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Anthocyanin as Neuroprotector for Methamphetamine-Induced Neurotoxicity

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Abstract---*Methamphetamines are chemicals that might affect brain function and causes the development of addiction and other brain pathologies. It increased dopamine stimulation and would increase the formation of free radicals leading to dopaminergic neurotoxicity. Various therapeutic targets have been developed to prevent or minimize the negative effects of methamphetamine use. Increased level of oxidative stress has been considered as a potential trigger for neurotoxicity hence the expected ability for the administration of antioxidants to prevent damages caused by free radicals. The administration of antioxidants is expected to provide protective effects and prevent further damages created by methamphetamine exposure. Anthocyanin is a type of flavonoid is a potentially effective neuroprotector candidate for preventing neuronal cell death reduction, and this compound works with various mechanisms.*
Keywords---*anthocyanin, methamphetamine, neurotoxicity, neuroprotector.*

1 Introduction

Drug and substance abuse has continuously become a significant global social issue. To date, the scale of the prevalence of drug and substance abuse worldwide is estimated to be 0.6% of the world adult population or equals about 29.5 million people (UNODC, 2017). This abuse has led to dependence or addiction that might cause both physical and mental effects, and even neurotoxicity or damages in the central nervous system (Sharma *et al.*, 2014; Lu R *et al.*, 2017; Allan *et al.*, 2016).

Psychostimulant substances including methamphetamines are chemicals that might affect the brain function and causes the development of addiction and other brain pathologies (Sharma *et al.*, 2014; Krasnova *et al.*, 2016). Long term and high dose short term use of methamphetamine could cause neurotoxic effect and incite several observable neurochemical changes, both in humans and animals. These changes are commonly found in striatum (caudate nucleus-putamen), hypothalamus, thalamus, cortex, and hippocampus (Yamada, 2008; Chen *et al.*, 2014; Salamanca *et al.*, 2015; Volkow *et al.*, 2015; Heinsleigh, 2017). The occurring significant and persistent changes in the transporter, receptor, or enzyme levels are observed during the withdrawal phase and they signify several fundamental changes in the neurons. This abnormal condition contributes to the development of the brain pathology of addiction (Volkow, 2015; Koob, 2009; Dewi & Mustika, 2018).

During methamphetamine administration, the increased dopamine stimulation would increase the formation of free radicals leading to dopaminergic neurotoxicity. Subsequently, persistent deficits of dopamine, tyrosine hydroxylase protein, and dopamine transporter (DAT) levels might follow *(Wu et al.*, 2006; McFadden & Vieira-Brock, 2016). In mice provided with 10 mg/kg methamphetamines four times, decreased levels of dopamine, tyrosine hydroxylase activity, and DAT was evident, as well as the decreased VMAT bonding in the striatum after 24 hours. The decrease or loss of dopamine markers shortly thereafter has been correlated with the process of neuronal degeneration leading to the loss of neuronal components, which has been proposed as a histological marker of

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neuronal damages and behavioral abnormalities (Moszczynska & Yamamoto, 2011; Anneken *et al.*, 2015; Moszczynska & Callan, 2017; Partama *et al.*, 2018).

Various therapeutic targets have been developed to prevent or minimize the negative effects of methamphetamine use. Increased level of oxidative stress has been considered as a potential trigger for neurotoxicity hence the expected ability for the administration of antioxidants to prevent damages caused by free radicals. The administration of antioxidants before methamphetamine exposure is expected to provide protective effects and prevent further damages created by methamphetamine exposure (Gholipour, 2016; McDonnell-Dowling & Kelly, 2017).

2 Mechanism of Methamphetamine-Induced Neurotoxicity

Neurotoxicity involves the central nervous system damage that might lead to complications and significant distress. It can be caused by neurotoxins, psychostimulants, or excessive use of drugs. Neurotoxic effects of methamphetamine have been correlated with the pattern and dose of usage. Severe neural damage might cause serious consequences including coma, paralysis, dementia, incoordination, and convulsion. Mild damage might lead to memory loss, disorders of communication and motor function, and concomitantly decreases the patient's quality of life (Kousik *et al.*, 2014; Sharma *et al.*, 2014). Methamphetamine affects brain functions hence the development of addiction and varied brain pathology. This psychostimulant could permeate the blood-brain barrier to become a serum protein and lead to a somewhat adverse effect on the brain's microenvironment, cell edema, and even neuronal death. The damage of the blood-brain barrier is the first stage leading to further processes of neurotoxicity (Sharma *et al.*, 2014; Yadnya *et al.*, 2016).

As a whole, several mechanisms are involved in the occurrence of methamphetamine neurotoxicity. Those include hyperthermia, oxidative stress, excitotoxicity, neuroinflammation, and other mechanisms such as microglial activation, blood-brain barrier dysfunction, and apoptotic pathway activation (Heinsleigh, 2017). Methamphetamine produces reactive oxygen species (ROS) such as OH^- (hydroxyl radicals), H_2O_2 (hydrogen peroxide), and $O2^-$ (superoxide anion) due to the increased dopamine auto-oxidation. ROS increases oxidative stress markers like lipid peroxidase and activates protease that triggers the cascade of cell death. The concurrently occurring mitochondrial metabolism dysfunction also induces neurotoxicity through inhibitions of the Krebs cycle and the electron transport chain. Other neurotransmitters such as glutamate (the main excitation neuron) also play an important role in the occurrence of neurotoxicity. Glutamate accumulation causes Ca^{++} influx leading to increased intracellular Ca^{++} level. This high intracellular Ca^{++} level triggers the intracellular cascade to activate protein kinase, phosphatase, NOS (nitrous oxide system) to produce NO, leading to endoplasmic reticulum stress and activation of the apoptotic pathway. Furthermore, the process of inflammation occurs, marked by the methamphetamine-induced activation of NFKB, leading to the transcription of proinflammatory cytokines in the microglia. The result is the increased levels of IL-6, IL-1β, TNF-α, MCP-1, dan ICAM-1 (Yang *et al.*, 2018).

4 The Therapy of Methamphetamine-Induced Neurotoxicity

Severe neurotoxicity induced by drugs or psychostimulants has been demonstrated in various studies. Efforts, as follow, have been attempted for developing neuroprotection from such damages (Sharma *et al.*, 2014):

a) 5-HT receptor modulator
   Psychostimulants induce hyperthermia by involving biogenic amine neurotransmitters. One potent biogenic amine that might be involved is 5-HT which affects the medication-induced body temperature regulation and modulates the release of other neurotransmitters through the receptor mechanism in the CNS. The serotonergic receptor has also been implied in the blood-brain barrier damage and edema. Serotonin receptor blockade inhibits the blood-brain barrier damage caused by various stressors and plays an important role in inhibiting the psychostimulant-induced neurotoxicity (Muller & Homberg, 2014).
b) Antioxidant components
   Increased oxidative stress has been proposed as one of the mechanisms leading to neurotoxicity due to the release of free radicals and lipid peroxidase. This state might damage the cell membrane and the blood-brain barrier, consequently leading to cell edema and damage. Several types of antioxidants have demonstrated protective effects from the process of neurotoxicity (Sharma, 2014). The administration of high dose amphetamine or methamphetamine increases free radicals, and antioxidant administration before the

amphetamine exposure has led to the delay of amphetamine-induced dopaminergic deficit (Brown & Yamamoto, 2003).

c) Neurotropic factors and its combination
The benefit of neurotrophic factors has been greatly studied in CNS trauma. The addition of exogenous neurotrophic factors, such as the combination of BDNF and GDNF, plays a role in inhibiting psychostimulant-induced neurotoxicity (Nikulina *et al.*, 2014).

d) *Nanodrug*
The psychostimulant-induced neurotoxicity might be exacerbated by several factors including nanoparticles, environment temperature, hypertension, or diabetes. The administration of nano-drug is effective due to its quick, widespread, and high-level penetration into the CNS (Sharma *et al.*, 2014).

5 Anthocyanin as Neuroprotector

Antioxidants are classified based on their molecular characteristics into enzymatic and nonenzymatic antioxidants. Based on their mechanism of action, antioxidants are grouped into primary and secondary antioxidants. Primary antioxidants search for free radicals and inhibit the oxidation through the chain reaction disruption. Normally they have reactive OH and NH that inhibit proton transfer to free radical species. Secondary antioxidants break hydroperoxide to stable non-radical products (Smetanska, 2018).

Flavonoid is one of the non-enzymatic antioxidants, and anthocyanin is a type of flavonoid. Other flavonoids and polyphenols have significantly contributed to the antioxidant activities within the body. Anthocyanin is a potent antioxidant found abundantly in fruits, vegetables, red wine, and purple sweet potato (Primayanti *et al.*, 2012). Antioxidant properties of anthocyanin in the purple sweet potato has been demonstrated in mice, rats, and rabbits (Jawi *et al.*, 2008; Jawi & Budiasa, 2011; Jawi *et al.*, 2012). Sweet potatoes decreased the plasma MDA level in rats with oxidative stress (Jawi *et al.*, 2008). Another study has investigated the effect of anthocyanin from the purple sweet potato in the cerebellum of the ischaemic stroke rate model induced by the Middle Cerebral Artery Occlusion (MCAO) technique. The study showed that the sweet potato-derived anthocyanine increased the cerebellar BDNF level and VEGF expression in rats experiencing an ischemic stroke. This might justify its use as one therapeutic modality for ischaemic stroke (Rahmawati *et al.*, 2018). The expression of cerebellar apoptotic cells of the rats with ischemic stroke decreased significantly ($p<0.01$) after 72 hours of reperfusion therapy with purple sweet potato anthocyanin (Tribuana Dewi *et al.*, 2018). The daily dose of 3 ml given for 7 days also increased the expression of Bcl-2 in the rat model experiencing an ischemic stroke. The potential mechanism proposed is the increased production of indigenous antioxidants and suppressed formation of malondialdehyde (Adnyana *et al.*, 2018).

Baicalein, a flavonoid derivate taken from *Scutellaria baicalensis* root, has demonstrated an ability to inhibit DAT loss in the striatum caused by the methamphetamine-induced neurotoxicity. This shows the neuroprotective effect of baicalein. The proposed mechanism is by inhibiting lipid peroxidation and neutrophil ROS production (Wu *et al.*, 2006). Pre-methamphetamine exposure intraperitoneal injection of isoliquiritigenin (ISL), another flavonoid with chalcone structure and active components from licorice (*Glycyrrhiza radix*), has significantly prevented methamphetamine-induced DAT and TH (tyrosine hydroxylase) reduction. ISL also suppresses methamphetamine-induced glial cell activation and inhibits nitric oxide synthase expression and NF-κB activation through blockade of phosphorylation (Lee *et al.*, 2009). The neuroprotective effect of polyphenol of green tea has been demonstrated in the nigral dopamine neuron. Pretreatment with polyphenol (-)- epigallocatechin-3-gallate (EGCG) prevents the degeneration of dopamine neurons in the substantia nigra through its antioxidant activity. Interestingly, green tea polyphenol inhibits the 3H-dopamine and 1-methyl-4- phenylpyridinium (MPP+) uptake, and protects the dopamine neurons from toxicity through the inhibition of the DAT activity (Chen *et al.*, 2007).

The neuroprotective effect of the anthocyanin has been studied with the whisker cut rat model. The rats were exposed to psychological and emotional distress that subsequently started the oxidative stress in the tissue. They displayed increased protein carbonyl and lipid peroxidase in the brain, heart, kidney, and liver. The rats were then fed with 100 mg/kg body weight anthocyanin extracted from the *Vaccinium myrtillis L* for 7 days. The administration of active anthocyanin in the brain depressed the stress-induced brain's oxidative stress and dopamine abnormalities (Rahman *et al.*, 2008). Anthocyanin and phenolic compounds from the boysenberry and blackcurrant have demonstrated a significant protective effect and restored the capacity of calcium buffering of cells affected by the oxidative stress induced by dopamine and amyloid β25-35 (Ghosh *et al.*, 2007).

Anthocyanin containing food is a potentially effective neuroprotector candidate for preventing neuronal cell death reduction, and this compound works with various mechanisms (Li *et al.*, 2017). One study has investigated the potential benefit of anthocyanin within the purple sweet potato (*Ipomoea batatas* L) extract provided to 35 smokers

for 14 days. Significant differences ($p<0.05$) were found for plasma MDA and NOx levels among groups (the control group, P1 group that received 15 ml purple sweet potato syrup, and P2 group that received 30 ml purple sweet potato syrup). The plasma MDA level decrease was 35.39% and 49.87% in P1 and P2 group, respectively, while the plasma NOx level increase was 7.78% and 14.68% in P1 and P2, respectively (Primayanti *et al.*, 2012). Anthocyanine within the purple sweet potato demonstrated stronger DPPH (1,1-diphenyl-2- picrylhydrazyl) radical finding activity than anthocyanine from red cabbage, grape peel, elderberry, or purple corn. Eight main components of anthocyanin within the purple sweet potato showed higher activity than *ascorbic acid* (Panda & Sonkamble, 2012). Anthocyanin is also effective in decreasing ROS production induced by ethanol. Its activity as an antioxidant plays an important role in neuroprotection (Chen & Luo, 2010).

Parkinson is a type of degenerative disease marked by the loss of dopaminergic neurons in the midbrain area. Anthocyanin from blueberry, grape seeds, and Chinese mulberry, significantly suppresses the rotenone that induces dopaminergic cell death through the activation of microglia and the mitochondrial repair dysfunction. Mitochondrial dysfunction could be caused by oxidative stress and this might initiate further neuronal damage (Li *et al*, 2017). Another example of antioxidants is vitamin C that could reduce the production of free radicals, maintain the glutathione homeostasis, and induce the expression of HO-1 (Yang *et al.*, 2018).

Anthocyanin has demonstrated significant neuroprotective properties from apoptosis induced by mitochondrial oxidative stress (MOS), which is also effective as GSH (glutathione) in protecting the CGNs (cerebral granule neuron). Bcl-2 inhibition leads to a significant decrease in mitochondrial GSH and this process is prevented by anthocyanine (Kelsey *et al.*, 2011).

Studies have been conducted to develop effective pharmacological strategies to manage methamphetamine-induced neurotoxicity. As described above, methamphetamine affects the dopamine reuptake and initiates dopamine oxidation. This initiates the production of ROS and RNS which would subsequently trigger the degeneration of dopaminergic terminals and neuronal apoptosis. This demonstrated that oxidative stress is one of the main mechanisms that play a role in methamphetamine-induced CNS damage. Pharmacotherapy with antioxidants could be administered to further explore effective strategies to protect neuronal cells from damages caused by methamphetamine-induced oxidative stress (Yang *et al.*, 2018).

6 Summary

Many studies have been conducted to develop effective pharmacological strategies to manage methamphetamine-induced neurotoxicity. Methamphetamine initiates dopamine oxidation and the production of ROS and RNS, as one of the main mechanisms that play a role in methamphetamine-induced neurotoxicity. Antioxidants work by slowing, preventing, or eliminating oxidative stress in the target molecule, directly searching for reactive oxygen species (ROS), or by indirectly enhancing the antioxidant defense and inhibiting ROS production. Antioxidants bind with free radicals to form stable new radicals through an intramolecular hydrogen bond in the subsequent oxidation. Anthocyanin is arguably the most potent antioxidant within the flavonoid group. Several new studies have demonstrated that anthocyanin could play a neuroprotective role in cases of neurotoxicity. Pharmacotherapy with antioxidants could be administered to protect neuronal cells from damages caused by methamphetamine-induced neurotoxicity.

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