

The Effect of Chronic Administration of Amphetamine-Type Stimulants on Oxidative Stress and Inflammation in Wistar Rats

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Received 01/06/2023, Revised 08/09/2023, Accepted 10/09/2023, Published Online First 25/12/2023,
Published 1/7/2024



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Abstract

This study aims to determine the effect of chronic administration of amphetamine-type stimulants at varying doses on inflammation and oxidative stress in Wistar rats. They were given methylphenidate and divided into 4 treatment groups. Furthermore, simple random grouping was carried out to divide the samples into 5 groups, each consisting of 9 rats. These groups included rats given only distilled water as the controls, as well as those given methylphenidate at doses of 10 mg/kg BW, 20 mg/kg BW, and 40 mg/kg BW for 4 weeks as the experimental groups. Statistical analysis was then performed using GraphPad Prism to compare the effects of oxidative stress, systemic inflammation, BDNF, and spatial memory of the Wistar rats. Chronic administration of stimulants led to a significant decrease in glutathione peroxidase levels as well as an increase in the release of IL-6 and tumor necrosis factor- α compared to the control group. Based on the results, the pathways involved in cognitive impairment, which were related to the use of amphetamine-type stimulants played a role in addressing the detrimental effect of substance abuse and their comorbidities.

Keywords: amphetamine-type stimulants, glutathione peroxidase, IL-6, inflammation, oxidative stress, tumor necrosis factor- α

Introduction

Based on a study conducted by the Global Burden Disease, drug dependence, including alcohol and prohibited substances, such as opioids, cocaine,

amphetamine-type stimulants, and cannabis poses a risk of causing paranoia, anxiety disorders, depression, and cognitive impairment, as classified

by World Health Organization's International Classification of Disease (ICD-10). Furthermore, several studies have shown that drug use disorders are more prevalent among men. The United Nations Office on Drugs and Crime (UNODC) stated that a significant number of people aged 15-64 years have used drugs¹. This finding is consistent with the National Narcotics Agency in Indonesia that people aged 15-35 years are more vulnerable to substance abuse. Methamphetamine, locally known as "sabu-sabu" has been abused by more than 33 million people worldwide and its use has continuously increased over the past decades². UNODC data showed that it was the most commonly used drug in Indonesia, ranking second after cannabis with a prevalence of 0.09%¹. A cross-sectional study in Medan also revealed that 55% of a group aged 21 years experienced severe dependence and required intensive therapy in rehabilitation centers³.

The use of crystal methamphetamine has remained a major concern in Indonesia, as indicated by the latest data on seizures, purity, and prices. Furthermore, there are several indications of an increase in ecstasy usage in recent years, which is produced domestically. The transnational organized criminal groups, both inside and outside Southeast and East Asian countries, target Indonesia as a transit and destination country for illicit drugs, specifically methamphetamine¹. Several studies have shown that the use of methamphetamine has negative effects on families, as well as causes loss of productivity, severe public health problems, and dependent on medical intervention resources. According to previous reports, it belongs to a group of synthetic drugs known as amphetamine-type stimulants, such as amphetamine, methylenedioxy-methamphetamine, methylphenidate, and other designer medication^{4,5}.

Methylphenidate is a stimulant used as a first-line treatment for Attention Deficit Hyperactivity Disorder (ADHD) in both children and adults⁶⁻¹⁰. Furthermore, its noradrenergic and dopaminergic activity in the reward brain area is associated with positive subjective effects, such as increased activity, alertness, energy, drug liking, good effects, and stimulation⁹. It also has similar features to cocaine, thereby increasing the potential for its abuse over the

past two decades^{10,11}. In recent years, all methylphenidate derivatives are classified as Schedule II drugs under the U.S. Controlled Substances Act, indicating a high potential for abuse¹⁰, which can lead to physical and psychological dependence^{10,12}. As one of the amphetamine-type stimulants, Methylphenidate has the potential for misuse and dependence in long-term use^{10,13}. This drug has the binding site at the dopamine transporter (DAT) and norepinephrine transporter (NET), which are responsible for the reuptake of dopamine and norepinephrine neurotransmitters from the synaptic cleft^{8,14,15}. This often leads to an increase in DA and NE levels in the synapse. Several studies have also shown that methylphenidate has the ability to increase extracellular dopamine in the striatum, nucleus accumbens, and prefrontal cortex^{8,10}.

Neurotoxicity often occurs due to the presence of harmful effects on the structure or function of the nervous system. This broad term encompasses the reversible or permanent damage caused by substances that affect neuronal components, lead to neuronal collapse, show histological signs of neuronal damage, and/or cause abnormalities in behavior¹⁶. Furthermore, the neurotoxic effects of stimulants include damage to dopaminergic and serotonergic terminals, neuronal apoptosis, oxidative stress, as well as activation of astroglia and microglia, which elicit a neuroinflammatory response in the brain^{4,17}. Stimulants have the ability to induce neurotoxicity primarily in certain brain areas, such as the hippocampus and amygdala^{18,19}.

Amphetamine-type stimulants have been reported to induce oxidative stress by generating free radicals, increasing H₂O₂ concentration, as well as reducing the catalase activity, and antioxidant levels, such as glutathione, and glutathione peroxidase (GPx) in the rat brain. Highly reactive atoms and reactive oxygen species can cause cellular damage^{16,18,20-22}. Inflammatory effects caused by the use of stimulants often lead to the production of IL-6, IL-8, and tumor necrosis factor by neuron cells, as well as myelin degeneration in rats^{4,16,20,23}.

Several studies have shown that medium to high doses of stimulants can damage dopaminergic and serotonergic neurons in experimental animals, but

recreational use in humans does not cause neuronal degeneration. In some humans, the use of methamphetamine can lead to a loss of functions due to persistent dopamine deficits as well as metabolic and structural abnormalities in the brain, leading to mild cognitive impairment^{4,16}. This cognitive impairment commonly affects various functions, including decision-making, response inhibition, planning, working memory, and attention²⁴.

In animals, behavioral impairment is often characterized by increased locomotion activity and stereotypical behavior, as well as deficits in prepulse and latent inhibition or sensitization of behavior. Furthermore, a previous study showed that amphetamine-type stimulants caused cognitive impairment in animals^{16,25}.

This study employed methylphenidate as a substitute for methamphetamine because they have similar effects. According to the Narcotics Law Number 35 of 2009, these drugs are Schedule I narcotics that are

not produced and their use for study purposes should be strictly regulated. Therefore, the use of amphetamine in Indonesia is often challenging due to these regulations and guidelines. As an alternative, an animal model with methylphenidate as a substitution for amphetamine was used because both substances had a similar pharmacological profile as amphetamine-type stimulants. Methylphenidate is a Schedule II psychotropic drug that has a strong addictive effect but can be used for both study and treatment (under a doctor's supervision).

At present, there is no effective treatment for cognitive impairment caused by the use of amphetamine-type stimulants^{5,18}. Therefore, this study aims to determine the effects of varying doses of methylphenidate on interleukin-6 (IL-6), and glutathione peroxidase (GPx) in Wistar rats given. The results of this study can provide a theoretical basis for interventions in cognitive impairment among chronic users of amphetamine-type stimulants.

Materials and Methods

Animal study

The animal experiment was performed after ethical approval by the local ethical committee of research in Universitas Sumatera Utara (Number 1188/KEP/USU/2021). All procedures were performed with consideration to minimize pain and discomfort. Twenty-eight Wistar rats, weighed 200-250 g, 12 weeks old were divided into 4 groups (n=7). Rats were acclimatized for 1 week prior to the experiment in room temperature with a 12/12-h dark/light cycle and had food and drinking water ad libitum. Each group was treated with various doses of methylphenidate (10,20 and 40 mg/kg BW) per oral for 4 weeks. Distilled water was given in the control group. Blood serum was collected at the end of the experiment from cardiac puncture under deep anesthesia.

Measurement of Glutathione Peroxidase (GPx), Interleukin 6 (IL-6) and Tumor Necrosis Factor- α (TNF- α)

Serum GPx, IL-6 and TNF- α detection was carried out with the ELISA Kit (BT LAB #E1242Ra, #0135Ra, and #E0764Ra, respectively) following the

manufacturer's instructions. In brief, 40 μ l serum and 10 μ l antibodies were plated into the wells and then mixed with 50 μ l streptavidin-HRP. After 60 minutes of incubation at 37°C, the plate was washed with buffer solution and then substrates were added to the mixture. After 10 minutes of incubation in the dark and 37°C, the stopping solution was added and the optical density was measured immediately in a microplate reader at 450 nm. To obtain quantitative analysis, standard solutions were measured in the same plate as samples²⁶⁻²⁸.

Statistical Analysis

Data were analyzed with the use of GraphPad Prism[®] version 9 for Mac (GraphPad Software, La Jolla, CA, USA, www.graphpad.com)²⁹. ANOVA test followed by Dunnett's post hoc test were used to compare the differences among groups. All data were expressed as mean \pm standard error of the mean (SEM). P value < 0,05 was accepted as significance³⁰.

Results and Discussion

Serum level of GPx, IL-6, and TNF- α after chronic oral administration is shown in Table 1. Methylphenidate (MPH) caused a decrease in GPx levels dose-dependently. Using one way ANOVA followed by post hoc test, a significant decrease was found in the group treated with 40 mg/kg MPH compared to the control group ($p < 0.05$), as shown in Fig. 1.

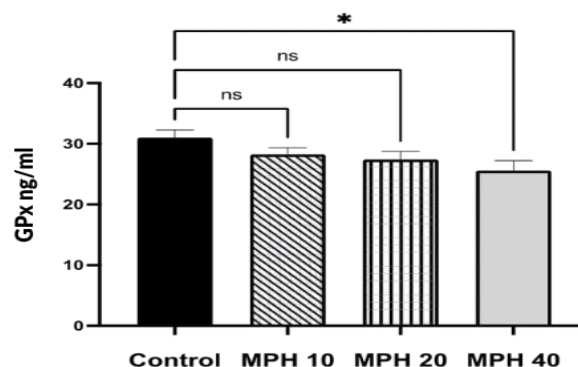


Figure 1. Serum level of GPx significantly decreased following 40 mg/kg methylphenidate chronic administration compared to control group. * $p < 0,05$ (ANOVA test followed by Dunnett's post test)

Table 1. The effect of various doses methylphenidate on GPx, IL-6, and TNF- α

Groups	GPx ng/ml	IL-6 pg/ml	TNF- α ng/L
Control	31.05±3.70	3.33±0.56	136.2±14.42
Methylphenidate (10 mg/kg)	28.26±3.28	3.56±0.26	140.0±10.18
Methylphenidate (20 mg/kg)	27.42±3.93	3.62±0.66	153.9±22.36
Methylphenidate (40 mg/kg)	25.60±4.87*	4.17±0.67*	158.9±17.91*

* $p < 0.05$; ANOVA with Dunnett's post hoc test compared to control.

Beside decreasing antioxidative capacity, chronic administration of high dose methylphenidate to Wistar rats caused an increase in IL-6 levels dose dependently. Significant increase of IL-6 level was found in the experimental groups treated with 40 mg MPH compared to the control ($p = 0.03$), as shown in Fig. 2.

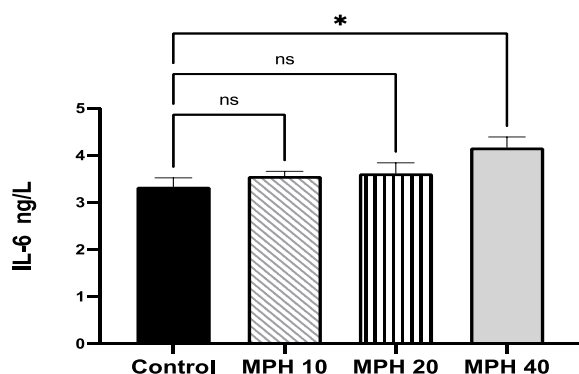


Figure 2. Serum level of IL-6 significantly increased in the group treated with 40 mg/kg methylphenidate chronic administration compared to control group. * $p < 0,05$ (ANOVA test followed by Dunnett's post test)

Increased inflammation after chronic high dose methylphenidate administration was confirmed by measurement of TNF- α level in serum. Our data confirmed that there was a dose-dependent increase in the mean TNF- α levels in the experimental groups given doses of 10 mg, 20 mg, and 40 mg of methylphenidate compared to the control. A one-way ANOVA test was then used to assess the comparative effects between the control and experimental groups, and the results showed a significant difference ($p = 0.04$). Multiple comparisons also revealed that groups that received 40 mg/kg methylphenidate differed significantly from the control, as shown in Fig. 3.

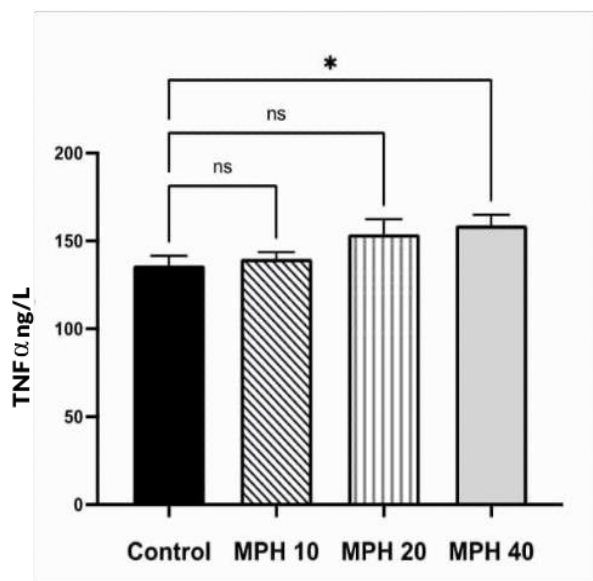


Figure 3. Serum level of TNF- α significantly increased in the group treated with 40 mg/kg methylphenidate chronic administration compared to control group. * $p < 0,05$ (ANOVA test followed by Dunnett's post test)

Several reports had shown that a high dependence on methylphenidate among humans caused neurodegeneration along with various harmful effects. Experimental studies also showed the effect of the drug on apoptosis activation, namely oxidative stress, inflammation, and ultimately cell death²³. The results of this study revealed that chronic administration of methylphenidate at varying doses of 10, 20, and 40 could decrease GPx levels in the blood serum of adult Wistar rats. This finding was in line with the previous research that its intake at doses of 10 mg/kg BW and 20 mg/kg BW significantly decreased the levels of GSH, superoxide dismutase, glutathione peroxidase, and glutathione reductase activity in the hippocampus and cerebral cortex. Chronic and acute administration of methylphenidate and methamphetamine-like substances could potentially cause various brain damage and disrupt the repair of the brain's antioxidant defense system, leading to the degeneration of dopaminergic neurons^{31,32}. Apart from the antioxidant function of GSH to prevent lipid peroxidation, it also acted as a neuroprotective agent against oxidative stress triggered by certain chemicals. Studies on rats given chronic methamphetamine showed the occurrence of cognitive decline and increased malondialdehyde

(MDA), TNF- α , and IL-1 β levels. These effects were caused by a significant decrease in superoxide dismutase (SOD), GPx, and glutathione reductase (GR) activity. Another study also reported that the chronic administration of methylphenidate could cause a decrease in SOD, GPX, and glutathione reductase activity levels^{23,33,34}.

Previous studies showed that the intake of methamphetamine and methylphenidate increased the inflammatory process through IL-6 and TNF- α ^{4,16,19,23,35,36}. The major neurotoxic effect induced by methylphenidate was the inflammatory process. Furthermore, inflammation involved the ability of the immune system to react to harmful stimuli and it relied on several molecules and enzymes. Among these molecules, interleukin played a role in modulating behavior at the cellular level and affected the signaling process³⁶. The acute administration of methylphenidate with varied doses of 2, 5, 10, and 20mg/kg caused an increase in the levels of inflammation markers in the hippocampus and cerebral cortex compared to the control. This increased level induced neurodegeneration in areas mediated by glutamate and α_2 -adrenergic receptors²³.

The administration of stimulants at low and high doses could affect neuroinflammation in the brain through the activity of glial cells, thereby triggering addictive behavior and neurotoxicity. Microglia are immune cells in the brain that can easily cause nerve damage due to the secretion of chemokines and cytokines when activated³⁷⁻³⁹. Furthermore, cytokines are endogenous immunomodulatory peptides whose functions are related to the activation of immune cell systems, cell death, and the survival of cells in response to damaging factors. For years, immune system mediators did not show effects on brain cell activity under physiological conditions. This change in activity only occurred under neuropathological conditions due to damage to the brain-blood barrier permeability. However, recent studies showed that cytokines played an important role in synaptic plasticity, neurogenesis, learning processes, and memory under normal physiological conditions along with their role in inflammatory and neuropathological immune processes⁴⁰. The role of these compounds in the learning of memories and synaptic plasticity had been studied extensively. The

outcomes of these processes depended on the specific cytokine, its concentration in the brain, the receptors available for binding and activating signal transduction pathways, as well as the conditions leading to its release⁴¹.

The presence of excessive astrocytes in the central nervous system could protect the brain and maintain its homeostasis. These cells also secreted various cytokines, including tumor necrosis factor, interleukins, and chemokines, which activated neurotoxicity. Previous studies also found the activation and proliferation of microglia in the central nervous system among patients with methamphetamine withdrawal, indicating a tendency for proliferation for at least 2 years. Methamphetamine could impair central and peripheral immune function, leading to the production of inflammatory cytokines, which enter the central nervous system by inducing glial cells to produce similar compounds. Furthermore, this caused high inflammatory conditions in the central

Conclusion

This study revealed that amphetamine-type stimulants, such as methylphenidate and methamphetamine could increase oxidative stress and inflammation. Furthermore, this suggested that

Acknowledgment

This study was carried out with TALENTA 2021 Fund (Grant Number: 352/UN5.2.3.1/PPM/SPP-

Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.

Authors' Contribution Statement

V. C. and M. I. designed the study. V. C. and M. I. performed the experiments. V. C. and M. I. performed the simulations. D. K. S., F. I. F., and M.

immunity^{38,41}. Studies on rats given methamphetamine showed impairment in the central and peripheral nervous immune systems as well as changes in cytokines (TNF- α , IL-6, dan IL- β) in peripheral plasma and brain regions³⁷. Other studies also revealed that immunomodulatory signals, such as TNF- α were important in regulating synaptic plasticity in specific brain areas with essential implications for understanding the pathophysiology of substance use disorders. Microglia and astrocytes were reported to release interleukin-6 in the central nervous system. Previous studies showed that acute exposure to IL-6 inhibited Long-term potentiation (LTP) in the hippocampus and tended to inhibit mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling. Furthermore, excessive expression of IL-6 in mice astrocytes caused a decrease in LTP in the dentate gyrus. LTP mechanisms are associated with the storage of memory and learning⁴¹⁻⁴⁴.

the pathways involved in neurotoxicity and cognitive impairment related to the use of these stimulants played a role in addressing the impact of substance use disorders and their comorbidities.

TALENTA USU 2021) from Universitas Sumatera Utara.

- The author has signed an animal welfare statement.
- Ethical Clearance: The project was approved by the local ethical committee at University of North Sumatra (1188/KEP/USU/2021).

M. A. expressed and purified all proteins. J. analyzed the data. A. S. R., E. E., S. I., A. Kh., and M. R. wrote the paper with input from all authors.

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تأثير الإدارة المزمنة للمنشطات من نوع الأمفيتامين على الإجهاد التأكسدي والالتهاب في فئران ويستار

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الخلاصة

تهدف هذه الدراسة إلى تحديد تأثير تناول المزمّن للمنشطات من نوع الأمفيتامين بجرعات متفاوتة على الالتهاب والإجهاد التأكسدي في فئران ويستار. تم إعطاؤهم ميثيلفينيديت وتم تقسيمهم إلى 4 مجموعات علاجية. علاوة على ذلك، تم إجراء تجميع عشوائي بسيط لتقسيم العينات إلى 5 مجموعات، تتكون كل مجموعة من 9 فئران. تضمنت هذه المجموعات الفئران التي أعطيت فقط الماء المقطر كعناصر تحكم، بالإضافة إلى تلك التي أعطيت ميثيلفينيديت بجرعات 10 مجم / كجم من وزن الجسم، و 20 مجم / كجم من وزن الجسم، و 40 مجم / كجم من وزن الجسم لمدة 4 أسابيع كمجموعات تجريبية. ثم تم إجراء التحليل الإحصائي باستخدام GraphPad Prism لمقارنة تأثيرات الإجهاد التأكسدي والالتهاب الجهازية و BDNF والذاكرة المكانية لفئران Wistar. أدى الاستخدام المزمن للمنشطات إلى انخفاض كبير في مستويات الجلوتاثيون بيروكسيداز وكذلك زيادة في إطلاق IL-6 وعامل نخر الورم ألفا مقارنة بمجموعة التحكم. بناءً على النتائج، لعبت المسارات المتورطة في الضعف الإدراكي، والتي كانت مرتبطة باستخدام المنشطات من نوع الأمفيتامين، دورًا في معالجة التأثير الضار لتعاطي المخدرات والأمراض المصاحبة لها.

الكلمات المفتاحية: المنشطات من نوع الأمفيتامين، الجلوتاثيون بيروكسيداز، الإنترلوكين 6، الالتهاب، الإجهاد التأكسدي، عامل نخر الورم ألفا.