

DESENSITIZATION OF PRE AND POST SYNAPTIC 5-HT-1A RECEPTOR RESPONSES FOLLOWING LONG TERM CONSUMPTION OF SUGAR RICH DIET: IMPLICATIONS FOR SUGAR-INDUCED OBESITY

BUSHRA JABEEN AND DARAKHSHAN J. HALEEM

Department of Biochemistry, Neurochemistry and Biochemical Neuropharmacology Research Unit,
University of Karachi, Karachi 75270, Pakistan

ABSTRACT

The present study concerns the effectiveness of a selective 5-hydroxytryptamine (5-HT) -1A receptor agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) in long term sugar diet treated rats. Male albino wistar rats were divided into control and test groups. Test animals were given sugar (5 g/10ml water) orally for three weeks. Food intakes and body weight of all rats were measured weekly. After three weeks control and test animals were further divided into two groups i.e. saline injected and drug injected. 8-OH-DPAT at a dose of 0.25mg/kg was injected to a group of normal diet treated and another group of sugar diet treated rats. Other two groups were injected with saline. 5-HT syndrome and food intakes at 2h and 4h were monitored. Then animals were decapitated to collect brain samples for the estimation of 5-HT and 5-hydroxyindole acetic acid (5-HIAA) levels by HPLC-EC method. We observed that weekly cumulative food intakes increased and body weights decreased in sugar diet treated rats. 8-OH-DPAT produced hyperactivity syndrome in both control and sugar treated rats. But these values were smaller in sugar diet than normal diet treated rats. Hyperphagic effects of 8-OH-DPAT were greater in normal diet than sugar diet treated rats. 5-HT and 5-HIAA levels were not altered. The results suggesting a desensitization of pre as well as postsynaptic 5-HT-1A receptors in rats treated with sugar diet are discussed in the context of a role of sugar diet in the precipitation of obesity and other neuropsychiatric illnesses.

Keywords: Sugar, 8-OH-DPAT, pre-synaptic 5-HT-1A receptor, hyperphagia, desensitization.

INTRODUCTION

Overeating is stimulated by the ready availability of food rich in fat and sugar. Appetite regulation and the understanding of rewarding effects of food in particular energy rich food (fat and sugar) has become of greatest interest for scientist. Serotonin (5-hydroxytryptamine; 5-HT), a neurotransmitter, has been implicated in the regulation of appetite (Curzon, 1990; Haleem, 1996; Reis *et al*, 2005). Brain serotonin levels are affected by many factors, including circulating levels of Tryptophan (TRP) and certain macronutrients (Halford and Blundell, 2000). It has also been reported that long term consumption of stabilized rice bran rich diet attenuates serotonergic response to stress (Jabeen *et al.*, 2007).

Intake of sugar rich diet increases brain 5-HT metabolism by a mechanism similar to the increase of carbohydrate (CHO) and insulin-induced increases of brain 5-HT (Fernstrom, 1983; Smolders *et al.*, 2001). Dietary CHO have been shown to raise brain serotonin turnover (Wurtman and Wurtman, 1995) by increasing the availability of TRP to the brain in humans (Piji *et al.*, 1993) as well as in animals (Fernstrom and Wurtman, 1972; Fernstrom, 1983) because the rate limiting enzyme of 5-HT biosynthesis exists only half saturated with its substrate (Fernstrom and Fernstrom, 1995). Multiple

receptors for 5-HT have been characterized. 5-HT-1A receptors are present on the soma and dendrites of 5-HT neurons and also on post synaptic neurons in various brain regions of the limbic system (Verge *et al.*, 1985).

Stimulation of somatodendritic receptors by a selective 5-HT-1A agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) decreases the synthesis and release of 5-HT from the nerve endings (Hutson *et al.*, 1989; Adell *et al.*, 1991; Haleem, 1999), which produces hyperphagia in experimental animals (Haleem, 1992; De Vry and Schreiber, 2000). This decrease at functional post synaptic receptor by 5-HT-1A agonist gives a measure of pre synaptic responsiveness (Haleem, 1999). Administration of 8-OH-DPAT induces hyperactivity syndrome, which is taken as a measure of post synaptic receptor responsiveness (Haleem, 1992; Haleem *et al.*, 2002). Previously it has been reported that prolonged consumption of sugar rich diet produces hyperphagia in rats that was associated with a decrease in brain 5-HT metabolism (Haleem *et al.*, 2000). The goal of our study here was to examine the pre and post synaptic receptor responses to 5-HT-1A agonist 8-OH-DPAT in long term sugar treated rats. It was hypothesized that the responsiveness of somatodendritic 5-HT-1A receptor is increased following long term administration of sugar rich diet. Greater effectiveness and availability of these receptors decreases the appetite suppressant effects of 5-HT in terminal regions to precipitate hyperphagia.

Corresponding author: e-mail: bushra_raza05@yahoo.com

MATERIALS AND METHODS

Animals

Locally bred male albino wistar rats weighing (200-220g) were housed individually under a 12 h light dark cycle (lights on at 6:00 h) in a quiet room with free access to cubes of standard rodent diet and tap water for at least 4 days before experimentation. All experiments were performed according to a protocol approved by the local animal care committee.

Drugs

8-OH-DPAT hydroxybromide (HBr) purchased from Research Biochemist (RBI, USA) was dissolved in saline (0.9% NaCl) and injected intraperitoneally (i.p.) at a dose of 0.25mg/ml per kg body weight. Control animals were injected with saline in a volume of 1ml/kg body weight.

Experimental Protocol

Twenty four animals were divided into two groups (I) control (II) sugar treated. Control rats were given normal standard rodent food and only tap water. Each animal of the latter group was given 5g of sugar in 10ml water/ day for three weeks. Standard rodent diet and tap water also available to the second group. During the treatment changes in body weight and food intake were monitored weekly.

After 3 weeks, the rats of the two groups were further divided into 2 subgroups. One of these was injected with saline in a volume of 1ml/kg body weight. Second group was injected with 8-OH-DPAT at a dose of 0.25mg/kg. Animals were injected in a balanced design to avoid order effect. 8-OH-DPAT elicited behavioral syndrome was monitored for 20 minutes, starting 5 minutes post injection. A weighed amount of food was placed in the hopper of the cages immediately after monitoring the activity. Food intakes were monitored 2h and 4h after injection. Then animals were decapitated using guillotine to collect whole brain samples and stored at -70°C. Concentrations of 5-HT and 5-HIAA were determined by HPLC-EC method.

BEHAVIORAL TESTS

8-OH-DPAT elicited 5-HT syndrome

Control and sugar treated rats were transferred in a Perspex activity cages (26x26x26cm) with sawdust covered floor 15 minutes before injecting 8-OH-DPAT between 10:00-11:00h. Hyperlocomotion elicited by 8-OH-DPAT was scored as described by Haleem (1992). The experiment was conducted on a group of four rats at a time. Control and sugar treated rats placed in a separate observation cages were injected with 8-OH-DPAT in a balanced design. The scoring period (5-25 minutes post injection) was divided into four sessions of 5 minutes continuously observed for 1 minute and similarly

observed for 1 minute at 5 minutes intervals in the next session for a total of 4 scoring sessions. In each session, the numbers of cage crossing were counted. A total of four scoring periods was later determined.

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

Brain samples were homogenized as described previously (Haleem and Parveen, 1994). 5-HT and 5-HT levels were determined by HPLC-EC as described before (Haleem *et al.*, 2002; 2004). A 5 um Shim-Pack ODS separation column of 4.0mm internal diameter and 150 mm length was used. Separation was achieved by mobile phase containing methanol (14%), octyl sodium sulfate (0.023%) and EDTA (0.0035%) in 0.1 M phosphate buffer of ph 2.9 at an operating pressure 2000-3000 psi on Shimadzu HPLC pump. Electrochemical detection was achieved on Shimadzu L-ECD-6A detector at an operating potential of 0.8 V.

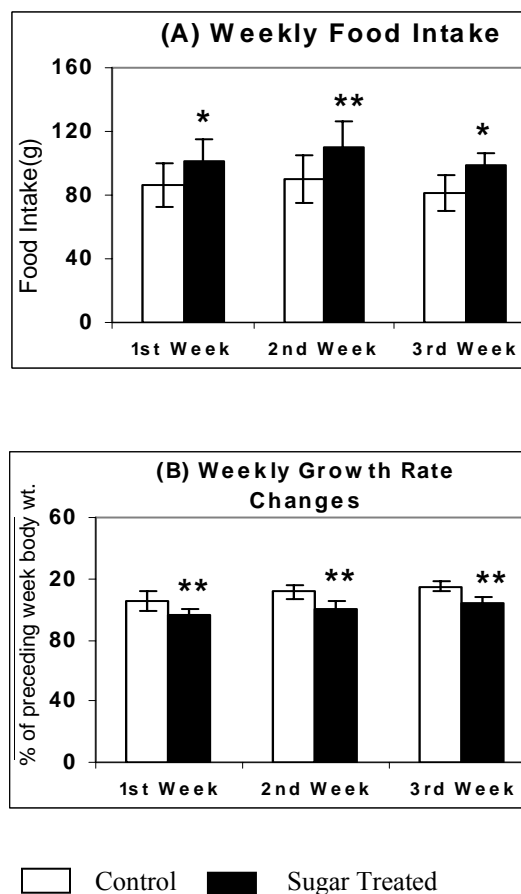


Fig. 1: Effects of 3 weeks sugar administration on weekly changes of food intake (A) and body weight (B). Values are means \pm SD (n=12). Significant differences by Newman-Keuls test, *p<0.05 and **p<0.01 from respective control rats following 2-way ANOVA.

STATISTICAL ANALYSIS

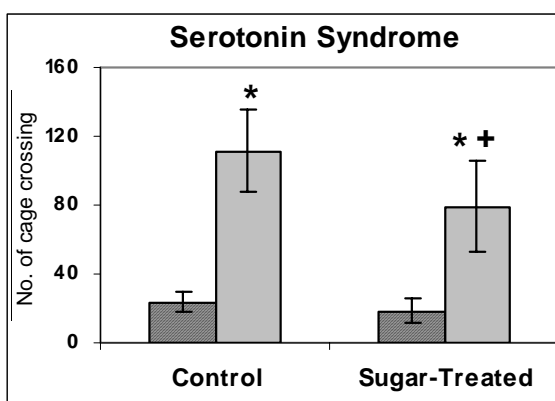
All data were analyzed by 2-way ANOVA. Post hoc comparison was done by Newman-Keuls test. $p < 0.05$ taken as significant.

RESULTS

Effects of three weeks oral sugar administration on food intake and growth rate

Figure 1 shows the effects of sugar (5g/10ml/animal/day) for 3 weeks on weekly food intakes and growth rate (as percentage of preceding week body weight). 2-way ANOVA (2-3-repeated measure design) revealed a significant sugar effect ($F=30.063$ $df=1,66$ $p < 0.01$) on weekly changes of food intake. The effect of weeks ($F=0.0069$ $df=2,66$ $p > 0.05$) was not significant. Interaction between week and sugar ($F=7.158$ $df=1,66$ $p < 0.01$) was significant. Post hoc comparison by Newman-Keuls test showed that food intake (including 5g of sugar) during the 1st week ($p < 0.01$), 2nd week ($p < 0.01$) as well as 3rd week ($p < 0.05$) was greater in sugar than control animals.

Data on weekly changes of growth rate analyzed by 2-way ANOVA (2-3-repeated measure design) revealed a significant sugar effect ($F=80.093$ $df=1,66$ $p < 0.01$) and week effect ($F=31.672$ $df=2,66$ $p < 0.01$). Interaction of sugar and weeks ($F=7.463$ $df=1,66$ $p < 0.01$) was also significant. Post hoc comparison (Newman-Keuls test) showed that in the groups of rats given sugar for three weeks, growth rates after 1st, 2nd and 3rd weeks were significantly smaller in sugar treated than control rats.



■ Saline injected ■ (0.25mg/kg) 8-OH-DPAT injected

Fig. 2: 8-OH-DPAT-induced hyperactivity syndrome behavior in control and sugar treated rats. Values are means \pm SD ($n=6$) 5 minutes after the saline or drug injections. Significant differences by Newman-Keuls test, * $p < 0.01$ from respective saline injected controls and + $p < 0.01$ from similarly injected control rats following 2-way ANOVA.

8-OH-DPAT-elicited syndrome in control and sugar treated rats

8-OH-DPAT (0.25mg/ml/kg i.p.) elicited 5-HT syndrome in control and sugar treated rats is shown in fig. 2. Data on cage crossing analyzed by 2-way ANOVA ($df=1,20$) indicated a significant sugar effect ($F=6.315$ $p < 0.05$) and drug effect ($F=97.50$ $p < 0.01$). Interaction between sugar and drug ($F=3.325$ $p > 0.05$) was not significant. Post hoc comparison made by Newman-Keuls showed that acute injection of 8-OH-DPAT (0.25mg/kg) significantly increased the mean values of cage crossing in control as well as sugar treated rats. Values were significantly smaller in sugar treated than control animals. Saline injected animals of the control and sugar treated groups exhibited comparable values.

Hyperphagic effects of 8-OH-DPAT in control and sugar treated rats

Fig. 3 shows the hyperphagic effects of 8-OH-DPAT in control and sugar treated rats. 2-way ANOVA ($df=1,20$) revealed a significant sugar effect ($F=6.223$ $p < 0.05$), drug effect ($F=17.894$ $p < 0.01$) and interaction between the two factors ($F=12.811$ $p < 0.01$) on 2h food intake. ANOVA performed on the data of 4h intake revealed non-significant sugar effect ($F=0.4897$ $p > 0.05$) but significant drug effect ($F=7.378$ $p < 0.01$) and also a significant interaction between sugar and drug ($F=13.608$ $p < 0.01$). Post hoc analysis by Newman-Keuls test indicated that injection of 8-OH-DPAT at a dose of 0.25 mg/kg significantly increased 2h and 4h food intake in control rats. The increases in sugar treated rats were not significant. These values of 2h and 4h intake were smaller in 8-OH-DPAT injected sugar treated than 8-OH-DPAT injected control animals. 2h and 4h intakes of saline injected sugar treated were higher than saline injected control rats. Differences were however not significant.

Effects of 8-OH-DPAT on the metabolism of serotonin in control and sugar treated rats

Fig. 4 shows the effects of 8-OH DPAT (0.25mg/kg) on 5-HT and 5-HIAA concentrations (ng/g of tissue) in the whole brain of control and sugar treated rats. 2-way ANOVA ($df=1,20$) indicated a non-significant sugar effect ($F=1.692$ $p > 0.05$), drug effect ($F=2.504$ $p > 0.05$) and a non-significant interaction between sugar and drug ($F=0.178$ $p > 0.05$) on 5-HT concentration. Effects of sugar administration ($F=1.69$ $p > 0.05$), 8-OH-DPAT ($F=2.332$ $p > 0.05$) and interaction between sugar and 8-OH-DPAT ($F=0.0595$ $p > 0.05$) were also not significant for 5-HIAA levels.

DISCUSSION

Other authors have reported that 5-HT-1A receptor agonist 8-OH-DPAT increases food intake of freely feeding rats (Haleem, 1992; DeVry and Schreiber, 2000). The mechanism is thought to be a selective stimulation of

5-HT autoreceptors in the raphe (Haleem, 1992; Haleem, 1996), so that serotonin release is decreased at the functional post synaptic hypophagic sites. We report that administration of 8-OH-DPAT produces smaller hyperphagia in sugar diet treated rats.

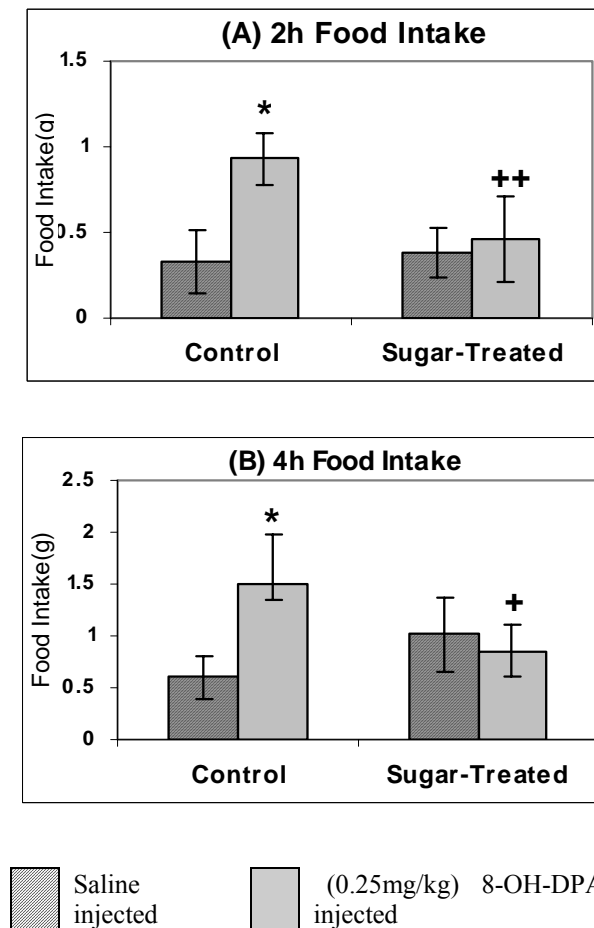


Fig. 3: Effects of 8-OH-DPAT on 2h (A) and 4h (B) food intakes of control and sugar treated rats. Values are means \pm SD (n=6). Significant differences by Newman-Keuls test, *p<0.01 from respective saline injected controls, +p<0.05 and **p<0.01 from similarly injected control rats following 2-way ANOVA.

Stimulation of somatodendritic 5-HT-1A receptors by 8-OH-DPAT decreases the activity of tryptophan-hydroxylase (Hutson *et al.*, 1986) and the availability of 5-HT decreases at post synaptic 5-HT-2C receptors (Liu *et al.*, 2005; Haleem *et al.*, 2004; Schuhler *et al.*, 2005) to produce hyperphagia. On the other hand, stimulation of post synaptic 5-HT-1A receptors by 8-OH-DPAT elicits hyperactivity syndrome (O'Connell and Curzon, 1996). Reports show that stimulation of pre as well as post synaptic 5-HT-1A receptors by buspirone (5-HT-1A agonist) and 8-OH-DPAT could attenuate restraint-induced behavioral deficits (Samad *et al.*, 2005).

Buspirone-induced decreases in brain 5-HT metabolism were greater in restrained than unrestrained animals, suggesting a greater responsiveness of somatodendritic 5-HT-1A receptor. In our result although 8-OH-DPAT-induced brain 5-HT and 5-HIAA levels were not different in both control as well as sugar treated rats as they were killed 4h post injections. However, a decrease in hyperphagia and hyperlocomotory effects of 8-OH-DPAT suggest desensitization of pre as well as post synaptic 5-HT-1A receptors in sugar rich diet treated rats.

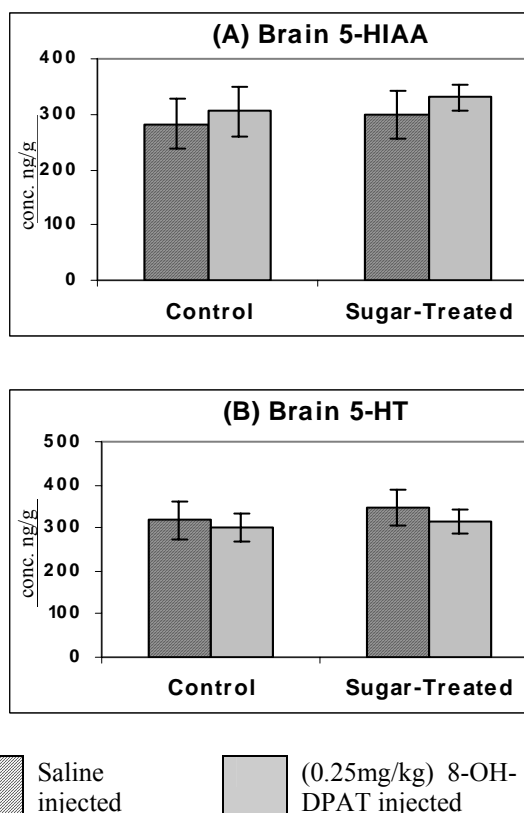


Fig. 4: Effects of 8-OH-DPAT (0.25mg/kg) on the levels of (A) 5-HT and (B) 5-HIAA in the whole brain of control and sugar treated rats. Values are means \pm SD (n=6). Differences by 2-way ANOVA were not significant.

In anorexia nervosa, a supersensitivity of hypophagic serotonin receptors provoked by decreased pre synaptic activity is involved in the manifestation of appetite suppression (Ploog and Prike, 1987). It is possible that supersensitization of 5-HT-2C receptor is involved to suppress the hyperphagic effect of 8-OH-DPAT in sugar treated rats.

Long term consumption of sugar rich diet has been found to produce hyperphagia in experimental animals (Haleem *et al.*, 2000), that did not contributed to weight gain. In the present study we observed decreased cumulative body weight gain together with increased food intake. It was

reported earlier that an increase in the activity of sympathetic nervous system (Young and Landsberg, 1980) in rats drinking sucrose solution produce hypercatabolism and reduction in body weight occurs without an effect on feeding centre (Bernandis and Bellinger, 1993). A high sucrose diet did not induce a greater body weight gain in obese rats but only improved stress tolerance (Kanazawa *et al.*, 2003). Hyperphagia is a well recognized symptom of untreated diabetes (Sahu *et al.*, 1992; Sipols *et al.*, 1994). Dietary sugars such as sucrose and fructose have been found to increase blood glucose levels (Beck-Nelson *et al.*, 1980; Liu *et al.*, 1984; Reiser *et al.*, 1986). One could suggest that decreased utilization of glucose may produce smaller body weight gain.

Adaptation to stress was associated with a decrease in the responsiveness of somatodendritic 5-HT-1A receptors and terminal 5-HT-1B receptor (Haleem *et al.*, 1999; Haleem *et al.*, 2002). Exposure to a stress including situation increases the effectiveness of negative feedback control over 5-HT metabolism via 5-HT-1A receptors (Samad *et al.*, 2006). When these receptors are desensitized their negative feedback action would become less effective. The present study suggest that desensitization of pre as well as post synaptic 5-HT-1A dependent responses may have a role in the prevalence of depression in people taking mostly sugar rich diet.

It has been shown that 5-HT exerts its strongest effect on appetite at the start of the natural feeding cycle, when carbohydrate is normally preferred (Leibowitz and Alexander, 1998). Dietary sugar is widely consumed as a part of meal particularly by children and this may lead to overeating. The most important cause of obesity is overeating (Ludwig *et al.*, 1999; McDevitt *et al.*, 2000). In our result 8-OH-DPAT-induced decreases in hyperphagic effect of sugar rich diet treated rats suggest that desensitization of somatodendritic pre synaptic 5-HT-1A receptor may help to control obesity.

CONCLUSION

In conclusion, the present study shows that long term intake of sugar may lead to a desensitization of somatodendritic as well as post synaptic 5-HT-1A receptors. Hyperphagic effects of sugar rich diet can not be explained in terms of a desensitization of somatodendritic 5-HT-1A receptors. However it is possible that not only post synaptic 5-HT-1A receptors but also 5-HT-2C receptors which are post synaptic and hypophagic are also desensitized to elicit hyperphagia after long term consumption of sugar rich diet.

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