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(54) Title: TREATMENT OF ADHD

(57) Abstract: A method is provided for treating a subject in need of therapy for attention deficit hyperactivity disorder (ADHD) and related CNS disorder symptoms of impaired learning, impaired planning, impaired problem solving, impulsiveness, attention deficit and aggression comprising administering to said subject an amount of a ketogenic material sufficient to produce a ketosis in the subject sufficient to provide therapeutic benefit in such behavioural disorders. Preferred materials produce a ketosis is such that the total concentration of acetoacetate and (R)-3-hydroxybutyrate in the blood of the subject is raised to between 0.1 and 30mM.

WO 2006/098767 A2

### TREATMENT OF ADHD

The present invention relates to a method for treating and preventing attention deficit hyperactivity disorder (ADHD) and related CNS disorders of cognition (as related to learning, planning and problem solving), impulsiveness, attention and aggression in children, adolescents and adults; such disorders include, but are not restricted to, the hyperkinetic syndrome and minimal brain dysfunction. More particularly, the invention relates to the unexpected advantages of using modalities to elevate plasma and brain concentrations of ketone bodies to treat ADHD and related CNS disorders of cognition (as related to learning, planning and problem solving), impulsiveness, attention and aggression.

ADHD is believed to result from a dysregulation in the function of two monoamine neurotransmitters in the brain, ie noradrenaline (or norepinephrine) and dopamine. It is also well known that ADHD and CNS disorders of cognition (as related to learning, planning and problem solving), impulsiveness, attention and aggression are treatable with sympathomimetic drugs, which either non-selectively enhance the function in the brain of dopamine and noradrenaline, eg dl-threo-methylphenidate, d-threo methylphenidate, dl-amphetamine or d-amphetamine, or selectively enhance noradrenaline, eg atomoxetine. However, there are several major clinical disadvantages to using these drugs including, but not limited to, the serious abuse liability of the psychostimulants, ie dl-threo-methylphenidate, d-threo-methylphenidate, dl-amphetamine or d-amphetamine (Schedule 2 Controlled Drugs in the UK and USA), and the actions of all of these drugs to produce serious side-effects of insomnia, anorexia and impaired growth.

It is known that ketone bodies (R)-3-hydroxybutyrate and acetoacetate can be utilized by the brain as alternative metabolic fuels to D-glucose and have neurological benefits. For example, it is known that both acute and chronic neurodegenerative states in mammals, eg man, can be treated by inducing ketosis. Such ketosis can be provided by restriction of diet, eg by starvation or exclusion of carbohydrate, or by administration of ketogenic materials, such as triglycerides, free fatty acids, alcohols (eg butan-1,3-diol), acetoacetate and (R)-3-hydroxybutyrate and their conjugates with each other and further moieties, e.g. esters and polymers of these. Ketogenic materials thus produce a physiologically acceptable ketosis when administered to a patient.

Further therapeutic indications for the application of ketosis include epilepsy, affective and related psychiatric disorders, which include, but are not restricted to, depression, anxiety, schizo-affective disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder, generalised anxiety disorder and post-traumatic stress disorder, impaired cognitive function resulting from neurodegeneration, pain, diabetes, dystrophies and mitochondrial disorders. In the case of epilepsy, the ketogenic diet has been applied in treatment of intractable seizures with some success for many years, although the mechanism by which the seizure suppression is achieved remains uncertain.

In the present invention, it has been surprisingly demonstrated that ketogenesis to increase the plasma concentrations of ketone bodies produces previously unanticipated changes in brain electrical activity similar to those evoked by stimulant drugs used in the treatment of ADHD and related CNS disorders of cognition with respect to learning, planning and problem solving, impulsiveness, attention and aggression. Moreover, this invention provides the additional therapeutic advantage that ketogenesis as a clinical treatment for ADHD and related CNS disorders of cognition associated with impairments of learning, planning and problem solving, impulsiveness, attention and aggression will be devoid of the serious side-effects of insomnia, anorexia and impaired growth because the animals displayed no signs of behavioural stimulation at the predicted therapeutic plasma concentrations of ketone bodies.

Analysis of brain field potentials ("Tele-Stereo-EEG") has been proven to be a very sensitive tool for the characterization of drug effects on the central nervous system (Dimpfel et al., 1986). After administration of a centrally active drug, quantitative changes in the brain field potentials can be considered as a characteristic fingerprint of that particular drug. "Fingerprints" of more than 100 compounds have been obtained including 8 established drug categories, e.g. stimulants, sedatives, hallucinogenics, tranquilizers, analgesics, antidepressants, neuroleptics, and narcotics. Different dosages of the same drug cause quantitative changes in electrical power. This methodology can, therefore, also demonstrate possible dose-response relationships. Direct comparison with specific reference drugs, or by discriminant analysis with reference to an extensive fingerprint database, permits the detection of any possible similarities with established drugs. In general, "fingerprints" show prominent differences for drugs prescribed for different indications and are similar for

drugs with the same indication (Dimpfel, 2003). Furthermore, the pattern of EEG changes in the rat is a useful tool in predicting possible changes in the EEG power spectrum in humans.

5 Applying this technique to ketogenesis, illustrated herein by direct administration of (R)-3-hydroxybutyrate sodium salt, the present inventors have been able clearly to show EEG changes consistent with the aforesaid action to be efficacious in the in the treatment of ADHD and related CNS disorders of cognition (as related to learning, planning and problem solving), impulsiveness, attention and aggression.

10 Thus in a first aspect of the present invention, there is provided a method of treating a subject in need of therapy for ADHD and related CNS disorder symptoms of one or more of impaired learning, impaired planning and impaired problem solving capability, impulsiveness, attention deficit and aggression comprising administering to said subject a therapeutically effective amount of a ketogenic material.

15 The therapeutically effective amount of ketogenic material will preferably produce a physiologically acceptable ketosis, as opposed to merely maintaining the normal physiological levels of ketones in the blood. Ketone bodies are utilised rapidly and it is possible to administer lower doses that are utilised without an increase in plasma levels being detected. The ketosis produced is preferably a state in which levels of  
20 one or both of acetoacetate and (R)-3-hydroxybutyrate concentrations in the blood of the subject are raised. Preferably the total concentration of these 'ketone bodies' in the blood is elevated above the normal fed levels to between 0.1 and 30mM, more preferably to between 0.2 and 15mM, and most preferably to between 0.5 and 8mM. For the purpose of maximising levels of such compounds in the CNS, it is desirable to  
25 saturate the transporter through which (R)-3-hydroxybutyrate crosses the blood brain barrier: this occurring at between 1 and 5mM.

In its broadest interpretation, the ketogenic material may be any of those used in the treatment of refractory epilepsy, such as creams and fats combined with low carbohydrate and possibly high protein, e.g. as set out in US 6,207,856 (Veech).  
30 However, in order to avoid undesirable consequences of such diets, preferred materials are selected from acetoacetate, (R)-3-hydroxybutyrate, salts, esters and oligomers of these and conjugates of these with other physiologically acceptable moieties, such as carnitine and other amino acids. Other acceptable materials are

metabolic precursors of ketones, those such as (R)-1,3-butandiol, triacetin, free fatty acids and triglycerides or saccharide esters.

Particular materials are known from the following references as set out in Table 1 below. Doses and formats are as described in the documents identified in the table. Typically the amount of ketogenic material required can be determined by measuring blood levels directly using a meter such as the Medisense Precision Extra (Medisense Inc, 4A Crosby Drive Bedford, MA 01730); BioScanner 2000 (formerly called the MTM BioScanner 1000) from Polymer Technology Systems Inc. Indianapolis, Indiana. In this manner the amount of ketosis derived from a set dose may be ascertained, and that dose iterated to suit the individual.

TABLE 1

Material	Type	Reference
Sodium(R)-3-hydroxybutyrate	Salt	US 4579955 US 4771074
(R)-1, 3-butandiol	Metabolic precursor	Gueldry & Bralet (1994) Metabolic Brain Diseases 9(2): 171-181
Acetoacetylbutandiol	Metabolic precursor	US 4997976 US 5126373
Dimer and trimer BHB	Metabolic precursor	JP 5009185 JP 2885261
Acetoacetyltri-3HB	Metabolic precursor	US 6207856
Mid-chain triglyceride	Metabolic precursor	WO 01/82928
Triolide	Metabolic precursor	WO 00/15216 WO 00/04895
(R)-3-hydroxybutyrate triglyceride	Metabolic precursor	US 5420335 US 6306828
(R)-3-hydroxybutyrate multimers/saccharides	Metabolic precursor	WO 00/14985 WO04077938

Typical dose ranges for example might be in the range 5 to 5000mg/kg body weight, particularly for an (R)-3-hydroxybutyrate containing material such as oligomeric (R)-3-hydroxybutyrate or its esters with, e.g. glycerol or (R)-butan-1,3-diol, more preferably 30 to 2000mg/kg body weight, most preferably 50 to 1000mg/kg body weight per day. Doses are conveniently given with meals when orally

administered, conveniently before or at the same time as such meals. Regular blood levels are more readily attained by dosing three or four times a day.

In a second aspect of the present invention, there is provided the use of a ketogenic material for the manufacture of a medicament for the treatment of ADHD and related  
5 CNS disorder symptoms of one or more of impaired learning, impaired planning, impaired problem solving, impulsiveness, attention deficit and aggression. Again, suitable ketogenic materials are as described for the first aspect of the invention and as exemplified in Table 1.

A third aspect of the present invention provides a pharmaceutical composition  
10 for treating ADHD and related CNS disorder symptoms of one or more of impaired learning, impaired planning, impaired problem solving, impulsiveness, attention deficit and aggression comprising as active ingredient a ketogenic material. The composition preferably includes diluent, excipient and/or carrier materials.

The present invention will now be described by way of the following non-  
15 limiting Examples and Figures. Further embodiments falling into the scope of the claims herein will occur to those skilled in the light of these.

## FIGURES

20 Figure 1: Changes in 24 variables and frequency changes in individual brain regions. Variance/co-variance was estimated on the basis of 88 groups from part of our database of reference drugs with a total of 674 experiments carried out under identical conditions. Variables: frequency range – brain region \* $F > 2.10$  corresponds to  $p < 0.05$  and \*\* $F > 2.80$  corresponds to  $p < 0.01$ . For evaluation of 24 variables: \* $F > 1.52$   
25 corresponds to  $p < 0.05$  and \*\* $F > 1.79$  corresponds to  $p < 0.01$ . Number of experiments:  $n = 12$  (100 mg/kg);  $n = 12$  (300 mg/kg);  $n = 11$  (600 mg/kg);  $n = 11$  (1000 mg/kg). F values – statistics for various time periods after a single intraperitoneal injection of sodium BHB (KTX 0101): 100, 300, 600 or 1000 mg/kg body weight.

30 Figure 2: Action of vehicle ( $n = 13$ ) on the electrical power of four rat brain areas. Time - dependent changes (percentage change of pre-drug values) in EEG spectral patterns (60 min each) during 300 min after i.p. single-dose application. Definition of frequency ranges: delta (1.25-4.5 Hz, red), theta (4.75-6.75 Hz, orange), alpha1 (7.00-

9.50 Hz, yellow), alpha2 (9.75-12.50 Hz, green), beta1 (12.75-18.50 Hz, light blue), beta2 (18.75-35.00 Hz, dark blue).

5 Figure 3: Action of BHB 100 mg/kg (n=12) on the electrical power of four rat brain areas. Time - dependent changes (percentage change of pre-drug values) in EEG spectral patterns (60 min each) during 300 min after i.p. single-dose application. Definition of frequency ranges see Fig. 2.

10 Figure 4: Action of BHB 300 mg/kg (n=12) on the electrical power of four rat brain areas. Time - dependent changes (percentage change of pre-drug values) in EEG spectral patterns (60 min each) during 300 min after i.p. single-dose application. Definition of frequency ranges see Fig. 2.

15 Figure 5: Action of BHB 600 mg/kg (n=11) on the electrical power of four rat brain areas. Time - dependent changes (percentage change of pre-drug values) in EEG spectral patterns (60 min each) during 300 min after i.p. single-dose application. Definition of frequency ranges see Fig. 2.

20 Figure 6: Action of BHB 1000 mg/kg (n=11) on the electrical power of four rat brain areas. Time - dependent changes (percentage change of pre-drug values) in EEG spectral patterns (60 min each) during 300 min after i.p. single-dose application. Definition of frequency ranges see Fig. 2.

25 Figure 7: Similarity of the "qEEG-fingerprints" of KTX 0101 (sodium BHB) in comparison to different drug classes using discriminant analysis during the period "20th to 50th min after single-dose application". Note the different shading for the classification of different drug actions.

30 Figure 8: Effect of intraperitoneal injection of various doses of KTX 0101 on plasma concentrations of (R)-3-hydroxybutyrate (BHB). Time-course of action for groups of 4-6 rats. Significantly different from baseline control values by t-test, \*p<0.05, \*\*p<0.01, \*\*\* p<0.001.

Figure 9: Effect of intraperitoneal injection of various doses of KTX 0101 on plasma concentrations of acetoacetate. Increase 30 minutes after dosing for groups of 6 rats. Significantly different from baseline control values by t-test, \*p<0.05, \*\*\* p<0.001.

## 5 EXAMPLES

### EEG measurements

Adult Fisher rats (4-6 month of age and day - night converted, bodyweight approximately 400 g) were implanted with 4 bipolar concentric steel electrodes using a stereotaxic surgical procedure. According to the coordinates of Paxinos and Watson (1982), all four electrodes were placed 3 mm lateral within the left hemisphere. Anterior coordinates were 12.2, 5.7, 9.7 and 3.7 mm for frontal cortex, hippocampus, striatum and reticular formation, respectively. A baseplate carrying the electrodes and a 5-pin-plug was fixed to the skull by dental cement attached to 3 steel screws fixed into the skull. Animals were given two weeks for recovery from the surgical procedure.

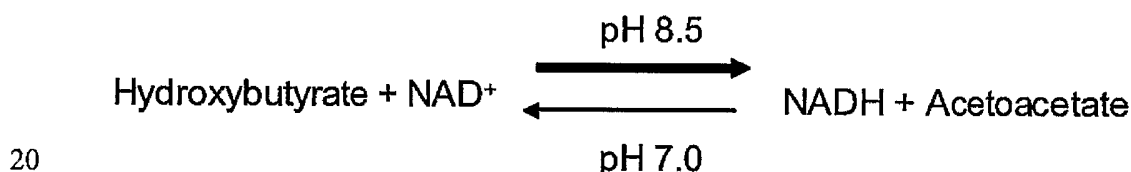
EEG signals were recorded from frontal cortex, hippocampus, striatum and reticular formation and were amplified and processed as described by Dimpfel et al. (1986). After automatic artefact rejection, signals were collected in sweeps of 4 s duration and submitted to Fast Fourier transformation. The resulting electrical power spectra were divided into 6 frequency ranges: delta (0.8 - 4.5 Hz); theta (4.75 - 6.75 Hz); alpha1 (7.00 - 9.50 Hz); alpha2 (9.75 - 12.50 Hz); beta (12.75 - 18.50 Hz); beta2 (18.75 - 35.00 Hz). Spectra were averaged in steps of 3 minutes each and displayed on-line. In an off-line procedure spectra were averaged to give 15 minute or longer periods for further statistical analysis.

Four doses of KTX 0101 (sodium (R)-3-hydroxybutyrate: 100, 300, 600 and 1000 mg/kg body weight) (supplied by Solvias AG, CH 4002 Basel, Switzerland, batch No: SO-1058.047.1.120) and a vehicle control (0.9% w/v saline) were administered intraperitoneally to a group of 12 animals using a crossover design with at least 3 drug holidays in between the applications. After a pre-drug period of 45 minutes for baseline recording, drug effects were observed continuously for 300 minutes. Changes of electrical power ( $\mu\text{V}^2/\text{W}$ ) are expressed as percentage of the 45 minute pre-drug values. Multivariate statistics were calculated according to Ahrens and Lauter (1974).

### Plasma determination of (R)-3-hydroxybutyrate and acetoacetate

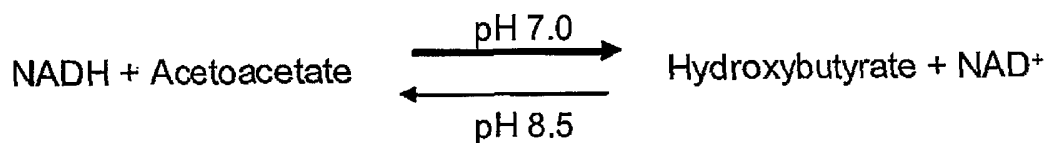
One hundred and seventy-one male Sprague-Dawley rats (weight range 200-250g) housed on a standard hour light/dark cycle were used. Animals had free access to a standard pelleted rat diet and tap water at all times. KTX 0101 (sodium (R)-3-hydroxybutyrate; 100, 300, 600 and 1000 mg/kg body weight) supplied by Sigma (H6501, Lot 111K2618) was administered by intraperitoneal injection. Control animals received the appropriate 0.9% saline vehicle via the same route. Animals were killed by CO<sub>2</sub> asphyxiation 0h, 0.5h, 1.0h or 2.0h after dosing and a terminal blood sample was collected by cardiac puncture. Blood was taken in lithium heparinised tubes and kept on ice prior to centrifugation to yield the plasma samples for analysis.

Commercial clinical assay kits for the determination of D-β-hydroxybutyrate were obtained from Randox Laboratories (Antrim, UK). The kit quantified NADH via the activity of β-hydroxybutyrate dehydrogenase measured as an increase in OD<sub>340nm</sub>. An alkaline pH is necessary to drive the reaction equilibrium towards the production of NADH and acetoacetate.



This spectrophotometric assay was modified for application to a 96 well microplate format. The reaction rate was then determined from the increase in OD<sub>340nm</sub> over a 1 minute time course, after allowing a necessary period for the reaction rate to settle.

The assay developed for the determination of acetoacetate was based on previously published clinical assays (Li et al, 1980; McMurray et al, 1984). A different assay buffer was prepared (0.1M Na<sub>2</sub>PO<sub>4</sub> adjusted to pH 7.0 with HCl) in order to shift the equilibrium of the reaction to production of β hydroxybutyrate and NAD<sup>+</sup>. Other modifications included the additional use of sodium oxalate at a final assay concentration of 20mM to inhibit lactate dehydrogenase (LDH) present in the plasma samples. The final optimised reagent, therefore, comprised 0.3mM NADH, 20mM oxalate, 0.5 U/ml β hydroxybutyrate dehydrogenase and 0.1M phosphate buffer pH 7.0.



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Acetoacetate was measured via the reduction in OD340nm over a 1 minute period after allowing for the reaction rate to settle.

## Results

### 10 EEG measurements

Intraperitoneal administration of 0.9% w/v saline produced no significant changes in the EEG power spectrum in comparison to the predrug values (Fig 2).

15 KTX 0101 (100 mg/kg body weight). Administration of this higher dosage of KTX 0101 resulted in frequency changes, especially within the hippocampus and somewhat less within the reticular formation. All regions showed a decrease of electrical power mainly with regard to alpha2 and to a lesser extent with regard to delta frequencies. In the hippocampus theta, alpha1 and beta1 power also decreased (Fig. 3). The effects lasted for 1-2 hours only. However, these changes were not  
20 statistically significant (Fig. 1).

KTX 0101 (300 mg/kg body weight). KTX 0101 300 mg/kg ip produced a consistent pattern of frequency changes characterized by decreases in alpha2 power throughout all brain regions. In addition, delta power changed throughout all regions albeit to a  
25 lesser degree. The pattern of changes (Fig. 4) lasted for exactly 2 hours. The changes were only statistically significant in the reticular formation (Fig. 1).

KTX 0101 (600 mg/kg body weight). KTX 0101 600 mg/kg ip produced a similar pattern of change to that seen after 300 mg/kg. The effects generally lasted for 2  
30 hours except for the reticular formation, where decreases in power persisted throughout the third hour (Fig. 5). The results were statistically significant, including the first hour within the striatum. Considering all 24 variables (6 frequencies at all four brain areas), the overall effect was also statistically significant (Fig. 1).

KTX 0101 (1000 mg/kg body weight). Administration of KTX 0101 1000 mg/kg induced an identical pattern of change, but with more prominent decreases of power lasting into the third hour and, with respect to the reticular formation, throughout the total experimental time of 5 hours (Fig. 6). Again, these changes were statistically significant, even for the 4th hour within the reticular formation (Fig. 1).

In summary, clear, dose- and time-dependent statistically significant changes could be observed after the administration of KTX 0101 within a dose range of 300 to 1000 mg/kg ip.

#### Plasma concentrations of (R)-3-hydroxybutyrate and acetoacetate

KTX 0101 (100, 300, 600 and 1000 mg/kg ip), when injected via the intraperitoneal route, produced clear dose-dependent increases in the plasma concentration of (R)-3-hydroxybutyrate (Fig. 8). The effect occurred rapidly after injection of KTX 0101 with the highest elevations in (R)-3-hydroxybutyrate being observed in the first 30 min sample. Thereafter, the concentration of this 2 ketone body decreased rapidly and had returned to control values by 1 hour after injection of KTX 0101 (Fig. 8). When the plasma acetoacetate levels were analysed in samples from a subgroup (24) of these rats, KTX 0101 also significantly increased the plasma concentration of acetoacetate 30 min after dosing at doses of 600 and 1000 mg/kg (Fig. 9).

#### Discussion

A single intraperitoneal injection of KTX 0101 in the range 100 to 1000 mg/kg induced clear, dose-dependent changes in the EEG power spectrum in freely-moving rats. At the 300 mg/kg dose, these changes were only statistically significant in comparison to vehicle in the reticular formation (Fig. 1). However at the 2 highest doses, significant changes were also observed in the frontal cortex, hippocampus and striatum (Fig. 1). The changes were maximal in the first 1 hour period after injection of KTX 0101. The observed changes affected all frequencies, except for the beta2 range, with the most prominent effects on the delta and alpha2 frequencies.

With regard to the specific frequency changes observed, theta activity has been shown to increase in response to drugs like the  $\alpha$ 2-adrenoceptor agonist, clonidine, which decrease noradrenergic function in the brain (Dimpfel and Schober, 2001);

thus, drugs which potentiate noradrenergic function would be predicted to decrease theta activity. Noradrenaline is known to have an important role in arousal, cognition, attention and vigilance (Biederman and Spencer, 1999). In ADHD and related CNS disorders disorders, increased function of this monoamine neurotransmitter is an important component of the therapeutic effects of the monoamine releasing psychostimulants, dl threo-methylphenidate, d-threo-methylphenidate, dl-amphetamine or d-amphetamine, and it is exclusively responsible for the therapeutic action of the selective noradrenaline reuptake inhibitor, atomoxetine. Decreases of alpha1 activity also indicate an elevated attentional state. Drugs acting to enhance dopaminergic function in the brain, eg dopamine precursors (L-DOPA), dopamine releasing agents (amphetamine) or dopaminergic agonists (SKF 38393), decrease alpha2 frequencies (Dimpfel et al., 1987). Thus, decreases in alpha2 activity are also generally associated with an increased state of arousal. Enhanced dopaminergic function in the brain is the second important component of the therapeutic mechanism of the monoamine releasing psychostimulants, dl-threo-methylphenidate, d-threo-methylphenidate, dl-amphetamine or d amphetamine, in ADHD and related CNS disorders disorders. Viewed overall, the ability of KTX 0101 to decrease theta, alpha1 and alpha2 frequencies is consistent with the hypothesis that this compound indirectly enhances both noradrenergic and dopaminergic function in the brain, and as a result of these actions, it will be beneficial in the treatment of ADHD and related CNS disorders of cognition, impulsiveness, attention and aggression in children, adolescents and adults.

The statistical differentiation of drug action is also possible using the mathematical tool of discriminant analysis. Having 6 frequency ranges and 4 different brain areas, the calculations are performed with 24 variables. The results for one time period are shown in Fig. 7. Note that in addition to the 2 projection axes, results from the third to fifth discriminant function are depicted by using an additive shading mixture (similar to that used in colour TV). Thus, not only is a two dimensional projection is used for classification of the EEG "fingerprint", but also the shading. This analysis of the EEG effects of BHB also places it in close proximity to the dopaminergic psychostimulants, d-amphetamine and cocaine, further supporting the hypothesis that KTX 0101 will be of therapeutic benefit in the treatment of beneficial in the treatment of ADHD and related CNS disorders of related CNS disorders of

impaired learning, impaired problem solving and impaired planning, impulsiveness, reduced attention and aggression in children, adolescents and adults.

Clear evidence that elevations in the concentrations of ketone bodies are responsible for the observed effects of KTX 0101 on the EEG patterns is provided by  
5 the pharmacokinetic analysis of plasma ketone bodies following injection of KTX 0101 (100, 300, 600 and 1000 mg/kg ip). Significant changes in the EEG patterns (Fig. 1) were only evoked by doses of KTX 0101, ie 300, 600 and 1000 mg/kg, which produced significant elevations of in the levels of plasma ketone bodies, ie (R)-3-hydroxybutyrate and acetoacetate (Figs. 8 and 9). Moreover, the greatest changes in  
10 EEG patterns occurred in the period 5 – 65 min (Fig. 1) which is consistent with the peak increases in the circulating concentrations of ketone bodies (Figures 8 and 9).

In summary, intraperitoneal injection of KTX 0101 over the dose range of 300 to 1000 mg/kg elevates the circulating concentrations of ketone bodies and has consistent effects on the conscious rat EEG fingerprint. The overall pattern of the  
15 change in the EEG power spectrum has similarities to the catecholamine enhancing drugs used for the treatment of ADHD and related CNS disorders of impaired learning, impaired problem solving and impaired planning, impulsiveness, reduced attention and aggression.

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## CLAIMS

1. A method of treating a subject in need of therapy for attention deficit hyperactivity disorder (ADHD) and related CNS disorder symptoms of one or more  
5 of impaired learning, impaired problem solving and impaired planning, impulsiveness, attention deficit and aggression by administering to said subject a therapeutic dose of a ketogenic material.
2. A method as claimed in Claim 1 wherein the therapeutic dose is sufficient to  
10 produce a ketosis in the subject sufficient to provide reduction in (ADHD) and related CNS disorder symptoms.
3. A method as claimed in Claim 1 wherein the disorder is selected from hyperkinetic syndrome and minimal brain dysfunction.  
15
4. A method as claimed in Claim 2 wherein the ketosis produced is such that the total concentration of acetoacetate and (R)-3-hydroxybutyrate in the blood of the subject is raised to between 0.1 and 30mM.
- 20 5. A method as claimed in Claim 1 wherein the treatment provides a total concentration of acetoacetate and (R)-3-hydroxybutyrate in the blood of between 0.2 and 15mM.
6. A method as claimed in Claim 1 wherein the treatment provides total  
25 concentration of acetoacetate and (R)-3-hydroxybutyrate in the blood raised to between 0.5 and 8mM.
7. Use of a ketogenic material for the manufacture of a medicament for the treatment of ADHD and related CNS disorder symptoms of impaired learning,  
30 impaired planning, impaired problem solving, impulsiveness, attention deficit and aggression.

8. A method or use as claimed in any one of Claims 1 to 6 characterised in that the ketogenic material is selected from the group consisting of triglycerides, free fatty acids, alcohols (eg butan-1,3-diol), acetoacetate and (R)-3-hydroxybutyrate and their conjugates with each other and further moieties, eg. esters and polymers of these.

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9. A method as claimed in any one of Claims 1 to 6 characterised in that the ketogenic material is a saccharide ester of a fatty acid, acetoacetate or (R)-3-hydroxybutyrate or oligomers thereof.

10

Time	5 - 65 min	65 - 125 min	125 - 185 min	185 - 245 min	245 - 305 min
24 variables					
100 mg/kg	0.63	0.34	0.57	0.28	0.26
300 mg/kg	1.23	1.24	0.55	0.42	0.63
600 mg/kg	1.89**	1.16	0.58	0.47	0.54
1000 mg/kg	2.72**	1.97**	1.28	1.27	1.03
Frontal cortex					
100 mg/kg	0.97	0.45	0.23	0.20	0.27
300 mg/kg	2.26	1.92	0.52	0.30	0.60
600 mg/kg	4.44**	1.67	0.41	0.36	0.85
1000 mg/kg	7.52**	3.18*	2.05	1.20	0.86
Hippocampus					
100 mg/kg	1.36	0.63	0.65	0.47	0.39
300 mg/kg	1.89	1.97	0.70	0.61	0.85
600 mg/kg	3.84**	1.94	0.52	0.45	0.19
1000 mg/kg	5.00**	2.66*	1.05	0.32	0.54
Striatum					
100 mg/kg	0.54	0.17	0.15	0.16	0.23
300 mg/kg	0.99	0.99	0.55	0.33	0.56
600 mg/kg	2.54*	0.72	0.80	0.87	1.50
1000 mg/kg	3.80**	1.83	0.59	0.27	0.62
Ret. Formation					
100 mg/kg	1.55	0.54	0.39	0.14	0.31
300 mg/kg	3.03*	3.14*	0.65	0.24	0.70
600 mg/kg	4.84**	3.10*	0.62	0.22	0.35
1000 mg/kg	6.28**	5.12**	2.57*	2.72*	2.26

FIGURE 1

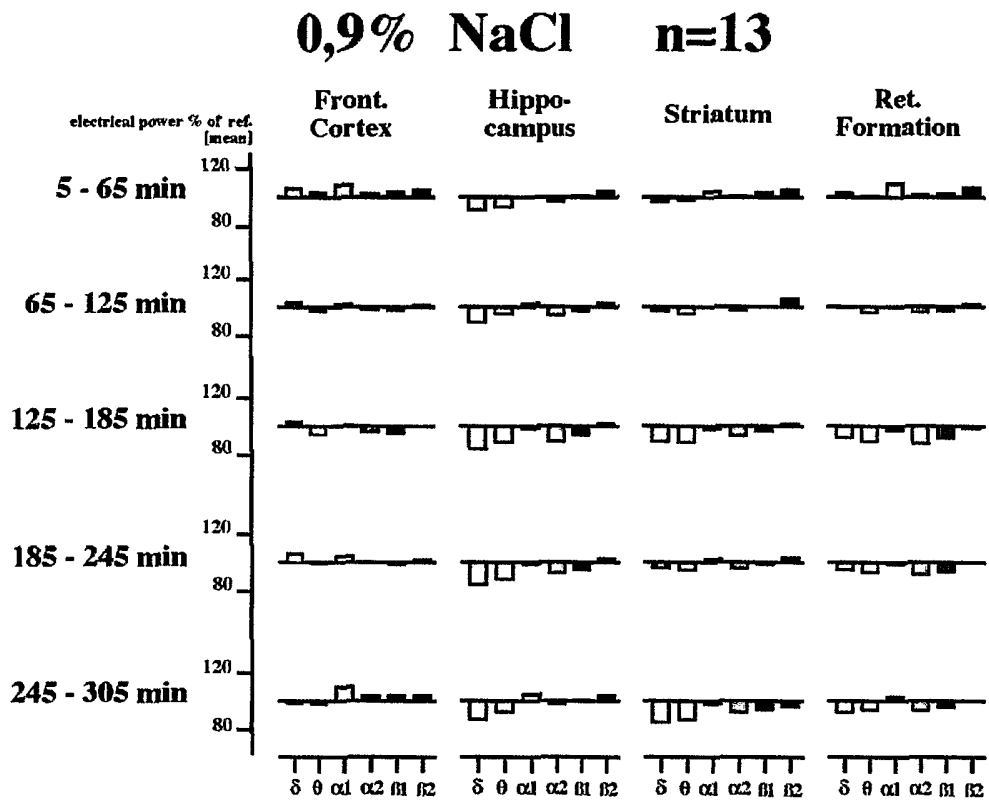


FIGURE 2

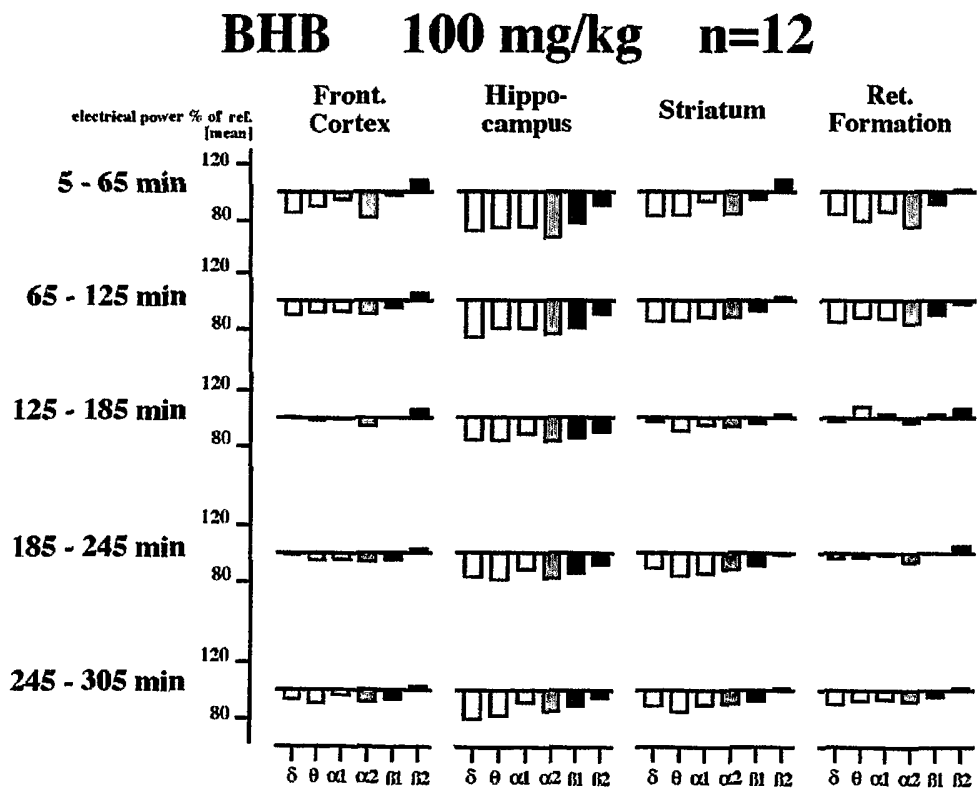


FIGURE 3

### BHB 300 mg/kg n=12

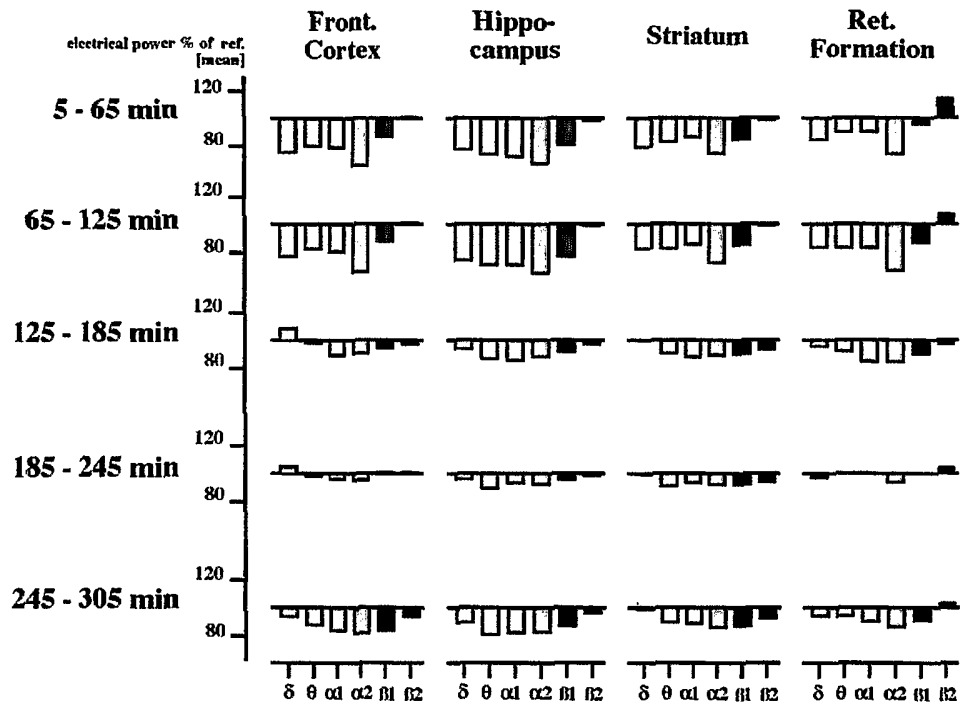


FIGURE 4

### BHB 600 mg/kg n=11

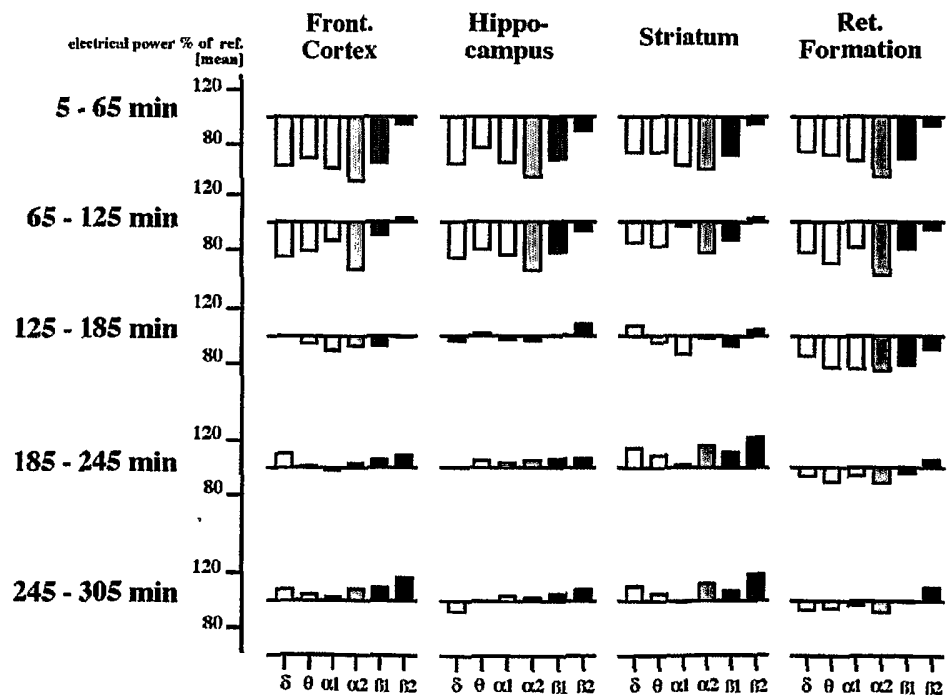


FIGURE 5

# BHB 1000 mg/kg n=11

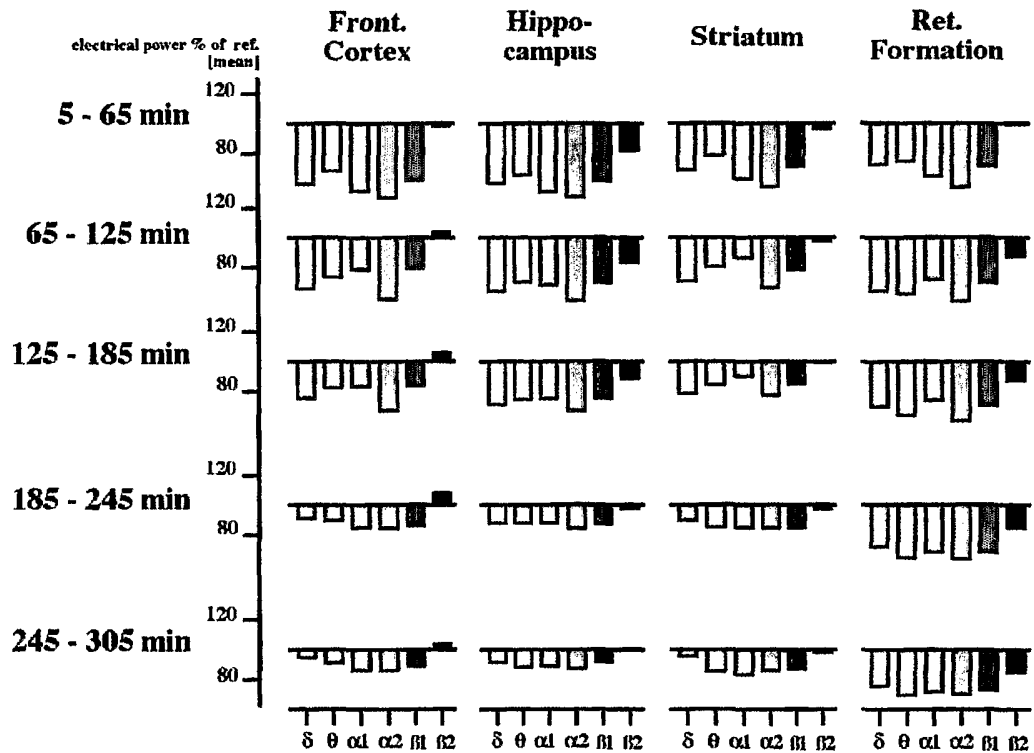


FIGURE 6

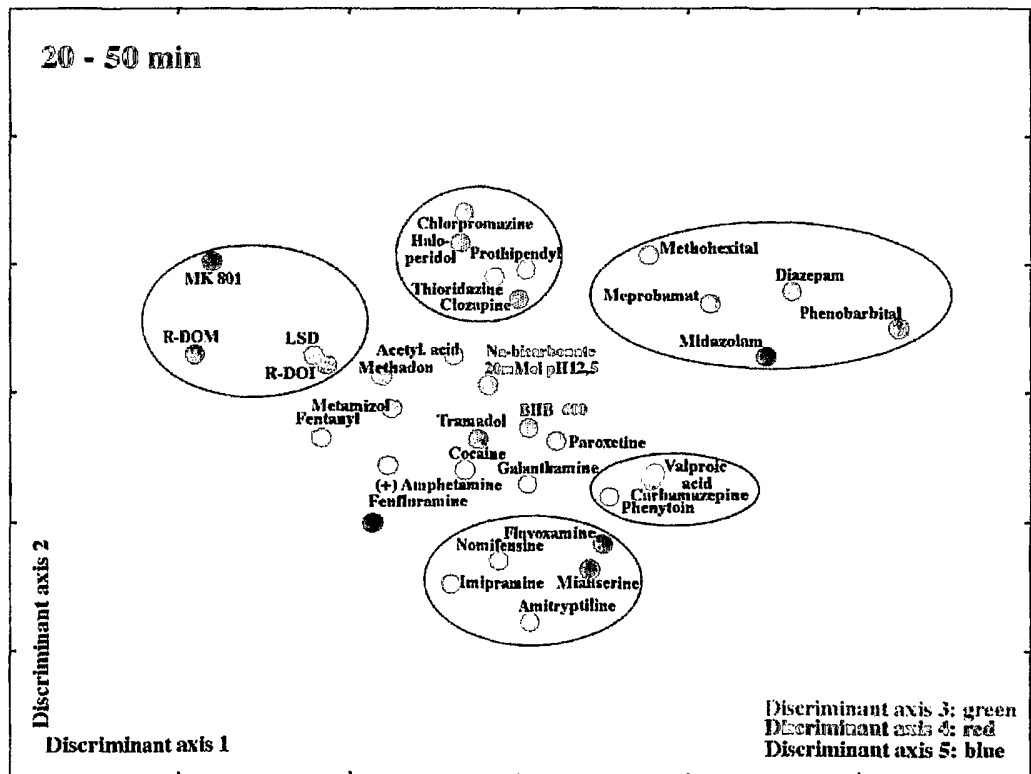


FIGURE 7

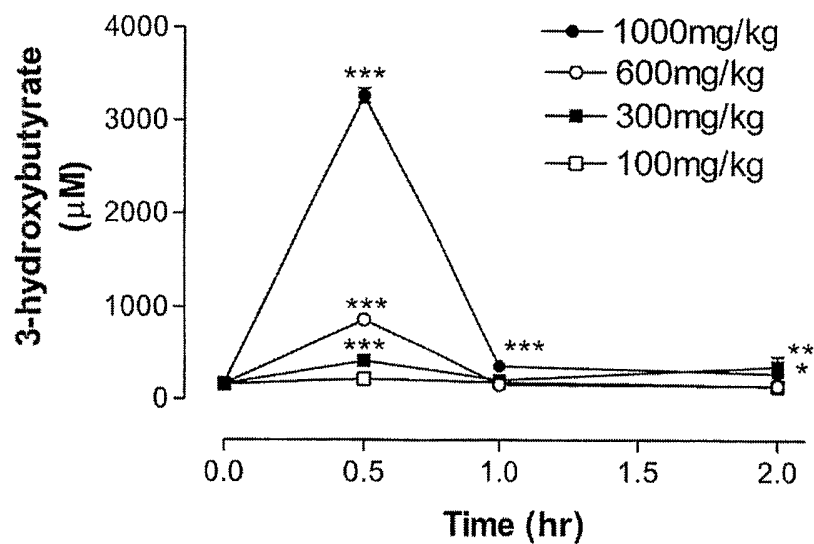


FIGURE 8

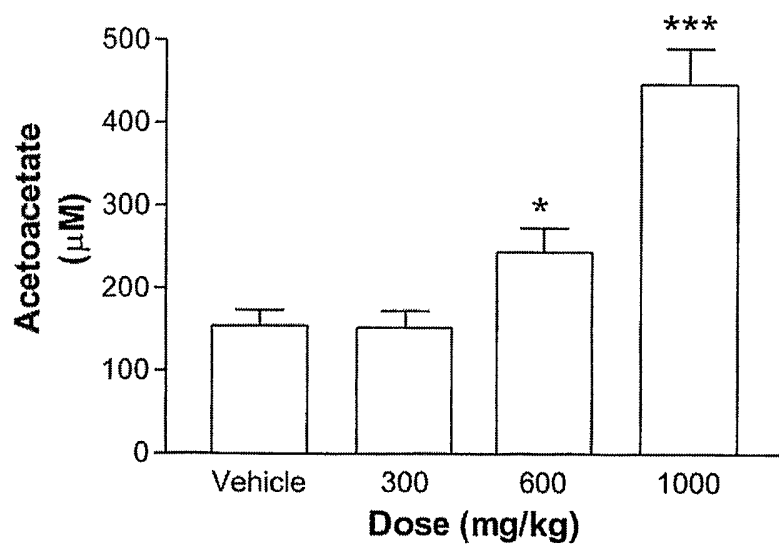


FIGURE 9