Title: MDMA and the Brain: A Short Review on the Role of Neurotransmitters in the Cause of Neurotoxicity

Running title: Neurotoxicity of MDMA

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Highlights

- MDMA is a popular recreational drug of abuse that has serious effects on animals’ behavior and mental health even though after the long abstinence. Hence, the choices of treatment for MDMA abusers who suffer from the symptoms need to be explored to reduce the effects. Unfortunately, the mechanism of action on how MDMA affects the body and brain needs to be studied first before the best treatment could be applied.

- MDMA administration was reported previously to cause the excessive release of both hippocampal glutamate and 5-HT concentrations mediated by the activations of NMDA receptors and 5-HT receptors. The condition contributes to the damage of the neurons in the brain.

- MDMA affects neurotransmitter systems in terms of the alteration of serotonergic, dopaminergic and GABAergic mechanism.

- MDMA also affect memory and learning due to the disruption of hippocampal function, mainly through the alterations of dopaminergic as well as NMDA receptors.

- Several treatments for MDMA neurotoxicity were reported from the previous study such as the manipulation of the reward pathway, protecting the neurons and regulating the normal level of 5-HT.

Plain Language Summary

The amphetamine-type stimulant drugs such as MDMA or ecstasy becomes the choice of drug abuse among young people and adults besides opioid. It is due to the excitement feelings experienced immediately after the administration. The side effects of MDMA are most prominent in the brain and behavior even though after a long time of abstinence. People who want to stop taking the drug usually failed to do so because of the withdrawal effects. Moreover,
other symptoms such as the lower performance in learning and memory and anxiety could disturb their everyday life. Considering this issue, this article reviews the neurotoxic effects of MDMA towards the neuronal brain and MDMA targeted proteins such as receptors and neurotransmitter systems that alter the brain and body functions so that when it comes to finding the treatments, researchers could target these areas for the treatment option. In the field of research, the new findings are always welcomed for the sake of people and community, especially in addiction.
ABSTRACT:

N-Methyl-3, 4-methylenedioxyamphetamine (MDMA) or ecstasy is a recreational drug of abuse. It is a synthetic substance that affects the body systems which requires more findings on its mechanism of actions and the choice of treatments. MDMA provides an immediate enjoyable feeling by stimulating the neurotransmitters release such as dopamine and serotonin in the brain. Unfortunately, abnormal regulation of the brain neurotransmitters, as well as the increase of oxidative stress, causes damage to the neuronal brain after the MDMA exposure. To date, only a few studies have been done regarding on its treatment. Thus, the treatments for the MDMA consequences need to be further explored mainly by targeting on its mechanism of action in the brain system. Hence, this article presents a short review regarding the recent findings relating to the role of neurotransmitters in the cause of MDMA neurotoxicity. It will be useful for the future research in the elucidating the potential treatment based on the targeted mechanisms to treat the neurotoxic effects of MDMA.

Keywords: MDMA, Neurotransmitter, Brain injuries, Memory, Therapy

1. INTRODUCTION:

Substances abuse remains a worldwide issue. Statistic of the total drug addicts in world drug report by United Nations on Drugs and Crime (UNODC) shows an increasing number of drug users every year. From 2006 until 2015, the global trends in an estimated number of drug users from the age of 15-64 years old increased from 208 million to 255 million, while people with drug user disorders increase from 26 million to 29.5 million (UNODC, 2017).
In conjunction with the biggest issue of opiate, the alleviating number of amphetamine-type stimulants (ATS) users and disorders are unnoticed, especially MDMA. MDMA has been declared as the illegal substance in most countries. Some countries such as Norway, Germany, and Canada have classified it under Schedule I, which is illegal to buy or possess without a license. National Survey on Drug Use and Health 2004 reported that more than 11 million people have tried MDMA for at least one time in their life (NIDA, 2006). Considering the new trend preference of the substance abuse, the effects caused by MDMA will be reviewed by focusing on the neurotoxicity and neurodegeneration. Besides, the targeted mechanism for the treatment of MDMA’s effects will be discussed.

Current understanding about the action of MDMA is on its effects towards the psychological changes and dependence. Psychological changes are explained as the euphoric effect, sharpened sensory perception, increase in social performance, increase in empathy, and greater tolerance of their feeling (Kalant, 2001). MDMA dependence is however still less understood, but it has been reported to be different from other drugs or alcohol (Degenhardt, Bruno, & Topp 2010). The biological mechanism that was believed to be involved in MDMA exposure are the changes of the serotonergic system which affects serotonin (5HT) and dopamine. Interestingly, there was a study that was not in line with the theory (Popova, Forsblad, Hashemian, & Jacobsson, 2016). This proven that there is still limited knowledge about the MDMA mechanisms. Therefore, more extensive researches are in needs in order to reveal strong evidence about the exact mechanism of MDMA toxicities.

Historical evidence showed that the mechanism of MDMA upon its administration is through its binding affinity towards the serotonin receptors (Liechti, Saur, Gamma, Hell, & Vollenweider, 2000). The activation of these receptors triggers a massive release of neurotransmitters. MDMA
also inhibit serotonin reuptake by its binding to the transporter protein, thus prolonging signaling at the synapses. Besides that, the MDMA bindings to the plasma membrane transporters are also translocated into the cytoplasm and promote nonexocytotic transmitter release (Verrico, Miller, & Madras, 2007). This causes the accumulations of the neurotransmitters in between the synapses, which can result in excitotoxicity. Although MDMA was reported to improve the emotional and personality problems in psychotherapy as mentioned earlier, in the long term, the effects can be more adverse. The massive release of serotonin that initially gives the psychotic symptoms can also give rises to the chemical damage to the cells that release it (Kalant, 2001).

Due to the disruption of the normal brain biological system, MDMA can cause damage to the brain structure and nervous system, which increases the loss of neurons and alters the brain functions. Therefore, three main focuses will be reviewed in this present article based on the recent studies on the effects of MDMA abuse, which include neuronal damage, neurotransmitters alteration and memory impairments.

1.1 Effects of MDMA on neuronal damage

Neuronal damage is the loss of brain cells either because of the alterations by toxic substances or certain diseases. Neuronal cell death can occur due to the increased production of free radicals by neurotoxins. Memory and learning impairment by MDMA is also resulted from the neuronal damages and dysfunction of the nervous systems. MDMA administration was studied to cause neurodegeneration by enhancing the release of free radicals. The previous study showed that the free radicals such as reactive oxygen generation inhibit the activity of mitochondrial complex-I (Karuppagounder et al., 2014). The inhibition of mitochondria cause the loss of energy, consequently cause neuronal death. Apart from that, the effects of MDMA was also observed in the changes MDMA hypothalamic–pituitary–adrenal (HPA) axis due to the increases of cortisol
levels, that show neuropsychobiological stress in MDMA users (Parrott et al., 1995). Besides that, an excessive autophagosome is also contributed into the neuronal damage induced by MDMA which was studied in cultured cortical neurons (Li et al., 2014). The recent finding on MDMA neurotoxicity in mice was suggested to be involved with the elevation of the neuronal nitric oxide synthase in the dopaminergic nigrostriatal system that occurred only in mice that received 28 drug administrations (Costa, Morelli, & Simola, 2018).

Apart from that, as mentioned previously, MDMA is a drug that was reported to have binding affinity for the specific serotonin receptor. The alteration of the serotonin receptor function (5HT1A) was found in repeated MDMA, following high doses MDMA administration (Bradbury, 2014). A study by Collins, Gudelsky, & Yamamoto, (2015) provides evidence that MDMA can also increase the glutamate release which was mediated by serotonin receptors. Subsequently, NMDA receptors are also activated, which then causes the loss of parvalbumin interneurons within the dentate gyrus of the brain. The loss of parvalbumin neurons in the brain upon MDMA exposure was supported by another study by Anneken, Cunningham, Collins, Yamamoto, & Gudelsky (2012), which further explained that the diminished number of the neurons were associated with the evokes of serotonin or 5-hydroxytryptamine (5-HT) in the hippocampus and the involvements of cyclooxygenase activity that contributes to the increase of glutamate in the dentate gyrus. It can be generally concluded that the excitatory of both hippocampal glutamate and 5-HT concentrations mediated by the activations of NMDA receptors and 5-HT receptors are part of the contributors to the neuronal damage. MDMA was also reported to have considerable effects on 5-HT activity and caused damage to the 5-HT neuritic tree (Mercer et al., 2017). Deficiency of serotonin transporter also modulated MDMA-mediated neurotoxicity in rats (Lizarraga et al., 2017).
In the long-term effect of MDMA exposure, it was proven that MDMA could reduce the level of serotonin in the cerebrospinal fluid of rats (Mueller et al., 2009; Mustafa et al., 2018). However, some researchers have suggested that MDMA may be able to cause a long-term 5-HT down-regulation without causing structural damage to serotonin neurons (Kish, 2002). The rationale is MDMA-induced serotonin deficit has been interpreted as neurotoxicity. Unfortunately, there is still ongoing debating whether the deficit of serotonin is reflecting the damage of the neurons (Baumann, Wang & Rothman, 2007). However, in clinical study, the brain imaging studies on MDMA users who had been abstinent for 20 weeks or longer have not revealed less SERT binding in the brains (Buchert et al., 2003). The brain imaging studies in human have, at the very least, provided evidence of altered serotonergic functioning in recreational ecstasy users.

Neurotoxic effects on dopamine neurons were also reported in rat exposed to MDMA at a low dose, indicated by the widespread reduction of the number of the neurons upon MDMA exposure (Cadoni et al., 2017; Costa, Morelli & Simola, 2017). Breivik et al., (2014) also reported that MDMA in long-term exposure affected the serotonergic and dopaminergic transport systems in the rat brain. Tao, Shokry, Callanan, Adams & Ma (2015) suggested that serotonergic transmissions play a role in MDMA-induced syndrome.

In chronic MDMA, serotonergic and GABAergic signaling impairments were the reason that contribute to the hippocampal protein deficits in adolescent and young adult rats, subsequently demonstrated the decreased of specifics structural cytoskeletal neurofilament proteins (Garcia-Cabrerozo & Garcia-Fuster, 2015). A recent finding by Mercer, Higgins, Lau, Lawrence, Beart., (2017) suggested that the damage to GABAergic neurons may be a secondary neurotoxicity in repeated and high dose administration of MDMA, not an initial primary action of MDMA. A
study by Costa, Morelli & Simola, (2017) reported that MDMA alters the expression of several proteins involved in GABA neurotransmission. MDMA altered proteins that are associated with GABA neurotransmission, such as the expression of the different GABA transporters (Simantov & Peng, 2004).

Hence, MDMA causes neurotoxicity in different mechanisms; either directly acts on the neuronal brain or by other indirect pathways. The future study for the treatment of the detrimental effects caused by MDMA should be focusing on the compounds that have the healing properties towards the abnormal neurotransmitter regulations and the damaged neurons.

1.2 Effects of MDMA on memory and learning

Series of published researches discovered that MDMA cause the impairment of learning and memory. A clinical study showed that MDMA users displayed relatively discrete declarative memory impairments which were quantified by hair analysis in duration of six month, and the pure chronic MDMA use was found to be associated with decreased performance in declarative memory (Wunderli et al., 2017). Another clinical study proved that MDMA users had significantly lower quality of working memory as compared to the control groups (Potter, Downey, & Stough, 2013).

The impairment of memory by MDMA was also studied in vivo. Memory deficit was detected in young mice exposed to MDMA that was explained by the increased expression of early markers of plasticity, observed through the reduction in dopaminergic markers in the substantia nigra (Abad, Camarasa, Pubill, Camins, & Escubedo, 2016). The previous study by Moyano & Frechilla, (2004) reported that acute MDMA in rat diminished the functions of hippocampal calcium and calmodulin-dependent kinase type II (CaMKII) and reduced the levels of synaptic
N-methyl-D-aspartic acid (NMDA) receptor subunits, which could explain the impairment of passive avoidance learning. NMDA receptor, a type of ionotropic glutamate receptors was reported to be also involved in the rewarding effects of MDMA (Garcia-Pardo, Escobar-Valero, Rodriguez-Arias, Minarro, & Aguilar, 2015). MDMA-treated rats also displayed a deficit in recognition memory in Novel Recognition Test (NORT), which was believed to occur due to the damage of dopamine neurons (Cadoni et al., 2017). Hence, the effects of MDMA on memory are seen through the alterations on dopaminergic as well as the disruption of NMDA receptors. Thus, the main focus of the researchers for the future studies should be on the treatment pointed through these targeted areas.

1.3 Previous studies on the therapeutic targets for MDMA toxicity

The toxicity effects induced by MDMA bring the researchers towards exploring for its treatments. Several therapeutic targets of MDMA abuse were suggested by the researchers. For example, Garcia-Pardo, Rodriguez-Arias, Minarro & Aguilar (2017) recently studied the role of nitric oxide (NO) pathway in MDMA rewards and they suggested the therapeutic option for MDMA abuse by manipulating the pathway. In the previous study, they suggested that NMDA receptor antagonism might be one of the therapeutic targets for MDMA-related problems (Garcia-Pardo et al., 2015). In addition, the potential treatments that were aimed to protect toxicity caused by MDMA were also studied. Dextromethorphan (DM) and its metabolite Dextrorphan (DX) were observed to may have a protective effect against MDMA-induced serotonergic toxicity in the brain (Finnegan, Skratt, Irwin, & Langston, 1990; Ma et al., 2016). Dextrorphan was believed to prevent the effects of serotonin depletion by MDMA in the striatum, hippocampus, and cortex (Finnegan et al., 1990).
In addition, ketopferon treatment has reduced the decreased number of parvalbumin-positive GABA interneurons in the dentate gyrus of the hippocampus upon repeated MDMA administrations. The ketoprofen unfortunately, did not prevent the 5-HT depletion in the hippocampus (Anneken et al., 2012). Another therapeutic option for MDMA abuse is Rilmenidine. Rilmenidine is one of the antidepressive agents (Laurent & Safar, 1992). Rilmenidine was found recently to protect against MDMA-induced injury via full preservation of 5-HT arbours that was shown through an image analysis (Mercer et al., 2017). Besides that, co-administration of acute MDMA and mephedrone had shown antidepressive-like activity and improved memory in mice (Budzynska & Michalak, 2017). Another natural substance was shown to prevent apoptosis induced by MDMA. Ginger was proven to reduce the activation of the caspase cascade that responsible for cell death (Asl et al., 2013).

Most of the recent studies and suggestions from the previous researchers regarding on the targeted treatment for MDMA abuse focused on attenuating neurotoxicity and neurotransmitters excitotoxicity in the brain. For the future findings, a great attention should be given to the potential therapeutic substances, either synthetic or natural substances that can attenuate the long-term effects of MDMA through those involved mechanisms.

**DISCUSSION**

In summary, people especially young people had chosen MDMA as their current preferences of the desired substance of abuse due to its stimulating effects. The energy that they get from the
stimulant's effects had been considered as an energy-giving for their basic life functions that makes MDMA as a drug of choices. However, the effects are satisfactorily detrimental to our body systems, particularly in neuronal cells. Therefore, it requires more advanced researches on that field either on the effects of MDMA on brain damage and behavior or the treatments for MDMA disorders.

**Ethical Considerations**
There are no ethical guidelines for the works of this review article.

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