For debate . . .

Is muscle the major site of insulin resistance in Type 2 (non-insulin-dependent) diabetes mellitus?

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Liver and muscle are the two major insulin-sensitive tissues responsible for maintenance of normal glucose homeostasis. In Type 2 (non-insulin-dependent) diabetes mellitus, both these tissues are resistant to insulin [1–5]. At the present time, muscle is widely regarded as the more important site [2, 5–8]. The main reasons for this view are the impressions that muscle is more insulin-resistant than liver, that muscle is more important than liver for glucose homeostasis, and that increased hepatic glucose output is a late event in Type 2 diabetes. In this article, I shall briefly examine some of the experimental evidence for these impressions and present arguments which question their validity.

Is muscle less sensitive to insulin than liver in Type 2 diabetes?

Strictly speaking, to answer this question, one must perform dose-response experiments and demonstrate that the ED_{50} for the action of insulin on muscle is increased to a greater extent than the ED_{50} for the action of insulin on liver. A great many glucose clamp experiments have been performed in subjects with Type 2 diabetes comparing suppression of glucose production (GP) and stimulation of glucose utilization (GU) as indices of insulin action on liver and muscle. Unfortunately, almost all these studies used only one insulin infusion rate and the plasma insulin concentration achieved (~ 100 mU/l) produced maximal or near-maximal suppression of GP. Thus, the results of such studies cannot be used to compare hepatic and muscle insulin sensitivity. Moreover, because of marked differences in the dose-response kinetics for the effect of insulin on GP and GU, use of such high insulin concentrations can lead to overestimation of the resistance of GU compared to GP; for example, GP can be suppressed by only $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, whereas GU can be increased by as much as $5\text{--}10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ depending on the insulin concentration used.

Three studies to date [1, 3, 4] have attempted dose-response experiments. In one study [1], non-diabetic and diabetic subjects were not adequately matched for age and gender. Furthermore, it was not possible, because of

the insulin doses used, to obtain reliable estimates of the ED_{50} for suppression of hepatic glucose output. The investigators did not conclude that muscle was the more insulin-resistant tissue. In the second study [3], subjects were well matched and the insulin doses used permitted estimation of the kinetic parameters of insulin action on both tissues; the ED_{50} s for suppression of GP and stimulation of GU were found to be comparably increased in diabetic subjects. In the third study [4], the ED_{50} for suppression of GP was increased two-fold in the diabetic subjects but, because of the limited insulin concentrations used, no kinetic parameters could be calculated for GU; however, the investigators did conclude that at physiologic insulin concentrations impaired suppression of GP contributes quantitatively more than defective GU.

Thus, the only study that has adequately compared hepatic and muscle insulin sensitivity in Type 2 diabetes found them to be equally impaired. Further studies are needed to substantiate these findings before they can be accepted as fact. Nevertheless, one can conclude that at present there are no data which demonstrate that muscle is less sensitive to insulin than liver. Furthermore, although clamp experiments have proven useful in quantifying the effect of insulin on GP and GU, it is worth emphasizing that the results of such experiments may not predict the alterations in GP and GU that occur under clinical conditions (e.g., meal ingestion, see below) in which plasma insulin and glucose concentrations are free to change and influence one another.

Does decreased muscle glucose uptake precede increased hepatic glucose output?

The finding that hyperinsulinaemic mildly hyperglycaemic individuals with Type 2 diabetes have “normal” GP and reduced systemic glucose clearance (GC) has been put forward as evidence that peripheral tissue (presumably muscle) insulin resistance is a more important early defect in Type 2 diabetes [7]. However, recent studies from our laboratory (Fig. 1 and Table 1) indicate that in four groups of age, weight and gender-matched in-

Fig. 1. Hepatic glucose output in age, weight and gender-matched subjects with fasting plasma glucose concentration between 4 and 8 mmol/l. (See also Table 1)

$r = 0.59, p = 0.001$

dividuals, rates of hepatic GP are linearly correlated with fasting plasma glucose concentrations even within the normal range. Furthermore, individuals with fasting plasma glucose concentrations between 6 and 7 mmol/l, whose muscle GU is normal or increased [9], have rates of GP that are significantly greater than those in individuals with plasma glucose concentrations between 4 and 5 mmol/l.

The reduction in systemic GC found in mildly hyperglycaemic subjects can be largely explained by reduced brain GC since brain glucose uptake does not increase appreciably as plasma glucose concentrations increase [9]. Because of this, systemic GC decreases even in non-diabetic subjects who are made hyperglycaemic [10]. Finally although muscle GC may be reduced in Type 2 diabetes [9], this may not be entirely due to insulin resistance, since hyperglycaemia reduces muscle GC in non-diabetic subjects [11].

GC, an index of the suitability of GU for the prevailing plasma glucose concentration, is calculated by dividing GU by the plasma glucose concentration. It is fallacious to compare GC, a derived rate, with an absolute rate for GP. There is no comparable expression to evaluate the suitability of GP, but a GP that is not reduced in a hyperglycaemic-hyperinsulinaemic individual must be inappropriate.

Additionally, it is important to point out that plasma glucose concentrations change because of absolute differences in rates of GP and GU – not because of differences in their suitability. For plasma glucose to increase, GP must exceed GU. This can occur because GU decreases, GP increases or a combination of these changes. No report [2, 9, 12–14] simultaneously examining GP and muscle GU in overnight-fasted subjects with Type 2 diabetes has found reduced muscle GU, whereas virtually all have found increased GP.

One may thus conclude that at the present time, there is no compelling evidence that decreased muscle glucose uptake precedes increased hepatic glucose output in Type 2 diabetes; indeed the data suggest the opposite.

Is muscle the more important tissue for glucose homeostasis?

It is possible that, although liver and muscle may be equally insulin resistant in Type 2 diabetes, a comparable degree of muscle insulin resistance may produce more

profound abnormalities because of the relative importance of muscle for glucose homeostasis. To examine this issue, I shall consider the postabsorptive (fasting) and postprandial states separately.

In the postabsorptive state, most GU occurs independent of insulin and only about 25% of GU ($\sim 2.5 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) is accounted for by muscle [13, 15–18]. In contrast, 100% of GP ($\sim 10 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) is due to the liver and is very sensitive to insulin [3]. Thus, a relatively minor ($\sim 25\%$) fluctuation in GP would exert an influence about four-fold greater on plasma glucose concentration than a comparable fluctuation in muscle GU.

Additional evidence favouring the importance of the liver in the postabsorptive state is the fact that plasma insulin concentrations found in the postabsorptive state have a more profound effect on GP than GU: a doubling of the basal plasma insulin concentration suppresses GP by about 30–50% [4, 19, 20] while having no effect on GU [4, 19].

Finally, as mentioned earlier, in hyperglycaemic-hyperinsulinaemic Type 2 diabetic subjects, hepatic GP is increased above normal and correlated with the fasting hyperglycaemia while muscle GU is either normal or increased [2, 9, 12–14]. Thus, hyperglycaemia and hyperinsulinaemia are able to compensate for muscle insulin resistance but not hepatic insulin resistance. It is, therefore, most likely that hepatic rather than muscle insulin resistance is the dominant factor responsible for the initiation and maintenance of fasting hyperglycaemia in Type 2 diabetic subjects.

In the postprandial state, the major determinants of plasma glucose fluctuations are the suppression of endogenous GP and uptake of glucose by splanchnic tissues, muscle and brain [13, 14, 18, 21, 22]. After ingestion of a meal or glucose load, endogenous GP is reduced by approximately 60%. A widely quoted study [23] has concluded that the great majority of an oral glucose load is taken up by muscle. In that study, 65 g glucose was calculated to be taken up by muscle of subjects whose splanchnic glucose output was only 61 g. Mathematically it is impossible for muscle GU to exceed the systemic delivery of glucose (in the absence of hypoglycaemia). Moreover, these calculations would leave no glucose to be taken up by brain, a physiologic impossibility. Thus, the validity of these observations is open to serious question. Other studies [13, 14, 18, 21, 22] indicate that muscle takes up about 30% of an oral glucose load and that brain and splanchnic tissues, respectively, take up 20–25% and 30–35% of the load.

Relating the results of these studies to overall glucose homeostasis after ingestion of a 70 g oral glucose load by a 75 kg normal subject (Table 2) indicates that muscle would take up 30 g glucose and splanchnic tissues would take up about 35 g glucose. In addition, however, the liver would reduce its output of glucose by about 25 g. Thus, changes in splanchnic GU and GP (a total of 60 g) would appear to be more important than changes in muscle GU (~ 30 g) for normal postprandial glucose homeostasis. Consequently, one would expect that hepatic insulin resistance would have a more profound effect on postprandial

Table 1. Hepatic glucose output in age, weight and gender-matched subjects with fasting plasma glucose concentration between 4 and 8 mmol/l

	Group 1	Group 2	Group 3	Group 4
Hepatic glucose output	10.6 ± 0.2	11.2 ± 0.2	11.7 ± 0.3 ^a	12.1 ± 0.2 ^a
Insulin	8.9 ± 0.5	10.5 ± 0.6	13.1 ± 1.1 ^a	10.8 ± 0.7
Body mass index (kg/m ²)	25.6 ± 0.9	25.8 ± 0.8	25.8 ± 0.8	26 ± 1.1
Age (years)	54 ± 3	49 ± 2	54 ± 2	51 ± 3

^a $p < 0.01$ vs Group 1 (See also Figure 1)

Table 2. Summary of postabsorptive and postprandial glucose homeostasis

	Normal subjects	Type 2 diabetic patients
Postabsorptive		
Hepatic glucose output/5 h	45 g	60 g
Muscle glucose uptake/5 h	11 g	14 g
Glycosuria/5 h	0	10 g
Tissue glucose uptake/5 h	45 g	50 g
Postprandial ^a		
Suppression of endogenous glucose appearance	25 g	15 g
Residual endogenous glucose appearance	20 g	45 g
Systemic appearance of oral glucose	55 g	55 g
Overall systemic glucose appearance	75 g	100 g
First-pass splanchnic glucose uptake	15 g	15 g
Splanchnic uptake of systemic glucose	20 g	22 g
Total splanchnic glucose uptake	35 g	37 g
Muscle glucose uptake	30 g	33 g
Brain glucose uptake	20 g	20 g
Adipose and other tissue glucose uptake	5 g	10 g
Glycosuria	0	15 g
Total tissue glucose uptake	75 g	85 g

^a Over 5 h after ingestion of 70 g glucose load in a 75 kg subject calculations based on data from Kelley et al. [18], Mitrakou et al. [14], Katz et al. [23], Firth et al. [13], Ferrannini et al. [21], Jackson et al. [22], and Marin et al. [29]

glucose homeostasis than a comparable degree of muscle insulin resistance.

This conclusion is supported by studies examining muscle GU and hepatic GP after glucose or meal ingestion in Type 2 diabetes [13, 14, 24–27]. No study has found reduced muscle GU [13, 14, 24–26], whereas all have found reduced suppression of GP [13, 14, 24, 25, 27]. Since there is no compensatory increase in first-pass splanchnic glucose uptake [13, 14], this reduced suppression of hepatic GP increases systemic delivery of glucose [13, 14, 24–26, 28]. It stands to reason, therefore, that postprandial hyperglycaemia in Type 2 diabetes should be attributed primarily to increased delivery of glucose to the systemic circulation.

As summarized in Table 2, Type 2 diabetes is usually characterized by increased tissue glucose uptake. Reduced effectiveness of glucose uptake by muscle and other tissues may exacerbate postprandial hyperglycaemia, but reduced GU cannot be the primary defect since tissue GU in absolute terms is not reduced, whereas GP in absolute terms is increased. Thus, as in the postabsorptive state, hyperglycaemia and hyperinsulinaemia in the postprandial state appear to be able to compensate for muscle insulin resistance but not for hepatic insulin resistance.

Summary and conclusions

Examination of experimental data, as well as physiologic considerations, fail to provide compelling support for the prevalent belief that muscle is the most important site of insulin resistance in Type 2 diabetes, rather they support the view that abnormal hepatic glucose production is the major factor responsible for both fasting and postprandial hyperglycaemia.

At the present time considerable resources are being applied to develop agents which improve GU in Type 2 diabetes; but GU is normal or increased in this condition [3, 5, 7, 13, 14, 24, 25]. It would seem preferable in the future that more effort be directed toward determining the mechanism(s) responsible for the abnormal hepatic glucose production and developing specific therapeutic agents to treat it. The mechanisms responsible for abnormal hepatic glucose production in Type 2 diabetes remain unclear, but factors such as hyperglucagonaemia, increased hepatic fat oxidation, increased availability of gluconeogenic substrates, impaired generation/effectiveness of intracellular insulin signals, and impaired insulin secretion all deserve consideration.

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