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Influence of Regular Physical Exercise on Increased Caloric Intake Triggered by Stressors

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Abstract

Benite-Ribeiro SA, Santos JM, Soares-Filho MC, Duarte JAR. Influence of Regular Physical Exercise on Increased Caloric Intake Triggered by Stressors. ARBS Annu Rev Biomed Sci 2010;12:30-45. Social distress may be a major source of allostatic load in contemporary life, contributing to the development of metabolic-related diseases in industrial societies. Indeed, the standard signals for vigilance and hypo-satisfaction, e.g. cortisol, seem to affect the individual feeding behavior, increasing the preference for high-caloric food. However, this preference can surpass the stressful period itself and become a habit, leading to several negative metabolic implications such as the enhanced risk to develop metabolic syndrome. Therefore, it is important to find effective ways to offset the harmful consequences of allostatic load on feeding. In particular, physical exercise has proven to be capable of counteracting the negative effects of psychosocial stress on feeding behavior. Consequently, physical exercise may be used to prevent the development of metabolic-related diseases, thus reiterating its recommendation as a way of protecting the organism against the stress side effects. Here, we analyze the outcomes of stress on feeding behavior (namely the enhanced calories intake) and the effect of physical exercise practice on food intake, considering the underlying signaling processes involved.

Keywords: HPA axis, food intake, leptin, insulin, physical activity, comfort food.

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1. Introduction

In the 1930s, Hans Selye (Selye, 1998) was the first to describe functional alterations of both the hypothalamo-pituitary-adrenal (HPA) axis and the sympathetic system caused by exposure to an unavoidable aversive situation (real or perceived). Because this response is independent of nature of the stimulus, Selye called this non-specific response the "general adaptive syndrome" (stress syndrome). This concept has been accepted for decades; however, it is currently a matter of debate, and a new model has been suggested.

The main reason for this debate is the central construct of Selye's model, which is based on the theory of homeostatic maintenance. The homeostasis concept (stability through constancy) is based on a proposal of Claude Bernard, in which vital regulatory mechanisms aim to preserve the constancy of the internal environment. Based on this concept, it might be assumed that the purpose of physiological regulation is to clamp each internal parameter at a "setpoint" by sensing deviations and providing feedback to correct errors; however, in physiology, there is a cumulative set of evidence showing that parameters are not constant. Variations, rather than signifying error, apparently exist to reduce error (Sterling, 2004). In fact, by an opposite view, the allostasis concept (stability through change) proposed by Sterling and Eyer (McEwen, 1998) state that the main aim of regulatory mechanisms is not to establish constancy, but it suggests that fitness under natural selection aims towards efficient regulation to prevent errors and minimize costs. Actually, most biologists agree that the main objective of regulatory systems is not constancy but both survival and reproduction. Obviously, some parameters must be closely regulated, such as temperature, pH and energy for the mammalian brain. However, to ensure fitness, the system works by using information gathered a priori to predict demand and then to adjust all parameters. Hence, allostasis considers a deviation from a setpoint as a response to predictions in order to meet anticipated demands, instead of a failure to defend the setpoint (Sterling, 2004).

Allostasis involves energy-flow adaptations (McEwen, 2005), including appetite and food intake, as well as energy storage and mobilization (Adam & Epel, 2007). The HPA axis and the cardiovascular, metabolic, immune and autonomic nervous systems protect the body by responding to internal and external aversive conditions; the price of this accommodation to stressors is called the allostatic load, defined as the wear and tear resulting from chronic over- or under-activity of allostatic systems (Bhatnagar & Vining, 2003; McEwen & Wingfield, 2003). The allostasis concept also attributes diseases, such as essential hypertension and type 2 diabetes, to sustained neural signals that arise from unsatisfactory social interactions. The homeostasis model attributes all pathologies to "defects" in reaching the set point, although this cannot explain the origin of essential hypertension, for example. Conversely, the allostasis model proposes that hypertension emerges from the combined responses of multiple neural effectors to a prediction of a "need for sustained vigilance" (Sterling, 2004).

Adaptation in the face of potentially stressful challenges involves activations of neural, neuroendocrine and immune mechanisms. The primary mediators of allostasis include the HPA axis hormones, catecholamines and cytokines, among others (McEwen, 2005). When these adaptive systems are turned on and turned off again efficiently and not overly frequently in the short term, the body is able to cope effectively with challenges that it might not survive, as an effective adaptive response. These allostatic mediators help the organism to face a brief aversive situation with vigilance. In some circumstances, such as hypervigilance, the regulatory systems may either be overstimulated or even work abnormally and favor the development of organic injuries, which was designated by McEwen and colleagues as "allostatic load" or the price for adaptation. Over long periods, allostatic load can lead to diseases (McEwen, 1998), such as metabolic syndrome and hypertension and cardiovascular diseases (Sterling, 2004). Many behaviors that regulate physiology are driven less by a promise of reducing anxiety than by an expectation of "reward" – some outcome that leads to a feeling of satisfaction. This feeling depends on neural activity in the ventral tegmental area of the midbrain, the nucleus accumbens and the prefrontal cortex. Thus, hyposatisfaction also triggers allostatic loads and elevates cortisol and related signals, the same way as physically and psychologically aversive agents. Because satisfaction cannot be stored and must be continuously renewed, it can be a potential source of allostatic load; for people of lower socioeconomic status, potential sources of satisfaction are less available, but food is abundant and cheap. So the allostasis model suggests that the brain overrides the local negative feedback (metabolic satiety signals) that controls what people eat (Sterling, 2004); overeating causes obesity, metabolic syndrome and cardiovascular diseases (Brindley & Rolland, 1989; Dallman et al., 2004; Hu et al., 2006; Torres & Nowson, 2007; Haskell-Luevano et al., 2009).

Levels of regular physical activity seem to directly or indirectly influence these mechanisms. Indeed, allostatic load in the presence of physical inactivity is associated with an increased risk for mental and physical illness; Tsatsoulis and Fountoulakis (2006) advocate that the practice of regular physical exercise may have a protective role in alleviating allostatic load and its negative health consequences. In fact, consistent findings suggest that physical exercise (PE) can lessen the harmful effects of allostatic load (Zheng et al., 2006). Further, the burden of a disease or an allostatic load is mainly set by two factors: the individual's perception of the stressful situation (mental fitness) and his general physical condition (physical fitness). Thus PE, or rather a good physical condition, could help an individual endure a chronic stressful situation (Tsatsoulis & Fountoulakis, 2006). Considering that improvement of physical and physiological conditions are caused by regular PE, is it wise to suppose that regular PE practice can counterbalance harmful allostatic load to some extent (aside from improvements in physical conditions)? In this paper, we will analyze the effects of allostatic load on feeding behavior and the effects of PE on enhanced caloric intake triggered by stress.

2. Allostatic Load and Overeating

Levels of stressful life events are a common phenomenon in the industrialized world and are considered to be responsible for the development of human psychopathologies such as anxiety and clinical depression (Kessler et al., 1985). "Psychosocial stressors" are the unpleasant stimuli prevailing in humans' contemporary lives and are present at a variety of degrees in distinct individuals and/or groups (Tamashiro et al., 2005). The social inequalities of Westernized societies are important predictors of disease (Sapolsky, 2005). However, low social status *per se* does not seem to account entirely for the effects on allostatic load level, but rather it is additive or interactive with the material consequences of the aforementioned low social status (Blanchard et al., 2001).

Under stressful conditions such as hypervigilance or hypo-satisfaction, the HPA axis is overactivated by one evolutionary adaptation - disorders of circadian and ultradian rhythms - (Harper et al., 1996; Herman et al., 2003) and the negative feedback control becomes faulty (Engelmann et al., 2004). These mechanisms are essential for an animal's survival during an emergence period (Bjorntorp, 2001). However, in a chronic state, in which glucocorticoid (GC) concentrations are elevated, corporal energy resources are redirected (Pecoraro et al., 2005; Tosevski & Milovancevic, 2006) and other markers can occur, such as increased glycemia (Epel et al., 2004; Buren & Eriksson, 2005); proteolysis, lipolysis and glycogenolysis (Widmaier et al., 1992), behavioral depression (Baranyi et al., 2005; Johnson et al., 2006; Bao et al., 2007) and negative effects on both memory and cognition (Sapolsky, 2000).

The overeating behavior triggered by allostatic load is common in both men and women (Van Strien et al., 1986; Greeno & Wing, 1994), overeaters exhibit eating preferences for fat-rich and highly palatable foods (the so-called comfort foods - CF) (Dallman et al., 2003); this happens in around 70% of the human population (Manson et al., 1990; Adam & Epel, 2007). Overeating behavior is apparently due to effects of GCs on the nucleus accumbens (NAcs). In some persons depression episodes and severe adverse life events may lead to anorexia nervosa (Ivarsson et al., 2000), but this will not discussed in the present paper. A variety of environmental stressors have shown to increase the reward effects of addictive drugs (Brady & Sonne, 1999; Lu et al., 2003), and to increase food intake (Mayer & Thomas, 1967; Rowland & Antelman, 1976; Oliver et al., 2000; Dallman et al., 2005). Increases in GC effects on the NAcs promotes elevations of dopamine (DA) within the shell of the NAcs (Thierry et al., 1976), which increases the reward effects and increases the salience or motivation for drugs of addiction and food (Tidey & Miczek, 1997).

Indeed, greater sensitization of the reward system can lead to excessive intake of highly palatable and caloric food (Dallman et al., 2003), which together with high GC and insulin plasma concentrations contributes to visceral fat distribution (Dallman et al., 2004; Pecoraro et al., 2004; Dallman et al., 2005). Moreover, there is a risk of metabolic injury or increasing the severity of pre-existing conditions related to metabolic deregulation (Buren & Eriksson, 2005; Abraham et al., 2007), which is exacerbated by high-calorie food intake accompanied by abdominal or visceral fat (AF) deposition, weight gain, and obesity (Dallman et al., 2004; Pecoraro et al., 2004). Cortisol is likely to favor visceral obesity because it regulates the differentiation and function of the adipose tissue. Furthermore, because clinical observations have long suggested a connection between AF and Cushing Syndrome (Bjorntorp & Rosmond, 2000).

The mechanisms by which GC exacerbate feeding behavior are controversial and will be briefly

discussed in the next section; however, the standard mechanisms of food-intake control will be addressed first. Obviously, it is important to note that these behavioral changes depend closely on individual genetic predispositions (Levin, 2007) and personality developments (Wolf & Crowther, 1983).

3. Control Mechanisms of Food Intake

Feeding behavior is evidently critical to survival because of its effects on energy allostasis. In this way, it is thought that the amount of energy consumed must be equivalent to the amount of energy spent; to assure this, there are a number of physiological signals that regulate food intake in long- and short-term fashions (Woods et al., 1998). Short-term regulation is mainly related to the prevention of overeating, and long-term regulation is related to the prevention of overeating and maintenance of normal energy stores in fat form (Konturek et al., 2005).

A range of meal-generated signals, called satiety factors, sets meal termination and hence meal size. In the prandial or post-prandial phases, satiety signals start in the gastrointestinal (GI) tract. Mechanoreceptors, which detect distension or food contact with the parts of GI such as the tongue, the oropharynx, the stomach, and the duodenum, might serve as satiety signals. Alternatively, chemoreceptors, which detect chemical presence of different sorts of nutrients that are secondary to food digestion, or the hormones and substances released by liver, pancreas or duodenum or even by the absorption of nutrients, might also generate satiety signals (Woods et al., 1998; Konturek et al., 2005). After reaching the brain through visceral afferent nerve fibers and through the blood, all these signals interact to finish a meal (Woods et al., 1998).

Acquisition of energy is regulated in a short-term way by hormones derived from the GI system such as ghrelin (Ariyasu et al., 2001; Ellacott & Cone, 2004), cholecystokinin (CCK) (Gibbs & Smith, 1977; Murphy & Bloom, 2004), and the bombesin family (Merali et al., 1999). Regulation of food intake must also respond to the long-term energy status of the organism through factors derived from energy-storage processes and from the status of the body's energy stores, such as fat storage or glucose-metabolism indicators (Halford, 2001), leptin from the adipocytes (white adipose tissues) (Moran & Phillip, 2003; Bojanowska & Nowak, 2007), and insulin or glucagon from pancreatic b and a cells, respectively (Geary, 1999; Moran & Phillip, 2003; Konturek et al., 2005; Bojanowska & Nowak, 2007).

These short or long-term signals are conveyed to the central nervous system (CNS) and integrated specifically by the hypothalamus to regulate the acquisition and expenditure of energy (Peruzzo et al., 2000). The arcuate nucleus (ARC) and other hypothalamic nuclei have classically been associated with regulation of body weight over the long term (Ellacott & Cone, 2004; van den Top et al., 2004; Konturek et al., 2005). Although they are regarded as structures linked to the regulation of meal initiation and termination, the role of nucleus of the tractus solitarius (Fan et al., 2004) and other brainstem nuclei (Grill & Kaplan, 2002; Berthoud & Morrison, 2008) will not be analyzed in the present paper.

Despite the complexity of the neuronal circuit for appetite control, the ARC of the hypothalamus is an important integration site for a number of neurological and circulatory factors (Morrison et al., 2005; Ellacott & Cone, 2006; Millington, 2007). In the ARC, there are two main populations of neurons involved in food intake regulation: neurons that synthesize anorexigenic neuropeptides including the proopiomelanocortin (POMC) and cocaine-and amphetamine related transcript (CART), and neurons that synthesize orexigenic neuropeptides such as neuropeptide Y (NPY) and agouti-related peptide (AgRP). The POMC/CART and NPY/AgRP neuronal populations project to the PVN or the lateral hypothalamus (LH), respectively. These areas are known to be essential in the regulation of food intake and energy expenditure (Grill & Kaplan, 2002; Murphy & Bloom, 2004; Dhillo, 2007; Millington, 2007). Neurons of the PVN express anorexigenic peptides, whereas LH neurons express orexigenic peptides. Hence, the equilibrium between outputs from the PVN and the LH plays a critical role in regulating feeding and energy allostasis (Figure 1).

Although this review aimed to focus on the control of caloric intake as mediated by insulin and leptin, whose effects on the control of food are affected by stress, some signals of short-term control will be briefly addressed.

Some of the short-term signals of food intake control are ghrelin, CCK and the bombesin family (bombesin, grastrin-releasing peptide and neuromedin B). The acylated form of the ghrelin, released during fasting and/or undernutrition, is a peptide produced mainly by oxyntic cells of the stomach and at low levels in the small intestine. Ghrelin induces food intake and positive energy balance via membrane potential oscillations (regular bursts of action potentials) of the neurons that express NPY and AgRP, which induces

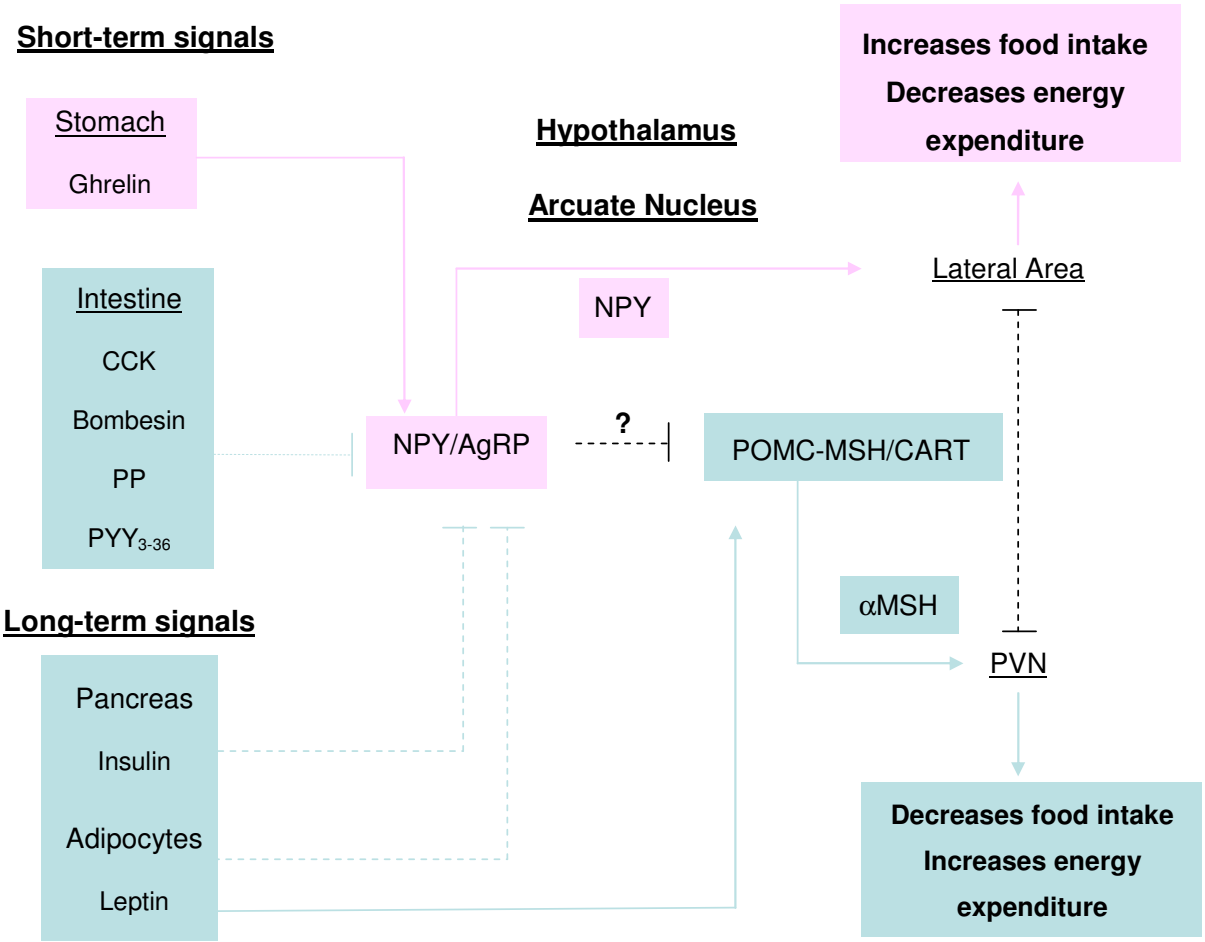

Figure 1: The short and long-term signals that control the food intake and the energy allostasis. The dotted lines refer to inhibition and the solid lines refer to excitation. The short-term control is performed by ghrelin, CCK, Bombesin, PP, PYY3-36 and GLP1 witch affect the NPY/AgRP neurons, but only ghrelin has orexigenic effect. Insulin and leptin inhibit NPY secretion whereas leptin also stimulates the POMC/CART anorexigenic control system. It has also been proposed that AgRP is a functional antagonist to the melanocortin receptors. NPY – neuropeptide Y; AgRP – agouti-related peptide; POMC – proopiomelanocortin; MSH – melanocyte-stimulating hormone; CART - cocaine-and amphetamine related transcript; PVN – paraventricular nucleus; CCK – cholecystokinin; PP – pancreatic polipeptide; PYY 3-36 – peptide YY; GLP1 – glucagon like peptide1.

their orexigenic effect on LH (Ariyasu et al., 2001; Inui et al., 2004; Asakawa et al., 2005; Stock et al., 2005). On the other hand, cholecystokinin is a GI satiety signal released from the duodenum that is stimulated by the presence of fat and proteins in the intestinal lumen. It was the first of the gut signals to be described to terminate feeding (Gibbs & Smith, 1977; Murphy & Bloom, 2004). Bombesin (BN) is polypeptide initially isolated from amphibian skin. In mammals, several BN-like peptides (e.g., Gastrin Releasing Peptide [GRP] and neuromedin B and C) are released from the GI tract in response to ingested food, and have been shown to reduce food intake (Gibbs et al., 1979).

For long-term energy control, leptin and insulin are the main signals. Both leptin and insulin circulate at concentrations that are proportional to body fat (Considine et al., 1996) and affect energy balance by reducing food intake and increasing energy expenditure.

Plasma levels of leptin follow a diurnal pulsating rhythm, which has not yet been fully elucidated. It is not still clear whether this rhythm is under direct control of the biological clock or whether it is a consequence of circadian rhythms of hormonal release and/or behavior. In diurnal animals, at midnight, during early morning, and in a moment between noon and mid-afternoon there is an increase of leptin levels. Because increases in nocturnal leptin secretion are modulated by feeding and prevented by fasting, the underlying mechanisms of the leptin rhythm are probably more closely dependent on meal-related timing than on the circadian clock or sleep cycles (Kalsbeek et al., 2001). Caloric intake is another important factor in leptin release regulation. Reductions in caloric intake promote lower fasting serum leptin levels than do increases in energy intake (Considine et al., 1996).

Leptin decreases food intake and increases energy expenditure through its effects on hypothalamic ARC (Jeanrenaud & Rohner-Jeanrenaud, 2001; Moran & Phillip, 2003). Erickson et al. (1996) advocate that leptin's final actions do not rely on a NPY decline (Erickson et al., 1996), but on its actions on the long form of the leptin receptor (LEPRB). It is also known that activation of the Janus-activated kinase (JAK) signal transducer by leptin and of the activator of transcription 3 (STAT3) signaling increases POMC neuronal activity in the ARC (Jeanrenaud & Rohner-Jeanrenaud, 2001; Moran & Phillip, 2003). The consequent results are a decrease in food intake and in expenditures of energy. However, other researchers advocate that leptin also inhibits hypothalamic Npy and AgRP gene expression and activates neurons within the PVN (van den Top et al., 2004; Morrison et al., 2005) via slow, progressive hyperpolarization (van den Top et al., 2004). In addition, Morrison et al. (2005) suggest that leptin activation of STAT3 is insufficient to inhibit expression of NPY or AgRP in the absence of the phosphatidylinositol 3-OH-kinase (PI3K) signaling activated by insulin (Morrison et al., 2005); yet it is possible that leptin also induces activation of PI3K (Plum et al., 2006).

Insulin is acutely secreted during and after a meal, whereas leptin is not. Insulin is mainly secreted from pancreatic beta cells and to certain extent from adipocytes. Similarly to leptin, circulating insulin concentrations are proportional to body adiposity, as its central receptors are located within hypothalamic ARC (Woods et al., 1998; Ellacott & Cone, 2006). It is recognized that insulin crosses the BBB and penetrates the CNS by a saturable, receptor-mediated transport process across capillary endothelial cells within the brain (Woods et al., 1998). This process induces tyrosine phosphorylation of the insulin receptor (IR) as well as insulin receptor substrate (IRS) 1 and 2, which, in turn, activate PI3K and protein kinase B (Akt) in the ARC (Niswender & Schwartz, 2003). The end result is that insulin decreases NPY gene expression in the ARC (Schwartz et al., 1992; Dallman et al., 1995; Niswender et al., 2004), therefore reducing food ingestion.

Plum et al. (2006) advocate that, both insulin and leptin increase the expression of POMC and decrease the expression of AgRP. Insulin binds to its receptor on POMC and AgRP neurons, stimulates receptor autophosphorylation, and activates the signal cascade (Plum et al., 2006). Both insulin and leptin signals converge at the level of PI3K (Xu et al., 2005); however, the hormones elicit distinct signaling events downstream of PI3K (Plum et al., 2006). Deficiency of either hormone results in hyperphagia and obesity (Bray & York, 1998; Morton, 2007).

4. The Effects of Glucocorticoids on Feeding

Increases in circulating levels of GC promote weight gain, centrally localized fat increments, hyperinsulinemia, hyperleptinemia, hyperglycemia, hypercholesterolemia, hypertriglyceridemia, and constitute risk factors for developing metabolic syndrome (Brindley & Rolland, 1989; Zakrzewska et al., 1999; Anagnostis et al., 2009). These effects can occur because the HPA axis and peripheral tissues become over-responsive to GC and because GC modulate the effects of NPY, insulin and leptin on eating behavior and energy-expenditure control when the systems become deregulated (Newcomer et al., 1998; Cavagnini et al., 2000; Pecoraro et al., 2004; Adam & Epel, 2007), raising food intake (Cavagnini et al., 2000).

Increasing circulating levels of GC exert diabetogenic effects through impairment of insulin-stimulated glucose uptake in peripheral tissues and promote increasing insulin plasma concentration, possibly because of the former's anti-insulin effect on the liver (Rosmond, 2003; Buren & Eriksson, 2005; Eriksson, 2007).

Another outcome of insulin properties can be observed when GC are regenerated in omental fat via the enzyme 11b-hydroxysteroid dehydrogenase type 1 (11bHSD1) (Bujalska et al., 1997; Masuzaki et al., 2001), which regulates access of GC to receptors in peripheral and brain tissues (thus strengthening the effects of GC), as they are able to regenerate GC from the inactive form in omentum (but not in the subcutaneous fat) (Bujalska et al., 1997). Consequently, this hormone is secreted directly to the liver via the portal vein (Masuzaki et al., 2001) and favors increased insulin secretion due to the anti-insulin effects of GC on this organ (Rosmond et al., 1998). Hepatic insulin resistance, as well as high plasma levels of both GC and insulin, is strongly associated with abdominal obesity, which occurs regardless of raised caloric food intake, such as in Cushing's disease (Delaunay et al., 1997; Michailidou et al., 2007). Yet the overexpression of 11bHSD1 in adipose tissue has been also correlated with hyperphagia (Masuzaki et al., 2001). Considering that 11bHSD1 derived from omental fat also causes hyperphagia, visceral obesity and energy deposit reshaping even in the absence of augmented CF intake, GC released from the omental fat might have a remarkable impact on systemic biology.

Regardless of the mechanisms of insulin resistance, the result is a misbalance between insulin and GC. Consequently, misbalances in energy equilibrium and feeding behavior. Increased GC concentration augments total caloric intake, whereas increased insulin levels prompt a higher preference for fat intake (la Fleur et al., 2005) and therefore raise calorie ingestion.

Larger GC doses may elevate body mass index (Bray et al., 1989) and leptin concentration, a state called leptin resistance (Zakrzewska et al., 1997). In this condition, leptin cannot efficiently reduce caloric intake, and overeating may occur (Zakrzewska et al., 1999).

Zakrzewska et al. (1999) assessed food intake in normal rats that had been received an intracerebroventricular dexamethasone infusion. These rats sharply increased their food intake relative to the control group and gained approximately 15 g by the end of the experimental period, which was shorter than three days. Meanwhile, control rats that were injected with a vehicle gained only 5 g during the same period. Plasma leptin levels rose from the first experimental day and reached, by the end, a value almost five times higher than that of the control group. The authors suggested that the rise in leptin levels was due to the intracerebroventricular glucocorticoid-elicited hyperinsulinemia, which triggered *ob* gene expression in adipose tissue and leptin secretion (Zakrzewska et al., 1999), in accordance with others studies (Cusin et al., 1995; Saladin et al., 1995). The stimulatory effect of intracerebroventricular glucocorticoids on food intake was a result of higher NPY levels in the arcuate nucleus. Despite increased insulin and leptin levels, the insulin NPY-inhibitor effect is not valuable in the presence of GC, and the exacerbated leptin levels are not able to increase POMC expression or decrease AgRP expression (Zakrzewska et al., 1999).

Morioka et al. (2007) suggested an additional interaction between insulin and leptin. In their opinion, increased leptin plasma concentrations must affect insulin release in a complex system within the b cells. In lean animals, leptin inhibits insulin secretion and thus protects the cells from the adverse effects of over-nutrition (Morioka et al., 2007). Adenosine-5'-triphosphate (ATP)-sensitive potassium channels (KATP) are responsive to ATP/ADP ratios, fatty acids and their derivatives. An increased ATP/ADP ratio stimulates depolarization of the b cell membrane via the closure of KATP channels; the result is a decrease in efflux of K+. Depolarization opens voltage-dependent calcium channels, and the intracellular levels of Ca2+ increase. The Ca2+ binds calmodulin and activates Ca2+/calmodulin-dependent protein kinase; protein phosphorylation results in insulin secretion (Kieffer & Habener, 2000). When hyperphagia causes over-nutrition, the resulting hyperleptinemia attenuates insulin secretion by hyperpolarizing the b cell membrane, by enhancing the KATP activity, or by decreasing the channel's sensitivity to the ATP/ADP ratio (Niswender & Magnuson, 2007). In a lean animal, this is a logical control system because insulin is lipogenic and leptin's secretion is directly proportional to the corporal adipose mass. Furthermore, leptin, in addition to its effect of reducing food intake, also restrains insulin secretion and lipogenesis. However, in obese people, this control is ineffective and both hyperinsulinemia and hyperphagia occur, in spite of hyperleptinemia (Zakrzewska et al., 1999; Nonogaki et al., 2007).

In conclusion, the interactions between the three hormones raise food intake of preferably caloric foods, which this often leads to abdominal fat accumulation and metabolic disease.

5. Physical Exercise versus Allostatic Load

Stress-related disorders have been often treated by specific drugs and therapies; however, valuable effects of PE have been noted in both behavior and emotion. In depression-suffering individuals, PE is an important instrument for improving depression symptoms (Babyak et al., 2000; Dunn et al., 2005). Furthermore, it has been verified in rats that PE can revert the harmful effects of allostatic overload on mood and behavior (Moraska & Fleshner, 2001; Greenwood et al., 2003; Zheng et al., 2006). It is important to point out that some studies detected increases in plasma concentrations of GC that were mediated by PE. Moreover, it is alleged that GC play an important role in allowing the body to cope with stress because they induce gluconeogenesis, which protects not only against the source of stress itself (in this case the PE) but also against inflammatory reactions and immune system activation (de Vries et al., 2000).

In an elegant experiment, Droste et al. (2003) observed that corticosterone plasma concentrations and adrenal hypertrophy degrees were higher in trained (voluntary exercise) than in sedentary mice during exercise protocols and during evaluation of responses to restraint (forced swimming). However, when animals were submitted to others' aversive situations (e.g., a novel environment), trained animals displayed lower corticosterone plasma concentrations than the sedentary ones. One striking parallel between the antidepressant effects of voluntary PE and those of antidepressant drugs is a reduction in CRH mRNA expression in the hypothalamic paraventricular nucleus (PVN) (Droste et al., 2003).

Likewise, Park et al. (2005) observed, in trained Sprague-Dawley rats, both a decline in GC receptor (GR) gene expression in the PVN and a rise in hypothalamic CRH mRNA expression, revealing a mechanism for the transient increase in basal HPA axis activity. The comparisons between rats subjected to forced swimming and sham-swimming rats (animals placed in water tanks for the same amount of time as the exercised rats, but without weights) showed that the sham-swimming rats did not exhibit the HPA axis adaptation displayed by the trained ones. While the trained rats adapted to both the PE protocols and the restraint, the sham rats did not. In addition, no change was detected in mineralocorticoid-receptor mRNA levels in the hypothalamus of the trained rats; conversely, a decline was seen in the hypothalamus of sham rats. This is important because mineralocorticoid receptors (MRs) are occupied at low GC concentrations, which modulates the tonic regulation of HPA axis activity (Park et al., 2005).

A number of studies on humans demonstrate reductions in plasma cortisol levels or in pituitary sensitivity to the GC, in both endurance-trained men and women (Duclos et al., 2001; Duclos et al., 2003; Hershberger et al., 2004; Jurimae et al., 2006). Meanwhile, there are few studies on the effects of PE on the HPA axis in sedentary as opposed to trained persons. Nonetheless, two reported a drop in plasma cortisol concentration after only a few weeks of training (Helyar et al., 1997; Chwalbinska-Moneta et al., 2005).

Chronic stress also has deleterious effects upon the hippocampus; GC decrease the expression of mRNA that encodes brain-derived neurotrophic factor (BDNF) (Berton et al., 2006; Duman & Monteggia, 2006; Gronli et al., 2006). In adults, BDNF is responsible for maintaining the morphology and viability of hippocampal neurons and influences synaptic transmission, learning and memory (Smith et al., 1995; Schaaf et al., 1999). Furthermore, BDNF lowers susceptibility to depression. In depressed subjects, there is a noticeable drop in the amount of BDNF and other neurotrophic factors in the limbic brain regions related to depression, such as the amygdala, prefrontal cortex and hippocampus. Antidepressant treatments revert or lessen this stress-induced fall in the BDNF expression (Duman & Monteggia, 2006). Physical exercise, as well as antidepressant drugs, causes BDNF upregulation (Neeper et al., 1995; Neeper et al., 1996; Oliff et al., 1998; Adlard & Cotman, 2004; Schulz et al., 2004; Sarbadhikari & Saha, 2006; Soya et al., 2007).

It has long been assumed that PE increases energy expenditure, but recently it has been suggested that PE also affects appetite and reduces food intake (Bi et al., 2005; Flores et al., 2006; Cintra et al., 2007).

In brief, concerning energy expenditure, regular PE practice might mitigate the harmful effects of stress on visceral fat and obesity. Regular PE plays an important role in weight loss and long-term weight maintenance, as shown in individuals who have maintained successful weight loss (at least 10% of initial body weight) for more than a year when engaged in regular and extensive PE programs (Ross et al., 2000; Wing & Hill, 2001). A further effect of PE on leptin and insulin occurs via the muscle interleukin 6 (IL-6)-releasing pathway that is formed during PE (Pedersen et al., 2004). Sensitivity of the hypothalamus to leptin and insulin is raised by IL-6, which increases energy expenditure (Pedersen et al., 2004; Flores et al., 2006).

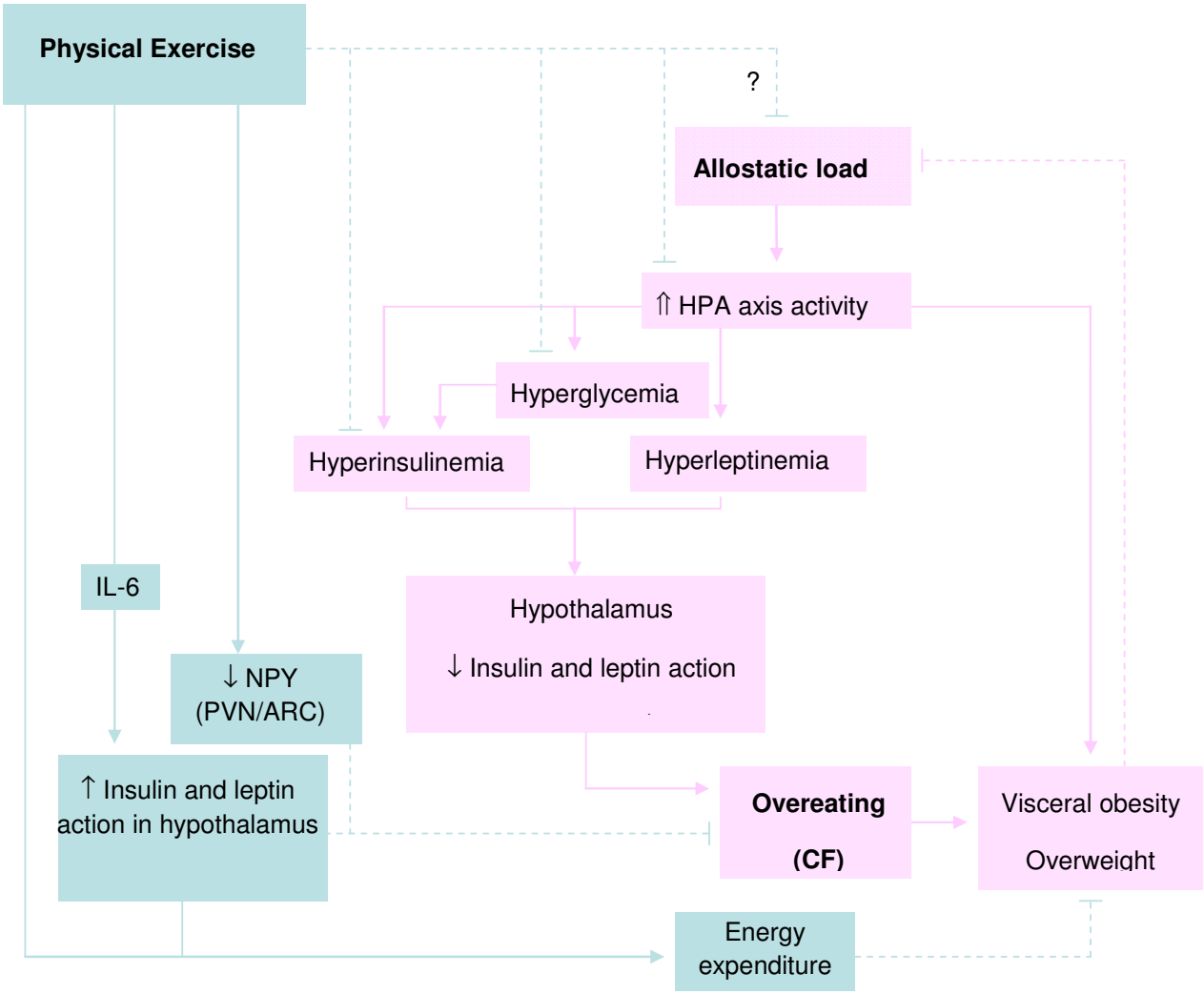

Figure 2: The effect of both the allostatic load and physical exercise on food intake, body weight and visceral obesity. The dotted lines refer to inhibition and the solid lines refer to stimulation. An allostatic load activates the HPA axis leading to a higher plasmatic glucocorticoids concentration. The rise in glucocorticoids concentration promotes an increase in leptin and insulin hormonal concentrations, as well as hyperglycemia which reinforces insulin secretion. The insulin and leptin actions on the ARC-Hypothalamus become impaired inducing a drop in the anorexigenic peptide secretion POMC as well as an increase in secretion of the orexigenic peptides NPY e AgRP. The imbalance between the orexigenic and anorexigenic peptides will result in overeating and a dietary preference for Caloric Food (CF), resulting in visceral obesity and overweight body. CF intake and abdominal fat deposition seem to improve the unpleasant psychological feeling caused by the allostatic load. On the other hand, the physical exercise practice decreases not only glycemia and glucocorticoids secretion but also insulinemia and leptinemia. These effects improve the insulin and leptin signalling process in the ARC and stabilize the POMC, NPY and AgRP secretions, resulting in beneficial effect on the control of food intake. It is likely that physical exercise acts directly on the NPY decreasing its secretion and diminishing the overeating behavior. Moreover, physical exercise stimulates production and secretion of the IL-6 (skeletal muscle) which improves the insulin and leptin signaling process in the hypothalamus, raising the energy expenditure and decreasing the food intake.
HPA- hypothalamo-pituitary-adrenal; NPY – neuropeptide Y; AgRP – agouti-related peptide; POMC – proopiomelanocortin; PVN – paraventricular nucleus; ARC – Arcuate Nucleus; IL6 – interleukin 6.

Regarding the regular PE effects on caloric intake, in particular the overfeeding triggered by allostatic load, there are few studies on the mechanisms by which exercise leads to reductions in appetite. However, there are reports indicating reductions in NPY expression in both the PVN and ARC (Shin et al., 2003) or increases of phosphorylation or activities of several proteins involved in leptin and insulin signal transduction in the hypothalamus, which improves central insulin and leptin signaling processes (Flores et al., 2006). The outcomes are decreases in circulating insulin concentration and food intake (Figure 2).

In Shin et al. (2003), sedentary diabetic rats (induced by streptozotocin) showed enhanced NPY expression in the PVN and ARC, whereas in diabetic trained rats there was a suppression of the diabetes-induced increment in NPY expression. In addition, animals exercising at moderate (running at a speed of 5 m/min for the first 5 min and at 8 m/min for the next 5 min, followed by running at 11 m/min for 20 min) and heavy (running at 5 m/min for 5 min, at 8 m/min for the next 5 min, and at 16 m/min for the last 20 min) intensity levels showed a minor suppression of NPY expression compared to animals trained at light intensity (5 m/min for 30 min), indicating that exercise intensity is an important factor for the modulation of NPY expression in the ARC of diabetic rats (Shin et al., 2003) and increasing BDNF expression.

Flores et al. (2006) demonstrated that intracerebroventricular insulin or leptin infusion, at doses that did not alter insulinemia or leptinemia, reduced food intake only in exercised rats, in comparison with sedentary rats. Exercised rats showed marked increases in the phosphorylation and activities of several proteins involved in leptin and insulin signal transduction in the hypothalamus. There was an increase in PI3-kinase activity in exercised rats after infusion of leptin and insulin that increased responsiveness to leptin and insulin in the exercised animals (Flores et al., 2006). As mentioned earlier, insulin and leptin signals converge at the level of PI3K (Xu et al., 2005) and induce reduction of appetite.

In humans, the existence of melanocortin-4 receptor single-nucleotide polymorphisms has been observed in obese patients (Vaisse et al., 1998; Krude & Gruters, 2000; Mergen et al., 2001). To clarify its importance, Haskell-Luevano et al. (2009) analyzed the effect of the voluntary exercise on food intake in melanocortin-4 receptor (MC4R) knockout mice. Initially, these mice presented obesity, hyperphagia, hyperinsulinemia and hyperleptinemia. At the end of the experiment, both exercising MC4R-knockout mice and wild-type controls which were housed in running wheel cages exhibited similar food intake and activity patterns, and consumed more food than sedentarily-housed control groups (wild-type). In addition, the MC4R-knockout exercised mice presented both fat and lean mass, similar to wild-type littermate mice. The main effects of exercise were observed in the comparison of food intake between sedentary MC4R-knockout mice with sedentary wild-type mice, which demonstrated that the sedentary MC4T knockout was hyperphagic. The MC4R knockout also presented higher serum levels of cholesterol, leptin, insulin and nonfasting glucose than all other groups (Haskell-Luevano et al., 2009), in accordance with another study (Irani et al., 2005). In addition, the exercising MC4R-knockout mice showed pancreatic islet-cell morphologies and other physiological parameters (circulating levels of nonfasting glucose, insulin and leptin) resembling those observed in the wild-type controls. Thus, this study supported the hypothesis that voluntary exercise can prevent the genetic predisposition towards MC4R-associated obesity and diabetes (Haskell-Luevano et al., 2009).

However, it is important to highlight that these apparently valuable effects of PE seem to depend on obesity etiology. Indeed, studies with rat models have shown that PE promotes reductions in weight gain and adiposity in diet-induced obese as well as in Otsuka Long-Evans Tokushima fatty rats, which lack central and peripheral cholecystokinin signaling pathways, but not in Zucker or Koletsky obese rats, which both congenitally lack leptin receptors (Bi et al., 2005).

6. Concluding Remarks

Stressors trigger an adaptive response that, among other hormones, increases release of glucocorticoids, which in turn exacerbate hypercaloric food intake in most humans, eventually leading to both hyperinsulinemia and hyperleptinemia. Nonetheless, insulin and leptin anorexigenic effects become disrupted over time, exacerbating further the preferential hypercaloric food intake that decreases allostatic load by increasing sense of reward. Furthermore the association between hypercaloric food intake and high plasma glucocorticoid concentration promotes fat deposition in the abdominal region, which favors an adaptive response during short stressor-exposed periods, but in the long run may gives rise to metabolic disease.

On the other hand, PE can mitigate the allostatic load via a reduction (or adaptation) of the HPA axis activity with concomitant decrease of both CRH mRNA levels and GR gene expression in the PVN; which

in addition to the non reduction in the MR mRNA amount, keep a negative feedback mechanism sensitive to the circulating GC. Furthermore, the PE practice can reduce the effects of harmful stressors by increasing the BDNF synthesis, an effect similar to those of anti-depressants drugs, by lessening the overfeeding caused by exacerbated GC, which together with the impairment of the insulin and leptin signaling at CNS, leads to an appetite decline. This way, PE has positive effects on the calorie intake and on the risk factors associated with both allostatic load and hypercaloric food ingestion. As well, advantageous results of regular PE may also be the regularization of blood pressure, blood glucose, and others risk factors of metabolic syndrome and cardiovascular diseases triggered by allostatic load.

Consequently, it is important to establish the level and kind of PE that have the desired effects, since the level of exercise influences the response to stressors and the signaling mechanism of insulin and leptin. It is also important to establish the physiological and behavioral effects of PE on different ages and the degrees and/or categories that are more appropriated, to different physical and physiological conditions (lean or obese, stressed or non stress, for example), to different ages as well to each gender. There is a need for longitudinal studies that monitor more effectively the PE effects on the CNS and endocrinal responses, both at the levels of the HPA axis and appetite regulation center, in non professional athletic subjects, because most studies have only examined the correlation between the variables, without investigating the adjacent mechanisms.

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