Insulin-mediated sympathoexcitation in obesity and type 2 diabetes

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Introduction

Obesity and type 2 diabetes mellitus represent major health problems in industrialized societies [1]. The insulin resistance characterizing these conditions frequently results in a compensatory and sustained hyperinsulinaemia. It has been recently recognized that hyperinsulinaemia, apart from stimulating glucose uptake in skeletal muscle, also exerts important and potentially pathophysiological effects on the cardiovascular system. For instance, research over the last decade has demonstrated that insulin promotes vascular smooth-muscle proliferation, renal sodium retention, elevations in blood pressure (BP), and increases in sympathetic nerve activity (SNA) [2].

Insulin causes sympathetic activation

Of these actions, an effect of insulin to increase SNA has been very consistent and the most well documented. In humans, acute insulin infusion during euglycaemic clamp generates elevations in muscle SNA, accompanied by increases in plasma noradrenaline levels. Similar infusion failed to increase SNA to skin, indicating preferential sympathoexcitation to skeletal muscle vasculature [2,3]. Although epidemiology has long demonstrated a link between insulin resistance, hyperinsulinaemia, and hypertension [2,3], studies in humans have yet to demonstrate chronic sympathoexcitatory effects of long-term insulin.

In rats, as in humans, acute insulin elicits increased lumbar SNA along with elevated plasma noradrenaline, and ganglionic blockade with hexamethonium produces exaggerated depressor responses in insulin-treated animals [2,3]. To demonstrate chronic sympathoexcitation, osmotic minipump administration of insulin generated long-term increases in plasma noradrenaline and elevations in BP. Interventions such as renal denervation and renin–angiotensin blockade that abolished insulin-induced BP increases also prevented increases in noradrenaline levels [4,5]. In addition, chronic pressure increases to insulin were attenuated...
by alpha-adrenergic receptor blockade [2,3]. Altogether, these studies have firmly established in both humans and experimental animals that insulin administration produces marked increases in SNA directed largely to skeletal muscle tissues.

**Hyperinsulinaemia and cardiovascular complications**

Increases in SNA, secondary to hyperinsulinaemia, may contribute to several cardiovascular complications characterizing obesity and type 2 diabetes. First, increased SNA and the associated release of noradrenaline result in alpha-adrenergic vasoconstriction and renal sodium retention, both important factors leading to the development of hypertension [2]. Although the relationship between hyperinsulinaemia and hypertension is still unclear [2,3], insulin-induced sympathoexcitation represents a major prohypertensive factor in disorders of carbohydrate tolerance. In diabetes, 35–75% of diabetic complications have been attributed to concomitant hypertension [1]. Specifically, hyperinsulinaemia accelerates the deterioration of glomerular filtration rate and exacerbates the development of diabetic nephropathy, an important cause of morbidity and mortality in type 2 diabetes. In addition, the presence of hypertension in diabetes enhances the development of macrovascular and microvascular disease in general [1]. As a second pathophysiological consequence, sympathetic activation promotes the development of atherosclerosis through trophic effects on the vasculature, by increasing platelet number and aggregability, and by promoting hypertension [2]. This action may describe, in part, why insulin is an independent predictor of coronary artery disease and why obesity is frequently associated with ischaemic heart complications and stroke [1]. In summary, insulin-induced sympathetic activation represents an important mechanism contributing to hypertension, atherosclerosis, and end-organ damage in disease states associated with insulin resistance and hyperinsulinaemia.

**Mechanisms of insulin-mediated sympathoexcitation**

Despite increasing evidence for a pathophysiological role of insulin-mediated sympathoexcitation, the underlying mechanisms and sites through which insulin increases SNA remain unclear. Insulin generates an endothelium-dependent vasodilatation which may activate the baroreceptor reflex, resulting in the observed increases in SNA [2]. Arguing against a baroreceptor mechanism, however, are observations in humans that euglycaemic hyperinsulinaemia increases SNA well before decreases in vascular resistance, or even in the absence of vasodilatation [6].

Over the last several years, we have been evaluating the possibility that insulin elevates SNA by activating specific sites in the central nervous system (CNS). In order to demonstrate a CNS origin of activation, we established that infusion of insulin into the third brain ventricle of rats evokes acute increases in lumbar SNA [3]. Interestingly, central neural administration of insulin failed to increase renal or adrenal SNA [3]. This pattern of sympathoexcitation, i.e. increased lumbar activity with no change in renal or adrenal outflow, is precisely the same type of activation observed when insulin is administered systemically during euglycaemic clamp. Thus, direct central neural administration of insulin generates a pattern of sympathoexcitation similar to that produced by systemic insulin.

In follow-up studies, we reasoned that if infusion of the hormone into the third cerebral ventricle increases lumbar nerve activity, destruction of third ventricular structures should abolish increases in sympathetic outflow to systemic hyperinsulinaemia. To evaluate this possibility, we subsequently lesioned tissues surrounding the anteroventral portion of the third ventricle (AV3V), a region clearly implicated in arterial pressure regulation and sympathetic neural control [3]. In this study, intravenously administered insulin produced a typical increase in lumbar SNA in sham-lesioned rats, whereas destruction of the AV3V abolished the increase in SNA, indicating that structures within or associated with the AV3V are crucial for activation of SNA in response to hyperinsulinaemia (Figure 1).

AV3V lesions may eliminate sympathetic responses to insulin by destroying cell bodies in the ablated area or by interrupting fibres of passage removed from the targeted region. Cell body regions within the lesion include the periventricular nuclei at the preoptic anteroventral hypothalamic level, the organum vasculosum, and other regions involved in cardiovascular control. Structural and physiological studies have shown that destruction of these nuclei results in a significant decrease in SNA (Figure 1).

![Fig. 1. Lumbar sympathetic nerve activity (SNA) in Sprague-Dawley rats. Baseline values were taken as 100%, and lumbar SNA responses to insulin and vehicle were expressed as a percentage (%) of the baseline level. Vehicle-infused sham-lesion (Sham-Vehicle) rats, and insulin-infused sham-lesion (Sham-Insulin), SFO-lesion (SFO-Insulin), and AV3V-lesion (AV3V-Insulin) rats are shown during baseline and at 0.6 and 0.13 U/h during euglycemic clamp (2 h). Entries are means ±SEM. During hyperinsulinaemia, lumbar SNA rose significantly in rats with sham or SFO lesions but did not change in rats with AV3V lesions. Reproduced with permission from Hypertension 1996; 29: 1020–1024, Copyright 1996, The American Heart Association.](image-url)
of the lamina terminalis (OVLT), the ventral portion of the median preoptic nucleus (MePO), and the medial edge of the preoptic nuclei. The lesion also interrupts a ventrally directed system of efferents originating from the subformical organ (SFO).

One way to determine which element of the AV3V is critical for sympathetic responses to insulin is to fractionate the lesion into its component neural systems. Therefore, in additional studies, we tested the hypothesis that AV3V lesions abolish sympathoexcitation to insulin by disrupting fibres of passage that arise from the SFO [7]. Findings from these experiments demonstrated that lesions of the SFO had no effect on sympathoexcitation to insulin (Figure 1), suggesting that the SFO itself and fibres originating from the SFO, which traverse and synapse with the median preoptic nucleus and the OVLT, both within the AV3V, are not essential in mediating elevations in lumbar SNA to hyperinsulinaemia. Interruption of sympathoexcitation to insulin by AV3V ablation, if not related to the SFO, could be mediated by several other brain regions. Likely candidates are regions located within the AV3V, such as the OVLT. In accord with a blood-monitoring role for the OVLT, this region contains receptors for insulin, angiotensin II, and atrial natriuretic peptide [7].

Interactions with the renin–angiotensin system

While our studies focused on the sites of sympathetic activation, others have recently begun to elucidate the mechanisms. For instance, hyperinsulinaemia, secondary to either insulin infusion or fructose feeding, caused increases in BP that were abolished by angiotensin-converting enzyme inhibition and by angiotensin II type I receptor blockade [4,8]. These observations suggest that insulin activates the renin–angiotensin system, which in turn stimulates increases in SNA to cause elevations in BP. An alternative hypothesis, that insulin increases sympathetic outflow to then activate the renin-angiotensin system, is unlikely because renin–angiotensin blockade abolished both BP and plasma noradrenaline increases to insulin [4]. If a primary increase in SNA activated renin–angiotensin, then blocking converting enzyme would not be expected to decrease sympathetic outflow, as indicated by the decreased noradrenaline levels. Although these observations indicate that the renin–angiotensin system is critical for insulin-induced hypertension, they provide no information on the specific sites of activation. Recently, Nakata and colleagues [9] found that sympathetically mediated increases in BP to insulin were abolished by intracerebroventricular administration of losartan, an angiotensin II type I receptor antagonist. These findings indicate that insulin activates CNS renin–angiotensin, which in turn stimulates sympathetic neural outflow to elevate BP. To support this possibility, several regions within the AV3V, such as the OVLT, lack a blood-brain-barrier and are responsible for monitoring blood concentrations of peptide hormones, such as insulin, and transmitting this information into the CNS. In addition, insulin has been shown to increase angiotensin II type I receptor density and elevate intracellular calcium transients to angiotensin II administration [10]. Furthermore, all of the components of the renin–angiotensin system have been found in the CNS, and the AV3V region is especially rich angiotensin II neurons [7,11]. In this region, angiotensin II acts as an excitatory neurotransmitter and direct administration of angiotensin II elicits increases in SNA and BP [11]. Altogether, these findings indicate that hyperinsulinaemia activates the renin–angiotensin system in the AV3V region, producing increased sympathetic-mediated vasoconstriction and hypertension.

Conclusions

In this brief review we have provided evidence that the hyperinsulinaemia that frequently accompanies obesity and type II diabetes activates components of the brain renin–angiotensin system, which in turn generates increases in sympathetic neural outflow. Such sympathetic activation could represent an important mechanism that contributes to the increased incidence of cardiovascular complications and diabetic nephropathy in disease states characterized by insulin resistance and hyperinsulinaemia.

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