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SYNCHRONOUS CONTROL OF METABOLIC ACTIVITY BY K^+ TRANSIENTLY AND REVERSIBLY LIBERATED FROM ADSORPTION SITES DURING MUSCLE CONTRACTION: AN EXTENSION OF ASSOCIATION-INDUCTION THEORY

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It has long been known that physiological activities of some living cells incur rapid and dramatic increase in metabolic activity. Thus muscle contraction can increase the flow of metabolites through the glycolytic system many hundred times,[1,2] suggesting that muscular activity involves a perfectly coordinated "switching on" of a number of "bottleneck" enzymes. To the best of my knowledge, no general theory has been advanced to account for these important experimental findings.

In recent years the reversible liberation of Ca^{2+} from the adsorbed (or in the opinion of others, sequestered) state has been widely accepted as the means for producing one type of synchronous activation of a multiunit system, the contraction of myofibrils.[3] I now suggest that the Ca activation of muscle contraction in turn causes a reversible liberation of K^+. The liberated K^+ then brings about the synchronized activation of bottleneck enzymes to achieve rapid increase in the production of ATP. This proposal is entirely reasonable if one assumes that in the resting cell the free K^+ concentration is very low—a concept intrinsic to the association-induction (AI) hypothesis.[4,5]

K+-sensitive enzymes are as a rule fully activated by K^+ at a concentration in the 10 to 30 mM range (ref. 4, p. 400). But this level is far *below* the 100 to 150 mM of total K^+ concentration found in living cells. According to the popular membrane-pump theory, all of this K^+ exists in the free state. It is not surprising that up to now little effort has been devoted to finding a physiological role for the K+-sensitivity demonstrated in a number of key metabolic enzymes.

In the last four years, however, extensive experimental studies from three different laboratories using a total of four different techniques have established unanimously and unequivocally the adsorbed state of the bulk of K^+ in muscle cells, confirming this key postulation of the AI hypothesis.[6-11]

According to the hypothesis, the free K^+ concentration in normal resting cells is only a fraction of that in the external medium (2.5 mM) and is thus at a range far below that needed for activating most of the K+-sensitive enzymes. K^+ liberation from adsorbed sites therefore would be essential if the concentration is to be raised to a level sufficient for enzyme activation.

Reversible loss of K^+ from activated cells has been reported repeatedly (see ref. 4, p. 450; also refs. 12, 13) most elegantly by Wilde and coworkers for contracting turtle heart.[14] This K^+ loss has also been shown not to be due to increase of K^+ permeability.[13,15] In view of recent confirmation of the adsorbed state of cell K^+, these findings concerning reversibility provided positive evidence for the plausibility of the present hypothesis. Other encouraging observations include the following:

(1) In muscle, two of the bottleneck enzymes (phosphofructokinase[16] and pyruvate kinase[17]) are known to be K+-activated enzymes, and a third key enzyme (phos-

phorylase b kinase) has been shown to be activated by increase of external K^+ concentration in a way not immediately related to the K^+ effect on the resting potential[18] (however, see ref. 19). Such increase of external K^+ concentration increases free K^+ in cells, according to the AI hypothesis.

(2) Increase of external K^+ concentration has been found to activate both glycolysis[20] and respiration[20,21] in excitable tissues. □

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