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Original article

Effectiveness of memantine on depression-like behavior, memory deficits and brain mRNA levels of BDNF and TrkB in rats subjected to repeated unpredictable stress

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ABSTRACT

Background: Previous clinical and preclinical studies have indicated that the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine, has neuroprotective properties as well as antidepressant effects. The present study was designed to examine behavioral and molecular effects of memantine administration in rats subjected to the repeated unpredictable stress (RUS) paradigm.

Methods: Rats were split into four groups at random including control + saline, control + memantine, stressed + saline and stressed + memantine. After 10 days of exposure to the RUS paradigm, rats were administered memantine (20 mg/kg) intraperitoneally (*ip*) for 14 days. Depression-like behavior and memory performance were assessed by measuring immobility time in the forced swim test and passive avoidance test, respectively. The mRNA levels of BDNF and TrkB in the prefrontal cortex and hippocampus were measured by real-time quantitative PCR.

Results: Our results demonstrated that the RUS paradigm caused depression-like behavior and impairment of memory retrieval in rats. We did not find significant changes in BDNF or TrkB mRNA levels in hippocampus, but mRNA levels of TrkB in the prefrontal cortex showed a significant downregulation. Administration of memantine reversed depression-like behavior and memory impairment and significantly increased BDNF and TrkB mRNA levels in both prefrontal cortex and hippocampus of stress exposed rats.

Conclusions: Our study supports the hypothesis that drugs with antagonistic properties on the NMDA receptor, such as memantine, might be efficient in treatment of major depression. Our results also suggest that upregulated mRNA levels of BDNF and TrkB in the brain might be essential for antidepressant-like activity of memantine in stress exposed rats.

Introduction

Major depressive disorder (MDD) is a devastating psychiatric disorder that involves high morbidity and mortality and has a worldwide prevalence rate at 15–20% in the general population [1–3]. There is an increasing amount of data indicating that cognitive disturbances, such as memory impairments, are core symptoms of MDD and that antidepressant treatment may improve cognitive dysfunctions along with mood improvement [4,5]. Exposure to stressful life events is a principal risk factor for the induction and progression of a depressive episode and several studies have demonstrated that activation of hypothalamic-pituitary-adrenal (HPA) axis is the most critical causal factor of MDD [6–10]. Higher activity of the HPA axis, and enhanced cortisol levels in plasma and cerebrospinal fluid, have been reported for depressed patients and effective antidepressant treatments have been shown to restore the function of the HPA axis [11–13]. Based on these findings, the repeated unpredictable stress (RUS) paradigm was designed and has been commonly used as an animal model of depression. The model has been demonstrated to induce considerable cellular and molecular effects on the brain as well as an enhancement of plasma corticosterone levels [14–18]. Monoamine-based antidepressants are usually prescribed for treatment of MDD, particularly selective serotonin reuptake inhibitors (SSRIs) that result in enhancement of the serotonin levels[5]. But because of side effects, latency in onset of action, and

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absence of response in 30–40% of patients, their clinical efficacy is low [19]. For these reasons novel, alternative, rapid acting and more effective antidepressant drugs are urgently needed. There is considerable evidence that increased glutamatergic neurotransmission plays an important role in the pathophysiology of depression [20]. Thus glutamate levels in blood, cerebrospinal fluid (CSF) and in the brain of depressed patients have been found to be elevated compared to healthy controls [21]. Notably, it has been described that glutamate through the NMDA subtype of ionotropic glutamate receptors (NMDAR) mediate normal physiological neural activities, however, in pathological conditions overactivation of NMDA receptors lead to neurotoxicity and neuronal damage in many neurological diseases [22]. Interestingly, antagonists of NMDA receptor such as memantine and ketamine have displayed antidepressive properties in several preclinical and clinical studies [19,23,24–31]. Ketamine, a high-affinity NMDA receptor antagonist, have a rapid and substantial therapeutic effect, however, the antidepressant effects of ketamine in MDD patients are transient and ketamine has severe adverse effects such as psychotomimetic and cognitive effects, which has limited its chronic use [32]. In contrast, memantine is a low-affinity non-competitive blocker of NMDA receptors and a safe and well-tolerated agent that clinically is prescribed for patients with Alzheimer's disease [33,34]. Unlike other NMDA receptor antagonists, memantine has neuroprotective properties that efficiently blocks excitotoxicity induced by hyperactivity of the NMDA receptors at therapeutically doses, thus restoring normal neurotransmission [22,35]. Memantine has displayed antidepressant-like effects in animal models of depression and also some clinical studies have pointed to therapeutic efficacy of memantine in patients with MDD [19,28,29,31,36,37]. However, the molecular mechanisms underlying the antidepressive properties of memantine in animal and clinical studies still have not been fully explored. In a previous pre-clinical study, memantine enhanced levels of brain-derived neurotrophic factor (BDNF) in the prefrontal cortex and normalized anhedonic behavior and corticosterone levels in a chronic mild stress (CMS) model of depression [36]. In addition, several studies have reported that stress diminishes the expression of BDNF in brain structures related to depression and antidepressants increases mRNA level of BDNF and its receptor, tyrosine kinase-coupled receptor (TrkB) reversing the effects of stress [36,38,39]. BDNF-TrkB signaling is known to be involved in synaptic plasticity and neuronal survival. Furthermore, according to the neurotrophic hypothesis of depression, reduced levels of BDNF in the hippocampus and frontal cortex is believed to be an essential causal factor for depression and upregulation of BDNF may be crucial for the therapeutic effects of antidepressant treatment [39,40]. Additionally, reduced levels of BDNF and other neurotrophic factors might play a role in atrophy of hippocampus and prefrontal cortex of patients with depression, brain areas known to be involved in learning and memory [39,41].

These studies lead us to a hypothesis that the antidepressive properties of memantine probably are caused by changes in gene expression of BDNF/TRKB signaling in the hippocampus and prefrontal cortex. Therefore, the current study was designed in order to investigate molecular mechanisms underlying antidepressant-like effects of chronic use of memantine in rats exposed to the repeated unpredictable stress paradigm.

Materials and methods

Animals

A total of 60 adult male Wistar rats weighing 250–270 g were housed 4 per cage (60 × 35 × 21 cm) except when isolation was employed as a stressor. Animals were kept at (22 ± 2 °C), on standard 12/12 h light/dark cycle, with lights on from 7 a.m. to 19 p.m., except when a reversed light/dark cycle was applied during the stress regime. Food and water was accessible ad libitum except when food or/and water deprivation was applied as a stress factor. The Ethic Committee of University approved the protocol of study and all experiments were conducted consistent with rules of the National Institutes of Health Guide for the care and Use of Laboratory Animals (NIH publications no. 80-23; revised 1996). All efforts were made to minimize the number of rats used.

Repeated unpredictable stress and drug injection

The RUS procedure was conducted for 10 days applying eight different kinds of stressors including: food deprivation, water deprivation, cage tilt, reversed light/dark cycle, isolation, group-housed in soiled cage, tail pinch in restrainer and restraint stress. Two of eight different stressors were presented to rats twice daily in an unpredictable sequential order, and at irregular times, according to an established paradigm [15,17,18]. Control rats were housed in their home cages during the 10-day period. The RUS procedure was stopped after 10 days and then *ip* injection of saline or memantine hydrochloride at a dose of 20 mg/kg (Sigma-Aldrich, Germany) was initiated once a day over 14 days. The drug treatment was administered in a volume of 1 ml/kg. The rats were randomly divided into 4 groups (n = 15 per group) including: control + saline; control + memantine; stressed + saline; stressed + memantine. The dose of 20 mg/kg of memantine applied in the present study was in accordance with previous studies [28,29,36]. Table 1 outlines the RUS paradigm and study design.

Forced swim test (FST)

FST was based on previous reports [24,26,42] and involves two individual exposures to swimming in a cylindrical transparent tank (tall: 80 cm; diameter:30 cm). The tank was half-filled with water (22–23 °C) to prevent rats touching the bottom of the tank. During pre-test session, rats did forced exposure to the water tank for 15 min 24 h after the pre-test session, the rats were tested for 5 min (test session), and the immobility time of rats were recorded in seconds. Memantine or saline was injected 60 min before the test session. First exposure to FST (pre-test session) was done on day 13 of chronic drug treatment, after the training phase in the passive avoidance test. On the 14th day, the last *ip* injections were performed and after 60 min the passive avoidance test was repeated. 5 min later the immobility time was recorded by exposure to 5 min swimming test.

Passive avoidance test

A step-through passive avoidance task was applied on days 13 and 14 of chronic drug treatment, 1 h after the last *ip* drug administration, to evaluate memory retention. The task procedure consisted of two phases: a training or acquisition phase and a retention phase with an inter-phase interval of 24 h. The step-through device comprised of two compartments, one bright and one black, of equal size (20 × 20 × 30 cm) detached *via* a decapitate door (7 × 9 cm). In the black chamber there was a grid floor built of stainless steel (2.5 mm in thickness) for delivery of 50 Hz electric shocks with 1 mA intensity for 3 s. A training trial was performed according to Monleon et al. [43]. On the first day of training (preacquisition trial), each rat was located in the bright section of the apparatus in a gentle way and after 30 s the door between two chambers was opened and the animal was able to move freely into the black section. When the animals completely entered into the black section, the door joining two chambers was closed and the rats were immediately removed to their homecages. The training

Table 1
Repeated Unpredictable Stress Paradigm and Experimental Schedule.

Day	1st stressor		2nd stressor	
	Time	Type	Time	Type
1	8 AM	food deprivation (24 h)	7 PM	Isolation housing (overnight)
2	10 AM	cage tilt (45°, 7 h)	5 PM	30-min restraint
3	8 AM	tail pinch in restrainer (1 min)	7 PM	group-housed in soiled cage (overnight)
4	8 AM	reversed light/dark cycle (24 h)	7 PM	30-min restraint
5	9 AM	water deprivation (24 h)	1 PM	tail pinch in restrainer (1 min)
6	8 AM	food deprivation (24 h)	7 PM	group-housed in soiled cage (overnight)
7	9 AM	reversed light/dark cycle (24 h)	7 PM	Isolation housing (overnight)
8	9 AM	water deprivation (24 h)	4 PM	30-min restraint
9	10 AM	reversed light/dark cycle (24 h)	7 PM	tail pinch in restrainer (1 min)
10	10 AM	cage tilt (45°, 7 h)	7 PM	Isolation housing (overnight)
11–24	Drug administration without stress			
23	training phase of Passive Avoidance Test pre-test session of Forced Swim Test			
24	retention phase of Passive Avoidance Test test session of Forced Swim Test Euthanize and collect samples			

(acquisition) phase was carried out 15 min after the preacquisition phase. In the training phase, after a 30 s adaptation period, the door between two chambers was opened and as soon as the rat paced into the dark chamber, the door was closed and a foot shock was applied (50 Hz, 1 mA, 3 s). The time delay before entering into the dark chamber was measured as the training latency. The rat was allowed to remain in the dark chamber for 20 s and was then removed. The recall of this aversive event, denoted inhibitory avoidance memory, was assessed 24 h after the training phase, and the step-through latency was recorded for each animal as an index of memory retention. The retention test was terminated when the animal stepped into the dark chamber or stayed in the light chamber for more than 300 s. During the retention phase the electric shock was not delivered.

Real-time quantitative PCR (qPCR)

2 h after the last drug administration, control rats and groups exposed to stress were decapitated, brains were removed, and prefrontal cortex and hippocampal tissue were immediately dissected, snap frozen on dry ice, and kept at −80 °C until further downstream analysis in order to quantify mRNA expression of BDNF and TrkB. Total mRNA was isolated from 50 to 100 mg of hippocampus and frontal cortex tissue using the Trizol™ Isolation Reagent Kit (Life Technologies, Carlsbad, CA, USA) in accordance with the instructions of manufacturer. Content and purity of extracted RNA was verified using spectrophotometry (Biochrom, UK). Synthesis of cDNA was performed by a reverse transcription kit based on the manufacturer's protocols (SuperScript III, Life Technologies, Carlsbad, CA, USA). Design of primers was performed using Primer-Blast software and Rattus norvegicus genome sequence data on the National Center for Biotechnology Information (NCBI) website. Table 2 shows Primer sequences of BDNF, TrkB and β-actin genes. qPCR was performed in triplicate by the QuantiTect® SYBR® Green PCR mastermix reagent kit (Ampliqon, Denmark) using StepOneplus Real-Time apparatus (Applied Biosystems, USA). The relative gene expression of the BDNF and TrkB was normalized to β-actin as the reference gene. The data analysis was performed by the comparative C(T) method [44].

Statistical analyses

All results were expressed as the mean ± SEM. Statistical analysis was carried out using a Kruskal-Wallis test followed by a Mann-Whitney *U* test in order to compare differences in the immobility time, training and retention latencies and mRNA levels of BDNF and TrkB between experimental groups. Statistical significance for all analyses was considered at *p*-value <0.05. Analysis of data was carried out using SPSS software (version 20).

Results

The Kruskal-Wallis test showed that the four groups are overall significant different regarding immobility time in the forced swim test ($\chi^2 = 34.890$, df = 3, $p < 0.001$). The Mann-Whitney test indicated a significantly increased immobility time of saline treated, stressed rats compared to the control group ($p < 0.001$; Fig. 1). The Mann-Whitney test also showed that 14 days of memantine treatment (20 mg/kg) significantly normalized the immobility time of stressed rats compared to the saline treated, stressed rats ($p < 0.001$; Fig. 1).

The Kruskal-Wallis test also revealed a significant difference in training latency (on day 1) ($\chi^2 = 31.555$, df = 3, $p < 0.001$) and retention latency (after 24 h) ($\chi^2 = 34.446$, df = 3, $p < 0.001$) among the four groups. The effects of the RUS paradigm and chronic administration of memantine on the training latency and retention latency in the step-through passive avoidance test are illustrated in Fig. 2. The Mann-Whitney test indicated that rats exposed to RUS have a significantly reduced training latency compared to non-stressed rats ($p < 0.001$, Fig. 2a). Interestingly, the treatment of stressed rats with memantine increased training latency relative to saline treated, stressed rats ($p < 0.001$, Fig. 2a). Furthermore stressed rats showed significantly shorter retention latency compared to control rats ($p < 0.001$, Fig. 2b). The Mann-Whitney

Table 2
Primer sequences of BDNF, TrkB and β-actin genes.

Gene	Forward primer	Reverse primer	Product length
BDNF	5′–CAATCGAAGCTCAACCGAAGAG –3′	5′– AACCCGGTCTCATCAAAGCC –3′	214 bp
TrkB	5′–CCAAGTTTGGCATGAAAGGTTTTG–3′	5′–GCAACAGTAGTCCCAGGAGTT–3′	139 bp
β-actin	5′– ACCCGCGAGTACAACCTTCT –3′	5′–ATACCCACCATCACACCCTGG –3′	203 bp

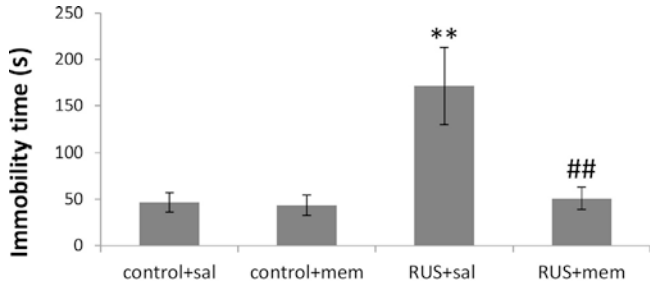

Fig. 1. The effects of the 14 days memantine administration (20 mg/kg) on the immobility time in the forced swim test in rats exposed to repeated unpredictable stress (RUS) paradigm. Bars illustrate means ± SEM. $^{**}p < 0.001$ *vs.* control + saline, ## $p < 0.001$ *vs.* RUS + saline, according to Mann-Whitney *U* test.

test indicated that chronic administration of memantine significantly increased retention latency in stressed rats as compared to that shown by saline treated, stressed rats ($p < 0.001$, Fig. 2b). The decrease in step-through latencies suggest impaired memory retention in the passive avoidance test.

The hippocampal mRNA levels of BDNF and TrkB are shown in Fig. 3. The Kruskal-Wallis test indicated a significant difference in mRNA expression levels of BDNF ($\chi^2 = 50.280$, df = 3, $p < 0.001$) and TrkB ($\chi^2 = 49.684$, df = 3, $p < 0.001$) in the hippocampus among the four groups. The Mann-Whitney test indicated that saline treated, stressed rats are not significantly different with respect to mRNA levels of BDNF and TrkB, in the hippocampus, in comparison with the control group ($p > 0.05$; Fig. 3), however, memantine administration to rats exposed to the RUS paradigm augmented mRNA levels of BDNF and TrkB, in the hippocampus, in comparison with all remaining groups ($p < 0.001$; Fig. 3). Interestingly, control

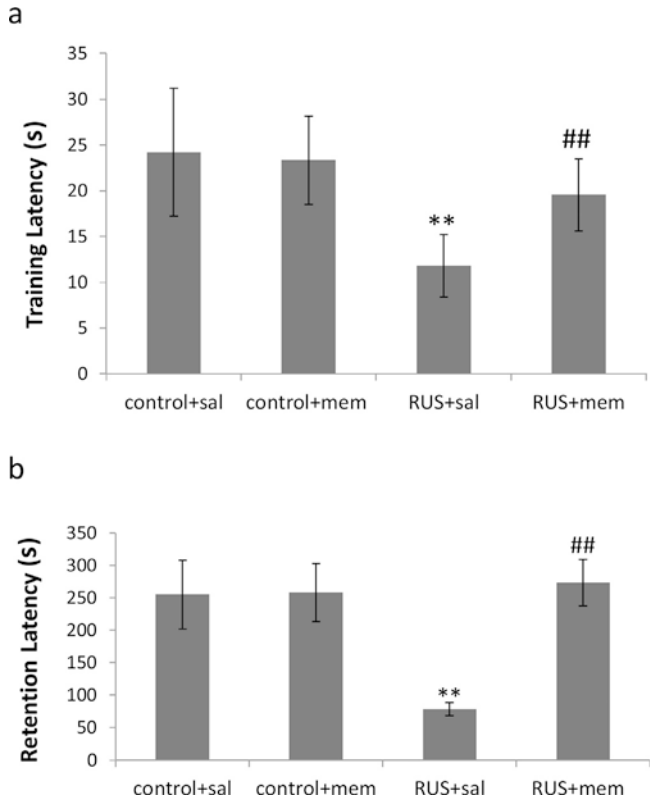

Fig. 2. The effects of the 14 days memantine administration (20 mg/kg) on latency to go into the dark chamber during training (a) or retention phase (b) in the passive avoidance test in rats subjected to repeated unpredictable stress (RUS) procedure. Bars illustrate means ± SEM. $^{**}p < 0.001$ *vs.* control + saline, ## $p < 0.001$ *vs.* RUS + saline, according to the Mann-Whitney *U* test.

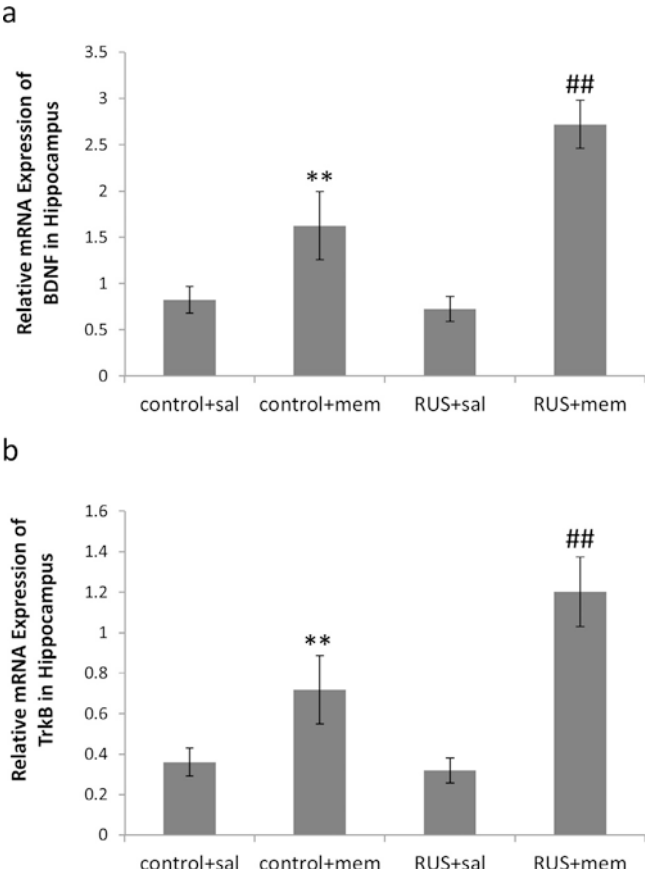

Fig. 3. The effects of the 14 days memantine administration (20 mg/kg) on the mRNA levels of BDNF (a) or TrkB (b) in the hippocampus of rats subjected to repeated unpredictable stress (RUS) paradigm. Bars illustrate means ± SEM. $^{**}p < 0.001$ *vs.* control + saline, ## $p < 0.001$ *vs.* RUS + saline, according to Mann-Whitney *U* test.

rats treated with memantine showed significantly augmented hippocampal BDNF and TrkB mRNA levels relative to saline treated control rats ($p < 0.001$; Fig. 3).

Fig. 4 illustrates prefrontal cortex mRNA levels of BDNF and TrkB. The Kruskal-Wallis test revealed an overall statistically significant difference in mRNA expression levels of BDNF ($\chi^2 = 50.087$, df = 3, $p < 0.001$) and of TrkB ($\chi^2 = 51.320$, df = 3, $p < 0.001$) in prefrontal cortex. Statistical analyses revealed that the RUS paradigm did not affect BDNF mRNA levels in the prefrontal cortex of stressed rats compared to control rats ($p > 0.05$; Fig. 4a). But the Mann-Whitney test did show that the RUS paradigm decreased mRNA levels of TrkB, in the prefrontal cortex, of stressed rats compared to saline treated control rats ($p < 0.01$; Fig. 4b). Stressed rats receiving memantine chronically was shown to have significantly augmented mRNA levels of BDNF and TrkB, in the prefrontal cortex, compared to vehicle treated, stressed rats ($p < 0.001$; Fig. 4). Interestingly, non-stressed rats injected with memantine showed significantly increased mRNA levels of BDNF and TrkB in the prefrontal cortex when compared to saline treated non-stressed rats ($p < 0.001$; Fig. 4).

Discussion

The intention of the current study was to track some of the mechanisms underlying antidepressant-like properties of memantine in rats with depression-like symptoms induced by exposure to stress. The present study demonstrated that: (1) RUS exposed rats have increased immobility time in the forced swim test; (2)

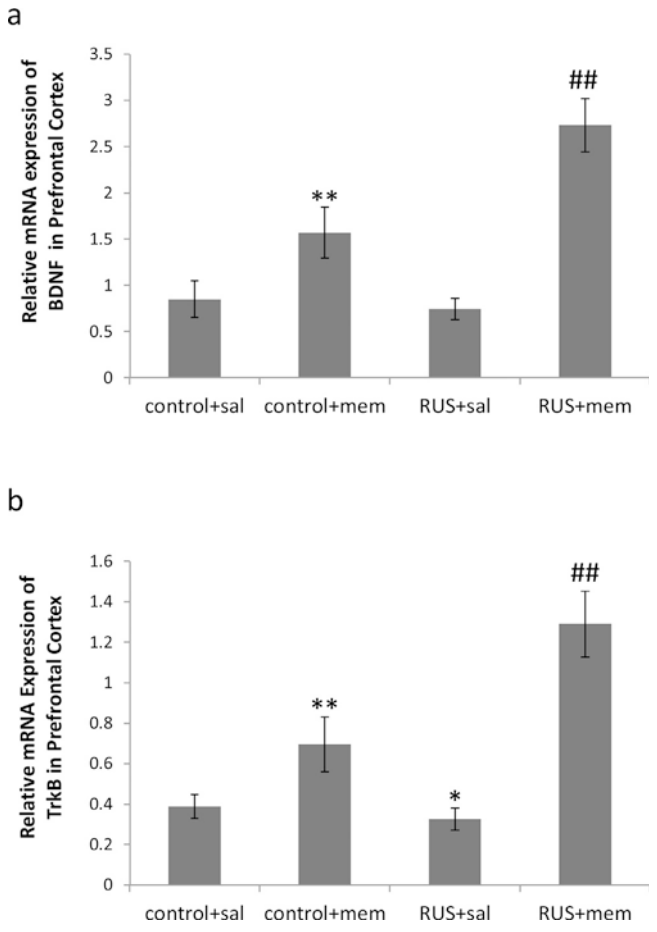

Fig. 4. The effects of the 14 days memantine administration (20 mg/kg) on the mRNA levels of BDNF (a) or TrkB (b) in the prefrontal cortex of rats subjected to repeated unpredictable stress (RUS) paradigm. Bars illustrate means ± SEM. $^{**}p < 0.001$ *vs.* control + saline, ## $p < 0.001$ *vs.* RUS + saline, * $p < 0.01$ *vs.* control + saline, according to the Mann-Whitney *U* test.

administration of memantine decreased the immobility time induced by stressful stimuli; (3) RUS rats showed reduced training latency in the passive avoidance test; (4) injection of memantine increased the training latency induced by repeated unpredictable stress; (5) RUS rats showed reduced retention latency in the passive avoidance test; (6) treatment with memantine increased the retention latency induced by RUS protocol; (7) memantine increased BDNF mRNA levels in the prefrontal cortex and hippocampus of non-stressed rats; (8) memantine increased TrkB mRNA levels in the prefrontal cortex and hippocampus of non-stressed rats; (9) memantine increased BDNF mRNA levels in prefrontal cortex and hippocampus of RUS rats; (10) RUS exposed rats did not show significant changes in BDNF mRNA levels in the prefrontal cortex and hippocampus; (11) RUS exposed rats revealed decreased mRNA expression of TrkB in the prefrontal cortex; (12) memantine increased mRNA level of TrkB in both brain regions in RUS exposed rats.

Our findings are consistent with a previous study that has shown memantine significantly raised BDNF and TrkB mRNA levels in the cerebral cortex, cingulate, retrosplenial, and entorhinal cortices in the rat brain [45]. Additionally, our results are in agreement with several studies reported previously, that demonstrate agents with antagonistic properties on the NMDA receptor, such as amantadine, memantine and ketamine, which in combination with traditional antidepressants decrease immobility time and significantly upregulate protein levels and mRNA expression of BDNF in the rat brain [46–48]. This feature of NMDA receptor antagonists in alteration of BDNF levels underpin the hypothesis that glutamatergic activation of the NMDA receptor is implicated in the regulation of BDNF levels in the brain [29,48]. Our findings also show that memantine is capable of reversing increased immobility time of stress exposed rats in the forced swim test to a comparable level of vehicle treated control rats. our data are in accordance with previous studies demonstrating that chronic stress induce depression-like behavior in rats and that chronic injection of memantine (20 mg/kg) lead to antidepressant-like activity in stressed rats [28,36]. Moreover, similar to previous studies, we observed that chronic stress does not affect BDNF levels in the rat brain [49]. However, some studies reported a downregulation of BDNF mRNA levels in the prefrontal cortex and hippocampus of the stressed rats [50–52]. The reason for this inconsistency is not clear, however, it has been suggested that some conditions, such as duration and severity of stressors as well as age of rats, might influence the levels of BDNF and its receptor, TrkB [52].

Interestingly, our results demonstrate that chronic treatment with memantine significantly increases BDNF and TrkB mRNA levels of both the hippocampus and prefrontal cortex of stressed rats. The present findings are in agreement with previous studies which suggested that increased BDNF and TrkB mRNA levels are a common antidepressant mechanism of action [38]. Our findings suggest that increased expression of BDNF and TrkB is involved in the molecular mechanism underlying antidepressant properties of memantine. In this regard, behavioral studies have shown that injection of BDNF into the brain generates antidepressant effects in behavioral depression tests [53,54]. In addition, it has been suggested that BDNF is implicated in the cellular and behavioral responses to stress [55,56]. Thus it has been proposed that downregulation of BDNF is implicated in stress induced neuronal atrophy in hippocampus [55,56]. BDNF belongs to the family of growth factors that has considered as an essential factors in differentiation, development, plasticity and survival of hippocampal neurons in the developing and adult brains [57]. It has demonstrated that repeated stress can produce neuronal death and atrophy in hippocampus and chronic treatment with the antidepressant tianeptine has been shown to avert such neuronal atrophy induced by stress [58–60]. Future studies are warranted to examine if chronic treatment with memantine has similar neuroprotective effects against chronic stress induced neuronal atrophy. In addition, our data show that RUS-exposed rats have significantly impaired memory retrieval in the passive avoidance test. Our findings are similar to previous evidence suggesting that chronic stress paradigms have a detrimental influence on learning and memory [61]. Disturbances in both HPA axis and cognitive functions, including learning and memory dysfunctions, are core elements in MDD and might be related to structural abnormalities induced by chronic stress in the hippocampus and the PFC [39,61,62]. It has been shown that BDNF is involved in long-term potentiation (LTP), a cellular type of synaptic plasticity resulting from long-term, activity-dependent alterations in the synaptic strength suggesting required molecular processes for formation of memory traces [63,64]. Several studies have shown that stress change LTP and synaptic plasticity and the NMDA receptor has a primary role in regulation of synaptic plasticity and LTP in the hippocampus [64].

Interestingly, in the present study, chronic treatment with memantine ameliorated memory impairments induced by the RUS protocol in rats. In contrast to memantine different classes of antidepressants have been found to impair memory function and consequently this has been designated as an SSRIs adverse effect [4,65]. Memory enhancing properties of memantine, observed in our study, may be attributable to our findings that the antidepressant mechanism underlying the action of memantine

is by increasing expression levels of BDNF and TrkB in the hippocampus and prefrontal cortex of RUS exposed rats. Actually, decreased BDNF and TrkB mRNA levels in response to stress and associated neuronal atrophy in two limbic structures, hippocampus and prefrontal cortex, and consequently their volume loss may underlie disturbances in memory and cognition in depressed subjects [39,66,67]. It has been demonstrated that chronic unpredictable stress may induce impairment of LTP in the prefrontal cortex, and memantine partially diminishes the deficit of synaptic plasticity induced by stress, suggesting LTP in the prefrontal cortex is NMDA receptor dependent [28]. On the other hand, it has been hypothesized that stressful events, probably through enhancement of release of glucocorticoids, stimulate glucocorticoid receptors (GRs) as well as receptors of corticotropin-releasing hormone (CRH) on the neurons and astrocytes and consequently leads to the retraction of synapses in the prefrontal cortex [68]. Glucocorticoids probably act by causing enhancement of glutamate release and hyperstimulation of NMDA receptors on the synaptic spines which consequently results in loss of synaptic spines and ultimately induces synaptic retraction [68]. The impact of glutamate excitotoxicity on the loss of synaptic spines possibly results in malfunctioning of cortical neural networks associated with major depression [21]. It has been demonstrated that memantine effectively blocks excessive activation of NMDA receptors and through the blockade of excitotoxicity the increased production of BDNF, and activation of the BDNF receptor TrkB in the brain, exerts its neuroprotctive properties [22,35,45].

Conclusion

Our data shows that increased immobility time in the forced swim test, in rats exposed to repeated unpredictable stressful stimuli, were diminished by administration of memantine. Moreover, the administration of memantine improved impairment of memory retrieval on the passive avoidance test, and increased mRNA levels of BDNF and TrkB in hippocampus and prefrontal cortex. We suggest further investigations to focus on: (1) clarification of the mechanisms underlying antidepressant properties of memantine; (2) dose-response assessments of chronic administration of memantine on learning and memory disturbances in animal models of depression. Finally, our findings strengthen the hypothesis that the NMDA receptor antagonist, memantine, may be effective in treatment of major depression and support the progression of new glutamatergic drugs with faster and stronger antidepressant properties.

Conflicts of interest

The authors report having no potential conflicts of interest.

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References

[1] Cuijpers P., Smit F. Excess mortality in depression: a meta-analysis of community studies. J Affect Disord 2002;72:227–36.
[2] Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry 2005;62:593–602.
[3] Murray CJL, Lopez AD. Global mortality, disability, and the contribution of risk factors: global burden of disease study. Lancet 1997;349:1436–42.
[4] Mutlu O, Ulak G, Çelikyurt IK, Akar FY, Erden F. Effects of citalopram on cognitive performance in passive avoidance, elevated plus-maze and three-panel runway tasks in naïve rats. Chin J Physiol 2011;54:36–46.
[5] Ulak G, Göçmez S, Erden F, Tanyeri P, Utkan T, Yildiz F, et al. Chronic administration of fluoxetine or venlafaxine induces memory deterioration in an inhibitory avoidance task in rats. Drug Dev Res 2006;67:456–61.
[6] McEwen BS. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. Metabolism 2005;54:20–3.
[7] Van Praag HM. Can stress cause depression? Prog Neuro-Psychopharmacology Biol Psychiatry 2004;28:891–907.
[8] Pariante CM. Depression, stress and the adrenal axis. J Neuroendocrinol 2003;15:811–2.
[9] Kendler KS, Thornton LM, Gardner CO. Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. Am J Psychiatry 2001;158:582–6.
[10] Charney DS, Manji HK. Life stress, genes, and depression: multiple pathways lead to increased risk and new opportunities for intervention. Sci Stke 2004;225.
[11] Holsboer F, Barden N. Antidepressants and hypothalamic-pituitary-adrenocortical regulation. Endocr Rev 1996;17:187–205.
[12] Linkowski P, Mendlewicz J, Leclercq R, BRASSEUR M, Hubain P, GOLSTEIN J, et al. The 24-hour profile of adrenocorticotropin and cortisol in major depressive illness. J Clin Endocrinol Metab 1985;61:429–38.
[13] Holsboer F, Gerken A, Stalla GK, Müller OA. ACTH, cortisol, and corticosterone output after ovine corticotropin-releasing factor challenge during depression and after recovery. Biol Psychiatry 1985;20:276–86.
[14] Kosten TA, Galloway MP, Duman RS, Russell DS, D'sa C. Repeated unpredictable stress and antidepressants differentially regulate expression of the bcl-2 family of apoptotic genes in rat cortical, hippocampal, and limbic brain structures. Neuropsychopharmacology 2008;33:1545–58.
[15] Perrotti LI, Hadeishi Y, Ulery PG, Barrot M, Monteggia L, Duman RS, et al. Induction of (FosB in reward-related brain structures after chronic stress. J Neurosci 2004;24:10594–602.
[16] Heine VM, Maslam S, Zareno J, Joëls M, Lucassen PJ. Suppressed proliferation and apoptotic changes in the rat dentate gyrus after acute and chronic stress are reversible. Eur J Neurosci 2004;19:131–44.
[17] Ortiz J, Fitzgerald LW, Lane S, Terwilliger R, Nestler EJ. Biochemical adaptations in the mesolimbic dopamine system in response to repeated stress. Neuropsychopharmacology 1996;14:443–52.
[18] Willner P, Muscat R, Papp M. Chronic mild stress-induced anhedonia: a realistic animal model of depression. Neurosci Biobehav Rev 1992;16:525–34.
[19] Ferguson JM, Shingleton RN. An open-label, flexible-dose study of memantine in major depressive disorder. Clin Neuropharmacol 2007;30:136–44, doi: http://dx.doi.org/10.1097/WNF.0b013e3180314ae7.
[20] Kim Y-K, Na K-S. Role of glutamate receptors and glial cells in the pathophysiology of treatment-resistant depression. Prog Neuro-Psychopharmacol Biol Psychiatry 2016;70:117–26.
[21] Hashimoto K. Emerging role of glutamate in the pathophysiology of major depressive disorder. Brain Res Rev 2009;61:105–23, doi:http://dx.doi.org/10.1016/j.brainresrev.2009.05.005.
[22] Xia P, Chen HV, Zhang D, Lipton SA. Memantine preferentially blocks extrasynaptic over synaptic NMDA receptor currents in hippocampal autapses. J Neurosci 2010;30:11246–50, doi:http://dx.doi.org/10.1523/JNEUROSCI.2488-10.2010.
[23] Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000;47:351–4.
[24] Garcia LSB, Comim CM, Valvassori SS, Réus GZ, Barbosa LM, Andreazza AC, et al. Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. Prog Neuro-Psychopharmacol Biol Psychiatry 2008;32:140–4, doi:http://dx.doi.org/10.1016/j.pnpbp.2007.07.027.
[25] Garcia LSB, Comim CM, Valvassori SS, Réus GZ, Stertz L, Kapczinski F, et al. Ketamine treatment reverses behavioral and physiological alterations induced by chronic mild stress in rats. Prog Neuro-Psychopharmacol Biol Psychiatry 2009;33:450–5.
[26] Garcia LS, Comim CM, Valvassori SS, Réus GZ, Andreazza AC, Stertz L, et al. Chronic administration of ketamine elicits antidepressant-like effects in rats without affecting hippocampal brain-derived neurotrophic factor protein levels. Basic Clin Pharmacol Toxicol 2008;103:502–6.
[27] Moryl E, Danysz W, Quack G. Potential antidepressive properties of amantadine, memantine and bifemelane. Pharmacol Toxicol 1993;72:394–7, doi:http://dx.doi.org/10.1111/j.1600-0773.1993. tb01351.x.
[28] Quan M-N, Zhang N, Wang Y-Y, Zhang T, Yang Z. Possible antidepressant effects and mechanisms of memantine in behaviors and synaptic plasticity of a depression rat model. Neuroscience 2011;182:88–97.
[29] Réus GZ, Stringari RB, Kirsch TR, Fries GR, Kapczinski F, Roesler R, et al. Neurochemical and behavioural effects of acute and chronic memantine administration in rats: further support for NMDA as a new pharmacological target for the treatment of depression? Brain Res Bull 2010;81:585–9, doi: http://dx.doi.org/10.1016/j.brainresbull.2009.11.013.

[30] Zarate CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A Randomized Trial of an NMDA antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006;63:856–64, doi:http://dx.doi.org/10.1001/archpsyc.63.8.856.
[31] Amidfar M, Khiabany M, Kohi A, Salardini E, Arbabi M, Roohi Azizi M, et al. Effect of memantine combination therapy on symptoms in patients with moderate-to-severe depressive disorder: randomized, double-blind, placebo-controlled study. J Clin Pharm Ther 2017;42:44–50.
[32] Katalinic N, Lai R, Somogyi A, Mitchell PB, Glue P, Loo CK. Ketamine as a new treatment for depression: a review of its efficacy and adverse effects. Aust New Zeal J Psychiatry 2013;47:710–27.
[33] Kavirajan H. Memantine: a comprehensive review of safety and efficacy. Expert Opin Drug Saf 2009;8:89–109.
[34] Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333–41.
[35] Volbracht C, Van Beek J, Zhu C, Blomgren K, Leist M. Neuroprotective properties of memantine in different in vitro and in vivo models of excitotoxicity. Eur J Neurosci 2006;23:2611–22, doi:http://dx.doi.org/10.1111/j.1460-9568.2006.04787.x.
[36] Réus GZ, Abelaira HM, Stringari RB, Fries GR, Kapczinski F, Quevedo J. Memantine treatment reverses anhedonia, normalizes corticosterone levels and increases BDNF levels in the prefrontal cortex induced by chronic mild stress in rats. Metab Brain Dis 2012;27:175–82.
[37] Rogóz Z, Skuza G, Maj J, Danysz W. Synergistic effect of uncompetitive NMDA receptor antagonists and antidepressant drugs in the forced swimming test in rats. Neuropharmacology 2002;42:1024–30, doi:http://dx.doi.org/10.1016/S0028-3908(02)00055-2.
[38] Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci 1995;15:7539–47.
[39] Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry 2006;59:1116–27.
[40] Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron 2002;34:13–25.
[41] Sandi C, Woodson JC, Haynes VF, Park CR, Touyarot K, Lopez-Fernandez MA, et al. Acute stress-induced impairment of spatial memory is associated with decreased expression of neural cell adhesion molecule in the hippocampus and prefrontal cortex. Biol Psychiatry 2005;57:856–64.
[42] Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. Nature 1977;266:730–2, doi:http://dx.doi.org/10.1038/266730a0.
[43] Monleón S, Vinader-Caerols C, Arenas MC, Parra A. Antidepressant drugs and memory: insights from animal studies. Eur Neuropsychopharmacol 2008;18:235–48.
[44] Schmittgen TD, Livak KJ. Analyzing real-time PCR data by the comparative CT method. Nat Protoc 2008;3:1101–8.
[45] Marvanová M, Lakso M, Pirhonen J, Nawa H, Wong G, Castrén E. The neuroprotective agent memantine induces brain-derived neurotrophic factor and trkB receptor expression in rat brain. Mol Cell Neurosci 2001;18:247–58, doi:http://dx.doi.org/10.1006/mcne.2001.1027.
[46] Réus GZ, Stringari RB, Ribeiro KF, Ferraro AK, Vitto MF, Cesconetto P, et al. Ketamine plus imipramine treatment induces antidepressant-like behavior and increases CREB and BDNF protein levels and PKA and PKC phosphorylation in rat brain. Behav Brain Res 2011;221:166–71, doi:http://dx.doi.org/10.1016/j.bbr.2011.02.024.
[47] Rogoz Z, Skuza G, Legutko B. Repeated co-treatment with fluoxetine and amantadine induces brain-derived neurotrophic factor gene expression in rats. Pharmacol Rep 2008;60:817–26.
[48] Amidfar M, Réus GZ, Quevedo J, Kim Y-K, Arbabi M. Effect of co-administration of memantine and sertraline on the antidepressant-like activity and brain-derived neurotrophic factor (BDNF) levels in the rat brain. Brain Res Bull 2017;128:29–33.
[49] Kuroda Y, McEwen BS. Effect of chronic restraint stress and tianeptine on growth factors, growth-associated protein-43 and microtubule-associated protein 2 mRNA expression in the rat hippocampus. Mol Brain Res 1998;59:35–9.
[50] Rasmusson AM, Shi L, Duman R. Downregulation of BDNF mRNA in the hippocampal dentate gyrus after re-exposure to cues previously associated with footshock. Neuropsychopharmacology 2002;27:133–42.
[51] Xu H, Chen Z, He J, Haimanot S, Li X, Dyck L, et al. Synergetic effects of quetiapine and venlafaxine in preventing the chronic restraint stress-induced decrease in cell proliferation and BDNF expression in rat hippocampus. Hippocampus 2006;16:551–9.
[52] Shi S-S, Shao S, Yuan B, Pan F, Li Z-L. Acute stress and chronic stress change brain-derived neurotrophic factor (BDNF) and tyrosine kinase-coupled receptor (TrkB) expression in both young and aged rat hippocampus. Yonsei Med J 2010;51:661–71.
[53] Siuciak JA, Lewis DR, Wiegand SJ, Lindsay RM. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). Pharmacol Biochem Behav 1997;56:131–7, doi:http://dx.doi.org/10.1016/S0091-3057(96)00169-4.
[54] Shirayama Y, AC-H Chen, Nakagawa S, Russell DS, Duman RS. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci 2002;22:3251–61 20026292.
[55] Duman RS, Malberg J, Nakagawa S, D'Sa C. Neuronal plasticity and survival in mood disorders. Biol Psychiatry 2000;48:732–9.
[56] Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. Arch Gen Psychiatry 1997;54:597–606.
[57] Lewin GR, Barde Y-A. Physiology of the neurotrophins. Annu Rev Neurosci 1996;19:289–317.
[58] Watanabe Y, Gould E, Daniels DC, Cameron H, McEwen BS. Tianeptine attenuates stress-induced morphological changes in the hippocampus. Eur J Pharmacol 1992;222:157–62.
[59] Watanabe Y, Gould E, McEwen BS. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. Brain Res 1992;588:341–5.
[60] Stein-Behrens B, Mattson MP, Chang I, Yeh M, Sapolsky R. Stress exacerbates neuron loss and cytoskeletal pathology in the hippocampus. J Neurosci 1994;14:5373–80.
[61] Henningsen K, Andreasen JT, Bouzinova EV, Jayatissa MN, Jensen MS, Redrobe JP, et al. Cognitive deficits in the rat chronic mild stress model for depression: relation to anhedonic-like responses. Behav Brain Res 2009;198:136–41.
[62] Mahableshwarkar AR, Zajecka J, Jacobson W, Chen Y, Keefe RSE. A randomized, placebo-controlled, active-reference, double-blind, flexible-dose study of the efficacy of vortioxetine on cognitive function in major depressive disorder. Neuropsychopharmacology 2015;40:2025.
[63] Patterson SL, Abel T, Deuel TAS, Martin KC, Rose JC, Kandel ER. Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. Neuron 1996;16:1137–45.
[64] Popoli M, Gennarelli M, Racagni G. Modulation of synaptic plasticity by stress and antidepressants. Bipolar Disord 2002;4:166–82.
[65] Arenas MC, Vinader-Caerols C, Monleón S, Martos AJ, Everss E, Ferrer-Añó A, et al. Are the effects of the antidepressants amitriptyline, maprotiline, and fluoxetine on inhibitory avoidance state-dependent? Behav Brain Res 2006;166:150–8.
[66] Hickie I, Naismith S, Ward PB, Turner K, Scott E, Mitchell P, et al. Reduced hippocampal volumes and memory loss in patients with early-and late-onset depression. Br J Psychiatry 2005;186:197–202.
[67] Bremner JD, Vythilingam M, Vermetten E, Nazeer A, Adil J, Khan S, et al. Reduced volume of orbitofrontal cortex in major depression. Biol Psychiatry 2002;51:273–9.
[68] Bennett Ao MR. Stress and anxiety in schizophrenia and depression: glucocorticoids, corticotropin-releasing hormone and synapse regression. Aust New Zeal J Psychiatry 2008;42:995–1002.