

Effects of Methamphetamine Administration on Serum Levels of Nitric Oxide in Male Rats

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Abstract— Drug abuse is a major problem in many societies that affect many physiological actions in organisms. The aim of this study was to investigate the effects of methamphetamine injection on serum level of nitric oxide in male rats. In this study, male Wistar rats were randomly divided into control, saline, and low dose of methamphetamine (2mg/kg), moderate doses of methamphetamine (4mg/kg) and the high dose of methamphetamine (6mg/kg) receiving groups. Methamphetamine was injected weekly for 45 days (once a week). At the end of experiments, blood samples were collected and consequently serum nitric oxide was measured. Data were compared between groups using one-way ANOVA. Serum level of NO decreased in rats receiving low dose of methamphetamine (2mg/kg) compared to control group ($P < 0.001$). Our results showed that methamphetamine injection can result in decreased serum levels of nitric oxide in male rats, which in turn may lead to impairing physiological function pertaining to NO system.

Keywords—Methamphetamine, Nitric Oxide, Rat.

I. INTRODUCTION

METHAMPHETAMINE is effective metabolites of amphetamine and its toxicity and pharmacological properties is similar to amphetamines. This substance is highly addictive and because of pleasure and euphoric state induction in humans is known as addictive drug [1]. Methamphetamine short-term use causes increased heart rate, blood pressure, respiratory rate and vasoconstriction and arrhythmias, while the long-term use may cause clogging of the arteries, atherosclerosis and pulmonary insufficiency [2]. Studies show that methamphetamine, can increase dopamine synthesis by increasing the activity of tyrosine hydroxylase [3] leading to dependency [4]. Recent studies also indicate a similar reduction in striatal dopamine in methamphetamine consumers [5].

Nitric oxide (NO) is one of the brain's neurotransmitters that its release takes place through the cGMP signaling pathway and by NMDA receptor activity due to entry of calcium ions into the cell and the enzyme nitric oxide synthase activation [6]. Researches indicated that nitric oxide and cGMP signaling pathway play an important role in opioid receptor responses in the immune and Cardio - vascular systems [7]. Also, molecule (NO) plays an important role in the expression, increased tolerance and dependency for methamphetamine [8]. In addition, the role of nitric oxide in the physiological function of muscle [9], endocrine glands

[10] and the reproductive system [11] is clear. Research about the effects of nitric oxide indicate that several factors can affect the serum levels of nitric oxide [12], [13] influencing different physiological functions [14]. Since there are few studies on the effects of methamphetamine on the serum nitric oxide system, this research was carried out to determine the effect of methamphetamine on serum levels of nitric oxide in male rats.

II. MATERIAL AND METHODS

A. Animals

In this experimental- laboratory study, adult male Wistar rats weighting 190 ± 10 grams were obtained from Pasteur Institute of Iran. Animals were kept in $2 \pm 25^\circ \text{C}$ with a light cycle of 12 hours light and 12 hours darkness. Animals had free accesses to laboratory chow and water. The animals were randomly grouped and animals in each group were adapted to the presence of the operator [15].

B. Protocol of Study

Animals were randomly divided into the control, receiving saline, low dose of methamphetamine (2mg/kg) [16], [17], moderate doses of methamphetamine (4mg/kg) [18], [19], and high dose of methamphetamine (6mg/kg) [19]. Receiving groups. Methamphetamine was injected weekly for 45 days. After completion of the experiment, animals were anesthetized with ether and blood samples were obtained using a cardiac puncture method. Blood samples were immediately collected in tubes at 3500 RPM/min and centrifuged for 10 min and the serum were prepared and serum NO levels were measured. This study was performed according to ethical guidelines relating to working with laboratory animals [20].

C. Statistical Analysis

Distribution of data was evaluated for normal distribution which was followed by statistical analysis using SPSS19 software and statistical method of ANOVA. Significant differences between groups were determined by using Game's-Howell post hoc test and difference in level of $p < 0.05$ was considered significant.

III. RESULTS

Table I indicates the serum level of nitric oxide in the experimental groups.

TABLE I
SERUM LEVEL OF NITRIC OXIDE IN RATS

Groups	Nitric Oxide ($\mu\text{mol/L}$)	P
Control	76.55 ± 3.95	—
Saline receiving	60.08 ± 6.1	NS
Methamphetamine (2mg/kg) receiving	47.52 ± 2.76	< 0.01
Methamphetamine (4mg/kg) receiving	74.1 ± 6.52	NS
Methamphetamine (6mg/kg) receiving	67.97 ± 9.14	NS

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The data represent the mean±SD of rats. The values of P (the result of one way ANOVA analysis) are expressed and compared to the control group. NS indicates non-significant difference compared with the control group at $\alpha < 0.05$.

Our results showed non-significant difference between saline and control receiving groups. According to which, injection method of methamphetamine had no effect on the results of the current study. The serum level of nitric oxide in rats receiving low doses of methamphetamine (2mg/kg) decreased significantly ($p < 0.01$), however, there was no significant difference between serum nitric oxide levels of rats receiving moderate or high doses of methamphetamine and control group.

IV. DISCUSSION

The results of this study show that there is not a significant difference in serum levels of nitric oxide among male rats receiving moderate or high doses of methamphetamine compared with the control group, but serum levels of nitric oxide were lower in rats receiving low dose of methamphetamine compared to control group. Our finding indicates that methamphetamine can influence NO system in low dose. In accordance with our finding, other studies indicate that methamphetamine may bring about the acute toxicity of brain [21], reduced release of dopamine and serotonin in the striatum, nucleus accumbens and olfactory tubercle [22] and the effect of methamphetamine on these areas is dose dependent. In line with our study, there are reports showing that methamphetamine administration leads to reduced nitric oxide production in hippocampus and striatum [23]. Meanwhile, methamphetamine use may have also several pathophysiological effects on endocrine system, cardiovascular system, liver, kidney and reproductive system, fetal development [24], [25], in which, the role of NO cannot be neglected.

V. CONCLUSION

Conclusively, the results of this study show that methamphetamine administration can result in decreased serum levels of nitric oxide in male rats. This may come from the inhibitory impact of methamphetamine on expression or activity of the nitric oxide synthase enzyme.

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