Insulin, Leptin, and Membrane Microviscosity in Blood Pressure Regulation

To the Editor:

We read with great interest the recent article by Vecchione and colleagues1 dealing with a possible link between insulin and leptin in the regulation of vascular tone in rats.1 The results of their presented study demonstrated that insulin and leptin cooperated in the modulation of vascular tone through enhancement of endothelial nitric oxide (NO) release. Vecchione et al proposed that direct cross-talk between insulin and leptin at the vascular level could have a major impact on the regulation of cardiovascular system in metabolic disorders and hypertension.

Numerous studies have already shown a strong relationship between obesity and hypertension.2,3 However, the contribution of insulin and leptin to the pathogenesis of hypertension is not fully understood. Recently, Sela et al4 demonstrated that polymorphonuclear leukocytes (PMN) in essential hypertension showed increased level of intracellular calcium content correlating positively with the individual’s blood pressure and plasma insulin. They proposed that, because PMN priming may lead to oxidative stress and inflammation, intracellular calcium and insulin are involved in the pathogenesis of hypertension-induced vascular injury. In a study we presented earlier, a relationship between membrane fluidity (a reciprocal value of membrane microviscosity) of erythrocytes and insulin was investigated in essential hypertension by means of an electron paramagnetic resonance method.5 The membrane fluidity of erythrocytes was significantly lower in patients with essential hypertension than in normotensive subjects. In addition, it was demonstrated that the higher the plasma insulin level, the lower the membrane fluidity of erythrocytes, which might indicate that hyperinsulinemia might be involved in the regulation of membrane fluidity of erythrocytes in essential hypertension. In an in vitro study, we showed that insulin alone and in combination with calcium decreased membrane fluidity of erythrocytes in essential hypertension.6 It is likely that the insulin-evoked decrease in membrane fluidity of erythrocytes may partially be mediated by the increased intracellular calcium content.7 The decreased membrane fluidity of erythrocytes might cause a disturbance in the blood rheological behavior and the microcirculation, which could contribute, at least in part, to the pathophysiology of hypertension.8,9 One hypothesis is that insulin might accelerate abnormalities in intracellular calcium metabolism and membrane function in blood cells such as PMN and erythrocytes, which could partially explain the vascular complications in hypertensive subjects with hyperinsulinemia. In contrast, it was demonstrated that leptin significantly increased the membrane fluidity of erythrocytes and improved the rigidity of cell membranes via the NO- and cGMP-dependent mechanism.10 The result might be consistent with the finding of Vecchione et al showing that leptin enhanced NO release. It is possible that insulin and leptin may exert opposite effects on membrane microviscosity of erythrocytes, although the precise mechanism underlying their modulatory effects on the membrane function is still uncertain. In this context, it can be speculated that a functional interaction between insulin and leptin may differ among tissues. It would be necessary to assess more precisely the roles of insulin and leptin and their contribution to the pathophysiology of hypertension.

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Response: Insulin–Leptin Interplay May Differ Among Tissues

We thank Tsuda et al for their letter in which they appreciate our study showing that both insulin and leptin evoke vascular endothelial nitric oxide release and, importantly, that the combination of two hormones potentiates their single effect on vascular nitric oxide production.3 The same authors have previously reported that insulin and leptin have contrasting effects on membrane fluidity in erythrocytes.2,3 In particular, they showed that insulin decreases the membrane fluidity of erythrocytes, and this effect is mediated by intracellular calcium.2 In contrast, leptin improves membrane fluidity in erythrocytes through a nitric oxide-dependent mechanism.3 The authors indicated that this latter evidence might be comparable to that observed in our study showing vascular nitric oxide release induced by leptin.1 However, our study demonstrated that insulin also has a positive effect on vascular nitric oxide,3 so that our results obtained on isolated vessels do not entirely explain the different action of insulin and leptin on the membrane fluidity of erythrocytes. Moreover, it is well known that at the vascular level, calcium is not a crucial element for insulin and leptin action on nitric oxide release,4,5 in contrast to that observed for insulin action on membrane fluidity of erythrocytes.2 Indeed, it has been reported that insulin, similar to that observed with leptin, also activates nitric oxide production in membranes of erythrocytes.6,7 but the impact of insulin-stimulated nitric oxide release or of the interaction of the two hormones on membrane fluidity of erythrocytes is still unexplored. However, several studies have shown that the combined effect of insulin and leptin can have promoting effects on some targets and conflicting in others. In particular, Kim et al reported that leptin and insulin cooperate to inhibit hepatic glucose output, but at same time leptin antagonizes insulin action on the gene expression for two key metabolic enzymes, glucokinase and phosphoenolpyruvate carboxykinase.8 Similarly, Szanto et al
reported that leptin exposure enhances insulin-induced tyrosine phosphorylation and PI3K-binding to IRS-1 while producing inhibition of insulin-evoked tyrosine phosphorylation and PI3K-binding to IRS-2.9

In conclusion, we agree with Tsuda et al that the interplay between insulin and leptin may differ among tissues, thus raising the demand for further studies focused on the several actions of the two metabolic hormones.

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