Central Involvement of Insulin in the Cardiometabolic Control: A Short Review

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Abstract

For several years the brain was not considered to be insulin responsive. However, different actions of insulin are being proven in mechanisms related to learning, memory, appetite, reproduction, body temperature control, conversion of liver glycogen to blood glucose, peripheral regulation of metabolism and cardiovascular control. With respect to the cardiovascular and autonomic nervous system, evidences indicate that insulin can modulate sympathetic neural outflow to lumbar, renal and adrenal nerves regulating renal function, hormone release and blood flow. In this way, studies suggest that the increase in blood pressure in hypoglycemia states is due to the increase in rostral ventrolateral medulla (RVLM) and the nucleus tractus solitaries (NTS)- important neural areas involved in the cardiovascular and autonomic control and considered a key point region in hypertension leading to sympahtoexcitation. The subfornical organ (SFO)-a circumventricular organ recognized for its ability to sense and integrate hydromineral and hormonal circulating fluid balance signals - is also responsive to insulin and participate in the cardiometabolic control. These recent findings suggest that insulin act in central areas involved in the cardiovascular balance and it is able to control this response. Thus, the goal of this review is to highlight the central action of insulin and its role in the cardiometabolic system.

Keywords: Insulin; Central nervous system; Sympathetic activity; Cardiovascular function; Metabolic function

Introduction

Insulin resistance, characterized as an impairment in insulin receptor-mediated signaling are directly associated with metabolic syndrome phenotypes including obesity, diabetes, hypertriglyceridemia, and hypertension [1-6].

Recently, different actions of insulin related to learning, memory, appetite, reproduction, body temperature control, hepatic production of glucose, and cardiovascular control are being studied, expanding the knowledge of the action of insulin beyond the regulation of glucose concentration in the blood. Central action of insulin involves release of neurotransmitters, cerebral cholesterol synthesis and mitochondrial function [7]. Thus, CNS insulin-mediated signaling - in addition to peripheral insulin action – has an important role in the control of cardio metabolic function [1,4,8-14].

Insulin infused intracerebroventricular was able to reduce hepatic venous glucose concentration (HVGC) in Wistar rats and this effect was totally blocked by atropine suggesting that insulin can suppress glucose release by the liver via parasympathetic pathways. To confirm this hypothesis, subdiaphragmatic vagus nerve activity was recorded during intracarotid infusion of insulin. Insulin was able to increase vagus nerve activity maintaining HGCG. Interestingly, all of these effects were impaired in the spontaneous hypertensive rats (SHR)- which has an insulin resistance and metabolic dysfunction [15]. It suggests that alterations in the autonomic system can lead to metabolic dysfunction through insulin or vice-versa [16]. It is important to highlight that insulin is able to cross the blood brain barrier so its actions can go further than the circumventricular organ region [17].
The transport of insulin through the blood brain barrier happens due to mechanism of saturable transport, that is facilitated by transporters mediated by insulin receptors in the endothelium that is activated especially in basal level of plasmatic insulin [18,19]. Furthermore, there are brain regions as the hypothalamus that lack an effective barrier, allowing faster access to insulin. Indeed, it was already shown that there is a fast insulin signalization on hypothalamus after a peripheral infusion of insulin [20]. In the central nervous system, insulin can be synthesized in hippocampus, prefrontal cortex and olfactory bulb and it is released by exocytosis [21,22], while insulin receptors are predominantly in olfactory bulb, hypothalamus, hippocampus, cortex and cerebellum and in less expression in striad, thalamus, mesencephalon and cerebral trunk [23,24] showing more concentration in neuronal cells and less concentration in glial cells [25].

Either central or peripheral insulin infusion evokes large increase in sympathetic outflow to cardiovascular organs suggesting that CNS-insulin pathway signaling is involved in the blood pressure [26-30]. However, insulin has different effects on blood pressure depending on the via of administration and pathological states. insulin can cross the brain blood barrier through a saturable transporter so, the translocation of insulin from the blood to the brain that can be altered in physiological and pathological states if these transporters are altered as occurs in diabetes disease, for example [17-19].

Furthermore, it was already established that insulin can be synthesized in the central nervous system such as hippocampus, prefrontal cortex and olfactory bulb [21,22]. Hyperinsulinemia can increase in the sympathetic nerve activity in a territory dependent way. For example, intracerebroventricular infusion of insulin in rodents, promotes reduction in food intake and alterations in SNA that can be characterized as an increase or reduction, depending of the territory, without changes in cardiovascular parameters such as blood pressure and heart rate [31-34,17]. There are evidence showing that insulin can act in hypothalamic neurons increasing white adipose tissue browning preventing diet induced obesity but how insulin is able to modulate the sympathetic neural outflow to cardiovascular system organ remains unclear.

Hypoglycemia states leads to blood pressure increase [35] and rostral ventrolateral medulla (RVLM) is presented as a key point region in hypertension response to glycemic reductions [36] and, as expected, the hyperglycemia in this region promotes blood pressure reduction [37]. RVLM is an important neural area involved in the cardiovascular control and is able to promote sympathetic vasmotor activity which has patterns topographically organized that is preferentially and selectively adjusted for different territories [38-40]. The RVLM area has pre sympathetic neurons which has an important role in blood pressure regulation [41]. The RVLM neurons projects to sympathetic pre ganglionar neurons in the intermedia lateral column, that regulates the activity of periphery sympathetic nerves, controlling the vascular resistance, cardiac debit and consequently the blood pressure [42].

For example, after a meal blood pressure decrease due to the redistribution of the blood to the splanchnic region and this phenomenon it is possible as a result of the increase in sympathetic activity to muscle vessels in response to the increase of plasma insulin. This compensatory mechanism is important for blood redistribution in the mesenteric region, without causing hypotension. However, people that have a deficit in the autonomic adjustments, specially mellitus diabetes, show hypotension postprandial [43,44].

Insulin itself can depolarize neurons in the RVLM through insulin receptors and the blockade of these receptors is able to promote hyperpolarization of this neurons [40]. Evidence shows that there is an interaction between insulin receptors and glutamate receptors since the infusion of NMDA receptors antagonist within the RVLM was able to blockade insulin effects on MAP and sympathetic activity [45-47]. Besides that, it is important to remember that insulin has the capability to cross the blood brain barrier and there is a correlation between insulin concentration on plasma and cerebrospinal fluid and can increase proportionally post prandial or by means of insulin peripheral infusion [48,49]. Likewise, interestingly, high levels of insulin in liquid celaraliquid, that occurs in the hyperinsulinemia state and insulin resistance, can stimulate neurons in RVLM via insulin receptors promoting elevation in blood pressure [40].

It is important to highlight that not just RVLM is involved in the insulin-cardiovascular effects. It was observed recently that subifornical organ (SFO) has insulin receptor signaling and it is involved in the insulin resistance, suggesting that selective insulin resistance in the SFO can contribute to cardiometabolic disease development [50]. Furthermore, it is important high spot that the baroreflex dysfunction is also involved in the cardiometabolic diseases and apparently insulin sensitivity is a mechanism involved in this dysfunction. It is already known, whether or not fasting hyperglycemia or hypertension are present, hyperinsulinemia and glucose intolerance coincide with impaired baroreflex-mediated control of heart rate (HR) [51-54]. Thereby, the Insulin has the ability to increase sympathetic nerve activity but also alter baroreflex and increase blood pressure variability contributing to cardio metabolic disorders [55,56].

Normally, an evoked rise in arterial pressure reduces heart rate via excitation of arterial baroreceptor afferent nerves that activate nucleus tractus solitarius (NTS) neurons in the brain stem. These neurons in turn excite cholinergic neurons in nucleus ambiguous to activate cardiac parasympathetic efferent nerves and GABAergic neurons in the caudal ventrolateral medulla (CVLM) to inhibit pre-sympathetic neurons in the RVLM in rats [57]. This baroreflex pathway is impaired in obese rats which is apparently associated with insulin sensitivity [58,59]. It was already shown...
in obese humans that weight loss improves insulin sensitivity and baroreflexes [60-62], but the relationship between these deficits has not been elucidated.

In addition to hypertension and impaired baroreflexes, young adult obese Zucker rats have hyperinsulinemia and glucose intolerance in the presence of normal fasting glucose levels [63]. As reported in humans, poor glycemic control in rats is associated with diminished short-term control of blood pressure even in the absence of other factors of metabolic syndrome. Streptozotocin-induced hyperglycemia in Sprague-Dawley rats produces diminished baroreceptor-mediated activation of the NTS without increasing body weight, insulin, or blood pressure [64], and this treatment also produces impaired baroreflexes and excess blood pressure variability which are improved by reducing blood glucose [65].

Neurons within barosensitive regions of the NTS can be excited by raising circulating glucose within a physiological range and by local changes in glucose concentration [66]. Within the NTS, glucose increases glutamate release from vagal afferent nerve terminals to enhance vagal activation of NTS neurons, and glucose produces excitatory postsynaptic effects in some NTS neurons [66,67]. In the setting of metabolic syndrome many of these homeostatic mechanisms are disrupted or lost altogether. Just as hyperinsulinemia promotes insulin resistance, hyperglycemia fosters glucose insensitivity within the NTS. Furthermore, with streptozotocin-induced hyperglycemia, glucose-mediated augmentation of NTS neuronal excitability is lost coincident with reduced expression and function of glucokinase within the NTS [68]. Thus, acute local changes in glucose concentration play an important role in facilitating the activation of NTS neurons by afferent inputs, and the loss of glucose-mediated enhancement of neurotransmission with chronic hyperglycemia likely contributes to diminished activation of the NTS in the setting of diabetes.

Conclusion

Taken all together we have summarized the effects of insulin in the central areas firstly involved in the cardiovascular and autonomic functions are also involved in the cardio metabolic insulin-effects. We also addressed some mechanisms could be involved in this effect, however the major integrated neural networks involved in the cardiovascular effects mediated by insulin still need to be better explained.

References


