Behavioral Responses in Rats Submitted to Chronic Administration of Branched-Chain Amino Acids

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Abstract Maple syrup urine disease (MSUD) is an inborn metabolism error caused by a deficiency of branched-chain α -keto acid dehydrogenase complex activity. This blockage leads to an accumulation of the branched-chain amino acids (BCAA) leucine, isoleucine, and valine, as well as their corresponding α -keto and α -hydroxy acids. Previous reports suggest that MSUD patients are at high risk for chronic neuropsychiatric problems. Therefore, in this study, we assessed variables that suggest depressive-like symptoms (anhedonia as measured by sucrose intake, immobility during the forced swimming test and body and adrenal gland weight) in rats submitted to chronic administration of BCAA during development. Furthermore, we determined if these parameters were sensitive to imipramine and *N*-acetylcysteine/deferolamine (NAC/DFX). Our results

demonstrated that animals subjected to chronic administration of branched-chain amino acids showed a decrease in sucrose intake without significant changes in body weight. We also observed an increase in adrenal gland weight and immobility time during the forced swimming test. However, treatment with imipramine and NAC/DFX reversed these changes in the behavioral tasks. In conclusion, this study demonstrates a link between MSUD and depression in rats. Moreover, this investigation reveals that the antidepressant action of NAC/DFX and imipramine might be associated with their capability to maintain pro-/anti-oxidative homeostasis.

Introduction

Maple syrup urine disease (MSUD; OMIM #248600), or branched-chain ketoaciduria, is an inborn metabolism error caused by a deficiency in the activity of branched-chain α -keto acid dehydrogenase complex (BCKDH). This deficiency leads to an accumulation of the branched-chain amino acids (BCAA) leucine, isoleucine, and valine, as well as their associated α -keto acids (BCKA) in tissue and body fluids (Chuang and Shih 2001; Treacy et al. 1992). The worldwide frequency is approximately 1:185,000 based on routine screening data from 26.8 million newborns (Chuang and Shih 2001). Individuals with MSUD usually present with poor feeding, convulsions, ketoacidosis, hypoglycemia, coma, ataxia, psychomotor delay, and mental retardation, as well as generalized edema and hypomyelination/ demyelination shown by magnetic resonance imaging studies of the central nervous system (Chuang and Shih 2001; Cavalleri et al. 2002; Ha et al. 2004; Schönberger et al. 2004; Zinnanti et al. 2009).

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Neurological sequelae of MSUD are likely caused by several interacting mechanisms. Proposed mechanisms of neurotoxicity include energy deprivation and osmotic dysregulation (Howell and Lee 1963; Land et al. 1976; Danner and Elsas 1989; Yudkoff et al. 1994; Zielke et al. 2002; Pilla et al. 2003; Sgaravatti et al. 2003; Ribeiro et al. 2008) and alterations in the concentrations of the neurotransmitters glutamate, aspartate, and aminobutyric in the brain (Dodd et al. 1992; Prensky and Moser 1967; Tavares et al. 2000; Yudkoff et al. 1994; Hutson et al. 2001). The brain injury in this disorder may also be related to a reduction of brain uptake of essential amino acids (Araújo et al. 2001; Wajner and Vargas 1999; Wajner et al. 2000), apoptosis of neural cells (Jouvet et al. 2000), oxidative stress (Bridi et al. 2003, 2005; Fontella et al. 2002; Barschak et al. 2006; Mescka et al. 2011), increased acetylcholinesterase activity in the brain (Scaini et al. 2012), and alterations of neurotrophin levels (Scaini et al. 2013a, b).

Hereditary disorders that cause neuropsychiatric sequelae provide a window into the biological foundations of mental illness. Anecdotal reports suggest that aging MSUD patients are at high risk for chronic neuropsychiatric problems, such as attention deficit disorder, depression, and anxiety (Strauss et al. 2006; Walterfang et al. 2013). Muelly and colleagues (2013) showed that the neurochemical deficiencies previously demonstrated in MSUD patients and experimental animals may persist in the chronic state, although to a lesser degree, and cumulatively contribute to neuropsychiatric morbidity. Therefore, in this study, we assessed anhedonia, measured by sucrose intake, immobility during the forced swimming test and body and adrenal gland weight in rats submitted to chronic administration of BCAA during development. Because previous observations suggested that oxidative stress may be involved in the pathophysiology of the neurological dysfunction of MSUD (Bridi et al. 2003, 2005; Fontella et al. 2002; Barschak et al. 2006; Mescka et al. 2011) and these variables suggest depressive-like symptoms (Katz et al. 1981b; Gamaro et al. 2003; Lucca et al. 2008), we also investigated the influence of the concomitant administration of *N*-acetylcysteine (NAC) plus deferoxamine (DFX) or imipramine in the behavioral tasks.

Materials and Methods

Animals

Male Wistar rats that were 7 days old (10–15 g) were obtained from the Central Animal House of Universidade do Extremo Sul Catarinense. The rats were weaned at 21 days of age. All rats were caged in groups of five, had free access to food and water, and were maintained on a 12-h

light-dark cycle (lights on 7:00 am) at a temperature of $23 \pm 1^\circ\text{C}$. All experimental procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the Brazilian Society for Neuroscience and Behavior recommendations for animal care. All experiments and procedures were conducted after approval from the Ethics Committee of the Universidade do Extremo Sul Catarinense was granted (protocol number 60/2010).

Chronic Administration of the BCAA Pool and Treatment with Antioxidants

The animals were divided into four groups: Group I – control (saline); Group II – Hyper-BCAA (H-BCAA); Group III – H-BCAA treated with a combination of NAC (20 mg/kg) and DFX (20 mg/kg); and Group IV – H-BCAA treated with imipramine (10 mg/kg). The animals received two subcutaneous injections per day of the BCAA pool (15.8 $\mu\text{L/g}$ body weight at 12-h intervals) containing 190 mmol/L Leu, 59 mmol/L Ile, and 69 mmol/L Val in saline solution, administered for 21 days starting at postnatal day (PD) 7 (last injection at PD 27) ($n = 12$, per group) (Bridi et al. 2006). Immediately after administration of the first injection of the BCAA pool, NAC was administered subcutaneously twice a day (at 12-h intervals) and DFX was administered once every two days for a total of 21 days (Di-Pietro et al. 2008). Imipramine, a standard antidepressant, was obtained from Novartis Pharmaceutical Industry (São Paulo, Brazil), and a dose of 10 mg/kg was injected intraperitoneally (i.p.) once a day over 21 days (Tuon et al. 2007). Twelve hours after the last injection of BCAA, the animals were submitted to behavioral testing. The choice of the administered doses and the ages of the rats were based on a previous study (Bridi et al. 2006), which showed that the administration of the BCAA pool to rats (similar doses and ages to those used in this study) resulted in increased levels of Leu, Ile, and Val in the blood and brain. Importantly, the dose of the BCAA pool mimicked the biochemical events observed in MSUD patients during crises, but in this model leucine levels in plasma and brain returned to basal values after 12 h the final BCAA injection, thus, we evaluate the chronic effects of daily episodes of metabolic decompensation.

Sweet Food Consumption (Anhedonia Test)

The consumption of sweet food was measured in all groups to evaluate anhedonia during the 7 days (PD 21–28). For this purpose, the animals were placed in an illuminated lightened rectangular box (40 cm $\times$ 15 cm $\times$ 20 cm) with a glass ceiling and floor and wooden sidewalls, and the box was divided into nine equal

rectangles by black lines. Ten Froot Loop(s) (Kellogg's® pellets of wheat, cornstarch, and sucrose) were placed in one extremity of the box. The animals were subjected to five 3-min trials, once daily for 5 days, to become familiarized with the food (PD 21–26). After being habituated, the animals were exposed to two test sessions of 3 min each, during which the number of ingested pellets was measured (PD 27–28). This task was performed during the light cycle by an observer who was blinded to the groups. The observer noted if the animal ate 1/4, 1/2, or an entire Froot Loop, in accordance with previous studies (Katz et al. 1981b; Gamaro et al. 2003).

During the first 5 days, the animals were exposed to a 22-h fasting before the count of Froot Loops, after the animals were exposed to standard food for 2 h. However in the test sessions (last 2 days), the animals were not fasting. These evaluations were performed because food deprivation, which is used in many behavior tasks as a motivating stimulus, may also be an acute stressor (Katz et al. 1981a; Gamaro et al. 2003). The behavioral tests were performed by the same person blinded to the experimental group. The number of black line crossings and rearings were measured during the first (PD 21) session to evaluate motor activity.

Body and Adrenal Gland Weight

Body weight was measured before administration of the BCAA pool (day 0) and 22 days (day 22) after the first administration of the BCAA pool. On the 22nd day, after consumption of the sweet food, the rats were anesthetized with a mixture of ketamine (80 mg/kg) and xylazine (10 mg/kg) administered i.p. After death, the adrenal gland was removed through laparotomy and weighed on an analytical scale (Krishnan and Nestler 2008; Katz et al. 1981b; Nestler et al. 2002; Gamaro et al. 2003).

Forced Swimming Test

This test was conducted according to previous reports (Porsolt et al. 1977) and used as a model for depressive behavior. The behavioral tests were performed by the same person blinded to the experimental group. Briefly, the test involves two exposures to a cylindrical water tank in which rats cannot touch the bottom and from which they cannot escape. The tank is made of transparent Plexiglas, is 80 cm tall, is 30 cm in diameter, and is filled with water (22–23°C) to a depth of 40 cm. The water in the tank was changed for each rat. For the first exposure, the rats were placed in the water for 15 min (training session). After 24 h, the rats were placed in the water again for a 5-min session (test session). The time of immobility was analyzed in the test session. The rats were judged to be immobile

whenever they stopped swimming and remained floating in the water, with their heads above the surface.

Statistical Analysis

The results are presented as the mean $\pm$ 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 was 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

As demonstrated in Fig. 1, chronic administration of BCAA decreased sucrose intake by 45.78% when compared with the control group. Treatment with imipramine and NAC plus DFX partially reversed the reduction of sweet food consumption by 52.83% and 45.78%, respectively, when compared with the H-BCAA group. Figure 2 shows that the chronic administration of BCAA produced no differences in the number of crossings or rearings between groups during the habituation to the open-field training sessions. These results demonstrated that there was no difference in the motor or exploratory activities between groups and that the results observed in Fig. 1 were not secondary to locomotor alterations.

Table 1 illustrates the effects of H-BCAA on body weight. Control animals significantly increased in body weight after the first administration, whereas H-BCAA animals did not. There was a 25.39% increase in adrenal gland weight in H-BCAA animals compared with the control group. Treatment with imipramine and NAC plus DFX prevented the increase in adrenal gland weight by 29.05% and 14%, respectively, compared with the H-BCAA group (Fig. 3).

The effects of H-BCAA administration on immobility time during the forced swimming test are illustrated in Fig. 4. In the H-BCAA group, we observed an increase in immobility time by 260, 61%, compared with the control group. Treatment with imipramine and NAC plus DFX reversed the increase in the immobility time by 55, 69% and 76, 61%, respectively, compared with the H-BCAA group.

Fig. 1 Effects of chronic administration of hyper branched-chain amino acids (H-BCAA), imipramine (IMI), and antioxidants (ATX) (*N*-acetylcysteine plus deferoxamine) on the consumption

of sweet food in the anhedonia test. Data are expressed as the mean $\pm$ the standard deviation of 12 rats. * $p < 0.05$ compared with the control group. # $p < 0.05$ compared with the H-BCAA group

Fig. 2 Effects of chronic administration of hyper branched-chain amino acids (H-BCAA), imipramine (IMI), and antioxidants (ATX) (*N*-acetylcysteine plus deferoxamine) number of crossings

and rearings of rats subjected to the open-field test. Data are expressed as the mean $\pm$ the standard deviation of 12 rats

Discussion

A number of metabolic disorders that affect the central nervous system can present in childhood, adolescence, or adulthood as a phenocopy of a major psychiatric syndrome, such as psychosis, depression, anxiety, or mania (Walterfang et al. 2013). In this study, we observed that rats submitted to chronic administration of H-BCAA have a decreased sweet food intake and increased adrenal gland weight, without any alteration of body weight compared with the control group. This mimics anhedonia, a key depressive symptom (Katz et al. 1981b; Willner et al. 1987, 1998). We also observed an increase in immobility time in the H-BCAA group during the

forced swimming test. Additionally, as described above, the H-BCAA group did not present with any locomotor activity impairments, reinforcing that the decreased sweet food intake and higher immobility time in the H-BCAA group were related to changes in the behavioral tasks (anhedonia and forced swimming tests).

Evidence from the literature shows that the causality of psychiatric illness is the result of two processes: the interruption of childhood/early adulthood neurodevelopmental trajectories in progressive illness, and the acute alteration of monoaminergic or excitatory/inhibitory neurotransmitter systems in acute or episodic illness (Walterfang et al. 2013). Moreover, neurotransmitter deficiency can be a primary

Table 1 Effects of chronic administration of hyper branched-chain amino acids (H-BCAA), imipramine (IMI), and antioxidants (ATX) (*N*-acetylcysteine plus deferoxamine) on bodyweight on day 0 (A) and day 22 (B). Data are expressed as the mean $\pm$ the standard deviation of 12 rats

	Body weight	
	Day 0	Day 22
Control	11.65 (1.06)	48.77 (4.53)
H-BCAA	11.78 (0.918)	48.94 (2.93)
H-BCAA + ATX	11.81 (0.99)	49.86 (3.22)
H-BCAA + IMI	11.63 (1.07)	47.62 (1.42)

Fig. 3 Effects of chronic administration of hyper branched-chain amino acids (H-BCAA), imipramine (IMI), and antioxidants (ATX) (*N*-acetylcysteine plus deferoxamine) on adrenal glandweight. Data are expressed as the mean $\pm$ the standard deviation of 12 rats. * $p < 0.05$ compared with the control group. # $p < 0.05$ compared with the H-BCAA group

cause of psychiatric disorders or entrain compensatory changes in receptor expression and synaptic structure that affect brain function. Neuronal energy depletion, osmotic dysregulation, and dysmyelination also likely contribute to the development of psychiatric disorders (Jou et al. 2009; Gardner and Boles 2011). Additionally, major depression is characterized by significantly lower plasma concentrations of a number of key antioxidants, such as vitamin E, zinc, and coenzyme Q10. Lowered total antioxidant status, or antioxidant enzyme activity, is another hallmark of depression (Kahnzole et al. 2003; Maes et al. 2000, 2009a, b). Several studies have shown evidence of oxidative damage to lipids, fatty acids, and DNA in depression (Forlenza and Miller 2006; Dimopoulos et al. 2008; Maes et al. 1999). These effects may occur on an ongoing basis or stem from developmental or cumulative aberrations of neurochemistry that lead to persistent modifications of receptor regulation and neurochemistry. In this context, studies have demon-

strated that metabolite accumulation in MSUD may affect myelin development (Taketomi et al. 1983; Tribble and Shapira 1983; Treacy et al. 1992) and inhibit the transport of tyrosine, tryptophan, and other essential amino acids across the blood-brain barrier, thereby limiting substrate availability for cerebral catecholamine, serotonin, and protein synthesis (Dodd et al. 1992; Prensky and Moser 1967; Tavares et al. 2000; Yudkoff et al. 1994; Araújo et al. 2001; Hutson et al. 2000; Wajner and Vargas 1999; Wajner et al. 2000).

Because the metabolites accumulating in MSUD induce oxidative stress (Fontella et al. 2002; Bridi et al. 2003, 2005; Mescka et al. 2011), which plays a critical role in the pathophysiology of depressive disorders, we also investigated whether free-radical generation could be involved in reduction in sucrose preference and higher immobility time. Corroborating this hypothesis, antioxidant administration prevented the decreased sweet food intake, increased immobility time, and increased adrenal gland weight.

Fig. 4 Effects of chronic administration of hyper branched-chain amino acids (H-BCAA), imipramine (IMI), and antioxidants (ATX) (*N*-acetylcysteine plus deferoxamine) on immobility time

during the forced swimming test. Data are expressed as the mean $\pm$ the standard deviation of 12 rats. * $p < 0.05$ compared with the control group. # $p < 0.05$ compared with the H-BCAA group

Though specific trials for antidepressant effects in depression are still lacking, NAC shows antidepressant-like activity in several preclinical models; studies corroborate the antidepressant-like effects of NAC in rats subjected to the forced swimming test (Ferreira et al. 2008) and in mice subjected to the tail suspension test (Linck et al. 2012). Additionally, the chronic administration of NAC resulted in a dose-dependent reduction in immobility time in bulbectomized rats and resulted in a significant increase in cellular antioxidant mechanisms (superoxide dismutase activity) in the frontal cortex, hippocampus, and striatum (Smaga et al. 2012). Arent and colleagues (2012) demonstrated that NAC and DFX, alone or in combination, reversed the stress-induced sweet food consumption decrease and oxidative stress in rats submitted to chronic mild stress. Magalhães and colleagues (2011) reported that adjunctive NAC may be useful for major depressive episodes in bipolar disorder.

NAC contributes to the maintenance of oxidative balance through the actions of the cysteine/cystine cycle. Like glutathione and GSSG, cysteine and cystine are coupled redox partners that help to prevent oxidative cellular dysfunction and injury (Iyer et al. 2009; Banjac et al. 2008; Vene et al. 2011). Hence, the actions of NAC are multifold and interrelated, with the production of glutathione, the cysteine/cystine cycle, and the action of the glutamate/cystine antiporter contributing to the maintenance of oxidative balance and cellular function. Note that NAC also acts on glutamatergic neurotransmission, both directly and indirectly (Berk et al. 2013). NAC is converted to cystine, which in turn facilitates the glutamate/cystine antiporter and the production of glutathione in glial cells

(Lafleur et al. 2006). In addition to the regulation of glutamate release, NAC, via GSH or its derivatives, has the capacity to modulate NMDA activity (Gilbert et al. 1991; Leslie et al. 1992; Varga et al. 1997). NAC regulation of the cystine/glutamate antiporter and mGluR2/3, as described above, can also regulate dopamine release from presynaptic terminals (Baker et al. 2002). NAC may also regulate dopamine release via the modulation of the redox status of the cell, via antioxidant effects of GSH and L-cysteine (JanÁky et al. 2007; Gere-Paszi and Jakus 2009). Additionally, Linck and colleagues (2012) have demonstrated that AMPA receptors play a key role in the mechanism of the antidepressant-like action of NAC by indirectly modulating the serotonin and noradrenaline pathways. Consistent with these mechanisms, reduced cerebral dopamine and glutamate levels have been observed in experimental MSUD animals (Dodd et al. 1992; Zinnanti et al. 2009) and postmortem brain tissue from a child who died of leucine intoxication (Prensky and Moser 1996).

Interestingly, we also demonstrated that the tricyclic antidepressant imipramine prevented the changes in the behavioral tasks observed in H-BCAA rats. Imipramine increases the levels of serotonin and/or norepinephrine by blocking reuptake of these neurotransmitters to presynaptic terminals, although an increase in monoamine levels occurs soon after drug administration, the effects of antidepressants emerge gradually over several weeks of continuous application, it is possible that in addition to an increase in monoamine levels, other more temporal neuronal events may be responsible for the action of imipramine (Yagasaki et al. 2006). The immobility is a parameter evaluated in the

forced swimming test and a reduction in sucrose preference in anhedonia test is interpreted as a depression-like behavior (Porsolt et al. 1977; Katz et al. 1981b; DellaGioia and Hannestad 2010; Réus et al. 2011), suggesting an imbalance in the noradrenergic and serotonergic neurotransmission. In fact, human and animal studies have showed low levels of dopamine and serotonin associated with high levels of BCAA (Wajner and Vargas 1999; Wajner et al. 2000; Araújo et al. 2001). In this context, we suggest that the alterations in monoamine metabolism evoke adaptive changes in intracellular signal transduction and prevent these changes in the behavioral tasks. In addition, previous studies reported that antidepressant treatments present an antioxidant action. Imipramine treatment reversed the lipid peroxidation in brain of Sprague Dawley rats induced by chronic ozone (Mokoena et al. 2010). Réus and colleagues (2010) recently showed that imipramine also presents antioxidant properties, reducing oxidative damage and increasing superoxide dismutase and catalase activity in the rat brain. Additionally, imipramine (10 and 20 mg/kg) restored depleted reduced glutathione levels and catalase activity and attenuated raised lipid peroxidation and nitrite concentrations in sleep-deprived mice compared to untreated sleep-deprived mice (Kumar and Garg 2009). Thus, the effects of imipramine in preventing the changes in the behavioral tasks observed in H-BCAA rats might be also associated with its capability to maintain pro-/anti-oxidative homeostasis.

Some limitations of this study should be taken into consideration, such as the fact that the antioxidant drugs and the antidepressants were given from the start of the BCAA administration and this will not be possible in humans unless it is known before birth that they have MSUD. Besides, we cannot rule out a possible effect of the branched-chain alpha-keto acids that were also produced considering an *in vivo* model of MSUD, since the analyses of plasma and brain levels branched-chain alpha-keto acids were not performed. However, the present findings demonstrate a link between H-BCAA and depression in rats. Moreover, this investigation revealed that the antidepressant action of NAC/DFX and imipramine might be associated with its capability to maintain pro-/anti-oxidative homeostasis. Besides, NAC/DFX and imipramine interact with distinct receptor systems, such as the glutamatergic and monoaminergic systems, which could produce synergic effects on brain pathways involved in the modulation of depressive-like behavior.

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Author Contribution

Giselli Scaini, Emilio L. Streck, and João Quevedo designed the study and wrote the protocol. Giselli Scaini, Gabriela C. Jeremias, Camila B. Furlanetto, and Diogo Domingui conducted the experiments. Giselli Scaini and Clarissa M. Comim undertook the statistical analysis; and Giselli Scaini and Emilio L. Streck wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of Interest

Giselli Scaini, Gabriela C. Jeremias, Camila B. Furlanetto, Diogo Domingui, Clarissa M. Comim, João Quevedo, Patrícia F. Schuck, Gustavo C. Ferreira, and Emilio L. Streck declare that they have no conflict of interest.

Informed Consent and Animal Rights

All institutional and national guidelines for the care and use of laboratory animals were followed. All experimental procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the Brazilian Society for Neuroscience and Behavior recommendations for animal care.

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