



(86) Date de dépôt PCT/PCT Filing Date: 2002/09/26

(87) Date publication PCT/PCT Publication Date: 2003/04/03

(45) Date de délivrance/Issue Date: 2011/04/05

(85) Entrée phase nationale/National Entry: 2004/03/26

(86) N° demande PCT/PCT Application No.: AU 2002/001320

(87) N° publication PCT/PCT Publication No.: 2003/026684

(30) Priorité/Priority: 2001/09/27 (US60/325,061)

(51) Cl.Int./Int.Cl. *A61K 38/06* (2006.01),
A61K 31/198 (2006.01), *A61P 25/18* (2006.01),
A61P 25/28 (2006.01)

(72) Inventeurs/Inventors:
BUSH, ASHLEY I., US;
COPLOV, DAVID L., AU;
BERK, MICHAEL, AU

(73) Propriétaire/Owner:
THE MENTAL HEALTH RESEARCH INSTITUTE OF
VICTORIA, AU

(74) Agent: KIRBY EADES GALE BAKER

(54) Titre : MODULATION DE PROCEDES PHYSIOLOGIQUES ET AGENTS UTILES A CET EFFET

(54) Title: MODULATION OF PHYSIOLOGICAL PROCESSES AND AGENTS USEFUL FOR SAME

(57) **Abrégé/Abstract:**

The present invention relates generally to a method of modulating glutathione metabolism in the central nervous system of mammals and to agents for use therein. More particularly, the present invention relates to a method of up-regulating glutathione metabolism in the central nervous system by up-regulating levels of glutathione precursor molecules. The method of the present invention is particularly useful, inter alia, in the treatment and/or prophylaxis of conditions characterised by aberrant, unwanted or otherwise inappropriate central nervous system oxidation homeostasis including, but not limited to, schizophrenia.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 April 2003 (03.04.2003)

PCT

(10) International Publication Number
WO 03/026684 A1

(51) International Patent Classification⁷: **A61K 38/06**,
31/198, A61P 25/18, 25/28

(74) Agents: **OBRANOVICH, Tania, D.** et al.; Davies Colli-
son Cave, 1 Little Collins Street, Melbourne, Victoria 3000
(AU).

(21) International Application Number: PCT/AU02/01320

(22) International Filing Date:
26 September 2002 (26.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/325,061 27 September 2001 (27.09.2001) US

(71) Applicant (*for all designated States except US*): **THE MENTAL HEALTH RESEARCH INSTITUTE OF VICTORIA** [AU/AU]; Locked Bag 11, Parkville, Victoria 3052 (AU).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BUSH, Ashley, I.** [US/US]; 91 Summer Street, Apartment 3, Somerville, MA 02143 (US). **COPOLOV, David, L.** [AU/AU]; 124 Finch Street, East Malvern, Victoria 3144 (AU). **BERK, Michael** [AU/AU]; 61 Montpellier Drive, Highton, Victoria 3216 (AU).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MODULATION OF PHYSIOLOGICAL PROCESSES AND AGENTS USEFUL FOR SAME

(57) Abstract: The present invention relates generally to a method of modulating glutathione metabolism in the central nervous system of mammals and to agents for use therein. More particularly, the present invention relates to a method of up-regulating glutathione metabolism in the central nervous system by up-regulating levels of glutathione precursor molecules. The method of the present invention is particularly useful, *inter alia*, in the treatment and/or prophylaxis of conditions characterised by aberrant, unwanted or otherwise inappropriate central nervous system oxidation homeostasis including, but not limited to, schizophrenia.



WO 03/026684 A1

- 1 -

MODULATION OF PHYSIOLOGICAL PROCESSES AND AGENTS USEFUL FOR SAME

FIELD OF THE INVENTION

5

The present invention relates generally to a method of modulating glutathione metabolism in the central nervous system of mammals and to agents for use therein. More particularly, the present invention relates to a method of up-regulating glutathione metabolism in the central nervous system by up-regulating levels of glutathione precursor molecules. The method of the present invention is particularly useful, *inter alia*, in the treatment and/or prophylaxis of conditions characterised by aberrant, unwanted or otherwise inappropriate central nervous system oxidation homeostasis including, but not limited to, schizophrenia.

BACKGROUND OF THE INVENTION

15

Bibliographic details of the publications referred to alphabetically by author in the specification are collected at the end of the description.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

Schizophrenia is a severe mental illness which affects approximately one person in a hundred. Symptoms characterising schizophrenia include delusions (false beliefs of persecution, guilt, grandeur or being under outside control), hallucinations (visual or auditory) and thought disorder (speech which is difficult to follow or jumping from one subject to another with no logical connection). Secondary symptoms of schizophrenia include loss of drive, blunted emotions, social withdrawal and/or lack of insight.

30 The onset of schizophrenia usually occurs during adolescence or early adulthood, although it has been known to develop in older people. Onset may be rapid, with acute symptoms

- 2 -

developing over several weeks, or it may be slow, developing over months or even years.

The causes of schizophrenia are not fully understood. However, during the last few years there has emerged a body of literature which supports an abnormality in oxidation homeostasis systemically and centrally in schizophrenia. The origin of this oxidative stress is still unknown. The brain in schizophrenia exhibits many chemical hallmarks of oxidative attack, in addition to indications of altered antioxidant defence. Any tissue under sustained radical attack may suffer a depletion of the key free radical/H₂O₂ scavenger in the brain, glutathione. Recently, reports have emerged that glutathione is indeed depleted in schizophrenia, and that the antioxidant enzymic activities related to glutathione metabolism are markedly perturbed. Do KQ, Trabesinger AH, Kirsten-Kruger M, Lauer CJ, Dydak U, Hell D, Holsboer F, Boesiger P and Cuenod M., (2000), *Euro J Neurosci*, 12:3721-8 have reported a significant decrease (-27%) in the cerebrospinal fluid levels of glutathione in drug-free schizophrenia patients compared to controls. This decrease is consistent with the previously reported decrease in the levels of the glutathione metabolite gamma-glutamylglutamine in the cerebrospinal fluid of such patients (Do KQ, Lauer CJ, Schreiber W, Zollinger M, Gutteck-Amsler U, Cuenod M and Holsboer F., (1995), *J Neurochem*, 65:2652-62). Furthermore, Do *et al.*, (2000) also found a 52% decrease in glutathione levels in the medial prefrontal cortex of schizophrenia patients compared to controls, using a non-invasive proton magnetic resonance spectroscopy method.

Intriguingly, other aspects of the glutathione metabolic pathway are also perturbed in schizophrenia. Decreased peripheral glutathione peroxidase (GPx) activity has been described in schizophrenia patients (Abdalla DS, Monteiro HP, Oliveira JA and Bechara EJ., (1986), *Clin Chem*, 32:805-7), and the decrease correlates with increased brain atrophy (Buckman TD, Kling AS, Eiduson S, Sutphin MS and Steinberg A., (1987), *Biol Psychiatry*, 22:1349-56). Plasma GPx positively correlates with psychosis rating scored in schizophrenia patients on or off medication (Yao JK, Reddy RD and van Kammen DP., (1999), *Biol Psychiatry*, 45:1512-5). GPx is the enzyme that catalyses the scavenging of H₂O₂ and other radicals by glutathione.

- 3 -

These biochemical changes have lead to a call for the critical study of antioxidants as schizophrenia treatments utilised adjunctively with antipsychotic medication. To date, research has focused on the use of indirect means of overcoming the defects in glutathione metabolism such as increasing the efficiency of other radical scavenging systems. For example, Vitamin C, Vitamin E (alpha-tocopherol), alpha-lipoic acid supplements and also selenomethionine have been investigated. Currently, investigators are focusing on the use of Vitamins E and C (Yao *et al.*, 1999, *supra*). Selenomethionine supplementation is well known to augment the activity of glutathione peroxidase (Duffield AJ, Thomson CD, Hill KE and Williams S., (1999), *Am J Clin Nutr*, 70:896-903). Vitamin E and selenium combined supplementation has already been reported to provide beneficial effects in the treatment of the FALS transgenic mouse model (Gurney ME, Cutting FB, Zhai P, Doble A, Taylor CP, Andrus PK and Hall ED., (1996), *Ann Neurol*, 39:147-57), demonstrating that the potential antioxidant benefits of such oral supplementation can also be transduced across the blood brain barrier in brain oxidation disorders. However, while being supportive of glutathione metabolism, in that these molecules can function as antioxidants, they are not the most efficient means of increasing glutathione levels in the brain. Accordingly, there is an on-going need to develop methods of treating schizophrenia, either in the form of adjunctive therapies to currently utilised treatments or as a replacement to the use of currently available antipsychotic medication.

20

In work leading up to the present invention, the inventors have determined that up-regulating glutathione metabolism in the central nervous system, and in particular in the brain, leads to a degree of normalisation of oxidative homeostasis in individuals suffering from schizophrenia and consequently a reduction in the occurrence and/or severity of schizophrenia related symptoms. More particularly, the inventors have determined that the central nervous system oxidative homeostasis, and particularly that of the brain, can be directly normalised via up-regulation of central nervous system glutathione metabolism. The inventors have still further determined that this can be easily and efficiently achieved by administering effective amounts of a glutathione precursor such as N-acetyl cysteine, which molecule is thought to be deacylated in the liver thereby elevating blood cysteine levels, which cysteine can then be transduced across the blood-brain barrier.

30

- 4 -

SUMMARY OF THE INVENTION

According to one aspect of the invention, there is provided the use of a glutathione precursor for the treatment or prophylaxis of a neuropsychiatric disorder in a mammal.

5

According to another aspect of the invention, there is provided the use of a glutathione precursor in the manufacture of a medicament for the treatment of a neuropsychiatric disorder in a mammal, wherein said glutathione precursor up-regulates antioxidant functional activity of the brain of said mammal.

10

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

15

One aspect of the present invention is directed to a method of up-regulating glutathione metabolism in the central nervous system of a mammal, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof.

20

Another aspect of the present invention provides a method of up-regulating glutathione metabolism in the brain of a mammal, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof.

25

Yet another aspect of the present invention provides a method of up-regulating glutathione metabolism in the brain of a mammal, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof wherein said glutathione metabolism
30 induces, up-regulates or otherwise augments antioxidant functional activity in said brain.

- 4a -

In still another aspect there is provided a method of up-regulating glutathione metabolism in the central nervous system of a mammal, said method comprising administering to said mammal an effective amount of N-acetyl cysteine or a derivative, homologue, analogue, chemical equivalent or mimetic thereof.

5

In still yet another aspect there is provided a method of up-regulating glutathione metabolism in the brain of a mammal, said method comprising administering to said mammal an effective amount of N-acetyl cysteine or a derivative, homologue, analogue,

- 5 -

chemical equivalent or mimetic thereof.

In yet still another aspect there is provided a method of up-regulating glutathione metabolism in the brain of a mammal, said method comprising administering to said
5 mammal an effective amount of N-acetyl cysteine or a derivative, homologue, analogue, chemical equivalent or mimetic thereof wherein said glutathione metabolism induces, up-regulates or otherwise augments antioxidant functional activity in said brain.

In a further aspect there is provided a method for up-regulating glutathione metabolism in
10 the brain of a human, said method comprising administering to said human an effective amount of N-acetyl cysteine or a derivative, homologue, analogue, chemical equivalent or mimetic thereof wherein said glutathione metabolism induces, up-regulates or otherwise augments antioxidant functional activity in said brain.

15 In a related aspect there is provided a method of normalising oxidative homeostasis in the central nervous system of a mammal, which mammal exhibits unwanted central nervous system oxidation, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof for a time and under conditions sufficient to up-regulate
20 glutathione metabolism.

In yet another further aspect there is provided a method of normalising oxidative homeostasis in the brain of a mammal, which mammal exhibits unwanted central nervous system oxidation, said method comprising administering to said mammal an effective
25 amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof for a time and under conditions sufficient to up-regulate glutathione metabolism.

Preferably said glutathione precursor is N-acetyl cysteine and still more preferably said
30 mammal is a human.

- 6 -

Yet another further aspect of the present invention relates to a method for the treatment and/or prophylaxis of a condition characterised by:

- 5
- (i) aberrant, unwanted or otherwise inappropriate oxidative stress; and/or
 - (ii) inadequate glutathione metabolism,

in the central nervous system of a mammal, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof.

10

Yet still a further aspect of the present invention relates to a method for the treatment and/or prophylaxis of a condition characterised by:

- 15
- (i) aberrant, unwanted or otherwise inappropriate oxidative stress; and/or
 - (ii) inadequate glutathione metabolism,

in the brain of a mammal, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof.

20

In yet still a further aspect the present invention relates to a method of treating a neuropsychiatric condition in a mammal, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof for a time and under conditions sufficient to induce, up-regulate or otherwise augment antioxidant functional activity in the brain of said mammal.

25

30 Preferably said glutathione precursor is N-acetyl cysteine.

- 7 -

More preferably said condition is schizophrenia, psychosis, bipolar disorder, manic depression, affective disorder, or schizophreniform or schizoaffective disorders.

Most preferably said condition is schizophrenia.

5

In another aspect the present invention provides a method for the treatment and/or prophylaxis of schizophrenia in a mammal, said method comprising administering to said mammal an effective amount of N-acetyl cysteine or derivative, homologue, analogue, chemical equivalent or mimetic thereof for a time and under conditions sufficient to
10 induce, up-regulate or otherwise augment antioxidant functional activity in the brain of said subject.

In yet another aspect the present invention relates to the use of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof in the
15 manufacture of a medicament for the up-regulation of glutathione metabolism and/or normalisation of oxidative homeostasis in the central nervous system of a mammal wherein said glutathione precursor induces, up-regulates or otherwise augments antioxidant functional activity in said central nervous system.

20 In still yet another aspect the present invention relates to the use of a glutathione precursor or derivative, homologue, analogue, chemical equivalent or mimetic thereof in the manufacture of a medicament for the treatment of a condition characterised by:

- 25
- (i) aberrant, unwanted or otherwise inappropriate oxidative stress; and/or
 - (ii) inadequate glutathione metabolism,

in the central nervous system of a mammal, wherein said glutathione precursor induces, up-regulates or otherwise augments antioxidant functional activity in said central nervous
30 system.

- 8 -

Preferably said central nervous system is the brain and still more preferably said glutathione precursor is N-acetyl cysteine.

Most preferably said condition is a neuropsychiatric disorder and still more preferably
5 schizophrenia, psychosis, bipolar disorder, manic depression, affective disorder, or
schizophreniform or schizoaffective disorders.

In yet still another aspect the present invention relates to a pharmaceutical composition
comprising a glutathione precursor as hereinbefore defined and one or more
10 pharmaceutically acceptable carriers and/or diluents. Said pharmaceutical composition
may additionally comprise molecules with which it is to be co-administered.

Yet another aspect of the present invention relates to modulatory agents, as hereinbefore
defined, when used in the method of the present invention.
15

- 9 -

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic representation of safe oral supplementation which promotes the glutathione radical scavenging biochemical pathway in the treatment of schizophrenia.

5 H_2O_2 generated by abnormal dopamine metabolism is scavenged first by reduced glutathione generating oxidized glutathione (GSSG) in a reaction catalyzed by glutathione peroxidase (GPx). H_2O_2 also contributes to the generation of lipid peroxide ($\text{LOO}\cdot$) radicals in adjacent neurons/synapses. The $\text{LOO}\cdot$ radical can propagate through poly-unsaturated fatty acids unless scavenged by *vitamin E*, which creates a vitamin E $\cdot$ radical.

10 Vitamin E is then restored by its radical being also reduced by glutathione, again generating oxidized glutathione, and also by *ascorbate*, generating semi-dehydroascorbate. Both of these reducing agents are themselves reduced from their oxidized state by *alpha-lipoic acid* (ALA) (Hagen TM, Ingersoll RT, Lykkesfeldt J, Liu J, Wehr CM, Vinarsky V, Bartholomew JC and Ames AB., (1999), *Faseb J*, 13:411-8). ALA requires cellular

15 energy to be reduced once it has been oxidized. GPx may not catalyse the reduction of vitamin E radicals by glutathione, but does catalyse the oxidation of glutathione by H_2O_2 . NAC is the rate limiting precursor for glutathione production. GPx activity is deficient in schizophrenia (Mahadik SP, Mukherjee S, Scheffer R, Correnti EE and Mahadik JS., (1998), *Biol Psychiatry*, 43:674-9), and oral *selenomethionine* (SeMet) supplementation is

20 a facile means of increasing GPx activity systemically and in the brain (Duffield *et al.*, 1999, *supra*).

Figure 2 is a graphical representation of average body weights (top panel) and daily fluid consumption (bottom panel) of wistar rats receiving normal water or 0.5% or 2% NAC.

25

Figure 3 is a graphical representation of baseline locomotor activity of rats receiving either normal water or 0.5% or 2% NAC solutions as drinking water. Data are pre-injection distance moved, averaged over three locomotor experiments $\pm$ SEM.

30 **Figure 4** is a graphical representation of the effect of injection of 0.5 mg/kg of amphetamine (top panel) or 5 mg/kg of amphetamine (bottom panel) on locomotor activity

- 10 -

of rats receiving normal water or 0.5% or 2% NAC to drink. Data is expressed as mean change of distance moved per 30 min period $\pm$ SEM.

Figure 5 is a graphical representation of the effect of 0.5 mg/kg of amphetamine on locomotor activity, 30-60 min after injection, of rats receiving either normal water, or 0.5% or 2% NAC to drink. Data are mean change of distance moved $\pm$ SEM compared to baseline values before injection.

- 11 -

DETAILED DESCRIPTION OF THE INVENTION

The present invention is predicated, in part, on the determination both that up-regulation of central nervous system glutathione metabolism, and in particular brain glutathione metabolism, improves aberrant oxidative homeostasis and that it can be achieved via administration of a glutathione precursor, in particular N-acetyl cysteine, to a mammal. Accordingly, this determination now permits the rational design of therapeutic and/or prophylactic methods for treating, either adjunctively or otherwise, conditions characterised by aberrant or otherwise unwanted oxidative homeostasis, or inadequate glutathione metabolism such as schizophrenia.

Accordingly, one aspect of the present invention is directed to a method of up-regulating glutathione metabolism in the central nervous system of a mammal, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof.

Reference to "central nervous system" should be understood as a reference to that part of the nervous system related to the brain and spinal cord. Preferably, the subject central nervous system region of interest is the brain.

The present invention therefore more particularly provides a method of up-regulating glutathione metabolism in the brain of a mammal, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof.

Reference to "glutathione metabolism" should be understood as a reference to any physiological process or pathway which is directly or indirectly regulated by glutathione or metabolic product thereof. "Direct" regulation of a physiological process or pathway by glutathione should be understood as a reference to any process or pathway which is modulated by the functional activity of glutathione or glutathione metabolites such as oxidised glutathione, reduced glutathione or gamma-glutamylglutamine. "Indirect"

- 12 -

regulation of a physiological process or pathway should be understood as a reference to any process or pathway which is modulated by the functional activity of a molecule which has itself undergone some form of modulation due to the functional activity of glutathione or a glutathione metabolite as detailed hereinbefore.

5

Without limiting the present invention to any one theory or mode of action, the physiological importance of glutathione is thought to be dependent on the highly reactive sulphhydryl group which is present in the molecule. The easy oxidation of this group to the corresponding disulphide allows participation of glutathione in oxidation-reduction
10 systems. Accordingly, glutathione is thought to play an important role in the protection of cells and tissues from oxidative damage. For example, glutathione is known to function as a scavenger of free radicals and H_2O_2 . In this regard, the scavenging functions of glutathione are thought to be catalysed by glutathione peroxidase.

15 In accordance with the present invention, the subject "glutathione metabolism" is preferably that which directly or indirectly results in up-regulation of antioxidant functional activity. However, it should be understood that regulation of glutathione metabolism for purposes other than modulating oxidative homeostasis are nevertheless encompassed by the method of the present invention. In terms of the preferred
20 embodiment of the present invention, the subject antioxidant functional activity should be understood as a reference to all forms of antioxidant functional activity which are either directly or indirectly modulated by glutathione or metabolites derived therefrom.

The present invention therefore preferably provides a method of up-regulating glutathione
25 metabolism in the brain of a mammal, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof wherein said glutathione metabolism induces, up-regulates or otherwise augments antioxidant functional activity in said brain.

30 Reference to "glutathione" should be understood as a reference to any form of glutathione or derivative, homologue, analogue, chemical equivalent or mimetic thereof. Without

- 13 -

limiting the present invention to any one theory or mode of action, glutathione is a tri-peptide containing a sulphydryl group which is widely distributed in living tissue. It is also known by the alternative name of α -glutamylcysteinylglycine or the abbreviation GSH. Glutathione is generally formed as a result of the actions of specific enzymes and
5 not as a direct result of the usual processes of peptide synthesis, being transcription and translation of a nucleic acid molecule specifically encoding said peptide. Glutathione is a molecule of the formula $\text{COOHCH}(\text{NH}_2)\text{CH}_2\text{CH}_2\text{CONHCH}(\text{CH}_2\text{SH})\text{CONHCH}_2\text{COOH}$ although it should be understood that the regulation of a physiological process or pathway by a derivative, homologue, analogue, chemical equivalent or mimetic of glutathione is
10 encompassed within the present invention. The first step in the synthesis of glutathione is the formation of a peptide linkage between the gamma-carboxyl group of glutamate and the amino group of cysteine to form gamma-glutamyl-cysteine. This is catalysed by gamma-glutamylcysteinesynthetase. Formation of this peptide bond requires activation of the gamma-carboxyl group, which activation is provided by ATP. The resulting molecule
15 is an intermediate which is then attacked by the amino group of cysteine. In this second step, which is catalysed by glutathione synthetase, ATP activates the carboxyl group of cysteine to enable it to condense with the amino group of glycine. Accordingly, glutathione is a molecule which is formed subsequently to the actions of enzymes on the rate limiting precursor cysteine. Glutathione cycles between a reduced thiol form (GSH)
20 and an oxidised form (GSSG) in which two tripeptides are linked by a disulfide bond.

In this regard, reference to a "glutathione precursor" should be understood as a reference to any molecule from which glutathione can be directly or indirectly derived. The subject molecule may be naturally or non-naturally occurring. Modification of a molecule in a
25 single step to form glutathione is an example of glutathione being directly derived from a precursor. Modification of a molecule to form an "intermediate" molecule, which intermediate molecule undergoes further modification to form glutathione is an example of glutathione being indirectly derived from the subject precursor. Cysteine is a naturally occurring precursor from which glutathione is indirectly derived. Specifically, cysteine is
30 catalysed to form γ -glutamyl cysteine prior to catalysis of this molecule to take up glycine and thereby form glutamine.

- 14 -

In accordance with a further aspect of the present invention, the inventors have determined that the acylated derivative of cysteine, N-acetyl cysteine, which is orally bioavailable, can supplement glutathione levels in the brain. Accordingly, in a preferred embodiment said glutathione precursor is N-acetyl cysteine or derivative, homologue, analogue, chemical
5 equivalent or mimetic thereof.

In accordance with this preferred embodiment there is provided a method of up-regulating glutathione metabolism in the central nervous system of a mammal, said method comprising administering to said mammal an effective amount of N-acetyl cysteine or a
10 derivative, homologue, analogue, chemical equivalent or mimetic thereof.

More particularly, there is provided a method of up-regulating glutathione metabolism in the brain of a mammal, said method comprising administering to said mammal an effective amount of N-acetyl cysteine or a derivative, homologue, analogue, chemical equivalent or
15 mimetic thereof.

Still more particularly, there is provided a method of up-regulating glutathione metabolism in the brain of a mammal, said method comprising administering to said mammal an effective amount of N-acetyl cysteine or a derivative, homologue, analogue, chemical
20 equivalent or mimetic thereof wherein said glutathione metabolism induces, up-regulates or otherwise augments antioxidant functional activity in said brain.

Derivatives include fragments, parts, portions, mutants, variants and mimetics from natural, synthetic or recombinant sources including fusion proteins. Parts or fragments
25 include, for example, active regions of glutathione or glutathione precursor. Derivatives may be derived from insertion, deletion or substitution of amino acids. Amino acid insertional derivatives include amino and/or carboxylic terminal fusions as well as intrasequence insertions of single or multiple amino acids. Insertional amino acid sequence variants are those in which one or more amino acid residues are introduced into a
30 predetermined site in the protein although random insertion is also possible with suitable screening of the resulting product. Deletional variants are characterized by the removal of

- 15 -

one or more amino acids from the sequence. Substitutional amino acid variants are those in which at least one residue in the sequence has been removed and a different residue inserted in its place. An example of substitutional amino acid variants are conservative amino acid substitutions. Conservative amino acid substitutions typically include
5 substitutions within the following groups: glycine and alanine; valine, isoleucine and leucine; aspartic acid and glutamic acid; asparagine and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine. Additions to amino acid sequences include fusions with other peptides, polypeptides or proteins or cyclising the peptide, for example to yield a pharmacologically active form.

10

Chemical and functional equivalents of glutathione or glutathione precursor molecules should be understood as molecules exhibiting any one or more of the functional activities of these molecules and may be derived from any source such as being chemically synthesized or identified via screening processes such as natural product screening.

15

The derivatives include fragments having particular epitopes or parts of the entire protein fused to peptides, polypeptides or other proteinaceous or non-proteinaceous molecules.

Analogues contemplated herein include, but are not limited to, modification to side chains,
20 incorporating of unnatural amino acids and/or their derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the proteinaceous molecules or their analogues.

Derivatives of nucleic acid sequences may similarly be derived from single or multiple
25 nucleotide substitutions, deletions and/or additions including fusion with other nucleic acid molecules. The derivatives of the nucleic acid molecules of the present invention include oligonucleotides, PCR primers, antisense molecules, molecules suitable for use in cosuppression and fusion of nucleic acid molecules. Derivatives of nucleic acid sequences also include degenerate variants.

30

- 16 -

Examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by reductive alkylation by reaction with an aldehyde followed by reduction with NaBH_4 ; amidination with methylacetimidate; acylation with acetic anhydride; carbamoylation of amino groups with cyanate; 5 trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS); acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; and pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with NaBH_4 .

The guanidine group of arginine residues may be modified by the formation of 10 heterocyclic condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal.

The carboxyl group may be modified by carbodiimide activation *via* O-acylisourea formation followed by subsequent derivitisation, for example, to a corresponding amide. 15

Sulphydryl groups may be modified by methods such as carboxymethylation with iodoacetic acid or iodoacetamide; performic acid oxidation to cysteic acid; formation of a mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; formation of mercurial derivatives using 4- 20 chloromercuribenzoate, 4-chloromercuriphenylsulphonic acid, phenylmercury chloride, 2-chloromercuri-4-nitrophenol and other mercurials; carbamoylation with cyanate at alkaline pH.

Tryptophan residues may be modified by, for example, oxidation with N- 25 bromosuccinimide or alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphenyl halides. Tyrosine residues on the other hand, may be altered by nitration with tetranitromethane to form a 3-nitrotyrosine derivative.

Modification of the imidazole ring of a histidine residue may be accomplished by 30 alkylation with iodoacetic acid derivatives or N-carboethoxylation with diethylpyrocarbonate.

- 17 -

Examples of incorporating unnatural amino acids and derivatives during protein synthesis include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminohexanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl
5 alanine and/or D-isomers of amino acids. A list of unnatural amino acids contemplated herein is shown in Table 1.

- 18 -

TABLE 1

	Non-conventional	Code	Non-conventional	Code
5	amino acid		amino acid	
	α -aminobutyric acid	Abu	L-N-methylalanine	Nmala
	α -amino- α -methylbutyrate	Mgab	L-N-methylarginine	Nmarg
	aminocyclopropane-	Cpro	L-N-methylasparagine	Nmasn
10	carboxylate		L-N-methylaspartic acid	Nmasp
	aminoisobutyric acid	Aib	L-N-methylcysteine	Nmcys
	aminonorbornyl-	Norb	L-N-methylglutamine	Nmgln
	carboxylate		L-N-methylglutamic acid	Nmglu
	cyclohexylalanine	Chexa	L-N-methylhistidine	Nmhis
15	cyclopentylalanine	Cpen	L-N-methylisoleucine	Nmile
	D-alanine	Dal	L-N-methylleucine	Nmleu
	D-arginine	Darg	L-N-methyllysine	Nmlys
	D-aspartic acid	Das	L-N-methylmethionine	Nmmet
	D-cysteine	Dcys	L-N-methylnorleucine	Nmnle
20	D-glutamine	Dgln	L-N-methylnorvaline	Nmnva
	D-glutamic acid	Dglu	L-N-methylornithine	Nmorn
	D-histidine	Dhis	L-N-methylphenylalanine	Nmphe
	D-isoleucine	Dile	L-N-methylproline	Nmpro
	D-leucine	Dleu	L-N-methylserine	Nmser
25	D-lysine	Dlys	L-N-methylthreonine	Nmthr
	D-methionine	Dmet	L-N-methyltryptophan	Nmtrp
	D-ornithine	Dorn	L-N-methyltyrosine	Nmtyr
	D-phenylalanine	Dphe	L-N-methylvaline	Nmval
	D-proline	Dpro	L-N-methylethylglycine	Nmetg
30	D-serine	Dser	L-N-methyl-t-butylglycine	Nmtbug
	D-threonine	Dthr	L-norleucine	Nle
	D-tryptophan	Dtrp	L-norvaline	Nva
	D-tyrosine	Dtyr	α -methyl-aminoisobutyrate	Maib

- 19 -

	D-valine	Dval	α -methyl- γ -aminobutyrate	Mgabu
	D- α -methylalanine	Dmala	α -methylcyclohexylalanine	Mchexa
	D- α -methylarginine	Dmarg	α -methylcyclopentylalanine	Mcpen
	D- α -methylasparagine	Dmasn	α -methyl- α -naphthylalanine	Manap
5	D- α -methylaspartate	Dmasp	α -methylpenicillamine	Mpen
	D- α -methylcysteine	Dmcys	N-(4-aminobutyl)glycine	Nglu
	D- α -methylglutamine	Dmgln	N-(2-aminoethyl)glycine	Naeg
	D- α -methylhistidine	Dmhis	N-(3-aminopropyl)glycine	Norn
	D- α -methylisoleucine	Dmile	N-amino- α -methylbutyrate	Nmaabu
10	D- α -methyllleucine	Dmleu	α -naphthylalanine	Anap
	D- α -methylllysine	Dmlys	N-benzylglycine	Nphe
	D- α -methylmethionine	Dmmet	N-(2-carbamylethyl)glycine	Ngln
	D- α -methylornithine	Dmorn	N-(carbamylmethyl)glycine	Nasn
	D- α -methylphenylalanine	Dmphe	N-(2-carboxyethyl)glycine	Nglu
15	D- α -methylproline	Dmpro	N-(carboxymethyl)glycine	Nasp
	D- α -methylserine	Dmser	N-cyclobutylglycine	Ncbut
	D- α -methylthreonine	Dmthr	N-cycloheptylglycine	Nchep
	D- α -methyltryptophan	Dmtrp	N-cyclohexylglycine	Nchex
	D- α -methyltyrosine	Dmty	N-cyclodecylglycine	Ncdec
20	D- α -methylvaline	Dmval	N-cyclododecylglycine	Ncdod
	D-N-methylalanine	Dnmala	N-cyclooctylglycine	Ncoct
	D-N-methylarginine	Dnmarg	N-cyclopropylglycine	Ncpro
	D-N-methylasparagine	Dnmasn	N-cycloundecylglycine	Ncund
	D-N-methylaspartate	Dnmasp	N-(2,2-diphenylethyl)glycine	Nbhm
25	D-N-methylcysteine	Dnmcys	N-(3,3-diphenylpropyl)glycine	Nbhe
	D-N-methylglutamine	Dnmgln	N-(3-guanidinopropyl)glycine	Narg
	D-N-methylglutamate	Dnmglu	N-(1-hydroxyethyl)glycine	Nthr
	D-N-methylhistidine	Dnmhis	N-(hydroxyethyl)glycine	Nser
	D-N-methylisoleucine	Dnmile	N-(imidazolylethyl)glycine	Nhis
30	D-N-methyllleucine	Dnmleu	N-(3-indolylyethyl)glycine	Nhtrp
	D-N-methylllysine	Dnmlys	N-methyl- γ -aminobutyrate	Nmgabu
	N-methylcyclohexylalanine	Nmchexa	D-N-methylmethionine	Dnmmet
	D-N-methylornithine	Dnmorn	N-methylcyclopentylalanine	Nmcpen

- 20 -

	N-methylglycine	Nala	D-N-methylphenylalanine	Dnmphe
	N-methylaminoisobutyrate	Nmaib	D-N-methylproline	Dnmpro
	N-(1-methylpropyl)glycine	Nile	D-N-methylserine	Dnmser
	N-(2-methylpropyl)glycine	Nleu	D-N-methylthreonine	Dnmthr
5	D-N-methyltryptophan	Dnmtrp	N-(1-methylethyl)glycine	Nval
	D-N-methyltyrosine	Dnmtyr	N-methyl- α -naphthylalanine	Nmanap
	D-N-methylvaline	Dnmval	N-methylpenicillamine	Nmpen
	γ -aminobutyric acid	Gabu	N-(<i>p</i> -hydroxyphenyl)glycine	Nhtyr
	L- <i>t</i> -butylglycine	Tbug	N-(thiomethyl)glycine	Ncys
10	L-ethylglycine	Etg	penicillamine	Pen
	L-homophenylalanine	Hphe	L- α -methylalanine	Mala
	L- α -methylarginine	Marg	L- α -methylasparagine	Masn
	L- α -methylaspartate	Masp	L- α -methyl- <i>t</i> -butylglycine	Mtbug
	L- α -methylcysteine	Mcys	L-methylethylglycine	Metg
15	L- α -methylglutamine	Mgln	L- α -methylglutamate	Mglu
	L- α -methylhistidine	Mhis	L- α -methylhomophenylalanine	Mhphe
	L- α -methylisoleucine	Mile	N-(2-methylthioethyl)glycine	Nmet
	L- α -methyllleucine	Mleu	L- α -methyllysine	Mlys
	L- α -methylmethionine	Mmet	L- α -methylnorleucine	Mnle
20	L- α -methylnorvaline	Mnva	L- α -methylornithine	Morn
	L- α -methylphenylalanine	Mphe	L- α -methylproline	Mpro
	L- α -methylserine	Mser	L- α -methylthreonine	Mthr
	L- α -methyltryptophan	Mtrp	L- α -methyltyrosine	Mtyr
	L- α -methylvaline	Mval	L-N-methylhomophenylalanine	Nmhph
25	N-(N-(2,2-diphenylethyl) carbamylmethyl)glycine	Nnbhm	N-(N-(3,3-diphenylpropyl) carbamylmethyl)glycine	Nnbhe
	1-carboxy-1-(2,2-diphenyl-N-methylamino)cyclopropane			

30 Crosslinkers can be used, for example, to stabilise 3D conformations, using homo-bifunctional crosslinkers such as the bifunctional imido esters having (CH₂)_n spacer groups with n=1 to n=6, glutaraldehyde, N-hydroxysuccinimide esters and hetero-bifunctional

- 21 -

reagents which usually contain an amino-reactive moiety such as N-hydroxysuccinimide and another group specific-reactive moiety.

Said derivative, analogue, chemical equivalent or mimetic thereof may be proteinaceous or
5 non-proteinaceous. The proteinaceous molecule may be derived from natural or recombinant sources including fusion proteins or following, for example, natural product screening. Said non-proteinaceous molecule may also be derived from natural sources, such as for example via natural product screening, or it may be chemically synthesised. The present invention contemplates chemical analogues of the glutathione precursor.
10 Chemical agonists may not necessarily be derived from the glutathione precursor but may share certain conformational similarities. Alternatively, chemical agonists may be specifically designed to mimic certain physiochemical properties.

The molecules which may be administered to a mammal in accordance with the present
15 invention may also be linked to a targeting means such as a monoclonal antibody, which provides specific delivery of these molecules to target regions.

The subject of the glutathione precursor administration may be any mammal including, but not limited to, humans, primates, livestock animals (e.g. horses, cattle, sheep, pigs and
20 donkeys), laboratory test animals (e.g. mice, rats, rabbits, guinea pigs), companion animals (e.g. dogs, cats) or captive wild animals (e.g. kangaroos, deer, foxes). Preferably, the mammal is a human.

According to this most preferred embodiment there is provided a method for up-regulating
25 glutathione metabolism in the brain of a human, said method comprising administering to said human an effective amount of N-acetyl cysteine or a derivative, homologue, analogue, chemical equivalent or mimetic thereof wherein said glutathione metabolism induces, up-regulates or otherwise augments antioxidant functional activity in said brain.

30 Without limiting the present invention to any one theory or mode of action, glutathione is thought to protect against oxidative damage due to its capacity to function both as a

- 22 -

scavenger of free radicals and as a substrate for the detoxification of H₂O₂, peroxynitrite, lipid peroxides and a variety of electrophilic compounds including redox-active metal ions (Freedman JH, Ciriolo MR and Peisach J., (1995), *J Neurosci*, 264:5598-605). Schizophrenia is a disease condition which is characterised by oxidative stress. As
5 detailed hereinbefore, emerging evidence suggests an abnormality in oxidation homeostasis both systemically and centrally in schizophrenia. Specifically, it is thought that abnormalities in an individual's dopamine metabolism leads to the production of free radicals and H₂O₂. These events, coupled with a loss in oxidative defences at sites of dopamine activity in the brain, may lead to the oxidative attack of neuronal structures,
10 thereby resulting in neural dysfunction and giving rise to the psychosis associated with schizophrenia. The inventors have determined that increasing glutathione levels in the brain results in a decrease in oxidative stress due to normalisation of brain oxidative homeostasis and therefore a decrease in the occurrence and/or severity of symptoms associated with schizophrenia. Still further, it has been determined that this normalisation
15 of brain oxidative homeostasis is partly due to the elevation of glutathione preventing the breakdown of dopamine.

Accordingly, in a related aspect there is provided a method of normalising oxidative homeostasis in the central nervous system of a mammal, which mammal exhibits unwanted
20 central nervous system oxidation, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof for a time and under conditions sufficient to up-regulate glutathione metabolism.

25 More particularly, there is provided a method of normalising oxidative homeostasis in the brain of a mammal, which mammal exhibits unwanted central nervous system oxidation, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof for a time and under conditions sufficient to up-regulate glutathione
30 metabolism.

- 23 -

Preferably said glutathione precursor is N-acetyl cysteine and still more preferably said mammal is a human.

Reference to "normalising" oxidative homeostasis should be understood as a reference to
5 improving oxidative homeostasis relative to the oxidative homeostasis status prior to treatment. The subject improvement may be partial or complete. Preferably, said normalisation is a decrease in oxidation in the central nervous system.

The use of N-acetyl cysteine in accordance with the method of the present invention is
10 particularly desirable since it has been determined that oral administration of N-acetyl cysteine, which is highly convenient, does result in the elevation of glutathione levels in the brain and therefore up-regulation of glutathione metabolism. N-acetyl cysteine rapidly and safely increases plasma cysteine levels due to rapid deacylation of N-acetyl cysteine in the liver to form cysteine. It should be understood, however, that the method of the present
15 invention is not intended to be limited to NAC to cysteine conversion occurring in the liver. Rather, the method of the present invention should be understood to encompass the occurrence of such conversions in any suitable file, such as, for example, the brain.

The development of the method of the present invention has facilitated the design and
20 application of therapeutic and prophylactic protocols for treating conditions characterised by aberrant, unwanted or otherwise undesirable oxidative stress and/or inadequate glutathione metabolism in the central nervous system and, in particular, the brain. Reference to "oxidative stress" should be understood as a reference to oxidation.

25 Reference to the treatment and/or prophylaxis of the subject condition should be understood as a reference to the treatment of any disease, injury or other condition, the symptoms, cause or side effects of which include aberrant, unwanted or otherwise undesirable oxidative stress and/or inadequate glutathione metabolism in the central nervous system. It should also be understood to encompass reference to conditions in
30 which one or more components or steps which would lead to aberrant, unwanted or otherwise undesirable oxidative stress and/or glutathione metabolism in the central nervous

- 24 -

system have occurred but which may not yet have resulted in noticeable symptoms. This includes, for example, conditions which occur as a side effect of a treatment regime for an unrelated disease condition.

- 5 Preferably, the subject condition is a neuropsychiatric disorder and still more preferably schizophrenia, psychosis, bipolar disorder, manic depression, affective disorder, or schizophreniform or schizoaffective disorders, psychotic depression, drug induced psychosis, delirium, alcohol withdrawal syndrome or dementia induced psychosis.
- 10 The method of the present invention preferably facilitates the subject condition being reduced, retarded or otherwise inhibited. Reference to "reduced, retarded or otherwise inhibited" should be understood as a reference to inducing or facilitating the partial or complete inhibition of any one or more causes or symptoms of the subject condition. In this regard, it should be understood that conditions such as neuropsychiatric disorders are
- 15 extremely complex comprising numerous physiological events which often occur simultaneously. In terms of the object of the subject method of treatment and/or prophylaxis, it should be understood that the present invention contemplates both relieving any one or more symptoms of the subject condition (for example, relieving one or more psychosis events) or facilitating retardation or cessation of the cause of the disease
- 20 condition (for example, reducing oxidative stress thereby minimising any further neuronal damage).

Accordingly, another aspect of the present invention relates to a method for the treatment and/or prophylaxis of a condition characterised by:

25

- (i) aberrant, unwanted or otherwise inappropriate oxidative stress; and/or
- (ii) inadequate glutathione metabolism,

- 30 in the central nervous system of a mammal, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue,

- 25 -

analogue, chemical equivalent or mimetic thereof.

More particularly the present invention relates to a method for the treatment and/or prophylaxis of a condition characterised by:

5 (i) aberrant, unwanted or otherwise inappropriate oxidative stress; and/or

(ii) inadequate glutathione metabolism,

10 in the brain of a mammal, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof.

Reference to "aberrant, unwanted or otherwise inappropriate" oxidative stress should be understood as a reference to excessive oxidation or to a physiologically normal level of oxidation, which level is inappropriate in the given circumstances or otherwise unwanted. It should also be understood that the subject unwanted oxidative stress may occur as a side-effect or other indirect consequence of a treatment regime for an unrelated condition, for example, due to the effect of anti-tumour drugs, radiotherapy, dopamine replacement therapy for Parkinson's disease or anti-psychotic medication.

20

Still more particularly, the present invention relates to a method of treating a neuropsychiatric condition in a mammal, said method comprising administering to said mammal an effective amount of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof for a time and under conditions sufficient to induce, up-regulate or otherwise augment antioxidant functional activity in the brain of said mammal.

25

Preferably said glutathione precursor is N-acetyl cysteine.

30 More preferably said condition is schizophrenia, psychosis, bipolar disorder, manic depression, affective disorder, or schizophreniform or schizoaffective disorders.

- 26 -

Most preferably said condition is schizophrenia.

Administration of the glutathione precursor or equivalent, derivative, homologue, analogue
5 or mimetic thereof, (herein referred to as the "modulatory agent"), in the form of a
pharmaceutical composition, may be performed by any convenient means. The
modulatory agent of the pharmaceutical composition is contemplated to exhibit therapeutic
activity when administered in an amount which depends on the particular case. The
variation depends, for example, on the human or animal and the form of modulatory agent
10 chosen. A broad range of doses may be applicable. Considering a patient, for example,
from about 0.1 mg to about 1 mg of modulatory agent may be administered per kilogram
of body weight per day. Dosage regimes may be adjusted to provide the optimum
therapeutic response. For example, several divided doses may be administered daily,
weekly, monthly or other suitable time intervals or the dose may be proportionally reduced
15 as indicated by the exigencies of the situation. The modulatory agent may be administered
in a convenient manner such as by the oral, intravenous (where water soluble),
intraperitoneal, intramuscular, subcutaneous, intradermal or suppository routes or
implanting (e.g. using slow release molecules). Preferably the agent is administered orally
and dosages of 1-10 grams per day are envisioned. More particularly the dosage is 2-6
20 grams per day. The modulatory agent may be administered in the form of
pharmaceutically acceptable nontoxic salts, such as acid addition salts or metal complexes,
e.g. with zinc, iron or the like (which are considered as salts for purposes of this
application). Illustrative of such acid addition salts are hydrochloride, hydrobromide,
sulphate, phosphate, maleate, acetate, citrate, benzoate, succinate, malate, ascorbate,
25 tartrate and the like. If the active ingredient is to be administered in tablet form, the tablet
may contain a binder such as tragacanth, corn starch or gelatin; a disintegrating agent, such
as alginic acid; and a lubricant, such as magnesium stearate.

Routes of administration include, but are not limited to, respiratorally, intratracheally,
30 nasopharyngeally, intravenously, intraperitoneally, subcutaneously, intracranially,
intradermally, intramuscularly, intraocularly, intrathecally, intracereberally, intranasally,

- 27 -

infusion, orally, rectally, *via* IV drip patch and implant. Preferably, said route of administration is oral.

5 In a most preferred embodiment, the present invention provides a method for the treatment and/or prophylaxis of schizophrenia in a mammal, said method comprising administering to said mammal an effective amount of N-acetyl cysteine or derivative, homologue, analogue, chemical equivalent or mimetic thereof for a time and under conditions sufficient to induce, up-regulate or otherwise augment antioxidant functional activity in the brain of said subject.

10

In another aspect the present invention relates to the use of a glutathione precursor or a derivative, homologue, analogue, chemical equivalent or mimetic thereof in the manufacture of a medicament for the up-regulation of glutathione metabolism and/or normalisation of oxidative homeostasis in the central nervous system of a mammal
15 wherein said glutathione precursor induces, up-regulates or otherwise augments antioxidant functional activity in said central nervous system.

Preferably said central nervous system is the brain.

20 Still more preferably, said glutathione precursor is N-acetyl cysteine.

As detailed hereinbefore, the inventors have determined that elevation of glutathione levels in a subject leads to normalisation of oxidative homeostasis, at least in part, by preventing the breakdown of dopamine. Accordingly, in a related aspect, the method of the present
25 invention is also useful for treating the symptoms of dopamine depletion, which are often observed in conditions such as schizophrenia, including apathy and inertia. In this regard, it should be understood that the occurrence of such dopamine-depletion related symptoms falls within the scope of a condition characterised by "aberrant, unwanted or otherwise inappropriate oxidative stress" since it is characterised by a cycle of excessive dopamine
30 breakdown.

- 28 -

In yet another aspect the present invention relates to the use of a glutathione precursor or derivative, homologue, analogue, chemical equivalent or mimetic thereof in the manufacture of a medicament for the treatment of a condition characterised by:

- 5 (i) aberrant, unwanted or otherwise inappropriate oxidative stress; and/or
- (ii) inadequate glutathione metabolism,

10 in the central nervous system of a mammal, wherein said glutathione precursor induces, up-regulates or otherwise augments antioxidant functional activity in said central nervous system.

Preferably said central nervous system is the brain and still more preferably said glutathione precursor is N-acetyl cysteine.

15

Most preferably said condition is a neuropsychiatric disorder and still more preferably schizophrenia, psychosis, bipolar disorder, manic depression, affective disorder, or schizophreniform or schizoaffective disorders.

20 In a related aspect of the present invention the mammal undergoing treatment may be human or an animal in need of therapeutic or prophylactic treatment.

Reference herein to "treatment" and "prophylaxis" is to be considered in its broadest context. The term "treatment" does not necessarily imply that a mammal is treated until
25 total recovery. Similarly, "prophylaxis" does not necessarily mean that the subject will not eventually contract a disease condition. Accordingly, treatment and prophylaxis include amelioration of the symptoms of a particular condition or preventing or otherwise reducing the risk of developing a particular condition. The term "prophylaxis" may be considered as reducing the severity of onset of a particular condition. "Treatment" may also reduce the
30 severity of an existing condition or the frequency of acute attacks (for example, reducing the severity of psychotic episodes).

- 29 -

In accordance with these methods, the modulatory agent defined in accordance with the present invention may be coadministered with one or more other compounds or molecules. By "coadministered" is meant simultaneous administration in the same formulation or in
5 two different formulations via the same or different routes or sequential administration by the same or different routes. By "sequential" administration is meant a time difference of from seconds, minutes, hours or days between the administration of the two types of molecules. These molecules may be administered in any order.

In this regard, although N-acetyl cysteine supplementation is thought to be the most direct
10 and efficient means of achieving the object of the present invention, this method may nevertheless be augmented through the use of indirect means of increasing the efficiency of other radical scavenging systems. For example, N-acetyl cysteine therapy maybe combined with the administration of supplements that bolster indirect participants in glutathione metabolism. These indirect participants of glutathione metabolism are herein
15 referred to as "para"-glutathione antioxidant systems since radicals propagate radially in terms of the biochemical chain reaction. Accordingly, glutathione, while central to the antioxidant pool, is not the sole means of removing radicals. Examples of agents which may be co-administered to augment normalisation of oxidative homeostasis include Vitamin C, Vitamin E (alpha-tocopherol), alpha-lipoic acid supplements and
20 selenomethionine.

Without limiting the present invention in any way, selenomethionine supplementation is known to augment the activity of glutathione peroxidase, the enzyme that catalyses the scavenging of radicals and H_2O_2 by glutathione. Alpha-lipopic acid has been shown to
25 facilitate the restoration of glutathione from oxidised glutathione and has been observed to attenuate oxidative damage in rodents. The actions of other supplements are schematically detailed in Figure 1. Vitamin E and selenomethionine supplementation are particularly desired since oral supplementation has been found to result in transduction of these molecules across the blood brain barrier in brain oxidation disorder. Suitable dosage
30 regimes of the supplemental molecules can be determined by the person of ordinary skill in the art.

- 30 -

The method of the present invention may also be combined with currently known methods of treatment such as the administration of anti-psychotic drugs.

5 In yet another aspect the present invention relates to a pharmaceutical composition comprising a glutathione precursor as hereinbefore defined and one or more pharmaceutically acceptable carriers and/or diluents. Said pharmaceutical composition may additionally comprise molecules with which it is to be co-administered. These agents are referred to as the active ingredients.

10

Although the method of the present invention is preferably achieved via the oral administration of a glutathione precursor, it should be understood that the present invention is not limited to this method of administration and may encompass any other suitable method of administration. In this regard, the pharmaceutical forms suitable for injectable
15 use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion or may be in the form of a cream or other form suitable for topical application. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a
20 solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of
25 microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum
30 monostearate and gelatin.

- 31 -

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilisation. Generally, dispersions are prepared by incorporating the various sterilised active ingredient into a sterile vehicle
5 which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

10

When the active ingredients are suitably protected they may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsule, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the
15 active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The
20 amount of active compound in such therapeutically useful compositions in such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 0.1 µg and 3000 mg of active compound.

25 The tablets, troches, pills, capsules and the like may also contain the components as listed hereafter: a binder such as gum, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavouring agent such as peppermint, oil of
30 wintergreen, or cherry flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be

- 32 -

present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavouring such as cherry or orange flavour. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound(s) may be incorporated into sustained-release preparations and formulations. The pharmaceutical composition may also comprise genetic molecules such as a vector capable of transfecting target cells where the vector carries a nucleic acid molecule encoding a modulatory agent. The vector may be, for example, a viral vector.

Yet another aspect of the present invention relates to modulatory agents, as hereinbefore defined, when used in the method of the present invention.

The present invention is further described by the following non-limiting examples.

- 33 -

EXAMPLE 1**N-ACETYL CYSTEINE TREATMENT AND THE BEHAVIOURAL EFFECT OF
AMPHETAMINE IN RATS****5 Methods***Animals*

Male Sprague Dawley rats (380-430g) were obtained from Department of Pathology, University of Melbourne. On arrival rats were housed in pairs in a temperature-controlled
10 (20-24°C) colony room maintained on a 12hr light-dark cycle (6am-6pm). Rats had continuous access to food and water (plain or treated) and were weighed on arrival and then daily from onset of experiment. Rats were allowed to adjust to the new environment for 3 days before starting the experiment.

15 Drug treatment

This experiment consisted of 24 rats in total. Eight rats received plain drinking water (controls), 8 rats received 0.5% NAC (Sigma) in their drinking water (low dose) and 8 rats received 2% NAC in their drinking water (high dose). Drug treatment was administered for 14 consecutive days. Bottles were cleaned and fresh drug solution was made up on days 4,
20 8 and 11. Body weights and amount of drinking water consumed per box were measured on a daily basis. After 7 days of drug treatment, behavioural testing began and continued until day 14 of treatment.

Locomotor activity

25 Locomotor activity was assessed in 8 automated photo cell cages, data being collected in 5-min intervals. Animals were placed individually in cages and baseline activity was measured during the first 30 minutes. After 30 minutes rats received a subcutaneous injection of either saline (vehicle), 0.5 mg/kg or 5 mg/kg amphetamine and locomotor activity was measured for a further 90 minutes. Drug treatment and time of day of the
30 experiment were both randomised (see table 1). Each rat received 3 locomotor sessions in total. A period of 3 days was allowed between locomotor experiments to ensure complete

- 34 -

elimination of amphetamine.

Statistics

Locomotor hyperactivity was obtained as total distance moved per 30 min, i.e. before
5 injection and 0-30 min, 30-60 min and 60-90 min after injection. In order to account for
slight variations in baseline activity, post-injection behaviour was expressed a change of
baseline activity. Average data for rats receiving water, 0.5% NAC, or 2% NAC was
compared using analysis of variance for repeated measures (ANOVA) using the Systat 9.0
software package.

10

Results

Body weights and water consumption

Average daily water consumption per box during the 14 days of treatment was
15 considerably lower when the rats received the 2% dose of NAC, compared to the 0.5%
dose and water controls. Water consumption ranged from 77-90 ml in control rats, 60-72
ml in low dose rats and 27-49 ml in high dose rats (figure 2). This was accompanied by a
marked decrease in body weight over the treatment period of the high dose rats compared
with controls (figure 2, table 2).

20

Effect of amphetamine on locomotor activity

All rats were tested three times: once after saline injection, once after injection of 0.5
mg/kg of amphetamine, and once after injection of 5 mg/kg of amphetamine (table 2).
Baseline locomotor activity before injection, averaged over these three sessions, tended to
25 be lower in NAC-treated rats than in water controls, but this difference did not reach
statistical significance (figure 3).

After injection of saline, as expected locomotor activity fell to a low level throughout the
remaining 90 min of the experiment. In contrast, injection of 0.5 mg/kg of amphetamine
30 induced a behavioural hyperactivity, with values for distance moved after injection
equalling or exceeding the initial spontaneous activity (figure 3). The overall effect of 0.5

- 35 -

mg/kg of amphetamine tended to be greater in rats receiving either 0.5% NAC ($F_{(1,14)}=5.11$, $P=0.04$) or 2% NAC ($F_{(1,13)}=4.3$, $P=0.06$) in the drinking water. The maximal effect of this dose of amphetamine was observed 30-60 min after injection (figure 4). This maximal effect was significantly greater in rats receiving either NAC dose compared to
5 water controls (figure 5).

Injection of 5 mg/kg of amphetamine initially induced marked behavioural hyperactivity, but activity fell to low levels later in the 90 min observation period. The overall effect of 5 mg/kg of amphetamine tended to be greater in rats receiving 2% NAC to drink, but this
10 difference failed to reach overall statistical significance. There was, however an overall significant interaction of treatment x time, reflecting the differing time-course of the effect of this dose of amphetamine between groups. This interaction was significant when comparing rats receiving 2% NAC with controls ($F_{(2,28)}=4.9$, $P=0.024$), but not when comparing rats receiving 0.5% NAC with controls. Thus, in rats receiving the 2% NAC
15 dose, locomotor hyperactivity was maintained longer than in controls (figure 4).

Analysis

The effect of amphetamine given to rats is to increase locomotor activity mediated by increased dopamine release in the nucleus accumbens in the ventral forebrain. The current
20 results show that NAC-treatment enhances the effect of amphetamine. This was seen as a greater maximal effect of 0.5 mg/kg of amphetamine in rats receiving either 0.5% NAC or 2% NAC, and as a prolonged effect of 5 mg/kg of amphetamine in rats receiving 2% NAC. These results confirm that NAC impacts upon the central neurometabolism of DA, making it more available in the nucleus accumbens. NAC, after being metabolised to cysteine in
25 the liver, is then converted to glutathione (GSH), which passes into the brain through the blood brain barrier. GSH scavenges hydrogen peroxide and other pro-oxidants, and prevents oxidation and breakdown of biochemicals like dopamine. By increasing the availability of GSH in the brain, less of the dopamine that is released by the action of amphetamine would be oxidized and broken down. This would make more dopamine
30 available to stimulate postsynaptic receptors, leading to the enhanced or prolonged behavioural effects which were observed.

- 36 -

These findings confirm that oral NAC treatment favourably impacts upon brain dopamine metabolism.

5

EXAMPLE 2**N-ACETYL CYSTEINE IN SCHIZOPHRENIA: A DOUBLE-BLIND,
RANDOMISED, PLACEBO-CONTROLLED TRIAL**

10 This study investigates a novel, tolerable and practical adjunctive therapy. In this study the efficacy and tolerability 3g daily of N-acetyl Cysteine (NAC) is compared to placebo in patients who are suffering from both acute and chronic schizophrenia and are on treatment with the atypical antipsychotic drugs olanzapine, risperidone and clozapine.

15 (i) *Study Group*

Two hundred patients aged 18-65 years meeting DSM-IV criteria for schizophrenia on a structured clinical interview (SCID) are studied. There is a group of 100 patients with chronic, stable schizophrenia on clozapine as well as 100 patients suffering from an acute relapse of schizophrenia, who are with risperidone and olanzapine. The patients are assigned randomly and consecutively to treatment with NAC or placebo in a double blind fashion.

20 (ii) *Inclusion and Exclusion Criteria*

25 To be included the patients are required to meet DSM-IV criteria for schizophrenia. The age is between 18 to 65, and both males and females are studied. The study population includes both inpatients and outpatients. Patients with abnormal renal, hepatic, thyroid or haematological findings are excluded from the study, as are patients who have an acute systemic medical disorder. Subjects who have had a neuroleptic depot preparation in the last month are excluded, and patients on psychoactive medications for other indications need to have been on those agents

30

- 37 -

for at least 1 month. Patients on mood stabilisers (lithium, valproate and carbamazepine) are excluded from the study. Also excluded are those patients who are unable to comply with either the requirements of informed consent or the treatment protocol.

5 (iii) *Measurements*

The patients are assessed on admission through a structural clinical interview (SCID, DSM-IV). A complete physical as well as a neurological examination is also done. The patient's psychiatric condition is measured on admission using the
10 Positive and Negative Symptom Scale (PANSS) Clinical Global Impression (CGI) improvement and severity scales, as well as the Global Assessment of Functioning Scale (GAF). In addition, the AIMS, Simpson-Angus and Barnes Akathisia scales is performed. These scales are repeated two weekly for eight weeks or on the day
15 of study termination if the patient withdraws prior to 8 weeks. A further extension phase under continued double blind treatment follows, with monthly evaluations to a total of 6 months. Adverse events are tabulated. Clozapine, olanzapine and risperidone blood level monitoring is done at baseline and at the end of 2 months of treatment to exclude potential drug interactions. Routine laboratory investigations assess renal, thyroid, haematological and hepatic function. A urine analysis is
20 done. Vital signs are monitored at each visit (blood pressure, pulse, weight).

(iv) *Study Procedure*

All patients are treated with either olanzapine or risperidone (acute treatment
25 group) or clozapine (chronic treatment group) prior to randomisation. All randomised patients receive NAC 4 capsules BD to a total dose of 3g daily, or placebo. Platelet glutamate receptor sensitivity, measured using spectrofluorometry, is done at baseline and at the end of the first and second month. All patients give written informed consent before enrolment. Patients are
30 withdrawn from the study if they withdraw consent or develop serious adverse events associated with the study drug. Discontinuation due to adverse events is

- 38 -

either at the request of the patient or the discretion of the investigator. The trial is approved by relevant research and ethics committees. The trial is conducted according to GCP guidelines.

5 (v) *Rationale for Dosage Strategy*

10 NAC is well tolerated by humans and used in the clinic as a mucolytic (for AIDS and cystic fibrosis treatment), for treatment of acetaminophen overdose where it prevents glutathione depletion in the liver, and is also available in the US as an over-the-counter supplement. Human dosing can be up to 5 g/day without adverse effects (Louwerse ES, Weverling GJ, Bossuyt PM, Meyjes FE and de Jong JM., (1995), *Arch Neurol*, 52:559-64). The capsules of NAC are 750 mg, and the maximum dose in a clinical trial so far has been 5 g/day. A dose of 3 g/day (4 capsules, 2 bid) sustains elevated plasma cystine levels.

15

(vi) *Analysis of Results*

20 Overall power to detect significant differences between the actual pattern of means; assuming a correlation of post-treatment scores with baseline measurements of 0.7 and an effect of the NAC adjunctive treatment such that the NAC group differs from controls by 0.75 standard deviations, power is maintained above 90% with 50 subjects in each group. Pairwise comparisons with 50 subjects per group enables effects smaller than 0.6 standard deviations to be detected with power of 80%. These effect sizes are in the small to moderate range. The experiment is this
25 capable of detecting difference between groups of clinical and scientific interest.

(vii) *Available Patient Population*

30 The trial is conducted in three sites over three years, Geelong and Werribee in Victoria Australia as well as in Johannesburg, South Africa. All three centres have significant numbers of patients who meet trial criteria. Geelong has 250 patients on

- 39 -

clozapine, Werribee 100 and Johannesburg many hundreds. Similarly, acute relapse of schizophrenia is amongst the most common clinical problems seen in all centres.

5

EXAMPLE 3

RATIONALE FOR DOSAGES OF SUPPLEMENTARY AGENTS

Selenomethionione

10 Tables are purchased with 200 ug. One per day is an acceptable long-term dose with no known adverse effects.

Vitamin E

15 400 IU of alpha-tocopherol is sufficient to increase CSF levels without causing adverse effects. Doses higher than 2000 IU/day may cause coagulopathies and can be a source of radicals itself (Bowry VW, Mohr D, Cleary J and Stocker R., (1995), *J Biol Chem*, 270:5756-63)

20 *Vitamin C*

500 mg of Vitamin C daily is sufficient to elevate plasma levels 60%. Excess Vitamin C may increase nucleic acid oxidation (Podmore ID, Griffiths HR, Herbert KE, Mistry N, Mistry P and Lunec J., (1998), *Nature*, 392:559)

25

Alpha-lipoic Acid

100 mg tablets are marketed. Doses of 600-1200 mg/day for three weeks have been shown to be tolerated with no adverse effects, and with reproducibly demonstrated benefit in
30 decreasing the symptoms of diabetic neuropathy (Ziegler D and Gries FA., (1997), *Diabetes*, 46 Suppl 2, S62-) (believed to be caused by oxidative radical damage).

- 40 -

Therefore we will use 600 mg/day in divided doses.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood
5 that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

- 41 -

Table 2: randomisation table for the locomotor hyperactivity experiments. Rats 1-8 received normal water, rats 9-16 chronically received 0.5% NAC in their drinking water, and rats 17-24 received 2% NAC. During the locomotor hyperactivity experiments, the animals were injected with either saline (SAL), 0.5 mg/kg of amphetamine (0.5), or 5 mg/kg of amphetamine (5).

Rat#	Injection		
	1 st dose	2 nd dose	3 rd dose
1	SAL	0.5	5
2	5	SAL	0.5
3	0.5	SAL	5
4	0.5	SAL	5
5	5	0.5	SAL
6	5	0.5	SAL
7	SAL	5	0.5
8	SAL	5	0.5
9	SAL	0.5	5
10	5	SAL	0.5
11	0.5	SAL	5
12	0.5	SAL	5
13	5	0.5	SAL
14	5	0.5	SAL
15	SAL	5	0.5
16	SAL	5	0.5
17	SAL	0.5	5
18	5	SAL	0.5
19	0.5	SAL	5
20	0.5	SAL	5
21	5	0.5	SAL
22	5	0.5	SAL
23	SAL	5	0.5
24	SAL	5	0.5

- 42 -

BIBLIOGRAPHY

Abdalla DS, Monteiro HP, Oliveira JA and Bechara EJ., (1986), *Clin Chem*, **32**:805-7

Bowry VW, Mohr D, Cleary J and Stocker R., (1995), *J Biol Chem*, **270**:5756-63

Buckman TD, Kling AS, Eiduson S, Sutphin MS and Steinberg A., (1987), *Biol Psychiatry*, **22**:1349-56

Do KQ, Lauer CJ, Schreiber W, Zollinger M, Gutteck-Amsler U, Cuenod M and Holsboer F., (1995), *J Neurochem*, **65**:2652-62

Do KQ, Trabesinger AH, Kirsten-Kruger M, Lauer CJ, Dydak U, Hell D, Holsboer F, Boesiger P and Cuenod M., (2000), *Euro J Neurosci*, **12**:3721-8

Duffield AJ, Thomson CD, Hill KE and Williams S., (1999), *Am J Clin Nutr*, **70**:896-903

Freedman JH, Ciriolo MR and Peisach J., (1995), *J Neurosci*, **264**:5598-605

Gurney ME, Cutting FB, Zhai P, Doble A, Taylor CP, Andrus PK and Hall ED., (1996), *Ann Neurol*, **39**:147-57

Hagen TM, Ingersoll RT, Lykkesfeldt J, Liu J, Wehr CM, Vinarsky V, Bartholomew JC and Ames AB., (1999), *Faseb J*, **13**:411-8

Louwerse ES, Weverling GJ, Bossuyt PM, Meyjes FE and de Jong JM., (1995), *Arch Neurol*, **52**:559-64

Mahadik SP, Mukherjee S, Scheffer R, Correnti EE and Mahadik JS., (1998), *Biol Psychiatry*, **43**:674-9

- 43 -

Podmore ID, Griffiths HR, Herbert KE, Mistry N, Mistry P and Lunec J., (1998), *Nature*, **392**:559

Yao JK, Reddy RD and van Kammen DP., (1999), *Biol Psychiatry*, **45**:1512-5

Ziegler D and Gries FA., (1997), *Diabetes*, **46 Suppl 2**, S62-6

- 44 -

CLAIMS:

1. Use of a glutathione precursor for the treatment or prophylaxis of a neuropsychiatric disorder in a mammal.
2. Use according to claim 1, wherein the mammal is a human.
3. Use according to claim 1 or claim 2, wherein said neuropsychiatric disorder is selected from the group consisting of schizophrenia, psychosis, bipolar disorder, manic depression, affective disorder, schizophreniform or schizoaffective disorders, psychotic depression, drug induced psychosis, delirium, alcohol withdrawal syndrome and dementia induced psychosis.
4. Use according to claim 3, wherein the disorder is schizophrenia.
5. Use according to any one of claims 1 to 4, wherein said glutathione precursor is N-acetyl cysteine.
6. Use of a glutathione precursor in the manufacture of a medicament for the treatment of a neuropsychiatric disorder in a mammal, wherein said glutathione precursor up-regulates antioxidant functional activity of the brain of said mammal.
7. Use according to claim 6, wherein said mammal is a human.
8. Use according to claim 7, wherein said neuropsychiatric disorder is selected from the group consisting of schizophrenia, psychosis, bipolar disorder, manic depression, affective disorder, schizophreniform or schizoaffective disorders, psychotic depression, drug induced psychosis, delirium, alcohol withdrawal syndrome and dementia induced psychosis.
9. Use according to claim 8, wherein said neuropsychiatric disorder is schizophrenia.

- 45 -

10. Use according to any one of claims 6 to 9, wherein said glutathione precursor is N-acetyl cysteine.

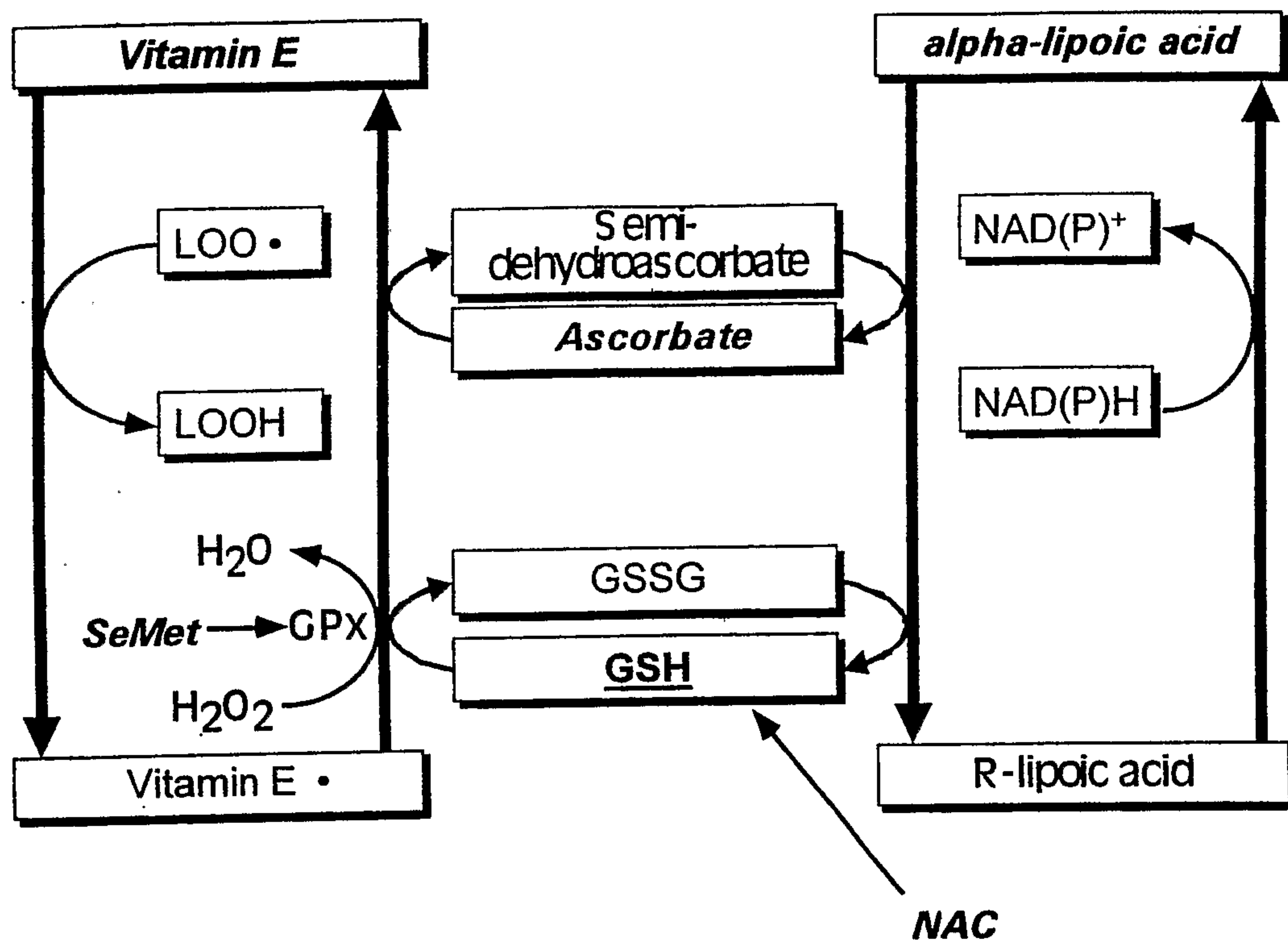
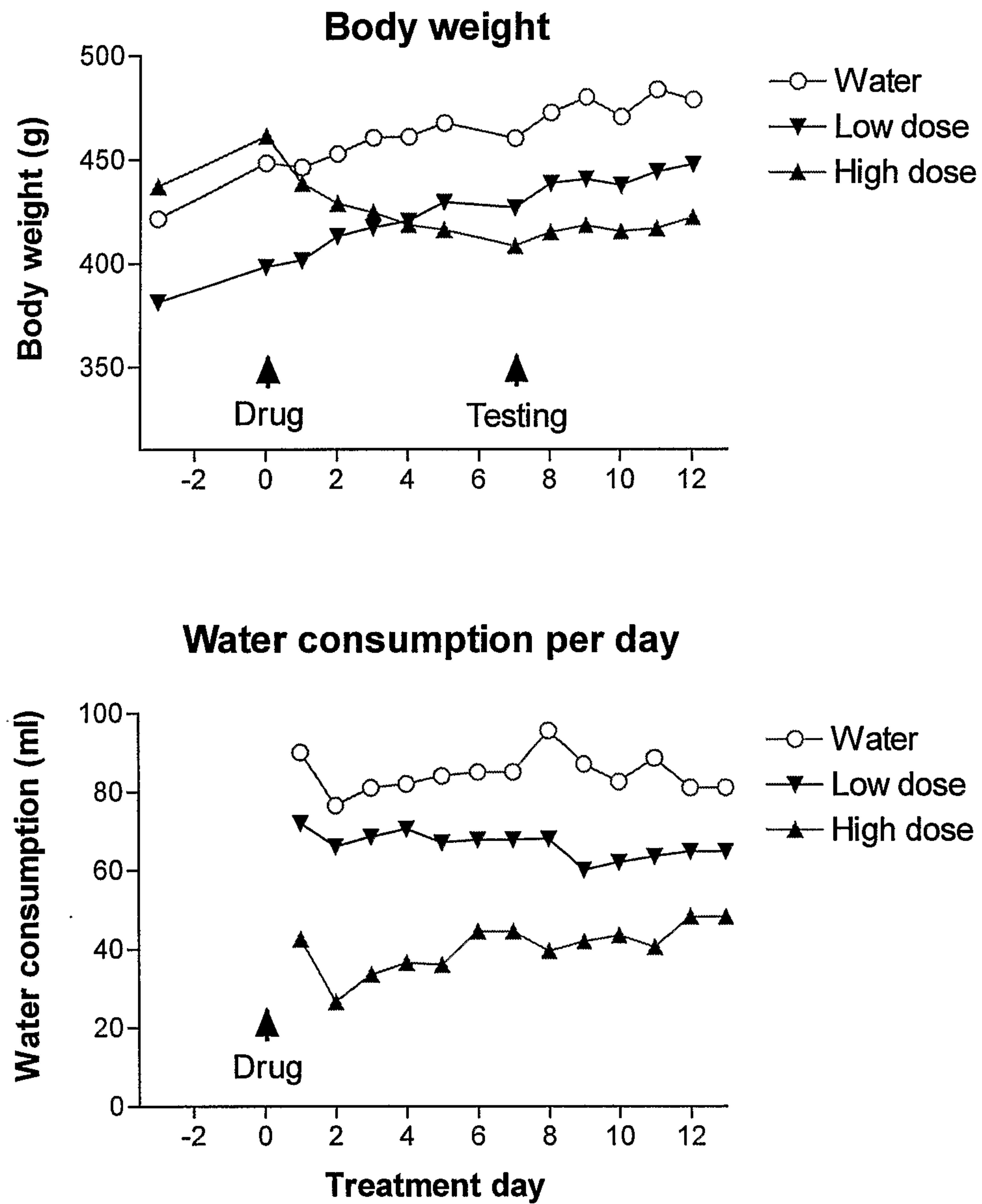
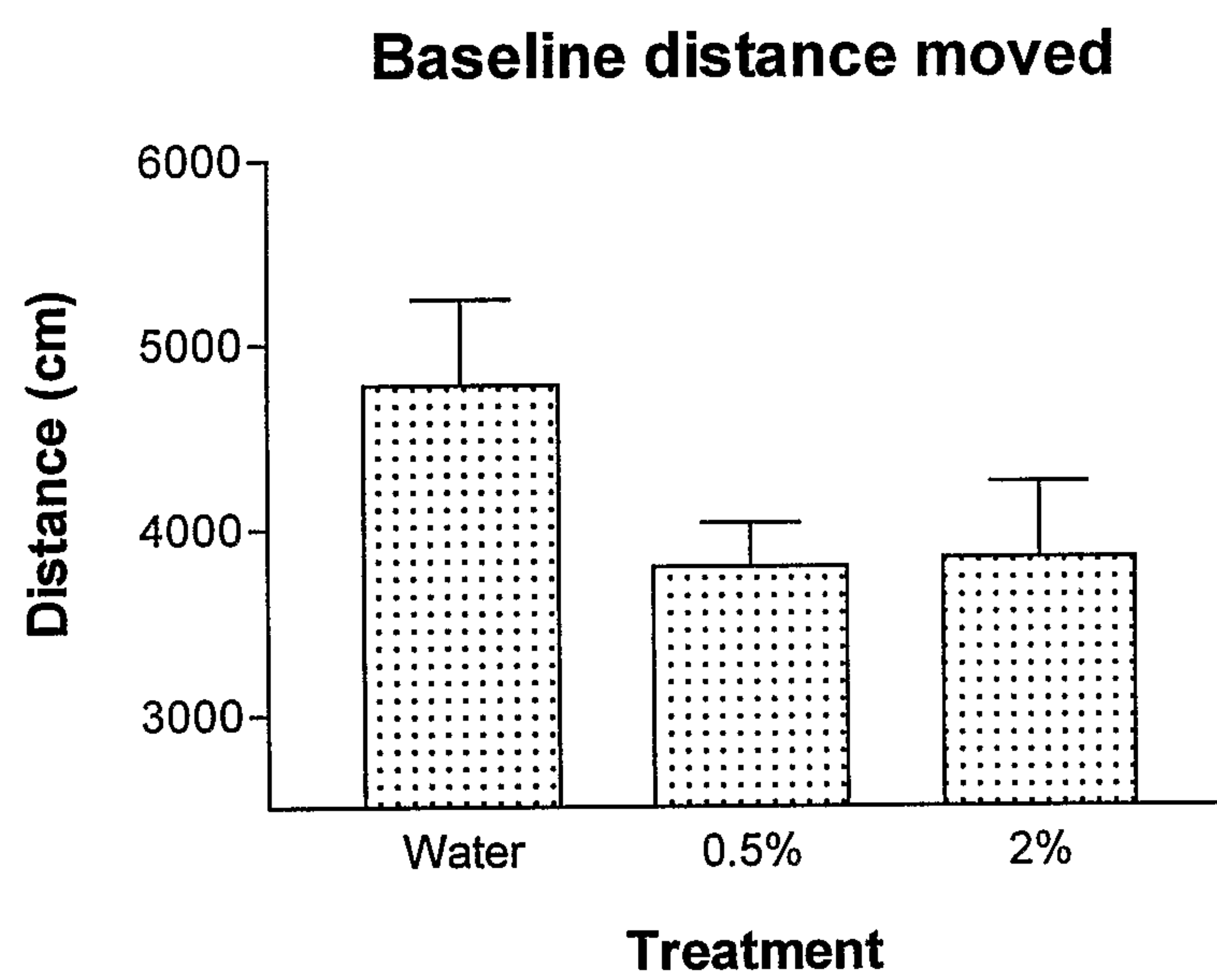
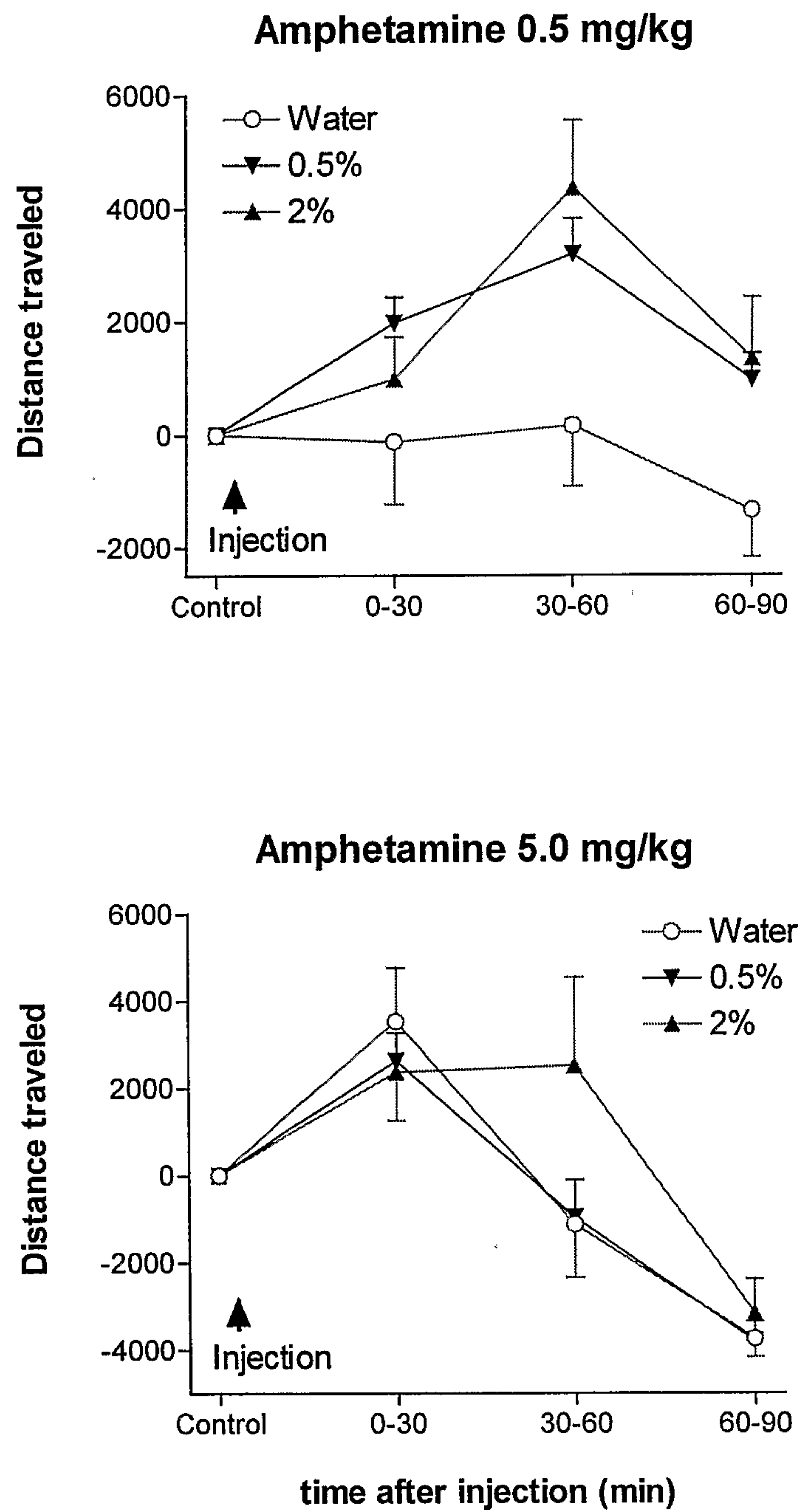
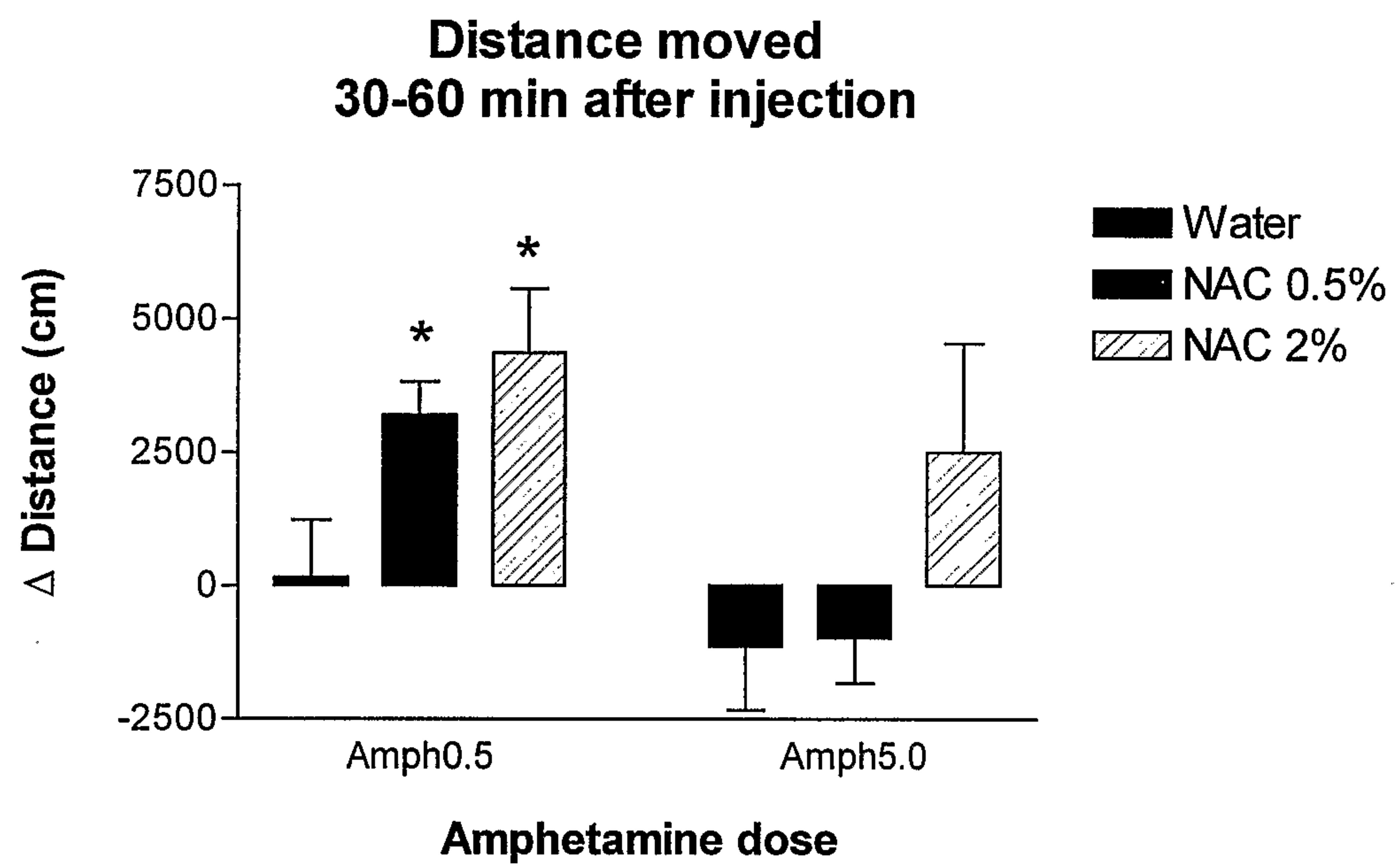


FIGURE 1

**FIGURE 2**

**FIGURE 3**

**FIGURE 4**

**FIGURE 5**