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Vascular insulin resistance in fructose-hypertensive rats

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Abstract

Evidence suggests that insulin has direct, potent and physiologically relevant vasodilatory effects. This has led to the hypothesis that in states of insulin resistance, insulin's vasodilatory effects may be blunted leading to an increase in vascular tone and blood pressure. To examine this proposition we studied the direct effects of insulin on the reactivity of aortae from control and insulin-resistant fructose-hypertensive rats to angiotensin II. Insulin incubation caused marked vasodepressor effects in control aortae. Strikingly, this effect was absent in aortae from fructose-hypertensive rats. These data suggest the presence of vascular insulin resistance in fructose-hypertensive rats and provide a hemodynamic basis for hypertension in states of insulin resistance. © 1997 Elsevier Science B.V.

Keywords: Insulin resistance; Vasculature; Fructose hypertension

The association between insulin resistance (resistance to the glucoregulatory actions of insulin), hyperinsulinemia and hypertension has been extensively explored during the last decade and remains an area of intense discussion and debate (Bhanot and McNeill, 1996). Although a strong and possibly causal relationship between hyperinsulinemia, insulin resistance and hypertension has been demonstrated in both clinical and experimental studies, the exact mechanisms and/or mediators linking these defects to hypertension remain unclear. A growing body of recent evidence suggests that insulin, in addition to its well known effects on carbohydrate, lipid and protein metabolism, exhibits potent and physiologically relevant vasodilatory effects (Baron, 1993). This has led to the hypothesis that in states of insulin resistance, insulin's vasodilatory effects may also be blunted which may lead to increases in vascular smooth muscle tone and hypertension. This is an attractive hypothesis which could provide a pathogenic link between insulin resistance and hypertension through increases in vascular reactivity (Baron, 1993). The present study was specifically targeted at examining this proposition. To this aim we examined the direct effects of insulin on reactivity of isolated aortae from control and fructose-hypertensive rats to angiotensin II. The fructose-hypertensive rat model is a widely used model of acquired hypertension, wherein feeding normal Sprague-Dawley rats a fructose-enriched diet results in hyperinsulinemia, insulin resistance and hypertension (Reaven et al., 1989; Verma et al., 1994). This model is ideally suited to examine the relationship between metabolic aberrations and blood pressure independent of any genetic contribution.

Male Sprague-Dawley rats (6 weeks of age) were procured locally and were divided into control ($n = 8$) and fructose ($n = 8$) groups. At week 7 (weeks denote age of rats), the fructose group was started on a 66% fructose diet to induce hypertension as described previously (Verma et al., 1994, 1996). At week 15, thoracic aortae from both groups of rats were carefully dissected out and cut into ring segments. The tissues were suspended on wire hooks in isolated tissue baths (under 2 g tension) containing modified Krebs-Ringer bicarbonate solution (containing 0.05% albumin) maintained at 37°C as described previously. No effort was made to remove the endothelium. After a 90 min equilibration period, isometric responses were recorded on a Grass 79 D polygraph as per the following protocol: (1) a cumulative dose-response curve to angiotensin II (10^{-12} to 10^{-5} M) in the absence of insulin and (2) a cumulative dose-response curve to angiotensin II in the presence of insulin (100 mU/ml for 2 h, Humulin N). The tissues were allowed to equilibrate for 60–90 min between steps 1 and 2. Systolic blood pressure, plasma glucose and insulin (5 h fasting values) were determined as described previously (Verma et al., 1994, 1996).

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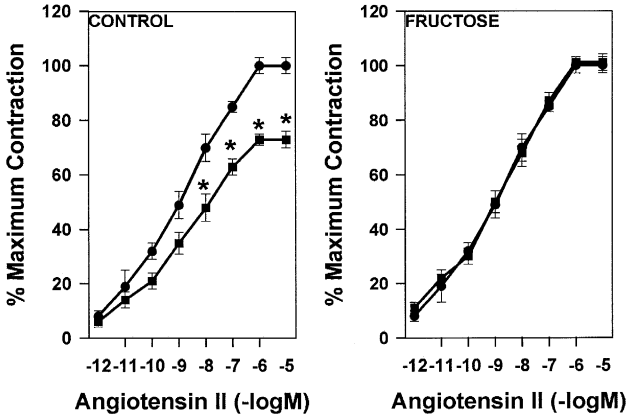

Fig. 1. Reactivity of isolated aortae from control ($n = 8$, left panel) and fructose-hypertensive rats ($n = 8$, right panel) to angiotensin II in the absence (●) and presence (■) of insulin (100 mU/ml for 2 h). Absolute tension values corresponding to 100% in g/mm^2: control 2.3 ± 0.1, control + insulin 1.53 ± 0.3, fructose 2.4 ± 0.2, fructose + insulin 2.2 ± 0.3.

The fructose group exhibited hyperinsulinemia (4.1 ± 0.5 ng/ml vs. control 2.2 ng/ml, $P < 0.05$), insulin resistance (5 h fasted insulin to glucose ratio: 0.53 ± 0.05 vs. control 0.27 ± 0.08, $P < 0.05$) and elevated blood pressure (153 ± 2 mmHg vs. control 129 ± 3 mmHg, $P < 0.05$) when compared to the control group. Fig. 1 depicts the effects of insulin on the contraction elicited by cumulative addition of angiotensin II in rat aortic rings from control and fructose rats. Insulin caused vasodepressor effects in control rat aortae; in the presence of insulin both the percent maximum contraction and the sensitivity were attenuated (percent maximum attenuation by insulin: 28 ± 3; pD_2 values: 7.49 ± 0.04 vs. control + insulin 8.10 ± 0.05, $P < 0.05$). Strikingly, insulin-induced attenuation of angiotensin II responses was absent in aortae from fructose rats. Neither a rightward nor downward shift of the angiotensin II dose-response curves were observed in fructose rats in the presence of insulin (Fig. 1, right panel).

Data from this study reinforce accumulating evidence indicating that insulin exerts effects on vascular smooth muscle tone and provide a hemodynamic basis for hypertension in insulin-resistant fructose-hypertensive rats. It is important to note that multiple drug interventions that possess insulin-sensitizing properties lead to concurrent decreases in plasma insulin levels and blood pressure in fructose-hypertensive rats (Bhanot and McNeill, 1996). By contrast, diverse antihypertensive-vasodilator agents have also been shown to improve insulin sensitivity and decrease plasma insulin levels (Kotchen, 1996). In the former case, the antihypertensive effects of insulin sensitizers have been attributed to their ability to counter hyperinsulinemia and thereby correct the hypertensinogenic mediator(s) linking insulin to blood pressure. On the other hand, the ability of vasodilator-antihypertensive agents to increase insulin sensitivity may be an indirect consequence of drug-induced vasodilation and hence an increased blood flow to insulin-sensitive tissues. As resting blood flow has been proposed to be an important determinant of insulin sensitivity (Baron, 1993), it has been speculated that some common mechanism (such as increases in vascular smooth muscle tone) may underlie both the expression of insulin resistance/hyperinsulinemia and hypertension. Thus on one hand, insulin resistance results in vasoconstriction while on the other hand vasoconstriction results in decreases in blood flow to insulin target tissues, which further worsens insulin resistance. Thus, if the cycle is interrupted by agents that directly improve insulin sensitivity or by vasodilators that improve blood flow, the final outcome is an improvement in insulin sensitivity, a decrease in plasma insulin levels and a decrease in blood pressure (Kotchen, 1996).

In summary, data from this study demonstrate for the first time the presence of vascular insulin resistance in fructose-hypertensive rats and suggest that in states of insulin resistance, insulin's vasodilatory effects are blunted, which may be important in the development and/or reinforcement of the hypertensive state.

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