Nootropic and anti-stress effects of rice bran oil in male rats

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Abstract Rice bran oil (RBO) is an important product of rice bran. It is considered to be one of the most important nutritious oil due to its favorable fatty acid composition and unique composition of naturally occurring biologically active antioxidant compounds. This study was designed to monitor the effects of oral intake of RBO on stress response in rats. RBO was extracted using hexane. Rats were divided into Control and test (RBO-treated). RBO-treated rats were given 0.2 ml/day RBO for 6 weeks. Food intake and body weight changes were monitored weekly. After 6 weeks open field activity and Morris Water Maze (MWM) test were performed. Results showed that weekly cumulative food intake but not body weight were lower in RBO-treated rats during 1st to 5th week of treatment, which were normalized at the end of treatment. Exploratory activity of RBO-treated rats in an open field was increased. Spatial memory in Morris water maze was enhanced in RBO-treated than control rats. An episode of 2 h restraint stress decreased the 24 h food intake of both control and RBO-treated animals. Behavioral deficits were lower in RBO-treated rats. Exposure of 2 h restraint stress increased brain serotonin (5-hydroxytryptamine: 5-HT) metabolism. These increases were lower in RBO-treated restrained than their respective control animals. Serotonergic neurotransmitter mechanism is implicated in stress. The findings of the study show beneficial effects of RBO in learning and memory functions. Moreover, the study also highlights the attenuating effect of RBO on stress induced behavioral and neurochemical effects in rats.

Keywords Memory · Restraint stress · Rice bran oil · Serotonin

Introduction

Rice is one of the most widely consumed foods over the world, feeding more people over a longer period of time than any other crop. Rice consists of endosperm and germ. Rice bran (RB) is a by product of rice milling process. In the past, human consumption of rice bran has been limited primarily because of the rapid onset of the rancidity in rice bran, but methods to stabilize rice bran and to extract its oil have now been developed.

Rice bran oil (RBO) is an important product of rice bran. Depending on the rice and degree of milling, the RB consist 12–23 % oil that has an unusually high unsaponifiable matter of 4 % concentration (Saunders 1985; Sugano and Tsuji 1997). RBO is an unconventional vegetable oil which in some populations is believed to be healthy (Sugano and Tsuji 1997). It is considered to be one of the most nutritious oil due to its favorable fatty acid composition and unique composition of naturally occurring biologically active antioxidant compounds (Rukmini and Raghuram 1991; Rogers et al. 1993; Xu et al. 2001; Rana et al. 2004; Mishra et al. 2012; Khuwijitjaru et al. 2009; Posuwan et al. 2013; Hansakul et al. 2011). The bioactive compounds in RBO are fats, antioxidants and minerals. Rice bran oil has a balanced FA profile that includes 47 % monounsaturated fats, 33 % polyunsaturated fats and 20 % saturated fats. The fat content is composed of triacylglycerols (87 %), free fatty acids (8 %) and unsaponifiable material (5 %) a host of minor constituents with proven nutritional benefits such as γ -oryzanol, tocotrienols, tocopherols, and squalene (Van Hoed et al. 2011; Tyagi et al. 2012). At the same time, rice bran oil differs from other vegetable oils because of its

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higher FFA content along with its unusually high contents of wax, unsaponifiable constituents, polar lipids (including glycolipids), and pigments (Tyagi et al. 2012).

The effects of stress or diet on health have been well studied. Interactions between monoamines and macronutrient intake have been frequently shown (Pham et al. 2000; Fernstrom 1977; Fernstrom et al. 1979; Haleem et al. 2000; Paez and Leibowitz 1993; Jorgensen 2007; Tsuji et al. 2012). Serotonin (5-HT) is a major neurotransmitter involved in the control of various functions. A role of 5-HT is described in stress and memory. Brain serotonin is also known to be involved in responses to stress (Adell et al. 1988; Meltzer 1989; Leonard 2005; Keeney et al. 2006; Nesic and Duka 2008) and adaptation to stress (Haleem 1999; Haleem and Perveen 1994).

RBO is regarded as a highly nutritional source due to significant amount of lipids (PUFAs) (Juliano 1985). The long chain PUFAs are fundamental components of membrane lipids in the CNS and also precursor of various bioactive mediators (Calviello et al. 2013). A reduction in PUFA content has been implicated in altered learning behavior leading to reduced synaptic vesicle density in brain particularly in hippocampus (Ikemoto et al. 2001). Hippocampus has a major role in memory function (Haider et al. 2007). A diet rich in PUFA can be beneficial for learning and memory functions and also in alleviating the stress effects (Zare et al. 2011). The present study was therefore designed to observe the effects of oral RBO intake on learning and memory performance and responses to stress in rats.

Materials and methods

Animals

Locally bred albino Wistar rats weighing 180–200 g were housed individually under a 12 h light dark cycle (lights on at 6:00 h) with free access to tap water and standard rat feed for at least 4 days before starting the experiment. All animal experiments were approved by the institutional ethics and animal care committee and performed in strict accordance with National Institute of Health Guide for Care and Use of Laboratory Animals (Publication No.85-23, revised 1985). All treatment and behavioral monitoring were done in a balanced design to avoid order and time effect.

Extraction of Rice Bran Oil (RBO)

Rice bran was obtained from Falak Rice Mills, F.B. Area, Karachi, through their milling process. It was stabilized by microwave heating 30 s to inactivate the lipases (Connor and Connor 1972). The oil was extracted through solvent (hexane BP 68 °C) extraction and was heated at 57 °C to remove

hexane residues completely (Benado 2006) and placed in desiccator for removal of moisture.

Experimental protocol

Animals ($n=24$) were divided into two groups ($n=12$); (I) Control (II) RBO treated. RBO treated rats were given 0.2 ml RBO/day and normal standard rodent food for 6 weeks. Control animals were given only standard rodent diet. During the treatment changes in body weight and food intake were monitored weekly. Exploratory activity in open field was monitored after 6 weeks of treatment. Water maze test for testing spatial memory was conducted next day.

After six weeks of RBO treatment, the rats of the two groups were further divided ($n=6$) into unrestrained and restrained. Animals of the latter group were immobilized for 2 h between 10:00–12:00 h. Animals of the unrestrained group were left in their home cages during this period. Cumulative food intakes for 24 h were monitored next day before exposing the animals to a second restraint period of 2 h. Rats were decapitated immediately after the termination of 2nd restraint period using guillotine to collect whole brain samples and stored at -70 °C. Unrestrained animals were also decapitated at the same time.

Morris water maze test

Morris Water Maze (MWM) test was performed to examine the effects on spatial memory (Morris 1981). Spatial memory was determined by noting the latency time (time in seconds taken by the rats to reach a non-visible platform). It is a circular pool of water with a diameter of 45 cm, height of 37 cm, and depth of 12 cm. The pool is a metal cylinder painted white on the inner surface. The escape platform is also made of metal cylinder with flat metallic top having a surface diameter of 8 cm, and it is placed 2 cm below the surface of water during water maze training. The pool is filled with water (23 ± 2 °C) which was made opaque with milk in order to obscure the platform to allow proficient tracking of the swim paths of the rats (Haider et al. 2011). In our experiment, we have assessed learning acquisition, the reference (long-term) memory and working (short-term) memory in terms of latency to locate the escape platform. The test is based on two phases: the training phase and the test phase. Memory functions of rats were tested by noting down the retention latency. The cut off time was 2 min for each session. Initially, the training session was performed during which each rat was placed into the water in such a way that their face was towards the wall of the tank. Each animal was given 120 s to find and mount onto the hidden platform by using distal extra maze cues. Cues must be visible and useful to rats. They must be far enough to require the rat to use spatial analysis, rather than association, to solve the task. If the rat

located the platform it was allowed to stay on it for 10 s. Time on the platform must be sufficient for them to feel the location and to see the exact position. If it failed to locate the platform during the allocated time, then it was guided gently onto the platform (Haider et al. 2007). The test consisted of three trials: learning acquisition (LA), STM (short-term memory) and LTM (long-term memory). After training of animals learning acquisition was tested immediately by noting the initial latency (IL; the time taken by each rat to relocate the hidden platform immediately after training). STM was assessed 60 min after training session, and LTM was measured after 24 h of training (Haider et al. 2012).

Determination of whole brain 5-HT and 5-HIAA by HPLC-EC method

Frozen brains samples were homogenized in extraction medium using an electrical homogenizer (Polytron; Kinematica). Estimation of 5-HT and 5-HIAA in the rat brain was done by HPLC-EC method as reported by Haider et al. 2011. Brain 5-HT was detected in a single sample (20 μ l) by reversed phase HPLC with electrochemical detector at an operating potential of +0.8. A 5 μ Shim-pack ODS separation column (purchased from Sigma Aldrich) of 4.0 mm internal diameter and 150 mm length was used as the stationary phase. Separation was achieved by a mobile phase containing methanol (14 %), octyl sodium sulfate (0.023 %) and EDTA (0.0035 %) in 0.1 M phosphate buffer at pH 2.9, which was passed through the column under a pressure of 2,000–3,000 psi at the flow rate of 0.1 ml/min.

Statistical analysis

Statistical analysis was done by using SPSS version 13.0. Results are represented as mean $\pm$ SD. Data for weekly changes in food intake and body weight was analyzed by 2-way

ANOVA (repeated measure design). Behavioral activities data was analyzed by Student's *t*-test. Restraint-induced behavioral and neurochemical data were analyzed by 2-way ANOVA. Individual comparisons were made by Newman-Keuls test.

Results

The present study aims to assess the effect of long-term administration of RBO on neurological functions including behavioral and neurochemical alterations.

Effects of RBO intake on weekly food intake and growth rate

The effect of long-term (6 weeks) RBO administration on food intake (Fig. 1a) and growth rate (Fig. 1b) showed a significant ($p<0.01$) decrease in food intake as well as in growth rate of RBO treated rats compared to control as shown in Fig. 1 (a and b). 2-way ANOVA performed on food intake data indicated non-significant effect of week ($F=3.131$ $df=4, 132$ $p>0.05$) and non-significant treatment effect ($F=0.0305$ $df=1, 132$ $p>0.05$). However, the interaction between treatment $\times$ week ($F=18.667$ $df=1, 132$ $p<0.01$) was significant. Post hoc comparison by Newman-Keuls test showed that RBO treatment significantly ($p<0.05$) increases food intake in 1st week as compared to control but its starts decreasing after 3rd week cumulative food intakes and in 4th week there is significant ($p<0.05$) decrease in food intake as compared to control and 1st week food intake. These decreases in food intakes were then normalized after fifth week of RBO administration. Analysis of Growth rate data showed significant treatment effect ($F=79.594$ $df=1, 132$ $p<0.01$), week effect ($F=173.03$ $df=4, 132$ $p<0.01$) and significant interaction ($F=119.71$ $df=1, 132$ $p<0.01$) between the treatment and week. Post hoc comparisons by Newman-Keuls test indicated that the long-term administration of RBO significantly ($p<0.01$) decreases weekly cumulative growth rate from 1st to 5th week as compared to the control rats.

Fig. 1 The effects of RBO intake on weekly food intake (a) and (b) body weight changes. Values are represented as mean $\pm$ S.D. Significant comparisons by post-hoc tests are shown as $+p<0.05$, $++p<0.01$ when compared with 1st week and $*p<0.05$, $**p<0.01$ when compared with their respective controls

Fig. 2 The effects of RBO treatment in rats on spatial memory assessed by water maze test in terms of learning acquisition (a), short-term memory (b) and long-term memory (c). Values are represented as mean+S.D. Significant comparisons by post-hoc tests are shown as $*p<0.05$

Effects of RBO intake on spatial memory

The effect of long-term RBO administration, for 6 weeks in rats on spatial memory was assessed by MWM is presented in Fig. 2 in terms of learning acquisition (a), short-term memory (b) and long-term memory (c). Analysis by *t*-test showed a non-significant increase in learning acquisition (difference in escape latency time between training and learning acquisition session) while a significant improvement in STM and LTM was observed which was evident by a significant ($p<0.05$) increase in latency time (to find the hidden platform) compared to control rats.

Effects of RBO intake on locomotor activity

The effect on locomotor activity following long-term RBO administration was assessed by open field test. Statistical analysis by *t*-test showed a significant increase ($p<0.05$) in square crossings in RBO treated group as compared to control shown in Fig. 3. It indicates that RBO treatment enhanced the locomotor activity of rats in the open field.

Effects of stress on food intake and growth rate

The effect of single 2 h restraint stress on 24 h food intake (Fig. 4a) and 24 h growth rate changes (Fig. 4b) of control and RBO treated rats showed a significant ($p<0.01$) decrease in food intake as well as in growth rate of both control and RBO treated rats as compared to their respective unrestrained group

as shown in Fig. 4 (a and b). Analysis of 24 h food intake data by 2-way ANOVA ($df=1, 20$) showed a significant stress effect ($F=23.091$ $p<0.01$), treatment effect ($F=407.91$ $p<0.01$) and significant interaction between the treatment and stress ($F=53.793$ $p<0.01$). Similarly 2-way ANOVA performed on growth rate data again indicated a significant stress effect ($F=14.196$ $p<0.01$), treatment effect ($F=296.98$ $p<0.01$) and significant interaction between stress and treatment ($F=27.96$ $p<0.01$). Post-hoc comparisons by Newman-Keuls statistics showed that exposure to restraint stress significantly decreases 24 h cumulative food intake in control ($p<0.01$) and RBO treated animals ($p<0.05$) as well as significantly decreases ($p<0.01$) growth rates of both control and RBO treated animals. These restraint-induced decreases in food intake and growth rate were smaller in RBO treated rats

Fig. 3 The effects of RBO treatment in rats on locomotion assessed by open field activity. Values are represented as mean+S.D. Significant comparisons by post-hoc tests are shown as $*p<0.05$

Fig. 4 The effects of single 2 h restraint stress on 24 h food intake (a) and 24 h growth rate changes (b) of control and RBO treated rats. Values are represented as mean+S.D. Significant comparisons by post-hoc tests are

shown as * $p<0.05$, ** $p<0.01$ when compared to their respective unrestrained groups and + $p<0.05$, ++ $p<0.01$ when compared to restraint control

as on comparing the stressed control rats with stressed RBO treated group, the food intake and growth rate of stressed RBO treated group was significantly ($p<0.05$ & $p<0.05$, respectively) higher than the stressed controls.

Effects on brain serotonin metabolism

The result of neurochemical estimations showed that following long-term RBO administration levels of 5-HT and its metabolite 5-HIAA in brain were significantly ($p<0.01$) decreased in RBO treated rats but after an episode of 2 h restraint stress the levels of brain 5-HT and 5-HIAA were significantly ($p<0.01$) increased in both control and RBO treated rats which is shown in Fig. 5 (a and b). Analysis of data on brain 5-HT concentration (Fig. 5a) by 2-way ANOVA ($df=1, 20$) revealed a significant treatment effect ($F=13.093$ $p<0.01$), stress effect ($F=10.674$ $p<0.01$) and a non-significant interaction ($F=0.48122$ $p>0.05$) between the two factors. Post hoc comparison indicated that exposure to stress significantly increased brain levels of 5-HT in both control ($p<0.01$) and RBO treated rats ($p<0.05$) as compared to their respective unstressed groups but this increase was significantly lower ($p<0.05$) in RBO treated group as compared to stressed controls. Analysis of 5-HIAA data by 2-way ANOVA also showed a significant treatment effect ($F=7.284$ $p<0.01$), effect of stress ($F=3.486$ $p>0.05$) and non-significant effect of interaction between treatment x stress ($F=0.379$ $p>0.05$). Post hoc comparison indicated that exposure to stress

increases brain levels of 5-HIAA in both control and RBO treated rats. This increase was significant ($p<0.05$) in control rats but in RBO treated rats the increment was not significant as compared to their respective unstressed groups. These results indicates that restraint-induced increases of brain 5-HT and 5-HIAA levels were smaller in RBO treated animals, thus revealing the protective effect of RBO on stress-induced neurochemical alterations.

Discussion

In a previous study long term consumption of stabilized rice bran (SRB) rich diet was found to attenuate restraint-induced behavioral deficits and serotonergic responses in rats (Jabeen et al. 2007). The aim of the present study was to monitor the long term effects of RBO (instead of SRB) on learning and memory and responses to stress in rats. In the present study administration of RBO for 6 weeks was found to initially increase then decrease the weekly cumulative food intake of rats while the growth rate of rats was significantly increased throughout the treatment. Previous reports indicated that RBO supplementation did not affect quantity of food consumption or growth rate (Sierra et al. 2005). It was noted in the present study that 2 h restraint stress decreased the 24 h food intake of both control and RBO treated rats. But these restraint-induced anorexiogenic effects were smaller in RBO treated animals.

Fig. 5 Effects of RBO and 2 h restraint stress on the levels of brain 5-HT (a) and 5-HIAA (b). Values are represented as mean+S.D. Significant comparisons by post-hoc tests are shown as * $p<0.05$, ** $p<0.01$ when compared to their respective unrestrained groups and + $p<0.05$, ++ $p<0.01$ when compared to restraint control

Stress-induced body weight changes were also smaller in RBO treated rats. This reduction in food intake and weight gain following RBO treatment may be attributed to the stress alleviating effects of RBO. Stress represents the reaction of the body to the stimuli that disturbs its normal physiological equilibrium or homeostasis (Kim et al. 2002). RBO by attenuating the stress-induced deficits may be considered as an anti-stress source.

The main components of RBO include antioxidants like γ -orynazole, tocotrienols (Rukmini and Raghuram 1991; Nicolosi et al. 1994), and unsaturated fatty acids such as β -sitosterol (Sharma and Rukmini 1987). RBO appears to be a richest source of tocopherol and tocotrienols (Van Hoed et al. 2011). Hence, RBO not only has a good fatty acid profile but also is a rich source of antioxidant, and micronutrients. The increased antioxidant activity has been shown to improve memory function (Haider et al. 2014). In the previous experiment (Jabeen et al. 2007), we observed that mixing of SRB with rodent diet stimulated the learning and memory of rats in Morris water maze test. In the present study we found that administration of RBO enhanced both short term memory and long term memory in Morris water maze test. The enhanced memory function following administration of RBO may indeed be attributed to its rich antioxidant content.

Serotonergic mechanisms have a role in the adaptive responses to stress. Evidence exist for a role of 5-HT in stress and adaptation to stress (Haleem and perveen 1994). In the present study immobilization stress increased brain 5-HT levels stressed controls while increases of brain 5-HT and 5-HIAA were attenuated by RBO in rats subjected to immobilization stress. Previously we have shown that administration of SRB lowered brain 5-HT levels. Rats exposed to an episode of 2 h restraint stress exhibited an increase in brain 5-HT and 5-HIAA concentrations (Kennett et al. 1986; Haleem and Perveen 1994; Haleem et al. 1998) that did not occur after repeated immobilization of 2 h/day for 5 days (Haleem and Perveen 1994) suggesting that adaptation occurs in serotonergic responses to stress. In the present study restraint-induced increases of brain 5-HT and also 5-HIAA were smaller in RBO treated than control rats. These beneficial effects may occur due to the presence of tocopherol, tocotrienol, γ -orynazole and other unsaponifiable compounds in RBO which make it a good source of antioxidants.

Conclusion

In conclusion the present study shows that prolonged consumption of RBO increases locomotor activity and enhances memory function in rats. An altered food intake and growth rate is also observed following the administration of RBO. Stress-induced increases of brain serotonin metabolism were attenuated by RBO treatment. These beneficial effects of RBO

may occur due to the presence of antioxidant compounds in RBO which may elicit neuroprotective effects and attenuate stress-induced behavioral and neurochemical deficits. It may further be suggested that use of RBO may be beneficial for memory function and helpful in combating the stressful events in everyday life.

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