Effects of exercise on glucagon-like peptide-1 (GLP-1)

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Abstract  Appetite and eating behaviour are controlled by a variety of peripheral signals that change in response to food intake and act in the hypothalamus and brainstem. Glucagon-like peptide-1 (GLP-1) is a brain-gut peptide that has a variety of physiological functions and is involved in appetite regulation. Abnormalities in the expression and secretion of GLP-1 have been shown to occur in obesity, diabetes, and hyperlipidemia, and improving these abnormalities has become an important challenge. Exercise has recently been shown to have an influence on GLP-1 concentrations. This short review aims to highlight the association between exercise and the blood kinetics of GLP-1 and discuss the relevance of GLP-1 in the regulation of appetite to prevent obesity.

Keywords: glucagon-like peptide-1 (GLP-1), exercise, appetite, obesity

Introduction

Physical activity is beneficial not only in the treatment of various diseases such as obesity, diabetes, and hyperlipidemia, but also in the maintenance of health. However, the physiological mechanisms underlying the beneficial effects of physical activity remain unknown. In recent years, hormones that influence energy balance have been detected in the gut. One of them is glucagon-like peptide-1 (GLP-1), which has been shown to suppress food intake and body weight gain. The present short review highlights the effect of exercise on circulating levels of GLP-1, which affects the regulation of appetite and energy intake.

Basis of GLP-1

GLP-1 is a satiety factor that is released into the circulation after a meal in proportion to the amount of food consumed, and the major source of postprandial GLP-1 release is the L-cells of the intestine. In addition, GLP-1 is the most powerful known incretin (i.e., insulin-releasing) in humans, and manipulation of the GLP-1 system has formed the basis of several major new treatments for type 2 diabetes. GLP-1 acts on the GLP-1 receptor, which is widely expressed throughout the central nervous system and peripheral tissues. For example, GLP-1 may act directly on gastric GLP-1 receptors to delay gastric emptying. Centrally, intra-cerebrovascular administration of GLP-1 increased c-fos expression in the hypothalamus. The brainstem is also thought to be an important site of action with increases in c-fos expression in the area postrema and the nucleus of the solitary tract being reported after a peripheral injection of GLP-1.

Excess body weight may be associated with a reduction in fasting GLP-1 levels and the postprandial response of GLP-1. In addition, GLP-1 has been shown to dose-dependently reduce appetite and food intake in lean and obese subjects, indicating an equal sensitivity to GLP-1 in these two groups. GLP-1 has also been shown to acutely reduce food intake by an average of nearly 12% without adverse effects. In addition, 5 days of prandial GLP-1 injections to obese subjects led to an average 0.55 kg weight loss.

Effect of exercise on GLP-1 levels in the short-term

One hour of cycling at 65% of maximal heart rate (HR) was shown to significantly increase GLP-1 plasma levels, and resulted in a subsequent decrease in hunger scores in young males and females of a normal body weight. We also demonstrated that a single bout of aerobic exercise caused significant increases in GLP-1 plasma levels, and decreases in subsequent energy intake in obese and non-obese subjects. Furthermore, increases in GLP-1 levels during exercise were significantly and negatively correlated with decreases in the amount of energy ingested. Regarding exercise intensity, GLP-1 levels were similar between high and moderate intensity exercise sessions in young healthy males. These findings suggest the intriguing possibility that exercise may partly function as a physiological regulator for GLP-1 release or metabolism and thus lead to appetite control.

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A 12-week supervised exercise training program (five times per week, 75% maximal HR) resulted in a significant reduction in body weight, with no significant changes in fasting GLP-1 levels\(^{19}\). We also demonstrated that a similar exercise training program (12 weeks, three times per week, 65% maximal HR) resulted in no significant changes in GLP-1 fasting levels in middle-aged obese women, consistent with the findings of a previous study (unpublished data). Martins et al. (2010)\(^{19}\) observed slightly higher postprandial GLP-1 levels in overweight/obese men and women after 12 weeks of exercise training. Chanoine et al. (2008)\(^{20}\) showed that an acute GLP-1 response to a liquid meal was enhanced by a 5-day aerobic exercise training program in normal weight and overweight adolescents. Similarly, we demonstrated a significant increase in GLP-1 levels after a single bout of exercise following 12 weeks of exercise training (Fig. 3). These results are likely to be important in developing new exercise programs for the prevention and treatment of obesity.

**Future outlook**

As described above, exercise is accompanied by an increase in GLP-1 plasma levels; however, the physiological mechanisms for this phenomenon remain unknown. In our preliminary study, rats were anaesthetized and subjected to 20 min hindlimb exercise\(^{\text{i in vivo}}\), at the end of which GLP-1 levels were measured. Hindlimb exercise was induced by electrical stimulation of the sciatic nerve with (SNA \([-]\)) or without (SNA \([+]) sciatic nerve deafferentation or vagotomy (VAG). The results showed that although hindlimb exercise induced increases in GLP-1 plasma levels, only sciatic nerve deafferentation attenuated this increase (Fig. 4). In other words, the increase in GLP-1 plasma levels observed during exercise may have been mediated by the sciatic nerve afferent pathway. Another group recently showed that this increase was mediated by skeletal muscle-derived interleukin-6 via a humoral pathway\(^{21}\). Further studies are required to elucidate the interplay between the two mechanistic pathways (neural and humoral) underlying the increase in GLP-1 plasma levels during exercise.

**Summary**

Exercise increases GLP-1 plasma levels regardless of the intensity of exercise and the species subjected to exercise. The mechanism underlying this increase is not yet fully understood; however, clear understanding of this mechanism may help us to develop new exercise programs for the prevention and treatment of obesity.
Fig. 3  GLP-1 plasma level responses to a single bout of exercise (A) and area under the curve for GLP-1 (B) after 12 weeks of exercise training. The mean values ± SEM of each parameter are presented. ***P < 0.001; pre versus post exercise training.

Fig. 4  GLP-1 plasma level responses to the hindlimb exercise (A) and area under the curve for GLP-1 (B) after sciatic nerve deafferentation SNA (-) or vagotomy (VAG) in the rats tested. The mean values ± SEM of each parameter are presented. **P < 0.01, *P < 0.05; SNA (+) versus SNA (-) session. ††P < 0.01, †P < 0.05; vagotomy versus SNA (-) session.

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