Hypothesis

Co-ordinated regulation of muscle glycolysis and hepatic glucose output in exercise by catecholamines acting via α-receptors

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Recent findings indicate that glucose uptake by contracting hindlimb [Acta Physiol. Scand. (1982) 116, 215–222] and heart [Biochem. Biophys. Res. Commun. (1982) 108, 124–131] of the rat is stimulated by epinephrine acting through α-adrenergic mechanisms. Since in exercise hepatic glucose output may be increased markedly by activation of α-adrenergic receptors and matched by the increase in muscle glucose uptake (maintaining blood glucose levels relatively constant), it is now proposed that a general co-ordination of glucose metabolism may operate via α-adrenergic receptor mechanisms. The basis for this proposal is discussed.

Glycolysis *Glucose uptake, output* *(Muscle)* *(Liver)* *Exercise* *Catecholamine* *Alpha-receptor*

1. EXERCISE AND GLUCOSE METABOLISM

Liver and muscle glycogen contribute significantly to the fuel homeostasis of the body. Liver glycogen is the primary source of blood glucose and hepatic glycogenolysis may be rapidly activated in response to exercise [3–5]. Muscle glycogen is used for energy production for the muscle fibres in which it is contained. Thus its contribution to glucose homeostasis is indirect: (i) by supplementing the use of blood glucose; and (ii) by providing gluconeogenic precursors for hepatic glucose synthesis.

Resting muscle takes up only a small amount of glucose [6,7]. Energy metabolism appears to be largely dependent upon free-fatty acid metabolism, as indicated by measurements of the local respiratory exchange and by direct determinations of free fatty acid and oxygen uptake [6–8].

Exercise gives rise to time- and work-intensity-dependent changes in fuel metabolism. For the human an initial net release of glucose by the exercising muscle [7] is followed by a large release of lactate [7]. As work continues glucose uptake increases progressively and the release of lactate subsides. For the exercising forearm net glucose uptake may be 15 times the basal value after 10 min and as much as 35 times after 60 min [3,7]. At 10 min the oxygen uptake appears to be used mainly for carbohydrate oxidation [7]. If exercise continues more than half of the oxidative metabolism is directed towards the oxidation of glucose taken up from the blood [7]. For the rat in vivo it appears that exercise and epinephrine act in concert to balance increased hepatic glucose output with increased glucose uptake by muscle [9]. Recent detailed studies using the perfused rat hind-quarter have now clarified this situation further. In this system, contractions by themselves were found to briefly increase glycogenolytic activity [10]. Physiological levels of epinephrine prolonged glycogen breakdown and increased the uptake of

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glucose and oxygen [10].

Blood flow changes during exercise favour increased oxygen (e.g., see review [11]) and fuel supply to the working muscle and the blood concentration of epinephrine increases [12–14]. However, despite the increased uptake of blood glucose it is clear that the hormonal response to exercise is characterized by a fall in plasma insulin and a rise in plasma glucagon [3,15,16]. The decrease in insulin concentration during heavy exercise is noteworthy since hypoinsulinaemia then occurs in spite of a moderate rise in the blood glucose level [3,17]. This trend suggests an inhibition of insulin secretion [18,19] that may be mediated by α-adrenergic receptors [20,21]. Nevertheless a permissive effect of insulin on exercise-induced glucose uptake is suggested, as in the absence of this hormone, glucose uptake fails to increase in response to contraction [22].

The rise in plasma glucagon levels during exercise [3] may be attributable to catecholamine activation of the β-adrenergic receptors of the A cells of the pancreas [23]. Since the rise in plasma glucagon appears to be slower to develop [3,15] than the increase in catecholamines [13,14], it may contribute less to the increase in hepatic glycogenolysis and more to the increase in gluconeogenesis that occurs later and during recovery. From known responses in other tissues it could be predicted that the effects of glucagon on skeletal and heart muscle glucose metabolism would be similar to the β-agonists. However, glucagon is considered to have no effect on skeletal muscle metabolism (e.g., see review [24]).

The net effect of the above tissue-specific changes in glucose production and utilization is that the blood glucose concentration changes only marginally during moderate exercise [3,17,24].

3. α-ADRENERGIC CONTROL OF HEART AND SKELETAL MUSCLE GLYCOLYSIS

The increased glucose uptake by muscle in exercise is largely accounted for in terms of increased glycolysis. The increase in glycogenolysis also requires that carbon flux is accelerated through the reactions of glycolysis after glucose 6-phosphate.

The rate controlling steps in muscle glycolysis have been examined in detail by numerous workers (e.g., see review [25] and references therein). Glucose transport, glucose phosphorylation, phosphofructokinase and triose phosphate dehydrogenase have each been implicated in the regulation of this pathway. For heart it has been shown that glucose transport is increased by insulin, work-load and anoxia [26] as well as by α-adrenergic agonists [27]. The properties of muscle hexokinase are such that regulation is probably achieved by the intracellular concentration of effectors (e.g., see review [26]); glucose 6-phosphate may have the most functional importance. Activation of phosphofructokinase in heart has been shown in this laboratory to be mediated predominantly by an α-adrenergic receptor mechanism [28]. Effectors of the enzyme do not appear to be involved and activation occurs via a Ca^{2+}-dependent mechanism which is independent of β-adrenergic receptor-mediated changes in cyclic AMP concentration and protein phosphorylation [28,29]. The activation of phosphofructokinase appears to result from increased affinity for the substrate fructose 6-phosphate and decreased sensitivity to the inhibitors, ATP and citrate (affording regulatory advantage to the enzyme only when hexose 6-phosphate concentrations are low and approaching the K_m). In addition, evidence for a key role of phosphofructokinase in the adrenergic control of cardiac glycolysis was obtained; the activity ratio of the enzyme correlated well with the rate of glucose uptake over a wide range of concentrations of epinephrine [2]. β-Adrenergic receptor-mediated activation of phosphofructokinase may occur at high concentrations of epinephrine coincident with the activation of phosphorylase [29]. From our own observations it seems reasonable to predict that a similar dose relationship exists between α- and β-adrenergic receptors for the control of glucose uptake in heart.

Epinephrine-mediated activation of skeletal muscle phosphofructokinase has also been reported [30] but the nature of the adrenergic mechanism involved was not characterized.

Glucose and non-metabolizable monosaccharide uptake by resting non-cardiac muscle has been studied by several groups. Both inhibitory and stimulatory effects of epinephrine have been reported. Walaas and Walaas [31] showed in early studies that epinephrine could decrease glucose uptake in rat diaphragm. Further examination of this

phenomenon in rat diaphragm revealed that both inhibition [32–35] and no effect [33,35] could be demonstrated depending on the ionic composition of the incubation media [33,35]. Newsholme and Randle [36] reported that 66 μM epinephrine increased the uptake of D-3-*O*-methylglucose, but not D-xylose in diaphragm. In 1978, Bihler and colleagues [37,38] reported that 10 nM–10 μM epinephrine inhibited the transport of 3-*O*-methylglucose in rat diaphragm and soleus. However, at very high concentrations (0.1–1 mM) transport was stimulated in diaphragm [37]. Both the inhibitory and stimulatory effects of catecholamines on 3-*O*-methylglucose transport were mediated by β-adrenergic receptors [37,38]. Saitoh et al. [39] reported an increase in glucose utilization and 3-*O*-methylglucose uptake by diaphragm which were each mediated by α-adrenergic receptors.

In an attempt to resolve these apparently conflicting data, the perfused hindquarter system has been used. Chiasson et al. [40] showed that 0.1 μM epinephrine increased basal glucose uptake and decreased glucose uptake when the latter was maximally stimulated by insulin (1 mU/ml). Chiasson et al. [40] ascribed both the stimulatory and inhibitory effects of epinephrine to β-adrenergic receptors, although a partial inhibition of epinephrine-stimulated glucose uptake was noted with the α-blocker. Epinephrine increased the free intracellular 2-deoxyglucose space but did not increase the uptake of 3-*O*-methylglucose by muscle of the perfused rat hindlimbs. In view of the observations that epinephrine can increase the uptake of 3-*O*-methylglucose into isolated rat adipocytes by a β-adrenergic receptor mechanism, Chiasson et al. argued that their observed stimulatory effects on glucose uptake by the hindlimb were due to effects on adipose tissue [40]. The inhibitory effect of epinephrine on muscle glucose uptake [40] was considered to be consistent with earlier explanations; i.e., that it resulted from inhibition of the hexokinase reaction due to the large rise in glucose 6-phosphate and fructose 6-phosphate induced by glycogenolysis (a β-receptor-mediated process [41]).

More recently, another group [1] have also applied the perfused hindquarter in an attempt to resolve these issues. Richter et al. [1] observed that at rest 2.4×10^{-8} M epinephrine significantly increased oxygen uptake, glucose uptake, lactate release and perfusion pressure of the perfused hindquarter. Phentolamine blocked the epinephrine-mediated increases in oxygen uptake, glucose uptake and perfusion pressure (the latter being decreased to less than control). Propranolol + epinephrine (which together accentuate the α-agonist activity of epinephrine) further increased glucose uptake over epinephrine used alone. Lactate release was decreased to less than epinephrine alone but remained higher than control (possibly suggesting an α-adrenergic receptor-mediated increase in lactate oxidation). Electrical stimulation increased all four parameters [1] and did not diminish the significant effect of epinephrine on glucose uptake [10]. The combination of epinephrine + propranolol retained highly significant stimulatory effects on glucose uptake, oxygen uptake and perfusion pressure [1].

It is not clear why such differing results have been obtained by the two groups ([1,10] and [40]) using the same technique of hindlimb perfusion. However, important differences in approach may have been relevant. Chiasson et al. [40] used the system at rest for all their studies and perfused in a non-recirculating manner during the experimental period. This group also used medium containing 10 mM glucose. Richter et al. [1,10] examined the effects of epinephrine at rest and during electrical stimulation. A recirculating mode was used and a physiological level of insulin (75 μU/ml) was present throughout all experiments [1,10]. This group used medium containing 6 mM glucose [1,10].

The observations made by Richter et al. [1] are consistent with our own findings for the Langendorff perfused beating rat heart, from which we have made speculations regarding mechanisms in skeletal muscle (e.g., see [29]). The studies with perfused hearts lead us to believe that the magnitude and duration of the β-adrenergic-mediated increase in the intracellular concentration of glucose 6-phosphate in non-contracting muscle is essentially non-physiological. Instead of a transient increase in concentration due to epinephrine (perhaps lasting only 3–5 min as in contracting heart [29]) the concentration of glucose 6-phosphate can remain elevated for 30 min or more in muscle at rest (e.g., [40]). Contracting muscle requires energy from metabolism

and thus accounts for the more rapid turnover of glucose 6-phosphate when compared with the resting state. Contracting muscle also affords the appropriate physiological environment for the inotropic effects of epinephrine to develop [1]. We have proposed that the positive inotropy, increase in glucose uptake and activation of phosphofructokinase in rat heart are mediated in a co-ordinated manner by an α-adrenergic receptor mechanism [42]. From the data of Richter et al. [1] it seems reasonable to propose that the same relationships may occur in skeletal muscle.

4. α-ADRENERGIC CONTROL OF HEPATIC GLUCOSE OUTPUT AND GLUCONEOGENESIS

There is now considerable evidence that catecholamines rapidly activate both hepatic glycogenolysis and gluconeogenesis in the rat through an α-adrenergic receptor mechanism that is independent of changes in the intracellular level of cyclic AMP (e.g., see [43] and references therein). The stimulation of carbohydrate metabolism by catecholamines is smaller in magnitude than that caused by glucagon or cyclic nucleotides [44–46] and is inhibited by α-blockers, but not by β-blockers [46,47]. Although it is regarded that catecholamines stimulate glycogenolysis by increasing the cytosolic concentration of Ca^{2+} and activating phosphorylase kinase [48–50], the mechanism by which α-receptor stimulation leads to increased gluconeogenesis is still controversial. Effects of epinephrine at pyruvate kinase-phosphoenol pyruvate carboxykinase and at phosphofructokinase-fructose 1,6-bisphosphatase have been claimed (e.g., reviews [51,52] and references therein). Hormone-mediated changes in concentration of the key regulator fructose 2,6-bisphosphate may have an important role to play in the α-adrenergic control of hepatic gluconeogenesis [53,54].

5. THE PROPOSED CO-ORDINATION OF MUSCLE AND HEPATIC GLUCOSE METABOLISM IN EXERCISE

Fig.1 outlines this proposal. The essential components are:

(i) Exercise in the mammal leads to increased sympathetic nervous system activity (norepinephrine) and release of adrenal medullary hormones (epinephrine and norepinephrine).

(ii) Post-synaptic adrenergic receptors in heart, pancreas, liver and skeletal muscle are activated.

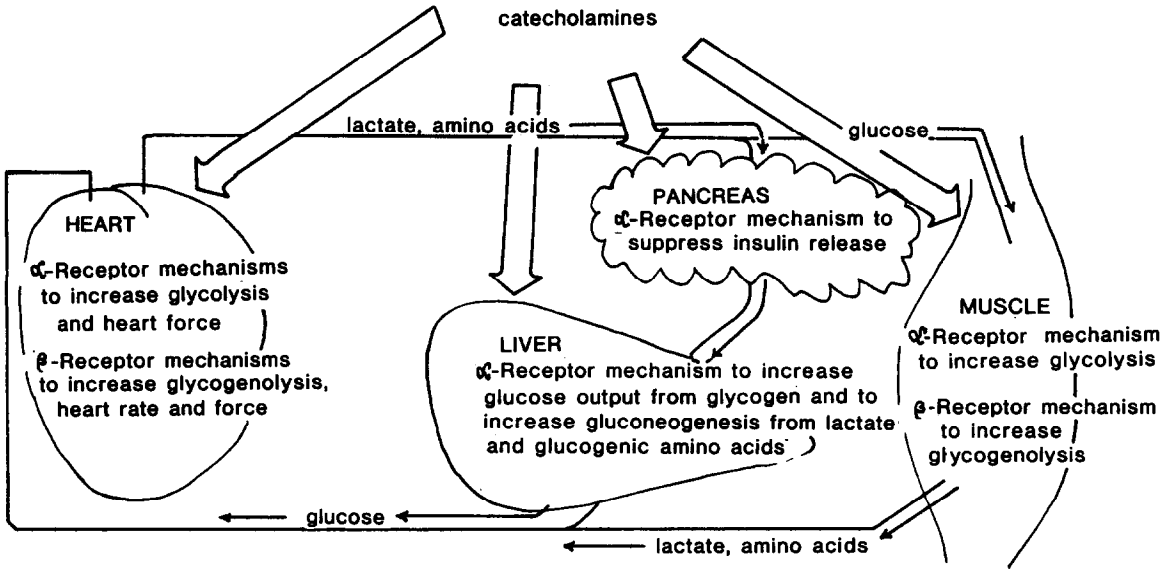

Fig.1. The co-ordination of muscle and hepatic glucose metabolism in exercise: a role for α-adrenergic receptors.

(iii) In heart, α-adrenergic receptor mechanisms act to increase glucose transport, the activity ratio of phosphofructokinase and force of contraction. Increased oxidation of lactate may also occur. If high levels of epinephrine are attained, β-receptor mechanisms act to stimulate glycogenolysis.
(iv) In pancreas, α-receptor mechanisms act to suppress insulin release.
(v) In liver, α-receptor mechanisms act to increase glucose output into the blood from glycogen and to increase gluconeogenesis.
(vi) In contracting skeletal muscle, α-receptor mechanisms act to increase glucose uptake and its utilization by reactions of glycolysis. Inotropy and oxygen uptake are also increased. β-Receptor mechanisms act to increase glycogenolysis.

6. QUESTIONS REMAINING

(1) The hypothesis proposed here would appear to be largely inconsistent with the observed effects of administering epinephrine in vivo. It is clear from studies of this latter kind that epinephrine administration gives rise to a decrease in glucose clearance [55–60]. However, in each of these studies non-exercising animal or human subjects were used. Under these conditions requirements for energy from glucose metabolism are minimal in muscle and events similar to adding epinephrine to non-contracting muscle preparations in vitro occur (see above). Thus a β-adrenergic receptor-mediated increase in muscle glycogenolysis may be the predominant biochemical response. Diminished peripheral uptake of glucose, together with hyperglycemia and a decreased hepatic glucose output, results [60]. In the few studies where epinephrine has been injected into exercising animals (e.g., [9]) the increased glucose uptake by contracting muscle has been viewed as the contributing factor in lowering blood glucose [9]. Further studies of this latter kind will help resolve the issue.

(2) This present proposal is largely based on observations made in rat tissues. The situation is less clear in other species. Exton [43] has argued that data support a role for α-receptors in catecholamine actions in hyperglycemia or hepatic glycogenolysis in mouse, cat, rabbit and guinea pig, but that the importance of α-receptors relative to β-receptors is uncertain. Data supporting the predominant role for β-receptor in the dog are questioned and the data indicating a role for α-receptors in man are considered to be incomplete [43].

(3) The question of target-tissue α-receptors in muscle requires thorough examination. For heart, sub-type characterization of the adrenergic receptors indicates that they are α_1 [61]. However, the membrane preparations used for sub-typing studies have not as yet been shown to be homogeneous preparations of sarcolemma from ventricular muscle cells. Thus the possibility remains that α-adrenergic effects on heart result indirectly from the vasoconstriction initiated by α_1-receptors in vascular smooth muscle cells. Similar reasoning could apply to skeletal muscle. As yet there has been no report of α-receptors on skeletal muscle sarcolemma.

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