MODERN MEDICAL MONOGRAPHS 12

POTASSIUM METABOLISM

in Health and Disease

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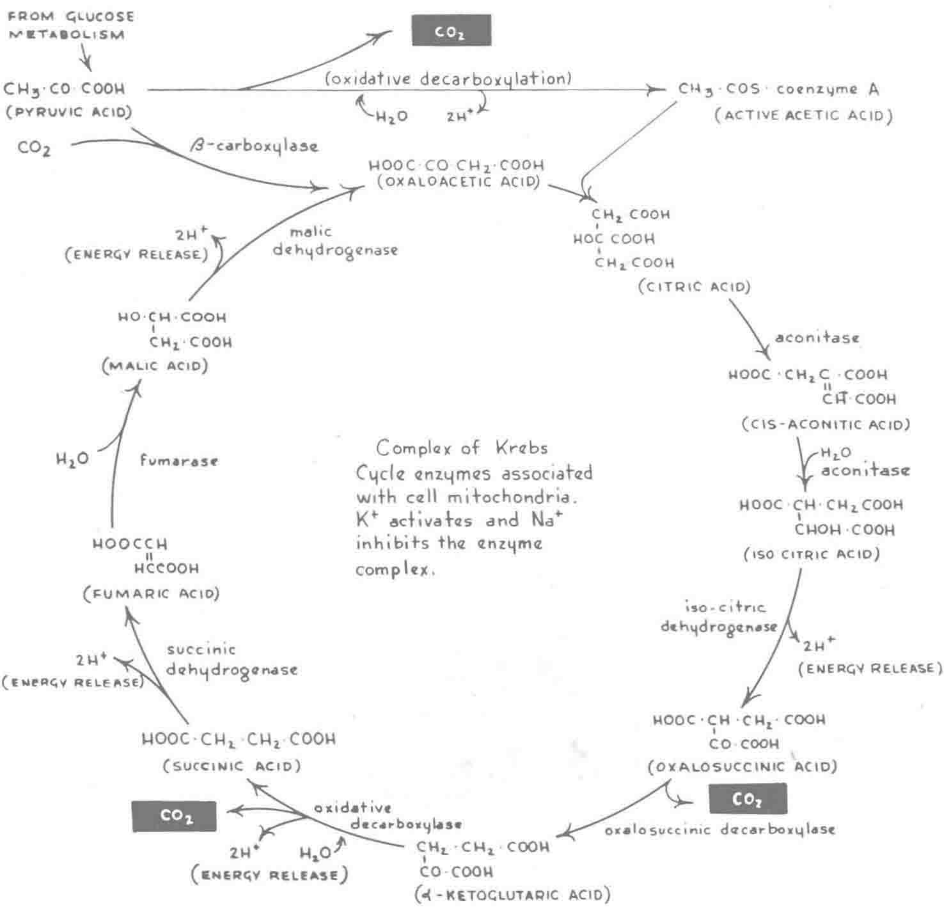
THE KREBS CYCLE

Energy Release in the Tricarboxylic Acid Cycle



A diagram summarizing energy production by intracellular oxidative reactions and the importance of potassium ion to these processes.

TO

JAMES SOMERVILLE MCLESTER, M.D., 1877–1954

Teacher, Critic, and Friend

Preface

Although the importance of the potassium ion in body metabolism has been recognized for more than a century, factual knowledge of the subject is still in its infancy. Renewed interest has been recently stimulated by the development of the relatively easy flame photometric method of determining the concentration of this important cation in the body fluids.

The purpose of this monograph is to present a review of this complex subject which may serve as a practical clinical guide in the diagnosis and treatment of abnormalities in potassium metabolism. The incentive to compile this treatise evolved from many interesting discussions with students, house staff and colleagues on the problem of potassium metabolism encountered here at the Jefferson-Hillman Hospital.

A comprehensive review of published reports indicating the importance of this element in the metabolism of man is herewith presented. We have thus drawn heavily on the reported experience of outstanding authorities in this field. Certainly all controversial points could not be treated in detail, but it is hoped that this compilation may encourage further interest in this subject inasmuch as some of the present enigmas in medicine may be better understood through further research in electrolyte metabolism.

The bibliographic references given are not intended to be complete, but are merely representative of the enormous literature that has rapidly accumulated during the past few years. Many other articles not mentioned here have furnished ideas and material for this manual. We would also like to give credit to the writings and intellectual impetus afforded by our associates: Dr. Virginia Whiteside-Carlson, Dr. Champ Lyons, Dr.

Tinsley R. Harrison, Dr. Robert Hogan, Dr. Basil Harris, and Dr. Haskell Ellison.

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Introduction

Proof of the essential role of the potassium ion in animal metabolism can be found in feeding experiments based on diets deficient in this mineral. In laboratory animals a potassium deficient diet causes retardation in growth, paralysis of voluntary and intestinal musculature, degeneration of cardiac tissue, and finally, death. Relatively recent advances in clinical laboratory methodology for determination of the alkali metal ions have facilitated the accumulation of data demonstrating that the effects of both potassium deficiency and potassium excess in laboratory animals are mirrored in human patients.

Advances in our knowledge of cell metabolism have demonstrated that the mechanisms of action of stimulatory and inhibitory substances alike most often involve effects on the delicately integrated enzyme systems, which are basic to the existence of all living cells. These effects may be direct and may involve the enzyme systems themselves, or they may be indirect and may result from modification of the environment in which the enzymes function. The physiologically important compounds classed as co-enzymes or activators are examples of substances having a direct action on cell enzymes, usually serving as integral parts of the catalytic centers of these systems. Ordinarily they are substances required in only trace amounts in the diet.

By contrast, other substances are described as "bulk" elements since they are required in the diet in relatively large amounts. Materials of this class are involved particularly in the maintenance of constant physiochemical properties of the aqueous solutions in which the enzymes function. The importance of potassium as a bulk element was early recognized. As the chief intracellular base ion it plays an obviously important role in the maintenance of pH within the normal narrow limits. This is essential for the successful integration of the activities of cellular enzymes. For a long time the importance of potassium as a bulk ion obscured its equally important role as an active component of various enzyme systems. In this latter role potassium functions as a trace element. This is a rapidly evolving field, and knowledge of potassium as an activator of specific enzymes, while still fragmentary, probably will soon be complete.

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CHAPTER I

Normal Potassium Metabolism

The predominantly intracellular position of potassium is emphasized by the fact that of the total of 4000 to 5000 milliequivalents (160 to 200 grams) present in the normal adult body, only 70 to 77 milliequivalents (2.7 to 3.0 grams) are found in the interstitial fluid and blood plasma. This contrasts with the distribution of the approximately 3000 milliequivalents (69 grams) of sodium contained in the body of the average adult, slightly over 2000 milliequivalents of which are found in the extracellular fluids*. The major amount of the remaining sodium is found in the bones, only a small fraction actually being within cells.

INTRACELLULAR POTASSIUM

1. *Potassium and Cell Metabolism*

The concentration gradient described above, apparently the result of both the active extrusion of sodium and uptake of potassium, is dependent upon continued, normal cell metabolism since the expenditure of energy is required to maintain the intracellular dominance of potassium. Accordingly, it is among the various enzymatic reactions carried on within cells, particularly those involved in the production of energy, that evidence should be sought for the part played by potassium in cell metabolism. Briefly, advances in biochemical research have focused attention on the so-called "high energy" phosphate compounds as the most important end products of energy-yielding metabolic reactions.

* See Appendix: Units Used in Body Fluid Measurements.

The compounds which contain high energy phosphate groups are of diverse chemical nature, comprising acid anhydrides of phosphoric acid, mixed anhydrides of phosphoric·acid and organic acids, and organic compounds containing phosphoric acid linked to nitrogen. Some of them occur only transiently as intermediate products in the oxidation of the food substances available to cells and transfer their high energy phosphate radicals to acceptor compounds. In this latter form the energy contained in these groups serves as the driving force for almost every type of work performed by the cells forming the various body tissues. Thus, the energy contained in these groups is used in muscle contraction, in the propagation of nerve impulses, in the performance of osmotic work, in the absorption of substances across cell walls, in the production of heat, and in the synthesis of the multitudinous compounds which characterize the various tissues.

The dominant position occupied by high energy phosphate groups in the body economy underscores the importance of those metabolic reactions, and their activators, which result in the synthesis of high energy phosphate compounds. Recent research has identified the potassium ion as an essential activator of several of these reactions, thus giving substance to earlier, empirical observations on the importance of this chemical element in normal growth and metabolism.

Carbohydrate Metabolism: The production of high energy phosphate compounds by body tissues is largely a function of *carbohydrate metabolism*, particularly that of glucose. In addition, when the carbon skeletons of amino acids and fatty acids are burned to carbon dioxide and water for the production of energy, the process involves the terminal oxidation cycle of glucose metabolism. It is by such means that carbohydrates, fats, and proteins are metabolically interrelated.

For the purpose of this discussion, the essential features of glucose utilization can be summarized as follows. There is a preliminary conversion (phosphorylation) of the sugar to a hexose phosphate with subsequent enzymatic steps leading to the formation of hexose diphosphate. These initial steps, which prepare the glucose molecule for splitting into smaller carbon compounds, are energy-consuming rather than energy-yielding reactions. In the process of phosphorylation, phosphate radicals from the most important of the high energy phosphate compounds of the body, adenosine triphosphate (ATP), are transferred to the hexose molecule. Of importance here is the finding that the potassium ion is an activator of the enzyme catalyzing the transfer of the second phosphate radical, with the production of hexose diphosphate. Subsequent splitting of the six carbon hexose diphosphate by enzymatic action into two three-carbon fragments and the resultant oxidation of these fragments lead to the production of high energy phosphate containing compounds, thus yielding a return on the energy investment originally made in the glucose molecule.

One of the intermediate three-carbon compounds formed is phosphoenol-pyruvate, which transfers its high energy phosphate group to adenosine diphosphate (ADP) to form ATP. The enzyme catalyzing this transfer, pyruvic phosphoferase, also has been shown to require the potassium ion as an activator. This enzyme is important also since the entry of lactic acid, accumulating as a result of muscular exertion, into the train of glucose metabolism is by way of the sequence: lactate $\rightarrow$ pyruvate $\rightarrow$ phosphoenol-pyruvate. If this sequence can proceed, the possibility exists for the resynthesis of lactic acid into glycogen. In the presence of a potassium deficiency the conversion of pyruvate into phosphoenol-pyruvate, under the influence of pyruvic phosphoferase and at the expense of ATP, will not proceed efficiently and lactic acid will accumulate. Thus it follows that a deficiency of potassium can interfere not only with initial steps in the enzymatic breakdown of glucose (glycolysis) but also with the harvesting of high energy phosphate groups formed during such oxidation, and with the re-centry of lactic acid into the metabolic chain.

The terminal stage in the utilization of the glucose molecule involves oxidation of the three-carbon intermediate compound, pyruvic acid, by a complex association of enzymes comprising what is usually called the *Krebs cycle* (frontispiece). By operation of the Krebs cycle the carbon atoms of pyruvic acid and the carbon skeletons of lipids and of amino acids are oxidized to carbon dioxide. Although biochemical research has not yet uncovered all the details of the reactions involved, it has been established that the oxidations occurring in the Krebs cycle are of the utmost importance in the production of high energy phosphate groups, the yield of ATP being many times that obtained during the oxidation of glucose to the three-carbon stage.

A further point of interest is that the enzymes of the Krebs cycle have been shown to exist as a complex associated with definite intracellular structures, the cell mitochondria. By special technics it has been possible to isolate the mitochondria of tissue cells and to study their metabolic requirements. One result of such work has been the demonstration of a requirement by mitochondria for potassium, if oxidative phosphorylation by Krebs cycle enzymes, with the production of considerable amounts of ATP, is to proceed. It has been further shown that potassium is bound by these cellular structures, the degree of binding varying with the activity of the oxidation processes. Such results have not only emphasized the importance of potassium to energy-producing chemical reactions but have also indicated that intracellular stores of this ion are not distributed homogeneously.

Finally, it has been found that the sodium ion inhibits the energy-producing oxidations of the mitochondria, once again demonstrating the antagonism existing between sodium and potassium ions. Aside from the inhibitory action ascribed to sodium, this ion also apparently stimulates enzymes (ATPase and apyrase) which catalyze the hydrolysis of ATP; such hy-