Original Research Article

Effect of a Combination of Naltrexone and Bupropion in High Fat Diet Induced Obesity in Rats

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Abstract

Background: Obesity is an ever-increasing global health problem. It is progressively becoming a major health problem in India among children and adolescents which leads to substantial increase in morbidity, and mortality. The use of antiobesity drugs in management of obesity is vital. Neuronal pathways are known to play a role in short-term regulation of appetite and satiety. Bupropion and Naltrexone leads to a synergistic effect on control of eating. **Objective:**(1) To evaluate the anti-obesity effect of a combination of naltrexone and bupropion. (2) To compare the anti-obesity effect of orlistat and a combination of naltrexone and bupropion in animal model of obesity. **Methods:** This study was a prospective study of 17 weeks duration. Obesity due to high fat diet was induced in rats over a period of 17 weeks. A combination of naltrexone and bupropion was administered for 5 weeks and various parameters like body weight, blood glucose, food intake & BMI were measured over a period of 5 weeks. **Results:** In this study upon administration of orlistat there was a gradual loss in weight in rats. The combination of Naltrexone and Bupropion showed significant ($P<0.05$) effect on reduction in body weight, reduction in food intake and reduction of BMI in obese rats

Key words: Anti-Obesity Drugs, Weight Loss Agents, high fat diet, Naltrexone, Bupropion, orlistat.

Introduction

Obesity is an ever increasing global health problem. It has a chronic course in which excess body fat accumulates, leading to adverse effects on health and life expectancy [1]. The worldwide prevalence of obesity has increased several times in recent decades owing to changing lifestyle patterns favouring sedentary habits & the intake of high calorie diet [2].Obesity is progressively becoming a major health problem in India with individuals with morbid obesity reaching 5% of the country's population [3]. As per ICMR-INDIAB study 2015, prevalence rate of obesity ranges from 11.8% to 31.3% [4], which is an alarming trend as we are one of the most populated country in the world. Obesity most often is caused by an imbalance between energy intake and expenditure triggered by overeating and physical inactivity; the pathophysiology of obesity is complex and still incompletely understood. Genetic and environmental factors interact in a complex way in the causation of obesity. Though obesity itself is rarely fatal but it bring along with it a cluster of disorders known as 'metabolic syndrome'. A modest decrease in body weight results in significant health benefits.

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A reduction in body weight of only 5% - 10% has shown to bring about significant fall in blood pressure and improved glycemic control in patients with diabetes [5]. Hypothalamus is the key brain centre involved in appetite regulation. Neuronal pathways are known to play a role in short-term regulation of appetite and satiety, while long-term weight control is more or less governed by hormonal stimuli released by the gastrointestinal tract and adipose tissue [6]. Within the arcuate nucleus there are two main populations of neurons involved in the regulation of food intake, the appetite inhibiting pro-opiomelanocortin (POMC) neurons, and the appetite stimulating neuropeptide Y (NPY) and agouti-related peptide (AgRP) co-expressing neurons [7]. Both the POMC and NPY/AgRP neuronal populations project to the paraventricular nucleus (PVN), which is known to be critical in the regulation of food intake and energy expenditure. Regulation of body weight is through these distributed brain circuits that use a variety of neuropeptides and transmitters, and are responsive to endocrine and metabolic signals. Targeting of these circuits with novel pharmaceutical drugs can be helpful in addition to lifestyle modification for the treatment of obesity. Anti-obesity medications can be categorized according to one of the three modes of action, inhibitors of fat absorption, inhibitors of the endocannabinoid system & modifiers of central nervous system neurotransmission of norepinephrine, dopamine and serotonin. Bupropion which is a dopamine and norepinephrine reuptake inhibitor and was approved for depression and smoking cessation showed modest weight loss in overweight and obese women [8]. Systemic administration of opioid agonists and antagonists affects the food intake, suggesting that the opioid system has a role in the regulation of feeding behaviour [9]. Naltrexone which is approved for the treatment of opioid addiction as well as alcoholism, is not known to be associated with weight loss.

However, the combination with Bupropion and Naltrexone leads to a synergistic effect on control of eating and response to food cravings as food cravings are reported to be an important obstacle to the ability of obese individuals to adhere to a diet.

All these drugs have been studied individually but there is no data available on direct comparison of these drugs on weight loss and glycemic control in obese patients. With this background this study was planned with an aim to study the comparative effects of Orlistat and a combination of Naltrexone and Bupropion on high fat diet induced obesity in rats.

Material and methods

Drugs which were used in the study:

1. Standard drug - Orlistat
2. Test drug – Combination of Naltrexone & Bupropion

Experimental animals

Wistar rats of either sex weighing between 90-110 grams were used for the study. Animals were kept in the animal house and were housed in a group of 3 animals per cage in polypropylene cages at 22±2 ˚C with 12-hour light/12 hours dark cycle. They had free access to water and food *ad libitum*. After 1 week of adaptation period, the animals were used for the study. The experimental protocol was duly submitted and approved by Institutional Animal Ethics Committee (IAEC) as per the CPCSEA guidelines.

Composition of high fat diet (HFD)

The high fat diet [10] was consisting of, Gram flour - 40%, Saturated fat - 25%, Coconut (dried) - 10%, Cheese - 5%, Condensed milk - 5%, Peanuts - 5%. The diet was made in the form of balls and were given to rats, in addition to free access to standard laboratory chow and water *ad libitum*. At the end of 12 weeks animals weighing between 130-200 grams were included in the study and were divided into below mentioned group I to group IV of six animals each.

Group I: It served as **Non-obese control (NOC)** and obesity was not induced in this group and it did not receive any treatment. This group was provided with standard laboratory chow and water for a period of 17 weeks.

Group II: It served as **Obese control (OC)** in which obesity was induced by HFD over a period of 17 weeks. This group did not receive any treatment.

Group III: It served as **Obese Orlistat (OO)** treated group in which obesity was induced by HFD over a period of 12 weeks. The same diet was further continued over the next 5 weeks period i.e., for a total of 17 weeks. This group received Orlistat (1.3 mg/kg body weight/day) suspended in 2% gum acacia emulsion which was given orally with the help of rat feeding needle, from week 13 to week 17 (for a period of 5 weeks).

Group IV: It served as **Obese Naltrexone plus Bupropion (ONB)** treated group in which obesity was induced by HFD over a period of 12 weeks. The same diet was further continued over the next 5 weeks period i.e., total 17 weeks. This group received a combination of Naltrexone (3mg/kg body weight/day) and Bupropion (33mg/kg body weight/day) dissolved in distilled water and given orally with the help of rat feeding needle from week 13 to week 17 (for a period of 5 weeks).

Weight measurement

Body weight was measured every week using the electronic weighing scale from 0-17 weeks. Weights were expressed in grams.

Food intake measurement

The food was given daily to rats and the remaining food in the cage was collected next day. The net food intake of each group for each week was calculated by measuring the difference between the food given throughout the week and the food remaining at the end of week and was expressed as gram/week/group.

Blood glucose estimation

Blood sugar was measured at 0, 4, 8, 12, 13, 14, 15, 16, and 17 weeks as mg/dl (milligram per deciliter) after overnight fasting and was estimated using tail clip method for blood collection.

Measurement of body mass index (BMI)

At the end of week 17 animals from group I to group IV were subjected to BMI estimation. It was calculated by measuring weight and measuring length from mouth to anus [11] with the help of Vernier Caliper. The BMI was expressed as gms/cm^2.

Statistical analysis

Body weight and blood glucose values were reported as Mean ± S.D, food intake was expressed in absolute values and body mass index (BMI) was expressed as mean. Statistical analysis was done using 'R' software as data analyzing tool. Data was analyzed using analysis of variance (ANOVA) to determine differences among groups. A p-value ≤ 0.05 was accepted as significant.

Observations and results

Body Weight

Feeding of high fat diet led to increase in weight in group II, III, & IV (table 1). Mean weight of rats in group III OO and group IV ONB gradually increased till week 12. After starting Orlistat (1.3 mg/kg/day) the weight of rats in group III OO started declining thereafter and was 139.9 ± 12.74 grams at the end of week 17 and after starting Naltrexone plus Bupropion (Naltrexone 3 mg/kg/day and Bupropion 33 mg/kg/day) the mean weight gradually started declining and was 140.6 ± 14.78gms at the end of week 17 in group IV ONB. Group II didn't receive any treatment and it showed further increase in body weight and was 169.1 ± 7.90 grams at the end of week 17. After normalization of mean weight at week 13 (table 2) for all groups the percentage change in weight was calculated for groups over a period of 5 weeks during which drugs were administered. It shows decline in weight in group III OO and group IV ONB.

Body Weight

Table 1: Body Weight of Groups (Mean Weight (in grams) ± SD)

Weeks	Group I NOC (Non-obese Control)	Group II OC (Obese Control)	Group III OO (Obese Orlistat)	Group IV ONB (Obese Naltrexone plus Bupropion)
0	98.5 ± 5.37	105.0 ± 4.38	101.2 ± 5.57	102.7 ± 7.36
1	99.9 ± 4.64	107.9 ± 3.53	104.4 ± 5.09	105.8 ± 6.91
2	100.2 ± 4.07	110.9 ± 4.56	107.6 ± 6.31	112.8 ± 7.79
3	102.4 ± 3.94	114.8 ± 4.99	110.8 ± 7.62	117.8 ± 7.00
4	105.0 ± 3.38	121.4 ± 5.76	115.5 ± 7.95	122.7 ± 8.13
5	107.7 ± 2.69	125.4 ± 5.35	119.0 ± 8.41	126.5 ± 9.95
6	109.4 ± 2.94	129.9 ± 5.26	123.2 ± 8.07	131.7 ± 11.01
7	110.7 ± 4.23	133.9 ± 3.94	127.6 ± 7.53	136.2 ± 11.31
8	111.8 ± 3.35	137.5 ± 3.14	133.0 ± 8.95	139.2 ± 12.14
9	113.5 ± 3.02	141.6 ± 1.99	137.0 ± 9.53	142.9 ± 12.73

10	115.9 ± 3.23	144.0 ± 2.94	141.9 ± 11.06	146.5 ± 12.00
11	118.1 ± 3.49	146.7 ± 3.99	146.1 ± 12.01	152.2 ± 12.18
12	119.9 ± 3.97	149.8 ± 5.89	150.0 ± 13.13	155.3 ± 13.24
13	121.8 ± 4.42	153.0 ± 6.51	148.8 ± 13.78	154.1 ± 12.70
14	124.7 ± 4.99	156.2 ± 7.67	146.4 ± 12.58	152.1 ± 12.97
15	127.6 ± 5.66	160.3 ± 7.57	143.8 ± 12.99	148.3 ± 13.80
16	129.0 ± 4.61	162.4 ± 7.05	141.8 ± 13.18	143.6 ± 14.24
17	132.1 ± 4.30	169.1 ± 7.90	139.9 ± 12.74	140.6 ± 14.78

Table 2: Percentage Change in Body Weight in GI-GIV during treatment

Weeks	Group I NOC (Non-obese Control)	Group II OC (Obese Control)	Group III OO (Obese Orlistat)	Group IV ONB (Obese Naltrexone plus Bupropion)
13	100%	100%	100%	100%
14	102%	102%	98%	99%
15	105%	105%	97%	96%
16	106%	106%	95%	93%
17	108%	111%	94%	91%

Food Intake

Food intake (table 3) of group I NOC and group II OC increased gradually over a period of 17 weeks. In group III OO after starting Orlistat the food intake attained a plateau from week 13 onwards. In group IV ONB after starting Naltrexone plus Bupropion the food intake started to decline from week 13 onwards and continued to decline till week 17.

Food Intake

Table 3: Food intake of Groups (grams/week)

Weeks	Group I NOC (Non-obese Control)	Group II OC (Obese Control)	Group III OO (Obese Orlistat)	Group IV ONB (Obese Naltrexone plus Bupropion)
1	122.9	147	144.6	138
2	133.8	164.2	152.6	144.52
3	144.87	172	166.7	151.22
4	149.7	183.2	184.1	170.55
5	155.32	196.99	198.23	230.32
6	150.33	211.73	212.1	225.55
7	160.45	230.67	236.76	240.48
8	157.89	245.87	248.87	279.75
9	161.32	267.22	251.62	275.54
10	160.43	270.89	271.34	270.81
11	154.32	263.44	263.75	281.21
12	158.94	261.43	269.71	272.24
13	167.89	268.84	270.75	265.32
14	167.58	269.62	269.57	260.56
15	168.97	270.32	268.53	258.39
16	170.43	271.38	270.47	252.56
17	169.51	270.43	272.54	247.73

Blood Glucose

There was a gradual reduction in blood glucose (table 4) in group III OO and group IV ONB after starting drug therapy.

Blood Glucose

Table 4: Blood Glucose of Groups (Mean ± SD in mg/dl)

Week	Group I NOC (Non-obese Control)	Group II OC (Obese Control)	Group III OO (Obese Orlistat)	Group IV ONB (Obese Naltrexone plus Bupropion)
0	98.50 ± 9.61	98.67 ± 10.41	98.17 ± 8.91	104.50 ± 17.44
4	104.67 ± 4.08	116.83 ± 11.07	129.17 ± 8.66	129.17 ± 13.82
8	103.83 ± 8.70	129.50 ± 5.32	128.00 ± 18.83	125.33 ± 23.02
12	107.83 ± 6.08	136.00 ± 5.51	147.17 ± 9.09	144.83 ± 9.45
13	111.67 ± 5.79	141.50 ± 6.72	146.67 ± 6.09	146.53 ± 7.68
14	113.83 ± 5.12	143.67 ± 7.63	142.83 ± 5.64	139.67 ± 5.20
15	117.50 ± 3.73	147.33 ± 9.03	137.67 ± 5.24	137.00 ± 7.56
16	118.17 ± 2.14	153.17 ± 7.49	136.17 ± 2.04	126.83 ± 6.88
17	120.83 ± 2.23	157.50 ± 8.55	134.17 ± 4.62	124.50 ± 4.23

Body Mass Index

Table 5 shows the mean BMI (in gm/cm^2) of each animal from group I-IV. Here group IV ONB has the lowest BMI and group II OC has the highest BMI.

Body Mass Index (BMI)

Table 5: Mean BMI (gm/cm^2) of GI-GIV

Animal No.	Group I NOC (Non-obese Control)	Group II OC (Obese Control)	Group III OO (Obese Orlistat)	Group IV ONB (Obese Naltrexone plus Bupropion)
A	0.49	0.44	0.36	0.51
B	0.52	0.61	0.55	0.57
C	0.59	0.52	0.60	0.56
D	0.53	0.60	0.62	0.41
E	0.49	0.66	0.55	0.54
F	0.57	0.61	0.56	0.56
Mean	**0.53**	**0.57**	**0.54**	**0.52**

Table 6: Repeated measures ANOVA summary

ANOVA summary	Body Weight	Food Intake	Blood Glucose
F	7.635	14.85	6.028
P value	0.0002	<0.0001	0.0022
P value summary	***	****	**
Significant diff. among means (P < 0.05)?	Yes	Yes	Yes
R square	0.252	0.4103	0.3611

Discussion

Obesity is a chronic disorder and an important risk factor for cardiovascular and metabolic syndromes. There is excess body fat accumulation, leading to adverse effects on health and life expectancy [12]. Currently there are many researches undergoing for the advent of safe and effective pharmacotherapy of obesity and are providing sound and promising results. Pharmacotherapy is an important adjunct to lifestyle modifications for induction and maintenance of weight loss. Among the animal models of obesity, rats that are fed a high-fat diet are considered useful; a high percentage of fat in the diet is considered to be an important factor in the development of obesity, leading to the accumulation of body fat [13]. In the present study it was observed that introduction of high fat diet to rats for a period of 12 weeks brought significant increase in body weight, blood glucose and BMI. Various other studies too have reported similar results with this methodology of obesity induction [14-16].

Body Weight

In our study weight changes were found in all the groups. Body weight of rats in group II OC to group IV ONB increased gradually from week 1 onwards, high percentage of fat in their diet can be considered as a leading factor in the development of obesity.

Group I NOC and group II OC did not receive any drug treatment for obesity and showed weight gain till the end of study owing to normal growth of the rats in group I NOC and due to high fat diet in group II OC respectively. Group III OO recorded a continuous increase in body weight till week 12 after which there was an observable decline from week 13 till week 17 after initiation of Orlistat (1.3 mg/kg body weight/day orally) (table no 1). Orlistat is known to act by binding and inhibiting lipases produced by the pancreas and stomach that act in the small intestine by breaking down dietary triglycerides into free fatty acids. Thus, reducing systemic fat absorption. Orlistat increase faecal fat loss with minimal systemic absorption [17]. This inhibition of gastric and pancreatic lipases may be responsible for decreasing dietary fat absorption from intestine in rats, thus leading to gradual decline in weight in group III OO. In group IV ONB (Obese Naltrexone plus Bupropion) Naltrexone (3 mg/kg body weight/day) and Bupropion (33 mg/kg body weight/day) was started orally at the beginning of week 13 and was continued till week 17. There was a significant decline in weight ($P<0.05$) in rats after NB administration (table 1 & 6). Bupropion causes inhibition of the synaptic reuptake of norepinephrine and dopamine thereby increasing dopamine activity and stimulating Pro-opiomelanocortin (POMC) neurons leading to their activation, this action leads to reduction in appetite and increase in energy expenditure [18]. Naltrexone an opioid receptor antagonist, blocks opioid receptors on the POMC neurons, preventing feedback inhibition and increasing POMC activity. Increased POMC signalling has been associated with decreased appetite, increased metabolism, and weight loss, whereas decreased POMC signalling is associated with hyperphagia and energy conservation [19]. These previous studies have demonstrated that the combination of Bupropion with Naltrexone leads to a synergistic effect on weight control. Thus we can assume that it can be co-related that the weight loss encountered in the present study in group IV ONB can be the combined result of the anorectic effect of Naltrexone and Bupropion.

Food intake

In our study, group I NOC which was given normal laboratory chow showed only modest increase in food intake throughout the study (table 3), whereas in group II OC food intake was higher than group I NOC (table 4). This can be attributed to rat's preference for high fat diet. In group III OO the food intake increased gradually till week 13 and even after starting Orlistat there was no significant change in food intake (table 3). Orlistat has inhibitory effect on dietary fat absorption [20] but as per literature search we could not find any effect on hunger and satiety. In group IV ONB which was fed high fat diet, food intake started to decline from week 13 onwards after starting Naltrexone and bupropion. There was significant ($P<0.05$) reduction in food intake in this group during the course of drug therapy (table 3 & 6). This can be explained on the basis of anorectic effect of Naltrexone and bupropion. It has been documented that different subtypes of adrenoceptor (AR) and dopamine (DA) receptors mediate bupropion's effects on the size of meals, on satiety and on satiation [21]. As discussed above combination of Naltrexone and Bupropion causes decrease in appetite, increase in energy expenditure and reduction in food intake by regulating POMC activity. The acute anorexic effects of Naltrexone and Bupropion in obese rats also replicate previously published data [22-23]. From the findings of group IV ONB we can say that Naltrexone and Bupropion has an anorectic effect in obese rats leading to decrease in food intake and subsequently causing weight loss.

Blood glucose

Blood glucose in group I NOC was within normal limits. As compared to group I NOC, the rise in blood sugar was significantly higher in group II OC (table 4). The continuous intake of calorie and fat rich diet lead to gradual development of obesity and increased blood glucose in group II OC rats. In group III OO there was a decline in blood glucose after starting Orlistat (Table 4). Orlistat has been shown to significantly reduces the incidence of type 2 diabetes in obese subjects [24]. On the basis of this clinical evidence we can draw an assumption that reduction in body weight can lead to improvement blood glucose levels, and this might be responsible for reduction in blood glucose in group III OO rats. In group IV ONB there was a significant decline in blood glucose after starting NB (table 4, 6). It can be said that due to anorectic effect of NB there was weight loss in

group IV ONB rats, reduction in weight loss then lead to normalization of blood glucose levels. This change is sometimes noticed in obese patients who demonstrate improvement in blood glucose with progressive weight loss. Reduction in weight (adipose tissue) leads to reduction in inflammation in adipose tissue thereby decreasing insulin resistance, which can be responsible for improvement in blood glucose levels [25].

Body mass index

In the present study it was found that group II OC showed maximum BMI. The minimum BMI was of group IV ONB (table 5). Group I NOC and group III OO had almost similar BMI values. Group IV ONB showed reduction in weight, blood glucose, as well as food intake. As per available literature it's known that the risk of high blood glucose and subsequent diabetes diagnosis was significantly more for individuals with higher BMI as compared to individuals with lower BMI [26]. The rats in group II OC were found to have high blood glucose and they also had the highest BMI among all the groups, whereas rats of group IV ONB had low blood glucose as well as low BMI.

Conclusion

The result of the present study helps in concluding that the combination of Naltrexone and Bupropion is an effective combination with significant effect on reduction in total body weight, reduction in food intake and reduction of BMI in obese rats. It also led to modest reduction in blood glucose. Current study can be further extended to include various other parameters like estimation of lipids, insulin level and leptin level.

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