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Review

Endogenous peptides as risk markers to assess the development of insulin resistance

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ABSTRACT

Insulin resistance, the reciprocal of insulin sensitivity, is known to be a characteristic of type 2 diabetes mellitus, and is regarded as an important mechanism in the pathogenesis. The hallmark of insulin resistance is a gradual break-down of insulin-regulative glucose uptake by muscle and adipose tissues in subjects. Insulin resistance is increasingly estimated in various disease conditions to examine and assess their etiology, pathogenesis and consequences. Although our understanding of insulin resistance has tremendously been improved in recent years, certain aspects of its estimation and etiology still remain elusive to clinicians and researchers. There are numerous factors involved in pathogenesis and mechanisms of insulin resistance. Recent studies have provided compelling clues about some peptides and proteins, including galanin, galanin-like peptide, ghrelin, adiponectin, retinol binding protein 4 (RBP4) and CRP, which may be used to simplify and to improve the determination of insulin resistance. And alterations of these peptide levels may be recognized as risk markers of developing insulin resistance and type 2 diabetes mellitus. This review examines the updated information for these peptides, highlighting the relations between these peptide levels and insulin resistance. The plasma high ghrelin, RBP4 and CRP as well as low galanin, GALP and adiponectin levels may be taken as the markers of deteriorating insulin resistance. An increase in the knowledge of these marker proteins and peptides will help us correctly diagnose and alleviate insulin resistance in clinic and study.

Contents

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1. Introduction

Insulin resistance is an important functional and clinical state characterized by a decrease in efficiency of insulin signaling for blood sugar regulation. As a consequence, myocytes, hepatocytes and adipocytes take up less glucose and the blood glucose concentration is elevated [93]. In nondiabetic individuals, a herald of the possibility of insulin resistance includes obesity, hyperinsulinemia, dyslipidemia, hypertension and impaired glucose tolerance [32,67,75]. The close relationship between insulin resistance and subclinical or clinical diseases has been observed, including cardiovascular diseases [34,97], neurodegenerative disorders [43,89], infectious diseases [41], cancer [11] and metabolic syndrome in both nondiabetic [10,37,47] and diabetic subjects [9,39]. Despite extensive investigations into insulin resistance, the precise mechanism is inadequately comprehended as yet. There are numerous factors involved in pathogenesis and mechanisms of insulin resistance, including the obesity, smoking, pregnancy, genes alteration, endocrine disorders, chromium lack and so on. Due to the ongoing worldwide epidemic of insulin resistance-related disorders [13], there is a pressing need to evaluate the insulin resistance status precisely and promptly. Quantifying insulin resistance in animal model and human is vitally important for basic scientific investigation and clinical practice [64].

Currently, a measure of plasma biomarker is an efficient predictor of insulin resistance and subsequent disorders, but validated risk-assessment methods about insulin resistance are not satisfactory enough in the clinical practice. To date a number of peptides and proteins, including galanin, galanin-like peptide (GALP), ghrelin, adiponectin, retinol binding protein 4 (RBP4) and C-reactive protein (CRP), have been identified as important biomarkers of developing insulin resistance, as they all respond to glucose intake in a dose-dependent manner. This review reports the updated information about these peptides, highlighting the effects of these endocrine peptide levels on insulin resistance and glucose homeostasis. It may foresee that this research line will help us better understanding and exploitation of the underlying mechanism of evolutionary insulin resistance to predict relative diseases.

2. Neuroendocrine peptides

2.1. Galanin

Galanin, a 29/30 amino-acid peptide, was isolated in 1983 from porcine intestine by Tatemoto and collaborators [92]. This peptide distributes widely throughout the peripheral and central nervous system as well as other tissues, such as the liver, skeletal muscle and adipose tissue, which are the main tissues to regulate insulin sensitivity and glucose disposal [24]. Galanin modulates a variety of biological functions, liking depression [80], feeding [25], pain threshold control [106], neuronal differentiation [2] and pituitary hormone release [96]. The galanin receptor family currently comprises three members, GalR1, GalR2 and GalR3 [100]. All of the subtype receptors distribute in the hypothalamus, hippocampus, amygdala, brainstem, thalamus, paraventricular nucleus (PVN), spinal cord and dorsal root ganglia. Of them, GalR3 seems to be the most important galanin receptor in both locus coeruleus and dorsal raphe nucleus of human versus GalR1 and GalR2 in the brain [49]. Activation of both GalR1 and GalR3 may inhibit adenyl cyclase leading to a decrease in the cAMP level via Gi/o receptors [45,99]. Excited GalR2, however, may result in hydrolysis of inositol phosphate and activation of phospholipase C through the Gq/11 pathway to enhance intracellular Ca^{2+} concentration [98]. This difference between signaling pathways may be related to the different functions of galanin. To date a lot of galanin receptor ligands have been developed to elucidate the specific roles of galanin receptors, such as GalR1 agonist M617 [8], GalR2 agonist M1145, M1153, M1160 and J18 [78–81], GalR2 antagonist M871 [82], GalR3 antagonist SNAP37889 and SNAP398299 [84].

Current research recommended galanin as a new potential plasma marker to assess insulin resistance and its complications in humans and animals. The plasma galanin level is higher in type 2 diabetic subjects and pregnant women with gestational diabetes mellitus than in healthy controls [23,51]. During a glucose tolerance test, galanin secretion in healthy volunteers and type 2 diabetic patients is positively correlative with the blood glucose level, which is dependent on insulin sensitivity [51,52]. In addition, a significant positive correlation between galanin level and blood glucose concentration or body mass index was found in women with gestational diabetes mellitus compared with controls [23]. These results demonstrate that the plasma galanin contents are closely associated with blood glucose levels and insulin sensitivity in humans.

Interestingly, growing evidence indicates that galanin may suppress insulin release from the pancreatic islets via activation of G(o)2, a member of the G(i/o) protein family [60,66,76,77,90]. An administration of galanin inhibits basal insulin secretion in a dose-dependent manner [60], which may be blocked by galanin antagonists [66,76,77]. However, the inhibitory effect of galanin on insulin secretion doesn't interfere its ability to benefit insulin sensitivity of subjects. Many studies provide convincing evidence that galanin may increase insulin sensitivity and carbohydrate utilization in animals. First, galanin promotes obesity and fat storage by facilitating utilization of more carbohydrate than fat in muscle. An acute injection of galanin significantly reduced circulating glucose levels, but increased carbohydrate metabolism over fat in muscle tissue [107]. And the chronic injection of galanin may contribute to the process of fat accrual in rats, specifically as fed with high fat content [107]. Second, animals with galanin metabolic disorder easily suffer from type 2 diabetes mellitus [50]. The galanin-immunoreactive cell number in pancreatic islets of diabetic rats is reduced also compared with nondiabetic rats [1]. And our recent study demonstrated that the plasma galanin levels in the male type 2 diabetic rats were significantly reduced compared with controls [35]. Third, the homozygous galanin transgenic C57BL/6J mice of the obese phenotype show an increase in metabolic rates of lipid and carbohydrate [72]. During the glucose tolerance tests galanin gene knockout mice had impaired glucose disposal due to a reduction in insulin-independent glucose elimination and insulin response [3]. Fourth, GalR1 knockout mice showed an impaired adaptation to a two week high-fat diet challenge, leading to decreased intake and consuming less daily energy than controls while maintained on low-fat diet and than heterozygote littermates. This suggests that galanin-GalR1 systems help animals adapt food intake and metabolism to changes in dietary fat as well as modulate glucose disposition [110]. Finally, our and Bu et al. studies indicated that administration of M35, a galanin antagonist, reduced 2-deoxy-[^{3}H]-D-glucose (2-DG) contents in myocytes and adipocytes, and glucose infusion rates in the hyperinsulinemic-euglycemic clamp test which was a direct assessment of insulin sensitivity in rat and human [12,33,35,42,55,108]. Quantitative densitometry revealed that M35 treatment significantly decreased glucose transporter 4 (GLUT4) mRNA expression levels and GLUT4 protein concentration in plasma membranes of myocytes and adipocytes compared with diabetic controls. The ratio of GLUT4 contents in plasma membrane fractions to total cell membranes was lower in the treatment-M35 group compared with diabetic controls. These results implicate that endogenous galanin elevates not only GLUT4 protein concentration and GLUT4 mRNA expression level but also the GLUT4 translocation from cytoplasm vesicles to cellular surface of myocytes to accelerate glucose uptake and