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Role of the Autonomic Nervous System in the Hemodynamic Response to Hyperinsulinemia—Implications for Obesity and Insulin Resistance

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Abstract

Purpose of Review Herein, we summarize recent advances which provide new insights into the role of the autonomic nervous system in the control of blood flow and blood pressure during hyperinsulinemia. We also highlight remaining gaps in knowledge as it pertains to the translation of findings to relevant human chronic conditions such as obesity, insulin resistance, and type 2 diabetes.

Recent Findings Our findings in insulin-sensitive adults show that increases in muscle sympathetic nerve activity with hyperinsulinemia do not result in greater sympathetically mediated vasoconstriction in the peripheral circulation. Both an attenuation of α-adrenergic-receptor vasoconstriction and augmented β-adrenergic vasodilation in the setting of high insulin likely explain these findings. In the absence of an increase in sympathetically mediated restraint of peripheral vasodilation during hyperinsulinemia, blood pressure is supported by increases in cardiac output in insulin-sensitive individuals.

Summary We highlight a dynamic interplay between central and peripheral mechanisms during hyperinsulinemia to increase sympathetic nervous system activity and maintain blood pressure in insulin-sensitive adults. Whether these results translate to the insulin-resistant condition and implications for long-term cardiovascular regulation warrants further exploration.

Keywords Obesity · Insulin resistance · Hyperinsulinemia · Sympathetic nervous system · Blood flow · Blood pressure

Introduction

Blood glucose levels increase following consumption of a meal. Increases in blood glucose promote release of insulin from the pancreas, which is essential for peripheral glucose uptake. In addition to its metabolic actions, insulin elicits profound vasodilatory effects in the peripheral circulation, promoting the delivery of insulin and glucose to tissues such as skeletal muscle [1•, 2–6]. Indeed, insulin-stimulated skeletal muscle vasodilation plays an important role in glycemic control [3, 5–7]. Consistent with this, impairments in insulin-mediated blood flow in adults with insulin resistance parallel with decrements in glucose disposal [1•].

At the level of the vascular endothelium, insulin binds the insulin receptor (IR) and activates downstream IR substrate 1/2/PI3K signaling, resulting in phosphorylation of endothelial nitric oxide (NO) synthase [8–10]. During hyperinsulinemia, the vasodilatory effects of insulin in skeletal muscle must be opposed by countercurrent vasoconstrictor mechanisms in order to preserve blood pressure. This is analogous to exercise-induced hyperemia, where Loring Rowell once stated, *"skeletal muscle is a sleeping giant whose blood flow must be under tonic vasoconstrictor constraint if hypotension is to be averted"* [11]. Insulin promotes endothelin-1-mediated vasoconstriction via activation of ERK1/2. Endothelin-1 is one key countercurrent mechanism to maintain blood pressure [8, 12, 13], but is not the sole opposing force to insulin-induced, NO-dependent vasodilation. Hyperinsulinemia also elicits an increase in the activity of the sympathetic nervous system [14–20]. In this regard, inhibition of local

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sympathetic vascular control (via regional sympathectomy) was shown to elicit a more rapid NO-mediated vasodilation in response to insulin compared to control [21]. Using an isolated forearm model, Lembo and colleagues further supported a crosstalk between insulin and the sympathetic nervous system [22, 23].

The insulin-mediated increase in sympathetic nervous system activity directed towards the skeletal muscle (muscle sympathetic nerve activity, MSNA) in insulin-sensitive individuals is gradual, occurring over approximately 30–60 min. This time course has been primarily attributed to the amount of time needed for insulin to transfer across the blood brain barrier [24–26]. In the brain, insulin increases sympathetic nervous system activity via actions within the arcuate nucleus [27–32]. Increases in central insulin also enhance the gain of the arterial baroreflex control of sympathetic nervous system activity [33, 34]. Recent evidence further supports a role for both the arterial baroreceptors [35–39] and carotid chemoreceptors [40] in insulin-mediated sympathoexcitation.

The purpose of this brief review is to summarize recent work by our group, in context of known findings, to provide new insights into the role of the autonomic nervous system in the control of blood pressure during hyperinsulinemia and consequent peripheral vasodilation (Fig. 1). We also highlight remaining gaps in knowledge as it pertains to the translation of findings to relevant human chronic conditions such as obesity, insulin resistance, and type 2 diabetes.

Role of Sympathetic Nervous System Activation in Restraining Insulin-Stimulated Vasodilation

As noted above, hyperinsulinemia elicits a prominent increase in MSNA in insulin-sensitive adults [14–20]. Activation of the sympathetic nervous system stimulates norepinephrine release from sympathetic nerve terminals, which ultimately binds α-adrenergic receptors and promotes vasoconstriction. With this, increases in MSNA during hyperinsulinemia have the potential to limit insulin-induced vasodilation via greater α-adrenergic mediated vasoconstriction [16, 20, 41]. Considering this scenario, we hypothesized that blunting MSNA would elicit a greater increase in femoral blood flow and vascular conductance during hyperinsulinemia compared to baseline [42••]. Using neck suction (to acutely unload the arterial baroreceptors and decrease MSNA), we observed no effect of hyperinsulinemia on the

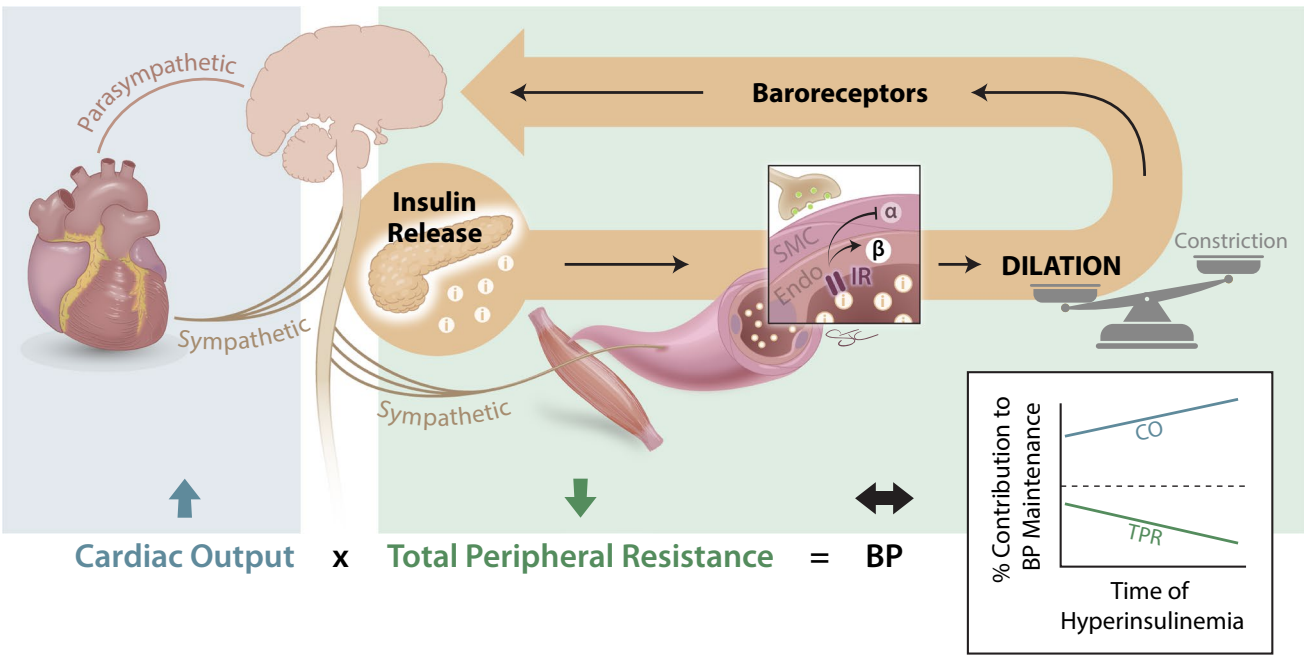

Fig. 1 Role of the autonomic nervous system in the hemodynamic response to hyperinsulinemia. Our findings in insulin-sensitive adults do not support the role of sympathetically mediated vasoconstriction as a principal mechanism to restrain insulin-induced skeletal muscle vasodilation for the maintenance of blood pressure during hyperinsulinemia. Both insulin-induced attenuation of α-adrenergic vasoconstriction and augmented β-adrenergic vasodilation likely explain these findings. Due to the lack of sympathetically mediated restraint of peripheral vasodilation during hyperinsulinemia, healthy individuals must heavily rely on increases in cardiac output to support blood pressure. Together, these results support a dynamic interplay between central and peripheral mechanisms during hyperinsulinemia to increase muscle sympathetic nerve activity and maintain blood pressure in insulin-sensitive adults. BP, blood pressure; Endo, endothelium; SMC, smooth muscle cells; IR, insulin receptor; i, insulin

skeletal muscle blood flow, vascular conductance, nor total peripheral resistance response to acute MSNA inhibition [42••]. Consistent with this, blocking α-adrenergic receptor-mediated vasoconstriction (with prazosin) was similarly shown to have no effect on insulin-stimulated blood flow [41]. Thus, we concluded that the role of the sympathetic nervous system in restraining peripheral vasodilation, particularly in healthy adults, is not augmented during hyperinsulinemia. On the other hand, neck suction did promote a greater decrease in blood pressure during hyperinsulinemia and this response was accompanied by greater decreases in cardiac output [42••]. Combined with the observation that cardiac output was markedly increased during insulin infusion, these results support the idea that neurally mediated increases in cardiac output, rather than restraint of peripheral vasodilation, may be critical to the preservation of systemic blood pressure during hyperinsulinemia (Fig. 1).

Given the lack of an effect of hyperinsulinemia on the peripheral vascular response to an acute reduction in MSNA, our understanding of the "net effect" of insulin on sympathetic control of blood flow and blood pressure remained incomplete. We therefore sought to extend these findings by examining the effect of hyperinsulinemia on sympathetic transduction (i.e., the dynamic vascular and/or blood pressure response to MSNA) [43•]. To do this, we employed a signal-averaging technique [44] to characterize changes in blood pressure and total vascular conductance following spontaneous bursts of MSNA at rest and during hyperinsulinemia. Consistent with our results using neck suction [42••], we observed no significant differences in the peak blood pressure nor vascular response to bursts of MSNA between rest and hyperinsulinemia (i.e., "net" sympathetic transduction was unchanged) [43•]. However, after taking into account the increase in MSNA burst height that occurs with hyperinsulinemia (presumably associated with greater efferent sympathetic activity), we found that sympathetic transduction for a given burst amplitude was blunted during insulin infusion [43•]. These findings lend further support to the idea that during hyperinsulinemia, a given amount of sympathetic activity is less capable of restraining insulin-stimulated vasodilation. Indeed, we went on to show that in young healthy men and women, acute sympathetic activation (via a cold pressor test) elicited less vasoconstriction in the setting of high insulin compared to control [45••]—however, contributing mechanisms remained unclear.

Role of Hyperinsulinemia in Attenuating Sympathetically Mediated Vasoconstriction

We were initially surprised to observe that insulin-mediated increases in skeletal muscle blood flow were not under considerable sympathetically mediated vasoconstrictor restraint [42••]. With this, we hypothesized that insulin may attenuate α-adrenergic receptor-mediated vasoconstriction [22, 23, 46–49]. In isolated aortic rings, we showed that insulin exposure blunted α_1-adrenergic-mediated vasoconstriction [42••]. We further demonstrated that the ability of insulin to blunt α_1-adrenergic-mediated vasoconstriction requires the following: (1) an intact endothelium, and (2) an unrestricted PI3K/Akt insulin-signaling pathway. Specifically, endothelium denudation and pharmacological inhibition of NO synthase or the upstream enzyme PI3K [50•, 51] abolished the insulin-induced suppression of α_1-adrenergic vasoconstriction. Similarly, insulin-induced suppression of α_1-adrenergic vasoconstriction was lost in aortic rings from insulin-resistant db/db mice [42••]. Accordingly, vascular insulin signaling is capable of attenuating sympathetically mediated vasoconstriction and that "sympatholytic" factor appears to be endothelial-derived and NO-dependent.

Norepinephrine release from sympathetic nerve terminals binds α-adrenergic receptors to elicit vasoconstriction; however, norepinephrine can also bind β-adrenergic receptors—which promote vasodilation. Crosstalk between insulin and β-adrenergic receptors was previously supported by the literature, particularly in the heart [52–56]. Thus, we hypothesized that insulin-induced attenuation of sympathetic vasoconstriction may be due to a potentiation of β-adrenergic receptor-mediated NO production [57]. In accordance, we found epinephrine and norepinephrine-induced vasoconstriction to be attenuated in isolated mouse arteries exposed to insulin. Importantly, the ability of insulin to suppress epinephrine and norepinephrine-induced vasoconstriction was lessened with propranolol, a non-specific β-adrenergic receptor antagonist [57]. In alignment with this observation, insulin-induced vasodilation within the human forearm is attenuated with intra-arterial infusion of propranolol [58]. Notably, we also showed that insulin enhanced β-adrenergic-mediated vasodilation in an endothelium and NO-dependent manner. These observations may be mediated via crosstalk between the insulin receptor and β-adrenergic receptors, as has been shown in cardiac tissue [56]. Together, these findings support the link between insulin and β-adrenergic signaling in the modulation of vascular tone (Fig. 1).

Role of Arterial Baroreceptors in Mediating Insulin-Induced Sympathoexcitation

Given the observed ability of hyperinsulinemia to attenuate sympathetically mediated vasoconstriction, the question arose as to the mechanism by which insulin-mediated sympathoexcitation is achieved. In addition to insulin's actions within the arcuate nucleus to increase efferent sympathetic activity [27–32], the peripheral vasodilator effect of insulin has been postulated to contribute to baroreflex-mediated

increases in MSNA during hyperinsulinemia [35–39]. We thus reasoned that rescuing peripheral resistance with co-infusion of the vasoconstrictor phenylephrine would attenuate the MSNA response to hyperinsulinemia [59••]. Consistent with this hypothesis, we found that co-infusion with phenylephrine returned MSNA and total peripheral resistance to baseline levels [59••]. Notably, a role of insulin-stimulated vasodilation and response of the arterial baroreflex in insulin-mediated increases in MSNA has been discounted previously on the basis that in healthy adults, blood pressure is unchanged during systemic insulin infusion [20]. In addition, increases in MSNA during hyperinsulinemia are observed prior to increases in leg blood flow [36]. Based on these data, the authors concluded that the ability of insulin to stimulate MSNA is dissociated from its acute hemodynamic action [36]. Similarly, Anderson and colleagues [20] argued that during hyperinsulinemia, the change in MSNA per unit reduction in blood pressure was much greater than what was observed with another peripheral vasodilator—again going against a peripheral baroreflex mechanism. Important to these conclusions is the assumption that the peripheral vasculature retains its sensitivity to sympathetic activation during insulin exposure; however, as discussed above, sympathetically mediated vasoconstriction is attenuated during hyperinsulinemia [42••, 43•, 45••]. In the context of prior findings, we propose that the peripheral vasodilator effect of insulin contributes, at least in part, to baroreflex-mediated increases in MSNA during hyperinsulinemia in insulin-sensitive adults [59••].

Role of Peripheral Chemoreceptors in Mediating Insulin-Induced Sympathoexcitation

A novel role for the carotid chemoreceptors in insulin-mediated activation of the sympathetic nervous system and glucose regulation has been recently proposed [40, 60–64]. Using a combination of acute hyperoxia [65] and low-dose intravenous dopamine [66, 67] (to acutely attenuate carotid chemoreceptor activity), we sought to examine the contribution of the carotid chemoreceptors to insulin-mediated increases in MSNA in healthy, insulin-sensitive individuals [68•]. Consistent with the work of others [69, 70], we observed a limited role for the carotid body chemoreceptors in basal MSNA in healthy adults. We further found no consistent, measurable effect of acute hyperoxia or dopamine on MSNA during hyperinsulinemia [68•]. We interpreted these results to mean that the carotid body chemoreceptors do not contribute to insulin-mediated increases in MSNA in young, healthy, insulin-sensitive adults. Additionally, the glucose infusion rate required to maintain euglycemia was unaffected by interventions targeting the peripheral chemoreceptors—further supporting the idea that the carotid body chemoreceptors do not contribute to insulin-mediated increases in MSNA and/or insulin sensitivity in young, healthy adults. However, through an exploratory post hoc analysis, we found that, in some individuals, hyperoxia may have had a greater effect on MSNA during insulin than at baseline. The individuals where this occurred were the least insulin-sensitive (lowest glucose infusion rate) and lend support to the idea that the carotid chemoreceptors' role in sympathetic regulation during hyperinsulinemia may be altered with progressive disease (e.g., obesity, insulin resistance, type 2 diabetes).

Perspectives

The increased prevalence of obesity worldwide has resulted in an increase in obesity-related disorders including hypertension, insulin resistance, and type 2 diabetes. Indeed, insulin resistance affects nearly one-third of the US population and precedes the development of type 2 diabetes. As shown by our group [71, 72] and others [73, 74], MSNA is nearly two times greater in obese, insulin-resistant adults compared to lean counterparts. Higher MSNA in obesity is directly associated with higher fasting insulin (i.e., insulin resistance) [75–79]. With this information, one might anticipate that the MSNA response to hyperinsulinemia is further augmented in obesity. However, the majority of currently available data refute the notion that MSNA responses to acute hyperinsulinemia are greater in adults with obesity compared to normal weight controls [74, 80–83]. Disconnect between the effect of chronic (i.e., insulin resistance) and acute increases in circulating insulin (i.e., a meal) on MSNA may be due to impairments in cellular insulin action within the peripheral vasculature in human insulin resistance (i.e., reduced insulin-induced vasodilation and/or augmented α-adrenergic-mediated constriction) [74, 80, 84]. Indeed, it is well established that adults with insulin resistance exhibit impaired insulin-stimulated skeletal muscle vasodilation [1•, 2, 7, 85]. Based on current understanding, one may speculate that obese, insulin-resistant individuals would not exhibit further elevation in MSNA during acute hyperinsulinemia due, in part, to these impairments in the peripheral vasodilatory response to hyperinsulinemia [74, 80, 84, 86] and consequently reduced stimulus on the arterial baroreflex. Of note, work from Straznicky and colleagues [83] refutes the notion that a blunted MSNA response in insulin-resistant adults is related to the magnitude of insulin-stimulated blood flow. Given that insulin attenuates sympathetically mediated vasoconstriction [45••], and this may be absent in the setting of insulin resistance [42••], future experiments directly addressing these questions in a cohort of insulin-resistant individuals are warranted. Furthermore, whether human obesity alters

the efficiency with which insulin enters the central nervous system [87, 88] and/or the sensitivity of important brain and/or peripheral (i.e., carotid chemoreceptors) regions to insulin stimulation remains untested.

In addition to a lack of clear understanding of the presence of central (brain) insulin resistance in obesity, it is not well known whether sex differences exist in the neural and/or vascular responses to hyperinsulinemia. Reviewed in detail elsewhere [89••, 90], insulin-mediated increases in MSNA occur similarly in normal weight male and female rats and humans (*unpublished observations from our group*). In contrast, recent data suggest that obesity prone male rats have a tenfold greater increase in sympathetic nervous system activity with insulin exposure, a phenomena not observed in obesity-prone female rats [91]. In agreement with these data, our group [92] and others [93, 94] have shown that obesity induced by Western diet feeding increases blood pressure in male animals only. Together, these data suggest that men may be sensitized to the action of insulin within in the brain, and this differs from the response in women; however, definitive data in humans are lacking.

Conclusion

In aggregate, our findings in insulin-sensitive adults do not support the role of sympathetically mediated vasoconstriction as a principal mechanism to restrain insulin-induced skeletal muscle vasodilation for the maintenance of blood pressure during hyperinsulinemia. Both insulin-induced attenuation of α-adrenergic vasoconstriction and augmented β-adrenergic vasodilation likely explain these findings. Due to the lack of sympathetically mediated restraint of peripheral vasodilation during hyperinsulinemia, healthy individuals must heavily rely on increases in cardiac output to support blood pressure. Together, these results support a dynamic interplay between central and peripheral mechanisms during hyperinsulinemia to increase muscle sympathetic nerve activity and maintain blood pressure in insulin-sensitive adults. Future research translating results to obesity and insulin resistance is warranted in order to enhance our understanding of the pathophysiology of obesity and diabetes, which will be necessary prior to the development of new therapeutic interventions.

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Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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