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Original Article

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



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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.

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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 potentially 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

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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 \times 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 \times 26 cm \times 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 \times 26 cm \times 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

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