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(54) **Title:** ANTIDEPRESSIVA FOR TREATMENT OF METABOLIC SYNDROME

(57) **Abstract:** The invention provides serotonin selective reuptake inhibitor for treatment, amelioration or prevention of metabolic syndrome and disorders associated thereto, including cardiovascular disorders, dyslipidemia, neuropathy, nephropathy, retinopathy, type 2 diabetes mellitus. In particular the method is intended for animals including human beings with hypothalamus-pituitary-adrenal axis (HPA axis) hyperactivity. Moreover, the method may be applied to animals, which have been subject to foetal stress, low gestational weight, low birth weight and/or preterm birth.

Antidepressiva for treatment of metabolic syndrome

Field of invention

The present invention relates to the use of serotonin selective reuptake inhibitor for the treatment of diseases not previously known to be affected by the selective reuptake inhibitors.

Background of invention

The hypothalamic-pituitary-adrenal axis (HPA axis) is a complex set of direct influences and feedback interactions between the hypothalamus, the pituitary gland, and the adrenal or suprarenal gland. These fine, homeostatic interactions constitute the HPA axis, which is a central part of the neuroendocrine system that controls reactions to stress and regulates various body processes including digestion, the immune system, mood and sexuality.

A key function of the HPA axis is the synthesis and secretion of vasopressin and corticotropin-releasing hormone (CRH), which then stimulate the secretion of adrenocorticotropic hormone (ACTH), once known as corticotropin. ACTH then stimulates the production of glucocorticoid hormones, such as cortisol in humans, by the adrenal cortices. Glucocorticoids in turn act back on the hypothalamus and pituitary in a negative feedback cycle to suppress production of CRH and ACTH.

The release of CRH from the hypothalamus is influenced by a number of factors, such as stress, cortisol in the blood and the sleep/wake cycle. In healthy individuals, cortisol rises rapidly after wakening, peaking within 30-45 minutes. It then gradually falls over the day, rising again in late afternoon. Cortisol levels then fall in late evening, reaching a trough during the middle of the night. An abnormally flattened circadian cortisol cycle has been linked with chronic fatigue syndrome (MacHale, 1998), insomnia (Backhaus, 2004) and burnout (Pruessner, 1999).

Glucocorticoids have many important functions, including modulation of stress reactions. An excess of glucocorticoids, however, can be damaging. Atrophy of the hippocampus in humans and animals exposed to severe stress is believed to be caused by prolonged exposure to high concentrations of glucocorticoids. Deficiencies

of the hippocampus may reduce the memory resources available to help a body formulate appropriate reactions to stress.

The HPA axis is also involved in the neurobiology of mood disorders and functional illnesses, including anxiety disorder, bipolar disorder, post-traumatic stress disorder, clinical depression, burnout, chronic fatigue syndrome and irritable bowel syndrome.

Selective serotonin reuptake inhibitors (SSRIs) are a group of antidepressant drugs used primarily in the treatment of depression, anxiety disorders and some personality disorders. SSRIs increase the extracellular level of the neurotransmitter serotonin by inhibiting its reuptake into the presynaptic cell, increasing the level of serotonin available to bind to the postsynaptic receptor. They have varying degrees of selectivity for the other monoamine transporters; for example, SSRIs have little binding affinity for the noradrenaline and dopamine transporters.

Summary of invention

The present invention discloses the use of serotonin selective reuptake inhibitor for the treatment of diseases not previously known to be affected by the selective reuptake inhibitors.

In one aspect, the present invention relates to a method for treating, ameliorating, and/or preventing metabolic syndrome and/or a disorder or condition associated with metabolic syndrome comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof.

Another aspect of the present invention pertains to a use of SSRI for the manufacture of a medicament for treating, ameliorating, and/or preventing metabolic syndrome.

In a third aspect, the present invention relates to SSRI for treating, ameliorating, and/or preventing metabolic syndrome.

Yet a fourth aspect of the present invention relates to a pharmaceutical composition comprising SSRI for treating, ameliorating, and/or preventing metabolic syndrome.

Embodiments of the four aspects mentioned above include treatment, amelioration, and/or prevention of disorders such as cardiovascular disorders, dyslipidemia, and/or type 2 diabetes mellitus, as well as conditions associated with said disorders, including obesity, in particular visceral obesity. Cardiovascular disorders include disorders selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, microangiopathy, macroangiopathy, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication. Moreover, embodiments include treatment, amelioration and/or prevention of neuropathy, nephropathy, and/or retinopathy.

In a preferred embodiment of the four aspects, metabolic syndrome is associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity. In another preferred embodiment, the animal including a human being referred to above has been subject to foetal stress, such as preterm birth, and/or low gestational weight, and/or low birth weight.

Another aspect of the present invention pertains to a method for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication.

Moreover, an aspect of the present invention relates to a method for treating, ameliorating, and/or preventing a disorder or condition comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy,

macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication, and wherein said animal has been subject to foetal stress.

Another aspect relates to a method for treating, ameliorating, and/or preventing a disorder or condition comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication.

A further aspect of the present invention relates to the use of SSRI for the manufacture of a medicament for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, with the proviso that the disease is not depression, anxiety disorders and other affective disorders, such as generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder or drug abuse.

Another aspect of the present invention relates to the use of SSRI for the manufacture of a medicament for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective

reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are as aforementioned.

A further aspect of the present invention relates to the use of SSRI for the manufacture of a medicament for treating, ameliorating, and/or preventing a disorder or condition comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are as aforementioned.

A ninth aspect relates to the use of a kit or pharmaceutical composition comprising SSRI for the treatment of the disorders as aforementioned.

Furthermore, an aspect pertains to a kit comprising a pharmaceutically effective amount of serotonin selective reuptake inhibitor for the treatment, amelioration and/or prevention of a disorder or condition as aforementioned.

In another aspect, the present invention relates to s method for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, with the proviso that the disease is not depression, anxiety disorders and other affective disorders, such as generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder or drug abuse.

Description of Drawings

Figure 1. Birth Weight and Subsequent Risk of Type 2 Diabetes: A Meta-Analysis, Thomas Harder, Elke Rodekamp, Karen Schellong, Joachim W. Dudenhausen and Andreas Plagemann, Odds ratios for type 2 diabetes mellitus in subjects with birth weights <2,500 g as compared with subjects with birth weights 2,500 g in a meta-analysis (1966–2005). Studies are ordered alphabetically by first author. The pooled

odds ratio (diamond) was calculated by means of a random-effects model. 95% confidence intervals (CIs) are shown in parentheses and as horizontal bars.

Figure 2. Characterization of 40 Days LBW Metabolism. Clamp Glucose Infusion Rate (GIR). Hyperinsulinemic Euglycemic Clamp Conditions. Data are means±sem. Differences are analyzed by use of two-tailed unpaired t-test.

Figure 3. Characterization of 40 Days LBW Metabolism. A. Rate of Peripheral Glucose Utilization. Hyperinsulinemic Euglycemic Clamp Conditions. B. Glucose Transport Activity in Gastrocnemius Muscle Tissue. Hyperinsulinemic Euglycemic Clamp Conditions Data are means±sem. Differences are analyzed by use of two-tailed unpaired t-test.

Figure 4. Insulin-Stimulated Glucose Metabolism in 40 Days Old Control and LBW Rats. A: Rates of insulin-stimulated glucose infusion (N=10-12). B: Rates of Peripheral Glucose Metabolism (Rd) (N=10-12). C: Rates of 2-Deoxy-Glucose Uptake in Gastrocnemic Muscle Tissue (N=10-12). Data are means±sem. Differences are analyzed by use of two-tailed unpaired t-test.

Figure 5. Hepatic Glucose Metabolism. A: Rates of fasting and insulin stimulated hepatic glucose production (HGP) in Control and LBW rats (N=10-12). B: Percent insulin suppression of HGP (N=10-12). C: Fasting and insulin stimulated hepatic PEPCK-mRNA Expression in Control and LBW rats (N=5-10). Data are means±sem. Differences are analyzed by use of two-tailed unpaired t-test.

Figure 6. Hepatic Insulin Action in 40 Days LBW Rats (1). Percent insulin suppression of HGP (N=10-12). Data are means±sem. Differences are analyzed by use of two-tailed unpaired t-test.

Figure 7. Hepatic Insulin Action in 40 Days LBW Rats (2). Hepatic Phosphoenol-Pyrovate-Carboxy-Kinase (PEPCK). mRNA Levels Assessed by RT-PCR. Data are means±sem. Differences are analyzed by use of two-tailed unpaired t-test.

Figure 8. HPA-Axis Regulation in LBW-Rats. A. 24 Hour Urine Corticosterone Excretion (N=8-12). Data are means±sem. Differences are analyzed by use of two-tailed unpaired t-test.

Figure 9. Corticosterone Secretion in Control and LBW Rats. A: 24-Hour urinary corticosterone excretion in Control and LBW rats (N=8-12). B: Plasma corticosterone increase above basal during restraint stress tests (N=6). Data are means±sem. Differences are analyzed by use of two-tailed unpaired t-test.

Figure 10. HPA-Axis Regulation in LBW-Rats. Immunohistochemical Staining for ACTH in Lateral Lobes of Rat PituitariesA. Representative Section of Con-Pituitary. Magnification: 1:100. (57 Positive Cells in Shown Section). B. Representative Section of LBW-Pituitary. Magnification: 1:100 (64 Positive Cells in Shown Section). C. Blinded Quantification of Number of ACTH Positive Cells. Data are means±sem. Differences are analyzed by use of two-tailed unpaired t-test.

Figure 11. Morphology and Number of Pituitary ACTH Secreting Cells and Fasting 8 A.M. Plasma ACTH Concentrations in Control and LBW Rats. B: Immuno-histochemical staining for ACTH in the lateral lobe of the pituitary in a Control rat. (Magnification: 1:100; 57 ACTH Positive Cells in Shown Section). A: Immuno-histochemical staining for ACTH in the pituitary lateral lobe of a LBW rat. (Magnification: 1:100; 64 ACTH Positive Cells in Shown Section). C: Quantification of ACTH positive cells in a random area of the lateral lobe of the pituitary in LBW rats. Number of ACTH positive cells expressed as percent of number of ACTH positive cells in Control lateral pituitary lobe (N=9-10). D: Plasma ACTH concentrations at 8 A.M. after 14 hours of fast in Control and LBW rats (N=9-10). Data are means±sem. Differences are analyzed by use of two-tailed unpaired t-test.

Figure 12. Birth weight Data are means±sem. Differences are analyzed by use of two-tailed unpaired t-test.

Figure 13. HPA-Axis Activity (1). Restraint Stress Corticosterone Secretion. Data are means±sem. Differences are Analysed by ANOVA & Newmann-Keuls Post Hoc Test. * $P<0.05$ LBWI-Saline vs. LBW-SSRI & vs. Control-Saline. # $P<0.01$ LBWI-Saline vs.

LBW-SSRI & vs. Control-Saline; P<0.05 Control-Saline vs. Control-SSRI. § P<0.01 LBW-Saline vs. LBW-SSRI.

Figure 14. HPA-Axis Activity (2). AUC60-90min Corticosterone Secretion during Stress. Data are means±sem. P-values displayed are results from ANOVA & Newmann-Keuls Post Hoc Test.

Figure 15. HPA-Axis Activity (3). 24 Hour Urine Corticosterone Excretion (Sampled in Metabolic Cages). Data are means±sem. P-values displayed are results from ANOVA & Newmann-Keuls Post Hoc Test.

Figure 16. Glucose-Insulin Homeostasis (1). After 5 Weeks of Escitalopram Treatment. Data are means±sem. ANOVA & Newman Keul post hoc test: * P<0.01 LBW-SSRI vs. LBW-Saline, Control-Saline & Control-SSRI. # P<0.05 LBW-SSRI vs. Control-Saline. § <0.01 LBW-SSRI vs. LBW-Saline.

Figure 17. Glucose-Insulin Homeostasis (2). After 5 Weeks of Escitalopram Treatment. Incremental Area Under The OGTT Curve. Data are means±sem. P-values displayed are results from ANOVA & Newmann-Keuls Post Hoc Test.

Figure 18. Glucose-Insulin Homeostasis (3). After 5 Weeks of Escitalopram Treatment. Insulin Levels Before and During OGTT. Data are means±sem. ANOVA & Newmann-Keuls post hoc test. *P<0.05 LBW-Saline vs. Control-Saline. #P<0.05 LBW Saline vs. Control-Saline & P<0.05 Control-Saline vs. Control-SSRI.

Figure 19. Glucose-Insulin Homeostasis (4). After 5 Weeks of Escitalopram Treatment. AUC of The Insulin Levels during OGTT. ANOVA & Dunnet´s Post Hoc Test: *P<0.05 LBW-Saline vs. Control-Saline.

Figure 20. Glucose-Insulin Homeostasis (5). After 5 Weeks of Escitalopram Treatment. HOMA-OGTT Index - Whole Body Insulin Sensitivity. ANOVA & Newman Keul post hoc test: *P<0.05 LBW-Saline vs. LBW-SSRI & vs. Control Saline; #P<0.01 LBW-SSRI vs. LBW-Saline. (See Masafumi Matsuda and Ralph Defronzo, Diabetes Care, vol. 22 (9) 1999).

Figure 21. Glucose-Insulin Homeostasis (5). After 5 Weeks of Escitalopram Treatment. Hepatic PEPCK mRNA Expression Levels. N=4-8 for all groups. Data are means±sem. P-values displayed are results from ANOVA & Newmann-Keul's Post Hoc Test.

Detailed description of the invention

The present invention relates to disorders associated with increased activity of the hypothalamus-pituitary-adrenal axis (HPA axis hyperactivity). HPA hyperactivity can be triggered by foetal stress, in particular conditions causing foetal growth retardation, low birth weight, low gestational weight and/or preterm birth. A hyperactive HPA axis has been linked to an increased risk of developing various disorders, including diabetes mellitus. Serotonin reuptake inhibitors (SSRIs) are a group of drugs, which down-regulate the activity of the HPA axis, and therefore, the present invention relates to the use of SSRI for the treatment of various disorders or conditions, which are associated with HPA axis hyperactivity and/or foetal stress.

Terms and definitions

To facilitate the understanding of the following description, a number of definitions are presented in the following paragraphs.

The term "treatment", as used anywhere herein comprises any type of therapy, which aims at terminating, preventing, ameliorating and/or treating a clinical condition as described herein. In a preferred embodiment, the term treatment relates to prophylactic treatment, i.e. a therapy to reduce the susceptibility of a clinical condition, a disorder or condition as defined herein.

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia (high blood sugar). Diabetes exists as an insulin dependent diabetes mellitus (type 1), and an insulin independent diabetes mellitus (type 2). In addition to those to forms, gestational diabetes exists, which occurs during pregnancy. This form, however, although having similar signs, symptoms, and consequences as type 1 and 2, have different causes and population distributions. A common cause of diabetes it that the beta cells of the pancreas is unable to produce sufficient insulin to prevent hyperglycemia. Type 1 is usually due to autoimmune destruction of the pancreatic beta cells, which produce insulin. The hallmark of type 2 is tissue-wide insulin resistance. Initially, the pancreatic beta cells will attempt to compensate for the insulin resistance by increased insulin

production. As a result, due to the exhausting insulin producing activity, type 2 diabetes mellitus, sometimes progresses to loss of beta cell function as well. Gestational diabetes is similar to type 2 diabetes mellitus, in that it involves insulin resistance. In gestational diabetes, the hormones of pregnancy cause insulin resistance in those women genetically predisposed to developing this condition.

Diabetes can cause many complications. Acute complications, such as hypoglycemia, ketoacidosis or nonketotic hyperosmolar coma, may occur if the disease is not adequately controlled. Serious long-term complications include cardiovascular disease; chronic renal failure; retinal damage, which can lead to blindness; nerve damage of several kinds, and microvascular damage, which may cause erectile dysfunction (impotence) and poor healing. Poor healing of wounds, particularly of the feet, can lead to gangrene, which can require amputation.

Types 1 and 2 are incurable chronic conditions. They are usually managed with a combination of dietary treatment and insulin supplementation. Careful control is needed to reduce the risk of long term complications, as described above. For type 2 diabetes mellitus, this can be achieved with combinations of diet, exercise and weight loss, various oral diabetic drugs, and insulin use for patients not responding to oral medication. Oral diabetic drugs help control blood glucose levels in people who still produce some insulin, which is the majority of people with type 2 diabetes. These drugs are not insulin and are usually prescribed to people with diabetes along with recommendations for making specific dietary changes and getting regular exercise. The drugs may lower blood glucose by stimulating the pancreas to release more insulin, or improve insulin's ability to move glucose into cells especially into the muscle cells. The oral diabetic drugs are often used in combination to achieve optimal blood glucose control. Adequate treatment of diabetes, as well as increased emphasis on blood pressure and cholesterol control as well as lifestyle factors, such as smoking cessation, exercise and keeping a healthy body weight, seems to improve the risk profile of the complications related to diabetes.

The term “insulin resistance” as used herein, relates to a condition in which the cells no longer respond well to insulin. As a result, the body secretes more insulin into the bloodstream in an effort to reduce blood glucose levels. It is often linked to obesity,

hypertension and high levels of fat in the blood. Many people with type 2 diabetes have insulin resistance.

Insulin-sensitivity can also be measured by hyperinsulinemic euglycemic clamp studies, oral glucose tolerance test (OGTT), fasting levels of circulating metabolites, levels of inflammatory cytokines, levels of hormones and adipokines.

Impaired oral glucose tolerance relates to the response to an oral glucose tolerance test. In this test, a fasting individual is subjected to an oral administration of glucose, and it is subsequently monitored how quickly the glucose is cleared from the blood. The test is indicative for diabetes and insulin resistance. Thus, the term “impaired oral glucose tolerance” as used herein, relates to a condition in which venous plasma glucose levels 2 hours after oral administration of a 1.75 gram dose of glucose per kg bodyweight is above 140 mg/dL but below 200mg/dL and/or where fasting venous plasma glucose is concentration is between 110 mg/dL and 126mg/dL. However in a specific embodiment of the present invention, impaired oral glucose tolerance relates to a state in which said venous plasma glucose concentration after oral administration of a 1.75 gram dose of glucose per kg bodyweight is above 130 mg/dL or above 132 mg/dL or above 134 mg/dL or above 136 mg/dL or above 138 mg/dL or above 142 mg/dL or above 144 mg/mL or above 146 mg/dL or above 148 mg/dL or above 150 mg/mL.

The term “hyperglycemia” as used herein, relates to a state of abnormally high levels of glucose in the blood. Specifically, hyperglycemia relates to a state in which fasting blood glucose level is consistently above 126 milligrams per deciliter (mg/dL) and/or venous plasma glucose levels 2 hours after oral administration of a 1.75 gram dose of glucose per kg bodyweight is above 200 mg/dL However in a specific embodiment of the present invention, hyperglycemia relates to a state in which fasting venous plasma glucose concentration is consistently above 110 mg/dL or above 112 mg/dL or above 114 mg/dL or above 116 mg/dL or above 118 mg/dL or above 120 mg/dL or above 122 mg/dL or above 124 mg/dL or above 128 mg/dL or above 130 mg/dL or above 132 mg/mL or above 134 mg/dL or above 136 mg/mL or above 138 mg/dL or above 140 mg/mL or above 142 mg/dL or above 144 mg/mL or above 146 mg/mL or above 148 mg/dL or above 150 mg/mL.

Fat is not uniformly distributed in the body. The major adipose depot, corresponding to about 80% is subcutaneous. The visceral fat depot resides inside the abdominal cavity. Thus, the term “visceral obesity” as used herein, relates to obesity with high amounts of visceral adipose tissues. Visceral obesity is frequently associated with high plasma triglycerides. The extent of visceral obesity can be determined by magnetic resonance (MR).

The term “cardiovascular disorders” as used herein refer to the class of diseases that involve the heart and/or blood vessels (arteries and veins). Therefore, the term “cardiovascular disorder” refers to any disease that affects the cardiovascular system. Particularly, cardiovascular disorders comprise atherosclerosis, arteriosclerosis, and arteriolosclerosis. Thus, in one embodiment of the present invention, the cardiovascular disorder is selected from the group consisting of atherosclerosis, arteriosclerosis, and arteriolosclerosis. However, atherosclerosis, arteriosclerosis, and arteriolosclerosis are also separate embodiments of the present invention, and can accordingly be claimed individually.

Atherosclerosis, a disease of the arteries, is one of the leading causes of death in the United States and Western Europe. The pathology of atherosclerosis and occlusive heart disease has been studied intensely. The earliest stage of atherosclerosis is the formation of "fatty streaks" in the carotid, coronary and cerebral arteries and in the aorta. These lesions are yellow in colour due to the presence of lipid deposits found principally within smooth-muscle cells and in macrophages of the intima layer of the arteries and aorta. Further, it is presumed that most of the cholesterol found within the fatty streaks, in turn, give rise to development of the "fibrous plaque", which consists of accumulated intimal smooth muscle cells loaded with lipid and surrounded by extra-cellular lipid, collagen, elastin and proteoglycans. The cells and the matrix form a fibrous cap that covers a deeper deposit of cell debris and more extracellular lipid. The lipid is primarily free and esterified cholesterol. The fibrous plaque forms slowly, and is likely in time to become calcified and necrotic, advancing to the lesion, which accounts for the arterial occlusion and tendency toward mural thrombosis and arterial muscle spasm that characterize advanced atherosclerosis.

The term “atherosclerosis” as used herein, relates to the disease of the arteries, which is characterized by formation of fibrous plaques that become calcified and necrotic,

advancing to a lesion, which may account for arterial occlusion and tendency toward mural thrombosis and arterial muscle spasm that characterize advanced atherosclerosis. It is understood, that the term “atherosclerosis” as used herein, relates to all the stages of development of that disease. Atherosclerosis may result in ischemic heart disease, thrombotic stroke, haemorrhagic stroke, as well as limb ischemia and claudication. The term “ischemic heart disease” as used herein, relates to any condition in which heart muscle is damaged or works inefficiently because of an absence or relative deficiency of its blood supply. Ischemic heart disease includes angina pectoris, acute myocardial infarction and chronic ischemic heart disease.

The term “thrombotic stroke” as used herein, relates to the disease state in which plaque formation inside a blood vessel blocks the flow of blood through the circulatory system. The term “haemorrhagic stroke” as used herein, relates to the disease state characterized by rupture of a vessel, which leads to internal bleeding, i.e. escape of blood to the extravascular space. In it understood that that term “haemorrhagic” as used herein, is meant to comprise all classes of haemorrhages.

The terms “limb ischemia” as used herein, relates to a restriction in the blood supply to the limbs, generally due to factors in the blood vessels, with resultant damage or dysfunction of tissue. Ischemia may result from a number of factors, including atherosclerosis. The term “claudication” as used herein, is related to limb ischemia and relates to a disease state with pain in the legs. Claudication usually occurs as a result of atherosclerosis.

Hypertension (or high blood pressure) is a condition, which occurs in the human population as a secondary symptom to various other disorders such as renal artery stenosis, pheochromocytoma, or endocrine disorders. However, hypertension is also evidenced in many patients in whom the causative agent or disorder is unknown. While such "essential" hypertension is often associated with disorders such as obesity, diabetes, and hypertriglyceridemia, the relationship between these disorders has not been elucidated. Additionally, many patients display the symptoms of high blood pressure in the complete absence of any other signs of disease or disorder.

It is known that hypertension can directly lead to heart failure, renal failure, and stroke (brain haemorrhaging). These conditions are capable of causing short-term death in a

patient. Hypertension can also contribute to the development of atherosclerosis and coronary disease. These conditions gradually weaken a patient and can lead to long-term death.

The exact cause of essential hypertension is unknown, though a number of factors are believed to contribute to the onset of the disease. Among such factors are stress, uncontrolled emotions, unregulated hormone release (e.g. dysfunctional renin-angiotensin-aldosterone system), excessive salt and water due to kidney malfunction, wall thickening and hypertrophy of the vasculature resulting in constricted blood vessels and genetic factors.

The treatment of essential hypertension has been undertaken bearing the foregoing factors in mind. Thus a broad range of beta-blockers, vasoconstrictors, angiotensin converting enzyme inhibitors and the like has been developed and marketed as antihypertensives. The treatment of hypertension utilizing these compounds has proven beneficial in the prevention of short-interval deaths such as heart failure, renal failure, and brain haemorrhaging. However, the development of atherosclerosis or heart disease due to hypertension over a long period of time remains a problem. This implies that although high blood pressure is being reduced, the underlying cause of essential hypertension is not responding to this treatment.

Hypertension has been associated with elevated blood insulin levels, a condition known as hyperinsulinemia, and therefore appears to be linked to diabetes mellitus. Insulin, apart from promoting glucose utilization, is also acts to promote protein synthesis and the formation and storage of neutral lipids. Additionally, insulin affects vascular cell growth and increase renal sodium retention, among other things. These latter functions can be accomplished without affecting glucose levels and are known causes of hypertension. Peripheral vasculature growth, for example, can cause constriction of peripheral capillaries, while sodium retention increases blood volume. Thus, a reduction of insulin levels in patients with hyperinsulinemia can prevent abnormal vascular growth and renal sodium retention caused by high insulin levels and thereby alleviates hypertension.

The term “hypertension” as used herein, relates to a state of abnormally increased blood pressure. Specifically, hypertension relates to a state in which blood pressure is

consistently above 140/90 mmHg over a period of more than 1 month. Systolic blood pressure is the top number. Diastolic blood pressure is the bottom number. However in a specific embodiment of the present invention, hypertension relates to a state in which blood pressure is consistently above 130/80 mmHg or 120/80 mmHg or 110/70 mmHg. Hypertension may have no known cause (essential or idiopathic hypertension) or be associated with other primary diseases (secondary hypertension).

Hypertension as well as cardiovascular disorder risk factors can be estimated by measurement of blood pressure and heart rate levels measured by telemetry, visceral fat pads, circulationg CVD risk factors: lipid profile, PAI1 etc., spontaneous physical activity and body temperature. The effects on left ventricular function of the heart can be measured by ultrasonical assessment of left ventricular function.

Hyperlipidemia is recognized as a primary risk factor in causing cardiovascular disease due to atherosclerosis. Thus, the treatment and prevention of cardiovascular disease emphasize the need for reduction of plasma cholesterol levels, and low density lipoprotein cholesterol in particular. Other independent risk factors include glucose intolerance, left ventricular hypertrophy, hypertension, and being of the male sex. Cardiovascular disease is especially relevant among diabetic subjects, at least in part because of the existence of multiple independent risk factors in this population. Successful treatment of hyperlipidemia in the general population, and in diabetic subjects in particular, is therefore of tremendous medical importance.

The terms “dyslipidemia” or “hyperlipidemia” as used herein, relates to disorders in the lipoprotein metabolism characterized by excess levels of blood lipids such as cholesterol, high-density lipoproteins and triglycerides. This condition is often associated with the occurrence of true diabetes and is often also accompanied by high blood pressure. A combination of these mentioned states are often referred to as “metabolic syndrome X” or “metabolic syndrome”, as explained elsewhere herein.

In a particular embodiment, the present invention relates to treatment of metabolic syndrome and/or a disorder or condition associated with metabolic syndrome in an animal including a human being, which has been subject to foetal stress. The term “foetal stress” is meant to comprise any event or condition, which may affect the foetus.

In preferred embodiments, foetal stress include preterm birth, low gestational weight and/or low birth weight.

The term "preterm birth" as used herein, is meant to comprise people born at less than 38 weeks of gestation, such as less than 37 weeks of gestation, less than 36 weeks of gestation, less than 35 weeks of gestation, less than 34 weeks of gestation, less than 33 weeks of gestation, less than 32 weeks of gestation, less than 31 weeks of gestation, less than 30 weeks of gestation, less than 29 weeks of gestation, less than 28 weeks of gestation, less than 27 weeks of gestation, less than 26 weeks of gestation, less than 25 weeks of gestation, less than 24 weeks of gestation, less than 23 weeks of gestation, less than 22 weeks of gestation, less than 21 weeks of gestation, or less than 20 weeks of gestation.

The term "low birth weight", as used herein, is meant to comprise weight at birth of less than 3600 grams, less than 3500 grams, less than 3400 grams, less than 3300 grams, less than 3200 grams, less than 3100 grams, less than 3000 grams, less than 2900 grams, less than 2800 grams, less than 2700 grams, less than 2600 grams, less than 2500 grams, less than 2400 grams, less than 2300 grams, less than 2200 grams, less than 2100 grams, less than 2000 grams, less than 1900 grams, less than 1800 grams, less than 1700 grams, less than 1600 grams, less than 1500 grams, less than 1400 grams, less than 1300 grams, less than 1200 grams, less than 1100 grams, and less than 1000 grams.

The term "low gestational weight", as used herein, depends on the gestational age of the foetus. Consequently the term low gestational weight is meant to comprise a weight at a gestational age of at least 40 weeks of less than 3600 grams, less than 3500 grams, less than 3400 grams, less than 3300 grams, less than 3200 grams, less than 3100 grams, less than 3000 grams, less than 2900 grams, less than 2800 grams, less than 2700 grams, less than 2600 grams, less than 2500 grams, less than 2400 grams, less than 2300 grams, less than 2200 grams, less than 2100 grams, less than 2000 grams, less than 1900 grams, less than 1800 grams, less than 1700 grams, less than 1600 grams, less than 1500 grams, less than 1400 grams, less than 1300 grams, less than 1200 grams, less than 1100 grams, or less than 1000 grams.
Moreover the term low gestational weight is meant to comprise a weight at a gestational age of at least 39 weeks of less than 2800 grams, less than 2700 grams,

less than 2600 grams, less than 2500 grams, less than 2400 grams, less than 2300 grams, less than 2200 grams, less than 2100 grams, less than 2000 grams, less than 1900 grams, less than 1800 grams, less than 1700 grams, less than 1600 grams, less than 1500 grams, less than 1400 grams, less than 1300 grams, less than 1200 grams, less than 1100 grams, or less than 1000 grams.

Low gestational weight also comprises a weight at a gestational age of at least 38 weeks of less than 2800 grams, less than 2700 grams, less than 2600 grams, less than 2500 grams, less than 2400 grams, less than 2300 grams, less than 2200 grams, less than 2100 grams, less than 2000 grams, less than 1900 grams, less than 1800 grams, less than 1700 grams, less than 1600 grams, less than 1500 grams, less than 1400 grams, less than 1300 grams, less than 1200 grams, less than 1100 grams, or less than 1000 grams, and at a gestational age of at least 37 weeks of less than 2800 grams, less than 2700 grams, less than 2600 grams, less than 2500 grams, less than 2400 grams, less than 2300 grams, less than 2200 grams, less than 2100 grams, less than 2000 grams, less than 1900 grams, less than 1800 grams, less than 1700 grams, less than 1600 grams, less than 1500 grams, less than 1400 grams, less than 1300 grams, less than 1200 grams, less than 1100 grams, or less than 1000 grams.

Low gestational weight also comprises a weight at a gestational age of at least 36 weeks of less than 2400 grams, less than 2300 grams, less than 2200 grams, less than 2100 grams, less than 2000 grams, less than 1900 grams, less than 1800 grams, less than 1700 grams, less than 1600 grams, less than 1500 grams, less than 1400 grams, less than 1300 grams, less than 1200 grams, less than 1100 grams, or less than 1000 grams, and at a gestational age of at least 35 weeks of less than 2400 grams, less than 2300 grams, less than 2200 grams, less than 2100 grams, less than 2000 grams, less than 1900 grams, less than 1800 grams, less than 1700 grams, less than 1600 grams, less than 1500 grams, less than 1400 grams, less than 1300 grams, less than 1200 grams, less than 1100 grams, or less than 1000 grams.

Furthermore, low gestational weight also comprises a weight at a gestational age of at least 34 weeks of less than 2200 grams, less than 2100 grams, less than 2000 grams, less than 1900 grams, less than 1800 grams, less than 1700 grams, less than 1600 grams, less than 1500 grams, less than 1400 grams, less than 1300 grams, less than 1200 grams, less than 1100 grams, or less than 1000 grams, and at a gestational age of at least 33 weeks of less than 2200 grams, less than 2100 grams, less than 2000 grams, less than 1900 grams, less than 1800 grams, less than 1700 grams, less than

1600 grams, less than 1500 grams, less than 1400 grams, less than 1300 grams, less than 1200 grams, less than 1100 grams, or less than 1000 grams.

Also, low gestational weight comprises a weight at a gestational age of at least 32 weeks of less than 2200 grams, less than 2100 grams, less than 2000 grams, less than 1900 grams, less than 1800 grams, less than 1700 grams, less than 1600 grams, less than 1500 grams, less than 1400 grams, less than 1300 grams, less than 1200 grams, less than 1100 grams, or less than 1000 grams, and at a gestational age of at least 31 weeks of less than 2200 grams, less than 2100 grams, less than 2000 grams, less than 1900 grams, less than 1800 grams, less than 1700 grams, less than 1600 grams, less than 1500 grams, less than 1400 grams, less than 1300 grams, less than 1200 grams, less than 1100 grams, or less than 1000 grams.

Finally, low gestational weight comprises a weight at a gestational age of at least 30, such as at least 29, for example at least 28, such as at least 27, such as at least 26, for example at least 25, such as at least 24 weeks, of less than 2000 grams, less than 1900 grams, less than 1800 grams, less than 1700 grams, less than 1600 grams, less than 1500 grams, less than 1400 grams, less than 1300 grams, less than 1200 grams, less than 1100 grams, or less than 1000 grams.

The term “retinopathy” as used herein refers to a noninflammatory degenerative damage to the retina of the eye. Retinopathy frequently occurs secondary to diabetes, but may also result from hypertension.

The term “neuropathy” as used herein refers to any disease that affects any part of the nervous system. Thus, neuropathy relates to any problem in peripheral nerve function (any part of the nervous system except the brain and spinal cord) that causes pain, numbness, tingling, swelling, and muscle weakness in various parts of the body.

The terms “microangiopathy” and “macroangiopathy” as used herein, refers to any disease resulting from complication in the small blood vessels (eyes, kidnneys, nerves), and large blood vessels (arteriosclerosis, cardiovascular disease), respectively.

The term “hypercholesterolemia” as used herein refers to the presence of high levels of cholesterol in the blood. Though not in itself a disease, hypercholesterolemia is secondary many disorders and can contribute to many forms of disease, for example

cardiovascular disease. Specifically, hypercholesterolemia relates to blood cholesterol levels above 200 mg/mL, preferably above 210 mg/mL, most preferably above 220 mg/mL, or above 230 mg/mL, or above 240 or above 250 mg/mL, or above 260 mg/mL.

The term "hyperinsulinemia" as used herein refers to a condition in which the level of insulin in the blood is higher than normal. Hyperinsulinemia is caused by overproduction of insulin

The term "an animal including a human being" is meant to comprise any animal. In a particular embodiment, the animal is a mammal, such as a rodent, for example a mouse and/or a rat. In a preferred embodiment, the animal including a human being is a human being.

The term "a subject in need thereof" as used herein, is meant to comprise animals including human beings, who has or is at risk of developing at least one of the diseases mentioned herein. In a specific embodiment, the subject also has HPA axis hyperactivity. In one embodiment, the subject is a mammal, such as rodents, for example mice and/or rats. Preferably the subject is a human being.

The term "genetic disposition" as used herein is meant to comprise any genetic variation, which increases the relative risk of developing a disorder or condition according to the present invention. A genetic disposition may be apparent from observations of a family history of the disorder or condition. The genetic variation may also be determined by biochemical and/or biological methods known to persons skilled within the art.

The term "obesity" as used herein relates to increased body weight caused by excessive accumulation of body fat. Obesity may for example be observed by assessing body mass index (BMI), defined as weight (W) in kg divided by squared height (H) in meters, i.e. (W (kg)/H^2 (M^2)). In the present invention, a human being is considered obese, when BMI is above 25, for example 26, such as 27, for example 28, such as 29, for example 30. In the context of the present invention, the term "obesity" preferably relates to visceral obesity.

HPA axis hyperactivity

In a preferred embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of an animal including human beings with HPA axis hyperactivity. HPA axis hyperactivity can lead to increased stress induced cortisol secretion and/or increased average daily cortisol secretion. Thus, in one embodiment, the methods, compositions, uses, SSRIs and kits of the present invention provides for the reduction of stress induced cortisol secretion and/or average daily cortisol secretion by treatment of HPA axis hyperactivity with SSRI drugs. Human beings with HPA axis hyperactivity display an increased level of circulating glucocorticoids. Thus, in one embodiment the methods, compositions, uses, SSRIs and kits according to the present invention can be used to treat human beings with increased levels of circulating glucocorticoids. In particular, the invention relates to the treatment of human beings with circulating levels of glucocorticoids in the bloodstream within the upper tertile of normal range or above normal range.

In one embodiment the methods, compositions, uses, SSRIs and kits according to the present invention can be used for treating human beings with increased level of stress induced glucocorticoid (e.g. cortisol in humans) in the plasma. In particular, the invention relates to the treatment of individuals with a stress induced increase above basal levels of glucocorticoid (e.g. cortisol in humans) in the plasma of at least 200 ng/mL, preferably at least 400 ng/mL, most preferably at least 500 ng/mL, or at least 600 ng/mL, or at least 700 ng/mL, or at least 800 ng/mL, or at least 900 ng/mL, or at least 1000 ng/mL, or at least 1100 ng/mL, or at least 1200 ng/mL, or at least 1300 ng/mL, or at least 1400 ng/mL, or at least 1500 ng/mL. In particular, the invention relates to the treatment of human beings with circulating levels of glucocorticoids in the bloodstream during stress within the upper tertile of normal range or above normal range.

Increased levels of urinary glucocorticoids are also indicative of HPA axis hyperactivity. Therefore, the present invention also relates to human beings with levels of 24 hours excretion urinary glucocorticoids (eg. Cortisol in humans) above 4 nmol/kg bodyweight, preferably above 6 nmol/kg bodyweight, most preferably above 8 nmol/kg bodyweight or above 10 nmol/kg bodyweight or above 12 nmol/kg bodyweight or above 14 nmol/kg bodyweight or above 16 nmol/kg bodyweight or above 18 nmol/kg bodyweight or above 20 nmol/kg bodyweight. In particular, the invention relates to the treatment of human

beings with urinary of glucocorticoids in the bloodstream within the upper tertile of normal range or above normal range.

HPA axis hyperactivity may also be determined by stress tests and measurement of basal ACTH levels. In a specific embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment of human beings with permanent HPA axis hyperactivity. The term "permanent HPA axis hyperactivity" as used herein, refers to HPA axis hyperactivity as define above, which last over a period of more than 1 month, preferably more than 2 months, or more than 3 months, or more than 4 months, or more than 5 months, or more than 6 months, or more than 7 months, or more than 8 months, or more than 9 months, or more than 10 months, or more than 11 months, or more than 12 months, most preferably more than 1 year, or more than 1.5 years, or more than 2 years, or more than 3 years, or more than 4 years, or more than 5 years, or more than 10 years or more than 15 years, or more than 20 years or more than 25 years, or more than 30 years.

The present invention also relates to the use of SSRI for the manufacture of a medicament for treating, ameliorating and/or preventing of an animal, including a human being, with HPA axis hyperactivity. In a specific embodiment, such HPA axis hyperactivity can be found in people, who have been exposed to foetal stress, as defined elsewhere herein.

The present invention relates furthermore to the use SSRI or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, or claudication.

Specifically, HPA axis hyperactivity can be found in people, who have been exposed to foetal stress.

HPA hyperactivity can be triggered by foetal stress, as defined elsewhere herein.

In addition, HPA axis hyperactivity is linked to an increased risk of developing various disorders, including diabetes mellitus. Therefore, the present invention also relates to disorders and conditions in individuals, who have been subject to foetal stress.

Thus, one embodiment of the present invention relates to a method for treating, ameliorating, and/or preventing a disorder or condition, comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, said animal having been subject to foetal stress, low gestational weight, and/or preterm birth, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication. Each of the disorders or conditions specified above is intended to be an individual embodiment. Consequently, a method for preventing each of them according to the present invention may be claimed individually.

It is appreciated that the disorders and conditions as defined in relation to a method for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, are also relevant for this embodiment.

In a further embodiment, the present invention relates to a method for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, said animal having been subject to foetal stress, low gestational weight, and/or preterm birth, wherein the disorders or

conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication. Each of the disorders or conditions specified above is intended to be an individual embodiment. Consequently, a method for treating, ameliorating, and/or preventing each of them according to the present invention may be claimed individually.

It is appreciated that the disorders and conditions as defined in relation to a method for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, are also relevant for this embodiment.

Disorders

In a preferred embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used to treat metabolic syndrome and/or a disorder or condition associated with metabolic syndrome. Metabolic syndrome is a cluster of metabolic risk factors in an individual. These risk factors are obesity, hypertension/cardiovascular disorders, type 2 diabetes mellitus, and dyslipidemia. Thus, the term “metabolic syndrome” according to the present invention is meant to comprise those risk factors. Metabolic syndrome is also sometimes referred to as metabolic syndrome X, syndrome X, insulin resistance syndrome, Reaven's syndrome or CHAOS.

Moreover a range of other disorders or conditions may be associated with metabolic syndrome. Such disorders and conditions comprise obesity, including visceral obesity, hyperglycemia, hypertension, dyslipidemia, and insulin resistance/impaired oral glucose tolerance. Metabolic syndrome is, thus, predictive of an increased risk of type 2 diabetes mellitus, atherosclerosis, including ischemic heart disease, thrombotic stroke, haemorrhagic stroke, and/or limb ischemia/claudication. Thus, in a specific

embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of disorders associated with metabolic syndrome, including type 2 diabetes mellitus; atherosclerosis, including ischemic heart disease, thrombotic stroke, haemorrhagic stroke, and/or limb ischemia/claudication. In another embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for treating, individuals with risk factors associated with metabolic syndrome, including without limitation overweight/obesity, including visceral obesity, hyperglycemia, hypertension, dyslipidemia, insulin resistance and impaired oral glucose tolerance.

In a particular embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of a cardiovascular disorder selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, microangiopathy, macroangiopathy, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication.

In a particular embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of neuropathy.

In a particular embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of nephropathy.

In a particular embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of retinopathy.

In a particular embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of dyslipidemia.

In a particular embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of a

condition associated with dyslipidemia selected from the group consisting of hypercholesterolemia, hyperlipidemia, obesity, and visceral obesity.

In a particular embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of a disorder associated with type 2 diabetes mellitus.

In a particular embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of a disorder associated with type 2 diabetes mellitus selected from the group consisting of hyperglycemia, hyperinsulinemia, obesity, visceral obesity, insulin resistance, and impaired oral glucose tolerance.

In a particular embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of diabetes mellitus, hypertension and/or cardiovascular disorders.

In a particular embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of diabetes mellitus.

In a particular embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of hypertension.

In a particular embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of cardiovascular disorders.

In another embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used for the treatment, amelioration and/or prevention of diabetes mellitus, and especially non-insulin dependent diabetes mellitus (Type 2 diabetes) including treatment or prevention of long-term complications, such as retinopathy, neuropathy, nephropathy, and micro- and macroangiopathy; treatment of

hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis or ischemia.

The present invention relates to a method for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity. This method comprises administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, with the proviso that the disease is not selected from depression, anxiety disorders and other affective disorders, such as generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder or drug abuse.

In particular, the present invention relates to treating, ameliorating, and/or preventing atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, or claudication. Each of the disorders or conditions specified above is intended to be an individual embodiment. Consequently, a method for treating, ameliorating, and/or preventing each of them according to the present invention may be claimed individually.

Thus, present invention relates to a method for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity,

dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication. Each of the disorders or conditions specified above is intended to be an individual embodiment. Consequently, a method for treating, ameliorating, and/or preventing each of them according to the present invention may be claimed individually.

Furthermore, the present invention relates to a method for treating, ameliorating, and/or preventing a disorder or condition comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication. Each of the disorders or conditions specified above is intended to be an individual embodiment. Consequently, a method for treating, ameliorating, and/or preventing each of them according to the present invention may be claimed individually.

Specifically, the present invention relates to a method for treating a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity in animal with one or more symptoms of the disorders or conditions specified herein. In one embodiment, the present invention relates to a method for treating a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome,

ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication. Each of the disorders or conditions specified above is intended to be an individual embodiment. Consequently, a method for treating, ameliorating, and/or preventing each of them according to the present invention may be claimed individually.

In one embodiment, the present invention relates to a method for treating a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, and hypertension, or selected from the group consisting of atherosclerosis, and hypertension.

In another embodiment, the present invention relates to a method for treating a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorder to be treated is atherosclerosis, hypertension, or cardiovascular disorders.

In yet another embodiment, the present invention relates to a method for treating a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are selected from the group consisting of type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, and hyperlipidemia, or selected from the group consisting of type 2 diabetes mellitus, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, and hyperlipidemia, or selected from the group consisting of type 2 diabetes mellitus, hypercholesterolemia, hyperinsulinemia, and hyperlipidemia.

In another embodiment, the present invention relates to a method for treating a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are selected from the group consisting of retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy.

In one particular embodiment, the present invention relates to a method for treating a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorder to be treated is type 2 diabetes mellitus.

However, embodiments of the present invention also relate to a methods for treating a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorder to be treated is hypercholesterolemia or hyperinsulinemia.

In another embodiment, the present invention relates to a method for treating a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are selected from the group consisting of overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication, or selected from the group consisting of obesity, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, and metabolic syndrome, or selected from the group consisting of obesity, visceral obesity, dyslipidemia, and metabolic syndrome, or selected from the group consisting of metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication, or selected from the group consisting of ischemia, ischemic heart disease, thrombotic stroke, and haemorrhagic stroke, or selected from the group consisting of ischemia,

ischemic heart disease, and thrombotic stroke, or ischemic heart disease, thrombotic stroke, visceral obesity, metabolic syndrome, or hyperglycemia.

In a particular embodiment, the present invention relates to a method for treating a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorder or condition to be treated is insulin resistance.

It is also an object of the present invention to provide use of SSRI for the manufacture of a medicament for the treatment, amelioration and/or prevention of a disorder or condition as defined herein. In particular, such use is intended for the manufacture of a medicament for the treatment, amelioration and/or prevention of metabolic syndrome and/or a disorder or condition associated with metabolic syndrome as defined herein.

It is also an object of the present invention to provide use of at least one serotonin selective reuptake inhibitor (SSRI) for the preparation of a pharmaceutical composition for the treatment of a clinical condition associated with HPA hyperactivity as defined herein. Thus, in one embodiment the present invention provides a use of SSRI for the manufacture of a medicament for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof,
with the proviso that the disease is not depression, anxiety disorders and other affective disorders, such as generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder or drug abuse.

Furthermore, the invention relates to use of SSRI for the manufacture of a medicament for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor

(SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication.

In yet another embodiment, the present invention relates to the use of SSRI for the manufacture of a medicament for treating, ameliorating, and/or preventing a disorder or condition comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication.

Another central object of the present invention is to provide SSRI for the treatment, amelioration and/or prevention of a disorder or condition as defined herein. In particular, SSRI is provided for the treatment, amelioration and/or prevention of metabolic syndrome and/or a disorder or condition associated with metabolic syndrome as defined herein.

The invention also provides SSRI for the treatment of a clinical condition associated with HPA hyperactivity as defined herein. In one such embodiment, the present invention relates to SSRI for for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity, with the proviso that the disease is not depression, anxiety disorders and other affective disorders, such as generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social

anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder or drug abuse.

The present invention relates to SSRI for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication.

Moreover, the present invention relates to SSRI for treating, ameliorating, and/or preventing a disorder or condition comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication.

In a preferred embodiment of the present invention, the disorder or condition is insulin resistance. In another preferred embodiment, the disorder of condition is type 2 diabetes mellitus. In another preferred embodiment, the disorder or condition is atherosclerosis, arteriosclerosis, arteriolosclerosis, or hypertension. In yet another preferred embodiment, the disorder or condition is cardiovascular disease.

Foetal stress

In a preferred embodiment, the methods, compositions, uses, SSRIs and kits of the present invention can be used to treat metabolic syndrome and/or a disorder or condition associated with metabolic syndrome in an animal including a human being that has been subject to foetal stress. Examples of conditions which can lead to foetal stress include, but are not limited to, preterm birth, low gestational weight, foetal alcohol syndrome, maternal malnutrition, maternal smoking, maternal stress, maternal depression, and/or maternal systemic disease. Thus, in one embodiment the methods, compositions, uses, SSRIs and kits according to the present invention can be used for treatment of human beings, who have been subject to foetal stress, in particular people, who have been subject to preterm birth, low gestational weight, foetal alcohol syndrome, maternal malnutrition, maternal stress, maternal depression, and/or maternal systemic disease.

In addition, foetal stress can be caused without limitation by the following pregnancy conditions: preterm birth and/or small for date/low birth weight, maternal age below 17 years, below 16 years, below 15 years, below 14 years, maternal age above 35 years, above 40 years, above 45 years, above 50 years, above 55 years, above 60 years, maternal cardiovascular disease, maternal diabetic vascular disease, preeclampsia, eclampsia, mother with previous preterm birth, mother with previous still birth, mother with previous small for date/low birth weight offspring, maternal rubella infection, maternal urinary tract infection, maternal infection of vagina and/or uterus, maternal parvovirus B19 infection, placenta tumours, placenta insufficiency, placenta abruption, placenta infections, foetal congenital malformations, foetal chromosome abnormalities, reduced foetal production of insulin and/or insulin like growth factors, intra uterine growth retardation (IUGR), polyhydramnious and twin pregnancies (e.g. monochoric or dichoric, monoamniotic or diamniotic, dizygotic or monozygotic twin pregnancies and twin pregnancies complicated by twin to twin transfusion syndrome and/or pregnancies with more than 2 foetuses, more than 3 foetuses etc.). Thus, these conditions are also claimed as separate embodiments of the present invention.

In one embodiment of the present invention, the methods, compositions, uses, SSRIs and kits can be used for treatments of individuals of preterm birth with low gestational

weight, or individuals with low gestational weight, or individuals of extreme preterm birth with normal gestational weight.

Prevention

It is within the scope of the present invention to provide methods, uses, SSRIs, compositions and kits for preventing metabolic syndrome and/or a disorder or condition associated with metabolic syndrome as defined elsewhere herein. The term "preventing" as used herein refers to any measure, which diminishes the relative risk of acquiring a disorder or condition as defined herein. Thus, any level of reduced susceptibility to a disorder or condition as defined herein in response to a treatment according to the present invention is comprised in the terms "preventing" or "prevention".

In particular, the present invention relates to a method for preventing (i.e. prophylactic treatment of) a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity in an animal including a human being, which does not yet suffer from or display any clinical symptoms of any of the disorders or conditions specified herein.

Thus, one aspect of the present invention relates to a method for preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication. Each of the disorders or conditions specified above is intended to be an individual embodiment. Consequently, a method for treating, ameliorating, and/or preventing each of them according to the present invention may be claimed individually.

It is appreciated that the disorders and conditions as defined in relation to a method for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, are also relevant for this embodiment.

The present invention also relates to a method for preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity in an animal, which does not yet suffer from any of the disorders or conditions specified herein, said method comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to said animal including a human being, wherein said animal has been subject to foetal stress, low gestational weight, and/or preterm birth.

Thus in one embodiment, the present invention relates to a method for preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, said animal having been subject to foetal stress, low gestational weight, and/or preterm birth, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication. Each of the disorders or conditions specified above is intended to be an individual embodiment. Consequently, a method for preventing each of them according to the present invention may be claimed individually.

It is appreciated that the disorders and conditions as defined in relation to a method for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor

(SSRI) to an animal including a human being in need thereof, are also relevant for this embodiment.

The present invention furthermore relates to a method for preventing a disorder or condition in an animal, which does not yet suffer from any of the disorders or conditions specified herein, said method comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to said animal including a human being, wherein said animal has been subject to foetal stress, low gestational weight, and/or preterm birth.

Thus in one embodiment, the present invention relates to a method for preventing a disorder or condition, comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, said animal having been subject to foetal stress, low gestational weight, and/or preterm birth, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication. Each of the disorders or conditions specified above is intended to be an individual embodiment. Consequently, a method for preventing each of them according to the present invention may be claimed individually.

Still, it is appreciated that the disorders and conditions as defined in relation to a method for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, are also relevant for this embodiment.

Genetic disposition

The present invention also pertains to a method for preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity in an animal, which does not yet suffer from or display any clinical symptoms of any of the disorders or conditions specified herein, said method comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to said animal including a human being, wherein said animal is genetically predisposed for at least one of the disorders or conditions, and has been subject to foetal stress, low gestational weight, and/or preterm birth.

Thus in one embodiment, the present invention relates to a method for preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, said animal being genetically predisposed for said disorder or condition, and having been subject to foetal stress, low gestational weight, and/or preterm birth, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication. Each of the disorders or conditions specified above is intended to be an individual embodiment. Consequently, a method for preventing each of them according to the present invention may be claimed individually.

As mentioned for previous embodiments, it is appreciated that the disorders and conditions as defined in relation to a method for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, are also relevant for this embodiment.

The present invention further pertains to a method for preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity in an animal, which does not yet suffer from any of the disorders or conditions specified herein, said method comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to said animal including a human being, wherein said animal is genetically predisposed for at least one of said disorders or conditions.

Thus in one embodiment, the present invention relates to a method for preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, said animal being genetically predisposed for said disorder or condition, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication. Each of the disorders or conditions specified above is intended to be an individual embodiment. Consequently, a method for preventing each of them according to the present invention may be claimed individually.

It is appreciated that the disorders and conditions as defined in relation to a method for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, are also relevant for this embodiment.

The present invention also relates to a method for preventing a disorder or condition in an animal, which does not yet suffer from any of the disorders or conditions specified herein, said method comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to said animal including a

human being, wherein said animal is genetically predisposed for at least one of the disorders or conditions, and has been subject to foetal stress, low gestational weight, and/or preterm birth.

Thus in one embodiment, the present invention relates to a method for preventing a disorder or condition comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, said animal being genetically predisposed for said disorder or condition, and having been subject to foetal stress, low gestational weight, and/or preterm birth, wherein the disorders or conditions to be treated are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, cardiovascular disorders, type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, overweight, visceral obesity, dyslipidemia, insulin resistance, impaired oral glucose tolerance, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication. Each of the disorders or conditions specified above is intended to be an individual embodiment. Consequently, a method for preventing each of them according to the present invention may be claimed individually.

It is appreciated that the disorders and conditions as defined in relation to a method for treating, ameliorating, and/or preventing a disorder or condition associated with Hypothalamus-Pituitary-Adrenal-Axis hyperactivity comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof, are also relevant for this embodiment.

Specific embodiments

In a preferred embodiment, the present invention relates to methods, uses, SSRIs, compositions and kits for treating, ameliorating, and/or preventing type 2 diabetes mellitus, comprising administration of citalopram, escitalopram, or fluoxetine to an animal including a human being in need thereof, said animal having HPA axis hyperactivity.

In another preferred embodiment, the present invention relates to methods, uses, SSRIs, compositions and kits for treating, ameliorating, and/or preventing type 2 diabetes mellitus, comprising administration of SSRIs to an animal including a human being, said animal having been subject to foetal stress, as defines elsewhere herein. In one embodiment, the SSRIs are selected from the group consisiting of citalopram, escitalopram, or fluoxetine.

In yet another preferred embodiment, the present invention relates to methods, uses, SSRIs, compositions and kits for treating, ameliorating, and/or preventing type 2 diabetes mellitus, comprising administration of citalopram, escitalopram, or fluoxetine to an animal including a human being, said animal having HPA axis hyperactivity, and having also been subject to foetal stress, as defines elsewhere herein.

Combination treatments

It is further envisaged that the compounds of the present invention may be used in combination with at least one other compound. By administration “in combination” is meant herein that said other therapeutic compound may be administered prior to and/or during (including in a co-formulation) and/or after treatment with the compounds of the present invention. In one preferred embodiment, the SSRIs mentioned herein are administered together with one or more other compounds in a "kit-of-parts" system, for simultaneous, sequential or separate administration.
Preferred SSRI antidepressants include, but are not restricted to, Fluoxetine (Prozac), Fluvoxamine (Luvox), Paroxetine (Paxil, Paxil CR), Sertraline (Zoloft), Citalopram (Celexa) and Escitalopram oxalate (Lexapro).

Serotonin reuptake inhibitors

Serotonin is localized in the central and peripheral nervous systems and is known to affect many types of conditions including psychiatric disorders, motor activity, feeding behaviour, sexual activity, and neuroendocrine regulation among others.

Serotonergic neurotransmission is modulated by clearance of serotonin (5-hydroxytryptamine or 5-HT). The clearance of 5-HT from the synaptic cleft is maintained by the serotonin transporter (SERT). The transporter therefore affects the magnitude and duration of the signalling, and thus plays a key role in the spatio-temporal fine tuning of serotonergic neurotransmission.

The serotonin transporter (SERT), which belongs to a family of sodium/chloride-dependent transporters, is the major pharmacological target in the treatment of several clinical disorders, including depression and anxiety. Activation of a low affinity allosteric site on SERT modulates the ligand affinity at the high affinity binding site. Serotonin (5-HT), as well as some SERT inhibitors possesses affinity for both sites.

SERT is a well established molecular target of drugs of abuse (cocaine and amphetamines), as well as a number of high-affinity antidepressants. Multiple classes of antidepressants including tricyclic antidepressants, 5-HT selective reuptake inhibitors and antidepressants with dual actions are directed towards SERT. They enhance serotonergic neurotransmission by inhibiting 5-HT reuptake in a competitive manner with inhibitory constants in the low nanomolar range (Barker and Blakely, 1995;Owens et al., 1997;Tatsumi et al., 1997).

Several high affinity SERT inhibitors (citalopram, paroxetine, sertraline, imipramine) can also act as allosteric ligands (Plenge and Mellerup, 1985;Plenge et al., 1991). The affinity-modulating or allosteric site has been shown to be present at all three monoamine transporters, which in addition to SERT also includes transporters for dopamine and norepinephrine (Plenge and Mellerup, 1997).

Serotonin-selective reuptake inhibitors (SSRIs), such as fluoxetine (PROZAC (E)), have traditionally been the mainstay of treatment for clinical depression. SSRIs exert their therapeutic effect by blocking the reuptake of serotonin into the presynaptic nerve terminal, thus increasing the synaptic concentration of serotonin. It is also believed that SSRIs increase the efficacy of the serotonin (5-HT) neurons by desensitizing 5-HT autoreceptors located on the presynaptic 5-HT nerve terminals. The ability of the 5-HT autoreceptors to inhibit the release of 5-HT decreases after long-term treatment with SSRIs, with the net effect being that a greater amount of 5-HT is released per impulse.

The following nonrestricting list contains a number of serotonin reuptake inhibitors, which may be used in the present invention: citalopram, escitalopram, fluoxetine, R-fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, desmehtylvenlafaxine, duloxetine, dapoxetine, vilazodone, nefazodone, imipramine, imipramine N-oxide, desipramine, pirandamine, dazepinil, nefopam, befuraline, fezolamine, femoxetine,

clomipramine, cianoimipramine, litoxetine,cericlamine, seproxetine, WY 27587, WY 27866, imeldine, ifoxetine, indeloxazine, tiflucarbine, viqualine, milnacipran,bazinaprine, YM 922, S 33005, F 98214-TA, FI 4503, A 80426, EMD 86006, NS 2389, S33005, OPC 14523, alaproclate, cyanodothepine, trimipramine, quinupramine, dothiepin, Loxapine, nitroxazepine, McN 5652, McN 5707, VN 2222, L 792339, roxindole, YM 35992, OI 77, Org 6582, Org 6997, Org 6906, amitriptyline, amitriptyline N- oxide,nortriptyline, CL 255.663, pirlindole, indatraline, LY 280253, LY 285974, LY 113.821, LY 214.281, CGP 6085 A, RU 25.591, napamezole, diclofensine, trazodone, EMD 68.843, BMY 42.569, NS 2389, sercloremine, nitroquipazine, ademethionine, sibutramine, desmethylsubitramine, didesmethylsubitramine and clovoxamine vilazodone. The compounds mentioned above may be used in the form of the base or a pharmaceutically acceptable acid addition salt thereof. Each of the serotonin reuptake inhibitors specified above are also claimed in individual embodiments. Accordingly, each of them and the use thereof may be claimed individually.

Typically, compounds such as citalopram, escitalopram, fluoxetine, R-fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, desmethylvenlafaxine, duloxetine, dapoxetine, vilazodone, nefazodone, imipramine, imipramine N-oxide, desipramine, pirandamine, dazepinil, nefopam, befuraline,fezolamine, femoxetine, clomipramine,cianoimipramine, litoxetine, cericlamine, seproxetine, imeldine, ifoxetine, indeloxazine, tiflucarbine, viqualine,milnacipran, bazinaprine, alaproclate, cyanodothepine,trimipramine, quinupramine, dothiepin, amoxapine, Loxapine, nitroxazepine, roxindole, amitriptyline, amitriptyline N- oxide, nortriptyline, pirlindole, indatraline, napamezole, diclofensine, trazodone, sercloremine, nitroquipazine, ademethionine, sibutramine, desmethylsubitramine, didesmethylsubitramine, clovoxamine vilazodone, N- [(1- [(6-Fluoro-2-naphthalenyl) methyl]- 4-piperidinyl] amino] carbonyl]-3-pyridine carboxamide (WY 27587),[trans-6- (2-chlorophenyl)-1, 2,3, 5,6,10b-hexahydropyrrolo- (2,1-a)isoquinoline] (McN 5707),(dl-4-exo-amino-8-chloro-benzo- (b)-bicyclo [3.3. 1] nona-2-6 alpha (10 alpha) -diene hydrochloride) (Org 6997), <RTI (dl- [2- [4- (6-fluoro-1 H-indol-3-yl)-3, 6-dihydro-1 (2H)-pyridinyl] ethyl] -3-isopropyl-6-(methylsulphonyl)-3, 4-dihydro-lH-2, 1, 3-benzothiadiazine-2, 2-dioxide (LY393558), [4- (5, 6-dimethyl-2-benzofuranyl)-piperidine] (CGP 6085),dimethyl- [5- (4-nitro-phenoxy)-6, 7,8, 9-tetrahydro-5H-benzocyclohepten-7-yl]-amine (RU 25.591), are suitable as SSRIs. The compounds mentioned above may be used in the form of the

base or a pharmaceutically acceptable acid addition salt thereof. Each of the serotonin reuptake inhibitors specified above is intended to be an individual embodiment. Accordingly, each of them and the use thereof may be claimed individually.

In another embodiment the serotonin selective reuptake inhibitor is selected from the group consisting of citalopram, escitalopram, fluoxetine, sertraline, paroxetinem fluvoxamine, venlafaxine, dapoxetine, duloxetine, viazodone, nefazodone, imipramin, femoxetine and clomipramine.

It is understood, that the SSRIs specified in the present invention comprise derivatives, analogs, prodrugs, and pharmaceutically acceptable salts thereof, as well as compounds with comparable effects on HPA axis regulation. Certain of the compounds of the present invention may exist as stereoisomers including optical isomers. The invention includes all stereoisomers and both the racemic mixtures of such stereoisomers as well as the individual enantiomers that may be separated according to methods that are within the skill of the art.

Formulation

In one aspect, the present invention relates to a pharmaceutical composition comprising SSRI for treating, ameliorating, and/or preventing metabolic syndrome and/or a disorder or condition associated with metabolic syndrome. In one embodiment, the pharmaceutical composition comprises an effective amount of at least one SSRI. In a preferred embodiment the present invention relates to a pharmaceutical composition comprising SSRI for the treatment, amelioration and/or prevention of a disorder or condition as defined elsewhere herein. The pharmaceutical composition is particularly suitable for treatment of an animal including a human being that has been subject to foetal stress as defined elsewhere herein, preferably low gestational weight, low birth weight, preterm birth and/or has a genetic disposition for a disorder or condition as defined herein.

In general, the serotonin selective reuptake inhibitors of the present invention will be administered as pharmaceutical formulations including those suitable for oral (including buccal and sublingual), rectal, nasal, topical, pulmonary, vaginal, or parenteral (including intramuscular, intraarterial, intrathecal, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The

preferred manner of administration is generally oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction.

To prepare the pharmaceutical compositions of this invention, an appropriate amount of the active ingredient (s), in salt form or base form, is combined in an intimate admixture with a pharmaceutically acceptable carrier, which can take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable for administration orally, rectally, percutaneously or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. As used in the specification and claims, unit dosage form refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient (s) calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

A compound or compounds of the present invention, together with one or more conventional adjuvants, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds or principles, and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled

capsules, semisolids, powders, sustained release formulations, or liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration; or in the form of sterile injectable solutions for parenteral use. For example, in one embodiment, formulations containing about one (1) milligram of active ingredient or, more broadly, about 0.01 to about ten (10) grams, per tablet, are suitable unit dosage forms.

The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms. The pharmaceutical compositions and dosage forms may comprise a compound or compounds of the present invention or pharmaceutically acceptable salts thereof as the active component. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about one (1) to about seventy (70) percent of the active compound. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term"preparation"is intended to include the formulation of the active compound with encapsulating material as carrier, providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges may be as solid forms suitable for oral administration.

Other forms suitable for oral administration include liquid form preparations including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, or solid form preparations which are intended to be converted shortly before use to liquid form preparations. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents, for example, such as

lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents.

Solid form preparations include solutions, suspensions, and emulsions, and may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The compounds of the present invention may be formulated for parenteral administration (e. g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (e. g., olive oil), and injectable organic esters (e. g., ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for constitution before use with a suitable vehicle, e. g., sterile, pyrogen-free water.

The compounds of the present invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavored base, usually

sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatine and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

The compounds of the present invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example, with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size for example of the order of five (5) microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), for example, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, or carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve.

Alternatively the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and

polyvinylpyrrolidine (PVP).

The powder carrier can for example form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e. g., gelatine or blister packs from which the powder may be administered by means of an inhaler.

When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient. For example, the compounds of the present invention can be formulated in transdermal or subcutaneous drug delivery devices. These delivery systems are advantageous when sustained release of the compound is necessary and when patient compliance with a treatment regimen is crucial. Compounds in transdermal delivery systems are frequently attached to a skin-adhesive solid support. The compound of interest can also be combined with a penetration enhancer, e. g., Azone (1-dodecylazacycloheptan-2-one). Sustained release delivery systems are inserted subcutaneously into the subdermal layer by surgery or injection. The subdermal implants encapsulate the compound in a lipid soluble membrane, e. g., silicone rubber, or a biodegradable polymer, e. g., polylactic acid.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Other suitable pharmaceutical carriers and their formulations are described in Remington : The Science and Practice of Pharmacy 1995, edited by E. W. Martin, Mack Publishing Company,19th edition, Easton, Pennsylvania.

Administration

For administration, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate for the indicated route of administration.

The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinylpyrrolidine, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water, polyethylene glycol, propylene glycol, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, benzyl alcohol, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

The pharmaceutical compositions may be made up in a solid form including granules, powders or suppositories or in a liquid form such as solutions, suspensions, or emulsions. The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers, etc.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules.

In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water.

Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The SSRIs of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base.

Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of this invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of this invention can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

The SSRIs of the present invention can be used for treatment of the diseases as disclosed herein in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate,ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate and undecanoate. Also, the basic nitrogencontaining groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride,

bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained. In particular embodiments of the present invention the SSRI used to treat the diseases as disclosed herein is the hydrobromide and the hydrochloride of citalopram, and/or the oxalate of escitalopram.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.
For example, the compounds according to the present invention may be administered before, during or after the administration of the serotonin reuptake inhibitor, provided that the time between the administration of said compounds and the administration of the serotonin reuptake inhibitor is such that ingredients are allowed to act synergistically on the CNS. When simultaneous administration of the compounds according to the present invention and a serotonin reuptake inhibitor is envisaged, a composition containing both a serotonin reuptake inhibitor and the compounds according to the present invention may be particularly convenient. Alternatively, the compounds according to the present invention and the serotonin reuptake inhibitor may be administered separately in the form of suitable compositions. The compositions may be prepared as described elsewhere herein.

Dosage

In general, the SSRI of the present invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. In one preferred embodiment of the present invention, the invention comprises a method for treating a disease or disorder in an individual as defined elsewhere herein. Said method comprises administering to said individual, in a pharmaceutically acceptable carrier, a sufficient amount of any of the compounds disclosed herein. By "effecient amount" herein is meant a dose that produces the therapeutic effects for which it is administered. The exact dose will depend on the disorder to be treated, and will be ascertainable by one skilled in the art using known techniques. For example, the compound of the present invention can be administered to an animal in an amount of from 1 μg/kg to about 100 mg/kg per day. In addition, as is known in the art, adjustments for age as well as the body weight, general health, sex, diet, time of administration, drug interaction and the severity of the disease may be necessary, and will be ascertainable with routine experimentation by those skilled in the art.

In another embodiment, suitable dosage ranges are typically 1-500 mg daily, preferably 1-100 mg daily, 70-200 mg daily, 70-150 mg daily and most preferably 1-30 mg daily, 30-70 mg daily, 40-60 mg daily, 45-55 mg daily or about 50 mg daily. In another embodiment, the suitable dose of SSRI is 10 mg/kg bodyweight daily, preferably 20 mg/kg bodyweight, and most preferably 25 mg/kg bodyweight or 30 mg/kg bodyweight or 40 mg/kg bodyweight or 50 mg/kg bodyweight or 60 mg/kg. The suitable dose depends upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, the indication towards which the administration is directed, and the preferences and experience of the medical practitioner involved. One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of the present invention to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease.

In a specific embodiment, the SSRI according to the present invention is administered once daily. In the first week of treatment, for example 10 mg is administered, whereafter the dose may be increased to 20 mg.

Examples

In the examples, the following abbreviations are used: ACTH: adrenocorticoid hormone, BW: Body weight, CVD: Cardiovascular disease, LBW: Low birth weight, CBG: glucocorticoid binding globulin, GCCR: Glucocorticoid receptor, G6Pase: Glucose-6-phosphatase, HPA-axis: Hypothalamic-Pituitary-Adrenal-axis, PCR: Polymerase chain reaction, PEPCK: Phosphoenolpyruvate Carboxy-kinase, IUGR: intra-uterine growth retardation, CRH: Corticotropin releasing hormone.

According to the Barker Hypothesis harmful events taking place during the foetal period can induce life long changes in different organs predisposing to development of disease (1). In accordance with this hypothesis, individuals born with a birth weight of less than 5.5 lbs (LBW) are insulin resistant (2-9) and have increased prevalence of type 2 diabetes (3;4;10). The mechanisms responsible for these changes associated with LBW are unknown.

Recently, foetal stress and high plasma levels of glucocorticoids have been suggested to lead to hypothalamic-pituitary-adrenal axis (HPA-axis) hyperactivity, which after birth may result in chronically excessive adrenal glucocorticoid secretion, and an increased risk for the development of type 2 diabetes (11;12). However, these findings have been contrasted by other studies that have found no change (13) or decreased (14) HPA-axis activity in LBW rat models.
In order to examine the role of the HPA-axis in causing LBW associated insulin resistance insulin stimulated liver and muscle glucose metabolism may be assessed as well as HPA-axis activity in a rat model of stress-induced LBW, as shown in the examples below.

Epidemiological human studies have shown show LBW individuals to possess an increased risk of childhood behavioral problems. Furthermore, LBW individuals demonstrate an increased prevalence of psychological distress and depression in adulthood (even when corrected for confounders such as maternal socio-economical status, maternal depression, maternal psychological distress, early separation from the mother, smoking, alcohol, age etc.) (Gale CR et al, Br J Psychiatry 184: 28-33, 2004)

Example 1

Low Birth Weight and Hepatic Insulin Resistance - Increased Hypothalamic-Pituitary-Adrenal Axis Activity and Hepatic Insulin Resistance in Low Birth Weight Rats

Insulin sensitivity due to foetal stress was examined in a rat model of LBW. During the last 7 days of gestation rat dams were treated with dexamethasone and insulin sensitivity was assessed in the LBW offspring by a hyperinsulinemic-euglycemic clamp. The LBW group had liver specific insulin resistance associated with increased levels of PEPCK expression. These changes were associated with pituitary hyperplasia of the ACTH secreting cells, increased morning plasma ACTH concentrations, elevated corticosterone secretion during restraint stress, as well as an approximately 70% increase in 24 hour urine corticosterone excretion. The data show that prenatal stress can result in chronic hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis resulting in increased plasma corticosterone concentrations, up-regulation of hepatic gluconeogenesis, and hepatic insulin resistance.

Research Design and Methods

Animals: From day 7 of gestation pregnant female Sprague-Dawley rats (Charles River, Wilmington, MA) were housed singly under temperature (22-23ºC) and light-controlled (12:12h light/dark cycle) conditions. On day 14 of gestation rats were randomized into 3 groups: Control, dexamethasone treatment, or foster-mother group. From day 14 to day 21 of gestation a daily subcutaneously injection of dexamethasone (Sigma Aldrich) was given as 150µg/kg dissolved in 4% ethanol/saline solution at an concentration of 200µg/ml as previously described (15). Control dams were injected with a similar volume of the 4% ethanol/saline solution. Foster mothers were left undisturbed until delivery. To avoid postnatal influence of either dexamethasone or saline treatment, newborn pups were transferred to a healthy non-injected foster mother immediately after birth. Rats were weaned at 3 weeks of age and further studies were performed in male rats only.

24-hour urine collection: To minimize stress rats were housed singly in metabolic cages for one hour on two successive days prior to the 24-hour urine collection. Urine was collected in plastic tubes and immediately centrifuged at 4,000 rpm for 10 minutes at

4ºC to remove contaminants from debris of food and feces. Afterwards, total urine volume was determined and urine was kept frozen at -20ºC until further analysis. Restraint Stress Test: Rats were placed in a restrainer for 90 minutes, tail vein blood samples were collected at 0, 15, 30, 45, 60, 75 and 90 minutes, immediately centrifuged at 8,000 rpm for 20 seconds and stored at -20ºC until further analysis. Plasma corticosterone concentrations were assessed using a commercially available kit (MPBiomedicals Inc., East Lansing, MI).

Urine Corticosterone Concentrations: Corticosterone levels in urine were determined by LC/MS/MS using an internal standard (Valleyview Rd, Pelham, NH, cat#D3009). Total 24-hour urine corticosterone excretion was subsequently calculated by multiplying urine-corticosterone concentration and total 24-hour urine volume. Plasma ACTH Levels: At 8 a.m. after an overnight fast resting rats were quickly anesthetized with isoflurane, blood was collected by cardiac puncture and immediately transferred to a pre-cooled Eppendorf tube (4ºC) pre-treated with aprotine and phenyl-methane-sulphonyl-fluoride (PMSF) to neutralize protease-activity. The samples were subsequently centrifuged for 30 seconds at 4ºC, quick-frozen on dry ice and stored at -70ºC until further analysis. Plasma ACTH concentrations were measured by a commercially available kit (MPBiomedicals Inc., East Lansing, MI).

In Vivo Glucose Metabolism: Five to seven days before the studies indwelling catheters were placed into the jugular vein extending into the right atrium for blood collections and into the left carotid artery extending into the aortic arch for blood collection and infusions as previously described (16). Catheters were tunneled subcutaneously and externalized at the neck region of the rat, filled with a poly-vinyl-pyrrolidine-heparine solution and closed with tape.

Rats were fasted overnight for 12 hours prior to the clamp experiment and were awake, un-stressed and freely moving during the study. The 2-hour basal period was begun with a primed (10 μCi)-continuous (0.10 μCi/min) infusion of 3H-D-glucose and baseline venous blood was collected during the final 30 minutes for determination of plasma concentrations of glucose and insulin and for 3H-D-glucose specific activity. The 3-hour euglycemic-hyperinsulinemic clamp was initiated with a primed-continuous insulin infusion at a rate of 4mU/(kg-min) (R-100, Humulin, Eli Lilly & Co., Indianapolis, IN) and an additional primed (30μCi)-continuous (0.30μCi/min) infusion of 3H-D-

glucose. Plasma glucose levels were kept at 100 mg/dL by a variable infusion of 20% D-glucose. During the last 90 minutes of the clamp blood was collected every 15 minutes for the determination of plasma steady state concentrations of glucose and insulin and 3H-D-glucose specific activity. At the end of the clamp rats were euthanized by an intravenous injection of pentobarbital and liver, epididymal fat, and gastrocnemius muscles were quickly freeze-clamped in situ using aluminum tongs pre-cooled in liquid nitrogen and stored at -80ºC.

Plasma Metabolite and Hormone Concentrations: Plasma glucose concentrations were measured on a Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Plasma insulin concentrations were measured using a RIA kit (LINCO Research Inc., MS). Plasma samples for the determination of steady state specific activity of 3H-D-glucose were de-proteinized by 0.3N Barium Hydroxide, followed by 0.3N Zink Sulfate. Samples were centrifuged for 5 minutes at 12,000 rpm and the supernatant was dried overnight. Dry samples were re-suspended in filtrated water and 3H-D-glucose activity was counted in a liquid scintillation analyzer (Packard 2200CA, Canberra Packard Ltd., Pangbourne, UK).

Glucose Transport Activity in Muscle: To estimate insulin stimulated muscle and fat glucose transport activity an intravenous priming dose of 20 μCi 2-[1-14C]-deoxy-glucose was administered at T=90 minutes during the euglycemic-hyperinsulinemic clamp. Plasma specific activity of 2-[1-14C]-deoxy-glucose was measured at 91, 93, 95, 100, 105, 115, 125 and 135 minutes and with the concentrations of plasma glucose used to calculate glucose uptake activity in gastrocnemius muscle and epididymal fat. The tissues were diluted 10-fold in water, homogenized, and placed in a heat-block at 100ºC for 10 minutes. After cooling to room temperature, samples were centrifuged for 5 min, and the supernatant was diluted 1:15 with water. The total activity of 2-[1-14C]-deoxy-glucose was calculated as the sum of phosphorylated (intracellular) and un-phosphorylated (extracellular) fractions of 2-[1-14C]-deoxy-glucose. These fractions of 2-[1-14C]-deoxy-glucose were separated on anion exchange chromatography columns (Bio Rad Laboratories, Hercules, CA (Cat#731-6211)) for determination of intracellular 2-[1-14C]-deoxy-glucose. Tissue specific glucose transport activities were calculated from the amount of intracellular 2-[1-14C]-deoxy-glucose, plasma 2-[1-14C]-deoxy-glucose activity, and mean plasma glucose concentrations.

Quantitative RT-PCR for PEPCK: mRNA was isolated by use of mRNeasy Kit (Qiagen Inc, Valencia, CA) for liver and adipose tissue, respectively, in combination with DNAase digestion. Two micrograms of RNA were reversely transcribed with an oligo-prime (Stratagene, La Jolla, CA) and a PCR reaction was performed with a DNA Engine OptiControl 2 System (MJ Research, Boston, MA) by use of SYBR Green QPCR dye Kit. The primers for the different genes were: PEPCK: 5'CAG GAA GTG AGG AAG TTT GTG G 3' (L) and 5' ATG ACA CCC TCC TCC TGC AT 3' (R). Product specificity was confirmed by running products on an agarose gel and mRNA levels (CT-values) were expressed relative to 18S using the comparative method (17).

Immuno-Histochemical Staining for ACTH in Pituitaries: All brain fixations took place between 9 and 11 A.M. after isoflurane anesthesia. The right ventricle of the heart was opened to ensure venous out-flow and the abdominal aorta and vena cava were clamped to prevent perfusion of the lower carcass. The brain tissue was pre-fixed for 15 minutes by an arterial infusion of 2% paraformaldehyde in cold 0.1M Na Acetate (pH=6.5). After the pre-fixation, the brain was fixed in situ by a 25 minutes infusion of cold 2% paraformaldehyde in 0.1% glutaraldehyde in 0.1M Na Borate (pH=8.5). The skull was opened and the pituitary was isolated and fixed over-night in a super-fixation solution. For the ACTH immuno-histochemical examination, the paraffin was removed from the six-micron thick paraffin sections, which were treated with 3% H2O2 for 3 minutes, washed with tris-buffered saline, and covered with 2% normal goat serum for 30 minutes. Sections were incubated overnight at 4°C with primary antibody [mouse anti-ACTH antibody (1:300, Dako-M3501)] and the following morning, rinsed with tris-buffered saline, incubated with biotinylated anti-mouse antibody for one hour, followed by a tris-buffered saline rinse and 1-hour incubation with a streptavidin-peroxidase complex. Immunoreactivity of the tissue was evaluated after treatment with di-aminobenzidine, a chromogen, and hematoxylin counterstaining. Four representative regions for each pituitary were examined in a blinded fashion, a digital picture was taken of each of these four regions of each pituitary, and the ACTH-positive cells were counted using a counting grid. The number of ACTH-positive cells is the average of the four pictures and expressed in percent of the average number of ACTH-positive cells in control pituitaries.

Glucose Metabolism: Basal and insulin stimulated rates of glucose production were calculated as the ratio of 3H-D-glucose specific activity of infusate to the plasma

specific 3H-D-glucose activity and rates of hepatic glucose production and insulin stimulated peripheral glucose uptake were calculated as previously described (16). Statistical Analyses: Comparisons between LBW and Control rats were performed using the two-tailed Student's t-test. P-values of <0.05 were considered statistical significant. Software from PRISM Software Corporation, Irvine, CA was used for all statistical calculations. Data are given as mean ± standard error of the mean (SEM).

Results

Body Weight and Fasting Plasma Metabolites: At birth the LBW group weighed 13% less than the Control group (Control: 6.6±0.1 g [N=100] vs. LBW: 5.8±0.1 g [N=68]; P<0.00001). However, the LBW group gradually caught up and at the time of study at 40 days of age the weight of the LBW and Control groups were similar (Control: 151.1±10.3 g [N=10] vs. LBW: 167.9±5.3 g [N=12]; P=0.20). Fasting plasma concentrations of glucose (Control: 105.6±3.0 mg/dL [N=10] vs. LBW: 112.4±2.5 mg/dL [N=12]; P<0.01) and insulin (Control: 6.2±0.8 mU/l [N=15] vs. LBW: 10.1±1.9 mU/l [N=16]; P=0.05) were slightly but significantly higher in the LBW compared to the Control group.

In vivo Glucose Metabolism: Rates of fasting hepatic glucose production (HGP) (Control: 8.1±0.8 mg/(kg-min) [N=10] vs. LBW: 9.3±0.6 mg/(kg-min) [N=12]; P=0.23) and the basal expression of PEPCK (Control [N=10]: 100.0±8.7% of Control levels [N=10] vs. LBW: 114.0±12.7% [N=10]; P=0.37) were similar between the groups. LBW rats were more insulin resistant than the Control rats as reflected by a 34% lower glucose infusion rate required to maintain euglycemia during the hyperinsulinemic-euglycemic clamp (Figure 4, panel A). In contrast, there were no differences between the rates of insulin stimulated peripheral glucose uptake between the groups (Figure 4, panel B) and accordingly, rates of insulin stimulated 2-deoxy-glucose uptake in gastrocnemius muscle were similar among the groups (Figure 4, panel C). Instead, this insulin resistance could entirely be attributed to severe hepatic insulin resistance as reflected by the lack of suppression of HGP during the clamp in the LBW compared to almost total suppression of HGP in the Control group (Figure 5, panel A and B).

The hepatic insulin resistance could be attributed to increased hepatic gluconeogenesis as reflected by the lack of suppression of PEPCK expression during

the clamp (Figure 5, panel C). Thus, after insulin stimulation PEPCK expression was 2.8-fold higher in the LBW than in the Control rats ($P<0.05$).

24-Hour Urinary Corticosterone Excretion: The 24-hour urine corticosterone excretion in the LBW group was 73% higher in the LBW than the Control group ($P<0.05$) (Figure 9, panel A).

Restraint Stress Test: The stress-induced increment above basal in plasma corticosterone concentrations from was increased by ~118% and ~120% in the LBW group at 75 and 90 minutes, respectively (Figure 9, panel B). In accordance with this, the total area under the curve from 60 to 90 minutes was ~106% higher in the LBW than in the Control group ($P<0.05$) (Figure 9, panel B, upper right corner).

Immuno-Histochemical Staining for ACTH: On histological examination, the pituitary gland appeared normal (Figure 11, panel A and B) but there were ~20% more ACTH positive cells in the pituitaries of the LBW rats as counted in 4 randomly chosen sections from the lateral pituitary lobes of each animal ($P<0.05$) (Figure 11, panel C).

Plasma ACTH Concentrations: Fasting plasma ACTH concentrations at 8 A.M. were ~2-fold increased in the LBW rats compared to the Control rats ($P<0.05$) (Figure 11, panel D).

Discussion

This model of LBW is the result of chronic foetal glucocorticoid exposure by daily dexamethasone administration to the dam throughout the last 7 days of pregnancy. This foetal glucocorticoid exposure causes reduced foetal growth and LBW and it is associated with the development of glucose intolerance and hypertension (15;18) comparable to the common observations in LBW humans (2;9;19-21). To study the earliest established metabolic effects of LBW, male rats were studied at 40 days of age (e.g. juvenile rats) when plasma glucose concentrations were normal but plasma insulin levels tended to be increased reflecting whole body insulin resistance.

These studies demonstrate that LBW, in a rat model of foetal stress, results in hepatic insulin resistance accompanied by impaired insulin suppression of mRNA expression of PEPCK, demonstrating impaired insulin suppression of hepatic gluconeogenesis. Furthermore, these alterations were associated with increased activity of the HPA-axis as reflected by increased plasma ACTH levels, an approximately 70% increase in 24-hour urinary corticosterone excretion and a prolonged increase in plasma

corticosterone levels during restraint stress. Consistent with these findings pituitary sections showed hyperplasia of the ACTH secreting cells.

In an earlier study Nyirenda et al. (15) found that foetal exposure to dexamethasone resulted in LBW, fasting hyperglycemia and glucose intolerance after an oral glucose challenge. In addition they found hepatic expression of mRNA PEPCK and PEPCK activity were increased. However, neither hepatic insulin sensitivity or HPA-axis activity were assessed in this study (15).

The model of LBW rats had normal fasting plasma glucose concentrations and normal rates of hepatic glucose production but severe hepatic insulin resistance as reflected by impaired suppression of hepatic glucose production during the hyperinsulinemic-euglycemic clamp compared to the control rats. This hepatic insulin resistance could be attributed to upregulation of hepatic gluconeogenesis as reflected by increased hepatic expression of PEPCK mRNA and increased PEPCK activity. Hepatic insulin resistance has been found in another model of LBW due to intrauterine stress caused by ligation of the maternal uterine arteries (13). In this model hepatic insulin resistance was associated with decreased hepatic insulin stimulated IRS-2 and Akt-2 phosphorylation and increased expression of PEPCK and glucose-6phosphatase mRNA. However, in contrast to our LBW model, these pups had normal birth weight and increased rates of hepatic glucose production. In addition, these authors did not find alterations in plasma corticosterone concentrations and speculated that hepatic insulin resistance in this model of LBW could possibly be ascribed to increased oxidative stress due to overproduction of reactive oxygen species in the liver (13). In vivo assessment of the HPA axis is very difficult in awake rodents and it is likely that the inability of these workers to detect increases in plasma corticosterone concentrations in their LBW model may be due to the oscillatory nature of corticosterone secretion and possible stress associated with blood collection, which may obscure differences between groups. To avoid these possible confounding effects we assessed 24-hour urinary glucocorticoid excretion in our study, since this measurement provides an integrated picture of adrenal glucocorticoid production, and it can be done in an awake animal with a minimal amount of stress. Using this approach we found that 24 hour urinary corticosterone excretion was increased by ~70% in the LBW group compared to the control group. These changes were associated with pituitary hyperplasia of the ACTH secreting cells, increased morning plasma ACTH concentrations, and elevated

corticosterone secretion during restraint stress. Taken together these data suggest that the increased corticosterone production in the LBW rats in our study can be attributed to increased HPA-axis activity.

It is well established that increased adrenal glucocorticoid production can result in increased rates of hepatic gluconeogenesis, due to increased expression of PEPCK (22,23) and in this study we show that hepatic insulin resistance was associated with increased mRNA expression of PEPCK and increased PEPCK activity. Inhibition of gluconeogenesis is much less responsive to insulin than inhibition of net hepatic glycogenolysis and increased gluconeogenic flux in this LBW model explains the observed hepatic insulin resistance during the hyperinsulinemic-euglycemic clamp (24).

Taken together, these data show that increased HPA-axis activity and hepatic insulin resistance, due to increased hepatic gluconeogenesis, is a major factor responsible for the impaired insulin action associated with LBW due to prenatal stress.

Example 2

SSRI for the treatment of LBW related disorders

Selective Serotonin Reuptake Inhibitors (SSRI) and related drugs are used to treat depression and other states potentially related to chronic stress and HPA-axis hyperactivity (e.g. chronic widespread musculoskeletal pain etc). Thus, in depressed and chronically stressed individuals with elevated cortisol levels, SSRI drugs are known to be capable of down-regulating HPA-axis activity and cortisol levels as the psychological state is improved (36; 38). In rats displaying HPA-axis hyperactivity, long-term SSRI treatment is also known to down-regulate this hormone axis. So, the HPA-axis down-regulating effect has been shown in both man and in animals displaying HPA-axis hyperactivity. In contrast, SSRI treatment of young healthy men has been shown to increase morning cortisol levels. In addition, SSRI also exerted a negative impact on glucose metabolism reflected by impaired oral glucose tolerance (25) Moreover, SSRI treatment of type 2 diabetic patients with depression has in some studies been demonstrated an improved glucose homeostasis whereas in others it had deleterious effect on glucose metabolism (25). In these studies, however, no data exist as regards the level of HPA-axis activity prior to SSRI treatment.

Based on these previous observations, we believe that SSRI is capable of down-regulating HPA-axis hyperactivity in individuals displaying HPA-axis hyperactivity whereas in individuals with normal HPA-axis regulation SSRI has the opposite effect resulting in a possible deleterious effect on glucose metabolism.

As foetal stress, including LBW appears to be linked to increased HPA-axis activity, SSRI treatment would be capable of
1) restoring, at least partially, HPA-axis activity in to a normal range
2) through diminishment of circulating glucocortioids, improving glucose homeostasis by reducing glucocortioid drive on hepatic gluconeogenesis.

These issues was addressed by studying the same rat model for LBW as in example 1. At an age of 40 days where the rats are known to exhibit HPA-axis hyperactivity and hepatic insulin resistance, the rats were treated with SSRI (oral mixture of Escitalopram (Cipralex®) diluted with 0.9% saline into a concentration of 1.4 mg/ml, pH adjusted to 4.95 and given at a dose of 10mg/kg twice a day as an intra-peritoneal injection) or saline. In addition, a group of normal birth weight controls were also treated with either SSRI or saline. After 5 weeks of treatment, an oral glucose tolerance test was performed by administration of 2.5g glucose/kg body weight as insulin and glucose levels were measured at 0, 30, 60 & 120 minutes after the administration of the glucose load. In addition, corticosterone secretion during restraint stress (rats were restrained in PVC tubes) was measured at 0, 15, 30, 45, 60, 75 and 90 minutes after initiation of restrain and 24 hour urine collection was carried out in metabolic cages to assess the average 24 hour corticosterone levels. After 6 weeks, rats were sacrificed after an overnight fast (basal state) or 90 minutes after initiation of an OGTT (postprandial state). PEPCK mRNA levels were measured in hepatic tissues in both the basal and the postprandial state (90 minutes after oral administration of 2.5g glucose/kg body weight).

Additional Methods
Insulin levels were measured with a commercial ELISA kit and urine & plasma corticosterone levels were detected by use of a commercial RIA kit. Blood glucose levels were assessed by use of strip-glucometer.

PEPCK mRNA levels were detected by use of specific primers by use of RT-PCR and mean normalized expression levels were calculated based on CT-values by using GAPDH as housekeeping gene through the comparative method.

Results

As can be seen in Figure 12, birth weights of foetally dexamethasone exposed rats were significantly lower than controls.

Restraint Stress Test: Despite the initial plasma corticosterone concentrations in saline treated LBW rats were similar to saline treated Controls, LBW rats exhibited significantly higher plasma corticosterone levels from 60 to 90 minutes after initiation of restrain as compared to Control-Saline reflecting a prolonged stress induced corticosterone secretion-pattern in LBW-Saline rats (Figure 13) and, hence, the area under the curve from 60 to 90 minutes was also significantly higher (Figure 14). 5 weeks of SSRI administration, however, normalized the corticosterone secretion pattern of the LBW rats and therefore plasma corticosterone concentrations of LBW-SSRI rats were the same to those of the Control-Saline at al times during restrain (Figure 13 & Figure 14). In the contrary, SSRI administration seemed to exert the opposite effect in the Control-SSRI group with a resulting increase in corticosterone secretion during the last 30 minutes of the restrain. The difference, however, was only statistically significant at 75 minutes after initiation of the stress test and the area under the curve for the last 30 minutes was also not significantly different from Control-Saline rats.

24 Hour Urinary Corticosterone Excretion: As can be seen in Figure 15, Saline treated LBW rats excreted approximately 40% on average more corticosterone than Saline treated Controls as measured by the total 24 hour urinary corticosterone excretion. 5 to 6 weeks of SRRI treatment, however, significantly lowered the urinary corticosterone content in LBW-SSRI, but not in Control-SSRI.

Oral Glucose Tolerance Test:

Blood glucose levels in LBW-Saline were the same as Control-Saline except for at 120 minutes where the blood glucose level was slightly higher in the LBW-Saline group (Figure 16). The total area under the curve, however, was not different comparing Saline treated LBW and Control rats (Figure 17). Instead, SSRI treated LBW rats had lower glucose levels at al times as reflected by a significantly lower AUC as compared

to LBW-Saline, but also when compared to Saline and SSRI treated Controls, respectively. In contrast, SSRI treatment had no influence on OGTT glucose levels in Controls.

Despite close to normal glucose levels in Saline treated LBW rats vs. Controls, insulin levels in LBW rats were significantly higher throughout the glucose challenge – both when looking at timed plasma concentrations, but also when comparing the total area under the curve (Figure 18 & 19). SSRI administration, however, tended to decrease LBW-SSRI insulin concentrations but this change did not reach statistical significance. In contrast, SSRI tended to increase insulin levels in the Control rats and this change was in fact significant at 120 minutes as comparing Control-Saline to Control-SSRI. From fasting levels of glucose and insulin together with insulin and glucose levels during the OGTT the HOMA-OGTT insulin sensitivity index was calculated. As can be seen in Figure 20, LBW-Saline rats exhibited lower whole body insulin sensitivity as compared to the Control-Saline group. 5 to 6 weeks of SSRI administration, however, significantly increased insulin sensitivity in LBW-SSRI rats and further LBW-SSRI did not differ from saline treated Controls. In contrast, however, SSRI treatment significantly reduced insulin sensitivity in Control-SSRI.

Hepatic PEPCK mRNA levels: As can be seen in Figure 21, basal/fasting PEPCK mRNA expressions were the same as comparing all 4 groups. In the postprandial state, however, LBW-Saline rats did not fully suppress hepatic PEPCK expression when compared to Control-Saline rats and PEPCK levels were therefore approximately 96% higher on average. SSRI administration, however, restored the ability for LBW rats to fully suppress PEPCK to a level comparable to Controls. SSRI on the other hand did not impact postprandial PEPCK levels in Controls.

In this example, a selective seronotine reuptake inhibitor (Escitalopram) has been employed for the treatment of insulin-resistant LBW rats exhibiting HPA-axis hyperactivity. As shown previously in 40 days old LBW rats, saline treated LBW rats displayed a prolonged elevation in corticosterone secretion during restraint stress as compared to saline treated control rats and correspondingly had an increased area under the curve from 60 to 90 minutes after initiation of restrain. More importantly, however, present data shows for the first time that Escitalopram administration is capable of normalizing the corticosterone stress response during restraint stress in rats subjected to foetal growth retardation. Hence, Escitalopram treated LBW rats displayed

plasma corticosterone levels from 60 to 90 minutes that were comparable to saline treated controls. Interestingly, however, SSRI administration led to increased plasma corticosterone levels during restraint stress in control animals. This increase was statistically significant at 75 minutes after initiation of restrain comparing SSRI treated to saline treated controls, respectively, whereas the difference as regards the 60 to 90 minutes AUC did not reach statistical significance. As the total urinary corticosterone excretion during 24 hours was assessed the same picture emerged: SSRI treatment lowered the elevated glucocorticoids levels of the LBW phenotype into a range comparable to those of saline treated controls. In contrast, SSRI treatment did not influence this parameter in the control phenotype.

As shown previously in 40 days old LBW rats, saline treated LBW rats were insulin resistant as compared to saline treated controls as reflected by increased insulin levels in the fasted state as well as during a glucose challenge. These differences were further summarized into the HOMA-OGTT index also showing impaired whole body insulin sensitivity in the LBW phenotype compared to controls. As previously shown during hyperinsulinemic euglycemic clamp conditions, an impaired suppression of hepatic PEPCK levels in the LBW phenotype was demonstrated as PEPCK mRNA expressions levels of fasted liver tissues was compared to expressions in liver tissues taken out after 90 minutes after administrating an oral glucose challenge (postprandial state). More interesting, however, SSRI treatment restored the ability for the LBW animals to fully suppress hepatic PEPCK levels. As PEPCK is the rate limiting enzyme of gluconeogenesis and as the activity of this enzyme is primarily regulated at gene expression level our findings suggest that SSRI administration is capable of normalizing hepatic gluconeogenesis in LBW rats. In contrast, SSRI caused a deleterious effect on insulin-sensitivity in rats born normal birth weight as reflected by increased insulin levels during OGTT (statistically significant at120 minutes) and an impaired HOMA-OGTT index.

In summary, present data shows for the first time that insulin-sensitivity can be improved in insulin-resistant LBW rats by treatment with a selective serotonin reuptake inhibitor. The present data shows that SSRI related drugs should be administered cautiously as individuals with normal HPA-axis activity might not benefit from these drugs as HPA-axis activity might instead increase and thereby deteriorate glucose metabolism.

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Antidepressiva for treatment of metabolic syndrome

Claims

1. A method for treating, ameliorating, and/or preventing metabolic syndrome and/or a disorder or condition associated with metabolic syndrome comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof.

2. The method according to claim 1, wherein said metabolic syndrome is associated with Hypothalamus-Pituitary-Adrenal-Axis (HPA-axis) hyperactivity.

3. The method according to any of the preceding claims, wherein said animal has been subject to foetal stress.

4. The method according to any of the preceding claims for the treatment, amelioration, and/or prevention of a cardiovascular disorder.

5. The method according to claim 4, wherein said cardiovascular disorder is selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, hypertension, microangiopathy, macroangiopathy, metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication.

6. The method according to any of the preceding claims for the treatment, amelioration, and/or prevention of neuropathy.

7. The method according to any of the preceding claims for the treatment, amelioration, and/or prevention of nephropathy.

8. The method according to any of the preceding claims for the treatment, amelioration, and/or prevention of retinopathy.

9. The method according to any of the preceding claims for the treatment, amelioration, and/or prevention of dyslipidemia.

10. The method according to claim 9, wherein said dyslipidemia is selected from the group consisting of hypercholesterolemia, hyperlipidemia, obesity, and visceral obesity.

11. The method according to any of the preceding claims for the treatment, amelioration, and/or prevention of a disorder associated with type 2 diabetes mellitus.

12. The method according to claim 11, wherein said disorder associated with type 2 diabetes mellitus is selected from the group consisting of hyperglycemia, hyperinsulinemia, obesity, visceral obesity, insulin resistance, and impaired oral glucose tolerance.

13. The method according to any of the preceding claims, wherein the disorders or conditions to be treated, ameliorated and/or prevented are selected from the group consisting of atherosclerosis, arteriosclerosis, arteriolosclerosis, and hypertension.

14. The method according to any of the preceding claims, wherein the disorders or conditions to be treated, ameliorated and/or prevented are selected from the group consisting of atherosclerosis, and hypertension.

15. The method according to any of the preceding claims, wherein the disorders or conditions to be treated, ameliorated and/or prevented is atherosclerosis.

16. The method according to any of the preceding claims, wherein the disorders or conditions to be treated, ameliorated and/or prevented is hypertension.

17. The method according to any of the preceding claims, wherein the disorders or conditions to be treated, ameliorated and/or prevented is cardiovascular disease.

18. The method according to any of the preceding claims, wherein the disorders or conditions to be treated, ameliorated and/or prevented are selected from the group consisting of type 2 diabetes mellitus, retinopathy, neuropathy, nephropathy, microangiopathy, macroangiopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, and hyperlipidemia.

19. The method according to any of the preceding claims, wherein the disorders or conditions to be treated, ameliorated and/or prevented are selected from the group consisting of type 2 diabetes mellitus, hyperglycemia, hypercholesterolemia, hyperinsulinemia, and hyperlipidemia.

20. The method according to any of the preceding claims, wherein the disorders or conditions to be treated, ameliorated and/or prevented are selected from the

group consisting of retinopathy, neuropathy, nephropathy, microangiopathy, and macroangiopathy.

21. The method according to any of the preceding claims, wherein the disorders or conditions to be treated is type 2 diabetes mellitus.

22. The method according to any of the preceding claims, wherein the disorders or conditions to be treated, ameliorated and/or prevented is hypercholesterolemia.

23. The method according to any of the preceding claims, wherein the disorders or conditions to be treated, ameliorated and/or prevented are selected from the group consisting of metabolic syndrome, ischemia, ischemic heart disease, thrombotic stroke, haemorrhagic stroke, limb ischemia, and claudication

24. The method according to any of the preceding claims, wherein the disorders or conditions to be treated, ameliorated and/or prevented is ischemic heart disease

25. The method according to any of the preceding claims, wherein the disorders or conditions to be treated, ameliorated and/or prevented is insulin resistance.

26. The method according to any of the preceding claims, wherein said animal has been subject to foetal stress, low gestational weight, low birth weight and/or preterm birth,

27. The method according to any of the preceding claims, wherein the birth weight of said animal was less than 3000 grams.

28. The method according to any of the preceding claims, wherein the birth weight of said animal was less than 2500 grams.

29. The method according to any of the preceding claims, wherein the birth weight of said animal was less than 2200 grams.

30. The method according to any of the preceding claims, wherein said animal including a human being was born at less than 37 weeks of gestation.

31. The method according to any of the preceding claims, wherein said animal including a human being was born at less than 30 weeks of gestation.

32. The method according to any of the preceding claims, wherein said animal including a human being has a genetic disposition for said disorder or condition.

33. The method according to any of the preceding claims, wherein said animal including a human being has a family history for said disorder or condition.

34. The method according to any of the preceding claims, wherein the SSRI is selected from the group consisting of citalopram, escitalopram, fluoxetine, R-fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, desmehtylvenlafaxine, duloxetine, dapoxetine, vilazodone, nefazodone, imipramine, imipramine N-oxide, desipramine, pirandamine, dazepinil, nefopam, befuraline, fezolamine, femoxetine, clomipramine, cianoimipramine, litoxetine,cericlamine, seproxetine, WY 27587, WY 27866, imeldine, ifoxetine, indeloxazine, tiflucarbine, viqualine, milnacipran, bazinaprine, YM 922, S 33005, F 98214-TA, FI 4503, A 80426, EMD 86006, NS 2389, S33005, OPC 14523, alaproclate, cyanodothepine, trimipramine, quinupramine, dothiepin, Loxapine, nitroxazepine, McN 5652, McN 5707, VN 2222, L 792339, roxindole, YM 35992, OI 77, Org 6582, Org 6997, Org 6906, amitriptyline, amitriptyline N-oxide,nortriptyline, CL 255.663, pirlindole, indatraline, LY 280253, LY 285974, LY 113.821, LY 214.281, CGP 6085 A, RU 25.591, napamezole, diclofensine, trazodone, EMD 68.843, BMY 42.569, NS 2389, sercloremine, nitroquipazine, ademethionine, sibutramine, desmethylsubitramine, didesmethylsubitramine and clovoxamine vilazodone.

35. The method according to any of the preceding claims, wherein the SSRI is Escitalopram oxalate

36. The method according to any of the preceding claims, wherein the SSRI is citalopram.

37. The method according to any of the preceding claims, wherein the SSRI is fluoxetine.

38. Use of SSRI for the manufacture of a medicament for treating, ameliorating, and/or preventing metabolic syndrome.

39. The use according to claim 38 comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof.

40. The use according to any of claims 38 and 39, wherein said metabolic syndrome is associated with Hypothalamus-Pituitary-Adrenal-Axis (HPA-axis) hyperactivity.

41. The use according to any of claims 38 and 40, wherein said animal has been subject to foetal stress.

42. The use according to any of claims 38 to 41, wherein the disorders or conditions to be treated, ameliorated and/or prevented are as defined in any of claims 4 to 25.

43. The use according to any of claims 38 and 42, wherein said animal including a human being has been subject to foetal stress, low gestational weight, preterm birth and/or has a genetic disposition for said disorders or conditions according to claims 26 to 33.

44. The use according to any of claims 38 to 43, wherein said SSRI is as defined in any of claims 34 to 37.

45. SSRI for treating, ameliorating, and/or preventing metabolic syndrome.

46. SSRI according to claim 45 comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof.

47. SSRI according to any of claims 45 and 46, wherein said metabolic syndrome is associated with Hypothalamus-Pituitary-Adrenal-Axis (HPA-axis) hyperactivity.

48. SSRI according to any of claims 45 and 47, wherein said animal has been subject to foetal stress.

49. SSRI according to any of claims 45 to 48, wherein the disorders or conditions to be treated, ameliorated and/or prevented are as defined in any of claims 4 to 25.

50. SSRI according to any of claims 45 and 49, wherein said animal including a human being has been subject to foetal stress, low gestational weight, preterm birth and/or has a genetic disposition for said disorders or conditions according to claims 26 to 33.

51. SSRI according to any of claims 45 to 50, wherein said SSRI is as defined in any of claims 34 to 37.

52. A pharmaceutical composition comprising SSRI for treating, ameliorating, and/or preventing metabolic syndrome and/or a disorder or condition associated with metabolic syndrome.

53. The pharmaceutical composition according to claim 52 comprising administration of a therapeutically effective amount of at least one serotonin selective reuptake inhibitor (SSRI) to an animal including a human being in need thereof.

54. The pharmaceutical composition according to any of claims 52 and 53, wherein said metabolic syndrome is associated with Hypothalamus-Pituitary-Adrenal-Axis (HPA-axis) hyperactivity.

55. The pharmaceutical composition according to any of claims 52 and 54, wherein said animal has been subject to foetal stress.

56. The pharmaceutical composition according to any of claims 52 to 55, wherein the disorders or conditions to be treated, ameliorated and/or prevented are as defined in any of claims 4 to 25.

57. The pharmaceutical composition according to any of claims 52 and 56, wherein said animal including a human being has been subject to foetal stress, low gestational weight, preterm birth and/or has a genetic disposition for said disorders or conditions according to claims 26 to 33.

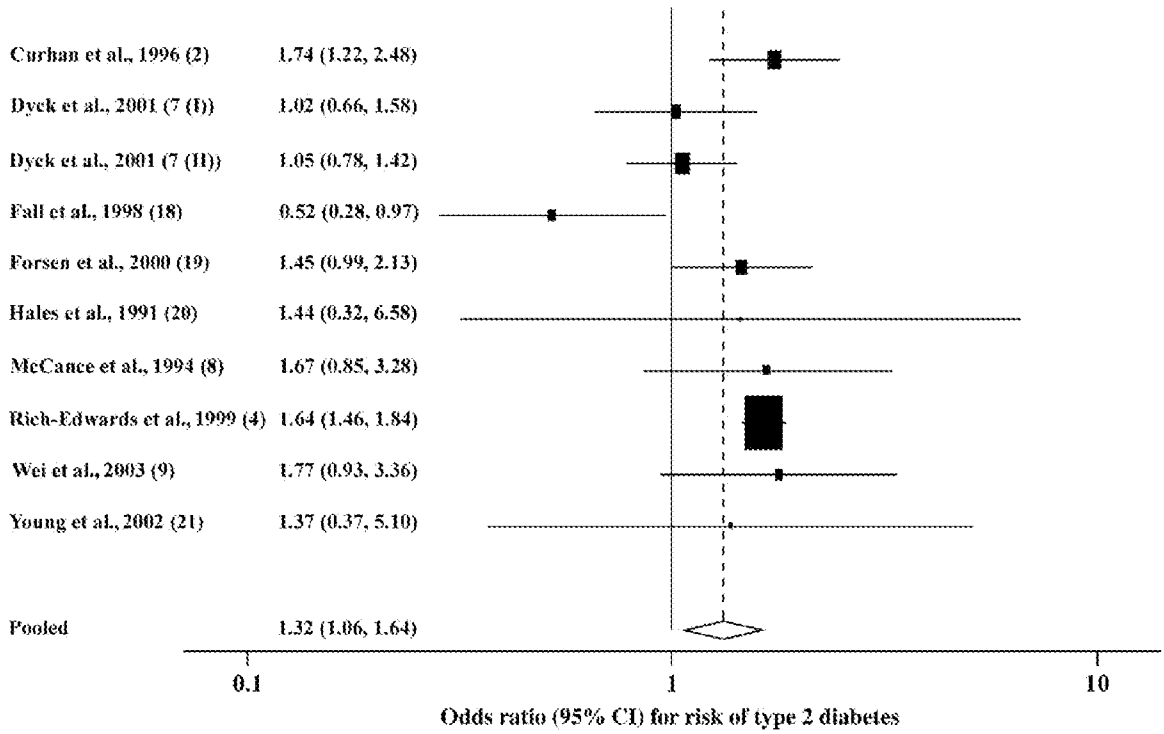
58. The pharmaceutical composition according to any of claims 52 to 57, wherein said SSRI is as defined in any of claims 34 to 37.

59. A kit comprising a pharmaceutically effective amount of serotonin selective reuptake inhibitor for the treatment, amelioration and/or prevention of a disorder or condition according to any of claims 4 to 25.

60. The kit according to claim 59, for administering of said compound to an animal including a human being in need thereof, as defined in claims 26 to 33.

61. The kit according to claims 59 and 60, further comprising instructions for administering of said compound.

Figure 1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Dyck et al., 2001 (7 (I)) 1.02 (0.66, 1.58)
Dyck et al., 2001 (7 (II)) 1.05 (0.78, 1.42)
Fall et al., 1998 (18) 0.52 (0.28, 0.97)
Forsen et al., 2000 (19) 1.45 (0.99, 2.13)
Hales et al., 1991 (20) 1.44 (0.32, 6.58)
McCance et al., 1994 (8) 1.67 (0.85, 3.28)
Rich-Edwards et al., 1999 (4) 1.64 (1.46, 1.84)
Wei et al., 2003 (9) 1.77 (0.93, 3.36)
Young et al., 2002 (21) 1.37 (0.37, 5.10)
Pooled 1.32 (1.06, 1.64)
0.1
1
10
Odds ratio (95% CI) for risk of type 2 diabetes

Figure 2

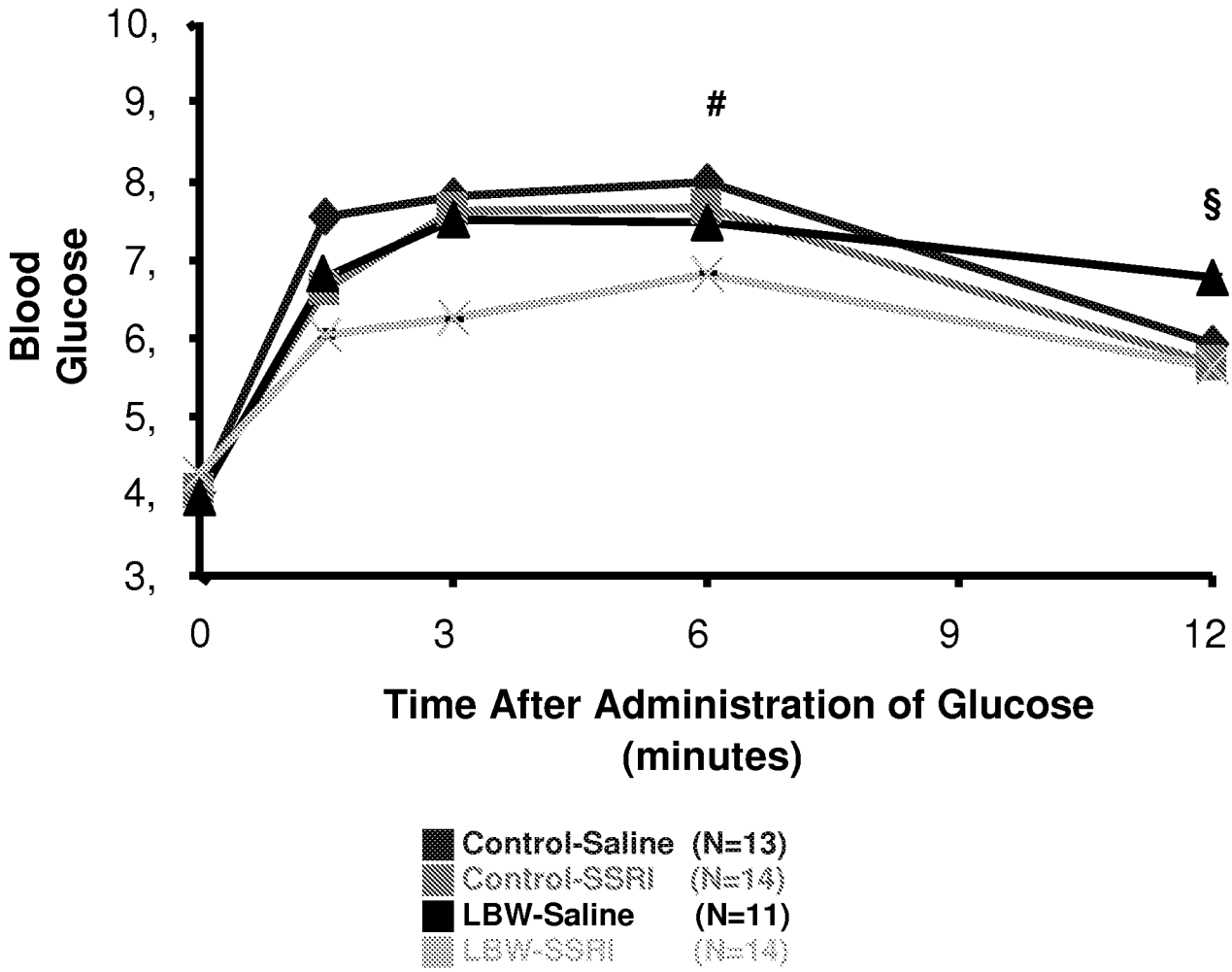

10,
9,
8,
7,
6,
5,
4,
3,
Blood Glucose
#
§
0
3
6
9
12
Time After Administration of Glucose (minutes)
Control-Saline (N=13)
Control-SSRI (N=14)
LBW-Saline (N=11)
LBW-SSRI (N=14)

Figure 3

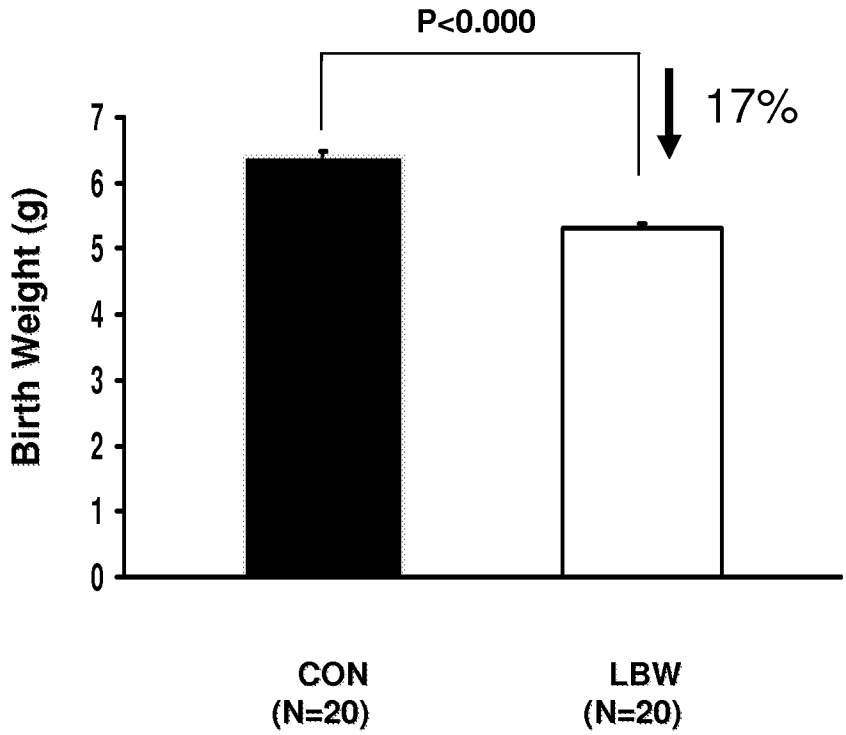


Figure 4

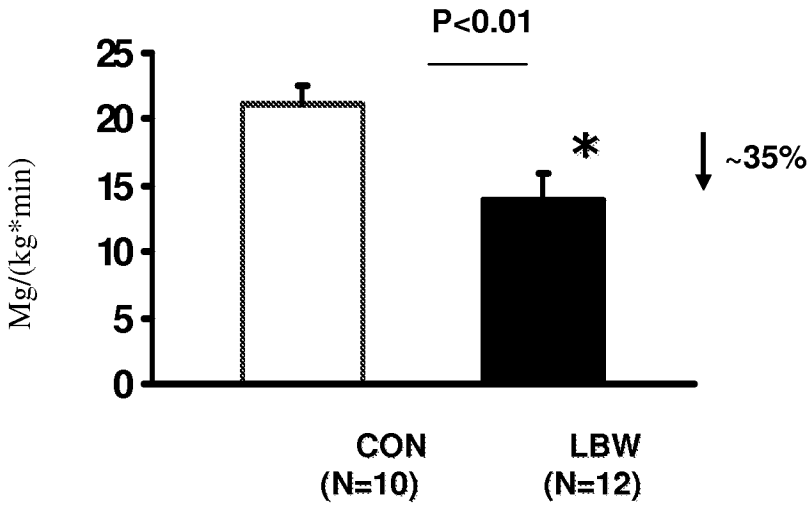


Figure 5

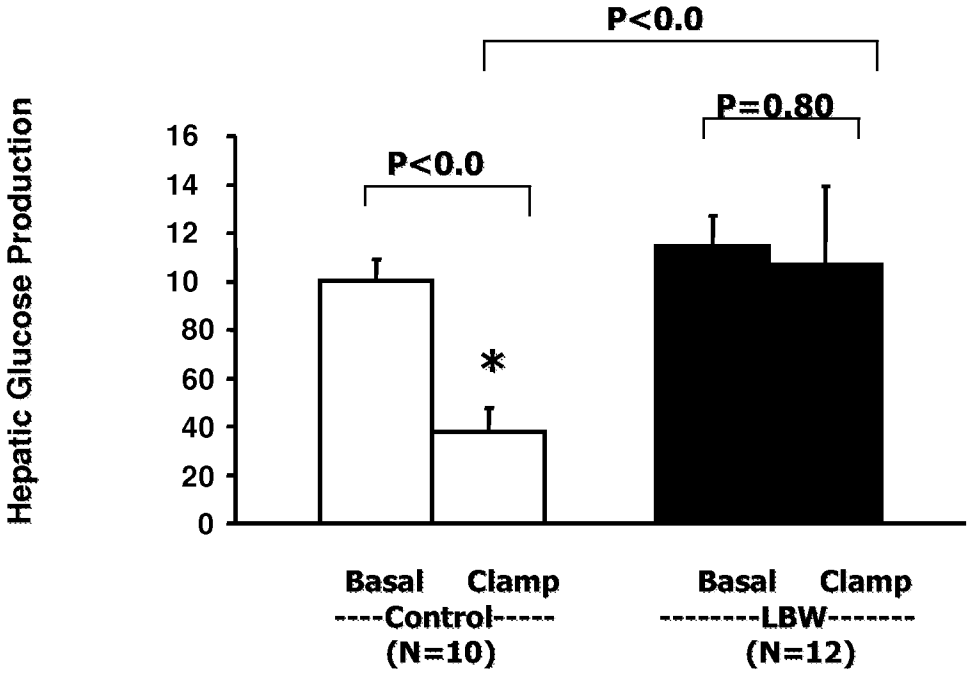
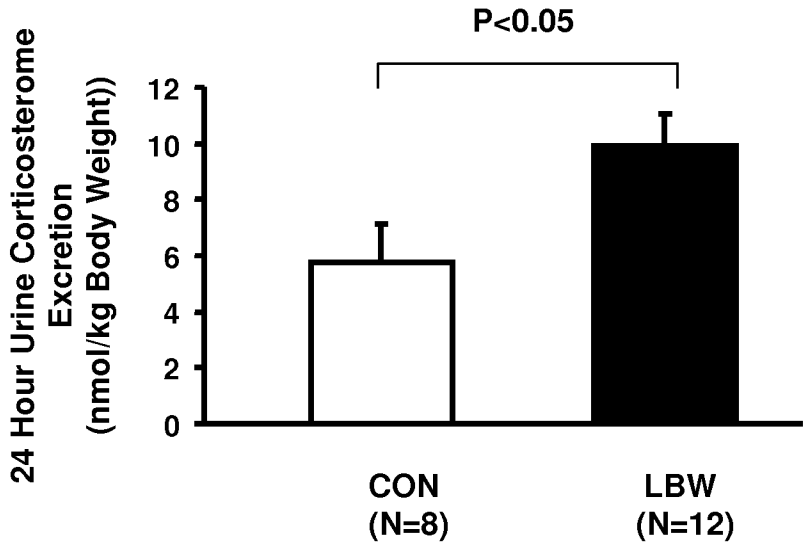

P<0.0
P=0.80
P<0.0
Hepatic Glucose Production
16
14
12
10
80
60
40
20
0
*
Basal Clamp
----Control-----
(N=10)
Basal Clamp
--------LBW-------
(N=12)

Figure 6

A


P<0.05
24 Hour Urine Corticosterome Excretion (nmol/kg Body Weight))
12
10
8
6
4
2
0
CON (N=8)
LBW (N=12)

B

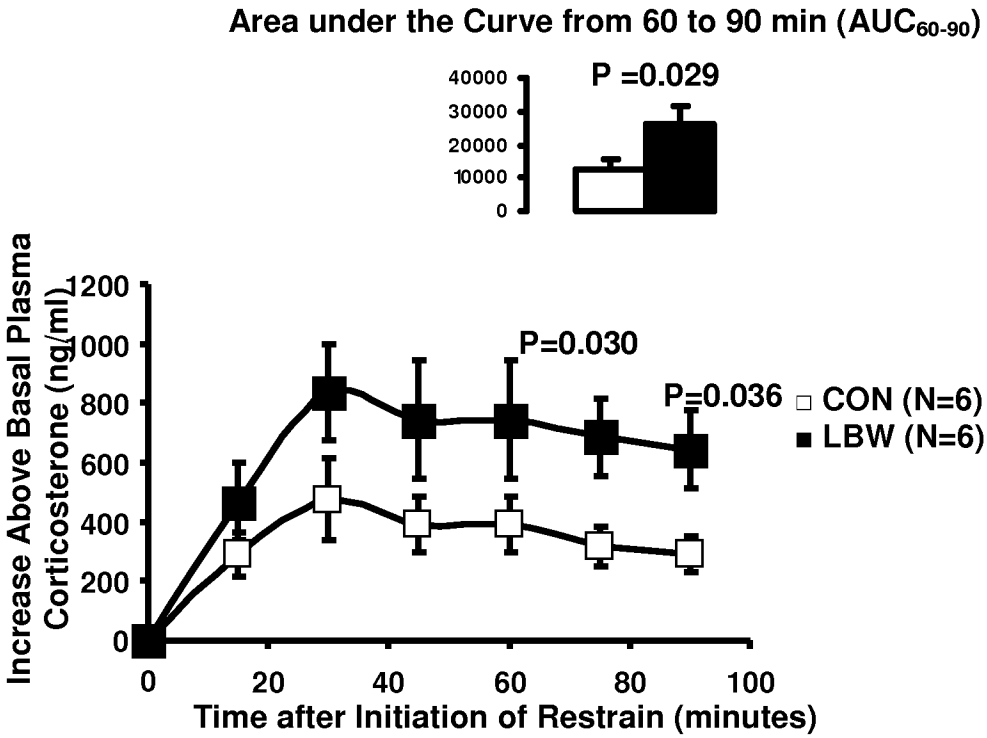
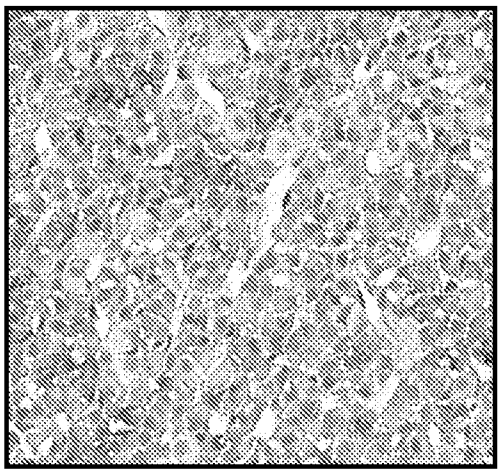
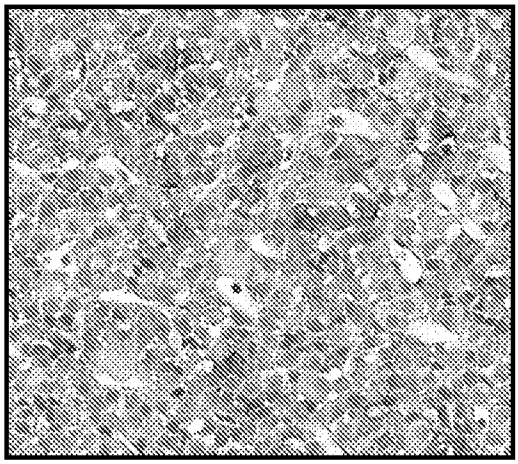

Area under the Curve from 60 to 90 min (AUC60-90)
P =0.029
40000
30000
20000
10000
0
Increase Above Basal Plasma Corticosterone (ng/ml)
1200
1000
800
600
400
200
0
P=0.030
P=0.036
CON (N=6)
LBW (N=6)
0
20
40
60
80
100
Time after Initiation of Restrain (minutes)

Figure 7

A



B



C

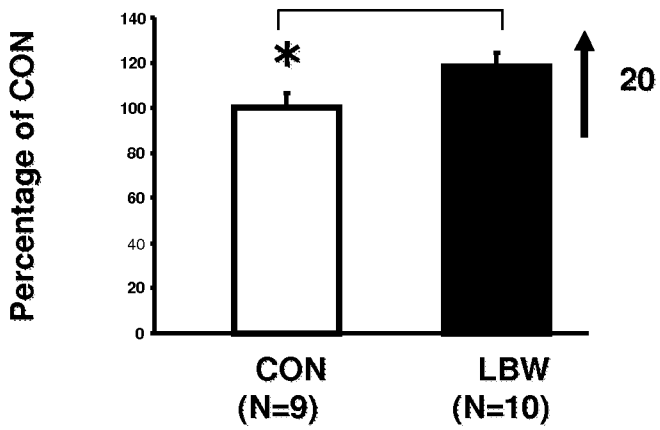


Figure 8

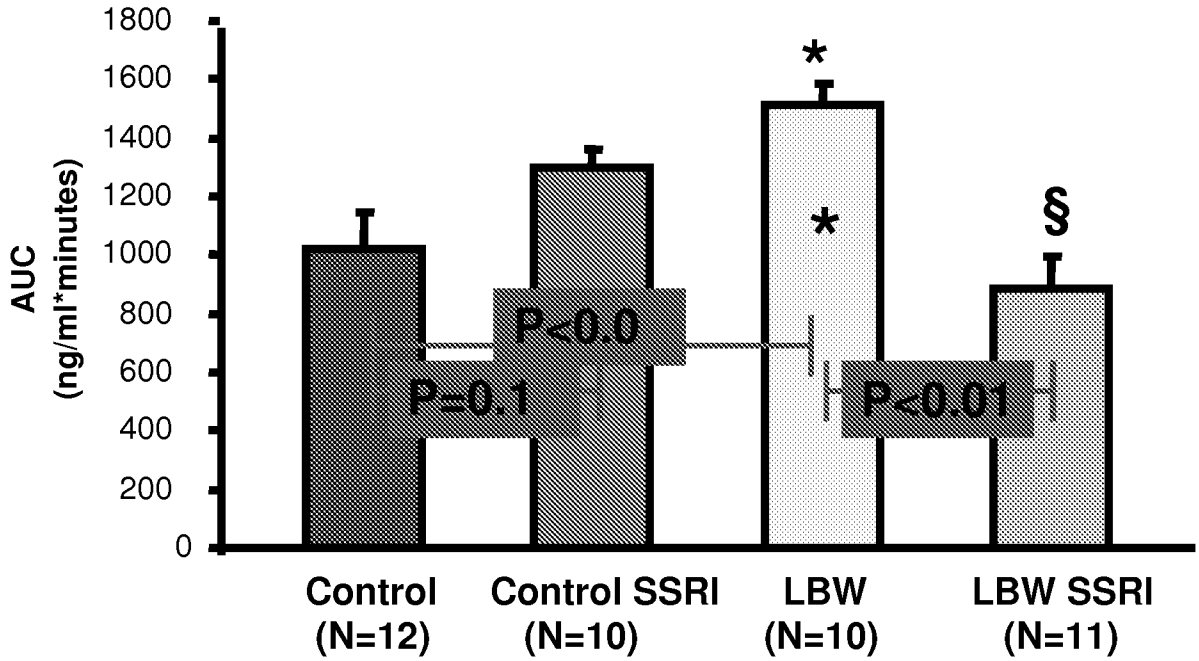

1800
1600
1400
1200
1000
800
600
400
200
0
AUC
(ng/ml*minutes)
*
*
§
P<0.0
P=0.1
P<0.01
Control
(N=12)
Control SSRI
(N=10)
LBW
(N=10)
LBW SSRI
(N=11)

Figure 9

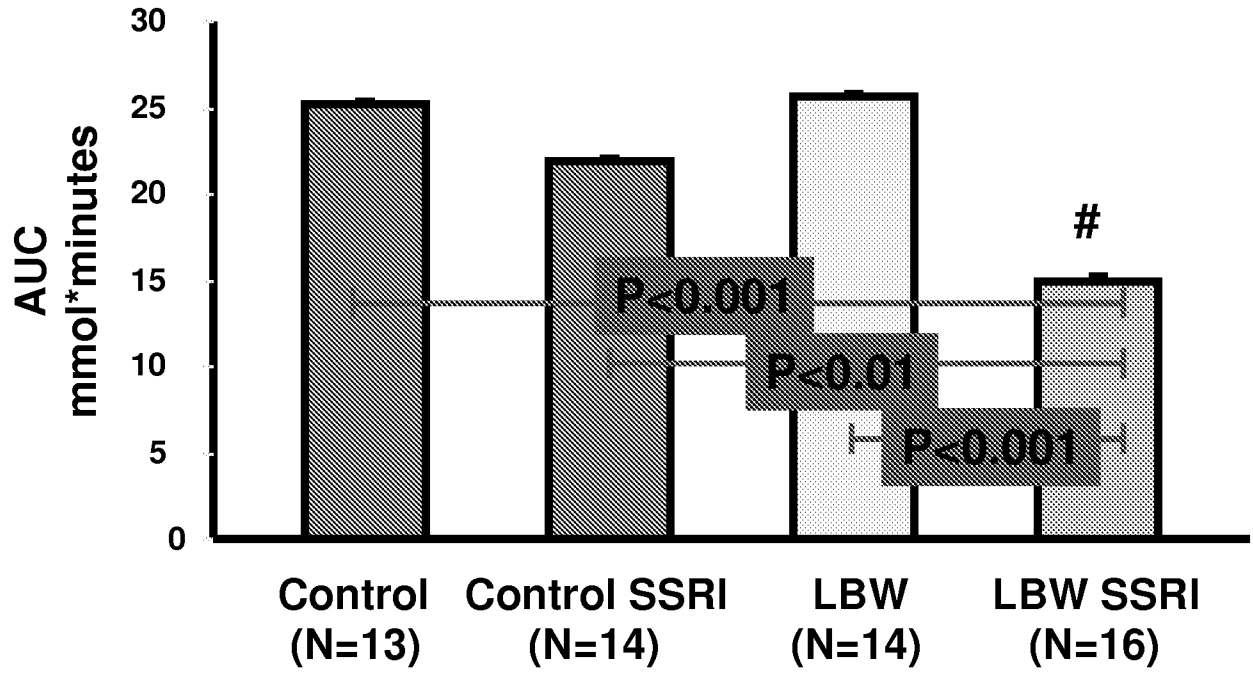

30
25
20
15
10
5
0
AUC
mmol*minutes
P<0.001
P<0.01
P<0.001
#
Control
(N=13)
Control SSRI
(N=14)
LBW
(N=14)
LBW SSRI
(N=16)

Figure 10

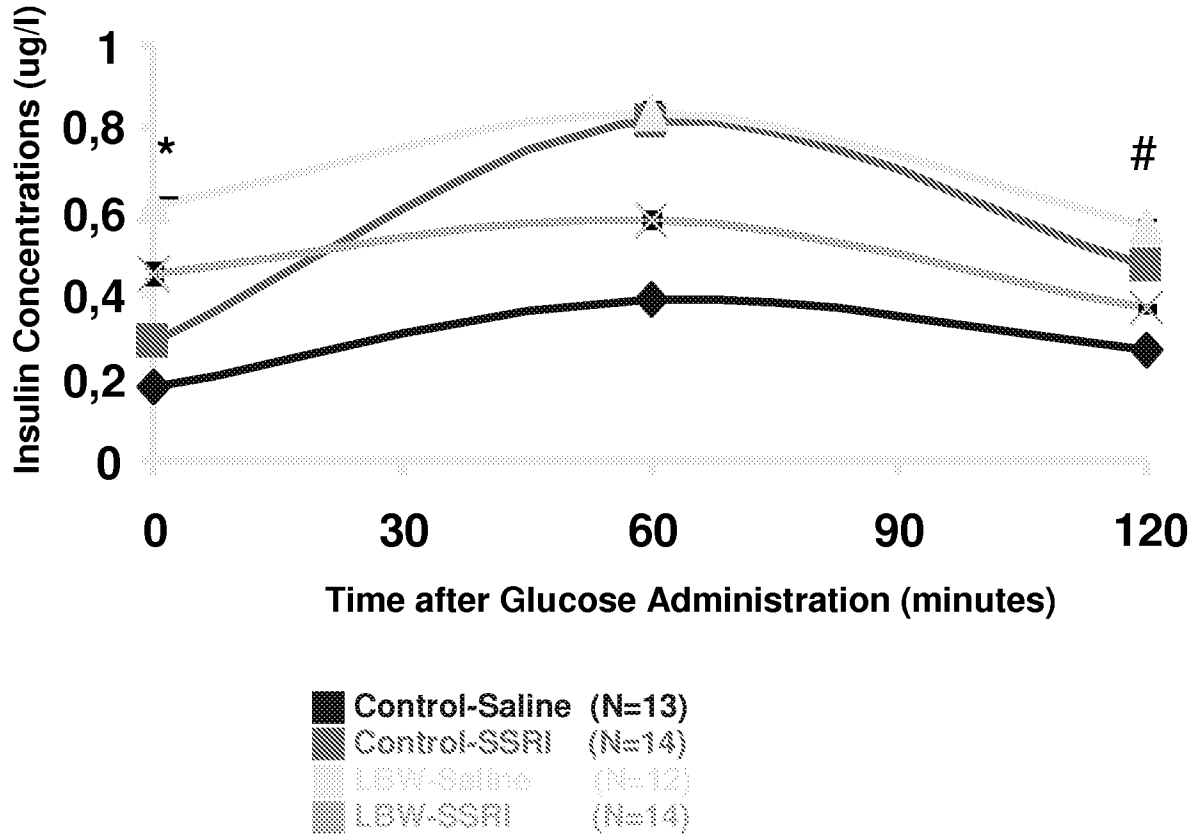

Insulin Concentrations (ug/l)
1
0,8
0,6
0,4
0,2
0
*
#
0
30
60
90
120
Time after Glucose Administration (minutes)
Control-Saline (N=13)
Control-SSRI (N=14)
LBW-Saline (N=12)
LBW-SSRI (N=14)

Figure 11

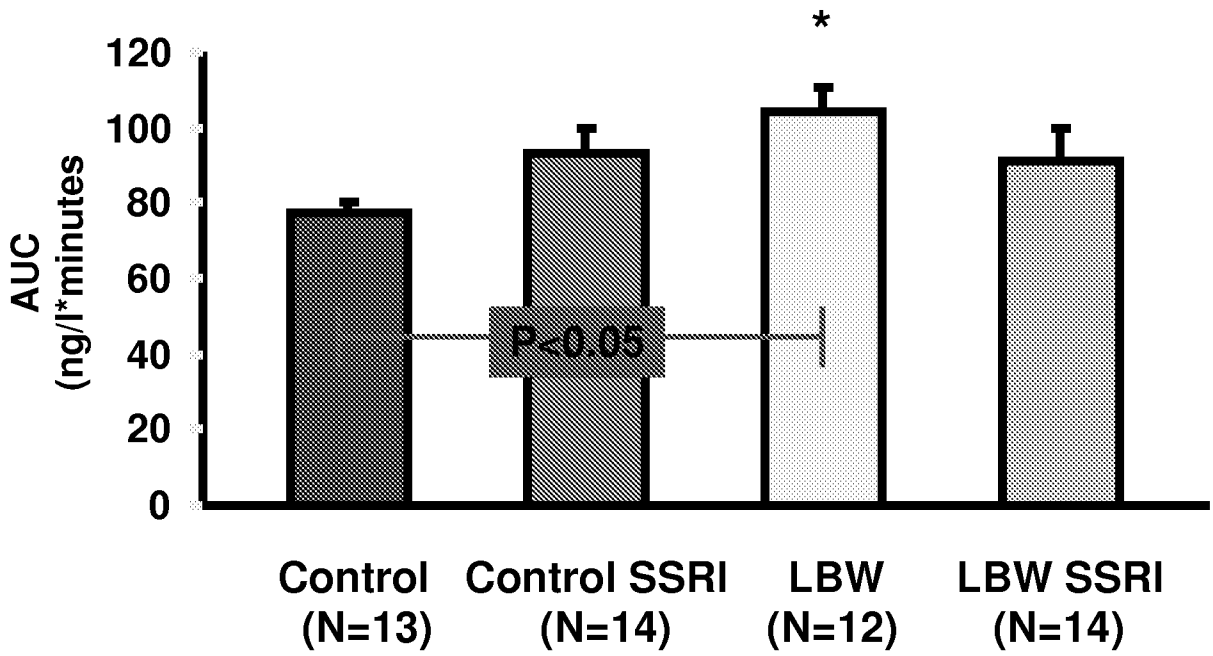

*
120
100
80
60
40
20
0
AUC
(ng/l*minutes
P<0.05
Control
(N=13)
Control SSRI
(N=14)
LBW
(N=12)
LBW SSRI
(N=14)

Figure 12

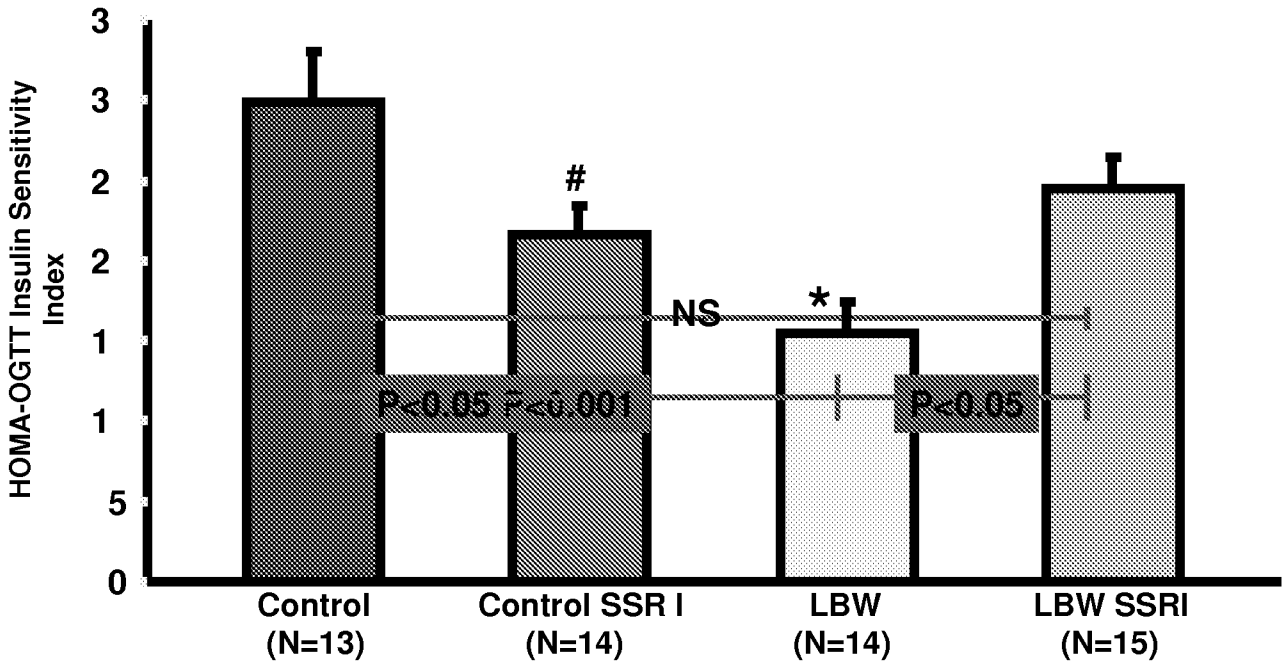

HOMA-OGTT Insulin Sensitivity Index
3
3
2
2
1
1
5
0
#
NS
*
P<0.05
P<0.001
P<0.05
Control (N=13)
Control SSR I (N=14)
LBW (N=14)
LBW SSRI (N=15)

Figure 13

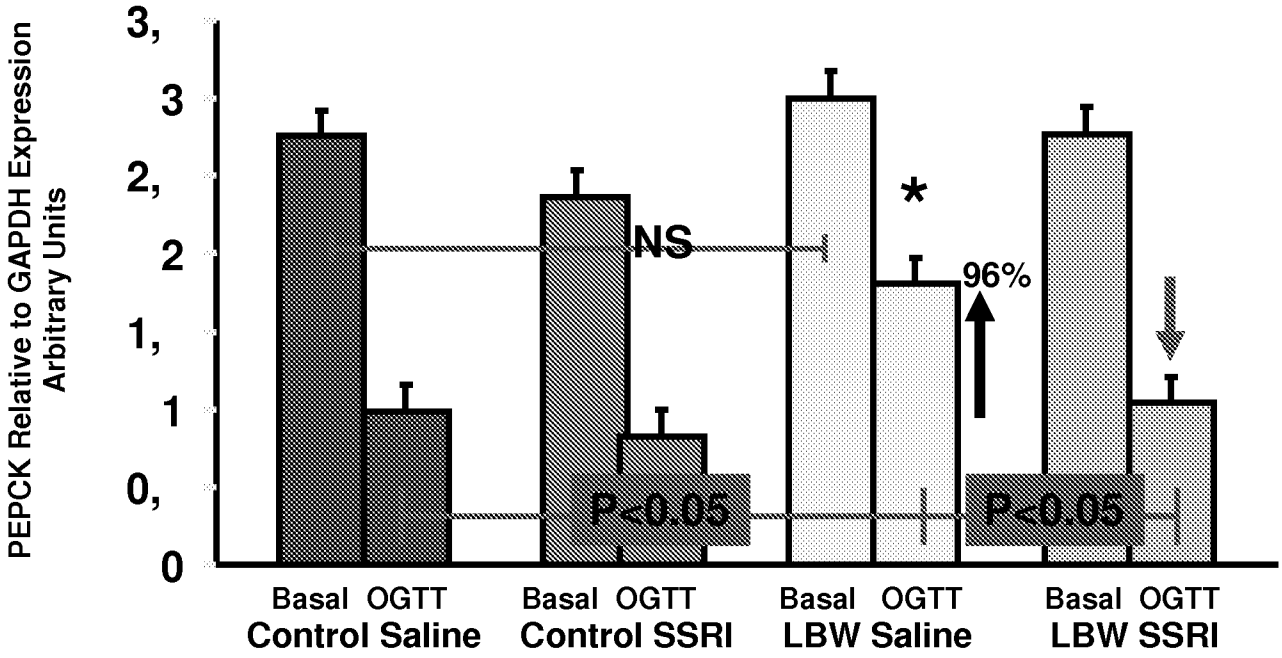

PEPCK Relative to GAPDH Expression
Arbitrary Units
3,
3
2,
2
1,
1
0,
0
NS
*
96%
P<0.05
P<0.05
Basal OGTT
Control Saline
Basal OGTT
Control SSRI
Basal OGTT
LBW Saline
Basal OGTT
LBW SSRI

Figure 14

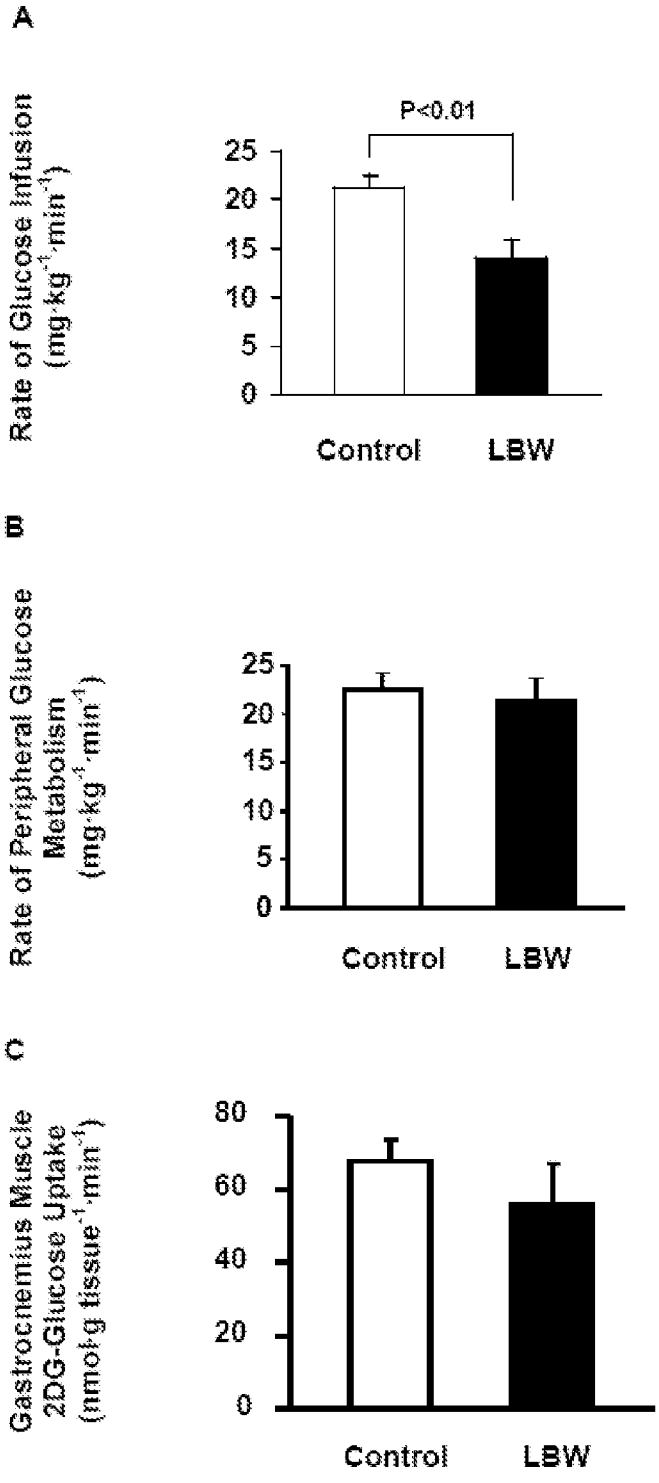

A
Rate of Glucose infusion (mg·kg⁻¹·min⁻¹)
P<0.01
25
20
15
10
5
0
Control
LBW
B
Rate of Peripheral Glucose Metabolism (mg·kg⁻¹·min⁻¹)
25
20
15
10
5
0
Control
LBW
C
Gastrocnemius Muscle 2DG-Glucose Uptake (nmol·g tissue⁻¹·min⁻¹)
80
60
40
20
0
Control
LBW

Figure 15

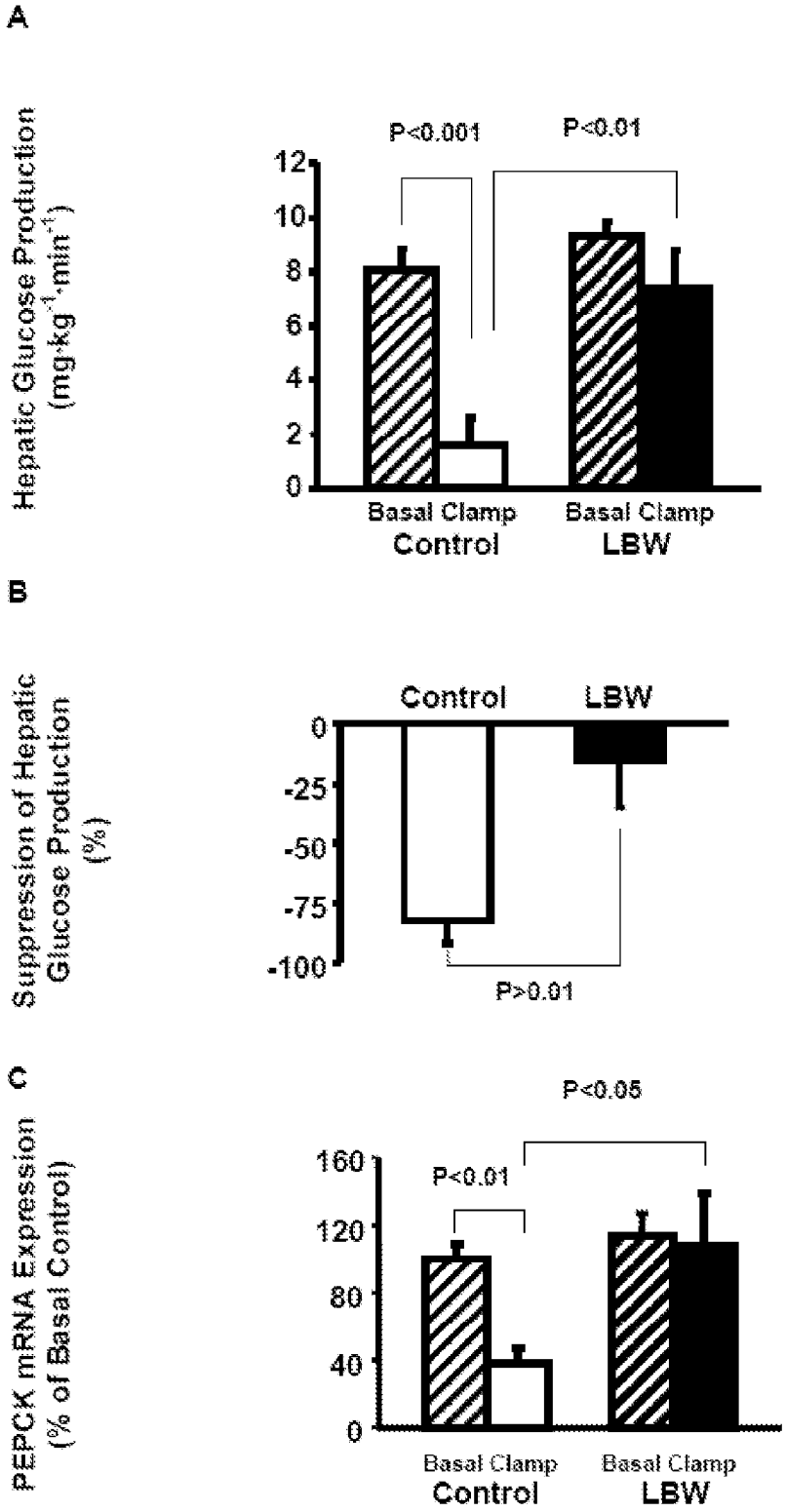
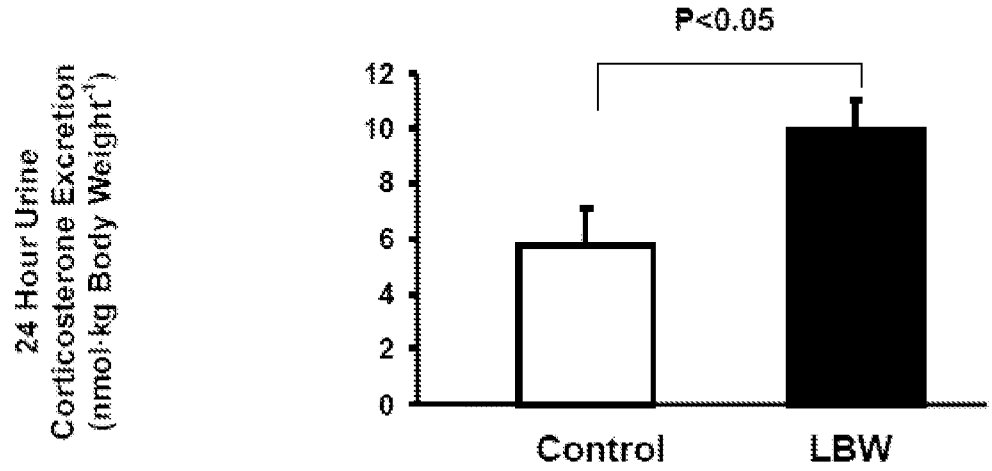

A
Hepatic Glucose Production
(mg·kg-1·min-1)
P<0.001
P<0.01
12
10
8
6
4
2
0
Basal Clamp
Control
Basal Clamp
LBW
B
Suppression of Hepatic
Glucose Production
(%)
Control
LBW
0
-25
-50
-75
-100
P>0.01
C
PEPCK mRNA Expression
(% of Basal Control)
P<0.05
P<0.01
160
120
80
40
0
Basal Clamp
Control
Basal Clamp
LBW

Figure 16

A


P<0.05
24 Hour Urine Corticosterone Excretion (nmol·kg Body Weight^{-1})
12
10
8
6
4
2
0
Control
LBW

B

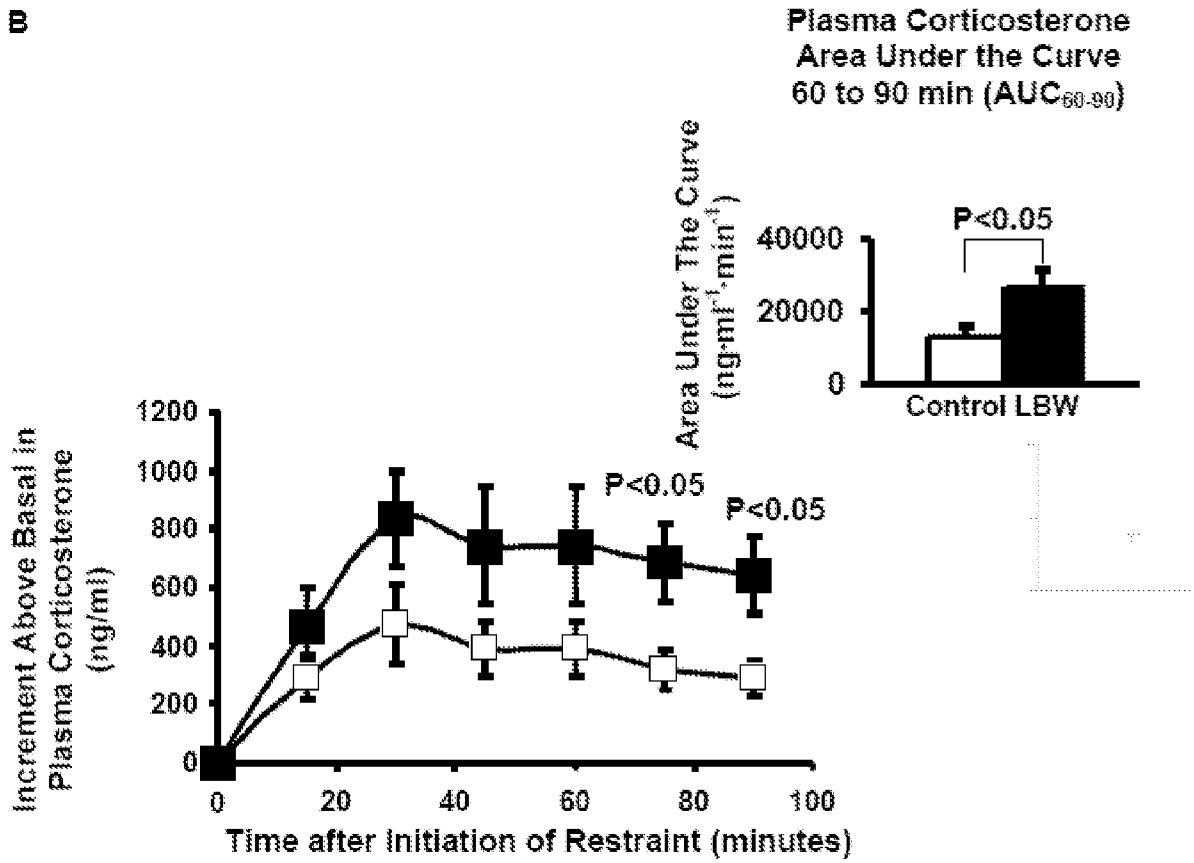

Plasma Corticosterone Area Under the Curve 60 to 90 min (AUC_{60-90})
Area Under The Curve (ng·ml^{-1}·min^{-1})
40000
20000
0
P<0.05
Control LBW
Increment Above Basal in Plasma Corticosterone (ng/ml)
1200
1000
800
600
400
200
0
P<0.05
P<0.05
0
20
40
60
80
100
Time after Initiation of Restraint (minutes)

Figure 17

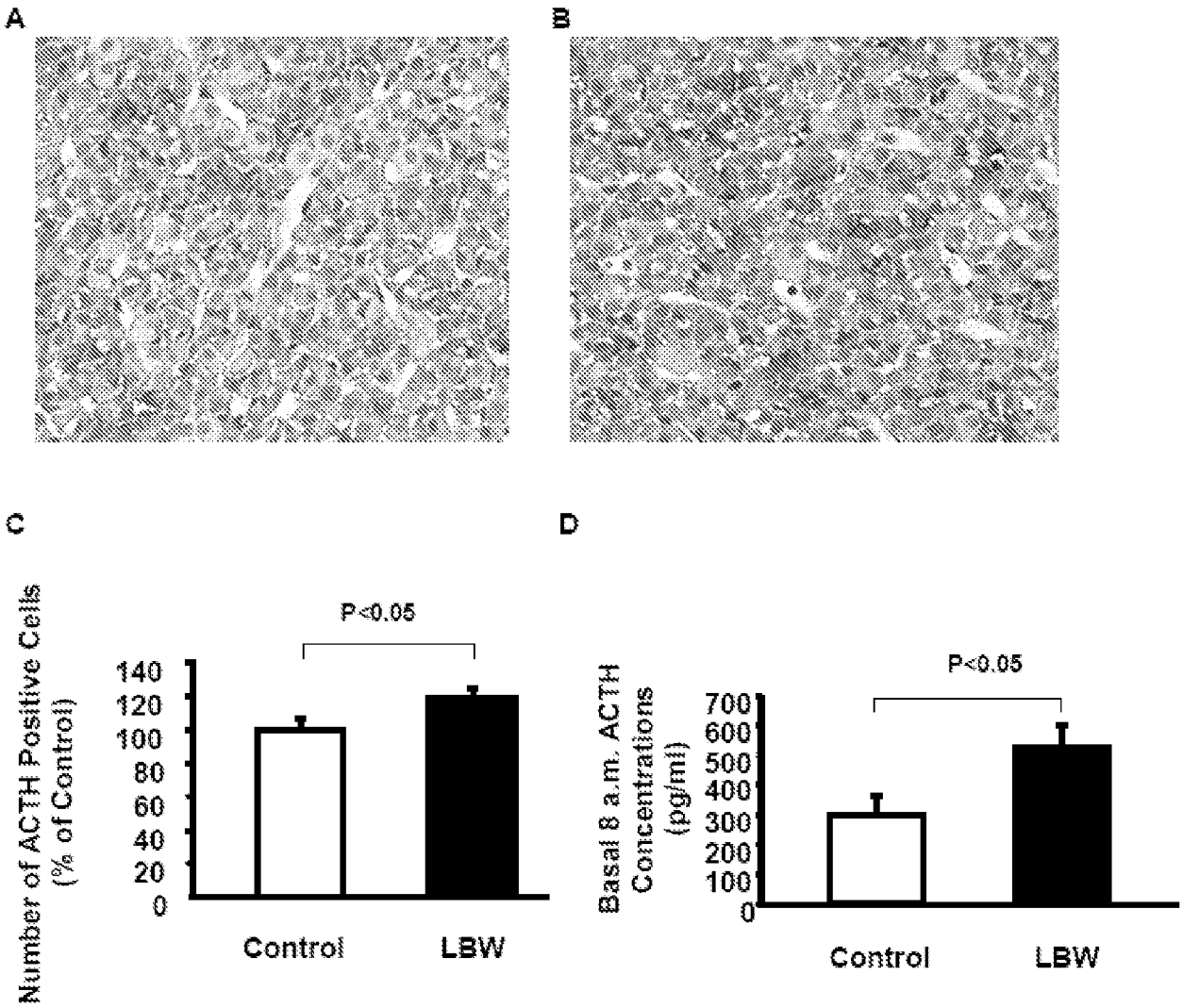
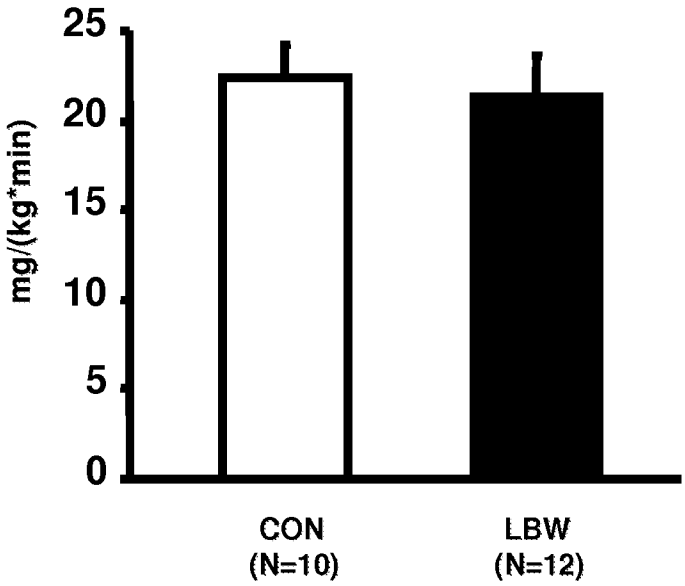

A
B
C
D
P<0.05
Number of ACTH Positive Cells (% of Control)
140
120
100
80
60
40
20
0
Control
LBW
P<0.05
Basal 8 a.m. ACTH Concentrations (pg/ml)
700
600
500
400
300
200
100
0
Control
LBW

Figure 18

A


25
20
15
10
5
0
mg/(kg*min)
CON
(N=10)
LBW
(N=12)

B

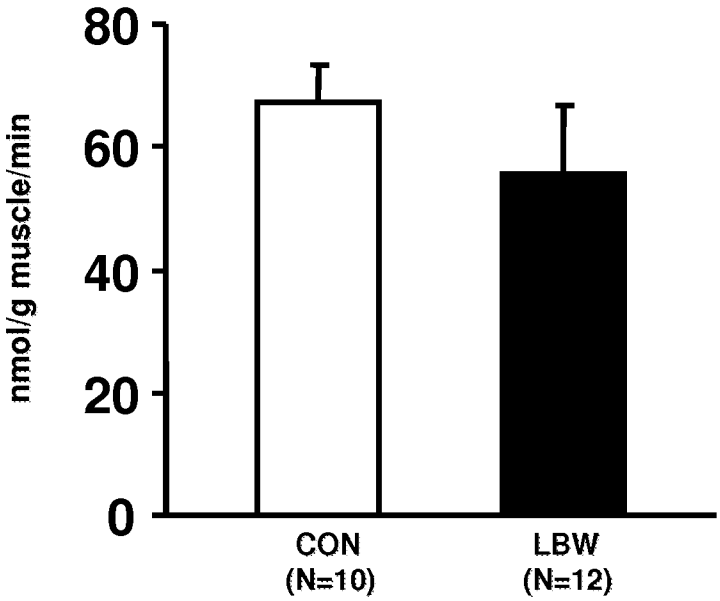

80
60
40
20
0
nmol/g muscle/min
CON
(N=10)
LBW
(N=12)

Figure 19

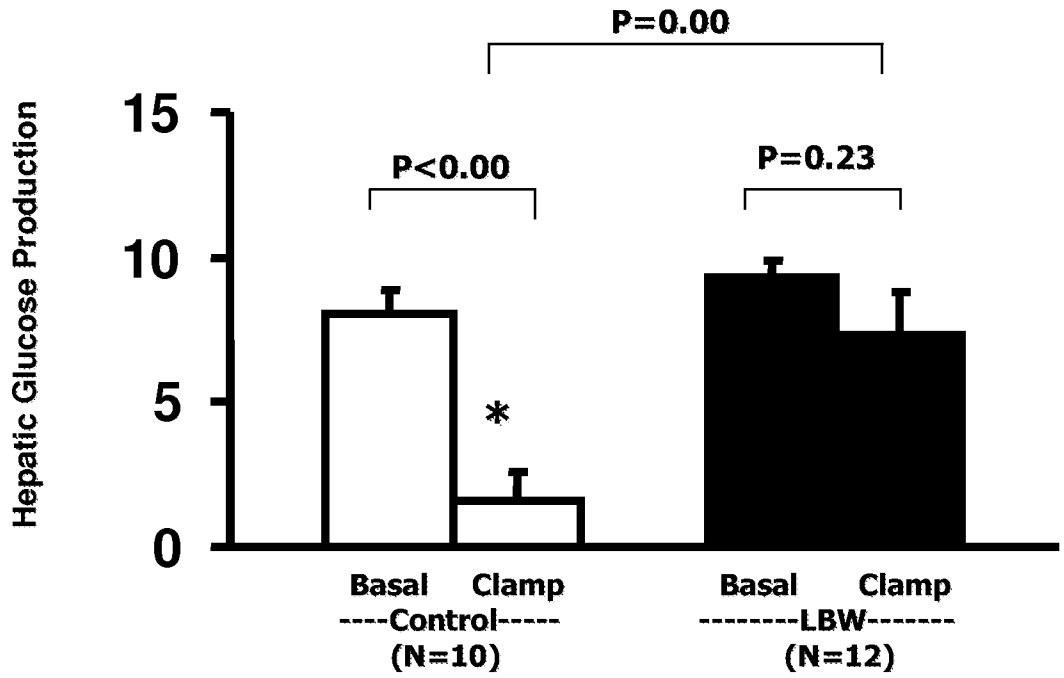

P=0.00
P<0.00
P=0.23
Hepatic Glucose Production
15
10
5
0
*
Basal
Clamp
----Control-----
(N=10)
Basal
Clamp
--------LBW-------
(N=12)

Figure 20

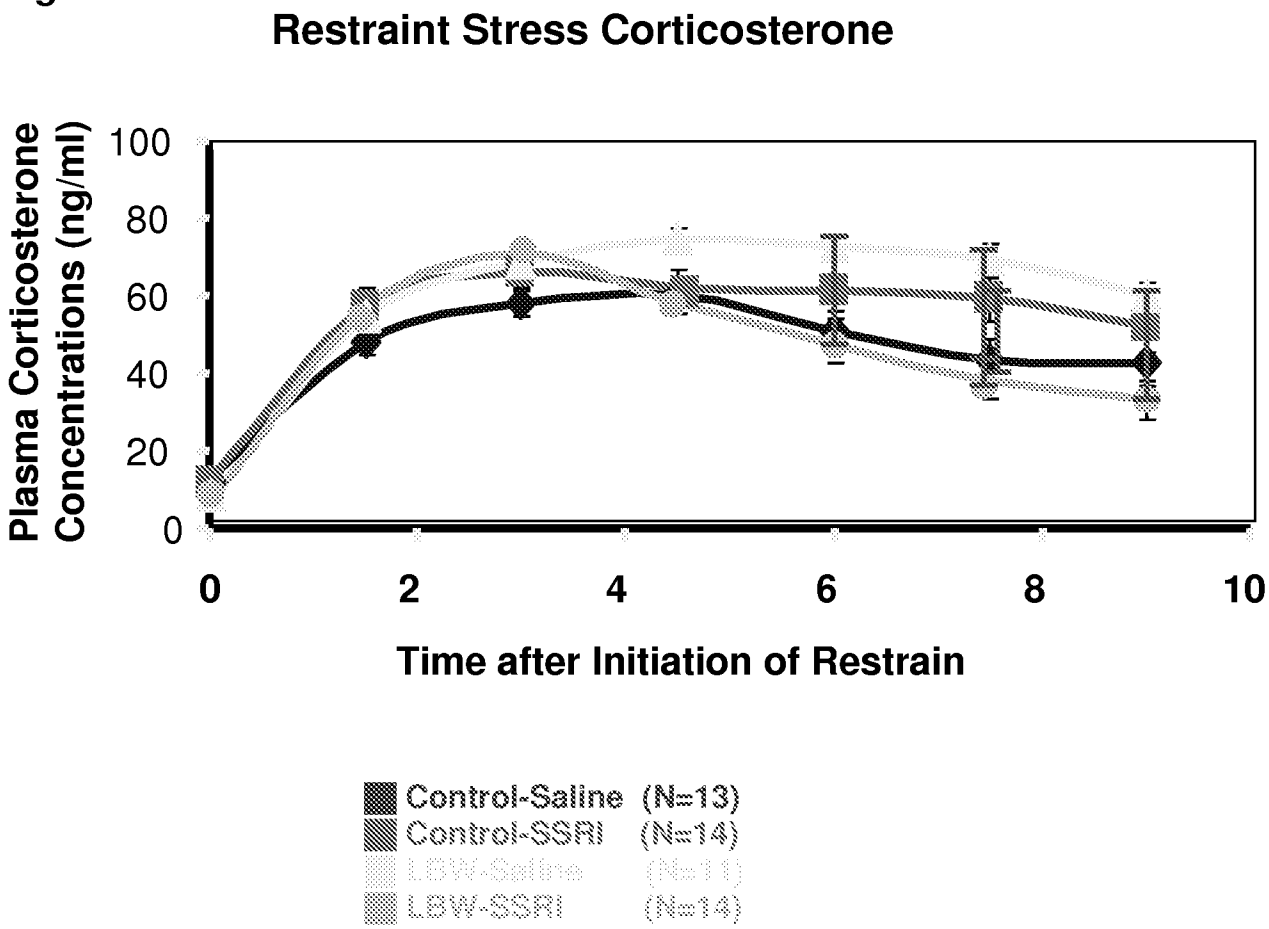
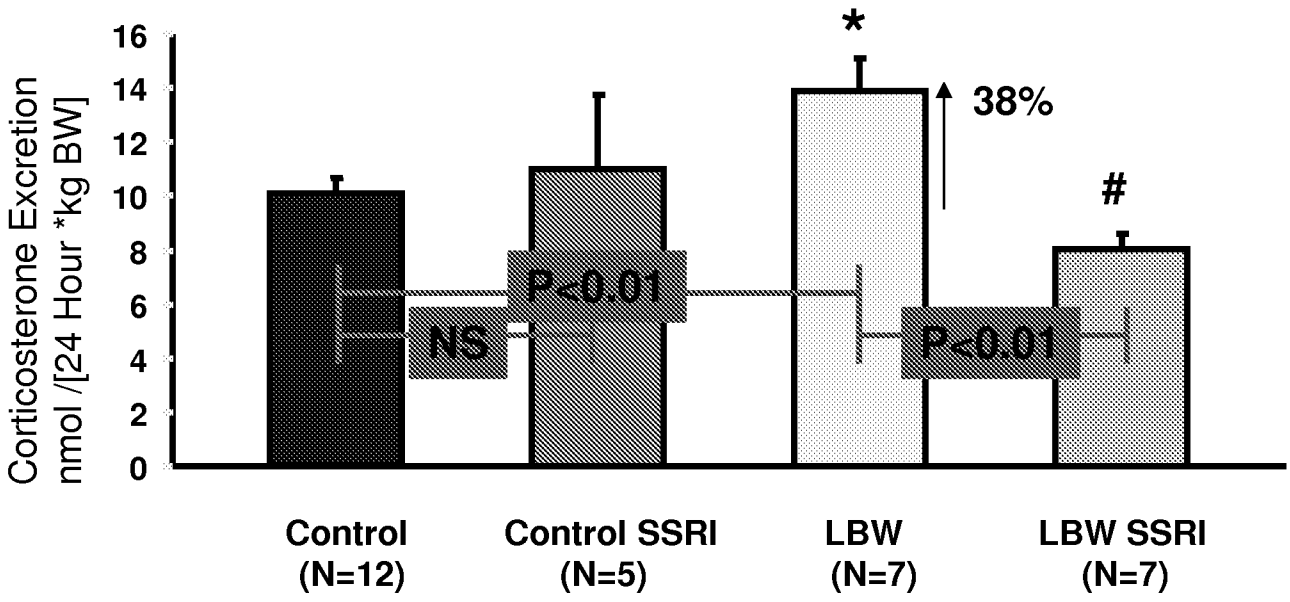

Restraint Stress Corticosterone
Plasma Corticosterone Concentrations (ng/ml)
100
80
60
40
20
0
0
2
4
6
8
10
Time after Initiation of Restrain
Control-Saline (N=13)
Control-SSRI (N=14)
LBW-Saline (N=11)
LBW-SSRI (N=14)

Figure 21


Corticosterone Excretion
nmol /[24 Hour *kg BW]
16
14
12
10
8
6
4
2
0
*
38%
#
P<0.01
NS
P<0.01
Control
(N=12)
Control SSRI
(N=5)
LBW
(N=7)
LBW SSRI
(N=7)

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2008/050122

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/343 A61K31/138 A61K31/135 A61K31/4525 A61K31/137
A61K31/496 A61K31/495 A61K31/55 A61P9/00 A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, SCISEARCH, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/072093 A (REGENT OF THE UNIVERSITY OF CA [US]; MONTEJO-PERNAS MARIA JULIA [US];) 4 September 2003 (2003-09-04) claims; examples	5,13,14, 16,17, 34,36, 49, 51-53, 56,58, 59,61
X	US 5 795 895 A (ANCHORS J MICHAEL [US]) 18 August 1998 (1998-08-18) columns 3,4; claims	10,12, 34,37

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 September 2008	10/10/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Venturini, Francesca

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZIEGLER, D. ET AL.: "impact of disease characteristics on the efficacy of duloxetine in diabetic peripheral neuropathic pain" DIABETE CARE, vol. 30, no. 3, March 2007 (2007-03), pages 664-669, XP002497029 paragraph [DISCUSSION]	6,18,20, 34,49, 51,56, 58,59,61
X	RAEDER MARIA B ET AL: "Obesity, dyslipidemia, and diabetes with selective serotonin reuptake inhibitors: the Hordaland Health Study" JOURNAL OF CLINICAL PSYCHIATRY,, vol. 67, no. 12, 1 December 2006 (2006-12-01), pages 1974-1982, XP009105711 ISSN: 0160-6689 page 1974, right-hand column, paragraph CONCLUSION - page 1975, right-hand column, line 3	1-61
P,X	EP 1 829 534 A (ESTEVE LABOR DR [ES]) 5 September 2007 (2007-09-05) page 2, lines 5-55; claims	1,9,10, 17-19, 22,34, 36,38, 39, 44-46, 49, 51-53, 56,58, 59,61
X	MAHEUX P ET AL: "Fluoxetine improves insulin sensitivity in obese patients with non-insulin-dependent diabetes mellitus independently of weight loss" INTERNATIONAL JOURNAL OF OBESITY, NEWMAN PUBLISHING, LONDON, GB, vol. 21, no. 2, 1 February 1997 (1997-02-01), pages 97-102, XP009105713 ISSN: 0307-0565 paragraphs [INTRODUCTION], [DISCUSSION]	1,11,12, 25,34, 37-39, 44-46, 49, 51-53, 58,59,61

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2008/050122

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	USPENSKY YU P ET AL: "Depressive disorders and their correction in complex treatment of metabolic syndrome patients" CARDIOVASCULAR THERAPY AND PREVENTION,, vol. 6, no. 3, 9 March 2007 (2007-03-09), pages 33-37, XP001538909 ISSN: 1728-8800 abstract -----	1,5, 9-14, 16-19, 21,25, 34,38, 39,42, 44-46, 49, 51-53, 56,58, 59,61

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/DK2008/050122

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03072093 A	04-09-2003	AU 2003217654 A1	09-09-2003
US 5795895 A	18-08-1998	NONE	
EP 1829534 A	05-09-2007	NONE	