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Original Article

Rice bran oil prevents neuroleptic-induced extrapyramidal symptoms in rats: Possible antioxidant mechanisms

Noreen Samad[*]

Department of Biomedical Engineering, Sir Syed University of Engineering and Technology, Karachi 75300, Pakistan

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ABSTRACT

Tardive dyskinesia (TD) is one of the serious side effects of long-term antipsychotic treatment. Chronic treatment with neuroleptic leads to the development of abnormal oral movements called vacuous chewing movements (VCMs). The oxidative stress hypothesis of TD is one of the possible pathophysiologic models for TD. Preclinical and clinical studies of this hypothesis indicate that neurotoxic free radical production is likely to be a consequence of antipsychotic medication and is related to occurrence of TD. Oxidative stress is implicated in the pathophysiology of TD. Rats chronically treated with haloperidol orally at a dose of 0.2 mg/kg/day for a period of 5 weeks developed VCMs, which increased in a time-dependent manner as the treatment continued for 5 weeks. Motor coordination impairment started after the 1st week and was maximally impaired after 3 weeks and gradually returned to the 1st week value. Motor activity in an open field or home cage (activity box) not altered. Administration of rice bran oil (antioxidant) by oral tubes at a dose of 0.4 mL/day prevented the induction of haloperidol-elicited VCMs as well impairment of motor coordination. The results are discussed in the context of a protective role of antioxidant of rice bran oil in the prevention of haloperidol-induced extrapyramidal symptoms.

1. Introduction

The therapeutic efficacy of antipsychotic drugs is generally believed to be due to their ability to block central dopamine D2 receptor [1–3]. Haloperidol, a typical antipsychotic, is a butyrophenone that acts primarily as a D2 dopamine receptor antagonist. Like most typical neuroleptics, haloperidol can cause extrapyramidal symptoms (EPS), including Parkinsonism and tardive dyskinesia (TD) [4].

TD, a syndrome of potently irreversible, involuntary hyperkinetic disorders that occurs during chronic neuroleptic treatment, is a major limitation of neuroleptic therapy [5,6]. The development of TD can be attributed to the potential toxic effects of prolonged typical neuroleptic administration. It has been shown that high concentration of this dopamine D2

* Department of Biomedical Engineering, Sir Syed University of Engineering and Technology, Karachi-75300, Pakistan.
E-mail address: noreensamad_ku@yahoo.com.

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receptor antagonist is cytotoxic for various cell types [7]. This could occur via an oxidative stress mechanism following the production of inhibitors of mitochondrial respiration [8,9].

Oxidative stress is implicated in the pathophysiology of various neurological disorders and also in development of TD [10]. Chronic treatment with neuroleptics increases free radical production and oxidative stress [11].

Rice bran is a brown layer present between rice and the outer husk of the paddy. Rice bran stabilized by heat treatment promptly after milling can be used as ingredients in food processing because of its high nutrient content such as fiber, lipid, protein, minerals, and tocopherols [12,13]. It is a good source of vitamins [14,15] and has been utilized by the baking, confectionary, and food-processing industries because of its impressive nutritive values [12]. Rice bran consists of 12–23% oil that has an unusually high unsaponifiable matter of 4% concentration [16].

Rice bran oil (RBO) is an important derivative of rice. It has some unique ingredients such as γ-oryzanol, β-sitosterol, and unesterified fatty acids, all of which may contribute to cholesterol reduction [17–20]. RBO has a high content of tocopherol and tocotrienol [21] with an antioxidant property [22,23]. RBO is considered to be one of the most nutritious oils due to its favorable fatty acid composition and unique combination of naturally occurring biologically active antioxidant compounds [22,23]. Inclusion of RBO in the diet has been shown to improve the antioxiogenic potential and protect against oxidative stress [24].

The objective of the present research was to determine the effects of long-term intake of RBO designed to investigate the effect of RBO on neuroleptic-induced EPS in rats.

2. Materials and methods

2.1. Animals

Locally bred male albino Wistar rats weighing 180–220 g purchased from HEJ Research Institute, University of Karachi, Pakistan were housed individually with free access to cubes of standard rodent diet and tap water 3 days before starting the experiment.

2.2. Drugs

Haloperidol (Serenace; G.D. Searle, Peapack, NJ, USA) purchased as oral drops of 2.0 mg/ml was given orally in drinking water at a dose of 0.2 mg/kg/day. RBO was extracted by the method of Hu et al [25] and given orally by oral tubes at a dose of 0.4 mL/day.

2.3. Experimental protocol

Sixteen animals were divided into four groups: (1) water+water; (2) water+RBO (3) haloperidol+water; and (4) haloperidol+RBO. They received the respective treatment for 5 weeks. Vacuous chewing movements (VCMs), motor coordination, exploratory activity in an open field and in a home cage were monitored weekly for 5 weeks.

2.4. Behavioral analysis

2.4.1. Open field activity

To monitor activity in a novel environment, an open field apparatus was used, consisting of a square area 76 cm × 76 cm with walls 42 cm high. The floor was divided by lines into 25 equal squares. To determine activity, a rat was placed in the center square of the open field. The numbers of squares crossed with all four paws were scored for 5 minutes.

2.4.2. Home cage activity

To monitor activity in a familiar environment, activity boxes were used. The rectangular Perspex activity cage consisted of small square area (26 cm × 26 cm × 26 cm) with sawdust-covered floor. Before monitoring the activity an animal was placed in it for 15 minutes for habituation. Numbers of crossings across the box were monitored for 10 minutes.

2.4.3. Rota-rod activity

Motor coordination was assessed for all rats on a rota-rod. The rota-rod had a 7 cm radius and a speed of 16 revolutions/minute. Prior to any treatment rats were trained in a single session until they attained 150 seconds on the rota-rod.

2.4.4. VCM quantification

Animals were placed individually in an activity box (26 cm × 26 cm × 26 cm) with sawdust-covered floor and were allowed to adapt the observation cage for a period of 15 minutes. VCMs were monitored during a 10-minute observation period. For calculation purposes, each burst of purposeless chewing was counted as one, if its duration was at least 3 seconds.

2.5. Statistical analysis

Data were analyzed by three-way ANOVA. *Posthoc* comparison was done by Newman–Keuls test with $p < 0.05$ taken as significant.

3. Results

Fig. 1 shows the effect of administration of haloperidol on activity in an open field in animal treated with water and RBO. Data analyzed by three-way ANOVA showed significant effects of haloperidol ($F = 6.75$; $df = 1,60$; $p < 0.05$), weeks ($F = 39.14$; $df = 4,60$; $p < 0.01$), and RBO ($F = 11.36$; $df = 1,60$; $p < 0.01$). Interactions between haloperidol and weeks ($F = 1.87$; $df = 4,60$; $p > 0.05$), haloperidol and RBO ($F = 2.15$; $df = 4,60$; $p > 0.05$), RBO and weeks ($F = 1.07$; $df = 4,60$; $p > 0.05$), and haloperidol, weeks, and RBO ($F = 2.02$; $df = 4,60$; $p > 0.05$) were not significant. Differences by Newman–Keuls test were not significant.

Fig. 2 shows the effect of administration of haloperidol on activity in a home cage (activity box) in animals treated with water and RBO. Data analyzed by three-way ANOVA showed significant effects of haloperidol ($F = 8.13$; $df = 1,60$; $p < 0.01$), weeks ($F = 14.21$; $df = 4,60$; $p < 0.01$), and RBO ($F = 40.81$; $df = 1,60$; $p < 0.01$). Interactions between haloperidol and weeks ($F = 1.60$; $df = 4,60$; $p > 0.05$), haloperidol and RBO

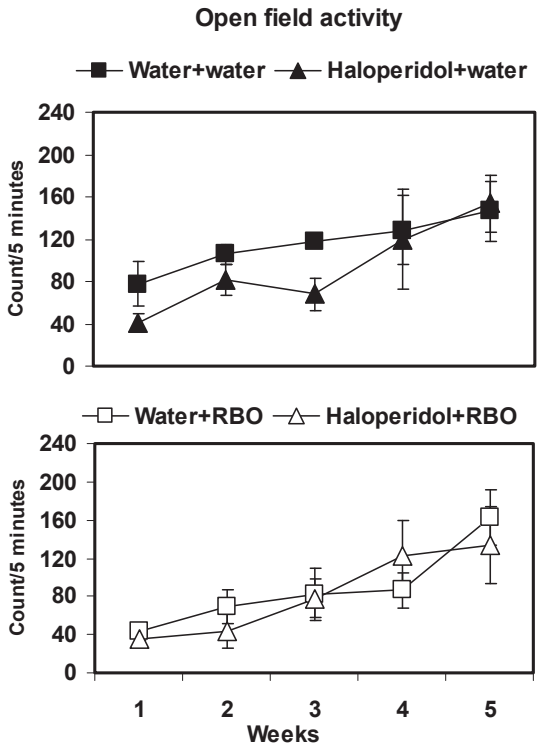

Fig. 1 – Effects of administration of haloperidol on activity in an open field in animals treated with water and rice bran oil (RBO). Values are means ± standard deviation ($n = 4$).

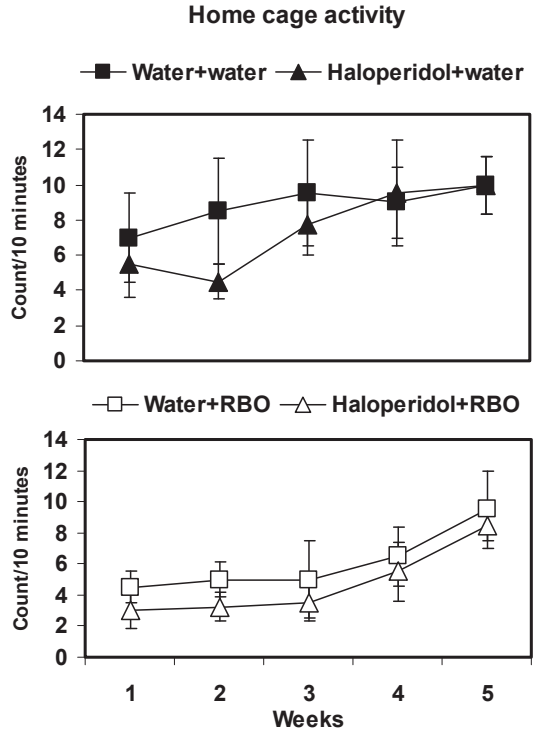

Fig. 2 – Effects of administration of haloperidol on activity in a home cage (activity box) in animals treated with water and rice bran oil (RBO). Values are means ± standard deviation ($n = 4$).

(F = 0.005; df = 4,60; $p > 0.05$), RBO and weeks (F = 2.18; df = 4,60; $p > 0.05$), and haloperidol, weeks, and RBO (F = 0.92; df = 4,60; $p > 0.05$) were not significant. Differences by Newman–Keuls test were not significant.

Fig. 3 shows the effect of administration of haloperidol on motor coordination in animals treated with water and RBO. Data analyzed by three-way ANOVA showed significant effects of haloperidol (F = 261.71; df = 1,60; $p < 0.01$), weeks (F = 4.11; df = 4,60; $p < 0.01$), and RBO (F = 147.89; df = 1,60; $p < 0.01$). Interactions between haloperidol and weeks (F = 4.11; df = 4,60; $p < 0.01$), haloperidol and RBO (F = 4.11; df = 4,60; $p < 0.01$), RBO and weeks (F = 3.43; df = 4,60; $p < 0.05$), and haloperidol, weeks, and RBO (F = 3.43; df = 4,60; $p < 0.05$) were significant. *Posthoc* analysis by Newman–Keuls test showed that administration of haloperidol impaired motor coordination after the 1st week. The impairment of motor coordination was maximum after the 3rd week and gradually returned to 1st week value. Administration of RBO prevented the haloperidol-induced impairment of motor coordination.

Fig. 4 shows the intensity of haloperidol-induced VCMs in animals treated with water and RBO. Data analyzed by three-way ANOVA showed significant effects of haloperidol (F = 344.39; df = 1,60; $p < 0.01$), weeks (F = 25.29; df = 4,60; $p < 0.01$), and RBO (F = 227.35; df = 1,60; $p < 0.01$). Interactions between haloperidol and weeks (F = 14.12; df = 4,60; $p < 0.01$), haloperidol and RBO (F = 278.98; df = 4,60; $p < 0.01$), RBO and weeks (F = 24.78; df = 4,60; $p < 0.01$), and haloperidol, weeks, and RBO (F = 23.11; df = 4,60; $p < 0.01$) were significant. *Posthoc*

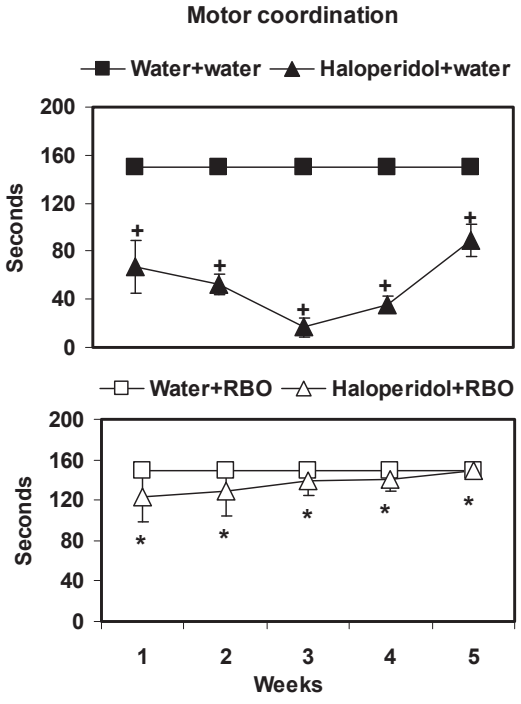

Fig. 3 – Effect of administration of haloperidol on motor coordination in animals treated with water and rice bran oil (RBO). Values are means ± standard deviation ($n = 4$). Significant differences by Newman–Keuls test: $^{*}p < 0.01$ from haloperidol plus water-treated animals, $^{+}p < 0.01$ from water-treated animals following three-way ANOVA.

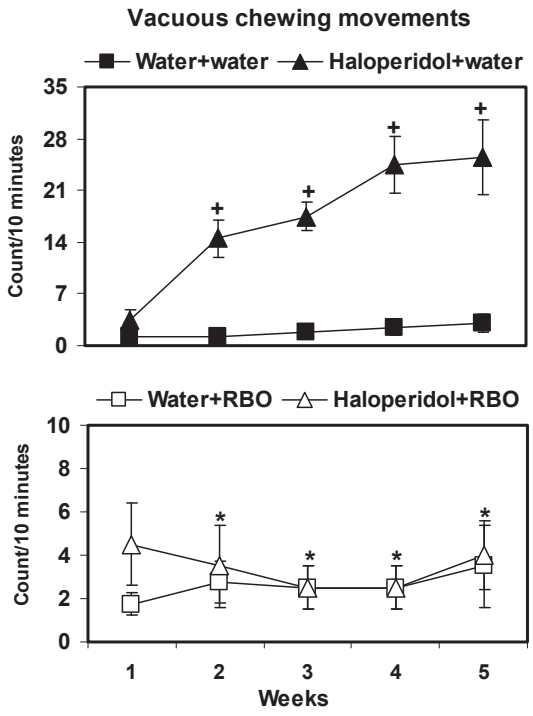

Fig. 4 – Intensity of haloperidol-induced vacuous chewing movements in animals treated with water and rice bran oil (RBO). Values are means ± standard deviation ($n = 4$). Significant differences by Newman–Keuls test: $^{*}p < 0.01$ from haloperidol plus water-treated animals, $^{+}p < 0.01$ from water-treated animals following three-way ANOVA.

analysis by Newman–Keuls test showed that administration of haloperidol elicited VCMS for 2 weeks, which increased in a time-dependent manner for 3–5 weeks. Administration of RBO prevented the induction of haloperidol-elicited VCMs.

4. Discussion

The major findings of the present study were that chronic administration of haloperidol increased VCMs in a time-dependent manner and impaired motor coordination as treatment continued for 5 weeks. Motor activity was not altered by oral repeated haloperidol treatment. The aim of the present study was to investigate the effect of RBO on haloperidol-induced EPS. Results show that RBO prevented the induction of haloperidol-elicited VCMs as well impairment of motor coordination.

An unbalanced production of free radicals is associated with chronic neuroleptic use [26] and might contribute to the onset of TD [27] and other movement disorders, such as dystonia and Parkinsonism [28].

Neuroleptics act by blocking dopamine receptors [29] and increase the turnover and metabolism of dopamine, which in turn could lead to an increased production of hydrogen peroxide [30,31], resulting in oxidative stress [32]. Dopamine is primarily metabolized through oxidation by monoamine oxidase to 3,4-dihydroxyphenyl acetic acid. This reaction produces hydrogen peroxide. Dopamine is also metabolized by auto-oxidation, yielding superoxide radical. Increased dopamine turnover by neuroleptics could lead to excessive production of these potentially damaging free radicals [33]. Oxygen free radicals are also reported to diminish the dopamine transporter function further increasing the extracellular dopamine levels [34].

Neuroleptics suppress the activity of certain detoxifying enzymes, leaving cells unprotected, especially if basal enzyme activity is low or the free radical-scavenging mechanism are less effective. Free radicals are highly reactive with specific cellular components and have cytotoxic properties [35] and neuronal loss in the striatum has been reported in animals treated with neuroleptics [36].

Oxidative stress in the hippocampus might inhibit neuronal plasticity and neurogenesis [37] and the behavioral deficits by antipsychotics may be mediated by oxidative stress [9]. Neuroleptics may also have direct cytotoxic effect via the production of toxic metabolites [38]. Reduced haloperidol is oxidized to a pyridinum metabolite in blood and brain [39], which is also thought to be a mitochondrial toxin. As reduced haloperidol concentrations are about five times higher in the elderly [40]; this could contribute to their predisposition to develop TD. It is well known that the antipsychotic drug haloperidol causes VCMs in rats, which are representative of side effects of TD. Haloperidol was disclosed to potentiate increases in oxidative stress or free radical-mediated levels of toxic metabolites in rat. Antioxidant has been used to combat haloperidol-induced VCMs in rats resulting from increases in oxidative cellular events [41]. Much preclinical evidence suggests that the inclusion of a naturally occurring and benign antioxidant compound as an adjunct to antipsychotics treatment may help guard patients against TD [42,43].

In the present study, activity in an open field and home cage were not altered by oral repeated haloperidol administration (Figs. 1 and 2). Chronic haloperidol treated animals exhibited VCMs for 2 weeks, which increased in a time dependent manner for 3–5 weeks (Fig. 3) and motor coordination was also impaired (Fig. 4), suggesting possible induction of free radical generation by chronic haloperidol treatment involved in the increase frequencies of VCMs and impairment of motor coordination.

RBO inhibited lipid peroxidation in erythrocytes and in all tissues initiated by free radical generation [19]. Antioxidants, such as tocopherol, tocotrienol, γ-oryzanol, and polyphenol and their components are present in rice bran. These compounds are free radical scavengers [16] and are normally consumed when tissues are exposed to oxidative stress [44] and protect neuronal cell from injury induced by oxygen free radicals *in vitro* and ischemia–reperfusion damage *in vivo* [45].

Toxicological studies show that intake of cellulose derived from agricultural waste such as maize cob, groundnut shell, or rice husks increased locomotor activity [46]. Similarly, standard rice bran diet increases exploratory activity in a novel environment [47]. In the present study motor activity was not altered by RBO.

The antioxidant activities of the four of the vitamin E and three oryzanol components purified from rice bran were investigated in a chronic model of cholesterol oxidation. All components exhibited significant antioxidant capacity and

inhibited cholesterol oxidation [48]. Previously, it was reported that vitamin E has neuroprotective properties [49,50] and may be of use for the treatment TD [51].

TD is a serious motor disorder related to antipsychotic therapy, whose pathophysiology is associated to oxidative stress [52]. Previous studies have shown that administration of B vitamins (B1:B6:B12 at 60:60:0.6 mg/kg) alone or the vitamin B cocktail along with haloperidol [52] and extract of *Ginkgo biloba* (antioxidant) and vitamin E [53] prevent the development of orofacial dyskinesia.

The findings of the present study support the notion that oxidative stress is involved in the elicitation of neuroleptic-induced VCMs and show that RBO given orally at a dose of 0.4 mL/day prevents the haloperidol-induced VCMs as well as impairment of motor coordination. It is suggested that antioxidant action of RBO is involved in the reversal of haloperidol-induced EPS.

Conflicts of interest

The author declares that there are no conflicts of interest.

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