Characterization of sodium-transport disorders in disease: different effects upon sodium and potassium of changes in the sodium pump and in membrane permeability

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The high potassium content and low sodium content of most animal cells differ strikingly from the contents in the extracellular fluid surrounding them. This arrangement is so widespread that it probably represents the optimal condition for intracellular processes. Such a system of cells and extracellular fluid is intrinsically unstable and will inevitably run downhill, with net movements of sodium into the cell. The weight of evidence suggests that the mechanism responsible for the maintenance of these ion gradients is an active transport system located in the cell membrane, which extrudes sodium from the cell while simultaneously moving potassium in the reverse direction. This process is thermodynamically 'uphill' and consequently energy-requiring; the immediate source of energy is ATP, which is continuously replenished by the processes of intermediary metabolism. The transport system, which has been most clearly defined, appears to consist principally of an ATPase inhibitable by cardiac glycosides and usually referred to as the sodium pump (Glynn & Karlish, 1975; Jorgensen, 1975).

The purpose of this review is to consider the different ways in which the transport of sodium and potassium may be altered by disease and therapy. We are particularly concerned to emphasize the time-dependent features of such alterations and also the very different implications of a primary change in the activity of the sodium pump as opposed to alterations in other transport processes. We have not attempted to review the literature on sodium-transport disorders, but have selected examples to point out the distinctions which we believe could help our understanding of these disorders. Before proceeding to the detailed argument, it is as well to make some general points concerning the terms to be used and also the nature of the techniques involved in the determination of the transport rates under discussion.

The cardinal feature of the sodium pump and the flux from which it derives its name is the transport of sodium from the cell interior to the extracellular fluid. The flux is measured as follows: the cells under study are incubated in a medium containing radioactive sodium until they have accumulated sufficient radioactivity for satisfactory counting. The cells are then washed and suspended in a medium free of radioactive sodium. Over an appropriate period of time either the loss of radioactivity from the cells or the gain of radioactivity by the extracellular fluid is observed. When the residual radioactivity in the cells is plotted against time, a smooth curve results, which converts to a straight line if the natural logarithm of radioactivity is substituted for radioactivity on the y axis. The slope of this line is the pseudo-first-order rate constant for sodium efflux and has the dimensions time$^{-1}$. This rate constant cannot be identified with the activity of the sodium pump alone as a proportion of the radioactive tracer leaving the cells does so by pathways independent of the sodium pump. The value for this latter rate constant may be determined by performing an identical experi-
ment in the presence of a sufficient concentration of ouabain to produce maximal inhibition of the pump. This also gives rise to a first-order rate constant which, when subtracted from the rate constant for total sodium efflux, gives the ouabain-sensitive sodium-efflux rate constant. It should be stressed that what has been measured or calculated is a rate constant, or the fractional loss of radioactive sodium with time. To derive the actual quantity of sodium actively transported by this process, the intracellular sodium content is multiplied by the corresponding rate constant. This figure is usually referred to as a unidirectional flux.

Potassium efflux is measured in a similar way, with radioactive potassium. Sodium and potassium influx may be determined by exposing the cells to an extracellular fluid containing the appropriate radioisotope for a known period of time. The gain in radioactivity (after correction for re-efflux) can be converted directly into an ionic flux since the specific radioactivity of the extracellular fluid is both constant and readily measured. Like sodium efflux, potassium influx is usually determined in the presence and absence of ouabain in maximally inhibitory concentrations.

The results obtained from the study of sodium transport in diseased cells are usually presented as the intracellular electrolyte values and the appropriate rate constant derived from the movement of the radioactive tracer. This contrasts with the physiological literature, where more commonly one finds the value of the unidirectional flux reported. The implications of this different mode of presentation of data are discussed below.

The reduction in cellular potassium and the increase in sodium which follows total inhibition of the sodium pump are well known, but in clinical investigation the problem is usually to describe the behaviour of the partially inhibited or impaired pump. Even a cursory examination of the literature shows that, in these clinical studies, although intracellular sodium is usually increased and the rate constant for sodium efflux is often decreased, the unidirectional flux of both sodium and intracellular potassium may be normal. This rather unexpected picture demonstrates that the well-known immediate effects of acute inhibition of sodium transport are only a stage on the way to a new steady state. A brief theoretical discussion of the effects of a reduction in the ouabain-sensitive rate constant for sodium efflux may help to show why the expected reduction in potassium is not always found.

At this stage, we should state two fundamental assumptions, which are generally made in sodium- and potassium-transport studies. First, that substantially all the sodium and the potassium in the cell can be regarded as freely available to the transport mechanisms; secondly, that for every three sodium ions removed from the cell by the sodium pump two potassium ions enter by the same mechanism (Post & Jolly, 1957; Garrahan & Glynn, 1967). There have been some reports of a small non-exchangeable pool of sodium (Keynes & Swan, 1959; Mullins & Frumento, 1963), but in human erythrocytes and leucocytes this has not been reported. In the presence of normal extracellular concentrations of sodium and potassium the 3:2 stoichiometric relationship also seems to apply to leucocytes (Hilton, Edmondson, Thomas & Patrick, 1975).

If we postulate an acute reduction in the ouabain-sensitive rate constant for sodium efflux without alteration of sodium influx, then the cellular sodium concentration must increase so that the product of intracellular sodium and the rate constant for sodium efflux again balance sodium influx. Thus the decrease in sodium efflux which accompanied the initial decrease in the rate constant for sodium efflux is not a permanent effect. Similarly, the decrease in cellular potassium associated with the initial fall in sodium transport will be temporary and cellular potassium will return towards a value only a little less than normal as the sodium transport rate is restored. This conclusion is substantiated by the results of Welt, Sachs & McManus (1964), who investigated the transport rates for sodium and potassium of the erythrocytes from subjects with renal failure. Those with high intracellular sodium concentrations and depression of the sodium-efflux rate constant exhibited a normal intracellular potassium and a normal rate of ouabain-sensitive potassium influx at this high intracellular sodium. If the sodium was artificially reduced to a normal value then potassium influx became subnormal. They commented that: 'It is our assumption that a defect in transport permits the accumulation of sodium up to a point where the impaired pump is able to maintain a new steady-state at the expense of a higher intracellular sodium concentration'. Funder & Wieth (1974) studied the effect on erythrocyte composition of clinical doses of cardiac glycosides sufficient to induce partial inhibition of the sodium pump. Although a consistent rise in intracellular sodium was found, intracellular potassium remained within the normal range. This study provides the clearest evidence for the contention that
intracellular potassium need not be greatly affected by moderate reduction in the ouabain-sensitive rate constant for sodium efflux. It should be noted that in the erythrocyte approximately 2–3 weeks were required for the new steady state to be achieved. Other cells with more active sodium-transport systems will achieve a new potassium equilibrium more rapidly. In this respect it is noteworthy that other workers, who have shown reductions in erythrocyte potassium after treatment with digoxin (Clifford & Beautyman, 1958; Astrup, 1974), had made their observations in the first few days of treatment, possibly before a new steady state had been achieved.

The changes in cell sodium and potassium we have discussed relate to a constant reference value (cell dry weight). It has to be accepted that the increase in cell cation consequent on an inhibition of the sodium pump will lead to an increase in cell water. If cell sodium and potassium and their transport rates are related to the variable of cell water or cell volume rather than dry weight, these changes will be at least partially obscured.

Reductions in the rate constant for ouabain-sensitive sodium efflux associated with an increase in intracellular sodium and a somewhat less constant change in intracellular potassium have been reported in a number of conditions, including uraemia (Welt et al., 1964; Welt, Smith, Dunn, Czerwinski, Proctor, Cole, Balfé & Gitelman, 1967; Edmondson, Hilton, Jones, Patrick & Thomas, 1975), hypertension (Edmondson, Thomas, Hilton, Patrick & Jones, 1975), hyperthyroidism (Smith & Samuel, 1970), malnutrition (Patrick & Golden, 1977) and liver disease (Alam, Wilkinson, Poston, Moodie & Williams, 1977; Alam, Poston, Wilkinson, Golindano & Williams, 1978; Owen & McIntyre, 1978). In most of these examples, a depressed rate constant for sodium efflux was associated with an elevated intracellular sodium and no change in the unidirectional flux for sodium. In erythrocytes from hyperthyroid patients, Smith & Samuel (1970) noted an increase in intracellular sodium coupled with a decrease in the rate constant for sodium efflux. Calculated sodium efflux was increased and, although influx was not measured in this study, it would clearly have been increased if we assume the cells were in a steady state. These results imply that hyperthyroidism alters not only the sodium pump but also the permeability of the erythrocyte membrane to sodium. If the rate constant for sodium efflux is held at a particular level, intracellular sodium will increase until the product of the rate constant for sodium efflux and intracellular sodium again equals the influx rate. If the stoichiometry of the sodium pump remains constant and membrane permeability to potassium is also unchanged then cellular potassium would actually increase. We are unaware of any pathological state in which these conditions obtain. However, there are examples of primary increases in membrane permeability, of which the haemolytic anaemia reported by Zarkowsky, Oski, Sha'afi, Shohet & Nathan (1968) is one of the most completely documented examples. In this disease intracellular sodium was approximately 100 mmol/l of cells and potassium was approximately 40 mmol/l of cells. Nevertheless, transport via the pump was increased 12-fold, sodium influx was increased 30-fold and potassium efflux was increased 15-fold. There appeared to be no abnormality of the pump despite the reversed sodium/potassium ratio and the disease is primarily one of increased membrane permeability. In view of the current interest in the role of sodium transport in energy expenditure one of the most interesting consequences of this condition was the threefold increase in glucose consumption and lactate production.

As we mentioned above, there appears to be a stoichiometric relationship between the transport of sodium via the pump and the utilization of ATP, with three sodium ions being extruded for the hydrolysis of one molecule of ATP (Sen & Post, 1964). There has been considerable debate as to the consequences for the whole organism of the activity of the sodium pump. Estimates of the proportion of basal energy devoted to this process vary from 5% (Chinet, Clausen & Girardier, 1977; Folke & Sestoft, 1977) to 45% (Edelman, 1976). Similarly experiments to assess the contribution of altered sodium transport to thyroid thermogenesis have also produced discrepant values varying from 90% (Ismail-Beigi & Edelman, 1970; Asano, Liberman & Edelman, 1976) to 5% (Folke & Sestoft, 1977). Results like these have even provoked the suggestion that the currently postulated transport systems, of which sodium transport is one of the most important, constitute a state of caloric catastrophe in that the sum of their energetic demands are greater than the total energy supply (Ling, Miller & Ochsenfield, 1973; Minkoff & Damadian, 1973). In debate Glynn has strongly attacked the theoretical basis of this latter argument (Cope & Glynn, 1977).
It has to be acknowledged that there are major methodological problems to be overcome in performing such experiments. The two approaches most commonly used have been to study energy consumption before and after inhibition of the sodium pump, either by the application of ouabain or by the removal of external sodium. Both these manoeuvres (which incidentally alter intracellular sodium in opposite directions) also cause cellular potassium depletion. This will itself lead to effects on intermediary metabolism, and in addition ouabain has the potential for affecting intracellular enzymes (Blatt, McVerry & Kimm, 1972; Horn, Walaas & Walaas, 1973). In experiments of this type, it may well be unsafe to assume that one is studying simply the deletion of one transport process, and that secondary processes, also energy-demanding, have not been activated. In general, the highest estimates of the energetic costs of sodium transport have come from studies on tissue slices, lower estimates being derived from perfused tissues. Whatever the ultimate explanation of these discrepancies, it remains a thermodynamic necessity that energy be expended in the maintenance of transmembrane gradients for sodium and potassium. Moreover, as Whittam (1961) pointed out, the hydrolysis of ATP is related to the flux of sodium via the pump (mmol unit time \(^{-1}\) unit mass \(^{-1}\)) and not to the rate constant itself. If we accept these arguments, sodium influx appears to be of prime importance as a pacemaker of sodium transport and at any rate one portion of energy consumption.

In many ways, the tissue most suited to the exploration of this concept is brown fat, one role for which is undoubtedly thermogenesis. Unfortunately no clear-cut explanation for the mechanism of this process has yet emerged. Horwitz (1976) has suggested an important if not dominant role for catecholamine-induced increases in membrane permeability leading to an increase in energy consumption and heat production. Himms-Hagen (1976), however, has emphasized the multifactorial nature of thermogenesis and tends to the view that changes in sodium transport play only a minor role in this process.

In summary, there is evidence that abnormalities of sodium and potassium transport are to be found in a number of widely differing clinical conditions. Such alterations are of importance in three major respects. They may result in changes in intracellular electrolyte composition with far-reaching secondary effects on cell metabolism. They may directly affect the membrane potential and the function of those specialized cells whose normal working is dependent on this. Changes in sodium transport involving an important alteration in the number of ions moved in unit time will alter the requirement for ATP at the plasma membrane.

By using theoretical arguments and examples drawn from the more complex situation found in clinical investigation, we have attempted to show that there are problems in direct extrapolation from the physiology laboratory to the patient but that, with care, the study of intracellular composition and electrolyte fluxes in disease can be rewarding in terms of an increased understanding of the complex of metabolic disorders that is a clinical entity in man.

Acknowledgments

J.P. was supported by a grant from the Wellcome Trust.

References


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