Vasodilator Response to Local Hyperinsulinemia

To the Editor:

Cardillo et al recently reported that systemic but not local hyperinsulinemia causes nitric oxide (NO)-dependent vasodilatation. They suggest that mechanisms stimulated only by systemic but not local hyperinsulinemia contribute to insulin-mediated vasodilatation. We believe that this conclusion is mistaken.

The changes in forearm blood flow during systemic and local hyperinsulinemia in their study were not directly comparable. Thus, although similar concentrations of insulin were achieved in both protocols, there was an artificial dissociation of insulin and glucose levels in the experiment with local hyperinsulinemia: in other words, no glucose supplement was administered in the local experiment, whereas euglycemia was maintained in the systemic study (using the clamp technique). It is likely, therefore, that glucose levels fell in the infused arm in the local experiment, whereas euglycemia was maintained in the other arm, no glucose supplement was administered in the local experiment, whereas euglycemia was maintained in the systemic study (using the clamp technique). It is likely, therefore, that glucose levels fell in the infused arm in the local experiment and that a discrepancy in forearm glucose uptake between the two conditions may have accounted for the different vasodilator responses to insulin observed.

In support of this alternative explanation, we have consistently shown that intra-arterial infusion of insulin at 5 mU/min (resulting in insulin concentrations of 100 μU/mL in deep venous effluent sampled from the infused forearm), using a strict experimental protocol with a double-blind crossover design and measurement of forearm blood flow ratio (infused: control arm), causes detectable but weak vasodilatation (approximately 20%). In contrast, insulin at the same dose and supplemented by D-glucose at 75 μmol/min (maintaining local venous euglycemia) causes early and significant (50% to 60%) vasodilatation in the human forearm. This response is not replicated when the stereoisomer L-glucose (which is not recognized by glucose transporters) is substituted. Our results strongly suggest that insulin causes direct, locally-mediated vasodilatation that is dependent on local glucose uptake. Furthermore, glucose-dependent insulin-mediated vasodilatation has been well-documented in in vitro experiments.

There have been conflicting reports on the direct vascular actions of insulin. While several investigators have shown insulin-mediated vasodilatation during systemic hyperinsulinemia in euglycemic clamp studies, local administration of insulin has been reported to produce either no change in blood flow or only a small response. Our study clearly suggests that the discrepancy between systemic and local insulin administration may result from artificially low rates of local glucose availability and uptake in the latter.

As under physiological circumstances, insulin is secreted by the B-cell in response to elevated glucose concentrations; however, concomitant hyperinsulinemia and hypoglycemia as used in the study by Castillo et al does not occur except when exogenous insulin is infused. We believe, therefore, that the local hyperinsulinemia model without concomitant D-glucose infusion is of questionable relevance in the investigation of the physiology of insulin’s vascular effects.

Shinichiro Ueda
Department of Medicine
Yokohama City University School of Medicine
Yokohama, Japan


Response

Ueda et al base their criticism of our study on the assumption that local hyperinsulinemia without glucose supplementation causes hypoglycemia that, in turn, could have prevented us from observing a vasodilator effect of insulin during local infusion of the hormone. However, local infusion of insulin, at the doses used in our study, does not induce systemic hypoglycemia (although not reported in the manuscript, plasma glucose levels in the affluent artery during experiments with local hyperinsulinemia were 4.8±0.1 mmol/L compared with 5±0.1 mmol/L at baseline). Therefore, the supply of glucose to the infused forearm was similar during local and systemic administration of insulin.

In other words, systemic euglycemia was maintained in both experiments (1) during systemic infusion of insulin by means of concomitant systemic administration of glucose and (2) during local infusion of insulin by the fact that the small doses of insulin did not influence systemic glucose levels. Further, in our studies with local insulin infusion, we observed a 4-fold increase in forearm glucose uptake (from 0.9±0.2 to 3.7±0.5 μmol/min/dL). If glucose uptake were a major determinant of the hemodynamic effect of insulin, as suggested by Ueda et al, we should have observed at least some degree of vasodilation in our study. Ueda et al refer to the results of their previous study2 to support the notion that local availability of glucose (and therefore glucose uptake) is an important determinant of insulin-mediated vasodilation. It must be noted, however, that in their experiments with local infusion of insulin, Ueda et al aimed to achieve euglycemia in the venous effluent by supplementing D-glucose to the infused forearm, which undoubtedly resulted in hyperglycemia in the local arterial vasculature. Thus, from the results of their study, we would conclude that it is the increases in the supply of glucose that induces a vasodilator effect of insulin; this does not necessarily imply a cause-effect relationship between glucose uptake and vasodilation. Finally, the impact of glucose uptake on the vasoactive effects of insulin was studied previously by Vollenweider et al, who performed experiments with systemic administration of insulin/glucose, glucose alone, or fructose. These authors observed that, for a comparable rise in carbohydrate oxidation (and therefore similar glucose metabolism), hyperinsulinemia evoked a much higher increase in limb blood flow compared with glucose alone (intermediate insulin...
levels) and fructose (low insulin levels), indicating that insulin per se, rather than insulin-mediated glucose uptake, is the mechanism triggering vasodilation in skeletal muscle. In summary, based on the results of our study, the reasoning summarized above, and the results of previously published investigations (including that by Ueda et al), we still believe that, during concomitant euglycemia, insulin has no or only a negligible direct vasodilator effect.

Carmine Cardillo, MD
Julio A. Panza, MD
Cardiology Branch
National Heart, Lung and Blood Institute

Vasodilator Response to Local Hyperinsulinemia
Shinichiro Ueda, John R. Petrie, Stephen J. Cleland, Henry L. Elliott and John M.C. Connell

Hypertension. 1999;34:e12-e13
doi: 10.1161/01.HYP.34.6.e12

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/34/6/e12

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/