ENDOCRINAL ASSOCIATION OF HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS WITH OBESITY

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Abstract
Obesity is a serious health condition that has been affecting individuals of all ages worldwide. Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and chronic stress exposure are implicated as main contributing factors for obesity development. This study is a systematic review of the research, based on all possible pathways that are involved in obesity involving HPA. The arcuate nucleus (ARC) and paraventricular nucleus (PVN) are involved in the interaction of HPA activity and energy intake. Neuropeptide Y and corticotrophin-releasing hormone (CRH) regulate the feeding behavior. Insulin and leptin levels also affect the HPA axis through different pathways and play a significant role in the pathogenesis of obesity. This review shows the relationship of the HPA axis with obesity. By decreasing the activation or by inhibition of different pathways the causes of obesity can be controlled. Recent therapies are being developed to decrease food intake and body weight regulations.

Keyword: HPA axis, obesity, neuropeptide Y, glucocorticoid, insulin, leptin

I. Introduction

In human’s obesity is a major common pathological process. Obesity occurs due to stress, environmental and genetic factors, and now become a serious consequence for health (Aguilar et al., 2011). Nowadays the increasing ratio of obesity is mainly related to the sedentary lifestyle and dietary factors (González et al., 2012). The most important reason for this pandemic health problem is the increased consumption of food rich in saturated fats, carbohydrates, and decreased intake of vegetables (Lange et al., 2011).

Furthermore, the major health consequences of obesity are cardiac and vascular diseases, atherosclerosis due to lipid metabolism changes, changes in hormones that have high metabolic activity like insulin cause cellular insulin resistance, increased risk of Diabetes mellitus type 2 due to decreased glucose tolerance, increased stroke risk due to high blood pressure, hyperleptinemia, and deficiency of growth hormone. These changes are collectively called metabolic syndrome (Juonala et al., 2011).
Commonly obesity occurs due to the dysregulation of energy balance when energy intake exceeds the expenditure of energy and excessive energy is stored as fats (Tremblay et al., 2004). Modern society elements like western diet stress, depression, and sedentary lifestyle all may dysregulate the HPA axis and cause a positive energy balance and contribute to the development of obesity. HPA axis is an important neuroendocrine axis that plays a significant part in the regulation of energy balance and stress response by the regulated secretion of glucocorticoid like cortisol (Tsigos et al., 2002).

**Hypothalamic-pituitary-adrenal (HPA) Axis**

The key adaptive neuroendocrine system of the human body is Hypothalamic-pituitary-adrenal (HPA) axis. Adrenocorticotropic hormone (ACTH) regulates the glucocorticoid secretion that is critical to life and is much essential to maintain energy balance and mammalian response to stressors (Pedersen et al., 2001; McEwen, 2007; Lupien et al., 2011).

The HPA axis has main components that regulate each other through their secretions like paraventricularis hypothalamic (PVN) that secretes corticotrophin-releasing hormone and arginine vasopressin (AVP). The secretion of PVN and AVP stimulates the pituitary gland which releases ACTH, then with the stimulation of ACTH, the cortex of adrenal gland secretes cortisol in humans and corticosterone in rodents (Yen et al., 1998; Wolkowitz et al., 2009).

Sequentially, in a negative feedback loop, glucocorticoids act through the pituitary and limbic structures mainly the hippocampus to regulate the activity of the neuron that produces CRH in the PVN and thus regulate the whole HPA axis (Bale et al., 2004; Roper et al., 2011). After the release of cortisol, it is transported in circulation and directed to the target peripheral tissue after binding to the corticosteroid-binding globulins, where the activity of 11β-hydroxysteroid dehydrogenase (11β-HSD) enzyme decides its availability. The inactive cortisone is converted into active cortisol by 11β-HSD1 isoform and cortisol is converted into inactive cortisone with the help of 11β-HSD2 isoform (Nieuwenhuizen and Rutters, 2008).
The HPA axis activity is managed by the complex interaction of cortisol with central intra and extra hypothalamic sites (Warne, 2009). The intra hypothalamic sites like arcuate nucleus (ARC) and paraventricular nucleus (PVN) are involved in the interaction of HPA activity and energy intake. Glucocorticoid receptors are frequently present in both PVN and ARC (Reul and De Kloet, 1986). Both play a regulatory role in energy intake regulation (Könner et al., 2007; Obici et al., 2002), through the activation of ARC afferents, signals that represent the nutritional status rush toward the PVN directly or indirectly through neuroendocrine output signals then PVN stimulates gut hormone release including oxytocin, vasopressin, and CRH (Tasker, 2006). The PVN receives its foremost input from ARC, where Neuropeptide Y (NPY) and Agouti-related peptide (AGRP) are co-localized (Hahn et al., 1998).

NPY and AGRP are orexigenic peptide hormones, however NPY neurons stimulate the CRH neurons in PVN and CRH release is activated that eventually stimulate glucocorticoid release that in turn decrease the hypothalamic CRH release and stimulate NPY activity, thus favor energy intake stimulation, forming a positive feedback loop (Warne, 2009). The interaction between orexigenic NPY neurons and anorexigenic CRH is necessary for the maintenance of healthy body weight. The biochemical mechanism of stress eating is due to increased NPY
NPY concentration in response to stress. Obesity is caused due to this NPY increased concentration in stressed people (Dube et al., 2007).

The receptor for insulin and leptin regulates NPY/AGRP neurons both are present abundantly in ARC (Schwartz, 2000). Leptin and insulin signals inhibit the NPY/AGRP neurons and these neurons are activated under low concentration of insulin and leptin (Hahn et al., 1998; Sipols et al., 1995).

**Neuroendocrinal association of insulin and leptin with HPA axis**

**Association of insulin**

The receptors of glucocorticoids are excessively present in both PVN and ARC (Reul and De Kloet, 1986). Leptin and insulin circulate in proportion to body fat mass, in ARC they carry the signals for the energy status of the body. When the energy stores of the body are low, the concentration of insulin and leptin will also be low, which eliminates the inhibition within ARC, and feeding behavior is stimulated. Thus, insulin act on orexigenic NPY/AGRP neurons and directly inhibit them while exciting the anorexigenic POMC/cocaine & amphetamine-regulated transcript (CART) (Schwartz et al., 2003). On the central and peripheral level glucocorticoid interfere with the signaling of insulin. Centrally, glucocorticoids stimulate energy intake by reducing the antagonizing effect of insulin on NPY neurons (Sato et al., 2005). In the periphery, the constant concentrations of glucocorticoid are related to the increases in plasma insulin concentration (la Fleur et al., 2004).

Chronically augmented glucocorticoid results in diabetogenic effects not only through hyperinsulinemia but they also impair the insulin-induced translocation of intracellular glucose transporters and by interacting with receptor binding in the skeletal and liver muscles (Yi et al., 2012). Eliminating or reducing insulin action (either by insulin deficiency or insulin resistance) eradicates the inhibitory effect and glucocorticoids stimulate feeding behavior (la Fleur et al., 2004). Insulin resistance causes NPY to increase that increases feeding and lead to obesity.
Fig 2: Neuroendocrinal association of insulin

Association of leptin

Leptin is an adipokine secreted by adipocytes characterized by Friedman et al. Leptin is a protein that is codified by ob gene (Zhang et al., 1994). Leptin derived from Greek word leptos means lean and has a molecular mass of 16kDa, made of 167 amino acids. Energy metabolism is regulated by leptin, it increases energy expenditure. Leptin is a metabolic signal for energy sufficiency (Maffei et al., 1995).

There is a hypothesis that within hypothalamus leptin influences neuropeptides that are involved in the intake of food and energy expenditure, including neuropeptide Y(NPY) and corticotrophin release hormone (CRH) (Campfield et al., 1995; Rohner-Jeanreanud et al., 1996; Schwartz et al., 1996; Stephens et al., 1995; Wang et al., 1997). NPY causes an increase in food intake and decreases the expenditure of energy (Billington et al., 1994; Clark et al., 1984), while the action of CRH is opposite (Krahn et al., 1988; Rohner-jeanreanud et al., 1989). Leptin modulates energy balance by decreases the synthesis and secretion of NPY and it increases the synthesis and secretion of CRH.

Leptin level is low during the day while it increases during sleep, so leptin level shows circadian rhythms (Sinha et al., 1996). It is postulated that the rise of leptin at night suppresses the appetite. Sleep deprivation causes a vigorous decrease in leptin levels (Knutson and Van Cauter, 2008). Routine short sleep durations are correlated with
low leptin in the morning, which probably leads to an increase in appetite through the activation of ARC in the hypothalamus and successively increases food intake (Taheri et al., 2004). This reduction in leptin level may stimulate the intake of food and eventually increases the risk for obesity and metabolic diseases.

The decreased level of circulating soluble leptin receptors (SLR) is associated with obesity (Ogier et al., 2002). These receptors are protein in nature and they circulate in blood and are directly related to leptin function (Ogier et al., 2002; Elmquist et al., 1999). This state explains the resistance to leptin in obese patients because they have high leptin level and low SLR (Holm et al., 2011; Levin et al., 2004). Decreased transport of leptin across blood brain barrier and decreased capability of leptin to initiate hypothalamic signaling in diet induced obesity (Caro et al., 1996; El-Haschimi et al., 2000; Rhee et al., 2011; De Lartigue et al., 2011) may be critical factor in the pathological process of leptin resistance that leads to failure to moderately compensate for positive energy balance that leads to obesity and unwanted weight gain.

Fig 3: Neuroendocrinal association of leptin

**Novel therapies for obesity**

Recent pharmacological approaches to prevent obesity through manipulations of the HPA axis have attention on 11β-HSD inhibitors that allow tissue-specific variations in the concentrations of cortisol without affecting circulating level. A non-selective inhibitor carbenoxolone act on 11β-HSD1 and 11β-HSD2. Some studies show that this inhibitor lowers the expression of 11β-HSD1 in adipose tissues while some do not (Sandeep et al., 2005; Pereira et al., 2012). One study shows that after 7 days administration of 300 mg carbenoxolone reduces glycogenolysis and lowers the cholesterol level (Andrews et al., 2003).
Topiramate produced a successive weight reduction in an obese patient. Topiramate causes weight loss by increasing the expenditure of energy, an appetite suppressant by decreasing caloric intake, and decrease energetic efficiency (Richard et al., 2000).

Genetically deleted and pharmacologically blocked NPY Y1 and Y5 receptors help to reduce weight and reduce food intake (Erondu et al., 2006). A selective antagonist for NPY Y5 receptor S-2367, known as velneperit induces weight loss (Sargent and Moore et al., 2009). It inhibits the binding of NPY to receptor and satiety induced.

GLP-1 (Glucagon-like peptide 1) receptors are present in brain activity through various neural circuitry involving peripheral GLP-1 signaling control body weight and food consumption regulations (Kanoski et al., 2016). Liraglutide (3.0 mg once-daily subcutaneous), is a GLP-1 analog and recently approved for the obesity treatment (Davies et al., 2015; Wadden et al., 2015).

II. Conclusion
Obesity occurs due to the dysregulation of energy balance. HPA axis produce orexigenic NPY and anorexigenic CRH that regulates energy balance. Insulin and leptin circulate in proportion to body fat mass, in ARC they carry the signals for the energy status of the body. Insulin and leptin have an inhibitory effect on NPY neurons. Their circulatory level determines the food intake or energy sufficiency. Insulin resistance and leptin resistance cause the increased food intake to lead to obesity. In the periphery inactive cortisone is converted into active cortisol by 11β-HSD1 isoform and cortisol is converted into inactive cortisone with the help of 11β-HSD2 isoform. The over-activity of these enzymes can cause obesity by disturbing the food intake balances. A non-selective inhibitor carbenoxolone act on 11β-HSD1 and 11β-HSD2, carbenoxolone reduces glycogenolysis and lowers the cholesterol level. Novel pharmacological studies show that the drugs like topiramate help to lose weight and future researches helps to produce targeted drugs that target the HPA axis for the control of obesity.

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