Short Communication

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Role of leptin and insulin on renal sympathetic nerve activity in high fat fed rabbits

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Abstract:

Using a rabbit model of obesity induced hypertension we have shown that a 3 week consumption of a high fat diet (HFD) induces elevated blood pressure (BP), heart rate, renal sympathetic nerve activity (RSNA) and plasma norepinephrine. Ganglion blockade completely abolishes the increase in blood pressure suggesting that this model of obesity hypertension is neurogenic. The changes are associated with elevation in plasma insulin and leptin which may be the basis for the development of long term obesity related hypertension. We found that 3 weeks of a HFD induces an increased sensitivity to the central sympatho- excitatory effects of leptin and also alpha-melanocyte stimulating hormone (MSH). We determined that the increase in BP and RSNA occur relatively quickly being detectable within 24 hours of commencing the diet. Also the main reason for the increases is the loss of pre-prandial reduction in cardiovascular measures. To determine the central mechanisms, we administered conscious rabbits with intracerebroventricularly (ICV) peptide antagonists of Leptin and Insulin. The insulin antagonist lowering BP slightly but had no effect on RSNA. By contrast leptin antagonist ICV abolished the hypertension and reduced RSNA. The antagonists had no effect in control rabbits. We conclude that increased RSNA associated with a HFD is due almost entirely to enhanced leptin signaling in the hypothalamus via MSH pathways.

Introduction:

Obesity is now a large-scale global epidemic that develops from a complex interaction between genotype and environment, including social, behavioral, cultural, physiological, and metabolic factors. The consequences of being overweight or obese include increased incidence of hypertension, hyperlipidemia and hyperinsulinemia, insulin resistance, and diabetes mellitus.Clinical evidence suggests that sympathetic activation participates not only in the initial elevation in blood pressure but also in maintaining the hypertension.Obesity is closely linked to increased sympathetic nerve activity (SNA) to the kidneys and skeletal muscle vasculature and is linked to the accumulation of body fat.

Our focus has been on the mechanism underlying the increase in blood pressure and, in particular, the role of the sympathetic nervous system in the development of the hypertensive state. We have demonstrated that 3 weeks of high-fat diet (HFD) feeding leads to increased mean arterial pressure (MAP), heart rate (HR), and renal SNA (RSNA) in rabbits. Importantly, we have shown that ganglion blockade completely abolishes the increase in blood pressure suggesting that this model of obesity hypertension is neurogenic.We suggested that the mechanism of the hypertension involved sympathetic activation and increased responsiveness to central sympathoexcitatory effects of leptin owing to increased plasma leptin arising from visceral fat accumulation. Leptin is an adipokine that plays an important role in regulating energy intake and energy expenditure, including appetite and metabolism, and acts as a key peripheral hormone in distinct neurons in the hypothalamus.Leptin is secreted primarily by adipocytes and is present in serum in direct proportion to the amount of adipose tissue. Chronic leptin infusion has been shown to increase HR and blood pressure in animal models via stimulation of the sympathetic nervous system.

In addition to the rise in leptin, we also observed a marked increase in plasma insulin in rabbits fed a HFD suggesting that insulin may also contribute to the hypertension and increased RSNA in rabbits particularly early in the onset of the HFD before significant accumulation of visceral fat. Thus, both leptin and insulin may contribute to the hypertension, and with the development of specific antagonists it is now possible to determine their relative roles. In the present study, we administered either the insulin receptor antagonist or the leptin receptor antagonist intracerebroventricularly to conscious rabbits at 1 or 3 weeks after the onset of a HFD.

Insulin is taken up into the brain from the blood stream by a receptor-mediated transport process. It functions as a peripheral regulator of nutrient storage and release as well as a key afferent signal to the central nervous system for energy balance.10 Insulin receptors are expressed in several regions of the central nervous system, with a high density in the hypothalamus. Neurons in the arcuate nucleus that express proopiomelanocortin and others that express neuropeptide Y, both express insulin receptors. However, the surprising finding was that although the central effects of the insulin antagonist were clear early on in those animals on a HFD, there was no effect of the insulin antagonist on RSNA. Similar to our findings, Vaz et al have re-

ported that in obese subjects, although fasting serum insulin concentrations are higher, serum insulin and renal noradrenaline spillover values are not quantitatively related, which shows that hyperinsulinemia per se does not lead to elevated RSNA. Furthermore, ICV infusion of insulin to rats increases lumbar SNA but not RSNA.Together with our finding, it would seem that the early increase in blood pressure to diet-induced elevation of insulin signaling may activate sympathetic vasomotor activity to beds other than the kidney. An additional suggestion is that the hypotension we observed to the central insulin antagonist was a result of reduced cardiac output, possibly related to the reduction in HR or in venous return (both can be decreased by inhibiting sympathetic activity). There is an established relationship between the ultradian rhythms of insulin secretion and the rhythms of autonomic function, presumably to cope with the metabolic load changes associated with the sleep/active cycle and to also coincide with the higher post prandial glucose. Thus, there is a conjunction between the metabolic and cardiovascular needs of high activity periods linked through hypothalamic circuitry, perhaps involving cardiac sympathetic activity (based on the known actions of central insulin on baroreflex curves in rats). We have reported a strong relationship between the changes in glucose levels and HR in a previous study of rabbits on a HFD. Thus, it follows that the HFD, being high in calories and leading to higher levels of plasma glucose and insulin, may inappropriately signal higher levels of HR and hence cardiac output and blood pressure at the level of the hypothalamus.

Interestingly, we did not see a reduction in HR with leptin at 3 weeks. However, this was in the presence of a rapid large fall in blood pressure, which would normally induce a reflex tachycardia. We have previously shown that the HR baroreflex curve shifts to the right and the upper plateau increases after 3 weeks of HFD. Thus, the leptin antagonist may reverse these changes and by altering the baroreflex curve allows for larger changes in blood pressure without influencing HR.

A strength of our current study was that we documented the effectiveness of the leptin and insulin antagonists. In separate experiments we used dose–response curves to determine initially the optimum pressor effect of leptin and insulin (at 3 weeks and 1 week of a HFD, respectively) and then pretreated rabbits ICV with the same dose of the antagonist before the agonist. We found that the pressor responses to leptin and insulin were abolished by the antagonist pretreatment. We also included control ICV injections of Ringer's solution, which had no effects on MAP, HR, and RSNA in both ND and HFD rabbits.

Conclusion:

We have now shown that the elevation of blood pressure and RSNA induced by a HFD for several weeks is predominantly mediated by central actions of leptin. Furthermore, central actions of insulin contribute a smaller proportion of the hypertension initially, presumably through sympathoexcitation but independently of RSNA. The rapid cardiovascular response to insulin elevation (or decrease after removal of a HFD) may reflect the role of insulin in the diurnal pattern of responding to circulating glucose and the metabolic load changes associated with the sleep/active cycle30 and to also coincide with the higher post prandial glucose. By contrast, there is a considerable delay in the renal sympathoexcitatory effects of leptin, which may allow for short-term regulation of sodium excretion in relatively limited periods of feast and famine. Future studies are now aimed at understanding why elevation of leptin for several weeks eventually leads to increased RSNA and blood pressure.