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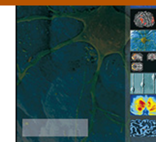

Effects of dehydroepiandrosterone (DHEA) and lactate on glucose uptake in the central nervous system

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ABSTRACT

Dehydroepiandrosterone (DHEA) prevents brain aging, enhances the cerebral metabolism and interacts with energy substrates. The interaction between lactate and DHEA on glucose uptake and lactate oxidation by various nervous structures was investigated and results demonstrate that the 2-^{14}C-deoxiglucose (2-^{14}C-Dglucose) uptake was stimulated by 10 mM lactate in the hypothalamus and olfactory bulb, inhibited in the cerebral cortex and cerebellum, and unaffected in the hippocampus. We also show that, in both the cerebral cortex and hypothalamus, ^{14}C-lactate oxidation was higher than ^{14}C-glucose oxidation ($p \leq 0.001$), demonstrating a relevant role for lactate as energy substrate. The interaction of lactate and 10^{-8} M DHEA was tested and, although DHEA had no significant effect on uptake in the cerebellum, hippocampus, or hypothalamus, 10^{-8} M DHEA increased the 2-^{14}C-Dglucose uptake in the cerebral cortex in the presence of lactate ($p \leq 0.001$), and in the olfactory bulb in the absence of lactate ($p < 0.05$). However, DHEA had no significant effect on ^{14}C-lactate oxidation. We suggest that DHEA improves glucose uptake in specific conditions. Thus, DHEA may affect CNS metabolism and interact with lactate, which is the most important neuronal energy substrate, on glucose uptake.

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1. Introduction

Dehydroepiandrosterone (DHEA) is a neurosteroid produced by neural tissue [3] that is able to modulate neuronal excitability, neurogenesis, cell survival, neurotransmitter receptors, and metabolism [8,17]. DHEA enhances mitochondrial oxidative capacity [27] and restored Na^+–K^+ ATPase activity of aging rat brains [32].

The brain is a highly oxidative organ that depends on a continuous glucose supply *in vivo* [12] although lactate is the most important ATP source for neurons during neuronal excitation [23,29]. It was described previously that astrocytes take up glucose, synthesize lactate, and transport the lactate to neurons, demonstrating the complex relations among cells and energy substrates in central nervous system (CNS) [22]. This anaerobical metabolism of CNS is the lactate shuttle hypothesis [22,23,28].

In vitro, lactate can decrease glucose uptake differently in specific regions of CNS [25]. So, as observed previously there are metabolic differences between structures of CNS [5,10,30]. Corroborating with these results, lactate is a preferential substrate for oxidation and it suppresses glucose oxidation by neurons in culture [14].

Age-related neurological disorders like Alzheimer's disease and endocrine diseases like Type 2 diabetes mellitus are conditions related to progressive accumulation of detrimental changes in the brain structure and function [2,11]. Memory disturbances in the elderly and in the initial stages of the disease of Alzheimer's disease patients are related to hypoxia, reduction in blood supply, and glucose hypometabolism in the cerebral cortex, hippocampus, and olfactory bulb [1,34,35,38]. It was postulated that the hypometabolism of neurodegenerative diseases could be reversed or minimized by DHEA, however this has not been clearly established in humans [2,13].

Therefore we tested the hypothesis that DHEA can alter the glucose metabolism of nerve tissues (cerebral cortex, hippocampus, cerebellum, hypothalamus, and olfactory bulb), and the possible interaction between DHEA and lactate, the most important metabolic substrate of neurons, on glucose uptake and lactate oxidation by various central nervous system structures.

2. Materials and methods

2.1. Materials

The reagents utilized in the experiments were analytical grade and were obtained from Merck SA, Porto Alegre, Brazil. Other

Abbreviations: CNS, central nervous system; DHEA, dehydroepiandrosterone; 2-^{14}C-Dglucose, 2-deoxi-1-^{14}C-glucose; KRb, Krebs Ringer bicarbonate; TCA, trichloroacetic acid; SNK, Student–Newman–Keuls.

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reagents were purchased as follows: hyamine hydroxide from Baker Chemical Company; L-[U-^{14}C] lactate (108.3 mCi/mmol), 2-deoxi-1-^{14}C-glucose (55 mCi/mmol), and D-[U-^{14}C] glucose (3.0 mCi/mmol), all from Amersham; DHEA from Calbioche; and 2-hydroxypropyl-β-cyclodextrin (Fluka). DHEA was dissolved in 10% of β-cyclodextrin. All solutions were prepared on the same day they were used.

2.2. Animals

Experiments were performed with adult male Wistar rats, weighing 250–300 g. Animals were housed in groups with free access to food and water, room temperature of approximately 22 °C, and a 12:12 h light–dark cycle. Rats were killed by decapitation and their brain was quickly removed and placed on a petri plate containing a humid filter paper with buffer at 4 °C. Different structures of CNS (cerebral cortex, hippocampus, cerebellum, hypothalamus, and olfactory bulb) were dissected, weighed, and sliced within 2 min. External and visual neuroanatomical landmarks were utilized as reference for dissection and both sides of the brain were used. Dissected tissues were randomly distributed in experimental groups.

The animals were not anesthetized prior to sacrifice. During all the experimental procedures, the animals were treated according to the Guidelines for Care and Use of Animals in Research issued by the National Institutes of Health. All efforts were made to reduce both animal suffering and the number of animals used. Animal experimentation protocols were approved by the Ethics Committee of the University.

2.3. The 2-deoxi-1-^{14}C-glucose (2-^{14}C-Dglucose) uptake

To measure 2-deoxi-1-^{14}C-glucose (2-^{14}C-Dglucose) uptake, tissue slices obtained from the various CNS structures (200 mg/tube) were incubated in (1) 0.5 mL Krebs Ringer bicarbonate (KRb) buffer pH 7.4 containing 0.15 μCi 2-^{14}C-Dglucose; (2) 0.5 mL KRb containing 0.15 μCi 2-^{14}C-Dglucose + 10 mM lactate; (3) 0.5 mL KRb containing 0.15 μCi 2-^{14}C-Dglucose + 10^{-8} M DHEA or 10^{-12} M DHEA; or (4) 0.5 mL KRb containing 2-^{14}C-Dglucose + 10 mM lactate + 10^{-8} M DHEA or 10^{-1} M DHEA [described and modified from [18]]. The 2-^{14}C-Dglucose is a non-metabolized glucose analog. Control groups (without lactate) were incubated with β-cyclodextrin at 10^{-6} M. The contents of the tubes were gassed with 95% O_2/5% CO_2 for 1 min and then closed. Tissues were incubated in a Dubnoff incubator with constant shaking at 37 °C for 1.5 h. After incubation, tissues were withdrawn, rinsed in cold incubation buffer (three times) and blotted with filter paper. Glucose uptake was immediately measured [21] and the results were expressed as tissue/medium (T/M) ratio, i.e., dpm/mL tissue fluid per dpm/mL incubation medium. Analysis of data was done in duplicate.

Time-course curve was performed using 2-^{14}C-Dglucose in cerebellar slices at 30, 60, 90 (1.5 h) and 120 min (data not shown). The peak occurred at 1.5 h of incubation then this time was chosen for the others experiments.

2.4. The D-[U-^{14}C] glucose or L [U-^{14}C] lactate oxidation

To measure glucose oxidation (CO_2 production), slices of brain structures (200 mg/tube) were incubated in tubes containing 1.0 mL KRb pH 7.4, plus: (1) 0.15 μCi [U-^{14}C] glucose + 5 mM glucose + 10 mM lactate + 10^{-6} M β-cyclodextrin; (2) 0.15 μCi L [U-^{14}C] lactate + 10 mM lactate + 10^{-6} β-cyclodextrin; (3) 0.15 μCi L [U-^{14}C] lactate + 10 mM lactate + DHEA 10^{-8}; or (4) 0.15 μCi L [U-^{14}C] lactate + 10 mM lactate [described previously by 7; [18]]. Contents of the tubes were gassed with 95% O_2/5% CO_2 for 1 min and then sealed with rubber caps. Slices were incubated in a Dubnoff incubator with constant shaking at 37 °C for 1.5 h. Incubation was stopped by adding 0.2 mL 50% TCA (trichloroacetic acid) through the rubber cap. Then, 0.2 mL of 1 M hyamine hydroxide was injected into the center of the tube. The tubes were left overnight at 25 °C to trap CO_2, after which the content was transferred to vials and assayed for CO_2 radioactivity in a liquid-scintillation counter [7]. Analysis of data was done in one replicate.

Table 1
Lactate effect on [2-^{14}C] deoxi-glucose uptake of rat brain structures.

Structure	Control	Lactate	p (control versus lactate)
Cerebellum	2.10 ± 0.23 (5)	1.21 ± 0.24 (6)	≤0.001
Cerebral cortex	3.35 ± 0.77 (6)*	1.61 ± 0.52 (8)	0.002
Hippocampus	2.32 ± 1.27 (4)	3.04 ± 0.46 (7)#	0.199
Hypothalamus	2.94 ± 1.64 (4)	7.24 ± 0.81 (5)&	0.001
Olfactory bulb	1.69 ± 0.14 (5)	2.88 ± 0.38 (5)#	≤0.001

Values are expressed as mean ± standard deviation (SD). Value for each n is represented in parentheses. Results are expressed as tissue/medium (T/M) ratio (that is, dpm/mL tissue fluid per dpm/mL incubation medium). See Section 2 for details. For structures incubated with the same medium: control (without lactate) or lactate (10 mM lactate) groups. One-way ANOVA was used to compare among structures in control or lactate groups, and for control versus lactate Student's t test was used. Differences between each nervous structure and inside the same group (control or lactate).

& Differences among all structures ($p \leq 0.001$).

Differences between hippocampus and olfactory bulb versus cerebellum and cerebral cortex ($p \leq 0.001$).

* Difference between cerebral cortex and olfactory bulb ($p = 0.041$).

2.5. Statistical analysis

Student's t-test was utilized to analyze lactate influence on glucose uptake by each CNS structure and in oxidation experiments. Data were analyzed statistically by One Way ANOVA and by Student–Newman–Keuls (SNK) multiple-range test to verify the differences in glucose uptake among tissues. Two-way ANOVA and SNK multiple-range test were utilized to indentify interactions between DHEA doses, incubation time, and lactate influence. Level of significance was set at $p < 0.05$ and data are presented as mean ± standard deviation (SD). All tests were performed using Sigma Stat software.

3. Results

3.1. Lactate effect on 2-^{14}C-Dglucose uptake by CNS structures

First, glucose (2-^{14}C-Dglucose) uptake was tested and compared between all CNS structures in a medium with or without lactate (Table 1). Note that in all tissues except the hippocampus, 2-^{14}C-Dglucose uptake was affected by presence of lactate. Next, we compared 2-^{14}C-Dglucose uptake of all structures incubated with lactate and with their respective controls. In the absence of lactate, 2-^{14}C-Dglucose uptake was the same among almost all structures and the only significantly increase value found was between cerebral cortex when compared to olfactory bulb ($p = 0.041$). However, the hypothalamus showed a great increase in 2-^{14}C-Dglucose uptake ($p \leq 0.001$) in the presence of lactate compared to the other structures. Cerebellum and cerebral cortex showed the lowest uptake values.

3.2. Substrate oxidation by CNS structures

The ^{14}C-lactate oxidation by the CNS structures studied was compared to ^{14}C-glucose oxidation in the presence of 10 mM of lactate (Table 2). No difference in ^{14}C-glucose or ^{14}C-lactate

Table 2
Oxidation of D-[U-^{14}C] glucose or L-[U-^{14}C] lactate in tissue slices of rat cerebral cortex and hypothalamus.

Structure	^{14}C-glucose + lactate	^{14}C-lactate	*p*
Cerebral cortex	473.4 ± 78.3 (6)	3190.8 ± 553.0 (5)	≤0.001
Hypothalamus	360.7 ± 116.5 (5)	2370.9 ± 796.2 (7)	≤0.001

Values are expressed as mean ± SD. The value of each *n* is represented in parentheses. Results are expressed as nmol of substrate oxidized to CO_2 h^{-1} g^{-1} tissue slices. See Section 2 for details. Student's *t* test was used to analyze differences between ^{14}C-glucose and ^{14}C-lactate groups. Differences observed in the table were obtained when comparing ^{14}C-lactate to ^{14}C-glucose in the same structure.

Table 3
Effect of 10^{-8} M DHEA on the oxidation of L-[U-^{14}C] lactate in tissue slices of rat cerebral cortex and hypothalamus.

Structures	Control	10^{-8} M DHEA	*p*
Cerebral cortex	3190.84 ± 552.95 (5)	2752.65 ± 184.39 (5)	0.131
Hypothalamus	2370.9 ± 796.21 (7)	2536.38 ± 1257.41 (8)	0.770

Values are expressed as mean ± standard deviation (SD). The value of each *n* is represented in parentheses. Results are expressed as nmol of substrate oxidized to CO_2 h^{-1} g^{-1} tissue slices. See Section 2 for details. Student's *t* test was used to analyze differences between control and 10^{-8} M DHEA groups. Differences observed in the table was obtained when control and 10^{-8} M DHEA are compared.

oxidation was observed between cerebral cortex and hypothalamus (data not shown).

3.3. DHEA effect on 2-^{14}C-Dglucose uptake in the presence or absence of lactate

Interaction of DHEA (10^{-8} or 10^{-12} M) and the presence or absence of lactate on 2-^{14}C-Dglucose uptake was evaluated. The 2-^{14}C-Dglucose uptake in the cerebellum (Fig. 1A, $p = 0.433$), hippocampus (Fig. 1B, $p = 0.561$), and hypothalamus (Fig. 1C, $p = 0.364$) was not affected by DHEA, regardless of lactate presence. Glucose uptake was enhanced in the cerebral cortex by 10^{-8} M DHEA in the presence of lactate (Fig. 1D, $p \leq 0.001$). In the olfactory bulb, stimulation of glucose uptake was observed in the absence of lactate for the same DHEA concentration tested in the cerebral cortex (Fig. 1E, $p = 0.009$).

3.4. DHEA effect on [^{14}C]-lactate oxidation

The ^{14}C-lactate was used to evaluate the possible oxidative action of DHEA because lactate is the most important energy substrate for the CNS, as shown in Table 2. The 10^{-8} M DHEA concentration was chosen because it produced a positive effect in 2-^{14}C-Dglucose uptake (Fig. 1D) by the CNS structures here studied. DHEA did not change the ^{14}C-lactate oxidation in either the cerebral cortex or the hypothalamus when compared to respective controls (Table 3).

4. Discussion

The brain is an oxidative-glucose-dependent organ [12], but lactate is the preferential ATP source for neurons of CNS structures as described by the lactate shuttle hypothesis [7,19,22,23,28]. It was previously reported that lactate addition to medium can affect glucose uptake *in vitro* [4,25]. Our study reveals that 10 mM lactate used in the culture medium differently affects each CNS structure tested.

Previous studies demonstrated that the regions of the brain do not use glucose uniformly, and showed differential storage of glucose as well as the localization of glycogen and relevant enzymes [5,10,30]. Therefore it is likely that different brain structures have different patterns of substrate metabolism.

We found that 2-^{14}C-Dglucose uptake in the cerebellum and cerebral cortex was diminished in the presence of lactate when compared to the uptake observed in the absence of lactate, which is consistent with the results published by Murata et al. [25]. Lactate has been shown to be the preferential oxidative substrate in the cerebral cortex [23]. Moreover, when cerebellar neurons were exposed to lactate *in vitro*, ATP concentration increased, suggesting lactate as an important energy source [1] leading to a decrease of glucose uptake.

Cerebral cortex has a great proportion of neurons, and when lactate and glucose are present at an equimolar concentration, 90% of neuronal metabolism is supported by lactate while only 10% of glucose is utilized as energy source for these cells [6,23].

Unlike the cortex and cerebellum, 2-^{14}C-Dglucose uptake in the hypothalamus was enhanced by almost two fold in the presence of lactate. We suggest that glucose neuron sensors, present in some hypothalamic nuclei [20], can alter the glucose uptake in response to the presence of lactate. When these neurons are exposed to glucose or lactate *in vitro*, ATP concentration decreases because they fire action potentials, demonstrating that these neurons are also sensible to lactate [1]. Decrease in ATP concentration can lead to increase glucose uptake. Another indication that lactate is the preferential energy substrate is our observation that in hypothalamus slices ^{14}C-lactate was more oxidized *in vitro* than ^{14}C-glucose, as described previously [7] and as seen in our results of cerebral cortex.

In the olfactory bulb, lactate also increased 2-^{14}C-Dglucose uptake. Energy deprivation is related to lactate oxidation to maintain energy status in the olfactory bulb [26]. Lactate can sustain a live tissue that is able to maintain 2-^{14}C-Dglucose uptake *in vitro*.

Only in the hippocampus was the 2-^{14}C-Dglucose uptake unaffected by lactate, a finding that agrees with a previous report [14]. Lactate is an important energy source for neurons during periods of extreme activity or following hypoxia–ischemia in the hippocampus [4] but glucose is preferred as energy by this tissue *in vitro* and can support synaptic transmission more efficiently [9,14,33].

The interaction between DHEA and lactate in glucose uptake *in vitro* was also investigated. DHEA serum levels decline with age and it has been proposed that restoring the circulating levels of these steroids may have anti-aging effects [18,32]. Mitochondrial respiratory and Na^+–K^+ ATPase activities from CNS also decline with aging and DHEA has been shown to reverse this process [27,32].

Oxidative metabolism dysfunction has been proposed to play a pivotal role in neurodegenerative diseases, including Alzheimer whose progression causes decrease of glucose uptake, and decreases enzymes activities [38]. The DHEA effect was tested in the present study because it is well recognized that DHEA modulates metabolism, and that the increase of glucose uptake can ameliorate the CNS metabolism of Alzheimer's patients [13].

Higher DHEA doses were previously shown to induce apoptotic effects and to decrease glucose uptake, and the supplementation of energy substrate glucose inhibited this process [31,36,37]. However, the doses used in the present work were lower and did not produce these previously reported negative effects [31]. In addition, the 10^{-8} M dose was chosen because it can stimulate glucose uptake in culture as described previously [16].

In our study, DHEA had no effect on glucose uptake in the cerebellum, hippocampus, and hypothalamus independently of lactate presence. In contrast, 10^{-8} M DHEA enhanced the 2-^{14}C-Dglucose uptake in the cerebral cortex in the presence of lactate and in the olfactory bulb in the absence of lactate, showing a tissue- and dose-dependent effect.

DHEA has been shown to attenuate glial reaction to denervation and to regulate glial plasticity in the olfactory bulb, demonstrating an important local action of neurosteroids [15]. In the present work, in the olfactory bulb DHEA enhanced the 2-^{14}C-Dglucose uptake only in the absence of lactate. It is likely that when present, lactate

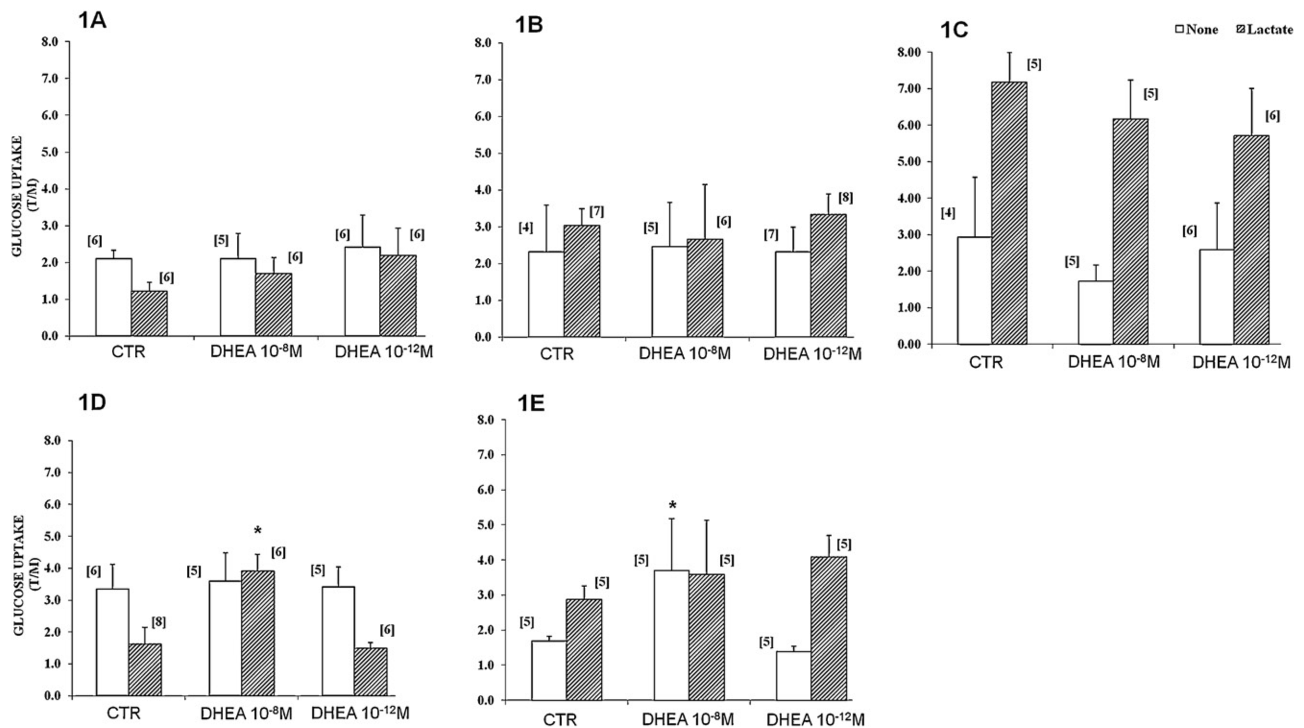

Fig. 1. Effect of DHEA (10^{-8} or 10^{-12} M) *in vitro* versus control (CTR) in 2-^{14}C-DG uptake, with or without (none) 10 mM lactate. White bars are results obtained in absence of lactate and grey bars were obtained in the presence of lactate. (A) Cerebellum ($p = 0.433$). (B) Hippocampus ($p = 0.561$). (C) Hypothalamus ($p = 0.364$). (D) Cerebral cortex: *statistical difference among DHEA versus 10^{-8} M CTR and DHEA 10^{-12} M (one-way ANOVA; $p < 0.05$); two-way ANOVA demonstrates difference between experimental groups ($p \leq 0.001$). (E) Olfactory bulb: *statistical difference among DHEA 10^{-8} M versus CTR and DHEA 10^{-12} M (one-way ANOVA; $p < 0.05$); two-way ANOVA demonstrates difference between experimental groups ($p = 0.009$). The values are expressed as mean ± SD. The value of each n is represented in brackets. The results are expressed as tissue/medium (T/M) ratio (that is, dpm/ml tissue fluid per dpm/ml incubation medium). See Section 2 for details.

is used as the most important ATP source [26] however the interaction between lactate and DHEA in glucose uptake remains to be elucidated.

In the cerebral cortex, DHEA enhanced 2-^{14}C-Dglucose uptake without any change in ^{14}C-lactate oxidation. *In vivo* cerebral cortex activation indicated by an increase in the metabolic rate is observed by a nonlinear coupling between glucose uptake (and lactate production) and oxygen consumption [19]. DHEA administration also enhances Na^+–K^+ ATPase activity in the cerebral cortex [32] and mitochondrial oxidative activity in a dose-dependent way [24,27]. Our results demonstrated that DHEA up-regulates glucose uptake by the cerebral cortex, without altering its oxidative capacity.

In our results DHEA enhanced 2-^{14}C-Dglucose uptake and did not influence lactate oxidation, so we cannot exclude that DHEA influenced astrocytes receptors because astrocyte takes up the great proportion of glucose in CNS [22]. The neurons had a preference to oxidize lactate instead of glucose [22] and as seen in our results lactate oxidation was not affected by DHEA. However we cannot exclude further DHEA actions in signaling pathways that increase metabolism or modulate other neuronal receptors. The structure-specific action needs to be clarified.

In addition, more experiments are also necessary to determine the DHEA action and the interaction between DHEA and lactate in glucose metabolism of CNS structures of old rats and hypometabolic tissues.

5. Conclusions

In conclusion, in the present study we demonstrated that lactate is a preferential oxidative substrate for various CNS structures and can alter glucose uptake by each structure differently. In addition, we showed that lactate and DHEA interact, increasing the 2-^{14}C-Dglucose uptake without affecting lactate oxidative metabolism. However, more studies regarding the molecular and metabolic interactions of this neurosteroid with other energy substrates and pathways (such as glycogen synthesis) are necessary.

Conflict of interests

The authors declare that they have no competing interests.

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