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Long-Term Administration of Rice Bran Oil Attenuates 5-HT1A Receptor Dependent Responses in Rats

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Abstract

Objective: To study the pre and post synaptic 5-HT1A receptor dependent responses in rats following Rice bran oil (RBO) treatment.

Methods: Male albino Wistar rats were first categorized into two groups. Standard rodent food was given to all groups. RBO-treated rats were given RBO (0.2 ml/day) daily for six weeks. After six weeks, the rats were subdivided into further two groups. Rats of first subgroup were injected with saline and second group with 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) at a dose of 0.25 mg/kg. 8-OH-DPAT-induced behavioral activity was monitored just after 5 minutes of injections till 25 minutes. One hour after saline or drug injections, animals were sacrificed. Plasma and brain samples were then stored for the estimation of cholesterol, glucose and corticosterone in plasma and concentrations of serotonin in brain.

Results: Intensity of serotonin syndrome produced by 8-OH-DPAT and the effects of the drug on plasma glucose and corticosterone were greater in RBO treated than control rats suggesting that the treatment decreases postsynaptic 5-HT1A receptor dependent responses. Drug-induced decreases of brain 5-HT metabolism, a measure of presynaptic 5-HT1A receptor dependent response were also attenuated in RBO treated rats.

Conclusion: Down regulation of 5-HT1A autoreceptor receptor mediated feedback control over 5-HT synthesis and release is possibly played a role to have opposed the depression like effects by RBO.

Keywords: Antidepressant; Rice bran oil; Serotonin; 5-HT 1A receptors; 8-OH-DPAT; Feedback control

Introduction

In the past, the intake of rice bran (RB) by humans was short due to the development of the quick rancidity, but these days stabilization methods and extraction of oil have been introduced [1,2]. Interest in RB is increasing because a number of studies suggest that the consumption of rice bran produces potential health benefits. Rice bran oil (RBO), an important derivative of rice bran [3] is a unique vegetable oil which is rich in unsaturated fats and is free of trans-fats [4]. It's ideal fatty acid constituents and presence of naturally producing biologically active and antioxidant compounds makes it nutritious oil. In addition, accumulating evidence suggests that RBO can lower blood cholesterol, boost immune response and may help prevent cancer [5-12].

5-Hydroxytryptamine (5-HT; serotonin) is implicated in the regulation of a number of physiological functions and treatment of many psychiatric illnesses. A possible role of 5-HT1A receptors in adaptation to stress and antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) is also well identified [13-15]. A high density of 5-HT1A receptor type occurs presynaptically on the cell body and dendrites serotonergic neurons where they act as auto receptors to regulate the synthesis, availability and release of the neurotransmitter [13]. The 5-HT-1A receptors are also located postsynaptically in almost every brain region. Postsynaptic receptors activation is known to regulate a number of physiological conditions, including antidepressant effects and adaptation to stress [13-15]. The activation of postsynaptic 5-HT1A receptors activates hypothalamo-pituitary adrenocortical (HPA) axis, resulting in an increase in circulating levels of corticosterone and glucose.

8-hydroxy-2-di-n-propyl amino tetralin (8-OH-DPAT), a selective agonist at 5-HT1A receptors is used as a tool to monitor 5-HT1A receptor dependent responses in rats. The drug activates pre as well as postsynaptic receptors. The activation of presynaptic receptors decreases 5-HT metabolism while activation of postsynaptic receptors elicits 5-HT syndrome and

increases plasma corticosterone and glucose [15]. Previously we have shown that long term administration of stabilized rice bran as well as RBO produces antidepressant like effects and facilitate adaptation to stress in rats [16,17]. For further evaluation mechanism concerned in the antidepressant like actions of RBO, the present study focuses 5-HT1A receptor dependent responses in rats treated with RBO for six weeks. In view of reported cholesterol lowering and stress reducing effects of RBO [4,6,18-20], effects of 8-OHDPAT on circulating corticosterone, cholesterol and glucose are also monitored. The aim of the study was to monitor the pre and post synaptic 5-HT-1A receptor dependent responses in rats following RBO treatment.

Material and Methods

Animals

Male Albino Wistar rats (weigh180-200 g) were bought from the Animal House of HEJ Research Institute of Chemistry, University of Karachi, Pakistan. Animals were caged separately in saw dust covered cages under a 12 hour light dark cycle (lights on at 6 hour) with free availability of tap water and standard rat food for minimum 4 days before starting the experiment. This was done to help animals adapt the new environment. All the experiments were carried out in accordance with the guidelines of the Local Animal Care & Ethical Committee. All injections and monitoring of behavior were done in a balanced design to avoid order and time effect.

Drugs

8-OH-DPAT hydroxybromide (HBr) taken from Research Biochemist (RBI, USA) was dissolved in saline (0.9% NaCl) and intraperitoneally (i.p.) injected at a dose of 0.25 mg/ml per kg body weight. It has been shown previously, that this dose activates both pre and postsynaptic 5-HT1A receptors [15]. Animals of the control group were injected with saline in a volume of 1 ml/kg body weight.

Evulsions of rice bran oil (RBO)

Rice bran was obtained through their milling process, stabilized by heating and then oil was separated out by the same method [17,21,22]. Microwave heating was used for stabilization to inactivate the lipases and oil was extracted through solvent (hexane BP 68°C) extraction.

Experimental protocol

24 Animals were categorized into two groups (I) Control and (II) RBO treated. RBO treated rats were orally given 0.2 ml RBO/day together with normal standard rodent diet for 6 weeks. Control animals were not given RBO but only standard diet. After six weeks of treatment, the rats of the two groups were again divided into two subgroups. Rats of the 1st subgroup were injected with saline and 2nd group was injected with 8-OH-DPAT at a dose of 0.25 mg/kg. Injections were done between 8:30 am and 9:30 am in a balanced design. 8-OH-DPAT evolved syndrome behaviors were monitored for 20 minutes, starting 5 minutes post injection. 1 hour after the drug or saline injections rats was decapitated to collect and store the plasma and brain samples.

Behavioral Test

8-OH-DPAT evolved 5-HT syndrome

15 minutes before injections, rats were placed separately to Perspex activity cages (26 cm × 26 cm × 26 cm) with sawdust covered floor. Injections were done between 10:00-11:00 hours. 8-OH-DPAT evolved syndrome behaviors were scored as previously described [23,24]. That experiment was conducted on a group of four rats at a time. Forepaw treading was scored for 1 minute, and every 5 minutes up to 25 minutes. 5-25 minutes post injection scoring period was divided into four sessions of 5 minutes each. Each animal in every scoring session was constantly watched for 1 minute and equivalently observed for 1 minute after 5 minutes pause in the next session for a total of 4 scoring sessions. The intensity of flat body posture was observed on a scale of 0-4 (absent to maximum). Total of four scoring periods were determined later.

Biochemical Estimations

Zlakits Method was used for the analysis of cholesterol in plasma [25]. Plasma glucose and plasma corticosterone levels were estimated by O-toluidine [26,27] and fluorimetric methods [28] respectively.

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

Chilled brain samples were homogenized in extraction medium using homogenizing pestle [29]. HPLC-EC method as before [30-32] was used to determine the levels of 5-HT and 5-HIAA in brain. 4 mm diameter and 150 mm length Shim-pack ODS column of 5 µm was utilized. Mobile phase which was used for separating contents having these composition, methanol (14%), Octyl sodium sulfate (0.0235) and EDTA (0.0035%) in 0.1 M phosphate buffer of pH 2.9 and that was passed through the column under a pressure of 2,000-3,000 psi at the flow rate of 0.1 ml/min. At an operating potential of 0.8 V electrochemical detection was achieved on L-ECD-6A detector.

Statistical Evaluation

Statistical evaluation was achieved by using SPSS version 13.0. Results are represented as means ± SD. All behavioral and chemical data were evaluated by 2-way ANOVA. Individual comparisons were made by Newman-Keul statistics.

Results

8-OH-DPAT- induced syndrome in control and RBO-treated rats

Flat body posture and fore paw treading syndrome produced by 8-OH-DPAT in both groups are shown in Figure 1A and 1B

respectively. Student's t-test analysis showed that flat body posture and fore paw treading were smaller in RBO treated as compared to control one.

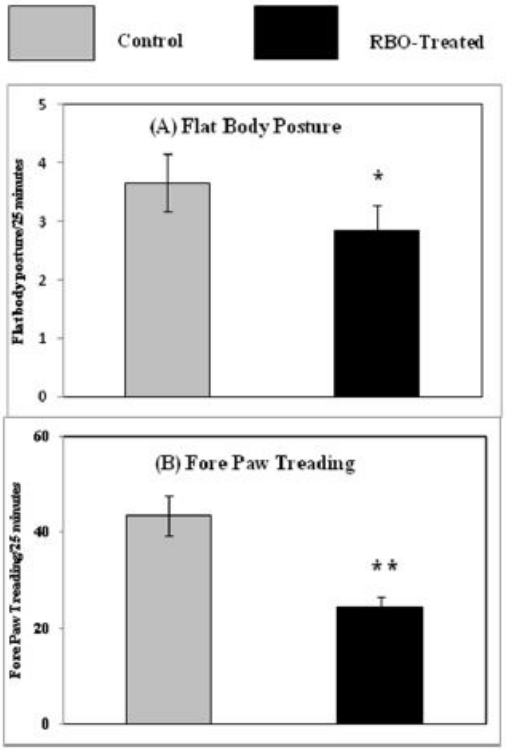

Figure 1: 8-OH-DPAT-induced serotonin syndrome: (A) Flat Body Posture and (B) Fore Paw Treading in control and RBO-treated rats. Values are means ± SD (n=6). Significant differences by t-test: $^{*}P<0.05$, $^{**}P<0.01$ from controls.

Effects on plasma cholesterol, glucose and corticosterone concentrations

Changes on the concentration of plasma cholesterol, glucose and corticosterone by 8-OH-DPAT in control and RBO treated rats are shown in Figure 2A-2C respectively. 2-way ANOVA (df=1,20) showed significant (p=0.01) treatment effects for cholesterol (F=24.768), glucose (F=37.883) and corticosterone (F=44.445); and significant (p=0.01) drug effects for cholesterol (F=20.017), glucose (F=57.808) and corticosterone (F=21.679). Interaction between the two factors was significant for glucose (F=13.997, p=0.01) but not for cholesterol (F=0.010, p=0.05) and corticosterone (F=1.612, p=0.05). Post hoc comparison indicated that 8-OH-DPAT-induced increases of plasma cholesterol and corticosterone were smaller in RBO treated than control rats. Drug-induced increases of plasma glucose levels were also smaller in RBO treated rats. Saline injected RBO treated rats also exhibited lower cholesterol and corticosterone levels.

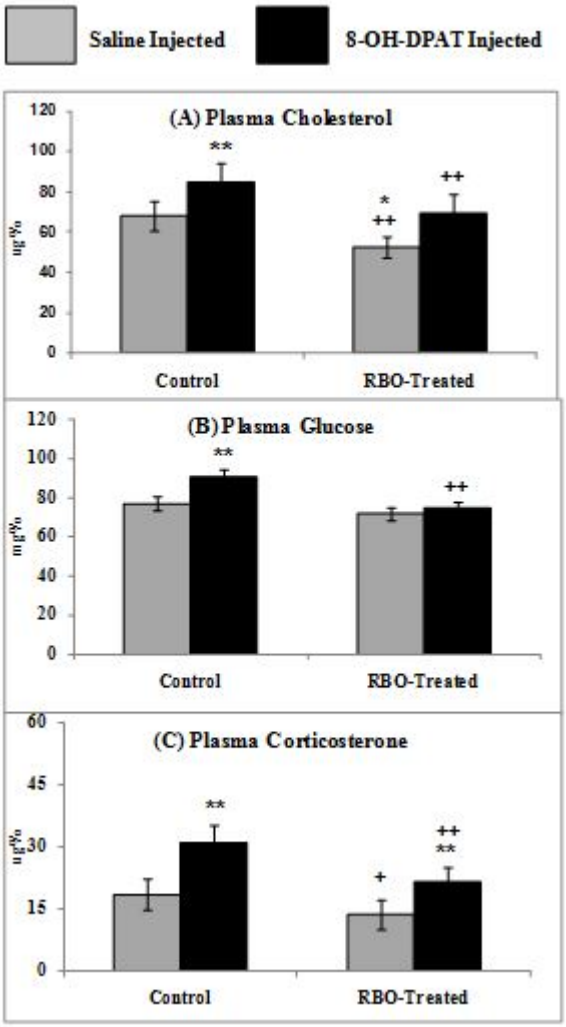

Figure 2: Effects of 8-OH-DPAT on the plasma levels of (A) Cholesterol (B) Glucose and (C) Corticosterone in controls and RBO-treated rats. Values are means ± SD (n=6). Significant differences by Newman-Keuls test: $^{*}P<0.05$, $^{**}P<0.01$ from respective saline injected rats; $^{+}P<0.05$; $^{++}P<0.01$ from respective controls following 2-Way ANOVA.

Effects in whole brain serotonin metabolism

8-OH-DPAT-elecited effects on the levels of brain 5-HT and 5-HIAA in control and RBO treated rats are shown in Figure 3. Data statistically analyzed by 2-way ANOVA (df=1,20) showed significant (p=0.01) RBO treatment effect for 5-HT (F=44.710), 5-HIAA (F=143.979). Drug effect was also significant (p=0.01) for 5-HT (F=77.852) and 5-HIAA (F=4.924, p=0.05) as well as significant (p=0.01) interactions between RBO × 8-OH-DPAT for 5-HT (F=155.205) and 5-HIAA (F=31.761). Comparison by Post hoc indicated that brain levels of 5-HT and 5-HIAA in control rats were deceased by 8-OH-DPAT injection. But decreases of 5-HIAA were smaller in RBO treated than control rats. The decreases of 5-HT did not occur in RBO treated rats by 8-OH-DPAT. Conversely, 8-OH-DPAT injected, RBO treated rats exhibited slightly higher levels of 5-HT than in saline injected RBO treated rats or 8-

OHDPAT injected control rats. Results suggested a down regulation of auto receptor mediated feedback control over 5-HT synthesis and release in RBO treated rats.

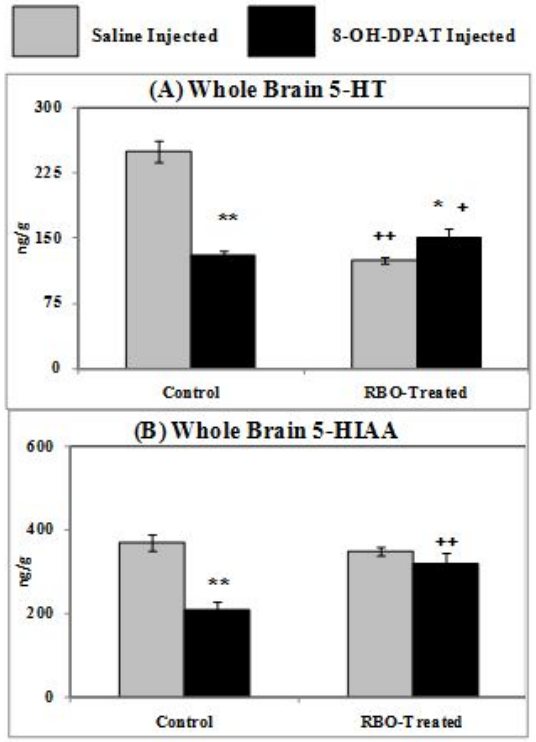

Figure 3: Effects of 8-OH-DPAT on the brain levels of (A) 5-HT and (B) 5-HIAA in control and RBO-treated rats. Values are means ± SD (n=6). Significant differences by Newman-Keuls test: $^{*}P<0.05$, $^{**}P<0.01$ from respective saline injected rats; $^{+}P<0.05$, $^{++}P<0.01$ from respective controls following 2-Way ANOVA.

Discussion

The basic purpose of the present study was to monitor responses mediated via the activation of pre and postsynaptic 5-HT1A receptors following RBO treatment. Activation of presynaptic 5-HT1A receptor is known to produce a feedback effect on the synthesis and release of 5-HT, which results in a decrease in 5HT metabolism. On the other hand, activation of postsynaptic 5-HT1A receptors increases activity of HPA axis resulting in an increase circulating levels of corticosterone and glucose. The behavioral syndrome following the 8-OH-DPAT injections is also produced via the postsynaptic 5-HT1A receptors activation. The current study shows that responses that depend on both pre and postsynaptic 5-HT1A receptor are attenuated in RBO treated rats. A number of studies showed that the injection of 8-OH-DPAT elicits hyperactivity syndrome by activating post synaptic 5-HT-1A receptors [15,33]. Specially, flat body posture and forepaw treading (5-HT syndrome components) are because of the action at post synaptic sites [33]. The behavior was not blocked by the inhibition 5-HT synthesis and is independent of pre synaptic machinery. As the administration of 8-OH-DPAT at a dose of 0.25 mg/kg produced smaller forepaw treading and flat body posture in RBO treated than control rats, so the findings tend to suggest that long term intake of RBO down regulates postsynaptic 5-HT1A receptors concerned in the of elicitation behavioral syndrome. Similarly, smaller increase in circulating corticosterone and glucose following the administration of 8-OH-DPAT in RBO treated than control rats suggests that postsynaptic 5-HT1A receptors [34,35] involved in the activation of HPA axis are also down regulated.

That activation of 5-HT-1A auto receptors present on the cell body and dendrites of serotonergic neurons decreases serotonin synthesis and release has been documented in many studies [36-38]. Because 8-OH-DPAT (0.25 mg/kg)-induced decreases of 5-HT metabolism were much smaller in RBO treated than control rats, we suggest long term administration of RBO down regulates 5-HT1A auto receptors.

It is tempting to relate the down regulation of presynaptic 5-HT1A receptors in RBO treated rats with the stress reducing effect of RBO, reported previously from our laboratory [17], because long term administration of selective serotonin reuptake inhibitors [39-41] and adaptation to stress [13,14,29,42] both down regulate presynaptic 5-HT1A auto receptors. On the other hand, it may be noted that a down regulation of presynaptic 5-HT1A receptors is expected to increase 5-HT and 5-HIAA levels in RBO treated saline injected animals, but the levels in the present study were smaller in these rats. It is however possible that in conditions that demand greater 5-HT neurotransmission, such as during stress, a down regulation of 5-HT1A receptors maintains 5-HT availability at postsynaptic sites to help cope the stress. Indeed, a greater sensitivity of 5-HT1A receptors impairs adaptation to stress [42] to predispose to depression.

Conclusion

In conclusion the current study shows that long term RBO intake down regulates presynaptic as well as postsynaptic 5-HT1A receptor dependent responses. A down regulation of presynaptic responses can prevent stress effects on serotonin neurotransmission to produce antidepressant like effect. A down regulation of postsynaptic 5-HT1A receptors involved in the activation of HPA axis and the elicitation of behavioral syndrome was also observed in the present study. Future studies on other behavioral and physiological responses may help to understand 5-HT1A receptor dependent neurotransmission in the antidepressant like effects or long term intake of RBO. Studies on partial 5-HT1A agonist buspirone and 5-HT1A antagonists may also be useful. Together with previous studies from our laboratory the present study tend to suggest that long term intake of RBO can reduce stress effects on behavior by decreasing 5-HT1A auto receptor mediated feedback control over 5-HT synthesis and release.

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