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Monosodium glutamate influences depressive behavior of two age groups of mice in forced swimming test: Vitamin B6 could remedy the situation

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ABSTRACT

Monosodium glutamate (MSG) could cause metabolic and neurotransmitters disturbance, and according to animal studies, it may cause neuronal damage. Vitamin B6 is a cofactor for various enzymes and can alter neurotransmitter levels. The aim was observing the effects of MSG administration alone and in combination with vitamin B6 on mood in two age groups of mice. MSG was administered either a single dose or long-term for 7, and 14 days in two age groups of mice (4–5 weeks or 9–10 weeks). Vitamin B6 (100 mg/kg) was administered six days consecutively. Depression was assessed by the forced swimming test (FST), higher immobility time denotes depressive-like behavior. A single dose of MSG (2.5 g/kg) increased immobility during the FST only in younger mice 179 sec ± 17 ($p < 0.05$, vs control 159 sec ± 8.5). Immobility time was higher than normal in young animals (191 sec ± 1.7) after seven or fourteen days of MSG exposure, it was also higher than control in adult animals on the 7th and 14th days (195 sec ± 8.7 and 203.6 sec ± 8 respectively). Vitamin B6 decreased the immobility time during FST in both age groups when it was administered prior to MSG single dose or in combination with MSG for the long term. In conclusion, MSG effects on depressive behavior depend on age and duration of exposure. Vitamin B6 as a cofactor of various neurotransmitter enzymes is promising in preventing the possible harmful effects of MSG on mood.

1. Introduction

Depression and anxiety are psychological diseases, characterized by mood and emotional disturbance, usually accompanied with reduced monoaminergic signaling, mainly of serotonin (5-hydroxytryptamine, 5-HT) [1]. The function of glutamate and γ-aminobutyric acid (GABA) are also altered in mood disorders [2]. Studies reported that GABA concentrations were abnormally lower in the plasma and cerebrospinal fluid (CSF) in major depression disorder individuals [3]. Glutamate is an excitatory neurotransmitter abundant in the brain. It acts on three different cell compartments presynaptic neurons, postsynaptic neurons, and glia [4]. Altered glutamate levels in diverse brain areas in patients suffering mood disorders have been reported in postmortem studies [5].

Studies performed by nuclear magnetic resonance spectroscopy of individuals with depression, revealed that the glutamate level in the occipital cortex was elevated while in the anterior cingulate cortex it was decreased [3,6].

Monosodium glutamate (MSG) with unique flavor-enhancing qualities is pervasively used as a food additive, it is one of glutamic acid salt forms, a non-essential amino acid. A growing body of evidence has shown that exposure to MSG resulted in severe metabolic disturbances in animals and humans [7–9].

In animal models, subcutaneous neonatal MSG treatment caused obesity through hypothalamic lesion that resulted in fat tissue accumulation, insulin resistance, hyperinsulinemia, and glucose intolerance [10]. Exposure to MSG induced neuronal damage in hippocampal CA1 pyramidal cells connected with learning impairment [11], hyperexcitability and motor behavioral alterations [12,13]. Moreover, it was proved that MSG could deplete the monoamine neurotransmitters of the hypothalamus region in treated rats [14,15].

Glutamate serves a multitude of roles in mammalian brain; where it is an important mediator of sensory information, motor coordination, emotions, and cognition, including formation and retrieval of the memory an energy substrate; also a potent neurotoxin [16].

Current evidence show that inadequate concentrations of B vitamins are associated with depression [17]. Evidently higher intakes of vitamin

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B6 and B12 could decrease depression in older adults [18] and they shows positive effects on general health as well as mood, and cognition [19]. Vitamin B6, folate, and vitamin B12 are biochemically involved in the metabolism of homocysteine, methionine, and other essential amino acids [18]. These B vitamins through their role as cofactors contribute to numerous catalytic reactions in the human body, which are required for neurotransmitter synthesis and functioning and myelination of the spinal cord and brain [18–21]. Thus they are involved in optimal functioning of the central nervous system.

GABA is one of the inhibitory neurotransmitters in the brain which is converted from glutamate by glutamate decarboxylase (GAD) enzyme that is essential in the balance of glutamate/GABA concentrations in the brain [16]. The GABA inhibitory effects play an important role in the protection of the brain neurons, vitamin B6 derivative pyridoxal 5-phosphate (PLP) is a cofactor of GAD [22]. Previously results showed that GAD activity is considerably reduced in the brain of old rats compared to the young animals [20]. That could influence the glutamate and GABA level concentration in favor of glutamate accumulations in certain brain regions [20].

Vitamin B6 beneficial effects on mood were proven before in mice model of despair [23]. The aim of this study was to evaluate: first the effect of MSG single dose and repeated doses for 7 and 14 days on depressive behavior in two age groups of mice. Second the effect of vitamin B6 pretreatment on depression following MSG single effective dose injection in two age groups of mice. Third the effect of vitamin B6 co-administration with MSG on depressive behavior after 7 and 14 days in two age groups of mice, by using the forced swimming test (FST).

2. Material and methods

2.1. Animals

Male albino mice either young, 4–5 weeks (21 g ± 1.5), or adult, 9–10 weeks (29.5 g ± 0.5), were housed in cages according to their ages; the minimum number of animal in each experimental group was seven. They were nurtured under a 12/12 h light/dark cycle (the lights were on from 6 am to 6 pm). Animals had free access to tap water and standard mice chow. They were placed in the experimental room 24 h before the test for acclimatization and the experiments were performed between 08:00 and 13:00 in the pharmacology laboratory in order to minimize circadian rhythm influence. All animal procedures were performed in accordance with guidelines for the Care and Use of Laboratory Animals Issued by The University of Medical Sciences (Ethical No: IR.MUI.REC.1395.3.866).

2.2. Locomotor test

The locomotor activity should be tested prior to behavioral tasks since variations in locomotor activity nonspecifically affect performance in many behavioral tests. Mice activity was measured in a plastic rectangular open field apparatus (Borj Sanat, Iran) divided by red beams into 15 zones in a 5 × 3 grid formation. Mice were placed facing the wall in the closest corner to the experimenter and they were allowed to explore the field for 3 min [24]. As the animals passed through the beams the number of zone entries was counted automatically and rears on hind-legs were counted manually. The total activity was calculated by summing the rears (vertical exploration) and the zone entries (horizontal exploration).

2.3. Forced swimming test (FST)

Depression was measured in mice by the FST [25], with some modifications, mice were forced to swim in 25 °C water in a glass beaker (diameter 12.5 cm) for 6 min and the measurements were done in the last 4 min of the test. The depth of water was about a level that the mice could neither touch the bottom of the container with their paws or tail nor could they escape it (12 cm). The total immobility time that is the time spent while the animal was floating staying still or using righting movements, was assessed. Swimming was considered animal movements which involved at least two limbs. The whole experiment was recorded by a camera and analyzed later. After 6 min, the mice were dried carefully and returned to their home cage. Each animal was subject to the FST following the locomotor test.

2.4. Drugs administration

MSG (Sigma, India) was administered subcutaneously (sc) either one single dose 2.5, 5 g/kg [26] an hour before the tests, or 2.5 g/kg for 2 weeks and tested on the days 7th and 14th, their related control group received saline. Meanwhile, in an attempt to use the minimum number of animal, the same animals have been used after 7 and 14 days. Vitamin B6 (pyridoxine HCl, 200 mg/ml, Caspian Tamin Industry, Iran) was injected 100 mg/kg intraperituneally (ip) [23] either six consecutive days before the MSG single dose (2.5 g/kg), or it was co-administered with MSG for 2 weeks, control animals were treated with saline alone. This was the dose of vitamin B6 that has previously induced antidepressant behavior in mice [23]. All of the drugs were diluted in saline and they were freshly prepared on demand, injections were adjusted for 10 ml/kg mice body weight.

2.5. Data processing and statistical analysis

Results were expressed as group mean ± SEM. Results were analyzed by one-way ANOVA, followed by Tukey's posttests, p values less than 0.05 were considered significant. The software programs used for data analyzing and making graphs were Excel 2010 and the GraphPad Prism 6.

3. Results

3.1. The effect of MSG single dose and after pretreatment with vitamin B6 on the FST

Acute MSG (2.5 and 5 g/kg) administration in young animals' increased immobility time during the FST; 179 sec ± 17 ($p < 0.05$, vs control 159 sec ± 8.5) and 200 sec ± 8 ($p < 0.001$, vs control) respectively (Fig. 1). While the single dose of MSG in adult mice did not increase the immobility time during the FST compared to their control counterpart that was 158 sec ± 2.8. It should be noted that the single

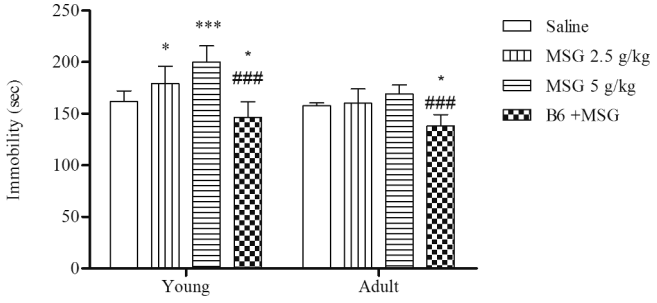

Fig. 1. The effect of acute MSG alone or following vitamin B6 pretreatment on depressive behavior in the forced swimming test in young and adult mice. The immobility time is the total time animals were immobile during the last 4 min of the total 6 min test. Vitamin B6 was injected (100 mg/kg ip) for 6 consecutive days before the MSG acute dose. Number of animals in each group was 8. Results are expressed as group mean ± SEM and analyzed by one-way ANOVA followed by Tukey's comparison tests. $^{*}p < 0.05$ and $^{***}p < 0.001$ compared with the control group; $^{###}p < 0.001$ compared with MSG 2.5 g/kg alone.

Table 1
Animal movements during the locomotor test.

	Vertical movement	Horizontal movement	Total activity
Young control	13.1 ± 2.9	137.0 ± 13.1	150.1 ± 14.42
Young MSG 2.5 g/kg	11.8 ± 2.4	139.7 ± 9.2	151.6 ± 9.6
Young MSG 5 g/kg	12.1 ± 3.8	142.6 ± 18.3	154.7 ± 21.0
Young MSG 2.5 g/kg + B6	9.8 ± 1.1	125.5 ± 8.4	135.3 ± 8.6
Adult control	13.3 ± 3.0	144.6 ± 9.1	158.0 ± 11.1
Adult MSG 2.5 g/kg	18.7 ± 3.6	168 ± 15.4*	186.7 ± 17.8*
Adult MSG 5 g/kg	15.6 ± 2.7	151.5 ± 13.7	167.2 ± 16.2
Adult MSG 2.5 g/kg + B6	12.2 ± 2.1	150.6 ± 16.8	162.8 ± 18.8
Young control (7 days)	11.3 ± 1.5	114.6 ± 9	126 ± 10
Young MSG (7 days)	13.3 ± 1.7	144.3 ± 9*	157 ± 11**
Young MSG + B6 (7 days)	12.6 ± 1.5	133.3 ± 9*	146 ± 9.5**
Young control (14 days)	8.8 ± 0.6	117 ± 6.7	125.8 ± 7.3
Young MSG (14 days)	10.7 ± 1.9	118.2 ± 6.5	129.0 ± 7.0
Young MSG + B6 (14 days)	10.0 ± 1.0	110.1 ± 7.0	120.1 ± 8.0
Adult control (7 days)	8.6 ± 1	116 ± 8	125.5 ± 8.3
Adult MSG (7 days)	9.6 ± 0.8	129.8 ± 12	139.5 ± 12.8
Adult MSG + B6 (7 days)	11 ± 4	129 ± 20	140 ± 24
Adult control (14 days)	10.3 ± 2.1	113.0 ± 9.4	123.3 ± 11.4
Adult MSG (14 days)	13.0 ± 1.7	127.1 ± 6.4	140.0 ± 7.8
Adult MSG + B6 (14 days)	12 ± 2.0	123 ± 11	136 ± 13

The total activity is the sum of vertical and horizontal movements. Number of animals in each group was 7. Two mice age groups: 4–5 weeks (young) or 9–10 weeks (adult). Vitamin B6 administration (100 mg/kg ip). The dose of long term MSG administration was 2.5 g/kg sc. Results are expressed as group mean ± SEM and analyzed by one-way ANOVA followed by Tukey's comparison tests. $^{*}p < 0.05$, and $^{**}p < 0.01$ compared with their control counterpart group.

dose of 7 g/kg was also administered but because of irregular locomotor activity and animal drowning it was not further analyzed. The results showed that treatments does not have the same effect on the immobility time of younger and older animals in the FST. Vitamin B6 treatment prevented the harmful effect of MSG (2.5 g/kg) on immobility time and significantly reduced it in both age groups of mice, which indicates vitamin B6 antidepressant effects. As it is presented in the Table 1, in young animals the total locomotor activity were not different from their corresponding control group, however, it was increased by 2.5 g/kg MSG in adult animals (total activity count 186.7 ± 17.8 vs 158 ± 11, $p < 0.05$).

3.2. The effect of long term MSG alone or simultaneously with vitamin B6 on the FST

After 7, and 14 days of the treatments animals were tested (Fig. 2). MSG caused increase in the immobility time in both of the age groups that was significantly higher compared with their control counterparts (young = 190 sec ± 2.2, and adult = 190 sec ± 6.3; $p < 0.05$ vs control). Vitamin B6 co-administration had significantly reduced the immobility time in both age groups (young = 130 sec ± 6.5, and adult = 140 sec ± 13; $p < 0.001$ compared with MSG alone). The animals' behavior during the FST after 14 days of therapy, also shows depressive behavior induced by MSG and antidepressant effects while vitamin B6 was co-administered in both of the age groups ($p < 0.05$ vs MSG alone) (Fig. 2).

According to the Table 1, after 7 days total locomotor activity in young animals treated with MSG alone and MSG plus vitamin B6 was higher than the control animals (total activity count 157.6 ± 11 and 146 ± 9.5 respectively vs control 126 ± 10, $p < 0.001$). But hyperactivity seemed to be soothed after 14 days of therapy. Locomotor activity in aged mice did not look affected by the treatments after 7 or 14 days. Animals weight did not change significantly compared to their control counterparts neither in adult nor in young animals (data not shown).

4. Discussion

The results of the present experiment extend the findings of MSG effects on behavior in a few ways. First, they show that MSG single dose could have different effects on behavior in young and adult mice. Second, while acute MSG caused depressogenic effect only in young mice, older mice are susceptible following long-term exposure to MSG. Third, vitamin B6 supplementation prevented the effect of either acute or long-term MSG administration in animals of the two age groups.

FST is the most widely used method for evaluating antidepressant activity [27]. The widespread use of this tool is mainly a result of its reliability across laboratories and ability to detect new antidepressant agents pre-clinically. The immobility is believed to reflect either a failure of persistence in escape oriented behavior (i.e. despair behavioral) or the development of passive behavior that frees the animal from active forms of coping with the stressful situation [28].

The single dose of MSG increased the immobility time in young animals while it caused no change in adult animals during the FST. This showed that MSG has the potential to induce depression in young mice, while older mice were invulnerable. Earlier studies in mice revealed that young, and aged mice had no differences in immobility in the FST and tail suspension tests [29,30]. Therefore different results that was observed in the two age groups could be the direct effect of MSG

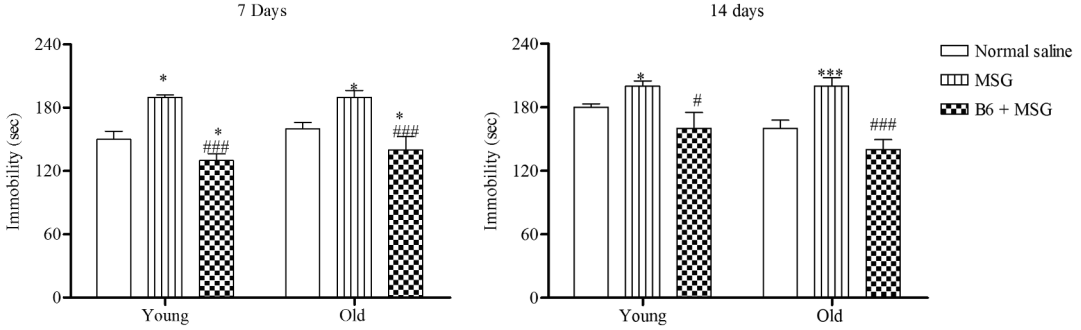

Fig. 2. The effect of long term MSG alone or simultaneously with vitamin B6 on depressive behavior in the forced swimming test in young and adult mice. The immobility time is the total time animals were immobile during the last 4 min of the total 6 min test. Vitamin B6 (100 mg/kg ip), MSG (2.5 g/kg, sc) were administered for 14 consecutive days, tests were performed on the 7th and 14th day. Number of animals in each group was 7. Control groups received normal saline. Results are expressed as group mean ± SEM and analyzed by one-way ANOVA followed by Tukey's comparison tests. $^{*}p < 0.05$, $^{***}p < 0.001$ compared with the control group; $^{\#}p < 0.05$, $^{\#\#\#}p < 0.001$ compared with MSG alone group.

depressogenic effect in the FST. It could be assumed that young animals are more vulnerable to possible harmful effects of MSG. The previous studies have shown that the neonatal period is more embracing to the neurotoxic effect of MSG due to the immature blood-brain barrier (BBB) [26]. Therefore plausibly single dose of MSG did not have depressogenic effects in adult mice because of the matured BBB. In addition age associated changes in brain neurotransmitters' metabolism are thought to be important and could possibly lead to many age-related symptoms [20]. Vitamin B6 had beneficial antidepressant effects in both age groups. This is supported by previous findings advocating vitamin B6 antidepressant effects [23]. In young animals following MSG administration total locomotor activity was similar to the control group, this further declares that increased immobility during the FST is because of depression induced by MSG. Locomotor activity was increased by 2.5 g/kg MSG in aged mice, but this effect was not noticeable by the higher dose. As far as we have gathered most of the studies on the behavioral outcomes of MSG are performed on neonate animals, while this study shows that adult mice brain could also be susceptible, but we came to a paradox since hyperactivity was not detected in MSG higher dose (5 g/kg). The amino acid glutamate serves a multitude of roles in the brain; it is not only an excitatory neurotransmitter but also it is the precursor of the inhibitory neurotransmitter GABA. These diverse neurotransmitters may be responsible for the different effects observed by various doses of MSG in the adult mice group.

The effect of long-term MSG administration on behavior during the FST was also determined in two age groups of mice. Long term MSG administration has induced depression in young mice tested on days 7 and 14. This was parallel with previous studies that proved exposure to MSG increased immobility in the FST in young rats [26]. But there are few differences in the study design since they administered MSG during the first 5 postnatal days and on the 60th day submitted to behavior tests. Interestingly our study showed that after 7 days the locomotor activity was increased and turned back to normal values after 14 days. An acute surge in hippocampal and intra-cerebroventricular glutamate concentrations was observed following MSG administration in neonates [13]. Increased animal activity in the locomotor test supports the hyperactivity induced by glutamate which also had deleterious effects on depression. Since the following study was based on observation on the downside biochemical data were not evaluated, but according to previous literature the possible mechanisms that may contribute to this interaction are proposed.

Previously MSG treatment caused some of the neurotransmitters and their metabolites to be depleted in the hypothalamus region of rat brain such as norepinephrine, serotonin, and dopamine [14]. Depletion of these neurotransmitters could also be responsible for MSG depressogenic effect that could be prevented by vitamin B6 co-administration. Evidently, vitamin B6 is the cofactor for various enzymes including the enzyme that converts L-dopa to dopamine and 5-hydroxytryptophan to serotonin; aromatic amino acid decarboxylase (AADC) [31]. After 14 days the harmful effects of MSG on locomotor activity returns to normal values, and the immobility time during the FST remains. In adult mice MSG induced depression that continued after 14 days, while vitamin B6 co-administration was able to compromise this deleterious effect. Evidently, GAD activity was significantly low in aged animals' that could shift the balance of glutamate and GABA concentration in favor of glutamate augmentation in the synaptic parts of certain brain regions [20]. It was also determined that vitamin B6 profoundly increased GAD activity in aged rats. Thus it could be deduced that vitamin B6 has returned the balance of brain glutamate/GABA to normal values. Ultimately the beneficial effect of vitamin B6 on AADC activity could also have played a role in overcoming MSG causing depression in adult mice that warrants further biochemical research. In addition researchers have also proved that MSG causes permanent changes in the behavior including convulsive susceptibility which persist until the adulthood age [32]. Therefore evaluating adulthood depressant effects of MSG after exposure in young mice is also suggested.

Although the extrapolation from studies with animals to humans should be done with caution, maybe MSG could induce different effects on mood of different age groups where younger ages could be even susceptible to a single dose and the adults when exposed chronically. Vitamin B6 supplements could be prevented these harmful effects, apparently, further clinical studies are warranted.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmip.2019.05.002.

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