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Memantine treatment reverses anhedonia, normalizes corticosterone levels and increases BDNF levels in the prefrontal cortex induced by chronic mild stress in rats

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Abstract Memantine is a N-methyl-D-aspartate (NMDA) receptor antagonist and several studies have pointed to the NMDA receptor antagonists as a potential therapeutic target for the treatment of depression. The present study was aimed to evaluate the behavioral and physiological effects of administration of memantine in rats exposed to the chronic mild stress (CMS) model. To this aim, after 40 days of exposure to CMS procedure, rats were treated with memantine (20 mg/kg) for 7 days. In this study, sweet food consumption, adrenal gland weight, corticosterone levels, and brain-derived-neurotrophic factor (BDNF) protein levels in the prefrontal cortex, hippocampus and amygdala were assessed. Our results demonstrated that chronic stressful situations induced anhedonia, hypertrophy of adrenal gland weight, and an increase of corticosterone levels in rats, but did not alter BDNF protein levels in the rat brain. Memantine treatment reversed anhedonia and the increase of adrenal gland weight, normalized corticosterone levels and increased BDNF protein levels in the prefrontal cortex in stressed rats. Finally, these findings further support the hypothesis that NMDA receptor antagonists such as memantine could be helpful in the pharmacological treatment of depression.

Keywords Memantine · BDNF · Chronic mild stress · Anhedonic behavior · Depression

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Introduction

Depression is a mood disorder, which affects up to 20% of the world population (Nestler et al. 2002; Manji et al. 2001). For more than 50 years, drugs that increase the synaptic availability of biogenic amines have been used to treat depression, but these antidepressant drugs require 2–4 weeks (or more) to produce a clinical improvement in depressive symptomatology (Skolnick et al. 2009). In addition, patients have a low (about 30%) remission rate (Krishnan and Nestler 2008). For these reasons new research has been conducted for more effective agents (Feier et al. 2011; Magalhães et al. 2011).

There is growing evidence that an increase of glutamatergic neurotransmission is involved with the pathophysiology of depression. In addition, studies have been suggested that NMDA receptor antagonists play an important role in the treatment of depression (Hashimoto 2009, 2011; Skolnick et al. 2009). In fact, patients with depression presented a significant increase of serum levels of glutamate, compared with healthy controls (Kim et al. 1982; Mitani et al. 2006), and several preclinical and clinical studies have demonstrated that NMDA antagonists, such as ketamine, memantine, amantadine and others, display antidepressant effects (Berman et al.

2000; Ferguson and Shingleton 2007; Garcia et al. 2008a, b, 2009; Moryl et al. 1993; Parsons et al. 1999; Quan et al. 2011; Réus et al. 2010; Roman et al. 2009; Zarate et al. 2006). The memantine is clinically used for neurological disorders, including Alzheimer's disease. In addition to the NMDA receptor, other systems are involved in the action of memantine, for example, serotonin and dopamine uptake, nicotinic acetylcholine, serotonin and sigma-1 receptors (for a review see Johnson and Kotermanski 2006).

Given the fact of the latency time being 3–4 weeks for antidepressants to exert their initial pharmacological effects, some studies have suggested that downstream neural adaptation (for example: the BDNF-TrkB receptor signaling pathway) rather than an elevation in synaptic monoamine levels itself may be responsible for their therapeutic effects (Hashimoto et al. 2004; Hashimoto 2011; Nestler et al. 2002). BDNF is a member of the neurotrophin family (Lewin and Barde 1997). A series of in depth studies have pointed to an involvement of BDNF in the pathophysiology of depression. In fact, postmortem studies have demonstrated that depressed subjects have decreased BDNF levels (Altar 1999). In contrast, antidepressants drugs induce an increase in BDNF levels in humans and animals (Pittenger and Duman 2008). Moreover, studies from many laboratories have showed that NMDA receptor antagonists induce increases in BDNF levels (Garcia et al. 2008a; Marvanová et al. 2001; Réus et al. 2010; Rogóz et al. 2008).

Animal models of depression are very important for our understanding of depression and antidepressant drug action, as well as for the development of new antidepressant treatments (Bylund and Reed 2009). The CMS is a widely used model of depression and it induces a lower consumption of sucrose (sweet food), changes in hypothalamic-pituitary-adrenal (HPA) axis and adrenal hypertrophy, which leads to corticosterone hypersecretion (Fortunato et al. 2010; Katz et al. 1981; Lucca et al. 2008, 2009a, b; Vollmayr and Henn 2003).

Studies evaluating the effects of memantine in rats submitted to a stress protocol, and linking the effects of memantine on behaviour and parameters linked to depression, such as glucocorticoids and BDNF have not been fully characterized. So, the present study aimed to investigate behavioral and physiological effects of repeated administration of memantine in rats submitted to the chronic mild stress procedure.

Experimental procedures

Animals

Male Adult Wistar rats (60 days old) were obtained from the UNESC (Universidade do Extremo Sul Catarinense,

Criciúma, SC, Brazil) breeding colony. They were housed five per cage with food and water available ad libitum (except for the stressed group during the period when the stressor applied required no food or water) and were maintained on a 12-h light/dark cycle (lights on at 7:00 a.m.). All experimental procedures involving animals were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals and the Brazilian Society for Neuroscience and Behavior (SBNeC) recommendations for animal care and with approval by local Ethics Committee under protocol number 059/2008.

Drugs and treatment

Memantine was obtained from APSEN Pharmaceutical Industry (São Paulo) Brazil, and a dose of 20 mg/kg was injected intraperitoneally once a day over 7 days (chronic treatment) after the CMS procedure. The protocol was performed in accordance with previous studies (Fortunato et al. 2010; Garcia et al. 2009) and the dose of 20 mg/kg of memantine was chosen because in a previous study from our group it showed a better effect on the forced swimming test (Réus et al. 2010). The treatments were administered in a volume of 1 ml/kg. To develop this study we employed 60 animals ($n=15$ per group) separated into four groups, as follows: 1) non stressed—saline; 2) non stressed—memantine; 3) stressed—saline; 4) stressed—memantine. The treatment with memantine was performed during the anhedonia test, once a day over 7 days, 60 min prior to the behavioral assessment.

Experimental procedure

The chronic mild stress (CMS) protocol was adapted from the procedure described by Gamaro et al. (2003). The animals were divided in two groups: control and stressed. The Control groups were kept undisturbed in their home cages during the 40 days of treatment receiving only ordinary daily care with daily supports of food and water. The 40-days chronic mild stress paradigm was used for the animals in the stressed group. Individual stressors and length of time applied each day as follows. The following stressors were used: (i) 24 h food deprivation was applied on days 2, 7, 15, 21 and 30; (ii) 24 h water deprivation on days 1, 10, 20 and 33; (iii) 1–3 h restraint on days 9, 23 and 31, (iv) 1.5–2 h restraint at 4°C on days 13, 26 and 34; (v) forced swimming for a duration of 10 or 15 min on days 8, 16, 27, 35 and 40; (vi) flashing light over a duration of 120–210 min on days 6, 14, 22, 28, 32 and 39; (vii) isolation on days 3, 4, 5, 17, 18, 19, 24, 25, 36 and 37. Stressor stimuli were applied at different times every day, in order to minimize its predictability. The Restraint test was carried out by placing the animal in a 25×7 cm plastic tube and adjusting it with

plaster tape on the outside, so that the animal was unable to move. There was a 1 cm hole at the far end for breathing. The Forced swimming was carried out by placing the animal in a glass tank measuring 50×47 cm with 30 cm of water at 23±2°C. The exposure to flashing light test was made by placing the animal in a 60×60×25 cm plywood made box divided in 16 cells of 15×15×25 cm with a frontal glass wall. A 40 w lamp, flashing at frequency of 60 flashes/min, was used.

Open-field test

The rats were treated with memantine (20 mg/kg), and saline 60 min before the exposure to the open-field apparatus, in order to assess possible effects of drug treatment on spontaneous locomotor activity. Analysis of the rats spontaneous activity was carried out in an open field apparatus, which is an arena 45×60 cm surrounded by 50 cm high walls made of brown plywood with a frontal glass wall. The floor of the open field was divided into 9 rectangles (15× 20 cm each) by black lines (Frey et al. 2006). Animals were gently placed on the left rear quadrant, and left to explore the arena for 5 min. The number of horizontal (crossings) and vertical (rearings) activities performed by each rat during the 3 min observation period were counted by an expert observer.

Sweet food consumption (anhedonia test)

After 40 days of treatment, the consumption of sweet food was measured to verify anhedonia. The animals were placed in a lit rectangular box (40×15×20 cm) with a glass ceiling, floor and side walls made of wood and divided into 9 equal rectangles by black lines. Ten Froot Loops (Kellogg's® pellets of wheat and sucrose) were placed in one extremity of the box. Animals were submitted to 5 sessions of 3 min each, once a day, in order to become familiarized with this food. After being habituated, the animals were exposed to two test sessions, 3 min each, where the number of ingested pellets were counted (Garcia et al. 2009; Lucca et al. 2009a, b). This task was undertaken during the light cycle and the evaluation was realized by an observer with no knowledge of the groups. Results were noted when the animal ate 1, 1/2, or 1/4 part of the Froot Loops, in accordance with previous studies (Gamaro et al. 2003; Katz et al. 1981). These evaluations were made since food deprivation, which is used in many behavior tasks as a motivating stimulus, may also be an acute stressor (Gamaro et al. 2003; Katz et al. 1981). At the seventh day after consumption of the sweet food, the rats were placed under anesthesia and blood was collected by cardiac puncture for subsequent analyses of corticosterone serum levels. After the decapitation of rats, the skulls were immediately removed and the prefrontal cortex, hippocampus and amygdala were quickly isolated by hand dissection using a magnifying glass and a thin brush (dissection was based on histological distinctions) described by Paxinos and Watson (1986) and it was stored at −70°C for analyses of BDNF protein levels. The adrenal gland was removed through laparotomy, and weighed in an analytical balance. Adrenal gland weight was used in this study as an indirect parameter of hypothalamic-pituitary-adrenal axis activation (Katz et al. 1981).

Corticosterone circulating levels

The rats were anesthetized with a mixture of ketamine (80 mg/kg) and xylazine (10 mg/kg) administrated i.p. and after blood was collected to evaluate corticosterone serum levels. Corticosterone levels were determined using enzyme immunoassay kits. The analyses were performed in a commercial laboratory (Biolabor Laboratório de Análises Clínicas, Criciúma, SC, Brazil), blinded to the experimental conditions.

BDNF analysis

BDNF levels in prefrontal cortex, hippocampus and amygdala were measured by anti-BDNF sandwich-ELISA, according to the manufacturers instructions (Chemicon, USA). Briefly, the rat prefrontal cortex, hippocampus and amygdala were homogenized in phosphate buffer solution (PBS) with 1 mM phenylmethylsulfonyl fluoride (PMSF) and 1 mM (EGTA). Microtiter plates (96-well flat-bottom) were coated for 24 h with the samples diluted 1:2 in sample diluent and standard curve ranged from 7.8 to 500 pg/ml of BDNF. The plates were then washed four times with sample diluent and a monoclonal anti-BDNF rabbit antibody diluted 1:1000 in sample diluent was added to each well and incubated for 3 h at room temperature. After washing, a peroxidase conjugated anti-rabbit antibody (diluted 1:1000) was added to each well and incubated at room temperature for 1 h. After addition of streptavidin-enzyme, substrate and stop solution, the amount of BDNF was determined by absorbance in 450 nm. The standard curve demonstrates a direct relationship between Optical Density (OD) and BDNF concentration. Total protein was measured by Lowry's method using bovine serum albumin as a standard, as previously described by Lowry et al. (1951).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) 16.0 was utilized for statistical analyses. All data is presented as mean±S.E.M. Differences among experimental groups were determined by one-way ANOVA followed by Tukey's *post hoc* test for sweet food intake,

locomotory activity, adrenal gland weight, ACTH circulating levels and BDNF protein levels. $P<0.05$ were considered statistically significant.

Results

As depicted in Fig. 1a, stressed rats treated with saline decreased sweet food intake, compared with control rats treated with saline ($p=0.03$). Statistical analyses revealed that treatment with memantine increased sweet food intake, when compared with stressed rats treated with saline. The Fig. 1b shows that the behavior of the rats subjected to the open-field test, after 40 days of chronic stressful stimuli, and that this did not alter the number of crossings ($p=0.21$) and rearings ($p=0.13$) displayed by all groups.

The effects of the CMS protocol in the adrenal gland this illustrated in Fig. 2. CMS procedure induced an

increase of adrenal gland weight in stressed rats treated with saline, compared with non-stressed rats injected with saline. Interestingly, the treatment with memantine reestablished to a normal range the adrenal glands weight in stressed rats ($p=0.02$).

Corticosterone levels this illustrated in Fig. 3. Rats subjected to the CMS paradigm, and treated with saline, displayed increased corticosterone levels compared with non-stressed rats injected with saline. However, the CMS-induced increases in circulating corticosterone levels were reversed by memantine ($p=0.02$).

Figure 4 shows the BDNF protein levels in the prefrontal cortex, hippocampus and amygdala. Stressed rats injected with saline did not alter BDNF protein levels in the prefrontal cortex, hippocampus and amygdala, but interestingly, the treatment with memantine in stressed animals increased BDNF protein levels in the prefrontal cortex ($p=0.01$).

Fig. 1 Effects of CMS procedure on sweet food consumption (**a**) and on the number of crossings and rearings (**b**) in the open-field test in rats repeatedly treated with memantine. *Bars* represent means±S.E.M. * $p<0,05$ vs. control saline; # $p<0.05$ vs. CMS saline, according to ANOVA post-hoc Tukey test
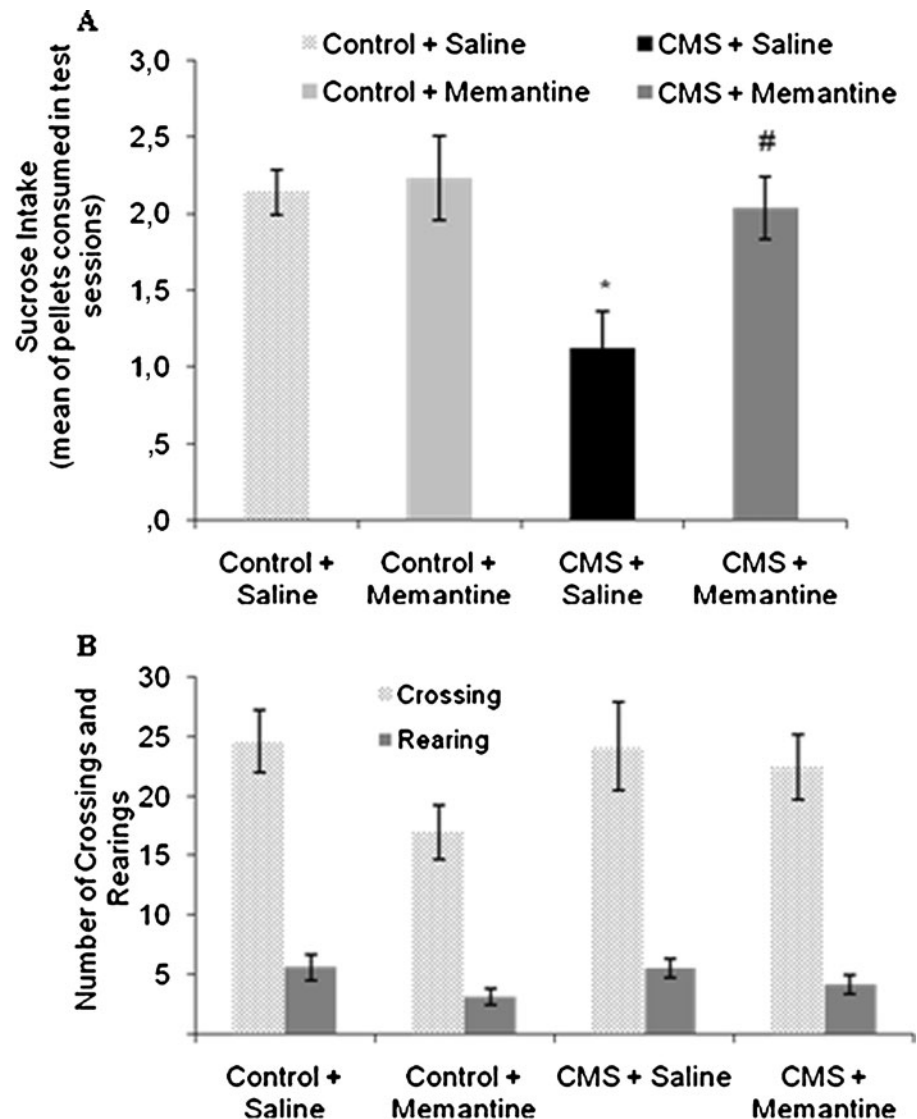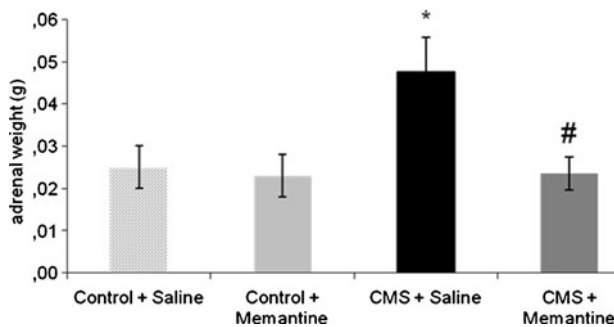
Fig. 2 Effects of CMS procedure on adrenal gland weight of rats repeatedly treated with memantine. *Bars* represent means±S.E.M. *$p<0.05$ vs. other groups; # $p<0.05$ vs. CMS saline, according to ANOVA post-hoc Tukey test

Discussion

In the present study we demonstrated that: (1) CMS rats displayed reduced sweet food intake, without significant changes in locomotor activity; (2) CMS rats displayed hypertrophy of adrenal gland, compared to non-stressed rats; (3) CMS rats displayed increase of corticosterone levels, compared to non-stressed rats; (4) administration of memantine reversed the anhedonic behavior induced by chronic stressful stimuli, and reversed the increase of adrenal gland weight and corticosterone levels; (5) memantine increased BDNF protein levels in the prefrontal cortex in CMS rats.

Memantine is used for treatment of moderate to severe Alzheimer's disease (Lipton 2004; Réus et al. 2008), it is a low-to-moderate-affinity non-competitive NMDA receptor (Rammes et al. 2008). Several recent studies have shown the role of memantine in depression. Our group recently demonstrated that acute and chronic treatments with memantine (5, 10 and 20 mg/kg) reduced immobility time in the rat forced swimming test, without affecting spontaneous locomotor activity (Réus et al. 2010). Other studies also showed that memantine enhances antidepressive-like effects in animals
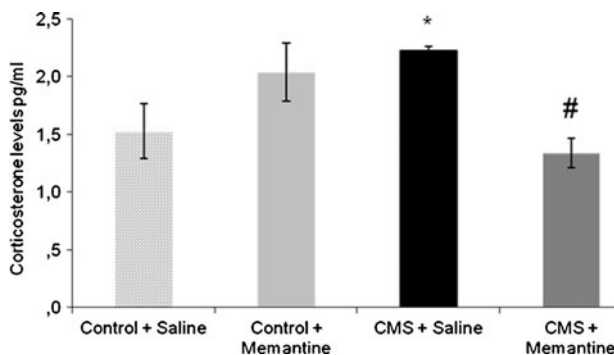

Fig. 3 Effects of CMS procedure on corticosterone circulating levels in rats repeatedly treated with memantine. *Bars* represent means±S.E.M. *$p<0.05$ vs. control saline and # $p<0.05$ vs. CMS saline, according to ANOVA post-hoc Tukey test
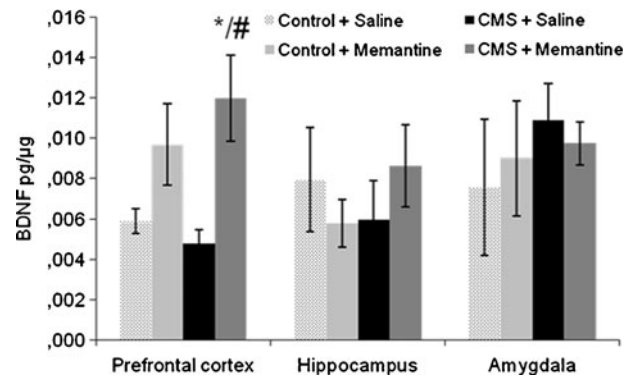

Fig. 4 Effects of CMS procedure on the BDNF levels in the rat prefrontal cortex, hippocampus and amygdala repeatedly treated with memantine. *Bars* represent means±S.E.M. */# $p<0.05$ vs. control saline and CMS saline, according to ANOVA post-hoc Tukey test

(Almeida et al. 2006; Rogóz et al. 2008). One open label study investigating the effect of memantine on depression demonstrated that the depressives symptoms improved within 1 week and reached and maintained maximal improvement from weeks 8 to 12 (Ferguson and Shingleton 2007). However, Zarate et al. (2006) in a randomized controlled trial it was concluded that memantine did not have antidepressant effects in patients with major depression.

Our results also showed that administration of memantine antagonized anhedonic behavior assessed in CMS, without affecting the consumption of sweet food in non-stressed rats. The present data is in agreement with literature studies, which show that rats exposed to the CMS procedure and treated with saline consumed less sweet food, compared to non-stressed rats treated with saline (Allaman et al. 2008; Garcia et al. 2009; Lucca et al. 2008, 2009a, b). In our data we have also shown an increase in adrenal gland weight in CMS rats, compared with non-stressed rats. Other groups also have shown an increase of rat adrenal weight after CMS paradigm (Garcia et al. 2009; Harro et al. 2001; Konarska et al. 1990; Lucca et al. 2008, 2009a, b). The hypertrophy of adrenal gland could increase corticosterone levels (O'Connor et al. 2000). In fact, we showed in this study an increase in the corticosterone levels in stressed rats. Moreover, an adaptive response to physical or psychological stress in the activation of the HPA axis, and consequently, a series of hormones are released, such as corticosterone. In addition, the high levels of glucocorticoids in the brain acting in turn to increase brain glutamate levels (Jacobs et al. 2000). In fact, glucocorticoids appear to exert their effects via a downstream action on NMDA receptors (Moghaddam et al. 1994). Additionally, in the present study memantine regulated hypertrophy of the adrenal gland and hormonal alteration, thereby; the effects of memantine in the present study may be related, at least in part, by its regulation of glucocorticoids via NMDA receptor. Indeed, glutamate antagonists can attenuate or block some of the

effects of chronic glucocorticoids excess on morphology in the hippocampus (Magariños and McEwen 1995).

Stress has profound effects on brain areas associated with mood, such as the prefrontal cortex, hippocampus and amygdala (Pittenger and Duman 2008). In the prefrontal cortex and hippocampus, both are reduced in size and activity in major depression; in contrast, in the amygdala's size and activity are increased (Drevets 2003). BDNF exerts its effects promoting the growth and development of immature neurons and enhancing the survival and function of adult neurons (Lindsay et al. 1994). The role of BDNF in depression has been extensively studied in recent years. Several forms of stress in preclinical studies, as well as postmortem human with depression reduce BDNF-mediated signaling in the hippocampus; on the other hand, chronic antidepressant treatment increases BDNF-mediated signaling (Karege et al. 2005; Nestler et al. 2002). However, the opposite effects have been shown. In fact, chronic stress increases BDNF levels in the nucleus accumbens (Berton et al. 2006). In the present study we demonstrated that the BDNF protein levels were not altered in the prefrontal cortex, hippocampus and amygdala in CMS rats, though our results have shown a tendency to decrease BDNF protein levels in the prefrontal cortex and hippocampus and to increase in the amygdala in CMS rats, suggesting that the effects of stress on BDNF levels may be related to the brain area. Allaman et al. (2008) demonstrated that exposure of the rats to the CMS paradigm does not alter BDNF mRNA expression in the hippocampus and in the basolateral amygdala, suggesting that BDNF mRNA levels were not modulated in these limbic brain structures during experimental conditions that cause anhedonia and chronic administration of the tricyclic antidepressant imipramine, which reverses CMS-induced anhedonia, does not regulate BDNF mRNA expression in the hippocampus and in the basolateral amygdala. Additionally, 7 days of treatment with antidepressant escitalopram activated intracellular pathways linked to BDNF and increased the levels of pro-BDNF in the rat prefrontal cortex (Alboni et al. 2010). In the present data we showed that 7 days of treatment with NMDA receptor antagonist memantine increased the BDNF protein levels in the prefrontal cortex from CMS rats. Fascinatingly, NMDA receptors and BDNF have important interactive actions as modulators of plasticity and survival. Furthermore, NMDA receptors play an important role in transcriptional regulation of BDNF formation (Yamada and Nabeshima 2004).

Some recent studies have demonstrated that NMDA receptor antagonists induced an increase in BDNF levels. Fluoxetine (10 mg/kg) in the hippocampus, and fluoxetine (5 and 10 mg/kg) and NMDA receptor antagonist, amantadine (10 mg/kg) in the cerebral cortex, significantly elevated the BDNF mRNA levels; in addition, joint administration of fluoxetine (5 or 10 mg/kg) and amantadine (10 mg/kg) induced a larger increase in BDNF gene expression in the cerebral cortex, but not in the hippocampus (Rogóz et al. 2009). Moreover studies from our group have shown that acute, but not chronic treatment with NMDA receptor antagonists, ketamine or memantine increase BDNF protein levels in the hippocampus (Garcia et al. 2009; Réus et al. 2010), suggesting adaptive mechanisms or the development of tolerance to the drugs effects on hippocampal levels. Additionally, Marvanová et al. (2001) showed that memantine increased BDNF mRNA levels in the limbic cortex in rat brain by in situ hybridization, suggesting new possibilities of pharmacologically regulating the expression of neurotrophic factors in the brain.

Other protective effects have been attributed to memantine. In vitro study showed that memantine in low concentrations (0.05–2 lM) could attenuate neuronal apoptosis induced by staurosporine, a protein kinases inhibitor and classical inducer of caspase 3-dependent apoptosis, in 7 day in vitro cortical neurons (Jantas-Skotniczna et al. 2006). In addition, Jantas et al. (2009) demonstrated that memantine can protect mouse primary cortical cultured neurons against staurosporine-evoked apoptosis in NMDAR-independent way by increasing phosphorylation of Akt and increasing BDNF protein level, providing a new insight into the anti-apoptotic action of memantine and its beneficial effects in chronic neurodegenerative disorders. Furthermore, memantine-injection promoted cellular proliferation in mice (Namba et al. 2010). It is important to note that memantine acts in other systems, involved with depression, such as 5-HT_3 receptor and this effect might contribute to its therapeutic efficacy (Rammes et al. 2001). However, has been shown that antidepressants, such as desipramine and fluoxetine were found to be low-affinity NMDA antagonists (Szasz et al. 2007), suggesting that classic antidepressant also acts in NMDA receptors, may contribute to the clinical effects of antidepressants.

In conclusion, our data suggest that the anhedonic behavior observed in rats subjected to chronic unpredictable stressful situations were reversed by treatment with memantine. In addition, administration of memantine reversed hypertrophy of adrenal glands, and corticosterone levels, which may have been regulated by controlling levels of glutamate by memantine. In fact, an increase in brain glucocorticoids activity can increase brain glutamate levels (Jacobs et al. 2000). Moreover memantine treatment increased BDNF protein levels in the prefrontal cortex, an effect seen by traditional antidepressant. Finally, these findings further support the hypothesis that NMDA receptor antagonists such as memantine could be helpful in the pharmacological treatment of depression. In addition, future double-blind, placebo-controlled studies would be necessary to confirm these observations in patients with major

depression and to evaluate whether memantine could be a new option for this impairment disorder.

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