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Acute administration of fenproporex increased acetylcholinesterase activity in brain of young rats

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ABSTRACT

Fenproporex is the second most commonly amphetamine-based anorectic consumed worldwide; this drug is rapidly converted into amphetamine, in vivo, and acts by increasing dopamine levels in the synaptic cleft. Considering that fenproporex effects on the central nervous system are still poorly known and that acetylcholinesterase is a regulatory enzyme which is involved in cholinergic synapses and may indirectly modulate the release of dopamine, the present study investigated the effects of acute administration of fenproporex on acetylcholinesterase activity in brain of young rats. Young male Wistar rats received a single injection of fenproporex (6.25, 12.5 or 25mg/kg i.p.) or vehicle (2% Tween 80). Two hours after the injection, the rats were killed by decapitation and the brain was removed for evaluation of acetylcholinesterase activity. Results showed that fenproporex administration increased acetylcholinesterase activity in the hippocampus and posterior cortex, whereas in the prefrontal cortex, striatum and cerebellum the enzyme activity was not altered. In conclusion, in the present study we demonstrated that acute administration of fenproporex exerts an effect in the cholinergic system causing an increase in the activity of acetylcholinesterase in a dose-dependent manner in the hippocampus and posterior cortex. Thus, we suggest that the imbalance in cholinergic homeostasis could be considered as an important pathophysiological mechanism underlying the brain damage observed in patients who use amphetamines such as fenproporex.

Key words: Acetylcholinesterase, Amphetamine, Dopamine, Fenproporex.

INTRODUCTION

Fenproporex is the second most commonly used anorectic substance in the world (Cohen 2009). Fenproporex was synthesized from amphetamine (AMPH) in 1965, in order to increase anorectic effect and reduce psychostimulant effect (Fogliatto 1998). Thus, the drug contains the nucleus of beta-phenethylamine and the pharmacological action of sympathomimetic amines, acting as an inhibitor of the hypothalamic hunger center, with lipophilic action (Coutts et al. 1986). Fenproporex is an anorectic acting catecholaminergic central nervous

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system is widely used in the short-term treatment of moderate to severe obesity since 1970 (Bell et al. 2001). Fenproporex promotes the reduction of food intake, through a change in the chemical control of nerve impulse transmission; the drugs presents a similar effect to that of amphetamine, including central nervous system stimulation, which acts by blocking the reuptake of norepinephrine and dopamine, thereby increasing the levels of these neurotransmitters in the synaptic cleft (Coutts et al. 1986).

Amphetamine compounds, including fenproporex, are classified as indirect-acting dopaminergic agents. These compounds have complex actions on the noradrenaline and dopamine presynaptic terminal, releasing or blocking neuronal reuptake of noradrenaline and dopamine. The end result of the actions of amphetamines in dopaminergic terminals is an increased concentration of dopamine in the synaptic cleft. The dopamine interacts with the dopamine D1 and D2 initiating a sequence of events that modifies neural activity and finally the expression behavior (Coutts et al. 1986, Hyman et al. 1996, Mattei and Carlini 1996). The dopamine system is among the most important neurotransmitter systems and its relationship to the cholinergic system has been widely studied (Hefco et al. 2004).

Acetylcholine (ACh) is one of the most studied excitatory neurotransmitter in the central nervous system. It is synthesized from acetyl coenzyme A (acetyl CoA) formed during cell respiration and choline, an important product of the metabolism of lipids (Taylor and Brown 1994, Soreq and Seidman 2001). It is important in the functions performed by the central nervous system, and has been associated with cognitive function, information processing sensory cortical organization of movement and control of cerebral blood flow (Scremin et al. 1997). Cholinergic transmission is mainly terminated by ACh hydrolysis by the enzyme acetylcholinesterase (AChE: EC 3.1.1.7), catalyzing the hydrolysis of ACh to choline and acetic acid (Marcel et al. 1998). AChE is one of the most important enzymes in many living organisms, including vertebrates and humans. It is essential to the normal functioning of the nervous system, since it rapidly terminates the action of ACh released into the synapse (Soreq and Seidman 2001). AChE is associated with brain development, learning, memory and neuronal damage (Ballard et al. 2005, Metz and Tracey 2005, Zimmerman and Soreq 2006). Moreover, it has also been reported that cholinesterase is involved in modulating glial activation, cerebral blood flux, amyloid cascade, and tau phosphorylation as well as acts as an adhesion protein in synaptic development and maintenance (Ballard et al. 2005, Silman and Sussman 2005).

Considering that fenproporex is rapidly converted in vivo into amphetamine leading to increased extracellular dopamine levels in brain and that AChE is an enzyme regulator involved in cholinergic transmission and can indirectly modulate dopamine release, the present study investigated the effects of acute administration of fenproporex on the enzyme activity of AChE in brain of young rats.

MATERIALS AND METHODS

Animals

Young male Wistar rats (100 - 120 g) were obtained from the Central Animal House of Universidade do Extremo Sul Catarinense. The animals were caged in groups of 5 with free access to food and water, maintained on a 12-h light-dark cycle (lights on 7:00 am), at a temperature of 23 ± 1ºC. All experimental procedures were carried out in accordance with the "Principles of Laboratory Animal Care" (NIH publication no. 80-23, revised 1996) and the Brazilian Society for Neuroscience and Behavior (SBNeC) recommendations for animal care, with the approval of UNESC Ethics Committee (protocols number 43/2009). Moreover, all efforts were made to minimize animal suffering as well as to use a reduced number of animals.

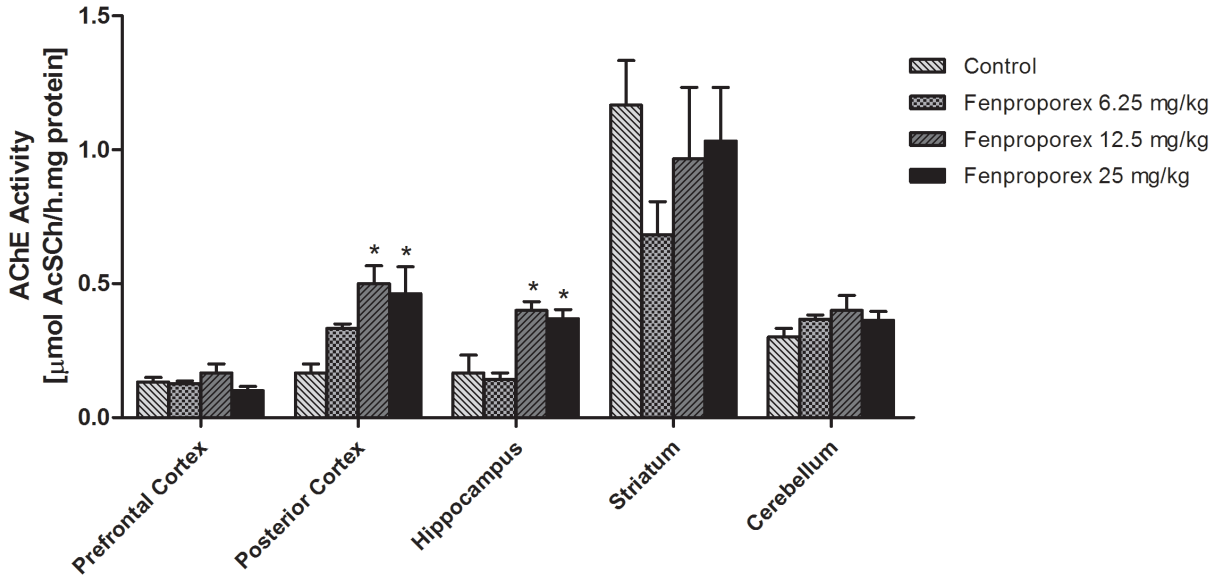

Figure 1 - Acetylcholinesterase activity after acute administration of fenproporex. Data were analyzed by one-way analysis of variance followed by Tukey test when F was significant. Values are expressed as µmol AcSCh/h.mg protein, mean ± S.D. (n=6). *Different from control; $p<0.05$.

Acute Administration of Fenproporex

Animals received a single intraperitoneal injection of Fen (6.25; 12.5 or 25 mg/kg,) or vehicle (2% Tween 80 in 0.9% physiological saline solution). The administration schedule was chosen on the basis of experiments previously performed in our laboratory (Rezin et al. 2014). Two hours after the injection the animals were killed by decapitation without anesthesia and the brain was excised on a Petri dish placed on ice. Prefrontal cortex, posterior cortex, hippocampus, striatum and cerebellum were homogenized in a 100 mM phosphate buffer containing 0.1% Triton X-100, pH 7.5. The homogenates were centrifuged at 800 x g for 10 min at 4°C and the supernatants were isolated and used for the evaluation of acetylcholinesterase activity.

AChE Activity

AChE activity was assayed according to the method of Ellman et al. (1961). The reaction mixture (2 ml final volume) contained 100 mM K^+–phosphate buffer (pH 7.5) and 1 mM 5,5′-dithiobisnitrobenzoic acid. The method is based on the formation of the yellow anion, 5,5′-dithio-bis-acid-nitrobenzoic, which is measured by absorbance at 412 nm during a 2-min incubation at 25°C. The enzyme (40-50 µg of protein) was preincubated for 2 min. The reaction was initiated by adding 0.8 mM acetylthiocholine iodide (AcSCh). All samples were run in duplicate or triplicate, and the enzyme activity is expressed in micromoles AcSCh per hour per milligram of protein. The protein levels were measured using the method of Lowry et al. (1951) with bovine serum albumin as the standard.

Statistical analyses

The results are presented as the mean ± the standard deviation. Tests for determining normality and equal variances were performed to examine whether the data qualified for parametric statistical tests. The data were normally distributed (Shapiro-Wilk, $p>0.05$) with equal variances among samples

(equal variances test, $p>0.05$). Therefore, a one-way analysis of variance (ANOVA) followed by Tukey HSD post-hoc tests were used to compare the means. The differences between groups were considered to be significant at $p<0.05$. All of the analyses were carried out on an IBM-compatible PC computer using Statistical Package for the Social Sciences (SPSS) software (Armonk, New York, USA).

RESULTS

We evaluated the effect of acute administration of fenproporex at three different doses on AChE activity in prefrontal cortex, cerebellum, hippocampus, striatum and posterior cortex of young rats. Acute administration of fenproporex increased the AChE activity in the hippocampus (12.5 and 25 mg/kg) and posterior cortex (12.5 and 25 mg/kg) (Fig. 1). Moreover, AChE activity was not altered in the prefrontal cortex, striatum and cerebellum after acute administration of fenproporex (6.25mg/kg, 12.5mg/kg and 25mg/kg), when compared with control group.

DISCUSSION

Fenproporex is an amphetamine-derived anorectic which is rapidly converted in vivo into amphetamine, used in obesity treatment. Consumption of a low daily dose, 10 mg, of fenproporex led to the detection of amphetamine, within 3 hours, in urine with peak urinary levels greater than 4.0 ng/mL (Cody et al. 1986). Silva et al. (2010) suggested that high concentrations of amphetamine are neurotoxic and can cause irreversible damage to serotonergic or dopaminergic neurons in brain. The mechanisms of neurotoxicity induced by fenproporex and amphetamine are mediated by multiple mechanisms, including the production of free radicals (Frey et al. 2006, Valvassori et al. 2008), DNA damage (Atianjoh et al. 2008, Gonçalves et al. 2013), mitochondrial dysfunction (Valvassori et al. 2010, Rezin et al. 2011, 2014, Feier et al. 2012), changes in Na+, K+-ATPase activity (Rezin et al. 2013) and mitochondrial apoptotic pathway through cytochrome c release (Oliveira et al. 2003, Jiménez et al. 2004).

ACh as a neurotransmitter has a crucial role in the central nervous system and is implicated in behavioral as well as learning and memory and neurodegenerative diseases (Berger-Sweeney et al. 2003, Schliebs and Arendt 2006). AChE activation leads to a fast acetylcholine degradation and a subsequent down stimulation of ACh receptors causing undesirable effects on cognitive functions (Tõugu and Kesvatera 1996, Soreq and Seidman 2001). Our results showed that acute administration of fenproporex in young rats increased AChE activity in the hippocampus and posterior cortex, further suggesting that fenproporex, in high doses, can have a neurotoxic effect on the cholinergic system. Considering these findings we speculate that increased AChE activity caused by fenproporex may lead to a reduction of cholinergic neurotransmission efficiency due to a decrease in ACh levels in the synaptic cleft, thus contributing to progressive cognitive impairment. In addition, several lines of evidence (Greenfield 1984, Inestrosa et al. 1996, Karpel et al. 1996, Layer and Willbold 1995) demonstrate non-catalytic activities for AChE, indicating that the enzyme plays a complex role in modulating cell growth and death. Jiang and Zhang (2008) showed that AChE isoforms participate in apoptosis in two ways: by promoting or suppressing cell death. Enhanced AChE variant expression may influence the expression of other group genes, including those involved in apoptosis (Ben-Ari et al. 2006).

Interestingly, AChE responds to various insults including oxidative stress. Alterations in the lipid membrane observed after fenproporex administration (Model et al. 2014) could be a decisive factor in the modification of conformational state of the AChE molecule and would explain changes in its activity (Das et al. 2001, Aldunate et al. 2004). It is well described in literature that psychostimulants have serious side effects and particular behavioral changes and is a potential for abuse. It is known

that amphetamine induces generation of free radicals via the oxidative catabolism of dopamine, suggesting that dopamine autoxidation can form reactive quinones that attack and potentially inhibit the function of intracellular proteins (LaVoie and Hastings 1999, Page et al. 2001). In addition to dopamine autoxidation, metabolism of dopamine by monoamine oxidase can incrase the production of H_2O_2 and iron-dependent reactive oxygen species (Spina and Cohen 1989). Based on these observations, we can suggest that AChE activation after acute administration of Fen may be mediated by the production of free radical production and consequent oxidative stress in the different brain regions.

Our results also indicate that acute administration of fenproporex did not alter AChE activity in prefrontal cortex, cerebellum and striatum. One possible explanation for the lack of fenproporex effect in these areas is the fact that there are a wide variety of molecular shapes of AChE, which differ in the type and solubility of the membrane binding, rather than catalytic activity (Das et al. 2001). Moreover, the brain is a complex biological structure, consisting of several regions which respond differently and, in part, to different types of neurons. Thus, within a homogeneous population of cells, there is great heterogeneity in terms of physiological and metabolic diseases (Sonnewald et al. 1998). Another important point to consider here are the different effects observed after acute and chronic administration of Fen in young and adult rats. Rezin et al. (2012) showed that chronic fenproporex administration in adult rats decreases AChE activity in prefrontal cortex and striatum, whereas our results showed that AChE activity was increased in hippocampus and posterior cortex after acute administration of fenproporex in young rats. The reason for these discrepancies is unknown but the different effects can be explained by the fact that juvenile and adolescent brain are highly plastic and develop rapidly, so they may be vulnerable to the actions of chronic drug treatment (Kuczenski and Segal 2005). Moreover, excessive stimulation of dopamine receptors during exposure to psychostimulants induces various molecular adaptive changes in the brain (Burrone and Murthy 2003, Nestler 2004). On the other hand, this age-related difference may be caused by pruning of synapses and receptors in adult animals. An overproduction of synapses and receptors from infancy to pubertal onset is followed by a pruning to adult levels during the transition from adolescence to adulthood (Huttenlocher 1979). Thus, it is possible that these molecular adaptive changes could be responsible for the differences in AChE activity observed between young and adult rats.

In conclusion, in the present study we demonstrated that acute administration of fenproporex exerts an effect in the cholinergic system, by altering AChE activity. Our results demonstrated that acute administration of fenproporex increased AChE activity in a dose-dependent manner in the hippocampus and posterior cortex of rats. Thus, considering the present findings, we suggest that the imbalance in cholinergic homeostasis could be considered an important pathophysiological mechanism underlying the brain damage observed in patients who use amphetamines such as fenproporex.

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RESUMO

O femproporex é o segundo anorexígeno à base de anfetamina mais consumido no mundo; esse fármaco é rapidamente convertido in vivo em anfetamina e atua através do aumento dos níveis de dopamina na fenda

sináptica. Considerando que os efeitos do femproporex sobre o Sistema Nervoso Central são ainda pouco conhecidos e que a acetilcolinesterase é uma enzima reguladora envolvida na transmissão colinérgica e que indiretamente pode modular a liberação de dopamina, o presente estudo investigou os efeitos da administração aguda de femproporex sobre a atividade da enzima acetilcolinesterase em cérebro de ratos jovens. Ratos Wistar machos jovens receberam uma única injeção de femproporex (6,25, 12,5 ou 25 mg/kg i.p.) ou veículo (Tween 80 2%). Duas horas após a injeção, os ratos foram mortos por decapitação e o cérebro foi removido para avaliação da atividade da acetilcolinesterase. Os resultados mostraram que a administração de femproporex aumentou a atividade da acetilcolinesterase no hipocampo e córtex posterior, enquanto que no córtex pré-frontal, estriado e cerebelo a atividade da enzima não foi alterada. Em conclusão, o presente estudo demonstrou que a administração aguda de femproporex exerce um efeito no sistema colinérgico causando um aumento na atividade da acetilcolinesterase, de um modo dose dependente, no hipocampo e córtex posterior. Assim, sugere-se que o desequilíbrio na homeostase colinérgica pode ser considerado um importante mecanismo fisiopatológico subjacente ao dano cerebral observado em pacientes que utilizam anfetaminas, como o femproporex.

Palavras-chave: Acetilcolinesterase, Anfetamina, Dopamina, Femproporex.

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