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m-CPP-induced behavioral and neurochemical alterations following longterm intake of rice bran oil in rats

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Abstract: Rice bran oil (RBO), a second product of rice bran consists of some extraordinary composition of biologically active and naturally produced antioxidant compounds. *meta*-Chlorophenylpiperazine (mCPP), a psychoactive drug of the phenylpiperazine class produces depressive and anxiogenic effects in humans and rodents. It is a postsynaptic 5-hydroxytryptamine (5-HT; serotonin) receptor agonist at 5-HT $_1$, 5-HT$_{1A}$, 5-HT$_2$ and 5-HT$_{2C}$ and antagonistic at 5-HT$_3$. The present study relates the hypophagic and neurochemical effects of m-CPP following prolong intake of RBO in rats. Male Albino Wistar rats were initially divided into Control and RBO treated groups. Control animals were given only standard rodent diet. RBO treated rats were given 0.2 ml RBO/day in addition to normal standard rodent food for 6 weeks. Animals of the two groups were again divided into 2 subgroups. Group one was injected with saline in a volume of 1ml/kg body weight. 2nd group was injected with m-CPP at a dose of 3 mg/kg. Food intakes were monitored 4h after the drug administration. Then animals were decapitated. Results showed that m-CPP produced hypophagia in control and also in RBO treated rats, but these effects were greater in RBO treated rats suggesting that the responsiveness of post synaptic hypophagic 5-HT$_{2C}$ receptors is stimulated by RBO treatment. In addition, m-CPP -induced 5-HT and tryptophan (TRP) levels were reduced in RBO treated than control rats. Plasma corticosterone and glucose levels following m-CPP were also found to be smaller in long term RBO treated animals. The results support the hypothesis that RBO can attenuate stress effects by changing the receptor responsiveness.

Key Words: Rice bran oil, Food intake, Hypophagia, Post synaptic 5-HT receptor, m-CPP, Rats, Stress
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INTRODUCTION

Meta-Chlorophenylpiperazine (m-CPP) is a serotonin (5-HT) agonist having antidepressant capacity[1]. It is an intermediate product of drug trazodone and nefazodone[2] and it leads to affect hormonal, physiological and behavioral responses. It is a strong 5-HT postsynaptic receptor agonist at 5-HT$_1$, 5-HT$_{1A}$, 5-HT$_2$ and 5-HT$_{2C}$ and antagonist at 5-HT$_3$ [3, 4]. Most of its binding affinity is presumably powerful at the 5-HT$_{1C}$ receptors[5]. Pharmacological studies provide evidence that increasing 5-HT functions at post synaptic 5-HT$_{2C}$ and 5-HT$_{1B}$ receptors produce decreased food intake[6] in experimental animals. m-CPP, that notably reduces food intakes in rats and humans[7] has high affinity for 5-HT$_{2C}$ receptors[8,9]. It could also be used to strengthen the effects of psychoactive drugs [10].

Rice bran oil (a byproduct of Rice bran) consists of 12–23% oil with high unsaponifiable matter[11]. It has some uncommon components like γ -orynazol, ß-sitosterol and unesterified fatty acids[12,13] to contribute cholesterol reduction[14,15]. High concentration of tocopherol and tocotrienol also exist in RBO with an antioxidant property[16,17]. Consumption of stabilized rice bran (SRB) and RBO in health and disease was already discussed in the context of its serotonergic together with antioxidant effects [18, 19].

The present study is designed to evaluate the hypophagic and neurochemical effects of m-CPP following prolong consumption of RBO in rats.

A number of studies in human and animal have shown that RBO is an affective as other oils in lowering serum cholesterol levels[15,20,21] and blood glucose[22]. Evidence shows that through central serotonin receptors, *m*-CPP acts to release cortisol, prolactin, growth hormone (GH) and Adrenocorticotropic hormone (ACTH). Due to the binding of m-CPP with serotonin transporter, its presynaptic functions have also been monitored[23]. Such type of effects have been studied in persons with psychiatric disorders and in normal controls[24, 25, 26]. Moreover, it has been reported that hyperglycemia produced by m-CPP was regulated by 5-HT $_{2C}$ and/ or 5-HT $_{2B}$ receptors and inturn adrenomedullary catecholamine release[27]. In this study following RBO administration m-CPP-induced changes in plasma cholesterol and glucose levels were also monitored.

MATERIAL AND METHODS

Animals

Albino Wistar rats, bred locally (weighing about180-200g) were housed singly under a 12h light dark cycle (lights on at 6:00 h) 4 days before experimentation. Tap water and standard rat food were freely available for at least 4 days before starting the experiment. All experimental animals were cared according to the approval of animal care committee and institutional ethics. Experiments performed in totally strict accordance with National Institute of Health Guide for Laboratory animals (Publication No 85-23, revised 1985). All treatment and behavioral monitoring were done in a balanced design to ovoid other effects.

Drug

m-CPP (2HCL) purchased from Sigma was dissolved in 0.9% NaCL (saline) and injected intraperitoneally (i.p.) at a dose of 3mg/ml per kg body weight.

Extraction of rice bran oil

Rice bran was obtained from a local Rice Mill through their milling process and stabilized by microwave heating process for 30 seconds to inactivate the lipases [28]. The oil was then extracted as described before[19], through (hexane BP 68°C) solvent extraction and heated at 57°C for complete removal of hexane residues[29] and placed in desicator to remove moisture.

Experimental Protocol

24 Animals were grouped into Control and RBO treated. Control animals were given only standard rodent diet. RBO treated rats were given 0.2 ml RBO/day and normal standard rodent food for 6 weeks. After 6 weeks, the rats of the two groups were again divided into 2 subgroups. Animals of the first group were injected with saline in a volume of 1ml/kg body weight. Animals of another group were injected with m-CPP at a dose of 3 mg/kg. All animals were injected between 9: 00 and 10:00h in a balanced design to avoid any order effect.

Determination of hypophagic effects

Just after the drug administration a weighed amount of food was placed in the hopper of the cages and food intakes during 4h were monitored. Then animals were sacrificed using guillotine to collect whole brain and plasma samples and stored at -70˚C.

Determination of plasma corticosterone, glucose and cholesterol

Immediately after decapitation of rats, blood was collected in tubes containing heparin and centrifuged at 3000 rpm for 15-20 minutes to get plasma for plasma corticosterone estimation by the method of Mattingly[30] as described by Haleem[31]. Plasma glucose and cholesterol levels were estimated by O-toluidine and Zlatkis methods respectively.

Determination of whole brain serotonin and its metabolite by HPLC-EC method

Using an electrical homogenizer (Polytron; Kinematica) frozen brain samples were homogenized as described previously[32]. Serotonin (5-HT) and its metabolite, 5-hydoxyindoleacetic acid (5-HIAA) levels were determined by HPLC-EC as reported before[33, 34]. A 5 um Shim-Pack ODS separation column was used, that have 4.0mm internal diameter and 150 mm length. Separation was performed by mobile phase enclosing methanol (14%), octyl sodium sulfate (0.023%) and EDTA (0.0035%) in 0.1 M phosphate buffer of pH 2.9, which was moved through the column under a pressure of 2,000–3,000 psi at the flow rate of 0.1 ml/m. Electrochemical detection was acquired on Shimadzu L-ECD-6A detector at an operating potential of 0.8 V.

STATISTICAL ANALYSIS

Analysis was done by using Statistical Package for Social Sciences (SPSS) version 13.0. Results are represented as mean ± SD. All Data were interpreted by 2-way ANOVA. Individual comparisons were

done by Newman-Keuls test. Post-hoc comparisons were made by Newman-Keuls test. P values P<0.05 were considered significant.

RESULTS

Figure 1 shows the effects of m-CPP on 4h food intakes of control and RBO treated rats. 2-way Analysis of variance (ANOVA ; 1,20 df) revealed a significant treatment (F=127.916 p<0.01) and drug effect (F=21.938 p<0.01). Interaction between treatment x drug (F=0.117 p>0.05) was non-significant. Newman-Keuls test indicated that injection of m-CPP at a dose of 3 mg/kg decreased 4h food intake of control and RBO treated rats in significant ratio. 4h intakes of RBO treated were higher than control rats.

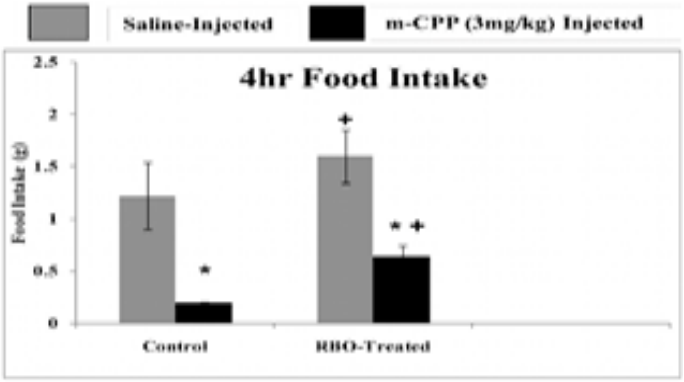

Figure 1: The effect of m-CPP on 4-h food intake in control and RBO-treated rats. Values are means + SD (n=6). Significant differences by Newman-Keuls test; *p<0.01 from respective saline injected and +p<0.05, ++p<0.01 from similarly injected control rats following 2-way ANOVA.

Figure 2 shows the effect of m-CPP on the levels of plasma cholesterol, glucose and corticosterone in control and RBO treated animals. ANOVA by 2-way method (1, 20 df) revealed significant (p<0.01) treatment effects for glucose (F=64.653) and corticosterone (F=73.485) but not for cholesterol (F=1.85 p>0.05), and significant (p<0.01) drug effects for glucose (F=58.711), corticosterone (F=5.326) and cholesterol (F=10.132). Interactions between the two components were non-significant for cholesterol (F=1.620 p>0.05), glucose (F=2.581 p>0.05) and corticosterone (F=0.679 p>0.05). Comparison by Newman-Keuls test indicated that m-CPP-induced increases of plasma glucose and corticosterone were reduced in RBO treated than control rats. m-CPP-induced plasma cholesterol levels were reduced in RBO treated rats. Saline injected animals exhibited decreased levels of cholesterol, glucose and corticosterone following RBO treatment.

Effects of single administration of m-CPP on the levels of plasma and brain TRP in control and RBO treated animals are shown in Figure 3. Data on plasma TRP concentration evaluated by 2-way ANOVA statistics (1, 20 df) indicated a significant treatment effect (F=43.97 p<0.01), drug effect (F=11.39 p<0.01) but an insignificant interaction (F=1.99 p>0.05) between the two. Analysis on brain TRP data showed a significant drug effect (F=8.82 p<0.01). Treatment effect (F=3.09 p>0.05) and interaction between treatment x drug (F=2.0 p>0.05) were not significant for brain TRP. Post-hoc comparison by Newman-Keuls indicated that administration of m-CPP significantly increased plasma and brain TRP. But these increases were little in RBO treated rats.

Effects of m-CPP on the levels of brain 5-HT and 5-HIAA in control and RBO treated rats are shown in Figure 4. Data on 5-HT evaluated by 2-way ANOVA (1, 20 df) showed a significant treatment (F=31.627 p<0.01) and drug (F=10.058 p<0.01) effects. Interaction between the two constituents (F=2.241 p>0.05) was not significant for 5-HT. ANOVA performed on 5-HIAA concentration indicated non-significant (p>0.05) effect of treatment (F=0.718) and drug (F=3.775). Interaction between the two (F=0.256) was also not significant. Post-hoc comparison indicated that administration of m-CPP produced reduction in brain levels of 5-HT in both control and RBO treated rats. Drug-induced 5-HT in RBO was smaller than control rats.

DISCUSSION

m-CPP, an intermediate product of antidepressant drug trazodone 2, has been noticed to produce marked physiological and behavioral effects both in human and animals. These effects have been considered due to the interaction of m-CPP with serotonergic receptors9, 21. Main purpose of the present study was to investigate the behavioral and neurochemical effects of m-CPP in RBO treated rats.

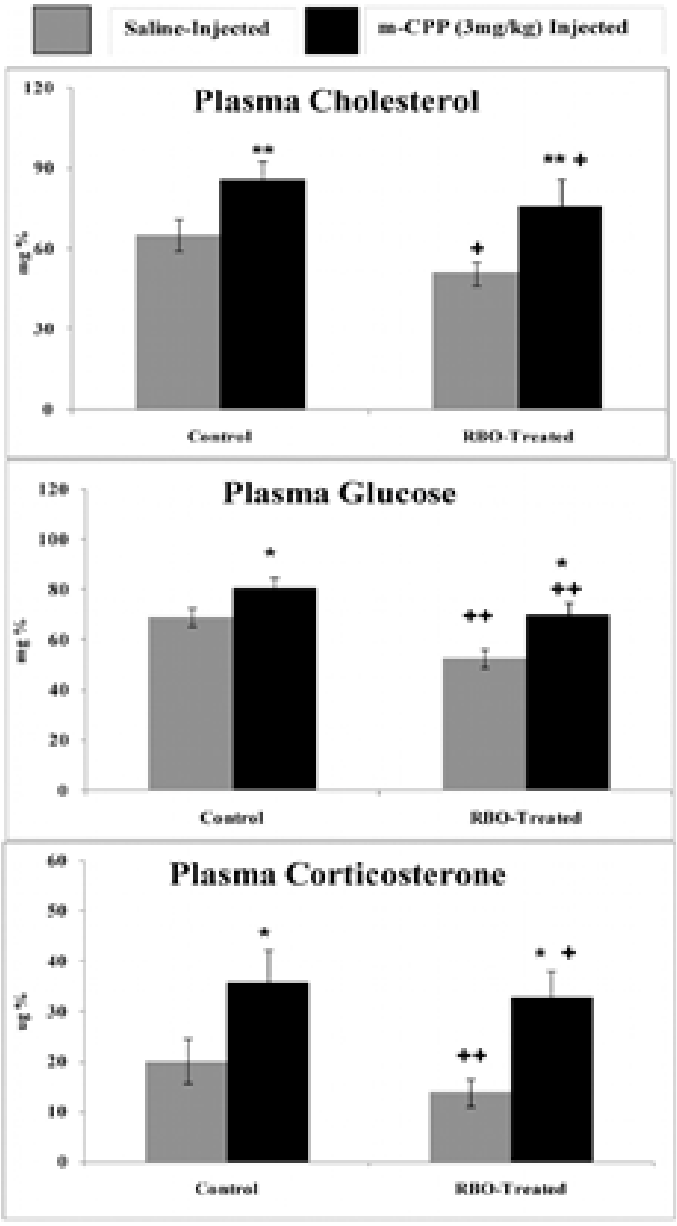

Figure 2: The effect of m-CPP on the levels of cholesterol, glucose and corticosterone in plasma of control and RBO-treated rats. Values are means + SD (n=6). Significant differences by Newman-Keuls test; *p<0.01 from respective saline injected and +p<0.05, ++p<0.01 from similarly injected control rats following 2-way ANOVA.

Hypophagic effects of m-CPP were greater in RBO treated rats as compared to controls. Other authors have shown that administration of m-CPP produced hypophagia in freely feeding as well as food deprived rats 6, (Schreiber and DeVry, 2002). m-CPP-induced hypophagia was found to be unaffected by the essential fatty acid composition of the diet 35. In our study we found that administration of m-CPP at a dose of 3mg/kg induced hypophagia in both control and RBO treated rats. But those

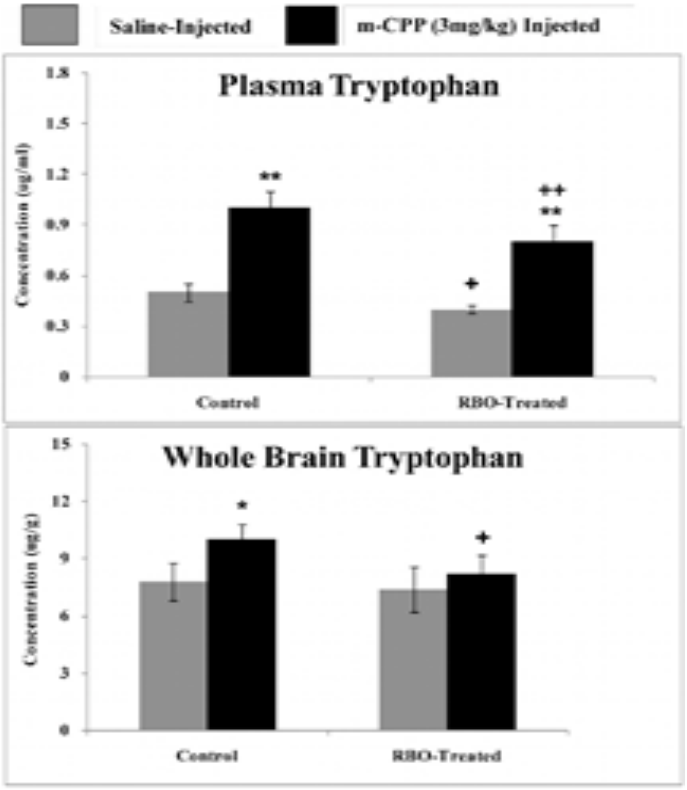

Figure 3: The effect of m-CPP on the levels of TRP in plasma and brain of control and RBO-treated rats. Values are means + SD (n=6). Significant differences by Newman-Keuls test; *p<0.05, **p<0.01 from respective saline injected and +p<0.05, ++p<0.01 from similarly injected control rats following 2-way ANOVA.

hypophagic effects of m-CPP were greater in RBO treated rats suggesting that the responsiveness of post synaptic hypophagic 5-HT2C receptors is stimulated by RBO treatment.

Administration of m- CPP has also been reported to increase plasma corticosterone and glucose levels[32]. In this study, all these increases following m-CPP were found to be smaller in long term RBO treated animals. The results are consistent that RBO can attenuate stress effects[19]. Recent study also indicated antinociceptive and antidepressant actions of RBO[36]. m-cpp, a metabolite of antidepressant trazadone binds to various serotonergic receptors mainly 5-HT_{2C} and α_2-adrenoreceptors.When the effects of m-cpp were investigated on serum cholesterol, the positive association between serum cholesterol and cortisol responses was possibly suggested[37]. Such type of association may provide an explanation for reported enhancement in depression, suicide and violence in subjects with low cholesterol[37, 38].

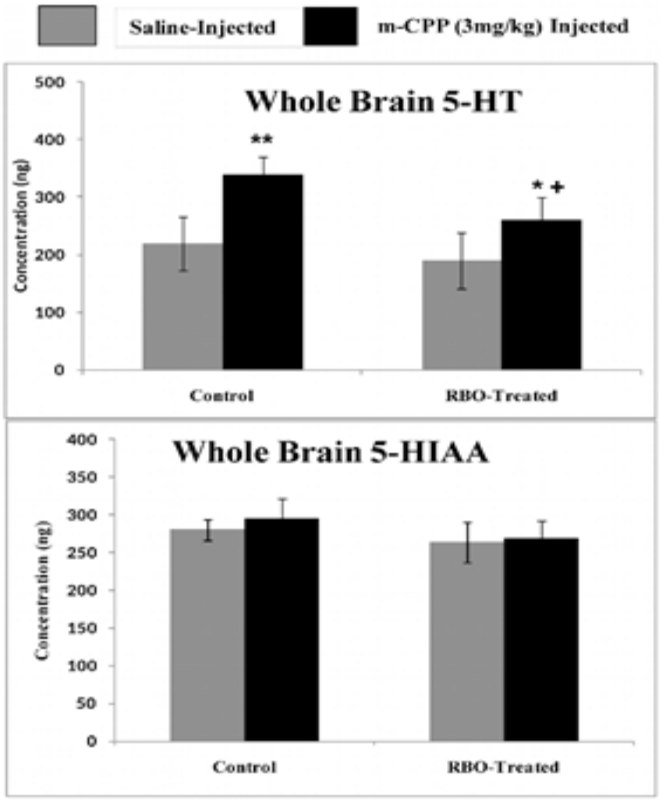

Figure 4: The effect of m-CPP on the levels of 5-HT and 5-HIAA in whole brain of control and RBO-treated rats. Values are means + SD (n=6). Significant differences by Newman-Keuls test; *p<0.01 from respective saline injected and ++p<0.01 from similarly injected control rats following 2-way ANOVA.

RBO is considered to decrease total and low density lipoprotein (LDL) cholesterol and increase high density lipoprotein (HDL) cholesterol levels due to its high content of unsaturated fatty acid especially Monounsaturated fatty acid[20, 21] (MUFA). We observed a smaller increase in m-cpp-induced plasma cholesterol levels following long term RBO treatment. It may also be due to antioxidant property of RBO [39-41].

In addition, we also observed that m-CPP - induced TRP and 5-HT levels were smaller in RBO treated than control rats. Decreased pre synaptic activity is often shown to produce a compensatory upregulation of post synaptic hypophagic receptors[42]. Evidence shows that simultaneous activations of 5-HT_{2C} and 5-HT_{2B} receptors underlied the high potency of m-CPP in reducing food intake, as compared to other compounds[6]. In the present study the concentration of 5-HT was decreased in RBO treated rats. Conversely, m-CPP-induced hypophagia was greater in RBO treated than control rats suggesting that a decrease in pre synaptic serotonin concentration is involved in upregulation of post synaptic 5-HT_{1C} receptors.

Administration of m-CPP has been shown to decrease 5-HT turnover and increase extracellular levels of 5-HT[43, 44] by regulating reuptake of 5-HT into synaptosomes. In the present study, this effect of m-CPP was greater in RBO treated than control rats. It may be concluded that decreasing 5-HT metabolism following prolonged RBO consumption increases the responsiveness of post synaptic hypophagic 5-HT_{2C} receptors.

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