Short- and long-term administration of buprenorphine improved gene expression of P2X4 and GABAA receptors in the hippocampus of methamphetamine rats

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ABSTRACT

P2X4 receptors modulate synaptic transmission and communication among neurons in the CNS. An increased level of neuronal P2X4 is associated with altered memory in the hippocampal region. Additionally, some evidence suggests that P2X receptors downregulate the GABAA receptors. In the microglia of drug users, methamphetamine (METH) modifies the expression of certain genes. Therefore, the alterations of P2X4 and GABAA gene expression on memory following treatment with/without buprenorphine (BUP) in METH rats were evaluated. Seventy-seven rats were allocated into eleven groups at random (n = 7). Control, METH (10 mg/kg), BUP (6 and 10 mg/kg) for 5 days, BUP (6 and 10 mg/kg) for 14 days, METH (10 mg/kg) + BUP (6 and 10 mg/kg) for 5 days, METH + BUP (6 and 10 mg/kg) for 14 days and withdrawal group. They received their treatments intraperitoneally. After memory assessment, the animals were decapitated, and the gene expression of P2X4 and GABAA receptors in the hippocampus was assayed using RT-PCR. The memory and P2X4 and GABAA receptor gene expression in METH rats were reduced compared to the control group. The administration of all the different BUP doses increased gene expression in (BUP 6 or 10 mg/kg. 5 days and BUP 10 mg/kg. 14 days) + METH groups compared to METH rats. These results demonstrated that METH toxicity severely decreased the level of P2X4 gene expression. Meanwhile, treatment of BUP led to increasing levels of the mentioned gene. Therefore, the potential role of P2X4 and GABAA receptor genes in modulating METH addiction is addressed.

1. Introduction

Methamphetamine (METH) is a common drug of abuse. There are multiple neuropsychiatric adverse events associated with the use of this addictive drug. A limited number of therapeutic options are available, but they are mainly ineffective [1]. Some reports showed that BUP treatment (as a semisynthetic drug, partial agonist μ receptor, antagonist δ, and K opioid receptors) could be recommended to treat METH withdrawal [2]. Molecular target(s) by which METH exerts its activity are unknown, which poses a critical barrier to the discovery of proper therapeutics. Recent studies have demonstrated the activation of microglial cells in response to these psychostimulant drugs, yet the mechanisms are not fully understood [3]. In this unknown mechanism, the extracellular adenosine 5'-triphosphate (ATP)-sensitive P2 purinoceptors are implicated as primary factors in initiating this disorder [4]. P2Xs are purinergic ionotropic receptors and cation-permeable channels [5]. P2X4 is a high calcium permeability subunit among the seven P2X subunits and represents the wide distribution in CNS neurons, glial cells, and peripheral tissues [5, 6]. Recent evidence has highlighted P2X4 subunits as potential targets in the regulating tasks of the nervous system, such as the regulation of neuropathic pain, neuroendocrine [7], hippocampal plasticity, epilepsy, ischemia, anxiety, and multiple sclerosis [5].

In addition, P2X4 expression of neurons is seen to be increased in mouse models of Alzheimer's disease (AD). As a result of increased P2X4 expression on excitatory neurons, memory processing is impaired, and activity-dependent synaptic plasticity is also altered, suggesting that increasing neuronal P2X4 expression observed in AD might contribute to its pathogenesis [8]. Furthermore, there were paradoxical reports about...
the effects of P2X4 receptors on other receptors. Some reports showed that this receptor inhibits γ-aminobutyric acid A [9]; however, other studies have indicated that this receptor modulates the N-methyl-D-aspartate glutamate receptor [10]. According to recent studies, P2X4 receptors may be inhibited by some drugs [11]; despite contrasting, findings remain controversial [12, 13]. In vitro and in vivo data indicate that P2X4 receptors may be significantly helpful targets for treating disorders associated with addiction [14]. On the contrary, based on studies on ethanol addiction, the amount of the inhibition is independent of ATP, and there is no alteration to the P2X4 channel deactivation [15].

Moreover, the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) is vital for operating the central nervous system (CNS). For instance, GABA limits the excitability of neuronal activity throughout the brain [16]. The predominant GABA receptors in the brain are A-type GABA receptors. It is estimated that 20%–50% of all synaptic connections contain ionotropic GABA receptors [17]. Furthermore, the GABA_a receptor enhances learning and memory performance [16]. The interaction of postsynaptic P2X4 and GABA_a receptors in the ventromedial nucleus of the hypothalamus promotes neuronal excitability by inhibiting GABA-mediated postsynaptic currents [18, 19]. Meanwhile, Cortical neurons have also shown P2X4-mediated attenuation of the GABAergic inhibition [20]. Activating P2X4 and GABA_a receptors in neurons may lead to neuropathic pain disinhibition [21, 22].

Considering the controversial information on the molecular target(s) of METH and the prominent role for P2X4 receptors during the drug abuse period, this study evaluated the alterations of the GABA_a and P2X4 gene expression and the effects of which on memory in METH-addicted rats following treatment with BUP.

2. Material and methods

2.1. Animals

Seventy-seven male Wistar rats (250 ± 50 g) were received from the Pastor Institute, Iran. The animals were kept in a room with a controlled temperature under lights from 7:00 a.m. to 7:00 p.m. (12:12 h light/dark cycle). Access to food and water was provided ad libitum for the rats. The Ethics Committee of Tabriz University confirmed animal protocols. Proper guidelines for the care and use of laboratory animals were followed in all processes for the preservation and usage of the experimental animals (NIH Guide for Care and Use of Laboratory Animals, 8th Edition, 2010). Figure 1 illustrates the timeline for procedures for two different duration of treatment (5 and 14 days).

2.2. Drugs

METH dissolved in sterile saline and obtained from Sigma-Aldrich. BUP was obtained from Tuyserkan Faran Shimi, Iran, and dissolved in sterile saline.

2.3. Groups

Seventy-seven Wistar rats were assigned to eleven groups at random (n = 7), including the

- Group 1: Control (saline), rats of the control group received saline (1 ml/kg [1]) for five days.
- Group 2: METH (10 mg/kg), in mentioned group, intraperitoneal METH was administered (10 mg/kg [1]) for 5 days. The animals were tested following the final treatment day.
- Group 3: BUP (6 mg/kg; for 5 days), in mentioned group, animals received intraperitoneal BUP (6 mg/kg) for 5 days.
- Group 4: BUP (6 mg/kg) + METH (10 mg/kg) group: in mentioned group, intraperitoneal BUP (6 mg/kg) + METH (10 mg/kg) were administered for 5 days [1, 23]. METH and BUP were administered 30 [24] and 60 [25] minutes before the test on the day of the water maze.
- Group 5: BUP (10 mg/kg; for 5 days) [26], rats in the BUP group received BUP (10 mg/kg) for 5 days.
- Group 6: BUP (10 mg/kg; for 5 days) + METH (10 mg/kg) group: METH rats received BUP (10 mg/kg) for 5 days [23].
- Group 7: BUP (6 mg/kg; for 14 days); in this group, animals received intraperitoneal BUP (6 mg/kg) for 14 days. After the final treatment day, the animals were tested.

![Figure 1. Schematic timeline of the experiment.](image-url)
Group 8: BUP (6 mg/kg) + METH (10 mg/kg) group for 14 days.
Group 9: BUP (10 mg/kg) [26] and treated for 14 days.
Group 10: BUP (10 mg/kg) + METH (10 mg/kg) group and treated for 14 days [27].
Group 11: Deprive group (Spontaneous methamphetamine withdrawal syndrome group): This group first received METH for five days. After 72 h without drug was assessed [28, 29].

After receiving the treatment intraperitoneally, the rats were tested. After that, the animals were quickly decapitated, and their hippocampus was removed and frozen in liquid nitrogen for the molecular test.

2.4. The Morris water maze test

Water (23–25 °C) was poured into a circular black pool (136 cm diameter, 60 cm height, and 30 cm depth). A circular rigid platform with a 10 cm diameter and 28 cm height was used to provide a route of escape from the water. The platform was placed to float approximately 2 cm below the water's surface. Fixed visual cues were present at several locations around the room outside the maze (i.e., hardware, computer, and posters). An infrared camera mounted above the maze tracked the rats' motions.

On each of the four consecutive days, four trials were performed. Each rat was put into the pool facing the sidewall at the start of each test. The pool area is divided into four quadrants based on four points arbitrarily designated as North, South, East, or West around the circle of the pool [30, 31, 32]. The rats were allowed to swim until they got to the platform and stayed there for 20 s. The experimenter guided the animals to the platform if they had not found it after 60 s and allowed them to stay on it for 20 s [33, 34]. They were taken out of the water, dried, and put back into the holding bin. Sixty seconds of swimming were allowed on the fifth day after removing the platform. On the last day, groups were compared based on time spent in the target quadrant [31].

2.5. The real-time polymerase chain reaction (RT-PCR) technique

The rats were quickly decapitated after memory assessment; For molecular analysis, the bilateral hippocampus was taken out and instantly frozen in liquid nitrogen. Total RNAs were isolated from hippocampus tissue samples using the TRIzol Pure RNA extraction buffer (Yekta Tajhiz, Iran) [35]. The next step included the detection of their purity and concentration using a Nanodrop Spectrophotometer [36]. Finally, reverse RNA transcription was performed using a reverse transcription kit (BIONEER). Triplicate real-time PCR was done to measure mRNA expression levels of P2X4 and GABAA using cDNA samples via the cDNA synthesis kit (BIONEER). Triplicate real-time PCR was done to measure mRNA expression levels of P2X4 and GABAA using cDNA samples via the cDNA synthesis kit (BIONEER).

The RT-PCR assay was performed on the RNA samples separated from the hippocampus of groups. The findings showed that the P2X4 gene expression level was decreased in the METH group compared to control rats (P < 0.001; Figure 3). The 5-day treatment by BUP induced a significant increase in the following groups of study: BUP group (6 mg/kg; P < 0.001), 10 mg/kg; i.p), METH + BUP (6 mg/kg; P < 0.001); 10 mg/kg; i.p) groups compared to METH group; however, the levels of P2X4 expression of BUP (6 or 10 mg/kg; i.p) groups treated for five days weren't considered significant compared to the control group (Figure 3).

2.6. Statistical analysis

Data were presented as mean ± SEM and analyzed by SPSS version 16. Statistical analysis was done using one-way analyses of variance (ANOVA) followed by Tukey's post hoc test. P < 0.05 was considered statistically significant.

3. Results

3.1. The measurement of the probe test component as an essential parameter in special memory

The results of the probe test showed a significant effect between treatments [F (10, 66) = 9.06; P < 0.001]. So, after administering the rats METH, there was a noticeable decrease in the amount of time spent in the target quadrant of the METH group (13.14 ± 1.26 s) in comparison with the control group (44.26 ± 2.49 s; P < 0.001). Also, the co-administration of METH + BUP (6 (P < 0.01) or 10 mg/kg (P < 0.01); for 5 days) or METH + BUP (6 (P < 0.01) or 10 (P < 0.001) mg/kg; for 14 days) increased the time spent in the target quadrant in comparison with the METH group. Also, a significant difference was observed in the group with withdrawal syndrome compared to control (P < 0.01) or METH (P < 0.05) rats (Figure 2).

3.2. The P2X4 expression alterations in METH rats with/without BUP treatment on day 5

The RT-PCR assay was performed on the RNA samples separated from the hippocampus of groups. The findings showed that the P2X4 gene expression level was decreased in the METH group compared to control rats (P < 0.001; Figure 3). The 5-day treatment by BUP induced a significant increase in the following groups of study: BUP group (6 mg/kg; P < 0.001), 10 (P < 0.001) mg/kg; i.p), METH + BUP (6 mg/kg; P < 0.001); 10 (P < 0.001) mg/kg; i.p) groups compared to METH group; however, the levels of P2X4 expression of BUP (6 or 10 mg/kg; i.p) groups treated for five days weren't considered significant compared to the control group (Figure 3).

3.3. The comparison of P2X4 gene expression alterations in METH rats with/without BUP treatment on day 14

The one-way ANOVA test revealed that the P2X4 gene expression levels between the groups with various BUP dosages and treatment durations were substantially different. There was a remarkable difference between METH group and [BUP (6 mg/kg, 14 days; P < 0.001); BUP (10 mg/kg, 14 days; P < 0.001)].

Moreover, the level of P2X4 expression in [BUP (10 mg/kg, 14 days; P < 0.05); METH + BUP (6 mg/kg, 14 days; P < 0.001); METH + BUP (10 mg/kg, 14 days; P < 0.001)] groups as compared to the control group was dramatically reduced (Figure 4).

3.4. The GABAA expression alterations in METH rats with/without BUP treatment on day 5

The results indicated that the GABAA gene expression level was decreased in the METH group compared to control rats (P < 0.001). The 5-day treatment by BUP induced significant increase in the following groups of study: BUP group (6 mg/kg; P < 0.001); 10 mg/kg; i.p), METH + BUP (6 mg/kg; P < 0.001); METH + BUP (10 mg/kg, 14 days; P < 0.001)) groups as compared to the control group (Figure 5).

3.5. The GABA A expression alterations in METH rats with/without BUP treatment on day 14

The one-way ANOVA test revealed a significant change in the GABA A gene expression between groups. Tukey's posthoc test indicated that the level of GABA A expression in hippocampus METH decreased compared to the control rats (P < 0.001). 14-days BUP treatment increased this

Table 1. Sequence of primers of studied genes.

| Gene name | Primer type | Primer |
|-----------|-------------|--------|
| P2X4 | Forward | CAGCCGTAAAGTGGGGCTCAT |
| Reverse | CCTTCTCCACACGACACCC |
| GABA A | Forward | TGGGAAGGTGGCATCAGGTAC |
| Reverse | GCTTCCCCCGGGACACATATT |
| GAPDH | Forward | CTCCTCGTCCTCCCTGGTCTC |
| Reverse | CGTCCCTCCCCCATCTCATA |
parameter in the BUP (6 \( P < 0.001 \); 10 \( P < 0.001 \) mg/kg; i.p) and METH + BUP (6 \( P < 0.001 \); 10 \( P < 0.001 \) mg/kg; i.p) rats compared to METH group. A significant difference between the withdrawal syndrome group and the control rats was also observed \( P < 0.001 \); Figure 6).

4. Discussion

The current research investigated the P2X4 and GABA\(\alpha\) gene expression alterations in METH rats following treatment with BUP. According to our data, in comparison to other groups, expression of P2X4 and GABA\(\alpha\) genes in the hippocampus of the METH group has significantly decreased. Studies have demonstrated that METH damages the neuronal dopamine system and is also believed to exert at least some of its neurotoxicity through microglial activation \[39\]. Severe deficits were observed following damage to the brain’s serotonergic and dopaminergic neurons, resulting in impaired recognition and memory in rats \[40\]. In line with our study, Gofman (2014) showed that in alcohol consumption, the P2X4 receptor might contribute to altering the microglial activity \[41\]. Contradictory, other studies suggested that the P2X4 receptor activation could cause dopamine hyperactivity and interfere with information processing \[42\].

Studies in individuals suffering from addiction suggest that dysfunctional GABA neuro-transmission plays a leading role in the process of addiction. Cigarette smoking history was associated with increased
limbic GABA\(_A\) receptor availability [43], whereas alcohol addiction was linked to lower limbic GABA\(_A\) receptor availability [44]. This research also considered changes in GABA\(_A\) receptor expression levels in the hippocampus of METH addict rodent models. According to the results, gene expression of this receptor was significantly reduced in the group with 10 mg/kg of METH for five days compared to the control. These findings align with prior research on the effect of METH addiction on GABA\(_A\) receptors, as data from several case-control studies have previously suggested that the GABA\(_A\) receptor subunit gene is moderately linked to METH use disorder [45].

Currently, no medications have been approved for the complete treatment of METH addiction; however, opioids are used to modify the pharmacodynamic actions of METH on dopaminergic systems by modulating the activity of dopamine (DA) neurons. Among opioids, BUP is known to be safer than others. There are few studies on the effects of BUP treatment on METH addict models. Kholghi et al. (2021) showed alterations in the dopaminergic response to METH in rat models treated with BUP [46].

Based on the results of our study, no significant differences can be observed in P2X4 gene expression in groups under treatment with BUP (6 or 10 mg/kg for 5 days) compared to the control group.

BUP has been known as a partial agonist of \(\mu\)-opioid receptors. Etare et al. (2017) demonstrated that administering METH or BUP can increase reaction times during hot plate and tail-flick tests, whereas

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**Figure 4.** The P2X4 gene expression alterations in methamphetamine (METH) rats with/without buprenorphine (BUP) treatment on day 14. Values are based on mean ± standard error of the mean (SEM), \(n = 7\), \(*P < 0.05\), \(**P < 0.01\), \(***P < 0.001\); * vs control group. ♦ vs METH group.

**Figure 5.** The GABA\(_A\) gene expression alterations in methamphetamine (METH) rats with/without buprenorphine (BUP) treatment on day 5. Values are based on mean ± standard error of the mean (SEM), \(n = 7\), \(*P < 0.05\), \(**P < 0.01\), \(***P < 0.001\); * vs control group. ♦ vs METH group.
coadministration of BUP + METH increases reaction time more than METH or BUP individually. As a result, synergistic effects could occur via the dopaminergic, serotonergic, and/or adrenergic systems [2]. Shahidi et al. demonstrated how the impact of various METH doses affected the expression of BDNF, long-term potentiation, and neuronal apoptosis [1].

There have been no studies on the relation between P2X4 or GABAA gene expression changes under the influence of BUP, which indicates the novelty of our research. Yet, regarding the effect of BUP on GABAA receptor expression following opioid addiction, it has been demonstrated that BUP enhances GABA expression while decreasing DA, implying that it can attenuate the neurotransmitter alterations seen in opioid dependence [47].

Based on the results of this study, there is a significant decrease in the levels of P2X4 and GABAA gene expression in the hippocampus of the addicted to METH groups and treated with doses of 6 or 10 mg/kg of BUP for 5 or 14 days compared to control group. In contrast with our study, other investigations showed that alcohol intake enhances the P2X4 receptor's expression, which affects microglia's ability to mobilize calcium, migrate, and phagocytosis [41]. On the other hand, the P2X4 receptor has a significant role in METH-induced microglial activation responses, according to research on different purinoceptor subtypes [48].

According to the probe test results, after METH administration, there was a significantly shorter amount of elapsed time in the target quadrant compared to the control group. Our findings supported that repeated METH injection impacted memory and learning [49]. Nevertheless, clinical investigations have also demonstrated a moderate dose METH enhances learning and memory function, including visuospatial perception and response speed [49]. There are also claims that preadolescent METH exposure improves the spatial learning of male rats [50, 51]. Conversely, some studies demonstrated various effects of different doses of METH on the nervous system [1, 52, 53, 54]. Therefore, compared to the other groups, the METH (10 mg/kg) group's preference scores, population spike amplitude, and BDNF expression significantly declined. On the contrary, METH (5 mg/kg) significantly elevated these variables compared to the control group. The parameters in the METH (1 mg/kg) and control groups were the same [1].

Our findings showed that, compared to the METH group, the coadministration of METH + BUP enhanced the amount of time spent in the target quadrant. This indicates that BUP slightly reduced the memory impairment caused by METH [55]. The endogenous opioid system might also be crucial in the memory impairment that stress causes [56]. Aligned with our results, the buprenorphine-benzodiazepine combination's positive enhancing effects may be associated, at least partially, with the buprenorphine's high sedative impacts leading to decreased anxiety [55]. Stimulation of κ-opioid receptors increases memory impairment due to the blockade of muscarinic receptors [57]. In agreement with other studies, it has been shown that BUP enhances short-term memory of social reward symptoms by acutely manipulating the opioid system [58].

5. Conclusion

Chronic intraperitoneal injection of METH to male rats reduced expression levels of P2X4 and GABAA receptors genes and memory. Prior research on the effect of METH addiction on GABAA receptors, as data from several case-control studies, has suggested that the GABAA receptor subunit gene is moderately linked to METH use disorder. Administration of BUP with low and high doses of 6 or 10 mg/kg in short and long periods of 5 or 14 days increased the P2X4 and GABAA gene expression levels compared to the METH group.

In general, it is hypothesized that altered expression of P2X4 and GABAA receptors in microglia due to the administration of different doses and periods of BUP to METH addicts could improve neuroinflammatory responses and memory in the CNS. Synergistic effects may develop due to the dopaminergic, serotonergic, or adrenergic systems.

Declarations

Author contribution statement

Shima Roshani, Hana Azizi Khoshsirat: Performed the experiments. Homeira Hatami Nemati: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.
Reihaneh Sadeghian: Performed the experiments; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interest’s statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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