

Review

INSULIN – A VASOACTIVE HORMONE

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ABSTRACT

Insulin is the single and the most important anti hyperglycemic hormone, whose metabolic actions are proven and are vital for the normal functioning of the body. Apart from being a metabolic hormone, insulin has been shown to be a vasoactive hormone also.

The vasodilatation caused by insulin results in increased skeletal muscle blood flow, which has been coupled to the increase in muscle glucose uptake. The mechanism by which insulin causes this effect is not very clear but the role of nitric oxide release by vascular smooth muscle cells, adenosine, cyclic AMP, cyclic GMP and role of insulin on $\text{Na}^+\text{-K}^+$ ATPase has been proposed. The mechanism seems to be a complex one and further understanding is required.

As various factors like insulin resistance and free fatty acid levels affect this vasodilatation, modulation of the vascular tone and skeletal muscle blood flow may be a novel therapeutic target to overcome the adverse effects of insulin resistance and reducing the complications associated with it.

KEY WORDS: Nitric oxide; Nitric oxide synthase; N-monomethyl L-Arginine ; Guanosine triphosphate

Insulin is the only hormone present in the body having anti-hyperglycemic effects. Apart from being the most important hormone in regulation of blood glucose levels, it also has vascular actions, which sometimes makes us consider insulin as a vasoactive hormone.

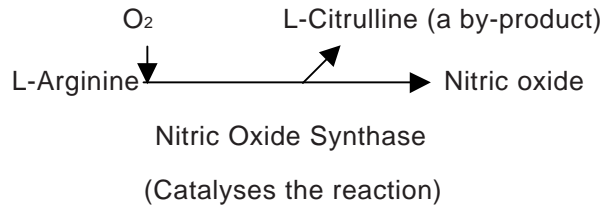
It has been observed that significant increase in limb blood flow occurs in response to systemic hyperinsulinemia, although there is marked variations in the results due to a number of confounding factors. Blood flow response to insulin is influenced by:

- i. the method used to quantitate blood flow
- ii. dose and duration of the insulin exposure
- iii. limb muscularity

- iv. states of insulin resistance like type 2 diabetes mellitus,
- v. plasma free fatty acid levels.

Different scientists have utilized various methods to measure blood flow across the limb like thermodilution technique, plethysmography (by slow approach or withdrawal method) or Doppler ultrasound technique. All these techniques have given different results for differing insulin concentrations. Thus till now, no standardized, universally accepted method of measuring blood flow across a limb has been found.

Insulin has been shown to cause peripheral vasodilatation and increased blood flow via a nitric oxide dependent mechanism. Nitric oxide is synthesized from L-Arginine by the following reaction:



Nitric oxide itself might inhibit the activity of nitric oxide synthase by interacting with the heme moiety of this enzyme. Physiological effects are produced after nitric oxide binds to the heme moiety of guanylate cyclase, leading to conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) in target cells (3).

Insulin displays a dose dependent effect to increase blood flow to skeletal muscle by causing nitric oxide dependent vasodilatation in skeletal muscle vasculature. Abrogation of insulin-mediated vasodilatation of human leg vasculature with the nitric oxide synthase inhibitor L-NMMA (N-monomethyl L-arginine) could reduce this flow. It has been proposed that via its effects of releasing nitric oxide from vascular endothelium, insulin reduces pre capillary arteriolar

tone and alters arteriolar vasomotion with a resultant increase and more homogeneous overall capillary perfusion termed as “functional capillary recruitment”, which allows greater capillary exchange of substrate. Insulin is also able to alter fixed permeability capillary recruitment ratio, further suggesting an increase in capillary exchange surface area or capillary recruitment. Thus a diminished vasodilator response to insulin might reflect an endothelial dysfunction. Limb muscle content is also an important contributor to blood flow, showing inter individual differences (4-8).

Different parts of the arterial tree have distinct hemodynamic functions. Terminal arteries and arterioles control peripheral vascular resistance and blood flow, while conduit vessels serve as a pressure buffering and blood carrying system. The contribution of nitric oxide to endothelium-dependent vasodilatation depends on the size of the artery and is more pronounced in larger arteries than in distal microvessels. Normal insulin action on the large vessels is to reduce arterial stiffness and this effect precedes the slow vasodilator effects of insulin in the periphery. However, this action of insulin has a slow time course and requires prolonged exposure of tissues to insulin for at least three hours (9,10).

Insulin also modulates the vascular tone by regulating vascular smooth muscle cell cation metabolism. In insulinopenic and insulin resistant states like diabetes mellitus, the $\text{Na}^+ - \text{K}^+$ ATPase activity (an ATP dependent enzyme), may lead to an accumulation of Na^+ . This leads to changes in $\text{Na}^+ - \text{Ca}^{++}$ exchange, with resultant increase in vascular smooth muscle cell Ca^{++} , which in turn causes vasoconstriction, an usual finding in these states. Insulin stimulates $\text{Na}^+ - \text{K}^+$ ATPase activity in vascular smooth muscle cells by translocation of preformed $\text{Na}^+ - \text{K}^+$ ATPase molecules to the plasma membrane, modification of the enzymes affinity for ATP, Na^+ and K^+ , stimulation of message expression of new pump units and secondary stimulation through the mass action effects of Na^+ (11,12).

Insulin increases the vascular smooth muscle cell content of both cyclic AMP and cyclic GMP, well known mediators of vasodilatation. It has been shown that the insulin induced cyclic GMP increase in vascular smooth muscle cells is due to nitric oxide formation (13,14).

Involvement of adenosine receptor has been also

hypothesized in insulin-induced vasodilatation. Through various experiments it was demonstrated that insulin induced increase in blood flow in the arm is more pronounced at the site of adenosine – uptake blockade by draflozine (an adenosine uptake blocker), whereas reduced blood flow has been seen during adenosine receptor antagonism by theophylline (an adenosine receptor antagonist), indicating mediation of insulin induced vasodilatation by adenosine. (15)

Hyperinsulinemia significantly increases choroidal blood flow and mean blood flow velocity in the ophthalmic artery, but retinal blood flow is not influenced. This effect over ocular hemodynamics is seen at physiological insulin levels (16). Insulin has a significant renal vasodilatory effect and it increases renal plasma flow. The vasoconstrictor response to angiotensin II can be attenuated by physiological hyperinsulinemia in isolated rat kidneys (16-18). No hemodynamic effects of insulin have been seen in the splanchnic circulation (19).

Insulin increases skeletal muscle blood flow despite increasing sympathetic activity. The mechanisms of these seemingly antagonistic effects are unclear. However, insulin may selectively antagonize adrenergic mediated vasoconstriction resulting in vasodilatation. Thus, insulin acts as an endogenous vasodilator (20,21).

Intra-arterial infusion of insulin in physiological doses causes forearm vasodilatation that is augmented by co-infusion of D-glucose, leading us to speculate that local insulin mediated vasodilatation may depend on insulin mediated glucose uptake. Thus it seems that there is a significant functional relationship between insulin’s metabolic and vascular actions, probably at the endothelial level. Thus the blood flow may play an important role in determining uptake, presumably through a capillary recruitment mechanism. ACE inhibitors may act in part to improve insulin sensitivity in diabetic patients by increasing flow to skeletal muscle. The blunted increase in skeletal muscle blood flow in response to insulin in type 2 diabetes appears to be due to the diabetic state per se (22,23).

In type 2 diabetic patients, both reduced skeletal muscle tissue permeability and blood flow has been observed. Insulin augments skeletal muscle blood flow in a dose dependent fashion over physiologic insulin concentrations (24).

In patients with chronic heart failure, insulin acts as a selective skeletal muscle vasodilator that leads to increased muscle perfusion primarily through redistribution of regional blood flow rather than by increased cardiac output. Thus it seems clinically beneficial to give insulin in situations like congestive cardiac failure (25).

Insulin resistant states, which by definition, exhibit diminished insulin mediated glucose uptake into peripheral tissue also display impaired insulin mediated vasodilatation as well as impaired endothelium dependent vasodilatation to the muscarinic receptor agonist acetylcholine. Free fatty acids elevation also causes endothelial dysfunction along with impaired insulin mediated vasodilatation. Thus a picture is emerging linking insulin action in peripheral tissues to its action on the endothelium (26,27).

Therefore a complex interaction between insulin mediated vasodilatation and skeletal muscle blood flow, serum free fatty acid levels, insulin mediated glucose uptake and endothelial dysfunction may be a central link between insulin resistance, blood pressure, impaired glucose tolerance and the risk of cardiovascular disease. An understanding of the primary mechanisms resulting in these phenotypes may reveal new therapeutic targets to prevent metabolic and cardiovascular complications in diabetes. As decreased rates of insulin mediated glucose uptake in type 2 diabetic patients are associated with defects, both in insulin's action to increase glucose permeability at the level of skeletal muscle and a blunted response to insulin mediated augmentation of skeletal muscle blood flow, from a therapeutic stand point, modulation of vascular system to increase skeletal muscle blood flow may represent a potential novel target for pharmacological intervention to improve insulin sensitivity, glucose tolerance and hyperinsulinemia in patients with insulin resistance.

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