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ROLE OF PERIPHERAL SEROTONIN IN STRESS INDUCED OBESITY

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ABSTRACT:

Background: Job stresses have been identified as one of the factors influencing eating behavior and lead to altered BMI. It is hypothesized that stress perception may alter serum levels of serotonin and possible correlation between serum serotonin and stress hormones help to understand stress related obesity in working women.
Methods: This cross-sectional study was conducted at Biochemistry Department, University of Karachi. One hundred adult women working 8 hrs/day were identified by stratified random technique from teaching institutes and banks. They were grouped as having perception of no/minimal, mild, moderate and severe, on the basis of the scores they achieved from answering the standardized questionnaire. The serum levels of stress hormones, leptin and serotonin were measured by ELISA. Appetite was measured by VAS for hunger and desire to eat.
Results: Applying ANOVA revealed that BMI of the women who perceived moderate and severe stress was significantly higher ($p<0.01$). Serum cortisol, noradrenalin and leptin levels increased with the level of stress perception ($p<0.01$) and displayed a negative correlation with serum serotonin. The serotonin levels in circulation decreased with elevated stress perception ($p<0.01$). The appetite showed a significant higher correlation with stress levels ($p<0.001$).
Conclusion: Working Pakistani women are moderately stressed and also have higher than normal BMI. Stress reactivity is associated with high cortisol, NA and leptin in circulation. The low serotonin levels in circulation may be considered as marker of stress. It is however not clear that the stress level and BMI in working women is greater than men working in same environment or women not in any job.

Key words: Obesity, Stress, Serotonin, Leptin, Stress hormones, Working Women

INTRODUCTION:

Obesity has been identified as a strong risk factor of metabolic and cardiovascular disorders. The incidence of obesity is rising alarmingly around the globe, consuming the major fraction of the research funds. The discovery of the obesity gene product leptin has led to the remarkable insight into the development of obesity[1]. Leptin is the protein secreted from adipose tissue in response to the nutrients in diet. It acts through hypothalamic receptors thereby decreasing food intake and increasing energy expenditure, thus regulating the weight gain[2]. Deficiency of leptin gene results in morbid obesity in rodents. On the contrary human obesity is associated with high serum leptin levels giving a picture of resistance mechanism[3]. Through years leptin has emerged as a multifactorial hormone involved in various hormonal activities, hypertension, metabolic disorders, bone diseases and many other functions of human body[4]. Leptin has also been found to be altered in various stressful events[5]. The role of serum leptin in stress is less studied. Stress is defined as any factor that tends to disturb the normal homeostasis of the body. It initially known to act via Hypothalamo-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS)[6] is now known to modulate a number of neuro-chemical and

physiological mechanisms[7]. A stressful event stimulate HPA axis resulting in increased cortisol levels in circulation. Higher circulating levels of corticosteroids cause mobilization of glucose, increased energy expenditure and appetite[8]. Stimulation of SNS results in increased release of noradrenalin (NA) at nerve endings and Adrenalin (Ad) from adrenal medulla. Stress reaction is also associated with increased central serotonin[9]. Serotonin is also found in periphery in the platelets where it functions as a platelet aggregating agent. It is synthesized by the essential amino acid tryptophan. Peripherally it is synthesized in the chromaffin cells and via blood it is transported to the platelets. The association of peripheral serotonin with the stress hormones during acute or chronic stress remains unclear.

It is reported that acute and chronic stresses alter appetite ranging from anorexia to bulimia nervosa during adolescence in women[10]. The stress hormones cortisol and NA increase appetite[11] while leptin decreases it[12]. Role of central serotonin as an anorectic agent is well documented[8].

Present study attempts to identify the serum levels of serotonin as the marker of stress induced obesity. Indeed estimations in humans cannot be performed directly in the brain. The study also investigates the correlations among the serum levels of stress hormones (cortisol and catecholamines), leptin and serotonin and the effects of perceived stress on obesity in Pakistani working women. It is hypothesized that stress perception may also alter serum levels of serotonin and possible correlation between serum serotonin and stress hormones may help to understand stress related obesity in working women.

MATERIAL AND METHODS:

It was an analytical cross sectional study. One hundred adult female subjects of ages ranging from 30 – 64 years, working at local hospitals, teaching institutions and bank offices were selected by stratified random technique for the study. An informed consent was obtained from all the subjects. Stress levels were monitored subjectively by a standardized questionnaire[13]. All participants submitted written consent for the use of information contained in the questionnaire and for the donation of serum samples. The study procedures were approved by the ethical committee for advanced research of University of Karachi

Monitoring levels of stress: Stress perception was calculated by evaluating social psychological and physiological stressors. The subjects were asked to respond each statement as never (1), rarely (2), sometimes (3), often (4) and always (5). The response number was added for one sample and stress level calculated as none/ minimal (52-58), mild (59-65), moderate (66-76), and severe (80-86).

Social stressors encompassed the aspects of satisfaction, social life, comfort, environment, behavior with other people during stress and the effect of change in the social surroundings.

Psychological stressor addressed the effect of workload on physical and mental well being, sound sleep at night, difficulty to control emotions and if there is any particular behavior during excess workload/stress.

Physiological stress encompassed the various physiological experiences during stress like quality of work at the start of the day, self control, perspiration breakout, tiredness at work, dryness of mouth and throat and yawning and dozing out at work.

Appetite: Subjective appetite was measured using visual analogue scale (VAS) method using 100 mm lines. The questions asked related to hunger (over the last month in general how hungry you have been feeling?) and desire to eat (over the last month in general how strong your desire to eat been?). The questions were weighted with the extremes at each end (0= not at all and 100=extremely). The VAS were administered in a single session and designed to reflect retrospective ratings of motivation to eat rather than the state of time[14].

Physical parameters: Body mass index of all the subjects was calculated by dividing weight in kilograms with height taken in meter squares.

Blood Sampling: After all aseptic measures 5 ml of venous blood was drawn from antecubital vein after answering the questionnaire for perceived stress. Blood was allowed to clot at 4°C and serum was separated and stored at -70°C until estimations of serotonin, leptin and cortisol by ELISA.

Determination of chemical variables: The chemical variables were determined by ELISA. The kit for serum leptin[15] and serotonin[16] were obtained from BioSource Europe S.A. The kit for cortisol[17] was obtained from The Equipar Diagnostics.

Statistical Analysis: All data are expressed as mean±SEM. Statistical analyses were performed by one-way ANOVA followed by Tukey's test for multiple comparisons

RESULT:

The Physical, chemical and behavioral parameters of various stress groups are shown in Table 1 as means ± S.E.M and 95% confidence interval given in parenthesis. Average age of the women who took part in the study was 41.49 ± 0.98 years. It was a multimodal data with 30, 35 and 42 years being the most frequent ages. 57% of the women perceived themselves as having moderate stress (70.91 ± 0.92, mode=68). BMI varied between 18 and 37. Average population was found to be overweight (27.28 ± 0.44 Kg/m^2) with a mode of 30 Kg/m^2. 38 % of the working class of women had the normal weight (22.63±0.334), while 62 % of the women had higher than normal BMI (26% overweight 27.22 ± 0.19 and 36% obese 31.52 ± 0.35).

The percentages of women who perceive stress of moderate level, predominated each BMI category (normal 63.16%, overweight 50% and obese 52.78%) Among the women with normal BMI, 13.6 % perceived no/minimal stress while 15.79% perceived it as mild stress. The perception of severe stress in women with normal BMI was significantly reduced to 7.89 % compared to mild and moderate stress ($p<0.05$). Overweight women with BMI ranging from 26 - 29.9 kg/m2 demonstrated similar perception of severe and no/minimal stress (15.38%), while 19.23% of women scored mild stress levels. The obese group of women had no individual with no/minimal stress perception. 19.44% of women scored mild stress level and significantly more number of women (27.278%, $p<0.05$) showed a severe level of stress perception.

A 2 tailed Pearson correlation was applied for finding correlation among the hormonal parameters with BMI, stress score and appetite. Serum leptin demonstrated a significant positive correlation with BMI($r=0.413$, $p<0.001$), serum NA ($r=0.197$, $p=0.049$), cortisol ($r=0.282$, $p<0.05$), stress level score ($r=0.433$, $p<0.001$) and Vas for hunger and desire to eat ($r=0.456$ and 0.451 respectively, $p<0.001$). Serum NA illustrated a strong positive correlation with ages of the women (0.274, 0.05), serum cortisol ($r=0.208$, $p<0.05$), stress level score($r=0.262$, $p<0.05$) and VAS of hunger ($r=0.214$,

Table 1: Behavioral, Physical and Chemical Parameters of Various Stress Group among Adult Working Women Population

Values are expressed as mean ± SEM, 95% confidence Interval is given in parenthesis.

Variables	No/minimal	Mild	Moderate	Severe
	N=9	N=18	N=56	N=17
Body Index (kg/m^2)	22.33± 1.12 (19.47,25.20)	26.56± 1.05 (24.26,28.76)	27.335± 0.56*[a] (26.19, 28.46)	29.63± 0.94*[a] (27.64, 31.63)
Serum leptin (ng/ml)	2.79±0.26 (2.11, 3.47)	4.13±0.26 (3.60, 4.67)	4.96±0.191*[a] (4.58, 5.34)	6.71±0.44*[(a,b,c)] (5.77, 7.64)
Serum Ad(pg/ml)	31.1± 3.38 (22.40, 39.80)	34.19±5.98 (21.61, 46.70)	36.19±3.52 (29.14, 43.24)	53.36±5.87 (40.98, 65.74)
Serum Noradrenalin (ng/ml)	207.87±38.04 (110.07, 305.66)	312.00±32.28 (244.44, 379.55)	360.88±21.71 (317.36, 404.39)	399.60±35.66*[a] (324.36, 474.84)
Serum Cortisol (ng/ml)	82.7±4.22 (71.86, 93.54)	107.32±5.60 (95.60, 119.04)	171.18±6.55*[(a,b)] (158.06, 184.30)	211.91±11.81*[(a,b,c)] (186.99, 236.82)
Serum Serotonin (ng/ml)	544.67±13.22 (510.68, 578.65)	282.83±15.46*[a] (250.47, 315.19)	266.94±13.94*[a] (239.01, 294.87)	192. 13±12.74*[(a,b,c)] (165.25, 294.87)
Stress Level Scores	58.67±3.60 (49.41, 67.93)	63.75±1.42 (60.77, 66.73)	71.98±0.77*[(a,b)] (70.38, 73.47)	79.78±2.53*[(a,b,c)] (74.44, 85.11)
VAS for Hunger	32.00±1.90 (27.12, 36.88)	50.15±3.22 (43.41, 56.89)	57.88±2.44*[a] (52.99, 62.76)	68.61±4.36*[(a,b)] (59.41, 77.81)
VAS for Desire to Eat	31.33±0.42 (30.25, 32.42)	52.20±3.74 (44.36, 60.04)	61.95±2.87*[a] (56.09, 67.71)	74.5±5.39*[(a,b)] (63.13, 85.87)

*p<0.05, a= compared with no/minimal stressed group, b= compared with mildly stressed group, c= compared with moderately stressed group

p<0.05) and desire to eat (0.216, p<0.05). Serum cortisol exhibited a strong positive correlation with BMI (r=0.274, p<0.05), stress level score (r=0.441, p<0.001) and VAS for hunger and desire to eat (r=0.285, p<0.05). Figure 2 illustrates the significant negative correlation with leptin and stress hormones (p<0.05)

Appetite measured by visual analog scale for hunger and desire to eat demonstrated highly significant positve correlation with the stress scores of various stress states (r=0.4612, r^2=0.2127, p<0.001) (Figure 2).

DISCUSSION:

A large and complex array of factors contributes to the obesity epidemic around the globe, including genetics, physiological and behavioral eccentricity of individuals by the influence of their social and physical environment. Our study addressed the status of stress levels contributing to the development of obesity in Pakistani adult female population, working 8 hours/day for more than 5 years. Mean BMI value suggested that most of women were overweight (27.28 ± 0.44 Kg/m^2). The scores obtained from