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Original Article

Exploring the Potential of 5-HT1 Receptor Subtypes as Therapeutic Targets for Obesity Treatment in Animal Models

Navpreet Kaur[1,2], Puja Gulati[1,*]

[1]Desh Bhagat University, Mandi Gobindgarh, Punjab, INDIA.
[2]G.H.G Khalsa College of Pharmacy, Guruar Sudhar, Punjab, INDIA.

ABSTRACT

Background: Serotonergic system plays an important role in the energy balance evidenced by various studies. The present study was designed to investigate the involvement of 5-HT1 receptor subtype in experimental obesity. **Materials and Methods:** In the present study effects of chronic administration of eletriptan (2.5 and 10 mg kg-1 day-1, .p.o) specific 5-HT1receptor agonist for 8 weeks along with high fat diet to the obese rats which were pre-treated with high fat diet feeding for 8 weeks on the various parameters of obesity were analysed. **Results:** Treatment with eletriptan (2.5 and 10 mg kg-1 day-1, .p.o) produced significant dose dependent decrease ($p<0.05$) in various parameters of obesity as compared to high fat diet group. Eletriptan positively modulate the parameters of obesity. The present data demonstrated that high fat diet induced obesity was prevented by 5-HT receptor agonist eletriptan. **Conclusion:** Above findings give the strong evidence of involvement of 5-HT1 receptor subtype in obesity.

Keywords: Serotonergic System, Eletriptan, 5-Ht1receptor Agonist, Obese Rats, High Fat Diet.

Correspondence:
Dr. Puja Gulati
Professor and Principal, Desh Bhagat University, Mandi Gobindgarh-147301, Punjab, INDIA.
Email: pujagulati@deshbhagatuniversity.in

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INTRODUCTION

Obesity refers to an excessive body fat and it is a major public health issue worldwide. It can be defined by the WHO as abnormal or extreme fat accumulations in adipose tissue that may impair health of human beings (World Health Organization, 2000). Persons are normally contemplated obese if their Body Mass Index (BMI) is more than 30kg/m^2 and considered overweighed when their Body Mass Index (BMI) ranges 25-30kg/m^2 (Schlesinger *et al.*, 2019). BMI is derived by dividing a person's weight by the square of the person's height. Obesity is the chief health trouble in the western world, in terms of greater chance of type 2 diabetes, cardiac problems, neoplasms and also in financial load to healthcare providers. The pervasiveness of obesity in the United States has amplified noticeably, not only among adults but children are also involved. The prevalence in juvenile obesity has risen from 4% during 1999-2004 to 6% during 2011-2012 (Arisaka *et al.*, 2020). Obesity occurs when the balance between calorie intake and calorie expenditure is disturbed, i.e. consumption of more calories than its utilization, leading to storage of surplus fat in the body. There are many environmental factors that prompt persons to put on weight, e.g. freely accessible high-calorie food and inactive life habits. Genetic factors also add to this disparity (Roberts *et al.*, 2022). There are a variety of treatment choices for obese people, that comprise therapeutic agents which can either reduce calorie intake or increase calorie expenditure, in the extreme cases surgical intrusion may be vital. The therapeutic agents are more reliable than the surgical involvement, even with exhaustive research on obesity pathogenesis; avaluable therapeutic approach to treat and cure this ailment is still deficient. At present, just a few FDA-approved anti-obesity drugs like orlistat, lorcaserin, phentermine-topiramate and naltrexone-bupropion are on hand, but they have remarkable adverse effects (Ahmad *et al.*, 2021). Various studies in last decades have recognized the importance of neural pathway in the hypothalamus in the regulation of body weight homeostasis. The numbers of neurotransmitters which affect the body weight-controlling neural pathways significantly expanded in recent years (Verhaegen and Van Gaal, 2021). Realizing the utility of neurotransmitters released from key neurons for energy balance regulation is crucial for depicting neural pathways and finally for designing useful therapeutic drugs against the obesity plague. Extensive efforts have been devoted for the expansion of treatments of obesity, which mainly target neurotransmitters in the brain that normalize calorie intake and energy utilization (Oxford University Press, 2017). Numerous neurotransmitters (GABA, dopamine, noradrenaline, Ach & serotonin) over and above peptides and amino acids are involved

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in the regulation of calorie intake but the brain mechanisms which are involved in the pathological over-eating and obesity are poorly understood (Blum *et al.*, 2020).

Evidence from a limited number of clinical studies examining the use of isoform-selective 5-HT receptor agonists as anorectic agents appears to confirm that stimulation of 5-HT2C and possibly 5-HT1B, reduces hunger, food intake and body weight in humans. These agents produced their actions through the modification of biogenic amine function. Studies identified a complementary role for the 5-HT1B receptor in feeding regulation (Yao *et al.*, 2021).

Activation of 5-HT1B receptor on arcuate NPY/Agrp cells inhibits neuronal activity, thereby derepressing the inhibitory GABAergic transmission from NPY/Agrp neurons to adjacent POMC (pro-opiomelanocotin) neurons. Thus 5-HT1B activation indirectly stimulates POMC cells, complementing the direct activation of these same neurons by the 5-HT2C receptor.

The clinical implication of these findings is that a combined 5-HT2C/1B receptor agonist should powerfully stimulate catabolic melanocortin pathways in the hypothalamus and this effect would lie downstream of at least some of the levels at which obesity-related leptin resistance occurs.

MATERIALS AND METHODS

Drugs and Chemicals

Casein (Modern Diary, New Karnal, India) and cholesterol (Thomas Baker, Mumbai, India) were used to prepare high fat diet. Atorvastatin (3R,5R)-7-[2-(4-Fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid was precured from Reine Lifesciences and Eletriptan 5-[2-(benzenesulfonyl)ethyl]-3-[[(2R)-1-methylpyrrolidin-2-yl]methyl]-1H-indole was purchased from Sigma-Aldrich. All the drugs were dissolved in dimethyl sulfoxide (DMSO; 10%, v/v). The estimation kits for serum glucose, cholesterol, triglycerides and HDL were obtained from (Reckon Diagnostics [P] Ltd. Vadodara, India). All other chemicals used in the present study were of analytical grade. All drug solutions were freshly prepared before use.

High Fat Diet-induced Obesity

Experimental obesity was induced by feeding high-fat diet (containing; powdered normal chow, 365 g; lard, 310 g; casein, 250 g; cholesterol, 10 g; Vitamin mix and mineral mix, 60 g; dl-methionine, 3 g; yeast powder, 01 g; Sodium Chloride (NaCl), 1 g was added to make 1.0 kg of diet), to rats (Qian *et al.*, 2015). The high fat diet contained 5.33 Kcal/g while the normal chow contains 3.80 Kcal/g. This diet provides 68% energy as carbohydrate, 20% as protein and 12% as fat to produce obesity in rats while as normal chow provides 65% of -energy as carbohydrate, 20% as protein and 4% as fat (Malik and Sharma, 2011).

Animal Treatment

Male wistar rats of 7-8 weeks of age were procured from the animal facility of the Institute. The animals were housed in polypropylene animal cages (two rats/cage) and maintained under controlled room temperature (25±2°C) with 12:12 hr light and dark cycle. The guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India were followed and prior permission was sought from the institutional animal ethics committee (approval no. GHG/2024/IAEC/P01/M05).

For conducting the study. Animals were fed with Normal Chow (NC) or High Fat Diet (HFD) for 8 weeks. Animals were divided into different groups and each group contains 6 animals. Animals fed on NC were continued on same diet for further 8 weeks and were assigned as group 1.

HFD fed animals randomized on the basis of their body weight and divided into different 6 groups (group 2 to 6) and these groups were continued on HFD for another 8 weeks. Group 2 was not given any treatment and assigned as HFD control. Group 3 was given DMSO 1 mL kg-1 day-1, i.p (Chung *et al.*, 2006, p. R1449) and assigned as vehicle control. Group 4 was given atorvastatin 5 mg kg-1 day-1, p.o. (Patricia and Georgina, 2006, p. 1) and assigned as standard control. Group 5 and 6 were given Eletriptan 2.5 and 10 mg kg-1 day-1, .p.o respectively (Garabadu and Krishnamurthy, 2014). All the animals had free access to water and the animals were inspected daily. Food intake and body weight were measured twice weekly.

At the end of the stipulated period, blood for various biochemical parameters was obtained by retro-orbital puncture under light ether anaesthesia and the animals were sacrificed by cervical dislocation. The blood was collected into tubes, serum separated and analyzed on the same day. The epididymal, mesenteric and retroperitoneal White Adipose Tissue (WAT) were dissected, cleaned of, weighed and stored in 10% buffered formalin solution for histological analysis. Lee index (Verma *et al.*, 2016) i.e. (Body Wt in gms) 1/3/(ano-nasal length in cm) an index of obesity, was calculated at the end of the experiment.

Histological Analysis and Morphometry

Epididymal adipose tissue was fixed in 10% formalin and then embedded with paraffin. Tissue sections (10 μm) were cut and mounted on microscope slides. After being air-dried, they were stained with hematoxylin and eosin and photographed at 100X magnification. At least two fields per slice and six slices per fat mass were analyzed for the purpose of quantifying adipocyte size.

Measurements

Serum glucose, triglyceride, total cholesterol and HDL cholesterol concentrations were measured by using commercially available kits.

Statistical Analysis

All values are expressed as Mean±Standard Deviation (STDEV). The significance of the differences between the means of various groups was established by one-way ANOVA followed by Tukey's multiple range tests using the GraphPad Prism 4 software. The *p* value <0.05 was considered to be statistically significant.

RESULTS

Administration of HFD for 8 weeks significantly ($p<0.05$) increased body weight of animals then the age-matched normal control rats and there was no significant difference of body weights of animals between the various treatment groups before initiation of treatment (Table 1).

Effect of Various Pharmacological Interventions on Body Weight, Adipose Tissue Weight and Lee Index: Obese rats after 16 weeks of HFD feeding had significantly increased body weight and total fat content then the age matched normal control rats. Lee index was also significantly increased in obese rats as compared to normal rats.

However, treatment with Eletriptan from 9-16 weeks attenuated HFD induced increase in body weight, adipose pads weight and lee index.

Administration of atorvastatin a standard drug from 9-16 weeks produced significant reduction in body weight gain, adipose pads weight and lee index in obese rats.

Effect of Various Pharmacological Interventions on Biochemical Parameters

Obese rats after 16 weeks of HFD feeding had higher glucose, triglyceride and total cholesterol level as compared to the age matched normal control rats. However, treatment with eletriptan from 9-16 weeks attenuated HFD induced hyperglycemia, hyper-triglyceridemia and hyper-cholesterolemia. Administration of dimethyl sulfoxide from 9-16 weeks did not affect HFD induce hyperglycemia, hyper-triglyceridemia and hyper-cholesterolemia. Administration of atorvastatin a standard drug for obesity from 9-16 weeks produced significant reduction in the level of glucose, triglyceride and total cholesterol in obese rats (Table 2).

Effect of Various Pharmacological Interventions on Daily Feed Intake (Kcal): In high fat diet model, a significant increase ($p<0.05$) in feed consumption (Kcal) was observed as compared to normal chow fed rats. Atorvastatin which was standard control in the present study significantly decreases the feed consumption as compared to HFD fed rats.

Administration of dimethyl sulfoxide from 9-16 weeks did not affect feed consumption of animals as compared to HFD fed rats. The food intake was significantly decreased by the administration of Eletriptan from 9-16 weeks (Table 2).

(a) adipocyte size of normal control animals; (b) adipocyte size of obese high fat diet control animals; (c) adipocyte size of vehicle control animals; (d) adipocyte size of standard control animals given Atorvastatin (5 mg/kg-1 day-1; (e) adipocyte size of animals given Eletriptan 2.5 mg kg-1 day-1; (f) adipocyte size of animals given Eletriptan 10 mg kg-1 day-1 (Figure 1).

DISCUSSION

In the present study, experimental obesity was developed by long term high fat diet treatment. The body weight gain observed in the present study is consistent with studies in animal models, suggesting that exposure to high concentrations of carbohydrates or HFD contribute to the development of overweight or obesity (Panchal *et al.*, 2011). Notably, metabolic disturbance results in elevation of plasma lipids (Nagarajan *et al.*, 2017) which is characterized by elevated TC, TG levels, LDL-C levels and

Table 1: Effect of Various Pharmacological Interventions on Body Weight of Animals at Different Time Intervals.

Groups	Initial Body Weight	Body weight at the end of 8th week	Body weight at the end of 16th week
Vehicle control (10% v/v DMSO, 1 mL kg-1)	$234.3^{a\pm}19.0$	$316.3^{a}\pm8.5$	$397.0^{a}\pm 13.0$
Atorvastatin (5 mg/kg, p.o)	$236.0^{a}\pm11.9$	$309.5^{b}\pm13.6$	$279.0^{c}\pm14.6$
Eletriptan (2.5 mg/kg)	$226.0^{b}\pm9.2$	$305.6^{bc}\pm9.5$	$290.0^{b}\pm16.1$
Eletriptan (10 mg/kg)	$229.0^{ab}\pm9.7$	$302.0^{c}\pm9.3$	$281.0^{c}\pm6.9$
Sum of squares			
Between groups	190.48	334.92	29299.45
Within groups	79.01	30.03	43.56
Mean square			
Between groups	63.49	111.64	9766.48
Within groups	9.87	3.75	5.44
F-value	6.42 ($p<0.05$)	29.73 ($p<0.01$)	1793.66 ($p<0.01$)

All values are expressed as Mean±standard deviation (STDEV), Two-way ANOVA followed by Tukey's multiple range tests. DMSO: dimethyl sulfoxide.

decreased serum HDL-C (Picchi *et al.*, 2011, p. 25). Further, feeding with high fat diet caused hyperglycemia in rats (Olson, 2012). Therefore, the serum lipid levels (total cholesterol, LDL, VLDL, HDL and triglycerides) and glucose levels were estimated in present study as the marker of hyperlipidemia and hyperglycemia. Hypercaloric diets can modify the 5-HT1B levels in the brain. There is a relationship between HFD intake and neurotransmitter concentration in the rat brain (Valladolid-Acebes *et al.*, 2012).

The role of 5-HT1B in the regulation of food intake is not well understood. The present study was undertaken to examine the role of 5-HT1B in experimental obesity by peripheral administration of 5-HT1B receptor modulators, Eletriptan in two different doses i.e. low and high dose. The present data demonstrated that in HFD rats, high dose of Eletriptan treatment significantly reduced food intake, Lee index and body weight increase; the weight of WAT was significantly decreased and the biochemical levels of glucose, TG, TC, LDL and VLDL was significantly improved by high dose of Eletriptan treatment. The last finding is of particular interest, since in earlier findings it had been shown that 5-HT1B receptor is having complementary role in feeding regulation (Foster-Schubert andCummings, 2016). Activation of this receptor on arcute NPY/Agrp cells inhibit neuronal activity, thereby depressing the inhibitory GABAergic transmission from NPY/Agrp neurons to adjacent POMC neurons. The result is that 5-HT1B activation indirectly stimulates POMC cells, complementing the direct activation of these same neurons by the 5-HT2C receptor. The clinical implication of these findings is that a combined 5-HT2C/1B receptor agonist should powerfully stimulate catabolic melanocortin pathways in the hypothalamus and this effect would lie downstream of atleast some of the levels at which obesity-related leptin resistance occurs. The present study, confirmed these findings by employing 5-HT1B receptor agonist, in high doses Eletriptan significantly decreases the parameters of obesity. To our knowledge, this is the first study in which the effects of Eletriptan on diet induced obese rats were examined and our results suggest that the effects of these pharmacological innervations on food intake and body weight were clearly dependent on 5-HT1B receptor modulation.

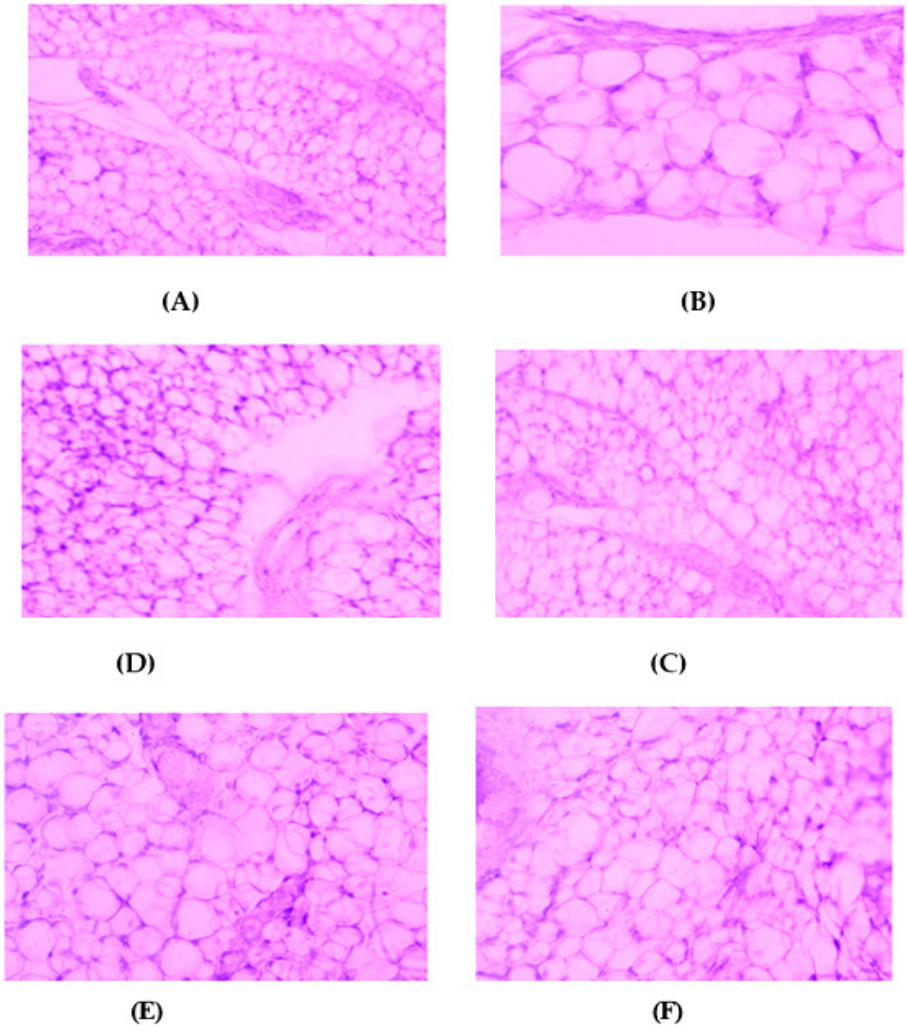

Figure 1: (A-F): Effect of Various Pharmacological Interventions on Adipocyte Size.

Table 2: Effect of Various Pharmacological Interventions on Various Parameters in Obese Rats.

Parameters	NC	OHFD-C	Vehicle Control (10% v/v DMSO, 1 mL kg-1)	Atorvastatin (/ kg, p.o)	Eletriptan (2.5 mg/kg)	(10 mg/kg)
Initial body wt (g)	221±8.3	230±6.1	231±9.7	236±10	226±1.2	231±1.7
Final body wt (g)	272±16.8	398±15.2[a]	396±12[a]	299±11.6[b]	319±10.4[b]	309±14.1[b]
Lee index	347±8.1	388±15.7[a]	393.18±13[a]	360±12.4[b]	370±14.1[b]	357±12.4[b]
Feed intake Kcal Day	92±2.1	112±7.6[a]	111±10.2[a]	86±12[b]	100±8.0[b]	98±6.1[b]
Epididymal fat	1.72±0.21	5.22±0.91[a]	5.24±0.8[a]	1.80±0.30[b]	2.01±0.11[b]	2.5±0.21[b]
Retroperitoneal fat	1.50±0.27	5.6±0.81[a]	5.5±0.73[a]	1.86±0.20[b]	1.96±0.1[b]	1.8±0.21[b]
Mesentric fat	2.6±0.17	5.4±0.92[a]	5.70±0.73[a]	2.5±0.30[b]	2.60±0.3[b]	1.9±0.2[b]
Glucose (mg dL^{-1})	95±5.1	151.5±5.41[a]	147.6±10.2[a]	96.1±4.01[b]	98±2.1[b]	94.1±1.65[b]
TG (mg dL^{-1})	65.7±4.2	145.5± 10.61[a]	144.2±10.1[a]	71.1±5.12[b]	73 .1±2.08[b]	71.5±4.12[b]
TC (mg dL^{-1})	94.9±4.0	162±11.61[a]	161.8±11.8[a]	94.2±4.19[b]	95.1±1.9[b]	92.5±4.19[b]
LDL (mg dL^{-1})	48.7±4.7	110.2±12.50[a]	110.8±10.5[a]	49±7.01[b]	50.1±1.4[b]	45.1±5.0[b]
VLDL (mg dL^{-1})	13.1±0.87	28.3±2.11[a]	28.1±2[a]	14.1±1.03[b]	14.7±0.7[b]	14.5±1.01[b]
HDL (mg dL^{-1})	32.4±2.10	23.1±2.90[a]	22.5±1.45[a]	31.1±2.45[b]	32±2.11[b]	33±1.2[b]

Data are presented as Mean±Standard Deviation (STDEV), assessed with 1-way ANOVA with Tukey-Kramer method, *n*=6. TG: Triglycerides, TC: Total cholesterol, LDL: Low-density lipoproteins, VLDL: Very low-density lipoproteins, HDL: High-density lipoproteins. [a]=p less than 0.05 versus Normal Control (NC), [b]=p less than 0.05 versus Obese high fat diet control (OHFD-C).

CONCLUSION

On the basis of above discussion, it may be concluded that 5-HT1B receptor has role in the body weight regulation. The 5-HT1B receptor modulation by its receptor agonist / antagonist alters the various parameters of experimental obesity. Eletriptan attenuated HFD induced increase in the body weight, visceral adipose pad weights and lee index, serum TC, TG and glucose levels. The present results suggesting that 5-HT1B receptor agonist could be new therapeutic reagent for obesity. These findings give the strong evidence of involvement of 5-HT1B receptor in obesity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

5-HT1B: 5-hydroxytryptamine receptor 1B; **LDL:** Low density lipoproteins; **HDL:** High density lipoproteins; **VLDL:** Very low density lipoproteins; **HDL-C:** High density lipoproteins cholesterol; **TC:** Triglycerides; **TC:** Total Cholesterol; **POMC:** Proopiomelanocortin; **NPY:** Neuropeptide Y; **WAT:** White adipose tissue; **BMI:** Body mass index; **HFD:** High Fat diet; **DMSO:** Dimethyl sulfoxide.

ETHICAL APPROVAL

The guidelines of committee for the purpose of control and supervision of experiments on animals (CPCSEA), Government of India were followed and prior permission was sought from the institutional animal ethics committee (approval no. GHG/2024/IAEC/P01/M05) for conducting the study.

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