The Kallikrein-Kinin System and Muscle Metabolism: Biochemical Aspects

by GÜNTER DIETZE, MATTHIAS WICKMAYR, INGOLF BÖTTGER, RICHARD SCHIFMANN, REINHARD GEIGER, HANS FRITZ and HELLMUT MEHNERT

Third Medical Department (Metabolism and Endocrinology), Academic City Hospital Schwabing, Munich, Kölner Platz 1, and Department of Clinical Chemistry and Clinical Biochemistry, Munich University School of Medicine, Munich, Nussbaumstr. 20, GFR

Abstract
Infusion of bradykinin (BK) into the brachial artery in front of skeletal muscle of the human forearm yielding arterial concentrations of about 10^{-12} mol/l caused not only acceleration of blood flow but also of glucose and branched-chain amino acid uptake into the muscle in healthy volunteers and maturity-onset diabetics. These effects were almost entirely abolished after inhibition of prostaglandin biosynthesis.

Papaverine, although causing identical acceleration of capillary blood flow, induced no metabolic action. Apart from causing enlargement of the capillary bed, bradykinin has another metabolic effect which was underlined by results obtained in the isolated perfused rat heart, indicating increased glucose uptake at constant rates of coronary blood flow.

In order to clarify whether kinins play a physiological role in muscle carbohydrate metabolism, the well-known work-induced acceleration of muscle glucose uptake was studied during the inhibition of kinin liberation from kininogen by application of a protease inhibitor (Trasylol®) and during additional substitution with synthetic BK. The glucose uptake under a defined work load was almost completely abolished by the protease inhibitor; application of BK restored the normal effect. Almost identical responses have been observed concerning the well-known hypoxia-induced acceleration of muscle glucose uptake. Furthermore, insulin-induced acceleration of glucose uptake into the resting forearm was reduced by half when kinin liberation from kininogen was inhibited by Trasylol®; additional application of synthetic BK restored the normal response.

From the data presented, one may suggest that kinins are involved in carbohydrate and amino acid metabolism of skeletal muscle, most probably by improving the action of insulin.

Introduction
That tissue hormones might play a role for glucose utilization of skeletal muscle was first discussed in the early sixties when CORI et al. [1], RANDLE and SMITH [2] and MORGAN et al. [3] observed an insulin-independent acceleration of glucose uptake into skeletal muscle during hypoxia and muscle work. Thereby, it was especially striking that this increase of glucose utilization occurred as under insulin through acceleration of glucose transport across the cell membrane [4] and through acceleration of glucose phosphorylation within the cell [3]. Since in the isolated tissue these effects could not be due to insulin, the liberation of a tissue factor was postulated which should exhibit insulin-like activity. Some years later, GOLDSTEIN [5] obtained evidence for the existence of such a tissue factor.

He infused glucose into eviscerated and nephrectomized dogs and then transfused the lymph of working dogs and of non-working dogs. Only the group which received the lymph from the working animals showed reduction of blood glucose. This led to the suggestion that a humoral factor or tissue hormone was liberated which was responsible for the observed effect. Recent studies exhibited further evidence that this factor was not only working on glucose but also on amino acid metabolism. Six of about twenty amino acids which generally are released from muscle were observed to be taken up increasingly during muscle work [6]. Furthermore, this factor was reported to be responsible for the acceleration of glycoegen synthesis which occurs in insulin-deficient diabetics after muscle work [7]. Also work-induced muscular hypertrophy was said to be caused by the factor [6].

Results and discussion
When E.K. Frey, who discovered kallikrein in 1925, stimulated us to study the effect of bradykinin on muscle metabolism in 1974, it
soon became apparent that the kinins can cause almost identical changes, as had been observed during muscle work. At concentrations of about $10^{-12}$ mol/l, bradykinin led to an acceleration of capillary blood flow and of muscular glucose uptake (Fig. 1) in healthy volunteers [8] and maturity-onset diabetics [9]. Further studies showed that it influenced also amino acid metabolism likewise [10]. These effects were almost entirely abolished after the inhibition of prostaglandin biosynthesis [8] which was in line with the present view that kinins exhibit their effects via prostaglandins. Control studies with papaverine, which accelerates capillary perfusion to a similar extent as bradykinin, showed no effect on muscle metabolism. This was underlined by recent data showing that kinins also increase glucose uptake into the hypoxic rat heart at constant coronary blood flow [11].

There is also a great deal of evidence from earlier studies emphasizing that kinins might play a role within the regulation of muscle metabolism during work. It was shown in the early thirties that pH lowering, which is known to occur during muscle work, activates kallikrein from prekallikrein, causing increased splitting of kinins from kininogen [12]. At the same pH range the activity of kinin-degrading enzymes such as kininase II were found to be inhibited leading to an accumulation of kinins [13]. Correspondingly, deep venous concentration of kinins was found to increase during work and hypoxia whereas kininogen, the precursor protein, was found to decline [14]. Finally, Goldstein, on the way to isolating the quested factor, arrived at an apparent molecular weight of about 1000 to 1200 which is almost entirely identical with that of kinins [15].

From these findings, one could speculate, if kinins are involved in muscle work, inhibition of their liberation from kininogen by a protease inhibitor should almost completely abolish the well-known acceleration of blood flow and of glucose uptake. The addition of exogenous kinins, e.g. synthetic bradykinin, should renormalize the hemodynamic and metabolic response. As can be seen from Figure 2 this has indeed happened [16]. The same effect could also be achieved if hypoxia was performed by a blood pressure cuff on the upper arm. The well-known acceleration of blood flow and of glucose uptake occurring during the posthypoxic phase could also be reduced by infusion of a protease inhibitor and was renormalized again by application of synthetic bradykinin (Fig. 3) [17].

Although the early studies performed in the isolated rat heart [1–3] do not support this view, it seems to be well accepted today that insulin is