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Type 2 diabetes mellitus as a disorder of galanin resistance

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ABSTRACT

The increasing prevalence of type 2 diabetes mellitus with its high morbidity and mortality becomes an important health problem. The multifactorial etiology of type 2 diabetes mellitus is relative to many gene and molecule alterations, and increased insulin resistance. Besides these, however, there are still other predisposing and risk factors accounting for type 2 diabetes mellitus not to be identified and recognized. Emerging evidence indicated that defects in galanin function played a crucial role in development of type 2 diabetes mellitus. Galanin homeostasis is tightly relative to insulin resistance and is regulated by blood glucose. Hyperglycemia, hyperinsulinism, enhanced plasma galanin levels and decreased galanin receptor activities are some of the characters of type 2 diabetes mellitus. The discrepancy between high insulin level and low glucose handling is named as insulin resistance. Similarly, the discrepancy between high galanin level and low glucose handling may be denominated as galanin resistance too. In this review, the characteristic milestones of type 2 diabetes mellitus were condensed as two analogical conceptual models, obesity-hyper-insulin–insulin resistance-type 2 diabetes mellitus and obesity-hyper-galanin–galanin resistance-type 2 diabetes mellitus. Both galanin resistance and insulin resistance are correlative with each other. Conceptualizing the etiology of type 2 diabetes mellitus as a disorder of galanin resistance may inspire a new concept to deepen our knowledge about pathogenesis of type 2 diabetes mellitus, eventually leading to novel preventive and therapeutic interventions for type 2 diabetes mellitus.

Contents

1. Introduction

The prevalence of type 2 diabetes mellitus is rapidly increasing worldwide and becomes an important health problem with its high morbidity and mortality (Malecki, 2004). The characters of this disease include an increase in the blood glucose level, a decrease in the blood

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supply of limbs and damage to the blood vessel, heart, retina, beta cell of pancreas, neurons with long axons reaching the limbs and other organs (Malecki, 2004). Epidemiological investigation demonstrated that there were 371 million people with diabetes in the world and expected to rise to 552 million by 2030 (Guariguata, 2012; Whiting et al., 2011). Diabetes mellitus is widespread in the United States according to the report of U.S. Centers for Disease Control and Prevention, with 24 million people diagnosed and 5.6 million undiagnosed. The National Institute of Health estimates that over 70 to 80 million people suffer from metabolic syndrome or other "pre-diabetic" conditions. The proportion of patients with type 2 diabetes mellitus to total diabetic patients is 90–95%. Blood glucose testing is a base for diagnosis and management of diabetes. Besides, an analysis of volatile organic compounds (VOCs) in the air exhaled from subjects offers a novel diagnostic approach for type 2 diabetes (Dowlaty et al., 2013; Greiter et al., 2010; Mazzatenta et al., 2013).

Despite many factors that result in type 2 diabetes mellitus, the insulin resistance is the core of our understanding of the etiology of type 2 diabetes mellitus. Most likely type 2 diabetes mellitus is caused by modification of insulin signaling, resulting in reduction in glucose uptake of myocytes, hepatocytes and adipocytes and elevation of blood glucose levels, i.e. development of insulin resistance (Perry et al., 2014; Taylor, 2012). However, besides insulin resistance other predisposing and risk factors for type 2 diabetes mellitus are still scarce to be identified and recognized. Therefore, further exploration of these predisposing and risk factors is urgently needed.

Recent studies have provided compelling clues that galanin plays an important role in the pathogenesis of age-related obesity and type 2 diabetes mellitus, and may be taken as a biomarker to predict these diseases (Fang et al., 2013b, 2014a, 2014b). Galanin, a 29/30 amino-acid peptide, was isolated in 1983 from porcine intestine by Tatemoto and collaborators (Tatemoto et al., 1983). This peptide distributes widely throughout the central and peripheral nervous systems as well as other tissues, such as the skeletal muscle, heart muscle, adipose tissue, pancreatic islet and carotid body (Fang et al., 2012b; Di Giulio et al., 2015; Lang et al., 2015). Galanin is involved in a multiplicity of physiological activities. As a hunger hormone, galanin can regulate energy metabolism and stimulate appetite (Fang et al., 2012a, 2012b). The galanin receptor family is currently comprised of three members, GAL1, GAL2 and GAL3 (Webling et al., 2012). All of the subtype receptors are G-protein-coupled receptors and distribute in the hypothalamus, amygdala, hippocampus, paraventricular nucleus (PVN), thalamus, brainstem, spinal cord and dorsal root ganglia (Webling et al., 2012). GAL3 seems to be the important galanin receptor in both the human locus coeruleus and dorsal raphe nucleus versus GAL1 and GAL2 in the rodent brain (Le Maître et al., 2013). GAL1 and GAL3 are known to couple to Gi/Go and inhibit adenylyl cyclase to decrease the cAMP levels (Webling et al., 2012). Excited GAL2, however, may result in hydrolysis of inositol phosphate and activation of phospholipase C through the Gq/G_{11} pathway to enhance intracellular Ca^{2+} concentration (Webling et al., 2012). These different signaling pathways may be related to different functions of galanin.

The results from human and animal studies supported that the characters of type 2 diabetes mellitus included obesity, insulin resistance, hyperglycemia, hyperinsulinism, enhanced plasma galanin levels and decreased galanin receptor activities. This review summarizes our recent studies and relevant papers to provide a new insight into above characters of type 2 diabetes, including insulin resistance, galanin resistance, and the relationship between galanin and obesity.

2. Insulin resistance

Numerous studies confirmed that the circulatory insulin level is increased rather than decreased in subjects with high blood glucose and type 2 diabetes mellitus (Malecki, 2004; Perry et al., 2014; Taylor, 2012). Hyperinsulinaemia precedes the development of type 2 diabetes (Johnson and Olefsky, 2013; Taylor, 2012). Consequently, the concept of insulin resistance was emerged. The development of insulin resistance means a progression from normal to impaired glucose tolerance. Molecular biology researches found that the mechanisms and symptoms of insulin resistance were causally linked to gene and molecule alterations, including modification of the insulin receptor substrate (IRS) that triggered insulin signaling pathways (Denley et al., 2007; Khan and Pessin, 2002; Tonks et al., 2013). IRS proteins interact with the regulatory subunit of phosphatidylinositol (PI)-3-kinase (PI3K), which catalyzes the formation of the lipid product phosphatidylinositol 3,4,5-trisphosphate (PIP3) to regulate the activity of downstream proteins such as protein kinase B (PKB) and atypical protein kinase C (PKC) (Denley et al., 2007; Khan and Pessin, 2002; Tonks et al., 2013). Both PKB and PKC play a crucial role in glucose transporter 4 (GLUT4) translocation through activation of Rab GTPase-activating protein (AS160), which is one of the substrates of PKB (Thong et al., 2007). 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 (Augustin, 2010; Leto and Saltiel, 2012). In the quiescent condition, the majority of GLUT4 are located in intracellular vesicles at the cytosol. As stimulus of insulin, more GLUT4 are translocated to plasma membranes via a complex pathway (Bogan et al., 2003; Geiger et al., 2006). Reduced GLUT4 translocation in response to insulin stimuli results in the most prominent defect in glucose transport into the cytosol, i.e., development of insulin resistance (Augustin, 2010; Leto and Saltiel, 2012). The important factors in lifestyle for development of insulin resistance are excessive caloric intake and scanty physical activity, which are easy to result in swell of fat cells in human and animal (Qi et al., 2008; Tuomilehto et al., 2001). Proliferated and swelled adipose tissues, as an active endocrine organ, can release bioactive mediators (adipokines), which are closely related to obesity-driven insulin resistance and diabetes mellitus (Zhang et al., 2012). In addition, impaired oxidative rates of fatty acid are also associated with insulin resistance, as fatty acids can interfere with the transmission of insulin signaling (Zhang et al., 2012). Whereas the healthy lifestyle, such as low fat diet, weight reduction and frequent physical activity may prevent and reduce the development of insulin resistance and diabetes (Qi et al., 2008; Tuomilehto et al., 2001).

The medical treatment for type 2 diabetes relies reduction in calorie intake and increase in regular physical exercise. Besides, a range of medications that can reduce blood glucose and increase insulin sensitivity should be properly taken, such as Metformin, Thiazolidinediones, Dipeptidyl peptidase-4 inhibitors, Glucagon-like peptide-1 agonist, Alpha-glucosidase inhibitors and Dapagliflozin (Adler et al., 2009).

3. Galanin and obesity

The compelling evidence supported that galanin is closely relative to body weight and obesity via regulation of feeding behavior in animals and humans (Fang et al., 2012a). An injection of galanin into the hypothalamus, particularly into PVN, stimulates food intake in food-sated rats (Kyrkouli et al., 1990). This effect is stronger in the rats as feed with the high-fat diet than with the standard diet (Tempel et al., 1988). The acute increase in central galanin content may augment food intake and fat consumption of mammals (Tempel et al., 1988), which may be blocked by the intracerebroventricular (i.c.v.) administration of galanin antagonists, M40 and C7, (Corwin et al., 1993) or antisense galanin mRNA (Akabayashi et al., 1994). Besides, repeated PVN injection of galanin versus saline during a 7-day test period significantly increased daily caloric intake and body weight of animals (Yun et al., 2005). Furthermore, galanin knockout mice decreased fat-rich diet intake by 48% than controls (Adams et al., 2008), while the obese phenotype of homozygous galanin transgenic C57BL/6J mice reduced energy expenditure and increased body weight (Poritsanos et al., 2009). Last, after chronic administration of galanin by mini-osmotic