Insulin and Membrane Microviscosity of Erythrocytes as Risk Factors for Stroke

To the Editor:
I read with great interest the comments by Dr Kernan and colleagues dealing with the insulin sensitivity in nondiabetic patients with a recent transient ischemic attack or ischemic stroke. The results of their presented study demonstrated that pioglitazone may be effective for improving insulin sensitivity with a concomitant decrease in fasting plasma insulin concentration in these patients. Kernan et al proposed that because the prevalence of impaired insulin sensitivity is high among patients with stroke, thiazolidinediones may improve the morbidity and mortality of this disease.

In a study we presented earlier, a relationship between membrane fluidity of erythrocytes and plasma insulin was investigated in patients with essential hypertension by means of an electron paramagnetic resonance method. Membrane fluidity (the reciprocal value of membrane microviscosity) is a physicochemical feature of biomembranes that is an important factor in modulating cell rheologic behavior. The membrane fluidity of erythrocytes was significantly lower in patients with essential hypertension than in normotensive subjects. The plasma content of insulin while fasting was significantly greater in hypertensive patients 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 a determinant of membrane fluidity of erythrocytes in essential hypertension. Barbagallo et al reported that insulin significantly elevated the intracellular calcium level of human erythrocytes in a dose- and time-dependent manner. With regard to the interaction between calcium and membrane fluidity, it was observed that calcium strongly decreased membrane fluidity of erythrocytes and other cells. In an in vitro study, we showed that insulin alone and in combination with calcium decreased membrane fluidity of erythrocytes in essential hypertension. It is likely that the insulin-evoked decrease in membrane fluidity of erythrocytes may be partially mediated by the increased intracellular calcium content. If the deformability of erythrocytes may be highly dependent on the membrane fluidity, the reduction in membrane fluidity might cause a disturbance in blood rheologic behavior and microcirculation, which could, at least in part, contribute to the risk factors of vascular complications.

In this context it can be speculated that the reduced plasma insulin level evoked by pioglitazone might restore the rheologic behavior of erythrocytes and microcirculation in patients with stroke. It is possible that the effect of pioglitazone could be beneficial for the protection against repeated attacks of stroke in patients with hyperinsulinemia.

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Response
Thiazolidinediones (TZDs), such as pioglitazone, have potent vasoprotective effects. They improve vascular reactivity, reduce monocye adhesion to endothelial cells and migration into nascent atheroma, retard vascular smooth muscle cell proliferation, decrease concentrations of circulating inflammatory cytokines, improve fibrinolysis, and favorably alter lipid metabolism. In recently published research, pioglitazone was shown to markedly reduce in-stent restenosis after coronary stent implantation. These favorable effects are thought to be mediated by binding of TZDs to a nuclear transcription factor, peroxisome proliferator-activated receptor γ.

Dr Tsuda proposes that TZD therapy for stroke patients may prevent recurrent vascular events by lowering serum insulin concentration and, consequently, improving erythrocyte deformability. In support of this proposal, Dr Tsuda describes his own research showing that insulin impairs erythrocyte fluidity and our research showing that pioglitazone lowers serum insulin after stroke in nondiabetic patients. It has been known for many years that type 2 diabetes is associated with impaired erythrocyte deformability, but this relationship is weak and of uncertain clinical importance. Abnormal erythrocyte deformability observed in hyperinsulinemic states may have a greater effect, for example, on small vessels (eg, retinal vessels) than on large vessels (eg, branches of the cerebral arteries).

The relationship between insulin and vascular health is complex. At high concentrations, insulin may stimulate endothelial cell proliferation and have other deleterious vascular effects. On the other hand, insulin is known to have potent vasodilatory and anti-inflammatory actions, and the improvement in hyperglycemia that results from insulin therapy in diabetic patients likely has additional beneficial effects.

We are not aware of any research on the effect of TZDs on erythrocyte deformability or viscosity. If such effects were found, investigators would have one more reason to begin clinical trials to test the effectiveness of these agents for secondary prevention of stroke. In our opinion, however, the principal vasoprotective effects of TZDs operate through other mechanisms.


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