Exercise for Appetite Management

New research published in the *Public Library of Science Biology (PLoSB) Journal* reveals that exercise can induce the sensation of satiety due to the triggering of specific neurons in the brain. A research panel at the University of Campinas Exercise in Brazil confirms they have found that an exercise stimulus can actually improve (or restore) sensitivity of neurons involved in the control of satiety, and therefore contribute to reduced caloric intake and weight loss over time.

Excessive caloric intake and sedentary lifestyle are two predominant factors that have led to the unprecedented prevalence of obesity currently seen within the American population. In mammals and humans, food intake and energy expenditure are securely regulated by specific neurons originating in the hypothalamus. The hypothalamus is a neuroendocrine control center in the brain that is capable of gathering data on the body's nutritional status by integrating neural and hormonal signals (such as insulin and leptin) that in turn can initiate negative feedback loop mechanisms for maintenance of metabolic homeostasis. Research has shown that when hypothalamic pathways that regulate insulin and leptin become impaired, consequent overconsumption of calories and an increased risk for obesity and type 2 diabetes can transpire. It is theorized that over-nutrition can cause systemic insulin and leptin resistance via abnormal activation of pro-inflammatory molecules in the hypothalamus; and this dynamic can lead to an irrepressible appetite response. Essentially, it seems that there is a link between metabolic inflammation in the hypothalamus and the dysfunction of hormonal signaling. The mechanisms behind this link are the activation of IKK, (an immune response enzyme) and endoplasmic reticulum (a network of membranes within the cytoplasm of cells where proteins and lipids are synthesized) stress. Based on these correlations, developing strategies to reduce the irregular activation of inflammatory signals and endoplasmic reticulum stress in hypothalamic tissues is crucial for the interest of improving insulin and leptin actions for the prevention (or treatment) of obesity and related metabolic diseases.

It is well known that structured exercise has the capacity to promote numerous health and fitness related benefits, such as bodyweight and visceral fat reduction, improved glycemic control, and reduced insulin resistance. Since the discovery of the cell-signaling molecule, Interleukin-6 (IL-6), research has verified that exercise also induces metabolic adaptations in other organs such as the liver, adipose tissue, and hypothalamus. IL-6 exhibits anti-inflammatory properties and appears to play a major role in the regulation of appetite, energy expenditure, and body composition. The effects of exercise on the regulation of caloric intake have not been thoroughly examined however. In the present study, the research team theorized that exercise can exert effects in the central nervous system (CNS) (e.g. hypothalamus) by modulating specific neurons responsible for the control of appetite and food intake. They therefore investigated the effects of exercise, mediated by IL-6, on IKK activation, endoplasmic reticulum stress, central insulin and leptin sensitivity, and food intake in diet-induced rats after bouts of physical activity.

To evaluate the impact of exercise on caloric consumption, the researchers measured total post-exercise energy intake for 12 hours in lean and diet-induced obese (DIO) rats after engaging in a bout of swimming and treadmill running. Lactate production was measured every 15 minutes to ensure that all of the rats were exercising at the same intensity during the bout. The exercise protocol did not have an effect on post-training energy intake in the lean rats, but it suppressed what is known as a hyperphagic (over-eating) response in the obese rats – to the extent that they consumed the same amount of calories as the lean rats. Chronic over-nutrition, as demonstrated in the DIO rats, has been shown to affect hormonal signaling and balance in a manner that causes overconsumption of calories due to an overactive CNS hunger mechanism; and the exercise stimulus seemed to have the ability to counteract this imbalance.

To extend the study hypothesis, the researchers also examined post-exercise food intake in leptin-deficient mice

(bred for obesity research, referred to as ob/ob mice) and wild type (WT) mice following the same aforementioned protocol. Food intake did not change in the WT mice but food consumption was reduced in the ob/ob mice. In both cases the data demonstrates that exercise modulates hypothalamic neuropeptides (neuron communication molecules) in a manner that can suppress food intake in obese rodents.

To summarize, in the absence of obesity, exercise does not have a direct effect on food consumption behavior as the anorexigenic or orexigenic pathways (neuroendocrine pathways of communication that cause either a lack of appetite or an increase in appetite, respectively) remain undistorted. Conversely, the study data reveals that exercise can aid in reorganizing the 'set point' of nutritional balance in rodents (potentially humans) that are obese and present with hormonal imbalance due to chronic over-nutrition. Exercise modulates dynamics in the hypothalamus that reduce the hyperphagic response in DIO rodents. The reduction in caloric intake was not associated with a concurrent loss of body fat or a stress response exasperated by the exercise bout; as no changes were found in epididymal fat pad weight or costicosterone (hormone that regulates stress and immune responses) levels after the bout.

To evaluate the effect exercise has on adjustments of insulin and leptin signaling within the CNS the research team utilized meticulous protocol to manipulate the presence or absence of pro-inflammatory molecules and IL-6 in the hypothalamus of rodents during exercise. One must first understand that skeletal muscle is actually an endocrine organ that can stimulate the production and release of cytokines (basically 'small' hormones that can communicate metabolic and immunological data between cells) during contraction to influence components of metabolism and indirect communication with the CNS. IL-6 is the first cytokine seen in circulation during exercise. This communicator has been shown to elicit pro-inflammatory and anti-inflammatory actions depending on systemic circumstances. The IL-6-mediated actions of focus during this study include the regulation of appetite, energy expenditure, and body composition; and their relationship to an exercise stimulus.

The researchers performed intra-hypothalamic injections to manipulate IL-6 levels in the non-control rodents to determine its potentially obesity-thwarting effects when released during exercise. Study data revealed that an increase in the presence of IL-6 in the hypothalamus is critical during exercise for the exertion of anti-inflammatory effects that reduce endoplasmic reticulum stress, and ultimately, hormonal communication imbalances. Western blot analysis (analytical technique used to detect specific protein and molecular action in a given tissue sample) was implemented to reveal this correlation. This relationship was solidified when intra-hypothalamic injection of anti-IL-6 antibodies were given to the non-control rodents prior to the exercise sessions, and endoplasmic reticulum stress reduction was not observed. Furthermore, the IL-6 injection reduced energy intake and decreased hypothalamic IKK, and endoplasmic reticulum stress in ob/ob rodents under resting conditions.

To further substantiate the relationship between IL-6 and CNS hormonal signaling, the study team gave an endoplasmic reticulum stress inducer (thapsigargin injection) to the lean rats. This would provide an environment to further illustrate the exercise-induced IL-6 effect on hypothalamic signal sensitivity enhancement. After the endoplasmic reticulum stress inducer was injected, the lean

rats engaged in the previously described exercise bout while receiving a complimentary dose of human IL-6. The exercise induced and pharmacological IL-6 offset the signal dampening effects of the thapsigargin in the lean rodents. Insulin and leptin release was maintained at normal levels due to proper signaling from the CNS.

Even though all of the actions involved in IL-6-mediated hormonal signaling are not fully understood, it has been concluded that IL-6 activation is essentially the first reaction in a cascade of dynamics leading to optimal metabolic neuroendocrine function. To state it simply, IL-6 initiates enhanced expression of another cytokine, IL-10, which then in turn has been shown to directly affect immunological and inflammatory markers such as IKK, that can lead to distorted CNS signaling and consequent over-nutrition/obesity.

Chronic overconsumption of food is directly linked with insulin and leptin resistance due to IKK activation and endoplasmic reticulum stress in the hypothalamus. Insulin has an effect on optimal metabolic action and storage while leptin communicates energy needs. In this study, it is established that exercise can suppress hormonal-driven overeating responses and hypothalamic inflammatory markers via expression of IL-6 in the hypothalamus. Disturbance of IL-6 action blocks the benefits of exercise related to appropriate caloric consumption and insulin and leptin resistance. The positive effects of IL-6 action are propagated by the anti-inflammatory cytokine IL-10 that has a direct inhibitory effect on IKK, and endoplasmic reticulum stress. Essentially, IL-6 and subsequent IL-10 release is necessary to suppress hyperphagia-related obesity. Inflammatory signaling in the hypothalamus links the beneficial physiological effects of exercise to the central action of insulin and leptin – crucial hormones in weight management.

As a conclusive summary, the study team led by Jose Barreto C. Carvalheira established that exercising obese rodents promoted restoration of hypothalamic neuro-endocrine communication and reduced caloric intake. As stated by Carvalheira, "In obese animals, exercise increased IL-6 and IL-10 protein levels in the hypothalamus, and these molecules were crucial for increasing the sensitivity of the most important hormones, insulin and leptin, which control appetite." According to this study's data, it appears that physical activity contributes to the deterrence and management of obesity not only via enhanced caloric expenditure, but also by positive hormonal modulation that can have an effect on orderly eating patterns. This knowledge has the potential to change the existing paradigm established between physical activity and weight loss. *(Public Library of Science Biology, 2010)*