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Methamphetamine-induced dopaminergic toxicity prevented owing to the neuroprotective effects of salicylic acid

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ABSTRACT

Aims: Methamphetamine (Schedule-II drug, U.S. Drug Enforcement Administration) is one of the most abused illicit drug following cocaine, marijuana, and heroin in the USA. There are numerous health impairments and substantial economic burden caused by methamphetamine abuse. Salicylic acid, potent anti-inflammatory drug and a known neuroprotectant has shown to protect against toxicity-induced by other dopaminergic neurotoxins. Hence, in this study we investigated the neuroprotective effects of salicylic acid against methamphetamine-induced toxicity in mice.

Main methods: The current study investigated the effects of sodium salicylate and/or methamphetamine on oxidative stress, monoamine oxidase, mitochondrial complex I & IV activities using spectrophotometric and fluorimetric methods. Behavioral analysis evaluated the effect on movement disorders-induced by methamphetamine. Monoaminergic neurotransmitter levels were evaluated using high pressure liquid chromatography-electrochemical detection.

Key findings: Methamphetamine caused significant generation of reactive oxygen species and decreased complex-I activity leading to dopamine depletion. Striatal dopamine depletion led to significant behavioral changes associated with movement disorders. Sodium salicylate (50 & 100 mg/kg) significantly scavenged reactive oxygen species, blocked mitochondrial dysfunction and exhibited neuroprotection against methamphetamine-induced neurotoxicity. In addition, sodium salicylate significantly blocked methamphetamine-induced behavioral changes related to movement abnormalities.

Significance: One of the leading causative theories in nigral degeneration associated with movement disorders such as Parkinson's disease is exposure to stimulants, drugs of abuse, insecticide and pesticides. These neurotoxic substances can induce dopaminergic neuronal insult by oxidative stress, apoptosis, mitochondrial dysfunction and inflammation. Salicylic acid due to its antioxidant and anti-inflammatory effects could provide neuroprotection against the stimulants or drugs of abuse.

1. Introduction

Methamphetamine (synonym = meth, chalk, ice, crystal) is a popular drug of abuse around the world that primarily affects the central nervous system and the cardiovascular system [29]. Methamphetamine abuse has enormously increased leading to enhanced emergency department visit resulting in huge medical expenditure. However, the major concern is the long-lasting health impairments that are associated with the chronic use of stimulants. Similarly, methamphetamine use leads to addiction as evident by compulsive drug use which is associated with eminent behavioral changes, additional functional and molecular alterations of the neuron and glial cells. Due to the biochemical and neurochemical changes, it can result in movement, mental and memory related functions. Researchers have examined the role of neuroinflammation, mitochondrial dysfunction and oxidative stress associated with the common substances of abuse and illegal street drugs [13]. The substantia nigra pars compacta region of the midbrain, which is mainly composed of neuromelanin pigmented dopaminergic neurons, controls the involuntary movement related functions of the body. It also has the highest density of microglia and iron in the brain. Postmortem investigation of Parkinson's and Alzheimer's disease patients exhibits prominent reactive gliosis, augmented oxidative stress and mitochondrial dysfunction which substantiate the role of mitochondria, oxidative stress and inflammation in neurodegeneration [2,3,14,16,27].

Methamphetamine displaces dopamine from the monoaminergic storage vesicles in the pre-synaptic neurons resulting in large amounts of monoamines released into the synaptic cleft and cytosol. Once released, the dopamine owing to its high chemical instability can be oxidized to highly reactive quinone adducts, which further augments reactive oxygen species levels. These reactive species can cause

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inhibition of mitochondrial ATP production that eventually leads to depolarized mitochondrial membrane potential and mitochondrial dysfunction. The combination of oxidative stress and mitochondrial dysfunction creates degeneration of the dopaminergic neurons in the nigrostriatal nerve terminals [26,36]. The central dopaminergic system that plays such an important role in the control of motor activity is comprised of a surprisingly small number of neurons. Due to this, it is especially vulnerable and even minor insults may lead to irreparable behavioral and biochemical deficits [7].

Thus, a drug that could provide neuroprotection against oxidative stress, mitochondrial abnormality and inflammation can prevent neuronal neurodegeneration associated with substances of abuse and street drugs like methamphetamine and its structural congeners.

Salicylic acid pharmacologically is characterized as analgesics or antipyretics [11]. Salicylic acid is a metabolite produced in the body following ingestion of acetylsalicylic acid (aspirin). Aspirin was the first-discovered member of the non-steroidal anti-inflammatory drugs (NSAIDs), which all have similar effects and most have inhibition of the cyclooxygenase as their principal mechanism of action. Today, aspirin is one of the most widely used medications in the world, with an estimated 40,000 metric tons of it being consumed each year. Salicylic acid is a known free radical scavenger [12] and possesses significant antioxidant properties. It has been shown to provide neuroprotection against MPTP induced neurotoxicity [17]. With the ability of salicylic acid for free radical scavenging, it could play a much needed neuroprotective role in not only nigral dopaminergic neurodegeneration, but also in numerous other neurodegenerative disorders. Our earlier studies show that administration of methamphetamine to mice produces a loss of dopaminergic neurons and a syndrome that behaviorally, biochemically, and neurochemically resembles Parkinson's disease [28]. Presently there are no specific therapeutic strategies that neutralize the explicit adverse actions of methamphetamine & its structural congeners, or therapies that prolong abstinence and decrease the abuse of methamphetamine. Hence, in this study, we use methamphetamine treated mice to establish the neuroprotective effects of salicylic acid. If salicylic acid proves to be a neuroprotectant, preventing methamphetamine-induced neurotoxicity, it could be used clinically for abuse and toxicity associated with designer drugs, substances of abuse and importantly can slow the progression of neurodegeneration.

2. Materials and methods

2.1. Animals

All the experimental procedures for this study pertaining to the neuroprotective effects of salicylic acid against methamphetamine-induced neurotoxicity were reviewed and approved by Institutional Animal Care and Use Committee (IACUC) at Auburn University. Male C57/Bl6 mice purchased from Charles Rivers were housed for 2–4 days prior to experiments in a temperature controlled room with a 12 h day and night cycle with free access to food and water. We also weighed the animals regularly to look for any changes.

2.2. Drug administration

C57/Bl6 mice were separated into 5 groups (control, methamphetamine only, high dose sodium salicylate only (100 mg/kg), sodium salicylate high dose (100 mg/kg) + methamphetamine and sodium salicylate low dose (50 mg/kg) + methamphetamine). The groups were given intraperitoneal (i.p.) injections once daily for one week with sterile water (control & methamphetamine groups), 100 mg/kg sodium salicylate (high dose), 100 mg/kg sodium salicylate (sodium salicylate high dose + methamphetamine group), and 50 mg/kg sodium salicylate (sodium salicylate low dose + methamphetamine group). On day 7 the methamphetamine, sodium salicylate high dose + methamphetamine and sodium salicylate low dose + methamphetamine groups were injected with methamphetamine (10 mg/kg i.p., twice, 2 h apart). The animals were sacrificed 5 days after the last injection.

2.3. Behavioral studies

Akinesia, Catalepsy and Swim test were performed based on previously established standard procedure [6,20,28,33].

2.4. Tissue preparation for in vivo biochemical assays

To avoid diurnal discrepancies of the changes in endogenous amines, enzymes, and other antioxidant molecules, control and drug treated mice were sacrificed by decapitation in the morning. Various brain regions were homogenized in 0.1 M phosphate buffer (pH 7.8) and centrifuged at 10,000g for 60 min at 4 °C and the supernatants were used for various assay [19,20].

2.5. Dopamine content

Striatum was dissected and analyzed for dopamine content using HPLC-electrochemical detector (HPLC-ECD) according to our previously published procedure [31].

2.6. Protein estimation

Protein was assayed using the coomassie plus protein assay reagent kit (Pierce, Rockford, IL). Bovine serum albumin (BSA) was used as a standard for protein measurement.

2.7. Mitochondrial complex I activity

Mitochondrial complex-I activity (NADH dehydrogenase activity) is measured spectrophotometrically based on the NADH oxidation. The mitochondrial complex-I activity is expressed as the amount of NADH oxidized/min/mg protein [24,34].

2.8. Mitochondrial complex IV activity

Complex IV activity was based on the cytochrome-C oxidation. The oxidation was measured spectrophotometrically. The absorbance was measured at 550 nm for 2 min and the enzyme activity was expressed as cytochrome-C oxidized/mg protein [24,34].

2.9. Mitochondrial monoamine oxidase (MAO) activity

Total monoamine oxidase activity was based on the amount of 4-hydroxyquinoline formed by the oxidation of kynuramine [18]. 4-hydroxyquinoline was measured fluorimetrically and the enzyme activity was expressed as 4-hyroxyquinoline formed/h/mg protein [19,20].

2.10. Assay of ROS production

The generation of ROS was measured and reported as relative fluorescence intensity [4]. Conversion of nonfluorescent chloromethyl-DCF-DA (2′,7′-dichlorofluorescin diacetate) to fluorescent DCF was used to monitor ROS production spectrofluorometerically using an excitation wavelength of 492 nm and an emission wavelength of 527 nm.

2.10.1. Super oxide dismutase (SOD) activity

Super oxide dismutase (SOD) activity was measured spectrophotometrically by Marklund and Marklund method [15] using pyrogallol as substrate at 420 nm.

2.11. Statistical analysis

Results are expressed as the mean ± SEM. The statistical significance was evaluated by the one-way analysis of variance (ANOVA) using SigmaStat version 3. Values of p less than or equal to 0.05 were considered significant.

3. Results

Methamphetamine (10 mg/kg) caused significant motor impairment as seen by catalepsy, akinesia and the swim score. Catalepsy was monitored by placing the control and drug treated mice on a flat horizontal surface with both the hind limbs on a square wooden block and the latency in seconds was measured to move the hind limbs from the block to the ground. Sodium salicylate (50 & 100 mg/kg) significantly blocked methamphetamine-induced catalepsy (Fig. 1a; n = 6, $p^a < 0.05$). Akinesia refers to the impaired ability to initiate movements and was measured by assessing the ability to move all the four limbs of the mice (initiate movements with the latency in seconds). Salicylic acid (50 & 100 mg/kg) significantly increased the ability to initiate movements in the methamphetamine treated mice (Fig. 1b; n = 6, $p^a < 0.05$). Methamphetamine reduced the movement as seen by decreased swim score. Salicylic acid treatment increased the swim score (Fig. 1c). Dopamine is the major neurotransmitter in the nigrostriatal tract and controls the movement. Administration of methamphetamine (10 mg/kg) caused a significant reduction in the levels of dopamine in the striatum. Sodium salicylate (50 &100 mg/kg) significantly blocked methamphetamine induced dopamine depletion (n = 6, $p = <0.05$), as compared to control animals (Fig. 2).

With regard to the mechanisms of neuroprotective effects of salicylic acid, we investigated the effect of salicylic acid on mitochondrial functions, oxidative stress and monoamine oxidase activity. Methamphetamine (10 mg/kg) exerted the neurotoxicity in mice by significantly inhibiting the complex I activity. Both the doses of sodium salicylate significantly enhanced the methamphetamine induced decrease in complex I activity (Fig. 3a; n = 6, $p^a < 0.05$). Neither sodium salicylate nor methamphetamine had a significant effect on complex IV activity (Fig. 3b; n = 6). Similarly, sodium salicylate and methamphetamine also had no significant effect on the total mitochondrial monoamine oxidase (MAO) activity (Fig. 4; n = 6). With regard to oxidative stress, we studied the effect on reactive oxygen species generation and superoxide dismutase activity. Methamphetamine caused significant generation of reactive oxygen species and sodium salicylate (50 & 100 mg/kg) significantly scavenged the reactive oxygen species (Fig. 5; n = 6, $p = <0.05$). Sodium salicylate had no significant effect on the superoxide dismutase activity (Data not shown).

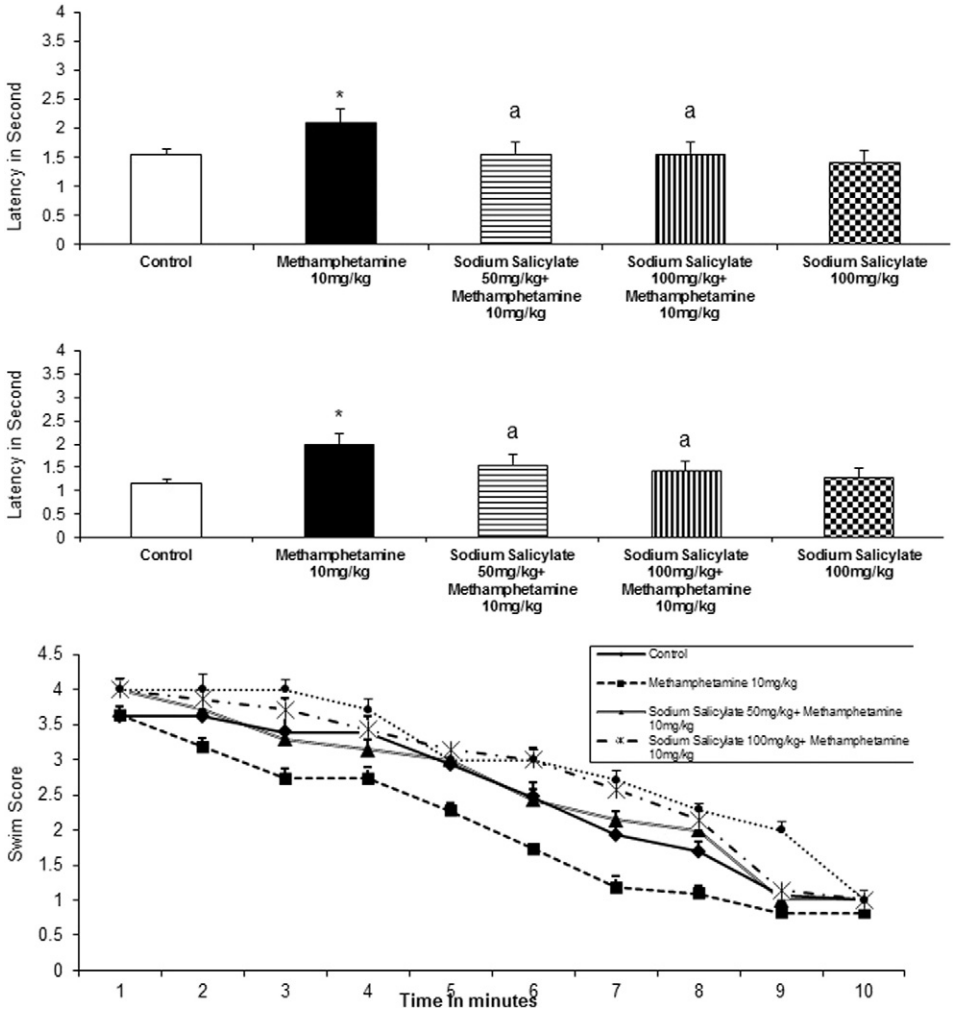

Fig. 1. Effect of salicylic acid on motor behavioral abnormalities-induced by methamphetamine: (a) Sodium salicylate (50 & 100 mg/kg) reduced methamphetamine induced behavioral abnormalities as seen in catalepsy. (b) Akinesia caused by methamphetamine treatment was blocked by Sodium salicylate (50 & 100 mg/kg). (c) Sodium salicylate (50 & 100 mg/kg) blocked methamphetamine induced decrease in swim score. *Significant (n = 6, $p^* < 0.05$) as compared to control animals. [a]Significant (n = 6, $p^a < 0.05$) as compared to methamphetamine treated mice.

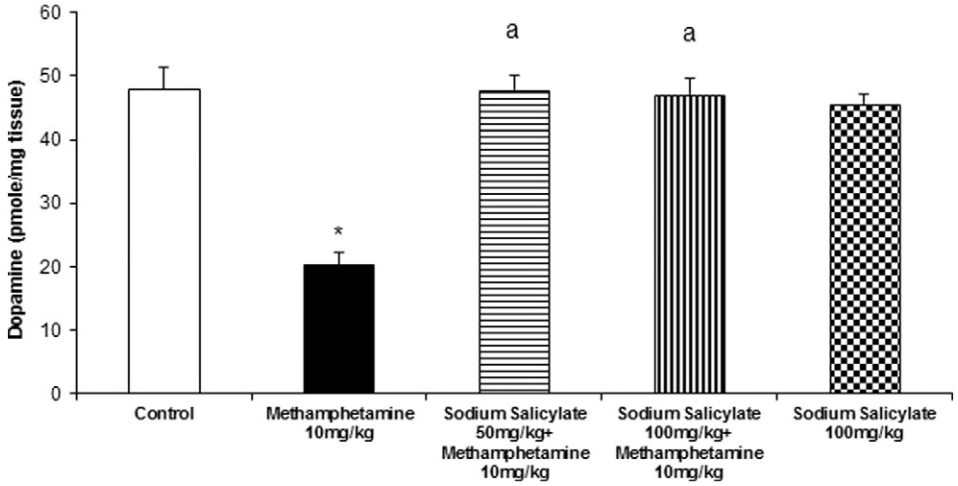

Fig. 2. Effect of salicylic acid on striatal dopamine content in mice: sodium salicylate (50 & 100 mg/kg) blocked methamphetamine mediated dopamine depletion in the striatum. *Significant ($n = 6$, $p^* < 0.05$) as compared to control animals. [a]Significant ($n = 6$, $p^a < 0.05$) as compared to methamphetamine treated mice. Dopamine content was expressed as pmol/mg tissue.

4. Discussion

Drug Abuse Warning Network (DAWN) reports that the current therapeutic approach for methamphetamine abuse is patient counseling, cognitive-behavioral rehabilitations in combination with family education and reassurance for non-drug-related activities. Few pharmacological approaches are effective in counteracting some adverse effects of substances of abuse. However, there is no single therapeutic drug that counteracts the explicit adverse effects of methamphetamine and prolongs abstinence which leads to the reduction in methamphetamine abuse. National Institute on Drug Abuse (NIDA) focuses on the new drug development or exploration of existing FDA approved medication to intervene

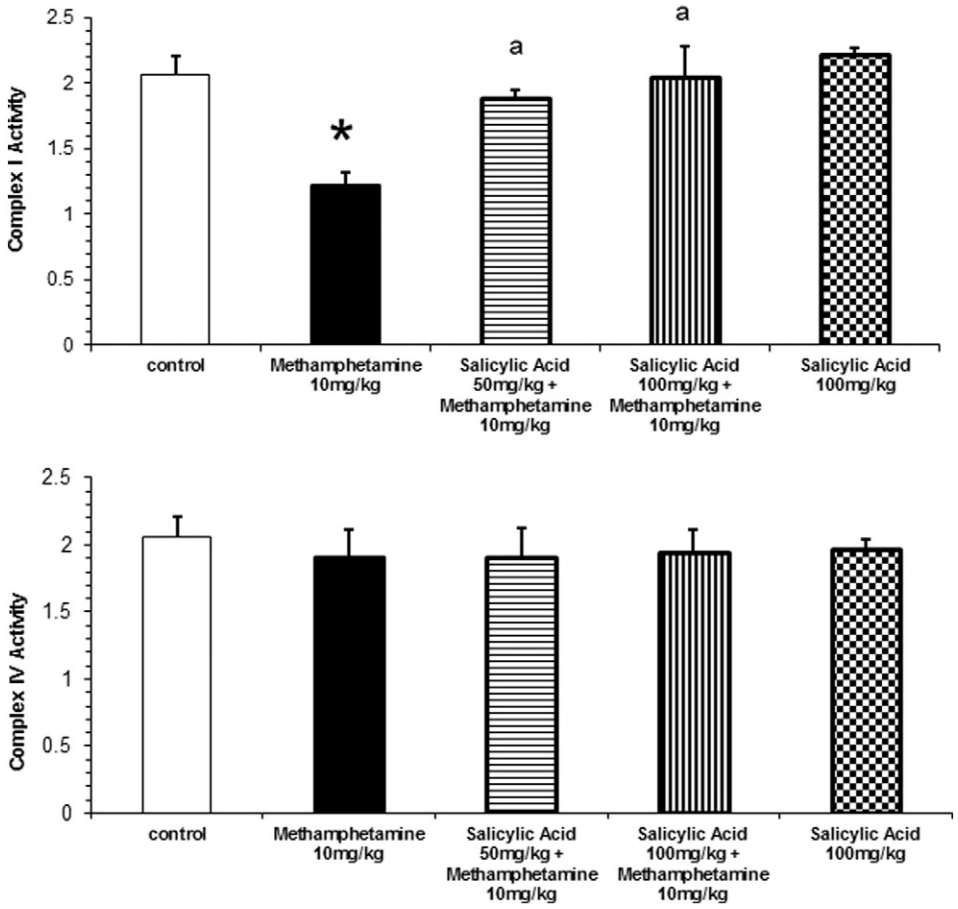

Fig. 3. Effect of salicylic acid on mitochondrial functions: (a) sodium salicylate (50 & 100 mg/kg) significantly protected against methamphetamine mediated decrease in complex I activity ($n = 6$). Activity expressed as μmol/min/mg protein. *Significant ($n = 6$, $p^* < 0.05$) as compared to control animals. [a]Significant ($n = 6$, $p^a < 0.05$) as compared to methamphetamine treated mice. (b) Effect of salicylic acid on mitochondrial complex IV activity: sodium salicylate (50 & 100 mg/kg) and methamphetamine caused no significant change in complex IV activity ($n = 6$). Activity expressed as μmol/min/mg protein.

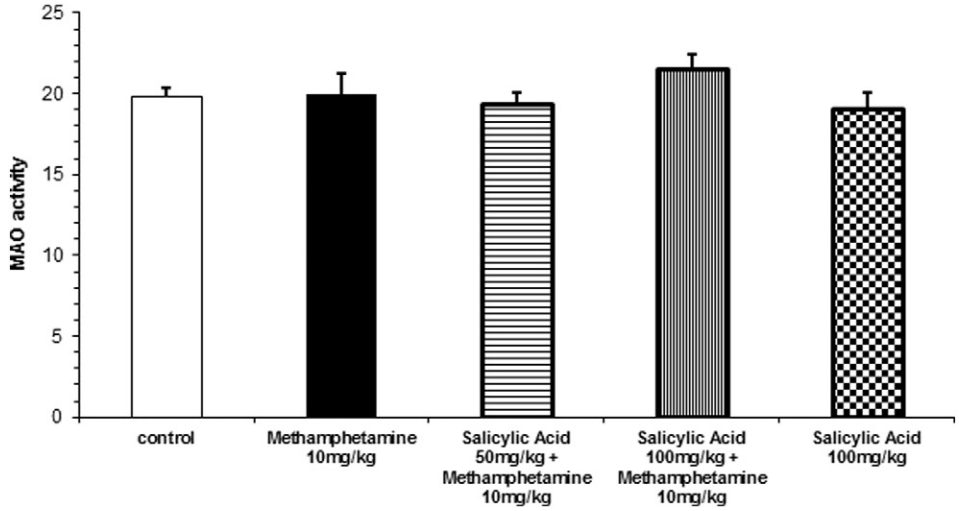

Fig. 4. Effect of salicylic acid on mitochondrial monoamine oxidase (MAO) activity: sodium salicylate (50 & 100 mg/kg) caused no significant change in MAO activity (n = 6). Activity expressed as 4-OHQ formed per mg protein.

methamphetamine addiction. In accordance with same principles, we constantly integrate our efforts in screening the most promising therapeutic candidates in our established battery of experiments against methamphetamine drug abuse. In our previous study, we investigated the neuroprotective effects of an anti-parkinsonian drug, amantadine. Amantadine (1 mg/kg, lower dose) possessed antioxidant effect but at high dose (10 mg/kg) aggravated the behavioral deficiencies of methamphetamine abuse [30].

Salicylic acid has been shown to prevent the dopaminergic neurotoxin, MPTP induced reduction in dopamine levels in mice. Salicylate inhibits the action of this specific dopaminergic neurotoxin on the mitochondrial electron transport chain, a common source of free radicals in the cell. Moreover, salicylic acid has been shown to block the neurotoxic effects of MPTP on the enzymatic defense system of the brain such as superoxide dismutase, glutathione peroxidase and catalase [9]. The reduction in glutathione levels induced by MPTP is significantly inhibited by salicylic acid. These results imply that salicylic acid is not only capable of scavenging free radicals, but also of enhancing the cell's own defense mechanisms against toxicity. In a MPTP mouse model of Parkinson's disease, salicylic acid blocked toxin-induced glutathione and dopamine depletion. This indicates its role as a hydroxyl radical scavenger and its neuroprotective properties. Interestingly, the same study for the first time showed that salicylic acid pre-treatment significantly improved motor impairments (akinesia and catalepsy) caused by MPTP administration [17]. Hence in this study, we wanted to investigate the neuroprotective (behavioral, neurochemical and biochemical) effects of salicylate against methamphetamine-induced neurotoxicity.

The alterations in the neuroimmune signaling pathway are a novel focus to study the crucial and comparatively not-well understood biological process in methamphetamine abuse. One reasonable explanation for that is the constantly increasing evidence for methamphetamine to activate microglia, alter the expression of pro-inflammatory factors leading to astrogliosis [22,25]. Moreover, inflammation is involved in the neurodegeneration associated with several neurodegenerative disorders like Amyotrophic Lateral Sclerosis, Huntington's disease, Alzheimer's disease and Parkinson's disease [1,8,17]. Mitochondrial abnormalities in the neuronal and glial cells alter some interleukin responses which is associated with the detrimental effects of neuroinflammation seen in neurodegenerative diseases. Thus, methamphetamine induced neuroimmune alterations result in the triggering of pathophysiological factors that result in the development of movement related disorder such as Parkinson's disease. Steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs) reduce inflammation, possess analgesic and antipyretic effect by inhibiting phospholipase and cyclooxygenase. Drugs that reduce inflammation have elicited neuroprotection which is not only because of their ability

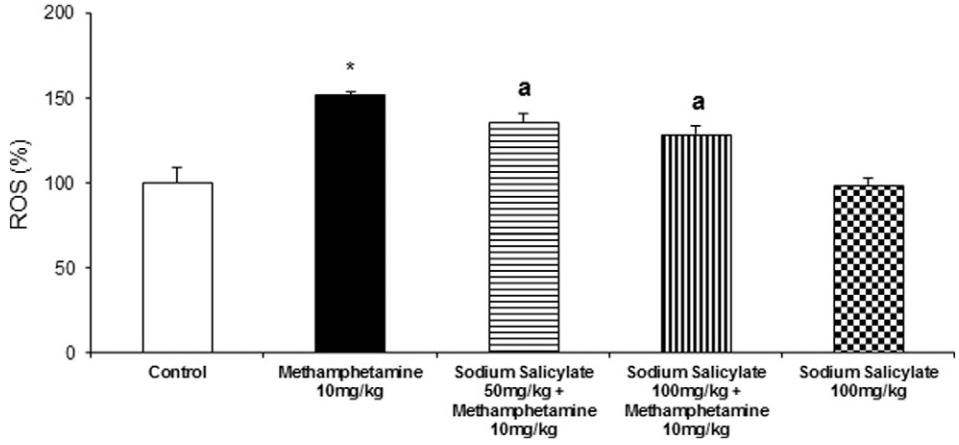

Fig. 5. Effect of Salicylic acid on mitochondrial ROS generation: sodium salicylate (50 & 100 mg/kg) significantly scavenged the methamphetamine induced generation of ROS. *Significant (n = 6, $p^* < 0.05$) as compared to control animals. [a]Significant (n = 6, $p^a < 0.05$) as compared to methamphetamine treated mice.

to inhibit cyclooxygenase but also due to the induction of other neuroprotective pathways [32]. These neuroprotective pathways involves antioxidant, anti-apoptotic, anti-excitotoxic and by enhancing the mitochondria functions [5,10,23].

In this study, we used methamphetamine treated mice model, that causes loss of dopaminergic innervation in the striatum and results in a syndrome that behaviorally, biochemically, and neurochemically resembles Parkinson's disease. Neurotoxic effects of various neurotoxins are different and specific to rodents such as mice, rats and hamster. With regard to MPTP, Golden hamster are resistant to MPTP as seen by no alteration in the content of dopamine in the nigrostriatal tract (substantia nigra and striatum) and the limbic system. Similarly rats are also resistant to the dopaminergic neurotoxicity induced by MPTP. This may be due to the monoamine oxidase-B content. Monoamine oxidase is the key enzyme that converts MPTP to MPP + the bio-active neurotoxin. Furthermore, monoamine oxidase inhibitors possess neuroprotective effects against neurotoxins and have numerous clinical benefits [21]. Due to the neuroprotective effects, deprenyl and rasagiline have been used in the therapy of Alzheimer's and Parkinson's disease. Hence, in this study we evaluated the effect of salicylic acid on monoamine oxidase activity. An earlier study evaluated the effects of salicylate on 3,4-Methylenedioxymethamphetamine (MDMA)-Induced neurotoxicity in rats. The MDMA-induced neurotoxicity was exerted by the initiation of superoxide and other toxic radicals leading to depletion of serotonin [35]. The neurochemical data from our current results showed that sodium salicylate (50 & 100 mg/kg) exhibited significant neuroprotection against methamphetamine induced dopamine depletion ($n = 6$, $p = <0.05$). The in vivo biochemical results showed that methamphetamine caused significant generation of reactive oxygen species and that sodium salicylate (50 & 100 mg/kg) showed significant neuroprotection against methamphetamine induced generation of reactive oxygen species and mitochondrial dysfunction. Due to the above neuroprotective properties, there was significant improvement in the motor behavior in mice. However, this study does not deal with the neurorestorative effects of salicylate against methamphetamine-induced neurotoxicity. Thus, the limitation of the current study can be overcome by treating salicylate after the methamphetamine administration.

5. Conclusion

Overall, these results indicate that salicylic acid is neuroprotective against neurotoxicity and dopamine depletion caused by methamphetamine administration in mice. Despite advances in pharmacotherapy that have improved quality of life, the mortality rate among drug abusers sufferers remains largely unchanged. Thus, salicylic acid can exert neuroprotection, prevent monoaminergic neuronal cell damage and could slow the progression of monoaminergic neurodegeneration.

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