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The effect of physical exercise on orexigenic and anorexigenic peptides and its role on long-term feeding control

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ABSTRACT

Over the past decades, life-styles changing have led to exacerbated food and caloric intake and a reduction in energy expenditure. Obesity, main outcome of these changes, increases the risk for developing type 2 diabetes, cardiovascular disease and metabolic syndrome, the leading cause of death in adult and middle age population. Body weight and energy homeostasis are maintained via complex interactions between orexigenic and anorexigenic neuropeptides that take place predominantly in the hypothalamus. Overeating may disrupt the mechanisms of feeding control, by decreasing the expression of proopiomelanocortin (POMC) and α-melanocyte stimulating hormone (α-MSH) and increasing orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP), which leads to a disturbance in appetite control and energy balance. Studies have shown that regular physical exercise might decrease body-weight, food intake and improve the metabolic profile, however until the currently there is no consensus about its effects on the expression of orexigenic/anorexigenic neuropeptides expression. Therefore, we propose that the type and length of physical exercise affect POMC/αMSH and NPY/AgRP systems differently and plays an important role in feeding behavior. Moreover, based on the present reports, we hypothesize that increased POMC/αMSH overcome NPY/AgRP expression decreasing food intake in long term physical exercise and that results in amelioration of several conditions related to overweight and obesity.

Introduction

The incidence of overweight among adults, children and adolescents in developed and in developing countries is rising [1–4]. Overweight and obesity are risks factors for type 2 diabetes (DM2) [5,6], cardiovascular disease [7–9], metabolic syndrome [10,11], and associated diseases. In order to avoid becoming overweight/obese, feeding behavior is critical so the amount of energy consumed must correspond to the amount spent.

Feeding control is assured through a number of physiological signals that regulate food intake in both short- and long-term fashion [12]. Food intake is controlled by the arcuate nucleus (ARC) of the hypothalamus through release of orexigenic and anorexigenic neuropeptides to the hypothalamic lateral area (LH) and the paraventricular nucleus (PVN) [13]. The release of these neuropeptides is regulated by endocrine and neuronal input, and when this signaling pathway fails, overfeeding can occur.

Over the past decades studies have shown that physical exercise can prevent obesity and its associated diseases [14–19]. In fact, it was demonstrated in human and in rodents that exercise could diminish high caloric and high fat food intake leading to an improved metabolic profile [7,20–22]. Moreover, a number of studies have addressed in general the effect of physical exercise on obesity, however the link with long term feeding control and energy expenditure is not well explored. Thus, in this article we analyzed recent studies that associate alterations in long-term feeding control and energy expenditure induced by overfeeding and by physical exercise.

The long term feeding control

Feeding behavior is controlled by a complex neuro-hormonal network that modulates alterations in food intake and energy expenditure [23,24]. Regulation of energy homeostasis responds to the long-term energy status of the organism through factors derived from energy-storage tissues and their status [25,26]. The ARC, PVN and LH of hypothalamus are important integration sites for neurological and circulatory factors [27]. The failure of signaling mechanisms of satiety and energy expenditure control can induce overfeeding.

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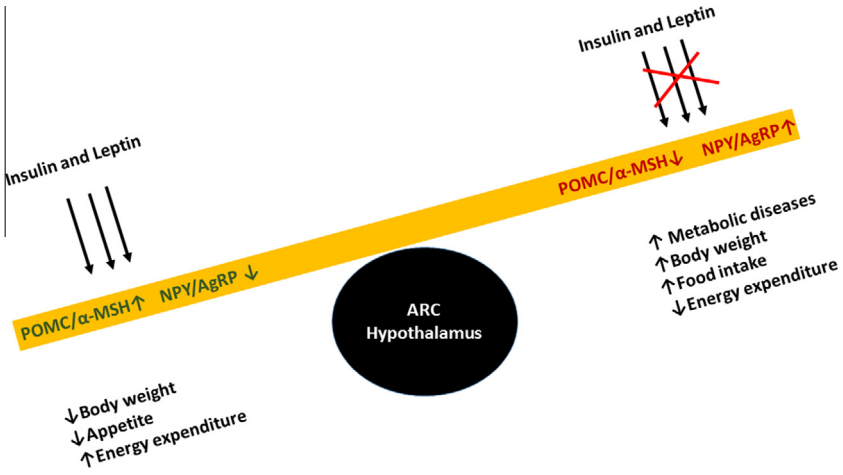

Fig. 1. Effect of leptin and insulin on arcuate nucleus (ARC) of the hypothalamus on anorexigenic neuropeptides proopiomelanocortin (POMC) and α-melanocyte stimulating hormone (α-MSH); and orexigenic neuropeptides neuropeptide Y (NPY) and agouti-related peptide (AgRP).

In the ARC, there are neurons that synthesize the anorexigenic neuropeptides proopiomelanocortin (POMC) and cocaine-and-amphetamine regulated transcript (CART); and neurons that synthesize orexigenic neuropeptides such as neuropeptide Y (NPY) and agouti-related peptide (AgRP) [13]. The humoral signal of long term feeding control is regulated mainly by leptin and insulin (Fig. 1). Leptin, a protein product of the *ob* gene, whose concentration is correlated with body fat percentage [28], regulates the POMC and NPY/AgRP neurons, by increasing the gene expression of POMC [29] and decreasing NPY/AgRP expression [30]. Upon binding of leptin to its receptor, long form of the leptin receptor (LEPRB) POMC and neuronal activity increases in the ARC by activation of both the Janus-activated Kinase (JAK) signal transducer and the activator of transcription 3 signaling (STAT3) [25]. The POMC gene encodes a desacetyl alpha melanocyte stimulating hormone (DA-αMSH) that generates the α melanocyte stimulating hormone (α-MSH), a well-studied anorexigenic peptide that mediates effects on food intake and energy expenditure through its binding and activation of MCRs, mainly MC4R [31,32]. A number of observations demonstrate that the MC4R has a pivotal role in controlling feeding behavior. MC4R knockout mice show an obese phenotype, due to severe hyperphagia [33,34] and mutations in the MC4R gene in humans are associated with an obese phenotype [35,36].

Hence, the equilibrium between outputs from the PVN and LH plays a critical role in regulating feeding and energy homeostasis. Circulating insulin, released by pancreatic β cells, crosses the blood brain barrier and repress NPY gene expression in the ARC thus decreasing energy intake [37,38]. However, it was suggested that the leptin–melanocortin pathway is the key intrinsic regulator of the energy homeostasis maintenance [35]. Moreover, in overweight and obesity, this signal transduction pathway is impaired, leading to hyperphagia [39–41], which might induce chronic metabolic diseases [10,42], DM2 [43,44], hypertension and heart diseases [7,45,46]. Therefore, strategies to inhibit the disruption of the feeding control pathway have been receiving extra attention by the scientific community.

The effects of physical exercise (PE) on orexigenic and anorexigenic hypothalamic peptides – the role of type, intensity and length of training

It has been well recognized that regular PE, resistance and endurance, can prevent the harmful effects of overweight on metabolism [47–50], attenuate overfeeding [22,51], maintain body weight loss [52], improve glucose uptake and prevent DM2 [53–55]. PE can also improve insulin and leptin signaling processes and signal transduction in the hypothalamus [56–59] by increasing activities of several proteins involved in their signal transduction in the hypothalamus [58,59], besides PE can also increase the long form of the leptin receptor (LEPRB [59]. Nevertheless, the effects of PE on the control of food intake are controversial [22,60,61].

Studies indicate that PE can promote alterations in the level of orexigenic and anorexigenic peptides [62]. Shin et al. (2003) [62] showed that sedentary rats with diabetes induced by streptozotocin (STZ) had enhanced NPY expression in both the PVN and ARC, whereas in diabetic exercised group the diabetes induced effect on NPY was suppressed. Moreover, in a comparison of PE protocols: light, moderate and heavy; the group assigned to light intensity PE showed the most potent suppressive effect on NPY expression [62]. On the other hand, Chen et al. (2007) [63] reported an increase in NPY after acute exercise in rats. These discrepancies might be due to difference in the animal condition healthy vs. diabetic but modulation of NPY expression in the ARC by PE waits for further clarification.

Moreover, elevation of POMC and MC4R was also shown to be an outcome of regular exercise [64,65]. After 7 weeks of training, the POMC level in the hypothalamus was increased immediately after acute and it remained high even during 3 h postexercise [64]. Moreover Caruso et al. (2013) [65] reported an up-regulation of POMC mRNA in rats submitted to voluntary exercise together with beneficial effects on body weight, adiposity and hormone profile. The increased POMC was observed even if the animals remained 3 weeks without engaging in physical exercise prior to the euthanasia, therefore, it is possible to hypothesize that the effect of exercise on POMC can last for a long period after a section of regular exercise [65]. Furthermore Haskell-Luevano et al. (2009) [47] analyzed the effect of voluntary exercise on food intake in knockout mice of the POMC downstream regulator MC4R. Exercised MC4R-knockout mice presented both fat and lean mass, similar to wild-type littermate mice, while sedentary MC4R-knockout mice showed obesity, hyperphagia, hyperinsulinemia and hyperleptinemia. In fact, the exercised group showed the same parameters resembling those observed in the wild-type controls. Interestingly, the beneficial effect of exercise was independent of NPY and POMC since when compared to sedentary groups no significant difference was observed [47]. The discrepancy in POMC response to PE in the Haskell-Luevano (2009) study in comparison to the other studies might be due to the strain of the animal.

Other factors such as the type and duration of the PE can also modulate effects on orexigenic or anorexigenic peptides. Carnier et al. (2013) [66] studied the effects of aerobic training (AT) and aerobic plus resistance training (ATRT) on the anorexigenic