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Research Report

Oxidative stress: A potential recipe for anxiety, hypertension and insulin resistance

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ABSTRACT

We recently reported involvement of oxidative stress in anxiety-like behavior of rats. Others in separate studies have demonstrated a link between oxidative stress and hypertension as well as with type 2 diabetes/insulin resistance. In the present study, we have tested a putative role of oxidative stress in anxiety-like behavior, hypertension and insulin resistance using a rat model of oxidative stress. Oxidative stress in rats was produced by xanthine (0.1%; drinking water) and xanthine oxidase (5 U/kg; i.p.). X+XO-treated rats had increased plasma and urinary 8-isoprostane levels (a marker of oxidative stress) and increased malondialdehyde (MDA) levels in the hippocampus and amygdala as compared to control rats. Serum corticosterone (a systemic marker of stress and anxiety) levels also increased with X+XO treatment. Moreover, anxiety-like behavior measured via open-field and light–dark exploration behavior tests significantly increased in X+XO-treated rats. Mean arterial blood pressure measured in anesthetized rats increased in X+XO-treated compared to control rats. Furthermore, plasma insulin but not glucose levels together with homeostasis model assessment (HOMA), an index of insulin resistance, were higher in X+XO-treated rats. Our studies suggest that oxidative stress is a common factor that link anxiety-like behavior, hypertension and insulin resistance in rats.

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1. Introduction

An increased risk of psychiatric impairment is widely believed to be accompanied with a chronic illness (Simon et al., 1995). Substantial literature supports this clinically important association (Roy-Byrne et al., 2008). In particular, comorbidity of anxiety disorders with chronic medical conditions like hypertension and type-2 diabetes mellitus is a topic of both clinical and policy interest (Roy-Byrne et al., 2008; Thomas et al., 2003). Interestingly, presence of anxiety is reported to contribute to an additional time of hospitalization due to the complications resulting from anxiety (Ball et al., 2002). Given the implications of comorbidity between anxiety, hypertension and type-2 diabetes mellitus, it is imperative to investigate whether there is a shared relationship underlying these conditions. Our studies point

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Abbreviations: HOMA, homeostasis model assessment; X+XO, xanthine and xanthine oxidase; MDA, malondialdehyde; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; OF, open-field; LD, light–dark

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towards a common factor, oxidative stress that more than likely is a contributing factor in the occurrence of comorbidity between anxiety disorders, hypertension and insulin resistance/type-2 diabetes mellitus.

In general, evidence for the involvement of oxidative stress in human disease is frequently cited (Salustri et al., 2010; Dean et al., 2009; Ko et al., 2010; Liu et al., 2008). Increased oxidative damage is likely to occur in most if not all human diseases, although it probably plays a significant pathologic role only in few. Recent studies including our own have shown direct involvement of oxidative stress with anxiety-like behavior in rodents (Salim et al., 2010; Hovatta et al., 2005; Gingrich, 2005; Masood et al., 2008; Souza et al., 2007; Bouayed et al., 2007; de Oliveira et al., 2007). Recent work also has suggested correlation of oxidative stress with hypertension and type-2 diabetes mellitus (Ko et al., 2010; Liu et al., 2008). Occurrence of oxidative stress, anxiety-like behavior, hypertension and type-2 diabetes mellitus have never been examined in the same study. In this study, using Sprague–Dawley rats, we induced oxidative stress by xanthine plus xanthine oxidase treatment for one week. This treatment increased oxidative stress markers, 8-isoprostane (in serum and urine) and malondialdehyde in blood plasma, hippocampus and amygdala brain regions of rats. Moreover, X+XO treatment increased anxiety-like behavior of rats examined via light–dark and open-field anxiety tests, when compared to the vehicle treated control rats. Furthermore, X+XO treatment increased blood pressure, insulin resistance and corticosterone levels. This suggests that induction of oxidative stress results in elevated anxiety, hypertension and insulin resistance. It is likely that oxidative stress is the common link that is responsible for increased incidence of comorbidity in these three chronic illnesses. Even though, there is a large volume of evidence suggesting anxiety as a risk factor for hypertension and other cardiovascular diseases, as well as type-2 diabetes mellitus, there remains paucity of information linking oxidative stress, hypertension, type-2 diabetes mellitus and anxiety, all in the same model.

In this study, we have employed a rat model in which we have induced oxidative stress using X+XO to assess direct involvement of oxidative stress in anxiety-like behavior, hypertension and insulin resistance.

2. Results

Oxidative stress was induced in rats by xanthine supplementation (0.1% in drinking water) and intraperitoneal injections at non-toxic dose of xanthine oxidase for 1 week. This treatment increased oxidative stress markers, 8-isoprostane (in serum and urine) and malondialdehyde in hippocampus and amygdala. The treatment also increased serum corticosterone levels, a generally considered marker of stress and anxiety (Kobayashi et al., 2009; Arranz et al., 2007). Moreover, X+XO treatment increased anxiety-like behavior of rats examined via light–dark and open-field anxiety tests, when compared to the control vehicle treated rats. Furthermore, X+XO treatment increased blood pressure of rats and insulin resistance as compared to vehicle-treated control rats (Fig. 1).

2.1. *Effect of X+XO treatment on general body parameters*

There were no significant changes observed in body weight, body temperature, food, or water intake habits in all groups of rats. All rats irrespective of treatment consumed similar amounts of rodent chow and tap water daily (Table 1).

2.2. *Effect of X+XO treatment on indices of oxidative stress and corticosterone levels*

Treatment with X+XO for 7 days caused significant increase in plasma (166%) and urinary (129%) 8-isoprostane as compared to vehicle-treated control rats (Fig. 2A, B). Also, treatment with X+XO for 7 days caused significant increase in markers of lipid peroxidation (MDA assay) in hippocampus (MDA: 153%) and amygdala (MDA: 101%) tissues (Fig. 2C). Serum corticosterone levels were examined for control (27.1 ng/ml) and X+XO treated (66.6 ng/ml) rats. X+XO treatment increased serum

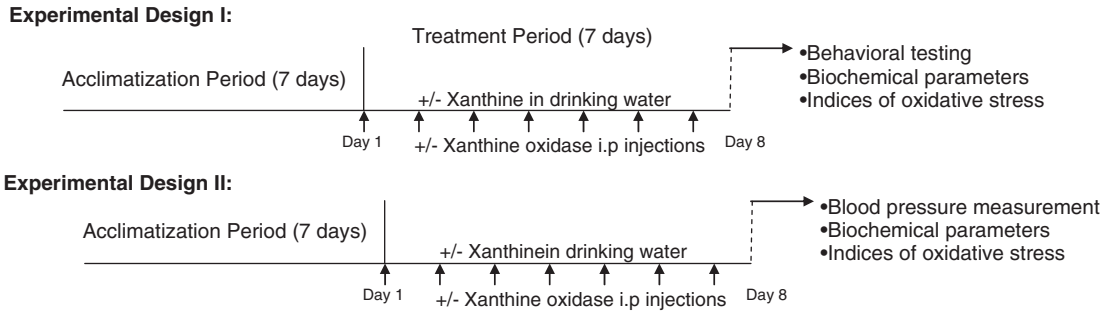

Fig. 1 – Schematic representation of the experimental plan. In experimental design I, the control group (n = 8–12 rats) received vehicle injections (saline) and drinking water *ad libitum* for 7 days. Another group of rats (n = 8–12 rats) received 0.2% xanthine supplementation in drinking water plus intraperitoneal injections at non-toxic dose of xanthine oxidase (5 Units/kg) once daily for 7 days. After 24 h of the last X+XO treatment, anxiety tests were conducted, brains harvested and biochemical and oxidative parameters measured. In experimental design II, rats were randomly selected into two groups (control and treated) as before. After 24 h of the last X+XO treatment, rats were anesthetized with inaction and blood pressure measurements were made, biochemical and oxidative parameters measured were analyzed in serum and urine.