Effect of Short Term Sibutramine Supplementation on Appetite Suppression and Related Metabolic Responses

Swati Jain, Saroj K. Verma, Vijay K. Singh and Som Nath Singh*

Nutrition Division, Defence Institute of Physiology and Allied Sciences, Lucknow Road, Timarpur, Delhi-110054, India

Abstract: The appetite suppressing property of Sibutramine is well reported. The present study was undertaken to investigate the appetite regulatory mechanism and associated metabolic changes induced in male *Sprague Dawley* rats by its short term supplementation. The effect of the drug on the regulatory hormones and biochemical variables was studied at an oral dose of 10 mg/kg body weight. There was a decrease in food intake of rats by 35.5% in comparison to their basal food intake as well as untreated controls. There was an increase in plasma levels of adiponectin, serotonin and a decrease in IGF-1 and corticosterone in the treated animals. The circulating levels of ghrelin marginally decreased with a corresponding increase in leptin and CCK in case of treated rats. These may be responsible for the anorectic effect of the drug.

Keywords: Sibutramine hydrochloride monohydrate, obesity, appetite, leptin, ghrelin, adiponectin.

1. INTRODUCTION

Obesity is increasing worldwide and has become a public health concern due to associated degenerative diseases and morbidity. Even though overweight and obesity are not life threatening but they qualify themselves as a disease entity [1]. The World Health Organization (WHO) estimates the number of overweight adult population to reach 2.3 billion by the year 2015 [2]. Lifestyle changes and behavioral therapy are required to a large extent along with preventive measures like diet and exercise to overcome this problem. Other management strategies to oppress weight gain are pharmacotherapy and surgical intervention. Appetite suppressants have been in use in the treatment of obesity since a long time. The approach of therapeutics for weight control therefore should lie with the utilization of agents that target both homeostatic and hedonic control mechanisms of the human body [3]. The efficacy of the drug depends on consumption of freely available food and by decreasing the reinforcing drive to consume food.

A centrally acting agent for weight loss is sibutramine hydrochloride which was introduced in 1997 and was licensed as a modality to promote weight loss for more than a decade. Formerly, sibutramine was evaluated for its use as an antidepressant. A study shows the underlying CNS actions of sibutramine through increased brain activity on presenting the images of food items to obese women [4]. Sibutramine was the only approved anti obesity drug till the concerns over the cardiovascular complications arose and caused its suspension and consequent withdrawal from the market in recent years. Ongoing clinical research on anti obesity drugs are hopefully going to produce better tolerated centrally acting agents that control appetite and have long term safety**.** Its mechanism of action is norepinephrine and serotonin reuptake inhibition. Through its twofold action it reduces the appetite as well as causes weight loss by stimulating thermogenesis in brown adipose tissue [1]. There are several studies that have proven and established the use of sibutramine as a known appetite suppressant but all of them have targeted its use in obese adults for the management of overweight/ obesity or diabetes through its long term administration. Sibutramine has a role in the management of adolescent and childhood obesity too. Short term efficacy of sibutramine has been shown for childhood obesity through positive effects on BMI [5]. Most of the pertinent studies show the short-term usefulness as the long-term effects of sibutramine are associated with the severity of complications [6].

It seems the short term intervention is safe which also encourages moderate and lasting effects on weight loss [7]. A diminished motivation to eat and a reduction in food intake in obese subjects have been reported on 14 days of supplementation with sibutramine [8]. Other short term studies that have employed sibutramine for a period of 12 weeks show the effects on mineral status [9] and on inflammatory markers [10]. Also a 6 week SCOUT trial (Sibutramine Cardiovascular OUTcomes) has been done for obese patients [11]. Only one study has reported the use of sibutramine for 5 days and studied the energy expenditure variables and physiological responses in

*Address corresponding to this author at the Nutrition Division, Defence Institute of Physiology and Allied Sciences, Defence Research Development Organisation, Lucknow Road, Timarpur, Delhi-110054, India; Tel: 91-1123883315; Fax: 91-1123914790; E-mail: nutrition-dipas@hotmail.com

ISSN: 2223-3806 / E-ISSN: 1927-5951/12

obese women [12]. The energy expenditure was found to be unaffected. They did not study any other biochemical parameters. Short term use of safe anorectics for suppression of the hunger sensations may improve human performance during critical missions such as military operations [13].

In the present study effect of short term administration of sibutramine (5 days) on appetite suppression was investigated by evaluating the appetite regulatory hormones and certain biochemical variables related to fuel metabolism.

2. MATERIALS AND METHODS

2.1. Animals

Male *Sprague Dawley* rats, weighing 200-250 g, bred and reared in the Experimental Animal Facility of our Institute were used in the study. Animals were maintained at a temperature (22º±1ºC), humidity (55-60%) and light-controlled room (lights on at 6:30 hrs, lights off at 18:30 hrs). Rats were provided commercial rodent diet supplied by M/S Golden feed Pvt Ltd., Delhi and water *ad libitum*. Food intake was monitored during the dark phase of the day since animals consume most of their food intake during the nocturnal period. All procedures and protocols used in the present study were approved by the Animal Care and Use Committee of the Institute and followed the guidelines documented in the National Institute of Health's Guide for the Care and Use of Laboratory Animals. The animals were randomly divided into two groups control and treated (n=12 in each group).

2.2. Sibutramine Hydrochloride Monohydrate Supplementation

Sibutramine hydrochloride monohydrate purchased from Cadila Healthcare Limited, Mumbai, India was used in the study. It was dissolved in water and a dose of 10 mg/kg body weight was given orally using rodent feeding needle for five days at 16.30 h in the evening 1 h prior to providing food. The dose used in the present study has been found effective in many behavioural studies [14-16].

2.3. Food Consumption and Body Weight Monitoring

Rats were individually housed in the metabolic cages (Ugo Basile Feeding and Drinking Analyzer). The cage had an aperture through which the animal could reach the pellet trough. The pellet trough was fastened to a scale pan, which could sense the load of the pellet and hence the quantity and frequency of food uptake at predetermined intervals was sent to the computer software for processing. Basal food intake of three days was recorded before observing any decrease in food intake by Sibutramine hydrochloride monohydrate treatment. Weighed amounts of food and water were added to the cage before beginning the experiment. The food intake was recorded for 12 h during the dark period. The first approach made towards the food by the rat was also recorded. Body weight was measured daily for five days.

2.4. Sample Collection for Biochemical Analysis

After completion of the five day treatment, rats were fasted overnight, anesthetized and sacrificed. Blood plasma was collected by centrifugation at 1000 × g for 10 min at 4ºC. The weight of the organs- liver, spleen, kidney, brain was recorded along with gastrocnemius muscle and epididymal fat tissue. For glycogen estimation the weighed portions of liver were dissolved in 30% KOH immediately after removal, precipitated with 95% ethanol in the presence of sodium sulphate. Ten percent liver homogenates (w/v) were prepared in 150 mm KCl using Polytron homogeniser and were centrifuged at 3000 × g for 15 min at 4ºC. The supernatants were divided into aliquots and frozen at -80ºC until assayed. Liver mitochondria were separated by differential centrifugation at 12,000 g for 30 min at 4 ºC and stored at -80 °C for Carnitine Palmitoyl Transferase-1(CPT-1) activity analysis.

2.5. Biochemical Estimations

Blood glucose was measured using glucose oxidase–peroxidase method. Tissue glycogen was estimated using the method of Montogomery [17]. CPT -1 activity was assayed using the method of Halperin and Pande [18]. Mitochondrial protein content was measured by the method of Lowry *et al*. [19]. Radio immunologic (RIA) kits from Phoenix Pharmaceuticals, Burlingame, CA were used for detection of plasma ghrelin, neuropeptide Y (NPY) and cholecystokinin (CCK) levels. Plasma leptin and adiponectin concentrations were measured with a commercially available rat ELISA kit from Ray Biotech, Inc., USA. Plasma insulin concentrations were determined using a direct ELISA kit bought from Mercodia, Uppsala, Sweden. Plasma samples were extracted using ethyl ether for corticosterone estimation and estimated using an ELISA kit (Neogen Corporation, USA). Plasma levels of insulin -like growth factor 1 (IGF-1) were analyzed with an EIA kit from Mediagnost, Germany. 5' adenosine monophosphate-activated protein kinase (AMP kinase) activity, levels of tri-iodothyronine(T3),

thyroxine(T4) and 5- Hydroxytryptamine(5-HT) in plasma were measured using kit from Cusabio biotech Co., Ltd.

2.6. Statistical Analysis

All the data are presented as mean ± SD and statistically analyzed using unpaired Student's *t*-test. The p value <0. 05 was considered significant change.

3. RESULTS

3.1. Effect on Food Intake

Sibutramine hydrochloride monohydrate (10 mg/kg) induced a decrease in food intake on a single dose administration of the drug over the 12 h duration. A decrease of 35.5% from their basal food intake was noted (Control: 18.3±3.14 g, Treated: 11.8±1.86 g, p<0.05). In addition, there was a delay of 30±8 min. in the first approach made towards food by the treated rats in comparison with control rats.

3.2. Effect on Body Weight and Organ Weights

The control rats gained weight (3.2 % increase) in five days while there was a slight reduction in the body weight (0.5%) of the treated rats. No significant differences in the vital organ weights and epididymal fat tissues were found between the groups (data not shown).

3.3. Effect on Blood Glucose and Liver Glycogen

There was a decrease in levels of blood glucose (21.7%) in the treated rats in comparison with untreated control rats. The drug induced a significant decrease in the hepatic glycogen content (p<0.05) (Table **1**).

3.4. Effect on Enzyme Activities

CPT-1 activity in the isolated liver mitochondria was found to be slightly increased in the treated group (Table **1**).

The AMPK activity measured in crude liver homogenates was significantly higher in the test group (Table **1**).

3.5. Effect on Appetite Regulatory Peptides

The hunger hormone, ghrelin levels dropped slightly but not significantly in the treated group. A small rise in the leptin concentration was seen in the treated group. The adiponectin exhibited a significant increase in the treated group (p<0.05) as compared to the control. The gut hormone, CCK and the orexigenic peptide, NPY showed no significant differences between the control and treated group. There were no changes between the plasma T3 and T4 concentrations of the treated and control rats. Plasma serotonin levels were found to be significantly increased in the treated group as compared to the control group (p<0.05). IGF-1 and corticosterone levels decreased (p<0.05) significantly in the treated group (Table **2**).

4. DISCUSSION

The use of Sibutramine monohydrate hydrochloride as a drug to combat obesity is known for more than a decade now.

In our study we assessed the effect of short term treatment with Sibutramine on food intake and regulatory metabolism of rats. We observed a significant reduction in food intake and a small decrease in body weight at a dose of 10 mg/kg body weight. An earlier study has reported similar results during the days 1-3 of their 7 day treatment [20]. The findings are inconsistent regarding the effect on body weight with sibutramine treatment. Levin and Dunn-Meynell [21] have stated that only with chronic administration of sibutramine there is a reduction in body weight through alteration of neuronal reuptake of serotonin and norepinephrine. We speculate that the dose used in the present study reduced the body weight gain in the rats but did not induce weight loss. This could be due to the short duration of the treatment and usage of a higher dose might lead to a significant

Table 1: Effect on Blood Glucose, Liver Glycogen, CPT-1 and AMP Kinase Activity

Variables	Control	Treated
Blood glucose (mg/dl)	61.44± 16.44	48.11± 6.58 *
Liver Glycogen (mg/g wet tissue)	0.72±0.34	0.38±0.26*
CPT-1 (µmol/min./mg protein)	37.26±7.38	40.08±5.53
AMP Kinase (pg/mg protein)	91.6±3.7	109.5 ± 16*

Expressed as mean ± SD (n=12), *p<0.05 in comparison with control.

Table 2: Effect of Sibutramine Supplementation (10 mg/kg Body Weight) for Five Days on Different Hormones in Plasma

Appetite Regulatory peptides	Experimental groups	
	Control	Treated
Insulin (ng/ml)	0.32 ± 0.01	0.30 ± 0.01
IGF-1 (ng/ml)	718.7±144.3	634±99.37*
Leptin (pg/ml)	1168 ±309.07	1263±366.10
Ghrelin (pg/ml)	2063 ± 351.68	2010±14.77
CCK (pg/ml)	166±17.28	173±19.09
Adiponectin (ng/ml)	150.4±112.07	249.7±73.93*
Plasma Serotonin (ng/ml)	13.29±3.24	27.5±17.35*
Corticosterone (ng/ml)	564.7±117.95	358.0±9.83 *
NPY (pg/ml)	1873.41±258.85	1976±141.24
T3 (ng/ml)	1.56+ 0.53	1.75+0.11
T4 (ng/ml)	50.84+2.79	51.78+2.28

Expressed as mean ± SD (n=12), *p<0.05 in comparison with control.

reduction in the body weight. Furthermore, it has been stated earlier that sibutramine treatment along with behaviour therapy and a reduced calorie diet induces a reduction in body weight [22, 23]

According to Chapelot *et al*. [24] even a single dose of sibutramine has a potent action on appetite control which gets altered according to the time and structure of the meal. They observed the hunger ratings to be lower than placebo 4 h after a single dose of sibutramine supplementation in young males. Our observations suggest similar results regarding the eating behaviour of rats.

Frassetto *et al*. [25] suggested that the serotoninergic effects of sibutramine may also be affected by the peripheral pathways and energy related parameters.The effects of sibutramine on glucose metabolism are variable. We observed a decline in blood glucose levels without a change in the plasma insulin. Fabris *et al*. [26] have shown reduced hepatic glucose production on 1 week treatment of sibutramine per se independent from weight loss on obese models that had a state of insulin resistance. On the other hand, some studies demonstrated no effect on plasma glucose and insulin levels even on long term administration of the drug [27,28]. The effects on insulin sensitivity would have been greater if our study period had been longer. Some studies have shown no effect of sibutramine on insulin levels [29,30]. Insulin is known to increase the production of IGF-1 and low IGF-1 levels are increased in response to high energy intake [31]. This explains the significant decline in the plasma IGF-1 levels in our study. IGF-1 could be a factor which influences appetite regulating centres directly or indirectly *via* peripherally produced hormones like leptin and insulin. Our data confirm here the view of earlier reports that the diminished changes in IGF-1 levels are related to an increase in leptin without much changes in insulin.

Glycogen is a readily accessible storage form of glucose in the liver and muscles and provides glucose to the body. The fall in blood glucose level of the treated rats can therefore be related to the depleted liver glycogen reserves in our study. To date, only one study has reported serotoninergic effects of sibutramine on glycogen reserves as increased glycogen concentration in diaphragm muscle of rats [25].

It is well known that sibutramine inhibits eating *via* noradrenergic and serotonergic mechanisms. There are a number of peripheral hormones which induce satiety and regulate the energy balance like leptin, insulin, CCK, glucagon- like peptide 1 and peptide YY. There is a possibility that sibutramine, being an anorectic affects the appetite regulatory peptides as well.

A decline in the ghrelin levels has an appetite lowering effect while leptin decline has appetite stimulating effects. There are very few studies reporting the effect of this drug on appetite and satiety peptide hormones. We demonstrated a slight increase in plasma leptin and a corresponding decrease in ghrelin levels due to the short study period which additionally

might be greater on usage of a higher dose. Baranowska *et al*. [32] suggested that NPY, insulin and leptin might be involved in the mechanism of action of sibutramine. However, they did not find any significant changes in these peptides when administered for 6 months to obese women.While a few studies reported a reduction in leptin levels dependent on weight loss, no significant change was observed even with a decrease in body fat [33]. Studies have also shown that changes in serum leptin levels were not statistically significant even after 3, 9 and 12 months of sibutramine administration [34, 35]. Bush *et al*. [36] have shown no effect of chronic sibutramine treatment on ghrelin levels in obese mice.

The NPY/AgRP neurons play an important role as they mediate the effect of ghrelin and since leptin receptors are present on NPY/AgRP neurons, leptin inhibits NPY. We did not find any similar association in our study. This could be explained, as it seems that the anorectic effects of sibutramine are not mediated through inhibition of ARC NPY neurons except in energy restricted state [37]. According to Casado *et al*. [15] it appears that NPY does not have a role in the hypophagic effect of sibutramine. They demonstrated no significant changes in NPY levels of obese rats at a dose of 10mg/kg body weight for a period of 2 weeks.

CCK is known to be a peripheral gastrointestinal satiety signal and a preabsorptive satiety factor that also induces a Behavioral Satiety Sequence (BSS). BSS is a result of caloric load in the gut. We demonstrate a small rise in plasma CCK, which indicates the role of sibutramine in hunger suppression. Sibutramine and CCK both preserve the BSS [38], but there is no study so far reporting its direct effect on CCK.

The positive effect of adiponectin on lipid oxidation is mediated by phosphorylation of AMPK which increases beta oxidation. Besides, the hepatic lipid metabolism is controlled by AMPK in a large part through modulating acetyl CoA carboxylase (ACC) and CPT-1 pathway [39]. We observed an increase in the level of phospho AMPK and plasma adiponectin. A study by Kang *et al*. [40] has shown similar results for AMPK and an increase in serum adiponectin with sibutramine administration has been reported [41, 42]. No previous studies have reported the effect of sibutramine on CPT-1 activity. CPT-1 activity is also increased by adiponectin [43]. We noticed a similar correlation in the adiponectin levels and CPT-1 activity. This depicts the role of sibutramine in lipid oxidation as well.

Additionally the appetite and metabolic rate are controlled through the peripheral effects of thyroid hormone that have clinical significance on appetite. Until now these effects were thought to be peripheral only, but only in a recent report it was shown that the local regulation of thyroid hormone in the central nervous system (CNS) plays an important role as well in appetite regulation [44]. In the present study T3 and T4 levels displayed no significant changes after the sibutramine supplementation. This might also suggest that there has been no increase in the basal energy expenditure that arises due to the high thyroid hormone status which also has a lessening adiposity effect. No significant reduction in the body weight of treated rats could also be related to no changes in the thyroid hormone status [45]. Controversial data exist on the long term use of sibutramine on thyroid hormones. Saleh and Bisher [46] has shown a highly significant increase in the total T3 and a highly significant decrease in the total T4 levels. These findings reflect abnormal changes in the thyroid gland. On the other hand Keskin *et al*. [47] have reported no significant changes in the serum levels of total T3 and T4 and suggests that thyroid hormones get affected by the extent of obesity too.

Glucocorticoids stimulate food intake by promoting NPY functions. The outcome of sibutramine administration *per se* on corticosterone levels has not been reported earlier. Sibutramine caused a significant decline in plasma corticosterone levels in our study indicating its anorectic properties. The results by Maes *et al*. [48] depict that serotonergic mechanisms alter the negative feedback of glucocorticoids on central HPA axis regulation. A study by Dronjak *et al*. [49] has shown no change in the plasma corticosterone levels of rats on chronic treatment with one noradrenaline reuptake selective inhibitor and the other being a selective serotonin reuptake inhibitor.

Apart from neurotransmitters and neuropeptides, the role of monoamines in eating has also been observed. Substantial literature strongly suggests 5-HT as a satiety agent and relationships exist between 5-HT neurons in the brain and control of food intake [50]. Sibutramine is the drug that increases synaptic 5-HT activity and therefore we observed a significant increase in the plasma serotonin levels.

In conclusion, we have shown the action of appetite regulatory peptides in response to short term administration of Sibutramine hydrochloride monohydrate *in vivo.* It has exhibited its anorectic

properties even on short term supplementation. This suggests that its associated side effects might get minimized when given for a short period. The extensive effects on carbohydrate and fat metabolic enzymes and substrates remain undetermined. Nevertheless the present study indicates that sibutramine can also be used as an experimental drug and positive control in studies related to development of appetite suppressants using experimental animals.

ACKNOWLEDGEMENT

Authors are thankful to Dr. Shashi B Singh, Director, DIPAS for encouragement and support to the study. Swati Jain is grateful to the Defense Research Development Organization for award of Senior Research Fellowship.

REFERENCES

[1] Równicka-Zubik J, Góra A, Sułkowska A. The obesity and way for treatment. Wiad Lek 2011; 64: 226-30.

[2] Roh C, Jung U, Jo SK. Screening of anti-obesity agent from herbal mixtures. Molecules 2012; 17: 3630-38. http://dx.doi.org/10.3390/molecules17043630

[3] Harrold JA, Dovey TM, Blundell JE, Halford JC. CNS regulation of appetite. Neuropharmacology 2012; 63: 3-17. http://dx.doi.org/10.1016/j.neuropharm.2012.01.007

[4] Oltmanns KM, Heldmann M, Daul S, *et al.* Sibutramine promotes amygdala activity under fasting conditions in obese women. Psychopharmacology (Berl) 2012; 221: 693-700. http://dx.doi.org/10.1007/s00213-011-2615-7

[5] McGovern L, Johnson JN, Paulo R, *et al*. Clinical review: treatment of pediatric obesity: a systematic review and meta-analysis of randomized trials. J Clin Endocrinol Metab 2008; 12: 4600-605. http://dx.doi.org/10.1210/jc.2006-2409

[6] Kanekar A, Sharma M. Pharmacological approaches for management of child and adolescent obesity. J Clin Med Res 2010; 2: 105-11.

[7] McTigue KM, Harris R, Hemphill B, *et al*. Screening and interventions for obesity in adults: summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2003; 139: 933-49.

[8] Barkeling B, Elfhag K, Rooth P, Rössner S. Short-term effects of sibutramine (Reductil) on appetite and eating behavior and the long-term therapeutic outcome. Int J Obes Relat Metab Disord 2003; 27: 693-700. http://dx.doi.org/10.1038/sj.ijo.0802298

[9] Sulibursk J, Bogdański P, Szulińska M, Pupek-Musialik D. Short-Term Effects of Sibutramine on Mineral Status and Selected Biochemical Parameters in Obese Women. Biol Trace Elem Res 2012; in press. http://dx.doi.org/10.1007/s12011-012-9425-6

[10] Joo NS, Kim SM, Kim KM, Kim CW, Kim BT, Lee DJ. Changes of body weight and inflammatory markers after 12-week intervention trial: results of a double-blind, placebo-control pilot study. Yonsei Med J 2011; 52: 242-48. http://dx.doi.org/10.3349/ymj.2011.52.2.242

[11] Weeke P, Andersson C, Fosbøl EL, *et al*. The weight lowering effect of sibutramine and its impact on serum lipids in cardiovascular high risk patients with and without type 2 diabetes mellitus - an analysis from the SCOUT lead-in period. BMC Endocr Disord 2010; 10: 3. http://dx.doi.org/10.1186/1472-6823-10-3

[12] Rotstein A, Inbar O, Vaisman N. The effect of sibutramine intake on resting and exercise physiological responses. Ann Nutr Metab 2008; 52: 17-23. http://dx.doi.org/10.1159/000114290

[13] Fischer K, Colombani PC, Wenk C. Metabolic and cognitive coefficients in the development of hunger sensations after pure macronutrient ingestion in the morning. Appetite 2004; 42: 49-61. http://dx.doi.org/10.1016/S0195-6663(03)00116-8

[14] Luscombe GP, Hopcroft RH, Thomas PC, Buckett WR. The contribution of metabolites to the rapid and potent down-regulation of rat cortical β-adrenoceptors by the putative antidepressant sibutramine hydrochloride. Neuropharmacology 1989; 28: 129-34. http://dx.doi.org/10.1016/0028-3908(89)90048-8

[15] Casado A, Rodríguez VM, Portillo MP, *et al*. Sibutramine decreases body weight gain and increases energy expenditure in obese Zucker rats without changes in NPY and orexins. Nutr Neurosci 2003; 6: 103-11. http://dx.doi.org/10.1080/1028415031000094264

[16] LeBlanc M, Thibault L. Effect of sibutramine on macronutrient selection in male and female rats. Physiol Behav 2003; 80: 243-52. http://dx.doi.org/10.1016/j.physbeh.2003.07.010

[17] Montogomery R. Determination of glycogen. Arch Biochem Biophys 1957; 67: 378-86. http://dx.doi.org/10.1016/0003-9861(57)90292-8

[18] Halperin ML, Pande SV. Fatty acyl group transport in mitochondria: carnitine palmitoyltransferase EC 2.3.1.23 and the carnitine-acylcarnitine translocase. Methods Enzymol 1979; 56: 368-78. http://dx.doi.org/10.1016/0076-6879(79)56034-0

[19] Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the folin phenol reagent. J Biol Chem 1951; 193: 265-75.

[20] Mulla MSA, Goyal VK, Jana S, Nirogi R. Safety Evaluation of Sibutramine in Wistar Rats. African J Basic Appl Sci 2010; 2: 128-34.

[21] Levin BE, Dunn-Meynell AA. Sibutramine alters the central mechanisms regulating the defended body weight in diet-induced obese rats. Am J Physiol Regul Integr Comp Physiol 2000; 279: R2222-R2228.

[22] Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. Lancet 2007; 369: 71-77. http://dx.doi.org/10.1016/S0140-6736(07)60033-6

[23] Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature 2000; 404: 661-71.

[24] Chapelot D, Marmonier C, Thomas F, Hanotin C. Modalities of the food intake-reducing effect of sibutramine in humans. Physiol Behav 2000; 68: 299-308. http://dx.doi.org/10.1016/S0031-9384(99)00176-6

[25] Frassetto SS, Della Santa Rubio A, Lopes JJ, *et al.* Locomotor and peripheral effects of sibutramine modulated by 5-HT2 receptors. Can J Physiol Pharmacol 2006; 84: 1239-44. http://dx.doi.org/10.1139/y06-082

[26] Fabris R, Granzotto M, Pagano C, *et al*. Effect of sibutramine on glucose metabolism in genetically obese (fa/fa) Zucker rats. Int J Obes Relat Metab Disord 2000; 24: S124-S126. http://dx.doi.org/10.1038/sj.ijo.0801297

[27] Godoy-Matos A, Carraro L, Vieira A, *et al*. Treatment of obese adolescents with sibutramine: a randomized, double-blind controlled study. J Clin Endocrinol Metab 2005; 90: 1460-65. http://dx.doi.org/10.1210/jc.2004-0263

[28] Berkowitz RI, Wadden TA, Tershakovec AM, Cronquist JL. Behavior therapy and sibutramine for the treatment of adolescent obesity. JAMA 2003; 289: 1805-12. http://dx.doi.org/10.1001/jama.289.14.1805

[29] Anagnostis P, Selalmatzidou D, Sapranidis M, *et al*. Comparative effects of sibutramine and orlistat on weight loss, glucose metabolism and leptin levels in non-diabetic obese patients: A prospective study. Indian J Endocrinol Metab 2012; 16: 146-47. http://dx.doi.org/10.4103/2230-8210.91214

[30] Berkowitz RI, Fujioka K, Daniels SR, *et al*. Effects of sibutramine treatment in obese adolescents: a randomized trial. Ann Intern Med 2006; 145: 81-90.

[31] Smith WJ, Underwood LE, Clemmons DR. Effects of caloric or protein restriction on insulin like growth factor-1 (IGF-1) and IGF binding proteins in children and adults. J Clin Endocrinol Metab 1995; 80: 443-49. http://dx.doi.org/10.1210/jc.80.2.443

[32] Baranowska B, Wolińska-Witort E, Martyńska L, *et al*. Sibutramine therapy in obese women--effects on plasma neuropeptide Y (NPY), insulin, leptin and beta-endorphin concentrations. Neuro Endocrinol Lett 2005; 26: 675-79.

[33] Stroubini T, Perrea D, Perelas A, *et al*. Effect of sibutramine on regional fat pads and leptin levels in rats fed with three isocaloric diets. Eur Cytokine Netw 2008; 19: 149-55.

[34] Sari R, Eray E, Ozdem S, Akbas H, Coban E. Comparison of the effects of sibutramine versus sibutramine plus metformin in obese women. Clin Exp Med 2010; 10: 179-84. http://dx.doi.org/10.1007/s10238-009-0080-y

[35] Derosa G, Maffioli P, Ferrari I, *et al*. Variation of inflammatory parameters after sibutramine treatment compared to placebo in type 2 diabetic patients. J Clin Pharm Ther 2011; 36: 592-601. http://dx.doi.org/10.1111/j.1365-2710.2010.01217.x

[36] Bush EN, Shapiro R, Brune ME, *et al*. Chronic treatment with either dexfenfluramine or sibutramine in diet-switched diet-induced obese mice. Endocrine 2006; 29: 375-81. http://dx.doi.org/10.1385/ENDO:29:2:375

[37] Zanella MT, Ribeiro Filho FF. Emerging drugs for obesity therapy. Arq Bras Endocrinol Metab 2009; 53: 271-80. http://dx.doi.org/10.1590/S0004-27302009000200019

[38] Halford JC, Wanninayake SC, Blundell JE. Behavioral satiety sequence (BSS) for the diagnosis of drug action on food intake. Pharmacol Biochem Behav 1998; 61: 159-68. http://dx.doi.org/10.1016/S0091-3057(98)00032-X

[39] Guo H, Liu G, Zhong R, Wang Y, Wang D, Xia M. Cyanidin-3-O-β-glucoside regulates fatty acid metabolism *via* an AMP-activated protein kinase-dependent signaling pathway in human HepG2 cells. Lipids Health Dis 2012; 11: 10. http://dx.doi.org/10.1186/1476-511X-11-10

[40] Kang JA, Lee K, Lee KM, *et al*. Desipramine Inhibits Histamine H1 Receptor-Induced Ca^{2+}. Signaling in Rat Hypothalamic Cells. PLoS One 2012; 7: e36185. http://dx.doi.org/10.1371/journal.pone.0036185

[41] Kim DM, Yoon SJ, Ahn CW, *et al*. Sibutramine improves fat distribution and insulin resistance, and increases serum adiponectin levels in Korean obese nondiabetic premenopausal women. Diabetes Res Clin Pract 2004; 66: S139-S144. http://dx.doi.org/10.1016/j.diabres.2003.12.008

[42] Polyzos SA, Kountouras J, Zavos C, Tsiaousi E. The role of adiponectin in the pathogenesis and treatment of non-alcoholic fatty liver disease. Diabetes Obes Metab 2010; 12: 365-383. http://dx.doi.org/10.1111/j.1463-1326.2009.01176.x

[43] Xu A, Wang Y, Keshaw H, Xu LY, Lam KS, Cooper GJ. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. J Clin Invest 2003; 112: 91-100.

[44] Amin A, Dhillo WS, Murphy KG. The central effects of thyroid hormones on appetite. J Thyroid Res 2011; 2011: 306510.

[45] Grover GJ, Mellström K, Malm J. Therapeutic potential for thyroid hormone receptor-beta selective agonists for treating obesity, hyperlipidemia and diabetes. Curr Vasc Pharmacol 2007; 5: 141-54. http://dx.doi.org/10.2174/157016107780368271

[46] Saleh A, Bisher AB. The Physiological alterations induced by Sibutramine anti-obesity drug on the functions of the thyroid gland and the liver: An experimental study on Wistar rats. Indian J Sci Technol 2010; 3: 1129-33.

[47] Keskin L, Sahin I, Bentli R, Senel S, Taskapan C. The effects of orlistat and sibutramine on serum thyroid hormone levels in obese subjects. Endocrine Abstracts, European Congress of Endocrinology; 2006: Glasgow, UK: British Endocrine Societies 2006; 11: P853.

[48] Maes M, Meltzer HY, D'Hondt P, Cosyns P, Blockx P. Effects of serotonin precursors on the negative feedback effects of glucocorticoids on hypothalamic-pituitary-adrenal axis function in depression. Psychoneuroendocrinology 1995; 20: 149-67. http://dx.doi.org/10.1016/0306-4530(94)00049-G

[49] Dronjak S, Spasojevic N, Gavrilovic L, Varagic V. Effects of noradrenaline and serotonin reuptake inhibitors on pituitary-adrenocortical and sympatho-adrenomedullar system of adult rats. Neuro Endocrinol Lett 2007; 28: 614-20.

[50] Fernstrom JD, Fernstrom MH. Monoamines and protein intake: are control mechanisms designed to monitor a threshold intake or a set point? Nutr Rev 2001; 59: S60-5, S66-8.

Received on 15-09-2012 Accepted on 20-10-2012 Published on 05-11-2012

DOI: http://dx.doi.org/10.6000/1927-5951.2012.02.02.8