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For debate

Insulin resistance syndrome: possible key role of blood flow in resting muscle

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Since the greater part of insulin-mediated glucose disposal occurs in muscle any reduction of muscle uptake has been perceived as "insulin resistance" (IR). In most cases, however, the mechanism is unexplained and the supposed connection with insulin must be seriously questioned. By definition, insulin is the normal rate-limiting factor for insulin-dependent glucose uptake. IR indicates that some other factor – not necessarily related to insulin – tends to take over this role. Although this new restricting factor is not well known in common IR, most likely it is to be found among the factors which set an upper limit for glucose uptake, when insulin is raised beyond physiological levels. The presence of such latent limiting factors in normal subjects is illustrated by the hyperinsulinaemic euglycaemic clamp curve. As soon as insulin begins to exceed the physiological range the curve begins to level off, indicating that glucose uptake has encountered some other limiting factor. Muscle blood flow may well be this factor [1].

The present discussion is an attempt to show how reduced blood flow in resting muscle may have a key role in the development of common IR. It may not only restrict glucose delivery to muscles and cause impaired glucose tolerance and Type 2 (non-insulin-dependent) diabetes mellitus but may also explain, or be explained by, fundamental features of the other disorders of the proposed insulin resistance syndrome [2–4].

Muscle blood flow and insulin-dependent glucose uptake in normal subjects

The hyperinsulinaemic euglycaemic insulin clamp has become something of an operational definition for IR. The metabolic conditions it imposes are therefore of special interest. For kinetic reasons, blood flow in muscles must be rate-limiting for their glucose uptake if a high insulin level is combined with a normal glucose level [5]. Glucose extraction of 20–30 % across the leg or forearm has been reported [6,7], but part of the venous blood came from tissues with low uptake. Therefore, we can assume that muscle uptake may have been as high as 40 %. With arterial blood glucose clamped at 5 mmol/l, venous blood leaving muscles would then contain 3 mmol/l. The interstitial fluid level would also be 3 mmol/l, or lower if equilibrium is not attained across the capillary wall. This level is crucial for the uptake, since the insulin-dependent glucose transporter has an apparent K_m of about 6–8 mmol/l [8, 9]. It therefore operates within the range where transport rate is directly dependent on the concentration. A lower rate of blood flow would cause a fall in delivery of glucose and a lower interstitial fluid level and thus a corresponding fall in the cell uptake rate [5]. That blood flow has this effect has been demonstrated in animals [10–12].

Another indication for glucose delivery being rate-limiting for cell uptake in the hyperinsulinaemic state comes from a more complex kinetic study in normal young male subjects [8]. Glucose disposal was studied at varying insulin (9 to 1700 mU/l) and glucose (5 to 22 mmol/l) levels. K_m-values were found to increase from 7–8 mmol/l for the lowest insulin level to about 30 mmol/l for the highest. The authors considered the increase to be apparent and caused by a shift in the rate-limiting step from cell membrane transport to "some step beyond". Although this step was not specified, the implication that it may be some of the enzymatic steps on the pathway to glycogen must be questioned. Assuming the insulin-dependent glucose transporter to be the only rate-limiting factor, Michaelis-Menten curves with identical K_m-values would be obtained for all insulin levels. If a high uptake rate would lead to some enzymatic step becoming overloaded, metabolites would accumulate backwards from the new rate-limiting step and prevent further increase of uptake. V_{max} for disposal at the highest glucose level would be suppressed, but glucose disposal at lower levels would be less influenced. This would cause an apparent reduction of the K_m-value (Fig. 1). If, on the other hand, high insulin-mediated cell uptake capacity would lead to glucose delivery becoming critical, it would affect the actual uptake most strongly at low blood glucose levels. The first part of the curve would then be suppressed more than V_{max}, leading to an apparent increase in K_m, in agreement with reported data. Therefore, even if the authors may have come to a

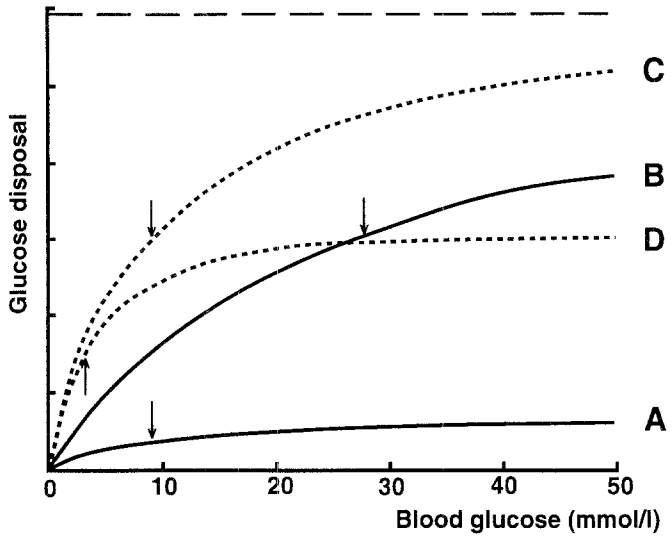

Fig. 1. Distortion of glucose disposal kinetics by a rate-limiting step before and after the cell membrane transport. A and B: Reported glucose uptake at basal and maximal (1700 mU/l) insulin levels [8]. C: Expected curve with K_m (↓) of curve A and V_{max} (— — —) of curve B. D: Uptake with transport capacity as in C but with an intracellular rate-limiting step. Arrows indicate K_m for the respective curve

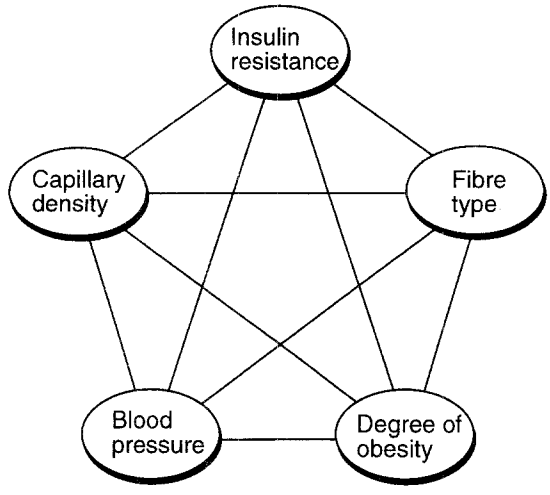

Fig. 2. Reported correlations (positive and negative) between some physiological variables

different conclusion, the report seems to indicate that the new rate-limiting factor, appearing at high insulin levels, is positioned prior to the glucose transporter. Blood flow and capillary diffusion are then the only candidates.

A third indication that blood flow in resting muscle is rate-limiting for insulin-dependent glucose disposal may be found in studies on the effect of muscle exercise. Exercise has a well-known, beneficial effect on the metabolic control in Type 2 diabetes and is also a powerful stimulator of insulin-dependent glucose uptake in normal subjects. That blood flow is the limiting factor is indicated by a study combining insulin clamp with bicycle exercise and measurement of blood flow and glucose uptake in the leg [13]. A close correlation was found between glucose uptake and leg blood flow ($r = 0.935$). Similar results were obtained for rat hindlimbs, stimulated electrically to contract [10].

A fourth indication for blood flow being rate-limiting for glucose uptake may be inferred from comparative physiology. The trans-membrane transport capacity of human erythrocytes exceeds the metabolic needs of the cells more than 10,000-fold [14]. An almost instantaneous equilibrium is therefore maintained between the erythrocyte and plasma glucose levels, making intracellular water space also available for transport to the tissues. Primates are reported to be unique in this respect, other mammalian erythrocytes having a high transporter capacity only during fetal life [14]. This may suggest that blood flow is rate-limiting for the delivery of glucose to some important tissue and that it has proved necessary during evolution to utilize the erythrocyte water for the transportation. Humans are also unique in having a very low blood flow rate in resting muscle, about 20 $ml \cdot min^{-1} \cdot kg^{-1}$ muscle, most other mammalians having flow rates of 50–100 $ml \cdot min^{-1}$ $kg \cdot ^{-1}$ [15]. Brain and placenta have been proposed as the organs which require additional glucose supply but muscle seems a much more plausible candidate. Most of the glucose taken up by brain and placenta is oxidized and glucose extraction can hardly increase beyond the limit set by oxygen supply. Extractable oxygen of fully saturated blood can at most oxidize glucose corresponding to 1 mmol/l. Glucose storage in muscle requires much less oxygen (theoretically about 6%) for the same amount of glucose to be taken up. Therefore, muscle should be able to extract more glucose, but uptake is restricted by the fall in the interstitial glucose level it causes and by the low blood flow rate. Glucose-transporting erythrocytes may help muscle to circumvent this problem.

Blood flow thus influences glucose uptake, but a reverse effect also exists. In normal males, leg blood flow increased from 250 to about 400 ml/min when basal insulin was raised to about 300 mU/l. A concomitant rise of the glucose level from 5 to 25 mmol/l further increased leg flood flow to about 650 ml/min [9, 16]. This implies that muscle blood flow and glucose uptake are coupled in a system of mutual reinforcement that might serve as a feedback system, adjusting disposal of glucose to the actual influx to the blood. These complex interactions emphasize the role of muscle blood flow in the pathogenesis of IR.

Muscle blood flow in the insulin resistance syndrome

Few studies have been performed on blood flow of resting muscle in IR and Type 2 diabetes and thus, it is not clear how blood flow may be influenced. Some authors have reported that the flow rate is less sensitive than normal to factors causing vasodilation, e. g. exercise [17, 18], glucose uptake (see below) or infusion of acetylcholine and glyceryl trinitrate [19]. The findings are consistent with the hypothesis that in IR the resistance vessels are in a constant state of relative dilation, possibly to compensate for restricting structural changes [17].

Basal leg blood flow in obese subjects did not differ significantly from that in lean subjects but increased much less when insulin and glucose were clamped at high levels

[9, 16]. Laakso et al. [20, 21] concluded that the difference in blood flow response had contributed significantly to the lower rate of glucose uptake in obese subjects and constituted "a novel mechanism of insulin resistance". Clamp studies were also performed on obese, Type 2 diabetic subjects with even lower insulin sensitivity and responsiveness. Leg blood flow response during the clamp was much lower than in non-diabetic subjects [20, 21]. The authors considered the decreased insulin responsiveness in the Type 2 diabetic group "to be largely due to reduced skeletal muscle blood flow".

Recently, the hypothesis was presented that "haemodynamic factors" are the link between IR and hypertension [22]. The most convincing arguments were compiled from reports on the metabolic effects of antihypertensive agents. Beta-receptor blocking agents and and thiazide drugs decrease cardiac output and blood flow. In addition they have well-known adverse effects, which increase IR and impair glucose tolerance [23–25]. Alpha-adrenergic antagonists and angiotensin-converting-enzyme inhibitors are peripheral vasodilators which increase blood flow and they have an alleviating effect on IR [24, 26, 27]. Calcium channel blockers also decrease vascular resistance, but only weak alleviating effects on IR have been noted [28]. It is remarkable that all major groups of antihypertensive agents affect IR exactly in the way that they would do, if muscle blood flow had a major role in the development of IR. The mechanism is probably via decreased delivery of glucose. The possibility of insulin delivery being the critical factor [29] seems less likely since it could not lead to decreased insulin responsiveness.

The same haemodynamic factors may contribute to IR-related dyslipidaemia. Antihypertensive agents affect plasma triglycerides essentially as they affect glucose, i. e. thiazides and beta-blockers clearly increase the level [24, 30–32], alpha-blockers clearly decrease it [30, 32–34], angiotensin-converting-enzyme inhibitors cause a slight decline [24, 30] and calcium-blocking agents have no clear effects [30]. The elevated triglyceride level is usually ascribed to increased synthesis although it is obvious that the catabolic rate also influences the level. Muscle endothelial lipoprotein lipase is decreased by 25–50% in obesity and Type 2 diabetes [35]. The fact that this enzyme is rate-limiting for triglyceride utilization does not mean that blood flow is not rate-limiting as well, rather the opposite. Only a few capillaries are perfused at rest with the number increasing proportionally as blood flow increases. More lipase is then brought into contact with the blood stream. Therefore, theoretically, muscle blood flow should be rate-limiting for the disposal of triglycerides.

Vascular and rheologic changes in conditions with IR

Long-term diabetes is associated with microangiopathy in many tissues, including skeletal muscles [36, 37]. Its main characteristic is thickening of the capillary basement membrane. The occurrence of microangiopathy is related to the aging process, hypertension, duration of diabetes and degree of metabolic control. In Type 2 diabetes the first signs may appear early in the history suggesting an independent, possibly genetic, cause. Opinions differ as to how blood flow is influenced in the early stages of diabetes but there is good reason to assume that microangiopathy over a long period of time leads to microvascular failure and decreasing blood flow [38].

Erythrocytes from diabetic patients, both Type 1 (insulin-dependent) and Type 2, show poor rheologic properties. Higher pressure has to be applied for cells to pass narrow capillaries with the same velocity as cells from non-diabetic subjects. Deviation of up to 50% from the value for non-diabetic subjects has been reported [39]. Reduced deformability and increased aggregation tendency are considered to be the cause [39, 40] and several investigators have found these changes to correlate with the metabolic control. Similar rheologic changes have been demonstrated in erythrocytes from diabetic mice, rats and rabbits and also in leucocytes from human diabetic patients.

Long-standing hypertension is accompanied by rarefaction of small blood vessels in various tissues, 40–50% in skeletal muscles [40], and similar changes have been noted in animal models of hypertension [41–43]. Moreover, capillary density correlates with the percentage of oxidative fibres in the muscles [44] and both these variables correlate with insulin resistance, blood pressure and degree of obesity [44–47] (Fig. 2). Though it is largely unknown the extent to which all these relationships are independent, this hub of related physiological quantities probably reflect fundamental mechanisms behind the insulin resistance syndrome. Together with diabetic microangiopathy and rheologic cell changes they might provide the basis for the proposed role of muscle blood flow in IR.

Conclusion

Insulin resistance and Type 2 diabetes are accompanied by a progressive deterioration of the microcirculation in many tissues. The mechanism behind this association is obscure but currently accepted data may be arranged to fit a pathogenic model with vascular and circulatory changes causing a decline of muscle blood flow that finally leads to the metabolic disorder.

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