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Review article

Crosstalk between exercise and galanin system alleviates insulin resistance

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ABSTRACT

Studies have demonstrated that aerobic exercise can enhance insulin sensitivity, however, the precise mechanism for this outcome is not entirely identified. Emerging evidences point out that exercise can upregulate galanin protein and mRNA expression, resulting in improvement of insulin sensitivity via an increase in translocation of glucose transporter 4 and subsequent glucose uptake in myocytes and adipocytes of healthy and type 2 diabetic rats, which may be blocked by galanin antagonist. In return, galanin can exert the exercise-protective roles to prevent excessive movement of skeletal muscle and to accelerate exercise trauma repair in exercise-relative tissues. Studies also implicated that combination of aerobic exercise and activation of galanin system may make more significant improvement in insulin sensitivity than that of either one did. These suggest that galanin system is essential for physical activity to alleviate insulin resistance, namely, the beneficial effect of physical activity on glucose uptake is at least partly mediated by galanin system. Besides, co-treatment with galanin and exercise is an effective therapeutic strategy for reducing insulin resistance.

Contents

1. Introduction

Insulin resistance is characterized by reduced glucose uptake and insulin sensitivity in skeletal muscle and adipose tissue in spite of normal or enhanced insulin stimulation. It is associated risk burdens of type 2 diabetes mellitus and cardiovascular disease which is a major public health problem.

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A growing body of evidence supports that regular exercise is a valuable primary care and community health strategy for healthy people to improve insulin sensitivity and for diabetes to lower insulin resistance (Fedewa et al., 2014; Ivy, 1997). After exercise the exercise-stimulated increase in glucose clearance is kept for a relative long duration. A deficiency of physical activity plays a vital role in development of insulin resistance and type 2 diabetes mellitus. However, the exact mechanism responsible for exercise-induced improvement of insulin sensitivity still not entirely identified. Some studies observed that exercise training can increase galanin expression and release which subsequently enhanced insulin sensitivity in skeletal muscle and adipose tissues via irritating glucose transporter 4 (GLUT4) expression and translocation (Guo et al., 2011; Jiang et al., 2009). To date, fourteen types of glucose transporters have been discovered, each having a specific function with different distributions (Augustin, 2010; Leto and Saltiel, 2012). Among these, GLUT4 is particularly important for maintaining glucose metabolism homeostasis and insulin sensitivity, since it is involved in glucose transport into myocytes and adipocytes in response to insulin stimuli. In the basal condition most GLUT4 is located at intracellular vesicles at the cytosol. Insulin acts as a trigger to transport GLUT4 to the plasma membranes of myocytes and adipocytes, which is closely associated with insulin sensitivity to increase glucose influx into cells (Bogan et al., 2003; Geiger et al., 2006). Any disruption in this pathway affects glucose transport into the cytosol, resulting in enhanced insulin resistance.

Galanin, a 29/30 amino-acid peptide, was originally isolated from porcine intestine by Tatemoto and collaborators (Tatemoto et al., 1983). This peptide distributes widely throughout the central and peripheral nervous system as well as other tissues, such as the skeletal muscle, heart muscle, adipose tissue and pancreatic islet (Fang et al., 2012a). Galanin has been implicated in versatile physiological effects, including regulating energy metabolism and stimulating appetite, so this peptide has been termed hunger hormone (Fang et al., 2012a,b). The galanin receptor family currently comprises three members, GalR1, GalR2 and GalR3 (Webling et al., 2012). All of these subtype receptors are G-protein-coupled receptors and distribute in extensive central and peripheral nervous systems.

This narrative review provides an overview related to the interaction between exercise training and galanin system, which may alleviate insulin resistance and type 2 diabetes. These will help us better understanding the intrinsic relationship among physical activity, galanin system and insulin resistance.

2. Interaction between exercise and galanin

2.1. Exercise stimulates galanin secretion

Physical activity, no matter acute or chronic, is an effective physiologic stimulus to accelerate galanin secretion (Guo et al., 2011; Epps et al., 2013; Jiang et al., 2009; Murray et al., 2010; O'Neal et al., 2001; Sciolino et al., 2012; Zhang et al., 2012a) (see Table 1). After a 20 min acute bout of exercise, the plasma galanin concentration in healthy volunteers was significantly higher than each basal value, reaching the peak at 15 min after the exercise (Legakis et al., 2000). As same, a 30 min swimming training enhanced the plasma galanin immunoreactivity in the glucose-treated rats (Milot and Trudeau, 1997). In the chronic exercise experiments, the galanin levels in rats were significantly elevated after 60 min swimming sessions for four weeks as compared with the corresponding sedentary controls. Our laboratory previously reported that galanin secretion is augmented by a training phase consisted of 60 min swimming sessions, 5 times per week during four weeks as compared with each pre-swimming level or sedentary controls (Guo et al., 2011; He et al., 2011; Jiang et al., 2009; Liang et al., 2012).

Physical exercise may increase not only galanin secretion in peripheral tissues, but also galanin gene expression in brain (Holmes et al., 2006). Murray et al. observed that treadmill running for four weeks significantly upregulated galanin mRNA expression level in the locus coeruleus region of rats as compared with sedentary controls (Holmes et al., 2006; Murray et al., 2010; Sciolino et al., 2012). Intriguingly, both voluntary and forced exercise were same to increase galanin mRNA expression in the locus coeruleus of rats (O'Neal et al., 2001). In a treadmill running experiment, the overall running distance was significantly correlated with prepro-galanin mRNA expression in the rats (Murray et al., 2010; O'Neal et al., 2001; Tong et al., 2001; Van Hoomissen et al., 2004). The longer overall running distance of rats, the higher galanin mRNA expression level was observed, presenting an exercise intensity-dependent increase in galanin mRNA expression which was associated with an augment of galanin synthesis and release (Holmes et al., 2006; Reiss et al., 2009; Sciolino et al., 2012). In line with these, our laboratory also found that the three weeks treadmill running significantly enhanced galanin mRNA expression levels in the hypothalamus of rats, further supporting that regular exercise is effective to increase endogenous galanin synthesis and secretion in the central nervous system (Zhang et al., 2012a).

To date it is poorly understood how exercise results in high expression of galanin protein and gene in brain. The only possible clue for it is the noradrenergic–galaninergic mechanism which plays an important role in this process (Sciolino and Holmes, 2012). The majority terminals of norepinephrine neurons show galanin-immunoreactivity in the locus coeruleus, the dorsal raphe nucleus, the dorsal and ventral dentate gyrus (Sciolino and Holmes, 2012). The exercise can boost noradrenaline release and galanin mRNA expression via activation of the α1-b adrenergic receptor in the dorsal raphe nucleus in a time-dependent manner compared with sedentary conditions (Sciolino and Holmes, 2012). The molecular mechanism how exercise up-regulates galanin expression and how these molecular factors interact with galanin system should be further clarified in the future.

2.2. Roles of galanin in exercise protection and exercise trauma repair

Several investigations have focused on that physical activity can reduce spinal hyperexcitability through a galaninergic mechanism to avoid excessive movement of skeletal muscle, which is helpful to avoid exercise-induced injury and to accelerate recovery after training (Qinyang et al., 2004). As co-localized with acetylcholine in the motor neurons, galanin may decrease acetylcholine release from the pre-junctional membrane at the neuromuscular junction to inhibit excessive movement of the flexor muscle (Burazin and Gundlach, 1998). Intrathecal pretreatment with galanin attenuated the spinal cord flexor reflex excitability induced by conditional stimulation of unmyelinated muscle afferents (Xu et al., 1991), and enhanced the threshold of innocuous mechanical stimulation (Verge et al., 1993). This pretreatment can relieve the convulsion and shorten the convulsive duration in the rats. After cut of the afferent fibers in the spinal cords, galanin still can inhibit the electrical stimulus-induced flexor contraction, which may be abolished by galanin antagonists, suggesting that it is a direct role of galanin to inhibit the motor neurons in the spinal cords (Wiesenfeld-Hallin et al., 1989).

In the damaged skeletal muscles galanin concentration was increased, resulting in inhibition of the excitation conduction from the primary sensory fibers to the second-level afferent neurons to reduce the activities of damage muscles and to avoid further damage of the tissues, meanwhile to irritate injury tissues proliferated