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Research Report

Increased oxidative stress in submitochondrial particles after chronic amphetamine exposure

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BD, bipolar disorder
ETC, electron transport chain
ROS, reactive oxygen species
SCZ, schizophrenia
SMP, submitochondrial particles
TBARS, thiobarbituric acid reactive substances

ABSTRACT

Previous studies have suggested that reactive oxygen species (ROS) production may play a role in the pathophysiology of many neuropsychiatric disorders, such as bipolar disorder (BD) and schizophrenia (SCZ). In addition, there is an emerging body of data indicating that BD and SCZ may be associated with mitochondrial dysfunction. We studied the effects of acute and chronic d-amphetamine on ROS production in submitochondrial particles of rat brain. Male Wistar rats were divided in two experimental groups: acute and chronic treatment. In the acute treatment, rats received one single IP injection of d-amphetamine (1, 2 or 4 mg/kg) or saline (control group). In the chronic treatment, rats received one daily IP injection of d-amphetamine (1, 2 or 4 mg/kg) or saline for 7 days. Locomotor activity was assessed with the open field task, and thiobarbituric acid reactive substances (TBARS) and superoxide production were measured in submitochondrial particles of the prefrontal cortex and hippocampus. Both acute and chronic amphetamine treatment increased locomotor behavior. Chronic amphetamine exposure induced a 3- to 6-fold increase of TBARS and a 1.5- to 2-fold increase of superoxide production in submitochondrial particles of prefrontal cortex and hippocampus ($P < 0.05$). No effects on superoxide or TBARS were observed with acute treatment. These findings suggest that amphetamine-induced mitochondrial ROS generation may be a useful model to investigate the hypothesis of altered brain energy metabolism associated with BD and SCZ. Further studies assessing the effects of mood stabilizers and antipsychotics in preventing mitochondrial oxidative stress are necessary.

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1. Introduction

There is an emerging body of data indicating that impaired energetic metabolism due to mitochondrial dysfunction may play a role in the pathophysiology of major mental disorders, such as bipolar disorder (BD) and schizophrenia (SCZ) (Ben-Shachar, 2002; Kato and Kato, 2000). Brain magnetic resonance spectroscopy studies have demonstrated decreased *N*-acetyl-aspartate (a marker of mitochondrial energy production) (Clark, 1998) and lower pH and phosphocreatine levels in BD and SCZ subjects (Gangadhar et al., 2004; Stork and Renshaw, 2005), further suggesting altered brain energy metabolism in vivo. Moreover, recent postmortem studies have reported changes in mitochondrial-related gene expression in BD and SCZ (Iwamoto et al., 2005; Munakata et al., 2005).

The central nervous system requires a high-energy supply due to its intense ATP-consuming processes. Thus, abnormal cellular energy metabolism may impair neuronal function and plasticity. Under normal conditions, mitochondria are the major source of reactive oxygen species (ROS), which are produced in the complexes of the electron transport chain (ETC) (Mattiasson, 2004). On the other hand, a shift in the antioxidant/pro-oxidant balance towards oxidative stress may inhibit ETC complexes, leading to decrease in ATP production and cellular dysfunction (Calabrese et al., 2001). It has been reported that amphetamines inhibited ETC complexes (Burrows et al., 2000), thereby impairing mitochondrial functioning. However, the effects of amphetamines on mitochondrial function are not fully understood (Brown and Yamamoto, 2003).

It is well known that dopamine (DA) antagonists are first-line agents in the treatment of manic and psychotic episodes (Falkai et al., 2005; Yatham et al., 2005). Given the proposed role of dopamine in the pathophysiology of BD and SCZ (Greenwood et al., 2006; Ben-Shachar, 2002), we studied the effects of acute and chronic amphetamine exposure on the generation of ROS in submitochondrial particles in the rat brain. More specifically, we decided to investigate the prefrontal cortex and hippocampus because alterations in these brain regions are thought to be associated with BD and SCZ (Soares and Mann, 1997; Antonova et al., 2004).

2. Results

Both acute and chronic d-amphetamine administration significantly increased locomotion and rearing behavior ($P < 0.05$; all active groups vs. saline; Figs. 1 and 2). As previously reported (Frey et al., in press), a single injection of 2 mg/kg of d-amphetamine induced higher locomotor activity than 1 or 4 mg/kg ($P < 0.05$; 2 mg/kg vs. 1 and 4 mg/kg). This difference between active groups was not observed in the chronic treatment.

Repeated d-amphetamine exposure increased superoxide ($F = 5.08$; $P = 0.017$; one-way ANOVA; Fig. 3) and TBARS ($F = 12.20$; $P = 0.001$; one-way ANOVA; Fig. 4) generation in the hippocampus (chronic treatment). We also found that repeated d-amphetamine treatment increased superoxide ($F = 5.27$; $P = 0.015$; one-way ANOVA; Fig. 5) and TBARS ($F = 9.29$; $P = 0.002$; one-way ANOVA; Fig. 6) generation in the prefrontal cortex. No significant effects on ROS generation were observed after a single d-amphetamine administration (acute treatment).

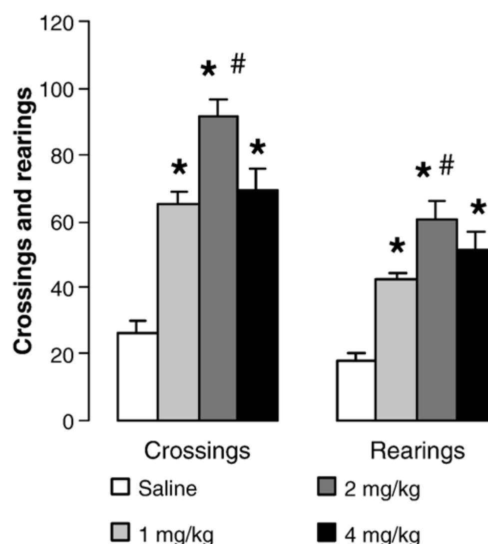

Fig. 1 – Numbers of crossings and rearings after acute d-amphetamine exposure ($n = 10$ per group). $^*P < 0.05$ (active groups vs. saline; Newman–Keuls test). $^\#P < 0.05$ (2 mg/kg vs. 1 and 4 mg/kg; Newman–Keuls test).

3. Discussion

We demonstrated that repeated d-amphetamine exposure lead to increased superoxide and TBARS formation in prefrontal and hippocampal submitochondrial particles in vivo. Amphetamine-induced generation of superoxide and products of lipid peroxidation (TBARS) from mitochondria may originate from several sources (Brown and Yamamoto, 2003). One potential source is the inhibition of mitochondrial ETC complexes (Burrows et al., 2000). Moreover, because amphetamine increases DA release from cytoplasmic vesicles, increased DA metabolism via monoamine oxidase (which is located in the outer mitochondrial membrane) may produce hydrogen peroxide and dihydroxyphenylacetic acid (Berman and Hastings, 1999). In addition, DA may undergo spontaneous auto-oxidation and form highly reactant DA quinones (LaVoie and Hastings, 1999). It has been postulated that mutations in mitochondrial DNA (mtDNA) could lead to increased ROS generation and vice versa (de Grey, 2005). Interestingly, recent studies have suggested that ROS generation may play a role in the increased mtDNA mutations observed in neuropsychiatric disorders, such as BD and SCZ (Marchbanks et al., 2003; Munakata et al., 2005).

We also found no effects on ROS production in submitochondrial particles after a single d-amphetamine administration. Recent reports have demonstrated that a single injection of larger doses of AMPH (5–7.5 mg/kg) increased lipid peroxidation in rat cortex and striatum (Bashkatova et al., 2002; Wan et al., 2000). Differences in drug regimens and animal strains may account for this discrepancy. Using

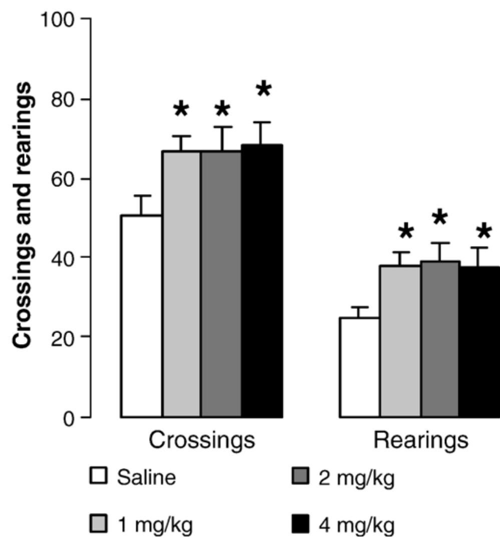

Fig. 2 – Number of crossings and rearings after chronic d-amphetamine exposure (n = 10 per group). $^*P < 0.05$ (active groups vs. saline; Newman–Keuls test).

dopaminergic cultured neurons, Lotharius and O'Malley (2001) found a rapid increase in ROS generation after d-amphetamine incubation. However, the authors found that only prolonged amphetamine exposure induced oxidative protein damage (Lotharius and O'Malley, 2001). Further evidence supporting the role of oxidative stress in AMPH-induced neurotoxicity is that the antioxidants α-phenyl-*N*-*tert*-butyl nitrone and *N*-acetylcysteine partially prevented amphetamine-induced DA depletion and lipid peroxidation in rat striatum (Wan et al., 2006). In humans, it has been reported increased lipid peroxidation and decreased SOD and CAT activity in erythrocytes of 3,4-methylenedioxymethamphetamine abusers (Zhou et al., 2003). In a postmortem study, Mirecki et al. (2004) showed moderate changes in SOD and oxidized glutathione in the caudate of methamphetamine users.

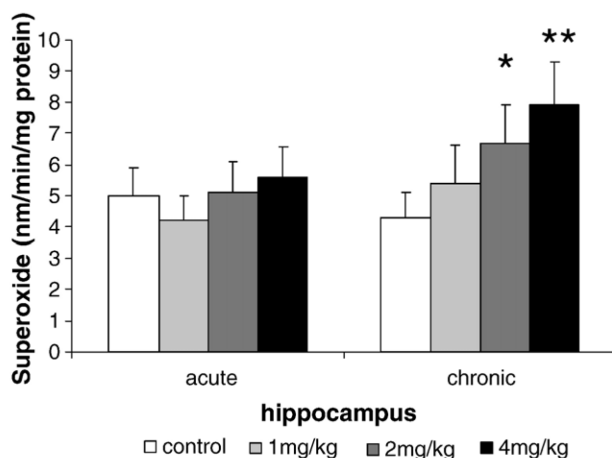

Fig. 3 – Superoxide levels in submitochondrial particles after acute and chronic d-amphetamine exposure (n = 4 per group). $^*P = 0.032$ (vs. saline; Newman–Keuls test). $^{**}P = 0.004$ (vs. saline; Newman–Keuls test).

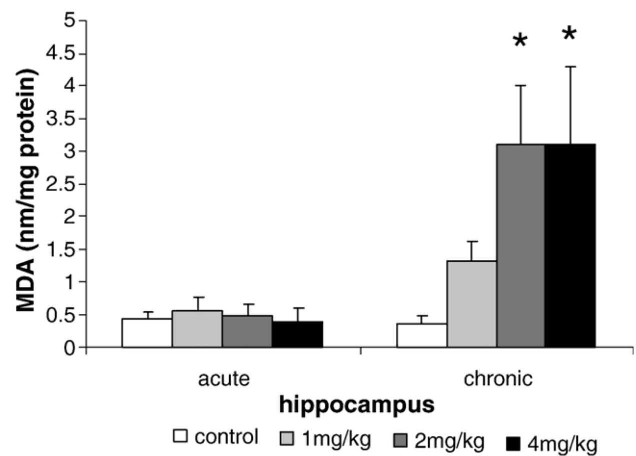

Fig. 4 – TBARS levels in submitochondrial particles after acute and chronic d-amphetamine exposure (n = 4 per group). $^*P < 0.001$ (vs. saline; Newman–Keuls test). TBARS: thiobarbituric acid reactive substances.

In the present study, we have used a relative low-dose d-amphetamine regimen (1–4 mg/kg) and previous data have demonstrated that much higher doses of amphetamine are necessary to induce cellular death in vivo (Ryan et al., 1990; Davidson et al., 2001; Krasnova et al., 2005). Interestingly, recent studies have found that ROS might act as intracellular messengers to mediate neuroprotective effects after brain ischemia (Liang et al., 2005; Mattiasson et al., 2003). More specifically, it has been demonstrated that superoxide produced in the mitochondria activates uncoupling proteins (Echtay et al., 2002) through the generation of lipid peroxidation products (Murphy et al., 2003), thereby lowering mitochondrial membrane potential and decreasing intramitochondrial ROS levels, like a negative feedback (Echtay et al., 2002; Mattiasson et al., 2003; Murphy et al., 2003). Using the same model, we previously showed that chronic, but not acute, d-amphetamine administration increased TBARS in brain homogenates in vivo (Frey et al., in press). Although speculative, we hypothesize that this initial, but limited (Calabrese et al., 2001), brain's ability to withstand oxidative stress might be overwhelmed after accumulate (chronic) amphetamine-induced ROS generation. Further studies are warranted to test this hypothesis. In this same vain, it has been demonstrated that chronic amphetamine exposure altered the activity of the major antioxidant enzymes in rat brain (Carvalho et al., 2001).

There is growing evidence supporting that glutamate may play a role in amphetamine-induced oxidative stress. It has been demonstrated that amphetamine augmented cortical glutamate efflux in rodents (Stephans and Yamamoto, 1994). Overstimulation of NMDA receptors induces abnormal Ca^{+2} influx, mitochondrial dysfunction and excessive free radical generation (Schinder et al., 1996). Interestingly, the administration of ionotropic (Sonsalla et al., 1989; Wan et al., 2000) and metabotropic receptor-5 antagonists (Battaglia et al., 2002) prevented amphetamine-induced neurotoxicity. In addition, the excess of free radicals generated by amphetamine exposure may interact with glutamate transporters in astrocytes and further increase glutamate concentration by

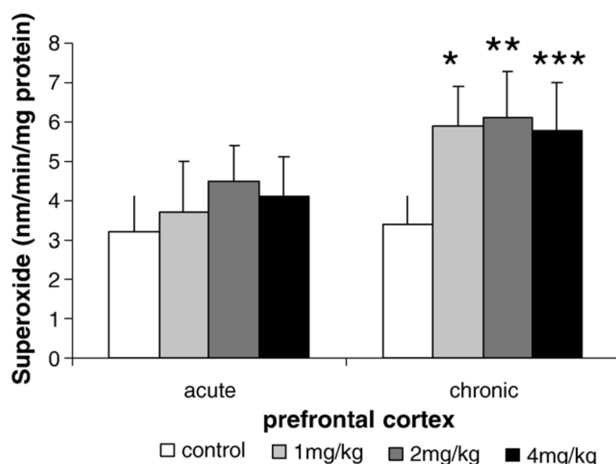

Fig. 5 – Superoxide levels in submitochondrial particles after acute and chronic d-amphetamine exposure ($n = 4$ per group). *$P = 0.009$ (vs. saline; Newman–Keuls test). **$P = 0.004$ (vs. saline; Newman–Keuls test). ***$P = 0.012$ (vs. saline; Newman–Keuls test).

inhibiting its uptake (Volterra et al., 1994). Although the activity of glutamate decarboxylase and choline acetyltransferase were not altered after high doses of amphetamine suggesting that GABAergic and cholinergic neurons may be spared (Hotchkiss et al., 1979), the role of other neurotransmitters in amphetamine-induced neurotoxicity remains to be elucidated (Ricaurte and McCann, 1992).

Thus, amphetamine-induced mitochondrial ROS generation may provide a useful model to test the hypothesis of altered brain energy metabolism associated to neuropsychiatric disorders. Studies addressing the effects of mood stabilizers and antipsychotics may provide new insights about their mechanisms of action. Additionally, a better understanding of how ROS generation impairs mitochondrial function may help to design novel therapeutics to reduce the cognitive decline observed in severe mentally ill subjects.

4. Experimental procedures

4.1. *Animals*

Adult male Wistar rats were obtained from our breeding colony. They were housed five to a cage with free access to food and water and were maintained on a 12-h light/dark cycle (lights on at 7:00 AM). All experimental procedures were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals and the Brazilian Society for Neuroscience and Behavior (SBNeC) recommendations for animal care.

4.2. *Experimental model*

The animals were divided into two groups: acute and chronic treatment. In the acute treatment, rats received a single intraperitoneal injection of saline (control) or d-amphetamine (Sigma, St. Louis, MO, USA) 1, 2 or 4 mg/kg. In the chronic treatment, rats received one daily injection of vehicle (control) or d-amphetamine 1, 2 or 4 mg/kg for 7 days. It has been previously demonstrated that at low-intermediate doses, amphetamine increased locomotor behavior, which was progressively reduced with higher doses due to the emergence of stereotyped behavior (Antoniou et al., 1998). Locomotor activity was measured 2 h (Bashkatova et al., 2002) after the last injection of AMPH, and the rats were sacrificed by decapitation immediately after the behavioral experiment. The prefrontal cortex and hippocampus were dissected, rapidly frozen and stored at −80 °C for posterior biochemical analysis.

4.3. *Locomotor activity*

The apparatus and procedures were described elsewhere (Barros et al., 2002; Frey et al., in press). The open field task was carried out in 40 × 60 cm open field surrounded by 50-cm-high walls made of brown plywood with a frontal glass wall. The floor of the open field was divided into 12 equal rectangles by black lines. Animals were gently placed on the left rear rectangle and were left to explore the arena for 5 min. Crossings of the black lines and rearings performed were counted.

4.4. *Oxidative stress in submitochondrial particles*

As an index of uncoupling of electron transporter chain (ETC), the generation of mitochondrial superoxide (O_2^-) was measured as previously described (Poderoso et al., 1996). In brief, superoxide anion production was determined in washed submitochondrial particles (SMP) using a spectrophotometric assay based on superoxide-dependent oxidation of epinephrine to adrenochrome at 37 °C (E480 nm = 4.0 mM cm). Mitochondria (1 mg/ml) were treated for 10 min, at 37 °C. SMP were obtained by freezing and thawing (three times) the mitochondria solution, washed (twice) with 140 mM KCl, 20 mM Tris–HCl (pH 7.4) and suspended in the same medium. The reaction medium consisted of 230 mM mannitol, 70 mM

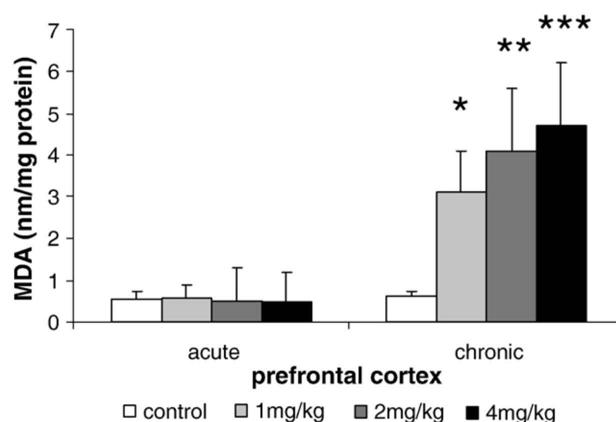

Fig. 6 – TBARS levels in submitochondrial particles after acute and chronic d-amphetamine exposure ($n = 4$ per group). *$P = 0.011$ (vs. saline; Newman–Keuls test). **$P = 0.001$ (vs. saline; Newman–Keuls test). ***$P < 0.001$ (vs. saline; Newman–Keuls test). TBARS: thiobarbituric acid reactive substances.

sucrose, 10 mM HEPES–KOH (pH 7.4), 4.2 mM succinate, 0.5 mM KH_2PO_4, SMP (1.0 mg protein/ml), 0.1 μM catalase and 1 mM epinephrine. Superoxide dismutase (E.C. 1.15.1.1.) was used at 0.1–0.3 μM final concentration as a negative control to confirm assay specificity. As a marker of lipid peroxidation, we measured the formation of thiobarbituric acid reactive species (TBARS) during an acid-heating reaction, as previously described (Esterbauer and Cheeseman, 1990). Briefly, the samples were mixed with 1 ml of trichloroacetic acid 10% and 1 ml of thiobarbituric acid 0.67%, and then heated in a boiling water bath for 15 min. TBARS were determined by the absorbance at 535 nm. All the results were normalized by the protein content, using bovine albumin as standard (Lowry et al., 1951).

4.5. *Statistical analysis*

Results were presented as mean ± SEM. Differences among experimental groups were determined by one-way ANOVA. Multiple comparisons were performed by a Newman–Keuls test. *P* values <0.05 were considered to indicate statistical significance.

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