

Prevalence of Depression in Animal Model of High Fat Diet Induced Obesity

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Abstract: The prevalence of obesity is substantially increased in developing countries and it is considerably associated with type 2 diabetes (T2DM), dyslipidemia, and hypertension. These symptoms are clustered to form metabolic syndrome. In accordance with the Researchers opinion, obese people are more likely to suffer from depression, a mental affliction that appears due to chronic stress, disturbs thoughts, behavior, and feelings. It has been addressed that the physiological impairments which are undergoing due to obesity can affect the metabolic activities which in turn give impact on brain and affect its functioning, because obesity itself seems to constitute a chronic stressful state thus, exacerbates the risk of depression. Present study intended to illuminate the anticipated links between obesity and stress. To make possible the study, animal model of obesity was accomplished by subjecting the Albino wistar rats with energy-dense diet (high fat diet) for 5 weeks; later on, chronic mild stress paradigm was implemented along with high fat feeding for 2 weeks. As expected, high fat feeding increased the adiposity in rodents. Obese animals presented the depressive symptoms more prominent than normal fat feeding rats. Present findings suggest that obesity could increase the depressive symptoms potentially involve in the recruitment of depression.

Keywords: High fat diet, Obesity, CMS, Depression.

INTRODUCTION

The physiological metabolism, undergoing inside the body, are extensively affected due to obesity. Obesity is considered as a medical condition, characterizes as abnormal or excessive fat accumulation that may impair health. It proceeds when energy uptake exceeds the energy expenditure or physical activity, leads to the enlarge store of body fat, particularly in adipose tissues. Although it is also interpreted that obesity is the result of consuming diet which is rich in fat [1] and significantly promotes other chronic diseases such as type 2 diabetes and cardiovascular disease [2, 3]. Beside these clinical diseases it is also thought to be a signal for depression [4], it has been addressed that the physiological impairments which are undergoing due to obesity can affects the metabolic activities which in turns give impact on brain and affect its functioning thus, exacerbates the risk of depression. As a consequences, the higher levels of depression in obese people were found [5, 6] since obesity itself seems to constitute a chronic stressful state and may cause HPA axis dysfunction [7]. There is a mutual relationship between obesity and depression as obese individual is prone to be at higher the risk of depression [8]. Moreover, stress induced chronic stimulation of the hypothalamic–pituitary–adrenal (HPA) axis plays a potential role in the development of obesity. The HPA

axis is not only the regulator of stress response, but is also tightly conducting appetitive behaviors [9]. Depressive symptoms are associated with weight gain because depression and obesity both are responded by the activity of HPA axis [10].

Under normal condition, adipocytes produce a hormone named as leptine which has influence on body weight through the regulation of fat storage inside the adipocytes. The level of leptin is observed to correspond with body fat [11] it regulates food intake through effect on hypothalamus to decrease food intake and increase energy expenditure [12]. Although leptin regulates the appetite but in obese individuals signaling of leptin is attenuated and they exhibit leptin resistance [13]. It has also been addressed that hypothalamic leptin receptor gene expression is suppressed in obesity [14]. CRH is found to be regulated by leptin, a hormone of HPA axis, since leptin signaling is resist in obesity CRH level will no longer regulate which in turns leads to the dysfunctioning of HPA axis [15]. Elevated level of cortisol, due to hyperactive HPA axis may alter different regions of brain and negatively affects the 5-HT metabolism [16] which has influence on body weight by suppressing appetite and reducing fat consumption [17].

METHODS AND CHEMICALS

Animals

24 male Albino Wistar rats weighing 120-180gm were purchased from The Dow University of Health and Sciences, Karachi, Pakistan and housed in individual cages and allowed to acclimatize to their surrounding

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with temperature ($25\pm 2^{\circ}\text{C}$) for one week. Animals had free access to a normal standard diet during acclimatizing time before starting experiment. All animal experiments, approved by the Institutional Ethics and Animal Care Committee, were conducted in strict accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals. All treatments and behavioral monitoring were performed in a balanced design to avoid order and time effects.

Experimental Protocol

Rodents were randomly divided into two equal groups, Normal Fat Diet (NFD) and High Fat Diet (HFD). According to the groups they treated with respective diet for 5 weeks. Afterwards, animals exposed to the schedule of chronic mild stress for next 2 weeks. Food intake, body weight, behavioral activity in familiar, novel as well as anxiogenic environment was monitored after 1st and last stress.

Composition of High Fat Diet

The normal diet group were fed a standard rat chow containing 4% fat, 67% carbohydrate, and 19% protein; whereas the HFD or high fat diet animals treated with a diet containing 35 % fat, 26% carbohydrate, and 26% protein. Dietary treatment was going as longer for 5 weeks. High-fat diet was designed in our laboratory. The high fat diet was rich in calories (high-fat diet = 5.2 kcal/g versus standard diet = 3.8 kcal/g).

Chronic Mild Stress

Table 1: CMS Type and Duration

Days	Stress	Duration
01	Cold stress 4°C	2 hours
02	light dark cycle	2 hours
03	Cage agitation	2 hours
04	White Noise stress	2 hours
05	Light stress	2 hours
06	Water deprivation	12 hours
07	Tilted cage	3 hours
08	Inescapable tail	1 hours
09	Wet cage	1 hours
10	Crowding	2 Hours

Behavioral Assessment

1. Food Intake

A weighed amount of food was placed individual cages and food intake monitored 24 hours of 1st first stress and then last stress. Intake of food was

monitored by placing the weighed amount of food in the Hooper of each animal's cage and measurement is done by weighing the food which was left at the time of measurement.

2. Body Weight

Changes in body weight were monitored to find out the effect of stress in obese rats. Each animal was allowed to sit with all four paws in the centre of a basket which was already placed in the balance machine to weigh the animals.

3. Locomotive Activity

Locomotive activity of rats was monitored in the familiar environment or activity box. The apparatus consists of square shape activity cage (26 x 26 x 26 cm), bedded with saw dust to provide familiar environment which is present in their cage. The rats placed in the center of activity cage and locomotive activity was monitored over the time period of 10 minutes and the number of cage crossing was noted during this period [18].

4. Exploratory Activity

To monitor the changes in locomotor/exploratory activity caused by the chronic mild stress Open field activity test is used for providing novel environment. This environment differs from home cage. It is used to explore the emotionality [19]. Animals were placed individually in the center of open field; consist of square area 76 x 76 cm with opaque walls 42 cm high. The floor is design with 25 equal squares. The time which was taken by animal to move on the center of the square was noted and then, in next 5 minutes the crossing of squares with all four paws was counted.

5. Anxiolytic Model

Crawley and colleagues introduced light/dark transition test for assessment of anxiolytic activity [20]. Apparatus consist of two equal compartments (26 x 26 x 26 cm), floored with the saw dust, one of the compartment is exposed into the light and second compartment is in dark. To monitor the activity a rat is place in the centre of the light compartment of the box. Entries and time spent with all four paws in the light compartment were monitored for a cut off time of 5 minutes [21]. Increased number of entries and time spent in light compartment are used as an indicator of reduced anxiety states [22].

Statistical Analysis

Results are presented as means \pm SD. Data on the effects of chronic mild stress on the food intake, growth

rate and locomotor activity, exploratory activity and anxiolytic activity were analyzed by three – way ANOVA (repeated measures design). Software used for the analysis was SPSS (version 17). Individual comparisons were made by Newman-Keuls test. Values of $p < 0.05$ were considered as significant.

RESULTS

Figure 1 shows the effect of CMS on body weight and food intake of HFD fed rodents was monitored on next day of 1st and last stress. Analysis on the data of body weight of HFD treated animals after Stress by three-way ANOVA, showed significant effects of HFD ($F=10.235$; $df= 1, 12$; $p < 0.01$), Stress ($F=16.787$; $df=1, 12$; $p < 0.01$) and Days ($F=298.217$; $df=1, 12$; $p < 0.01$). However, interaction among Days, HF diet and stress ($F=0.256$; $df= 1, 12$) were found to be non significant. Exposure to CMS decreased growth rate in HFD as well as in NFD treated rats. Significant decreased was found after last stress ($p < 0.05$). Increased growth rate found in both unstressed as well as stressed animals of HFD group after 1st stress as compared to respectively

treated NFD animals. After last stress growth rate decreased in HFD treated animals significantly as compared to NFD treated stressed group animals. In HFD treated animals, growth rate found to be decreased in both unstressed as well as stressed group animals after last stress as compared to respectively treated animals of unstressed or stressed group of 1st day of stress.

Figure 2 shows the effect of CMS on food intake of HFD fed rodents was monitored on next day of 1st and last stress. Data on food intake of HFD treated rats after CMS analyzed by three-way ANOVA (repeated measure design) showed significant effects of HFD ($F=31.920$; $df= 1, 12$; $p < 0.01$), Stress ($F= 13.134$; $df=1, 12$; $p < 0.01$) and Days ($F= 413.849$; $df=1, 12$; $p < 0.01$). However, interaction among Days, HF diet and stress ($F=0.387$; $df= 1, 12$) were found to be non significant. Post-hoc analysis by Newman-Keuls test showed that food intake decreased after last stress ($p < 0.05$) in both Normal diet treated stressed animals and HFD treated stressed animals as compared to similarly treated

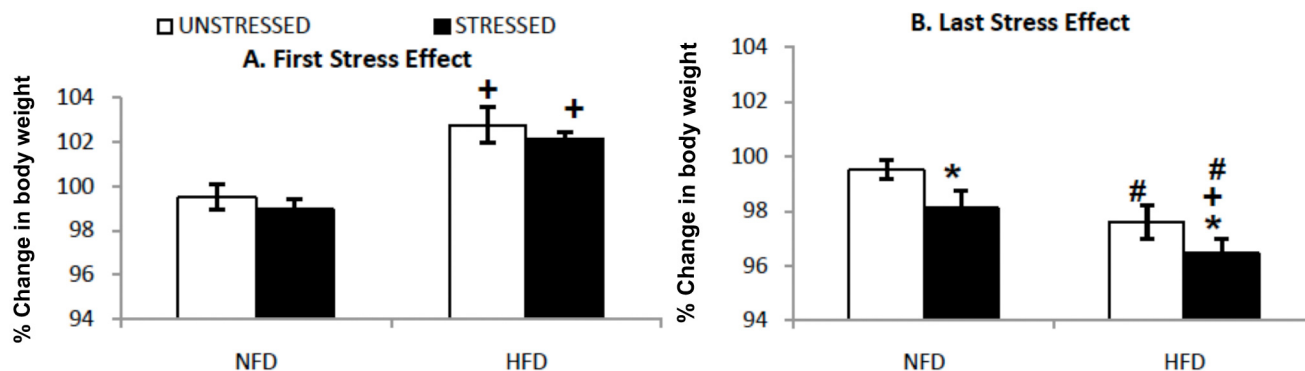


Figure 1: Effect of Chronic mild stress on growth rate of HFD treated Rats. Values are means \pm SD ($n=6$) as monitored on next day of 1st and last stress. Significant differences by Newman-Keuls test: * $p < 0.05$, ** $p < 0.01$ from respective unstressed animals; + $p < 0.01$ from respective NFD treated animals; # $p < 0.05$, ## $p < 0.01$ from respective 1st Stress NFD or HFD treated Unstressed or Stressed animals, following three-way ANOVA (repeated measures design).

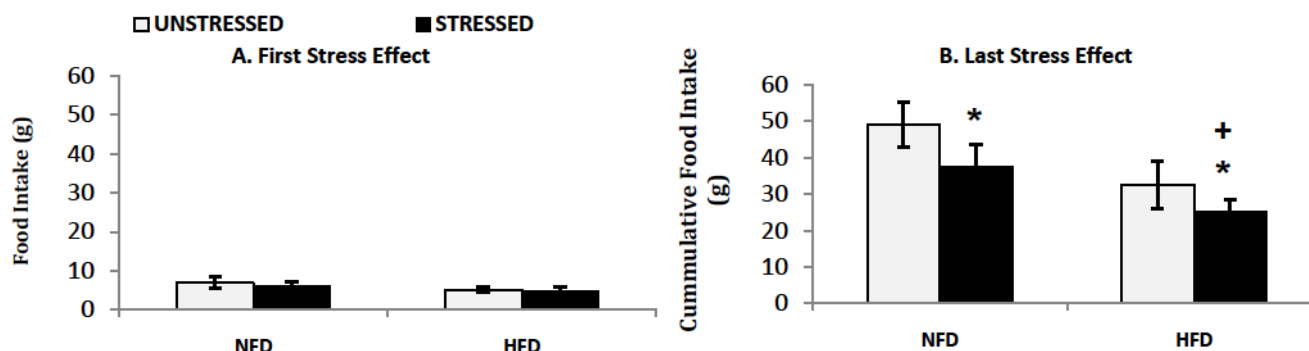


Figure 2: Effect of Chronic mild stress on food intake of HFD treated Rats. Values are means \pm SD ($n=6$) as monitored on next day of 1st and last stress. Significant differences by Newman-Keuls test: * $p < 0.05$, ** $p < 0.01$ from respective unstressed animals; + $p < 0.01$ from respective NFD treated animals; # $p < 0.05$, ## $p < 0.01$ from respective 1st Stress NFD or HFD treated Unstressed or Stressed animals, following three-way ANOVA (repeated measures design).

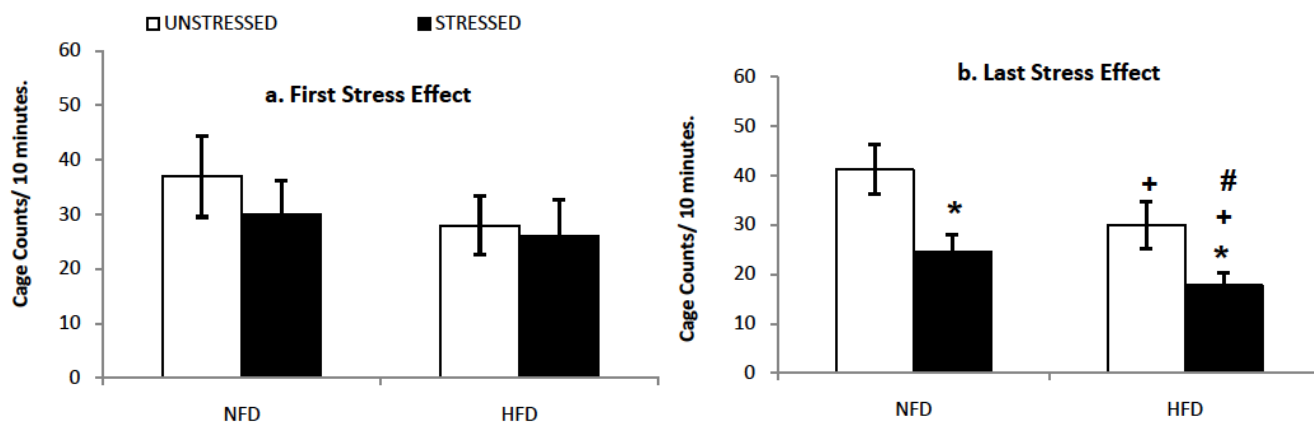


Figure 3: Effect of Chronic mild stress on activity in activity box of HFD treated rats. Values are means \pm SD (n=6) as monitored on next day of 1st and last stress. Significant differences by Newman-Keuls test: * $p < 0.01$ from respective unstressed animals; + $p < 0.01$ from respective NFD treated animals; # $p < 0.05$, ## $p < 0.01$ from respective 1st Stress NFD or HFD treated Unstressed or Stressed animals, following three-way ANOVA (repeated measures design).

unstressed animals. After last stress significant decreased ($p < 0.05$) in food intake was found in HFD treated animals as compared to NFD treated stressed animals.

Figure 3 shows the effect of CMS on activity of rats treated with HFD in activity box was monitored after 1st and last stress (Figure 3). Analysis of the number of cage crossing of stressed HFD treated animals by three-way ANOVA, showed significant effects of HFD ($F = 11.216$; $df = 1, 12$; $p < 0.01$), Stress ($F = 16.878$; $df = 1, 12$; $p < 0.01$). However the effect of and Days ($F = 1.009$; $df = 1, 12$) and the interaction among Days, HFD and stress ($F = 0.006$; $df = 1, 12$) were found to be non significant. Post-hoc analysis by Newman-Keuls test showed that after last stress NFD fed rats significantly decreased their locomotory activity ($p < 0.05$) as compared to HFD fed rats when compared with their

respective unstressed controls. It shows NFD fed stressed animals were less active than HFD stressed animals and other unstressed controls.

Figure 4 Shows the effect of CMS on open field activity shows the effect of CMS on number of square crossing in open field in order to monitored exploratory activity of rats treated with HFD was monitored on next day of 1st and last stress. Analysis of the number of square crossing of stressed HFD treated animals by three-way ANOVA, showed significant effects of Days ($F = 21.392$; $df = 1, 12$), HFD ($F = 13.148$; $df = 1, 12$; $p < 0.01$), Stress ($F = 15.596$; $df = 1, 12$; $p < 0.01$). However the effect of the interaction among Days, HFD and stress ($F = 0.355$; $df = 1, 12$) were found to be non significant. Post-hoc analysis by Newman-Keuls test showed exposure to a schedule of CMS decreased number of square crossed in NFD as well as HFD

a. Number of square crossed

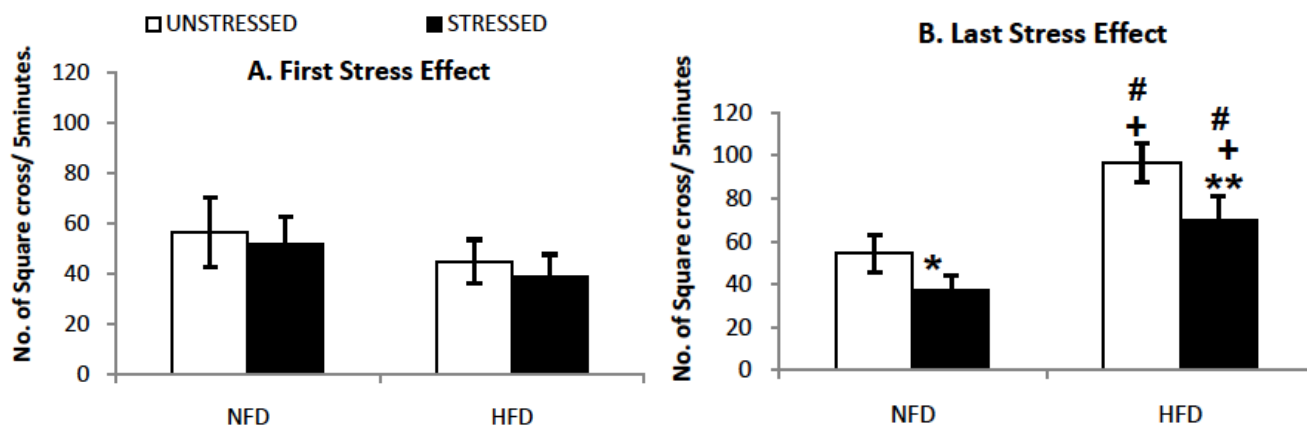


Figure 4: Effect of Chronic mild stress on activity in novel environment of HFD-induced obese rats. Values are means \pm SD (n=6) as monitored on next day of 1st and last stress. Significant differences by Newman-Keuls test: * $p < 0.05$, ** $p < 0.01$ from respective unstressed animals; + $p < 0.01$ from respective NFD treated animals; # $p < 0.01$ from respective 1st Stress NFD or HFD treated Unstressed or Stressed animals, following three-way ANOVA (repeated measures design).

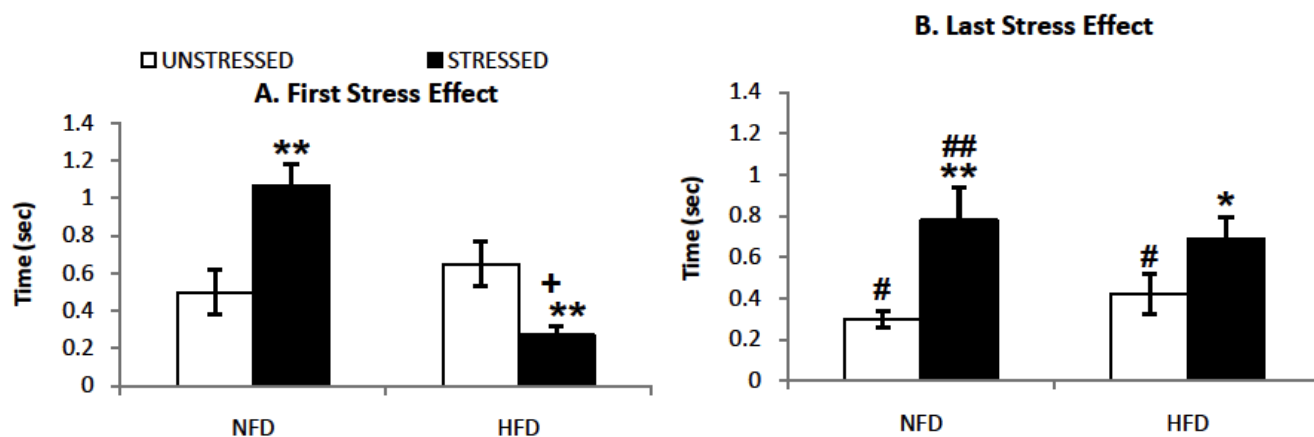


Figure 5: Effect of Chronic mild stress on activity in novel environment of HFD-induced obese rats. Values are means \pm SD (n=6) as monitored on next day of 1st and last stress. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from respective unstressed animals; +p<0.01 from respective NFD treated animals; #p<0.01 from respective 1st Stress NFD or HFD treated Unstressed or Stressed animals, following three-way ANOVA (repeated measures design).

treated animals. Significant increased in activity was seen in NFD (P<0.05) and HFD (P<0.01) after last stress as compared to similarly treated unstressed animals. In HFD treated animals, activity increased in both unstressed and stressed animals. Significant increase was found after last stress as compared to NFD treated unstressed or CMS animals. After last stress, activity in novel environment increased in HFD treated unstressed as well as CMS animals significantly (p<0.01) as compared to similarly treated unstressed or CMS animals from 1st day of stress schedule.

Figure 5 Shows the effect of CMS on open field activity shows the effect of CMS on latency time in open field in order to monitored exploratory activity of rats treated with HFD was monitored on next day of 1st and last stress. Analysis of the data on latency time of stressed HFD treated animals by three-way ANOVA,

showed significant effects of HFD (F= 13.584; df= 1, 12; p<0.01), Stress (F=22.165; df=1, 12; p<0.01) and interaction among Days, HFD and stress (F=10.519; df= 1, 12; p<0.01). However the effect of Days (F=3.345; df=1, 12), were found to be non significant. Post-hoc analysis by Newman-Keuls test showed that CMS exposure increased time required to move in open field of both NFD and HFD treated animals. Significant increased in time was seen after 1st stress in NFD (p<0.01) and after last stress in HFD (p<0.05) as well as NFD (p<0.01) as compared to respectively treated unstressed animals after 1st and last stress. Exposure to chronic stress decreased activity significantly in HFD treated animals as compared to similarly treated unstressed animals after 1st last. After last stress, latency time decreased in NFD treated animals as compared to NFD treated animals of stressed group of 1st day of stress schedule. In HFD

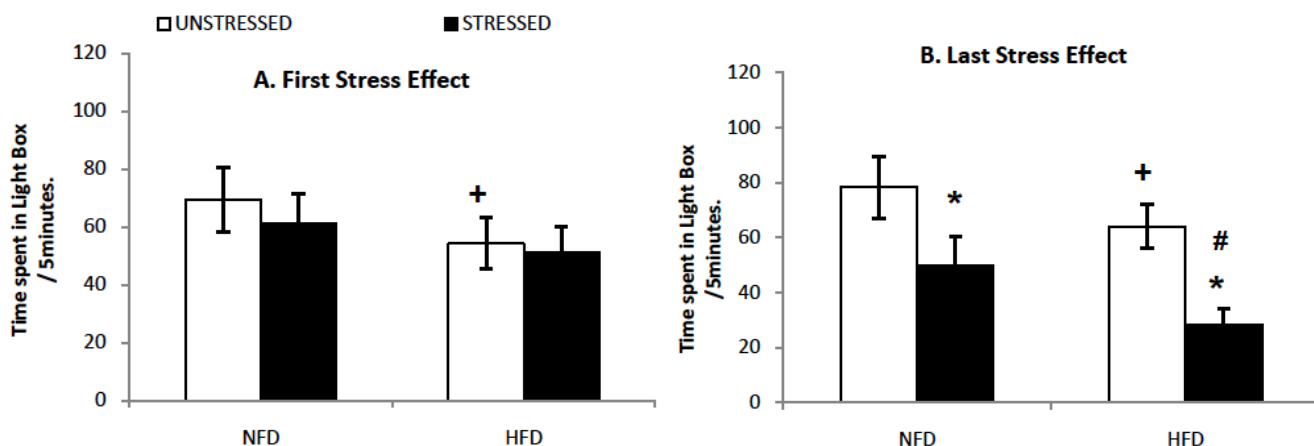


Figure 6: Effect of Chronic mild stress on Light Dark Box activity of rats treated with HFD. Values are means \pm SD (n=6) as monitored on next day of 1st and last stress. Significant differences by Newman-Keuls test: *p<0.01 from respective unstressed animals; +p<0.01 from respective NFD treated animals; #p<0.01 from respective 1st Stress NFD or HFD treated Unstressed or Stressed animals, following three-way ANOVA (repeated measures design).

treated animals, decreased activity was seen in unstressed animals on repeated monitoring. Significant decreased was found after last stress as compared to unstressed animals of HFD treated animals from 1st day of stress.

Figure 6 Shows the effect of CMS on time spent in light box in order to explore anxiolytic behavior of rats treated with HFD, as monitored on next day of 1st and last stress. Analysis of the data on time spent of stressed HFD treated animals by three-way ANOVA, showed significant effects of HFD ($F=17.856$; $df=1, 12$; $p<0.01$), Stress ($F=26.951$; $df=1, 12$; $p<0.01$). However the effect of Days ($F=1.687$; $df=1, 12$) and interaction among Days, HFD and stress ($F=1.106$; $df=1, 12$), were found to be non significant. Post-hoc analysis by Newman-Keuls test showed that CMS decreased activity in NFD as well as HFD treated animals. Significant decreased in activity was seen after last stress in HFD ($p<0.01$) and NFD ($p<0.05$) treated animals as compared to similarly treated unstressed animals. After last stress, activity decreased in unstressed HFD treated animals as compared to NFD treated unstressed animals of similar day. Time spent in light box by HFD treated animals decreased after last stress significantly ($p<0.05$) as compared to similarly treated animals of stressed group from 1st day of stress.

DISCUSSION

The aim of the present study was focus on the association between depression-like state and lipid metabolism in rats submitted to the chronic mild stress with high-fat diet. Present work exposed the obese animal to a schedule of CMS to produce behavioral deficits and revealed the impacts of CMS on obesity, the prevalence of depression in obesity and the metabolic alterations in fat rich body in the adverse situation. For this purpose, a model of high fat diet-induced obesity was applied to laboratory rats. Dietary profile is a crucial factor behind the reason of extraordinary body weight. Weight gain was seen to be higher in rats fed fat rich diet continuously probably due to the insufficient utilization of fats for energy purpose and their excessive storage in adipose tissue [23]. It suggest that high fat feeding proceeds the deposition of fats in adipose tissue which in turns develop leptin resistance, a hormone that regulates body weight by controlling fat accumulation in adipose tissues, thereby exhibit leptine resistance [13]. CMS induced decreased body weight in obese rats is due to hyperactive HPA, present study provides evidence which is supported by

another study [24] that body weight of CMS exposed high fat feeding animals was decreased more than normal fat feeding (Figure 1) because exposure to chronic mild stress results in significant behavioral deficits in a wide range of animal models have been resulted to induce significant changes in behavioral parameters [25]. Excessive fat in a diet promotes the accumulation of fats molecules inside the adipose tissues out of proportion, alters their morphology and undergoing mechanisms. Results from present study revealed that consumption of high fat diet induces hyperphagic effects it may be due to fat-rich diets generally increases food intake in male and female rodents regardless of the degree of saturation [26-30]. In present study, Figure 2 shows the relation between monoaminergic neurochemistry and macronutrient intake, exposure to CMS reduces food intake but in fat rich animals the effects of CMS are more prominent. CMS induced hypophagia is encouraged by using high fat is reported earlier [24]. CMS induced behavioral deficits in experimental model could be used reliably as animal model of depression [31].

The increased prevalence of obesity has been attributed to a decreased physical activity. In the present study results are suggesting that obesity decrease the physical activity gradually. Different behavioral tests (Figures 3 and 4), Home cage activity and open field test, provides observation about physical locomotor activity [18]. Adiposity has often seen to negatively associated with physical activity [1]. In Figure 2 results shows that rats with high fat diet intake were shown to be less active physically over the normal diet using rats, it suggests that Stress-induced suppression of home cage locomotor activity was also reduced by obesity it could be due to decreased serotonergic function which is encourage by CMS [16] results the depressive symptoms [32]. Conversely, High fat-induced obese rats have been shown to increase their active behavior in novel environment compared to normal fat using controls (Figures 4 and 5). An evidence [33] Supported the idea that high fat feeding are inversely related to anxiety, while anxiogenic condition are also indicated (Figure 6) by high fat induced obesity. Additionally, CMS exacerbates its effect on anxiety so that rats with HFD showed more anxiogenic over the normal diet rats.

CONCLUSION

Present work concluded that there are considerable impacts of dietary nutrient in the body response towards energy metabolism and behavior as well. It

does not only participate in the induction of obesity by altering the morphology of adipose tissue, but also impairs the neurochemical mechanisms which holds up the homeostasis and responsible for balance the body under adverse situation. In this regards, fats are more often claimed as responsible for these impairment because, unlike other macronutrients, they are specialized to store inside the tissues, adipose tissue, and initiates metabolic disturbance.

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Received on 12-04-2015

Accepted on 18-08-2015

Published on 25-08-2015

DOI: <http://dx.doi.org/10.6000/1927-5951.2015.05.03.6>

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