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Research Article

The Role NMDA Receptors within the Nucleus Accumbens in Acute Stress in Male Wistar Rats

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ABSTRACT

Introduction: Glutamate receptors are shown to play an important role in mediation of stress effects. In the present study, the effect of intra-core part of the nucleus accumbens (NAc)memantine(a NMDA receptor antagonist) injection on the metabolic effects of acute stress in the male Wistar rats was investigated.

Materials and Methods: Fifty five male Wistar rats were underwent to surgical cannulation and by lateral 23 gauge guide cannula were placed in their core part of nucleus accumbens. Seven days later, the animals received electro foot shocks for 60 min. Five min before stress session, memantine (0.1, 1 and 5 µg/rat) was administered bilaterally into the core part of the NAcThe metabolic signs of stress including food and water intake, anorexia time, andcorticosterone level changes were measured.

Results: Administration of 5 µg/rat memantine into nucleus accumbens core resulted in increased food and water intake and decreased anorexia time, and plasma corticosterone level. Memantine in both 0.1 and 1µg/rat had not effects.

Conclusion: These results indicated that NMDA glutamate receptor inhibition by memantine in thecore part of the nucleus accumbens could prevent metabolic responses to acutestress.

Keywords: Glutamate NMDA Receptors; Memantine; Nucleus AccumbensCore; Stress; WistarRat

INTRODUCTION

Stress as a bio-psycho-social phenomenon can overcome to several body functions and may induce metabolic disturbance in the living organisms as well (Yari-Beigi et al., 2017; Ranjbaran et al., 2017; Javadifar et al., 2016). In addition, several gastrointestinal, cardiovascular, and neurological diseases also are thought to be related to stress (McEwen, 2000). Several brain regions including the hippocampus, amygdala and prefrontal cortex are shown to be related to the stress responses in the central nervous system (McEwen , 2000; McEwen, 1999; McEwen, 1995). Among the important brain areas which is shown to be involved in emotional, locomotion, and also mediation of stress responses is the nucleus accumbens (Ranjbaran et al., 2017; Javadifar et al., 2016). The nucleus is lies in the forebrain area and composed of two distinct parts namely the shell and core part. The shell part is composed of the neuronal arborization including the nerve cells' dendrite and axons with the scanty number of inter neurons. This part is shown to

play a role in mediation of emotion to motion. The second part of the nucleus is the core part which is composed mainly from the medium sized spiny GABAergic interneurons and also some neurons with long axons which project to the other parts of the brain including the ventral tegmental area. Memantineis used for moderate to severe Alzheimer's disease treatment. It is considered as a low affinity noncompetitive NMDA glutamate receptor antagonist who may block the effects of glutamate signaling(1).It is find that NMDA glutamate receptors may be involve in the stress effects mediation (Sandi, 2011; Numakawa et al., 2009; Lehner M, 2017; Yuen et al,., 2009). So, it may be interesting that the effect of NMDA glutamate receptor inhibition in the core part of nucleus accumbens on metabolic responses to stress be studied. The aim of this study is to evaluate the effect of administration of memantine into the core part of the nucleus accumbens on the metabolic disturbances induced by electro foot-shock in male Wistar rats.

MATERIALS AND METHODS

Adult male Wistar rats (220-300 g), Pasture Institute, Tehran, Iran, were housed 4/cage on a 12/12-h light–dark cycle at constant room temperature (22^{o}C) with food and water ad lib. All experiments were performed in the period between 9:30 and 15:30 h. The experiments were conducted in accordance with the institutional guidelines for the Care and Use of Laboratory Animals from Baqyiatallah University of Medical Sciences ethical committee.

Six groups of animals were used in these experiments (n=6/group). The control group received intra-accumbenssaline (1 µlit/rat) before each stress exposure session. Theexperimental group received intra-accumbensmemantine (memantine hydrochloride, Sigma-Aldrich, Germany) in doses of 0.1, 1 and 5 µg/rat before each stress. Surgical cannulation was performed as follows: The animals were anesthetizedwith ketamine hydrochloride (75 mg/kg, ip) (Alfasan Worden, Netherland) and diazepam hydrochloride (5 mg/kg, ip) (Merck KgaA, Germany) and apaired of 21 gauge guide cannula was placed stereotaxicallyin the core part of nucleus accumbens.The coordinates for cannula place were A: 1.8 mm rostral to the bregma; L: 1.5 mm lateral to the midsagittal; V: 6.0 mm ventral to the surface of the level of skull. Drug administration into the core part of the nucleus accumbenswas performed by a 30-gage injection cannula and polyethylene tubing system attached to a Hamiltonian syringe.

Intra accumbensmemantine administration was performed 5 min before each stress session. After drug injection, the rats were placed in the communication box where they were exposed to an electro foot-shock for 100 s (40 mv).After the stress session completion, the animals were returned to their home cages, food and water intake were measured 24 h later and anorexia time of the animals were measured. Later, the animals were sacrificed and their adrenals were removed and fixed in 4% formalin for further weight determination.

Blood sampling was conducted from the animals' retro orbital sinus for evaluation of plasmacorticosterone level.

All data were shown as mean±SEM. Data were analyzed using two-way analysis of variance (ANOVA) with stress and memantineas the main factors. Tukey post hoc test was conducted when interaction reached significance. $P<0.05$ was considered as statistically significant.

RESULTS

Effects of memantine on food intake in stressed animals

As it is shown in the Fig. 1, intra core part of the nucleus accumbens administration of memantine can increase food intake in the animals as compared with control group [$F(5, 1)=2.41$, $P<0.001$].

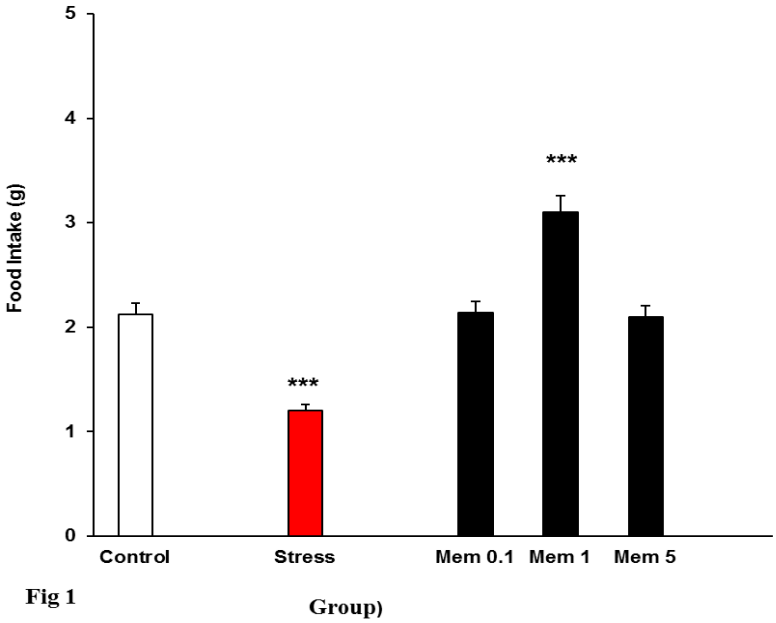

Fig. 1. Food intake in stressed rats after memantine administration.Each point mean±SEM for 6 rats. (***P<0.001)

Effects of memantine on water intake in stressed animals Water intake in the animals was reduced in the memantine treated animals as compared with the control group [F(1, 5)=2.13, P<0.001] (Fig. 2).

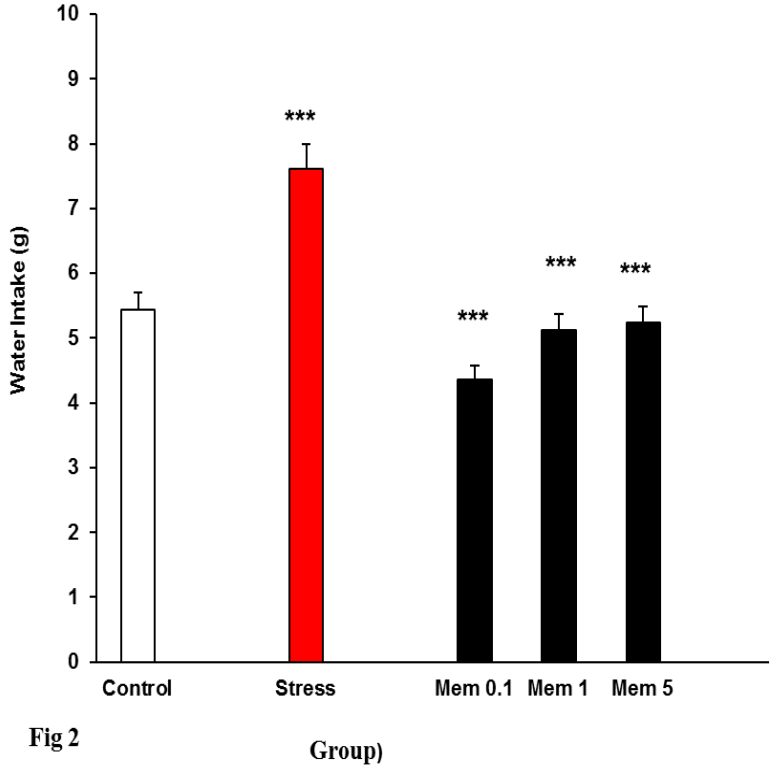

Fig. 2. Water intake in stressed rats after memantine administration.Each point mean±SEM for 6 rats. (***P<0.001)

Effects of memantine anorexia in stressed animals

Fig. 3 Shows the anorexia time in the animals which received memantine (0.1, 1, 5 µg/rat) in their Core part of the nucleus accumbens. As it is clear, memantine administration could reduce the effect of stress on anorexia time [$F(1, 5)=2.43$, $P<0.001$].

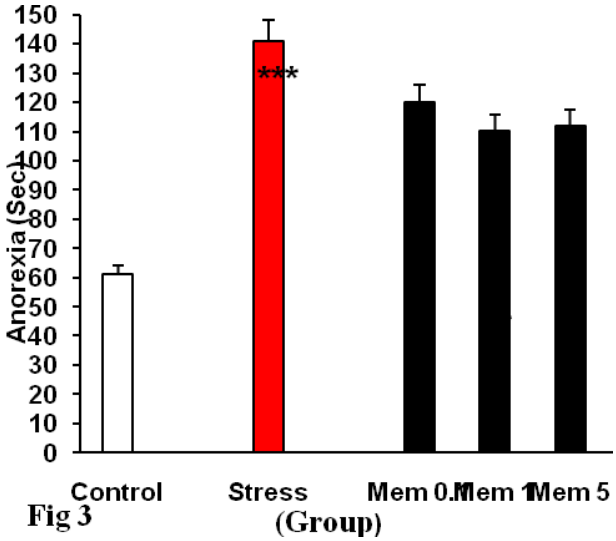

Fig. 3. Anorexia in stressed rats after memantine administration.Each point mean±SEM for 6 rats. (***P<0.001)

Effects of memantine on plasma corticosterone level in stressed animals

Fig. 4 illustrates the plasma corticosterone level groups. Intra accumbens injection of memantine reduces the plasma corticosterone level in the stressed animals as compared with the control group [$F(5, 1)=3.12$, $P<0.001$].

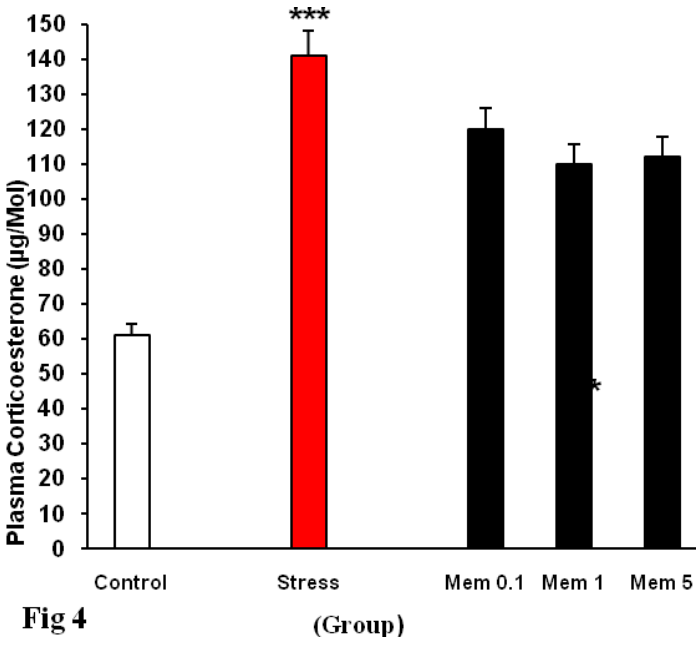

Fig. 4. Plasma corticosterone level in stressed rats after memantine administration.Each point mean±SEM for 6 rats. (***P<0.001)

DISCUSSION

In our experiments, the stressed animals showed increased in food and water intake as well as plasma corticosterone level. In addition, their time to food intake was increased. In addition, memantine micro injection in to the core part of nucleus accumbens enhanced food and water intake and reduced anorexia, and plasma corticosterone level. Acute stress has shown to produce a wide range of metabolic, neural, and cardiovascular consequences (Sapolsky, 1999). The stress responses are thought to be mediated by the hormone corticosterone which released during stress from the adrenal glands (McEwen, 2000). During the stress, it is accepted that the hypothalamus-pituitary-adrenal (HPA) axis is activated and corticosterone released in to the plasma as a response (Pacak and Palkovits, 2001). Our data are in accordance with the previous studies showed that different types of stress can increase plasma corticosterone level in rats and mice (Ranjbaran et al., 2017; Ghobadi et al., 2016). However, previous studies did not provide a wide spectrum of metabolic changes produced by acute stress and it was needed to be more studied (Ranjbaran et al., 2017; Ghobadi et al., 2016). Our data indicated that the animals after stress consume more food and water and memantine reduces these increments. It is interesting that intra-core part of nucleus accumbens injection of memantine (as a NMDA glutamate receptor antagonist) can interfere with stress action on food and water consumption. It is now clear that nucleus accumbens and its core part are involved in food consumption (Koob et al., 1978). Regarding that acute stress can initiate neuronal processes in the central nervous system that are mediated by glutamatergic system (Popoli et al., 2012), it is not surprising that inhibition of these receptors can inhibit the stress effects on food and water consumption. The effect of stress on food and water consumption is well known and it is hypothesized that amygdala and paraventricular nucleus (PVN) of hypothalamus are involved in this processes (Pacak and Palkovits, 2001). The corticotropin realizing factor (CRF)released from these brain areas are shown to play a central role in this regard (Pacak and Palkovits, 2001). However, the role of core part of nucleus accumbens in this regard is not well understood. Anatomical and histochemical studies have revealed that the nucleus accumbens composed of two distinct parts namely shell and core parts (Jongen-Relo et al., 1994). These two parts are connected to each other and also the shell part is connected to the central nucleus (CeA) of amygdala (Jongen-Relo et al., 1994). It is interesting that outward projections from the CeA reached the shell part of the NAc and so, one can concluded that activity of the amygdala during the stress, can affects the NAc shell and perhaps core (McEwen, 2000). Since the core part of the NAcreceived several glutamatergic inputs from amygdala and frontal cortex (Jongen-Relo et al., 1994), it can be reasoning that stress can affect the core part of the NAc both via central nucleus of amygdala and frontal cortex as well.

Other part of the present study has revealed that stress increases the anorexia in the animals and memantine reduces stress enhancement on anorexia. Anorexia is considered as one of the commonest signs of the stress and is believed to be related to the CRF effects (Pacak and Palkovits, 2001). Our data indicated that at least a part of this phenomenon may be related to the glutamate neurotransmission in the core part of the NAc. However, this finding needed to be further evaluated especially in regard to the role of the NAc in mediation of the metabolic effects of acute stressIt can be concluded that memantine injection in to the core part of the nucleus accumbens can reduces the metabolic effects of the acute stress. Our finding insisted the role of glutamate neurotransmission in the core part of the NAc in mediation of stress effects.

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