Extended Abstract

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Annual Congress on Advancements in Neurology, Neuroscience and Pediatric Neurology June 18-19, 2018 Rome, Italy - Differential Expression of the Insulin Receptor in Primary Sensory Neurons Innervating Somatic and Visceral Organs

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Insulin is a major hormone regulating the energy metabolism of the organism. Besides its endocrine effects, insulin may modulate distinct neural functions through insulin receptors (InsRs) expressed in neurons of the central and peripheral systema nervosum . Neuronal localizations of insulin and InsRs have been first described in the central nervous system mostly in areas involved in the regulation of energy balance and food intake. Later studies disclosed widespread brain distribution of InsRs, and also that of insulin, which is of peripheral (plasma) rather than neuronal origin. Available data indicate that most insulin is made in the pancreas, and there is no convincing evidence that insulin can be synthesized in the brain. In recent years, several studies indicated functional interactions between the insulin receptor (InsR) and the Transient Receptor Potential Vanilloid Type 1 receptor (TRPV1) co-expressed in a subset of Primary Sensory Neurons (PSNs) of unidentified target innervation. The aim of this study was to reveal the target-specific expression of the InsR and its co-localization with TRPV1 in adult rats. Adult male Wistar rats (n=12) weighing 300-350 g were used. Three days later representative serial sections were cut from Th10-13 and L3-S1 dorsal root ganglia. Immunohistochemistry and quantitative morphometry were wont to analyze the expression of InsR and TRPV1 in bWGA-labeled somatic and visceral PSNs. The largest proportions of retrogradely labeled InsR-positive neurons were identified among PSNs serving the pancreas (~54%) and the urinary bladder (~52%). InsR-positive neurons innervating the hind paw skin and the gastrocnemius muscle amounted to ~22% and ~21% of labeled neurons. The majority (~64%) of the labeled PSNs exhibited TRPV1 immunoreactivity. Co-localization of the TRPV1 and the InsR was observed in ~16%, ~15%, ~29% and ~30% of labeled cutaneous, muscular, pancreatic and urinary bladder PSNs. Our quantitative morphological data provide evidence for the co-localization of InsR and TRPV1 in PSNs innervating somatic and visceral organs and demonstrate a preponderance of InsR-immunoreactivity among PSNs which innervate visceral targets. These findings suggest that visceral spinal PSNs might be more sensitive to the modulatory influence of insulin than PSNs innervating somatic organs.

InsR, as a member of the receptor tyrosine kinase family, has a heterotetrameric structure with two extracellular α and two transmembrane glycoprotein β subunits which contain the tyrosine kinase domain. Insulin activates the InsR by binding to the α subunit of the receptor which induces the phosphorylation of tyrosine residues of intracellular proteins such as the insulin receptor substrate (IRS) proteins. Phosphorylation of IRS proteins initiates the activation of phosphatidylinositol-3-kinase (PI3K) which, in turn, activates protein kinase B (Akt) and protein kinase C (PKC) cascades, and growth factor receptor bound protein 2/son of sevenless protein cascade which activates mitogen-activated protein kinase (MAPK). The Akt cascade is involved within the translocation of the glucose transporter 4 into the cell wall, regulation of glycogen, protein and lipid synthesis and glucose intake, while MAPK is related to the modulation of gene expression, proliferation and cell growth. Besides its fundamental significance in energy metabolism, a significant role of insulin in modulation of neural functions has emerged. InsRs are expressed mostly on nociceptive TRPV1 receptor expressing PSNs innervating somatic and visceral organs with

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predominance in the latter. InsRs are involved in mechanisms of organ pathologies, especially inflammatory processes of both the exocrine and endocrine pancreas. Experimental evidence indicates a pivotal role of TRPV1 receptor expressing PSNs in the pathomechanism of acute pancreatitis. Pancreatic TRPV1 receptor- and InsR-expressing peptidergic afferent nerves are also implicated in the mechanism of insulitis and islet dysfunction contributing to the development of type 1 diabetes mellitus. Summarizes the mostly interrelated functional roles of insulin and the InsR and the TRPV1 receptor at system, organ and cellular levels. Although the significance of modulation of TRPV1 receptor function in the therapeutic management of pain, inflammatory states and neurogenic dysfunction, such as overactive bladder is now well established, further studies are warranted to exploit the possible therapeutic value of the observations summarized in this review. InsRs expressed on PSNs play a significant role in the mechanisms of neurite outgrowth of cultured PSNs and axonal regeneration in vivo. The exploration of the possible significance of these findings in relation to the mechanism and therapy of neuropathic pathologies associated with diabetes mellitus awaits future studies.

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