creasing with wind velocity, spreads space charge upward and lowers its density near the surface (*9, 10*). That the space charge layer near the sea is due primarily to the electrode effect is consistent with the data obtained over a lake (Fig. 3). Here the space charge layer cannot be due to the bubbling mechanism since this produces negative space charge with fresh water [S. G. Gathman and W. A. Hoppel, *J. Geophys. Res.* **75**, 1041 (1970)]. Although the electrode effect appears to be the dominant mechanism on calm or low-wind days, the bubbling mechanism can contribute significantly to the positive space charge layer close to the ocean on windy days [(*10*); D. C. Blanchard, *J. Atmos. Sci.* **23**, 507 (1966)].
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30. Recently I have begun such measurements in flights over the Atlantic Ocean and the Gulf Stream off Virginia, utilizing new horizontal electric field instrumentation in addition to the original vertical field instrumentation. The vertical field measurements have indicated circulation patterns spaced 1 km apart, presumably roll vortices, at times when meteorological conditions favored their formation. The horizontal field records at low altitudes (5, 15, 50, and 150 m) generally were characterized by higher-frequency oscillations, thus suggesting that the aircraft was passing through rising air plumes spaced about 100 to 300 m apart as found over land [J. Warner and J. W. Telford, *J. Atmos. Sci.* **20**, 313 (1963); *ibid.* **24**, 374 (1967)]. The horizontal spacing increases with altitude, thus suggesting that smaller eddies merge into larger ones as the air rises. This has also been reported over land and discussed in the above references. The relatively closely spaced plumes were detected both on days when the 1-km circulation patterns have been detected (presumably roll vortices) as well as on days when these were not in evidence. The horizontal field measurements nicely complement the vertical field data in that each appears to be especially sensitive to a particular size of circulation pattern.
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32. I acknowledge the suggestions of D. Latham, University of Miami, regarding flight paths close to the ocean which were important in recording convection patterns in this regime. I thank D. Blanchard, B. Lettau, and B. Vonnegut, State University of New York at Albany, for valuable discussions during this research program; H. Dolezalek, Office of Naval Research, Washington, D.C., who provided extensive critical evaluation during preparation of the manuscript; B. Leary, airport manager, and the Pan American Airlines staff, Rock Sound International Airport, Eleuthera, for their help during field operations in the Bahamas; and D. Mitchell, Governor's Harbor, Eleuthera, who measured ocean temperatures. This research was supported in part by the Atmospheric Science Program, Office of Naval Research, under contracts N 00014-71-C-0156 and N 00014-74-C-0336.

Membrane Transport: Its Relation to Cellular Metabolic Rates

Glucose transport into animal cells is adapted to their metabolic rate and often controls rates of glucose use.

J. Elbrink and I. Bihler

It is a truism to say that the various activities of the cell membrane are functionally integrated with the metabolic and other properties of the cell. For example, the cell membrane must provide for access of metabolic substrates at rates consistent with the cell's metabolic activity. It is of interest, therefore, to consider how membrane transport processes in different types of tissues are related to metabolism and other cellular functions and how various factors modulating these functions find expression at the membrane transport level. We discuss here one example of such integration between membrane transport and intracellular events, the interaction between the transport of glucose and its metabolism in the tissues of vertebrates. This choice is justified by the importance of glucose for the animal organism and the extensive information available on its distribution and metabolism. Even though certain animal tissues may use non-carbohydrate substances preferentially (*1*), all of them are able to use glucose and some use it almost exclusively; this substrate is constantly available, and its concentration in the blood is kept remarkably stable. Also, as discussed below, carbohydrate metabolism is subject to control by metabolic, hormonal, and other factors.

Owing to its essentially lipid nature, the cell membrane represents an effective barrier to the passage of hydrophilic molecules, unless specific transport pathways exist. Thus, glucose enters human erythrocytes 10,000 times faster than calculated for diffusion across the lipid membrane layer (*2*). The membrane transport of glucose and related monosaccharides is characterized by saturation (Michaelis-Menten) kinetics, chemical specificity, and other features indicating that its transfer across the cell membrane involves transient interaction with a limited number of specific membrane constituents, commonly referred to as carriers (*2–4*). Several nonmetabolized analogs of glucose are available permitting study of membrane transport in isolation from any subsequent metabolic transformation. From the point of view of energy requirements, the sugar transport systems in the absorptive epithelia of the small intestine and the proximal tubule of the kidney may be described as active—that is, capable of moving the substrate against an electrochemical gradient and requiring metabolic energy for this function. In most other animal tissues sugar transport is by energy-independent facilitated diffusion which leads to equilibration of sugar across the membrane and mediates equally its rapid flux in and out of the cell. The net flux will depend on the substrate concentrations at the two faces of the membrane and on kinetic parameters reflecting the carrier's affinity for the substrate and its capacity. The latter embodies both the number of carriers and their "mobility" (or rate of reorientation) within the membrane (*5*). The kinetic constants expressing affinity and capacity vary widely for transport systems in different tissues. The chemical specificity of the facilitated diffusion systems for sugars appears to be very similar but differs from that of the active transport systems; in both groups, however, D-glucose is the preferred substrate (*2*). As shown below, in some tissues facilitated diffusion of sugars depends exclusively on the substrate concentrations and the fixed properties of the carrier. In other tissues, such as muscle and adipose tissue, the properties of the sugar carrier are variable and are con-

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Table 1. Properties of glucose transport and metabolism in typical vertebrate tissues.

Transport	Intracellular glucose level	Metabolism
	Erythrocytes (nonregulated system)	
Rapid	High	Slow, stable; breakdown only
	Muscular tissue (regulated system)	
Variable; rate limiting	Very low	Variable; breakdown and storage
	Liver (nonregulated, large-capacity system)	
Very rapid uptake and release	High	Variable; breakdown, storage, and synthesis

trolled by hormonal and other factors, conferring upon the transport system added flexibility in adjusting to the metabolic requirements of the cell.

In this article emphasis will be put on the relationship between the metabolism of sugars and their facilitated diffusion in various tissues. We shall show that variability of the glucose carrier is characteristic of tissues with greatly variable metabolic rate and that membrane transport is an important control point of glucose metabolism in such tissues. We shall also review evidence suggesting that transport may be controlled in two ways: In "demand" regulation changes in metabolic and other activities of the cell provide a feedback signal for adjusting the rate of transport; in "supply" regulation the signal originates from the availability of the transport substrate itself. Some qualitative aspects of kinetics will also be discussed, but details of the carrier's chemical specificity will not be considered because this parameter is not affected by changes in cellular activity. It should be mentioned, however, that the chemical specificities of transport mechanisms and of metabolizing enzymes show a certain complementarity. Thus, the specificity of sugar transport complements that of the phosphorylating enzymes (*6*), thereby limiting the number of sugars which may gain access to the metabolic machinery and increasing the selectivity of the cell as a whole.

Erythrocytes and the Lens of the Eye

In the mature mammalian erythrocyte metabolic energy is required mainly to maintain the structural integrity of the cell, but it is not required for functional activity. Glucose is the principal substrate, and the main energy-providing pathway is anaerobic glycolysis; the hexose monophosphate shunt accounts for only about 10 percent of glucose metabolism and oxidative phosphorylation is absent (*7*). Sugar transport in erythrocytes is rapid and is not rate limiting for glucose utilization. For example, in human red cells incubated in 5 millimolar glucose entry is about 250 times faster than utilization (*3*). Thus, transport supplies more than sufficient amounts of substrate for the stable and relatively low metabolic requirements of the cells, and an appreciable intracellular pool of free glucose is present. The most thorough and extensive studies on sugar transport were done on human erythrocytes and no evidence for hormonal or metabolic regulation of sugar transport has been obtained (*8*). The penetration of glucose in adult erythrocytes of various species other than primates is, in general, much slower, and glucose transport and metabolism appear to be roughly correlated with each other. However, in most species tested free glucose is present in the cells.

In the lens of the eye, metabolism also serves primarily for the continuing turnover of cellular constituents and for the maintenance of structural integrity. It is not required directly for function because changes in the convexity of the lens are achieved entirely by the action of the ciliary muscles. Although some glucose is normally oxidized by the lens via the Krebs cycle and the hexose monophosphate shunt, and some is reduced to sorbitol, anaerobic glycolysis is the primary pathway for energy production from glucose (*9*). Sugar transport in the lens resembles that in erythrocytes. There is an intracellular pool of free glucose and of other reducing sugars (*10*) and transport is, therefore, not rate limiting for glucose utilization. Our recent experiments (*11*) also indicate that sugar transport in the lens is not subject to regulation by several factors found effective in some other tissues; as in erythrocytes, sugar transport is not stimulated by insulin.

These characteristics of sugar transport in erythrocytes and the lens are outlined in Table 1. In these two tissues the fixed capacity of the sugar transport system appears to be more than adequate to supply their stable energy requirements. Since facilitated diffusion mediates transport both in and out of the cells and since free glucose is present inside, some efflux of sugar will take place and net entry in the steady state will be less than unidirectional influx; a moderate increase in the rate of utilization will, therefore, result only in a lower stationary concentration of intracellular glucose and decreased efflux. In these tissues reserve fuels in the form of glycogen or triglycerides are either absent or unimportant as sources of energy, and insulin and other factors regulating sugar transport have no effect. Indeed, in view of their stable energy requirements these tissues would not derive any evolutionary advantage from a transport system subject to regulation. This simple "open" arrangement is, however, not without potential drawbacks. For example, in galactosemia (*12*) the increased concentration of galactose in blood and aqueous humor leads to greater entry of this sugar into the lens, followed by its enhanced metabolic conversion to dulcitol, eventually causing "sugar cataract" formation (*12*).

Other tissues which probably belong to this group include placenta and bone (see Table 2). In placenta, the penetration of glucose is not rate limiting for its utilization and the transport system does not appear to be sensitive to insulin (*4*). Sugar transport in bone has not been investigated extensively; however, an appreciable pool of intracellular glucose appears to be present and sugar transport is not affected by insulin (*13*). Glucose transport in Ehrlich ascites tumor cells appears to occur by two processes, both of which are insulin independent (*14*). Recent evidence suggests that one of these is an active process depending on metabolic energy (*15*).

Muscle

Skeletal, cardiac, and smooth muscle are excitable contractile tissues whose mechanical activity and, consequently, energy requirements may vary greatly. In these tissues the transport of glucose is normally rate limiting for its utilization (*16, 17*) and, as will be shown, the activity of the sugar transport system is modulated by contractile activity as well as by various hormonal and metabolic factors. Muscle of all types also contains glycogen stores.

Skeletal muscle. In this tissue metabolic energy is generated by both aerobic and anaerobic metabolism. In contrast to cardiac muscle, the latter pathway plays an important role under normal physiological conditions in providing energy during contractile activity. Even though the oxygen consumption of skeletal muscle rises greatly during heavy exercise and the aerobic oxidation of glucose and other substrates is much increased, aerobic metabolism alone is unable to satisfy the increased energy requirements during rapid con-

tractile activity. Additional energy is obtained by the anaerobic metabolism of glucose taken from the circulation and of stored glycogen (*18*). The steady-state intracellular concentration of glucose in resting muscle is so low as to be hardly measurable; its rate of utilization is, therefore, limited by the rate of transport into the cell (*16*). The observed increase in glucose utilization during muscular exercise thus necessarily entails stimulation of the transport step. Such stimulation is also seen with nonmetabolized glucose analogs (*19, 20*), confirming that this effect on transport is separate from any stimulation of subsequent metabolic steps. This increase may be seen as an example of "activity" or "demand" regulation, a feedback from the energy-consuming activity of the cell to the membrane transport system. In skeletal muscle the rate of sugar transport seems to be related to the frequency of muscle contractions, whereas variations in the work load are without effect (*20*). The evidence indicates that the stimulus for increased transport may be provided by events associated with excitation-contraction coupling, and it has been suggested that calcium ions may act as a link between muscular contraction and transport regulation (*21*). A hormonal substance (MAF, muscular activity factor), which stimulates sugar transport and is released only by contracting muscle, has also been proposed as mediator of the stimulatory effect (*22*). These two mechanisms need not be mutually exclusive since MAF may act by influencing the fluxes or distribution of calcium ions.

Sugar transport in muscle is also increased in vivo and in vitro by anoxia (*23, 24*). This is another example of demand regulation providing an increased supply of substrate in response to greater metabolic requirements stemming, in this case, from less efficient energy generation under anoxic conditions. It should be emphasized that the well-known activation of glycolytic enzymes during anoxia cannot by itself lead to increased anaerobic glucose utilization (Pasteur effect) unless the rate-limiting step of sugar transport is accelerated as well. The mechanism of the feedback to membrane transport is not completely understood. It was originally proposed (*23*) that the sugar carrier may be inactivated by conversion to a phosphorylated form and that the cellular level of adenosine triphosphate (ATP) might, therefore, exert a negative feedback effect. However, in some instances there is little correlation with total ATP levels (*25*); evidence from mammalian skeletal (*23*) and cardiac (*24*) muscle has specifically implicated the availability of oxidative (mitochondrial) ATP, raising the possibility of feedback from some other oxidation linked factor.

Table 2. Summary of facilitated diffusion systems for the membrane transport of sugars in vertebrates.

Nonregulated systems
Mature mammalian erythrocyte (*2, 8*)
Lens of the eye (*10, 11*)
Liver (*80, 81*)
Probably nonregulated
Ehrlich ascites tumor cell (*14, 15*)
Placenta (*4*)
Bone (*13*)
Regulated systems
Skeletal muscle (*16, 20, 23, 26, 33, 44*)
Cardiac muscle (*17, 19, 24, 28, 40, 43*)
Smooth muscle (*50*)
White adipose tissue (*53, 55, 56*)
Avian (nucleated) erythrocytes (*90*)
Probably regulated leukocytes (*76–82*)
Uncertain
Brain (*60–62, 66, 70, 71*)
Spinal cord (*76*)
Nerve (*77, 78*)

We have suggested that sugar transport may be controlled by a negative feedback from the sodium pump (*26*). This is consistent with observations that the sodium pump in mammalian skeletal and cardiac muscle is almost exclusively dependent on oxidative metabolism (*27*) and that inhibition of the sodium pump by ouabain or by potassium-free medium causes an increase in sugar transport in heart and diaphragm muscle (*26, 28*). Our data (*29*) indicate that the intracellular level of sodium ions is involved, rather than the activity of the sodium pump as such. The presence in the muscle cell membrane of a sodium-calcium exchange mechanism (*30*) suggests the possibility that the stimulation of sugar transport in the above described conditions may in fact be mediated in some way by calcium ions (*31*), as proposed previously for muscular contraction (*21*). The participation of calcium ions in the modulation of sugar transport would also be consistent with observations that ions antagonistic to calcium (*31*), and drugs known to "stabilize membranes" (*32*), inhibit the increase in sugar transport caused by a multiplicity of factors, including insulin.

Perhaps the foremost influence on sugar transport in muscle is that of insulin, whose direct effect on the membrane transport of sugar is well established (*33*). This hormone affects the same transport system as do the other regulatory factors: Stimulation by all the modulators appears to be additive unless the transport system has already reached its maximal capacity (*20, 26*). Kinetic studies have generally been interpreted as indicating an effect of insulin on the "mobility" of the sugar carrier (*34*).

Insulin is essentially an anabolic hormone promoting the synthesis of energy reserves, glycogen and triglycerides, and stimulating protein synthesis in general (*35*). Its most prominent function is in the regulation of interorgan cooperation in the disposal and distribution of metabolic substrates. The hormone's role is greatest in intermittently feeding species, such as predators and man, where periods of caloric excess alternate with periods of fasting, requiring efficient mechanisms for the storage and subsequent release of nutrients. Not surprisingly, therefore, stores of glycogen and triglycerides are found in insulin-responsive tissues. The release of insulin from the pancreatic beta cells is controlled by the blood level of certain metabolic substrates, in man primarily glucose and some amino acids. Other nutrients are more important in some other species, for example, amino acids in fish and short chain fatty acids in ruminants (*36*). Thus, when the blood level of these nutrients rises, normally following a meal, more insulin becomes available and stimulates nutrient utilization by the target tissues. This type of regulation may, therefore, be termed "supply" or "storage" regulation because the described sequence of events is set in motion by the increased availability of substrates for the synthesis of energy reserves.

It is now clear that some of the effects of insulin, such as stimulation of glycogen synthesis, inhibition of lipolysis, stimulation of amino acid transport and of protein synthesis, and effects on ion fluxes and membrane potentials, are independent of its effect on glucose transport and respond differently to inhibitors (*37*) and to adenosine 3′,5′-monophosphate (cyclic AMP) (*38*). Nevertheless, the various effects are complementary to each other (*35*), so that the increase in the transport of glucose is coordinated and integrated with a shift of its intracellular metabolism toward the synthesis of energy stores.

Cardiac muscle. As in skeletal muscle, the rate-limiting step for glucose utilization is membrane transport (*17*). Under normal physiological conditions mammalian cardiac muscle derives its energy nearly entirely from oxidative phosphorylation, but the capacity for anaerobic glycolysis is present (*39*). Anoxia strongly stimulates sugar transport in vitro (*17*) but the significance of such an effect under mild hypoxic conditions in vivo remains to be evaluated; it has been suggested that glycolysis may be of major importance in maintaining cardiac function in certain amphibians (*39*). As in skeletal muscle, sugar transport in the heart is also increased by contraction, and there is a direct relationship

between sugar transport and both contraction frequency (*28*) and work load (*19, 40*). Sugar penetration is also stimulated by inotropic concentrations of epinephrine (*41*) and ouabain (*28, 42*); this appears to be linked to the increase in contractile force caused by these drugs. Thus, in cardiac muscle, activity regulation seems to provide several mechanisms for adjusting the supply of substrate as required by the metabolic pattern and the work load of the heart.

Because sugar transport and glycogen synthesis in the heart are stimulated by insulin (*17*), storage regulation also takes place; but the role of glycogen as a reserve fuel in the heart is not well established. Although glycogenolysis may be demonstrated in vitro, there is no strong evidence for glycogen utilization in vivo. In addition, myocardial glycogen levels are increased in fasting and diabetes, a response opposite to that of skeletal muscle (*39*).

The inhibition of glucose transport and utilization by alternative oxidative substrates, for example, free fatty acids, may be seen either as regulation by the supply of metabolites or as a feedback from altered cellular metabolism. During oxidation of fatty acids, the transport of glucose, as well as its metabolism, are repressed in the heart (*43*) and in skeletal muscle (*44*). The effect depends on the oxidation of fatty acids and not merely on their presence, because it is antagonized by inhibitors of fatty acid oxidation. While the enzymatic aspects of the negative feedback on glucose phosphorylation have been elucidated (*45*), the effect on membrane transport, also seen with nonmetabolized glucose analogs, is not understood at present. Since fatty acids, ketone bodies, and other oxidative substrates are, in fact, the preferred substrates of muscle (*18, 19, 39, 46*), this effect is of great importance. It is well established that the availability of free fatty acids for oxidation in vivo leads to a considerable sparing of glucose (*47*). This is a physiologically very useful arrangement in starvation and intense exercise, since it preserves glucose for oxidation by the brain which normally is absolutely dependent upon it (*48*).

Smooth muscle. Less is known about the transport and metabolism of sugars in smooth muscle. It appears that anaerobic glycolysis is of even greater importance in this tissue than in skeletal muscle. Glycogen is present but little is known about its physiological role (*49*). Sugar transport in several types of smooth muscle occurs by facilitated diffusion and is rate determining for glucose utilization (*50*). Furthermore, our recent studies on the detrusor muscle of rat and rabbit urinary bladder have demonstrated that sugar transport is increased by muscular contraction, insulin, and anoxia or inhibition of the sodium pump. The present data would indicate that all of the agents and conditions which stimulate sugar transport in skeletal muscle are also operative in smooth muscle, and that both activity and storage regulation occur.

Other hormones stimulate sugar transport in certain types of muscle, for example, estrogens in uterine muscle (*51*) and androgens in the levator ani (*52*). These effects are probably an expression of the general stimulatory influence of sex hormones on their target tissues, and most likely represent an increase in the number of carriers rather than a regulatory effect on their activity. This interpretation is supported by the existence of a time lag between the stimulus and its effects and by the dependence of the effects on protein synthesis.

The factors and conditions which regulate the activity of sugar transport in the three types of muscle appear to be almost identical. The only major difference is the absence of load-dependent transport stimulation in skeletal, as compared to cardiac, muscle. The relationship between glucose transport and metabolism in muscle is summarized in Table 1.

Adipose Tissue

White adipose tissue is functionally specialized for the synthesis, storage, and release of fat. Lipogenesis prevails when the supply of glucose (and fats) is plentiful and lipolysis predominates during fasting periods. These effects are controlled and in part mediated by hormonal factors. In this tissue the transport of glucose is also rate limiting for its utilization, and no significant levels of free glucose are normally present in the cells (*53*). Sugar transport is increased by insulin (*53*) which, by increasing the availability of glucose for the formation of glycerol phosphate, also increases triglyceride synthesis; the hormone also has a glucose-independent antilipolytic effect (*54*). As in muscle, when oxidative metabolism is inhibited or uncoupled from energy production, glycolysis is enhanced and sugar transport is stimulated (*55*). Inhibition of the sodium pump also enhances sugar transport (*55, 56*) and, like insulin, shifts metabolism toward the increased synthesis of glycogen and lipids and decreased lipolysis (*56*). Catecholamines, apart from stimulating lipolysis, have also been reported to increase sugar transport in adipose tissue and isolated fat cells (*57*). This effect is not seen in adipose cell "ghosts" which are devoid of lipids (*58*), suggesting that the increase in sugar transport may be linked to the interference with oxidative metabolism by the high levels of intracellular fatty acids set free by lipolysis; it was shown that under these conditions ATP levels are depressed (*59*) and the sodium pump is inhibited (*56*). The physiological significance of this effect, if any, is at present not clear. The above relationships indicate that, as in muscle, those factors which govern the metabolic utilization of glucose also influence the activity of sugar transport in a coordinated fashion.

Brain

Evidence for sugar transport systems in the brain has been obtained only fairly recently. Experiments in vivo suggest that facilitated diffusion of sugars occurs at the level of the capillary endothelial cells (*60*); observations on brain slices (*61*) and synaptosomes (isolated nerve endings) (*62*) indicate that membrane transport of glucose may also take place at other sites including, presumably, the membranes of glial and neuronal cells. The transport of sugars between the cerebrospinal fluid and the brain is also facilitated (*63*) while in the choroid plexus active transport of some sugars has been demonstrated (*64*). The kinetic parameters and other properties of sugar transport measured in vivo and in brain slices appear to be very similar (*65*), but transport in synaptosomes apparently differs in several regards (*62*). Data from the usual highly heterogeneous brain preparations are, therefore, difficult to interpret. Another major uncertainty concerns the concentration of glucose within the brain cells. In contrast to earlier views, it has recently been argued that there is hardly any free glucose in the cells and that membrane transport may, therefore, be rate determining for cerebral glucose utilization (*66*). The argument depends on the size assumed for the extracellular space and on the comparison of transport and phosphorylation kinetics; some uncertainty still prevails about the precise magnitude of these parameters.

Normally, brain metabolism depends almost exclusively on glucose oxidation (*48*), but it is now known that the brain is capable of utilizing ketone bodies if their concentrations in the blood are sufficiently high as, for example, during prolonged starvation (*67*). Glucose utilization is increased in vitro by hypoxia and by electrical stimulation (*48*) but, as discussed above, present knowledge is insufficient for us to say whether or not this is accom-

panied by activation of the transport system. There is some indirect evidence for the simultaneous activation of sugar transport and metabolism (*48, 66, 68*) and such an arrangement would appear likely by analogy to other tissues. However, one cannot exclude the possibility that the intracellular glucose pool may be sufficient to supply the accelerated metabolism. Glycogen is present in the brain and is utilized rapidly in a variety of conditions (*69*), but the role of insulin in the brain remains controversial. Most studies indicate that insulin has no effect (*70, 71*). However, a slow entry of insulin into the cerebrospinal fluid has been demonstrated (*72*), and an effect of intracisternally administered insulin on glycogen synthesis has been observed (*70, 73*). An effect of the hormone on glucose uptake by the human brain in vivo has also been reported (*74*) and some newer studies with brain slices also indicate an effect of insulin on glycogen synthesis (*75*); some of these data suggest an effect on sugar transport. No effect of the hormone was observed in synaptosomes (*62*).

Data on sugar transport in other neuronal tissues are scant. Effects of insulin in the spinal cord have been reported but the results remain controversial (*76*). Effects of insulin have also been described in isolated peripheral nerve (*77*) and ganglia (*78*).

Although some of the evidence described above is indirect or still controversial, it nevertheless seriously challenges the older view that sugar transport in the brain resembles that in the erythrocyte (*4*). Future work, perhaps with homogeneous cell populations, should provide more conclusive evidence on whether sugar transport in the brain is of the erythrocyte or the muscle type.

Liver

This organ has a key function in glucose homeostasis and is the most important site of insulin-dependent glycogen synthesis and storage. The conversion of fructose and galactose to glucose, as well as glucose formation from other metabolites (gluconeogenesis), also takes place in this organ. The extent and pattern of glucose metabolism in the liver varies greatly and so does its relative contribution to total metabolic activity. Although earlier studies suggested that the liver was freely permeable to glucose and other sugars (*79*), newer work has shown that monosaccharides enter the liver cells by a specific facilitated diffusion process (*80*) which is not affected by insulin (*81*). The liver contains substantial amounts of free glucose and penetration is thus not rate limiting for its utilization. As opposed to other tissues, glucose efflux from the liver cells is of major physiological importance; glucose derived from glycogenolysis is being discharged from the liver when the plasma level of glucose is low or under the influence of, for example, glucagon or catecholamines. It would appear that the capacity of the sugar transport system in the liver is sufficient, without any alteration in its properties, for rapid efflux under these conditions, as well as for rapid influx during glycogen synthesis. With such an arrangment there is no need for two different regulatory systems to enhance sugar transport in these opposed conditions. In other words, even though glucose utilization is variable in this tissue, its penetration across the cell membrane is not rate limiting, and the transport system appears to have a sufficient capacity to provide for the high rates of influx or efflux without regulation.

Other Tissues

There is evidence for both activity and storage regulation of sugar transport in leukocytes. Glucose utilization of polymorphonuclear leukocytes and macrophages is increased in phagocytosis (*82*), and leukocytes of diabetic patients show a decrease in glucose utilization and glycogen levels; insulin in vivo corrects this defect but evidence on effects of insulin added in vitro is contradictory (*83–85*). It has been proposed (*83*) that in these cells membrane transport is not rate limiting for glucose utilization nor sensitive to insulin but other data suggest that insulin affects both transport and metabolism as is the case in all other insulin-responsive tissues. Thus, an effect of insulin in vitro on the transport of a nonmetabolized sugar has been described (*85*) and in one study no measurable free glucose was found within the cells, unless the rate-limiting transport step was stimulated by insulin in vitro (*86*). In lymphocytes an insulin-sensitive facilitated diffusion system for sugar transport has been recently characterized (*87*). Its activity is increased during blast transformation under the influence of the mitogenic agents, phytohemagglutinin and concanavalin A; this effect is rapid and does not require protein synthesis. A similar rapid increase of sugar transport in lymphocytes was reported for α-adrenergic agents (*88*). Viral transformation of some cell lines in tissue culture has also been described as leading to rapid activation of sugar transport (*89*). Although the picture is still incomplete, there is thus increasing evidence that changes in cell activity, for example, phagocytosis or preparation for cell multiplication, and hormonal effects may modulate sugar transport concurrently with their effects on leukocyte metabolism.

In contrast to mammalian erythrocytes, sugar transport in the nucleated erythrocytes of birds is subject to regulation (*90*). These cells are also more active metabolically and are capable of oxidative phosphorylation, as well as of anaerobic glycolysis. No measurable free glucose was found within the cells and glucose transport is, therefore, rate limiting for utilization. Inhibition of oxidative phosphorylation, anoxia, and epinephrine stimulated sugar transport; such stimulation was associated with a decrease in ATP levels, giving rise to a revival of the hypothesis implicating ATP as a regulator of sugar transport (*23*). Insulin had no effect on sugar transport in these cells nor were appreciable amounts of glycogen present. Sugar transport in mammalian reticulocytes, the nucleated precursors of erythrocytes, has not been studied. By analogy with avian erythrocytes one would predict their sugar transport system also to be regulated and to undergo transformation to the simple unregulated type on maturation; amino acid transport in reticulocytes has been shown to lose its sodium and energy dependence upon maturation of the cells and to revert to simple facilitated diffusion (*91*).

Conclusions

The data discussed above are summarized in Tables 1 and 2. In tissues where sugar transport is subject to regulation three main characteristics stand out. First, the cells contain only very low concentrations of free glucose. The rate of glucose metabolism is, therefore, largely determined by the amount of substrate admitted to the intracellular enzymes, and the transport step is thus one of the control points of glucose metabolism. Second, the rate of glucose metabolism in these tissues is variable, requiring that sugar transport be modulated to satisfy the changing substrate requirements. A negative feedback from the energy-providing systems or from the energy charge of the cell to the membrane transport step appears to operate here, in addition to the regulatory mechanisms controlling metabolic enzymes. A third characteristic is that, while there are some differences in what modulating factors are effective in a particular tissue, they all act by rapidly altering the efficiency of one and the same specific transport process, perhaps by a common mechanism.

With the exception of avian erythrocytes, all of these tissues respond to insulin and contain energy reserves in the form of glycogen and triglycerides. Also, all of them have a capacity for both aerobic and anaerobic metabolism and exhibit the Pasteur effect. The dependence of sugar transport on contraction is seen, of course, only in contractile tissues. These relationships are summarized in Fig. 1. As for the nature of the common regulatory mechanism, we have suggested (*31*) that the effect of the various modulators may be mediated by the binding of calcium ions to specific sites at the internal face of the cell membrane, resulting in altered "mobility" of the sugar carrier.

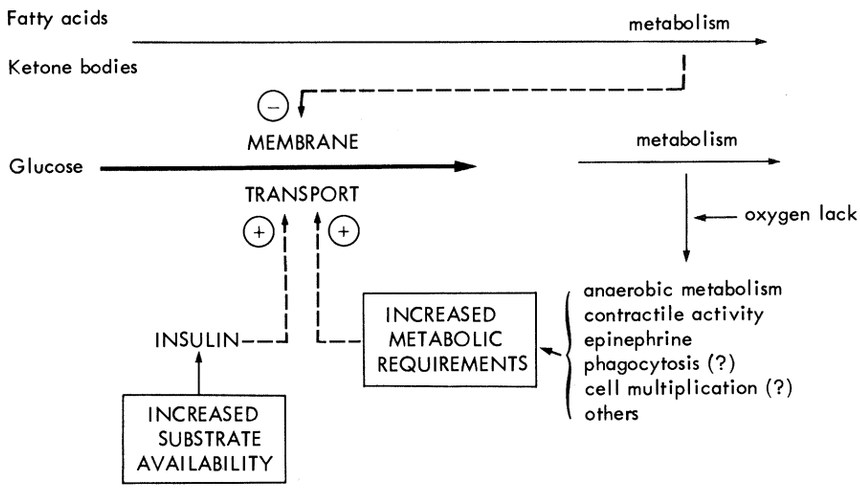

Fig. 1. Factors that regulate the membrane transport of sugars in vertebrates. Regulatory influences are indicated by dashed lines, + activating, – depressing. Only factors modulating the activity of the sugar carrier are shown. Interventions which alter sugar transport by increasing the nonspecific permeability of the cell, or by blocking the carrier, are not listed.

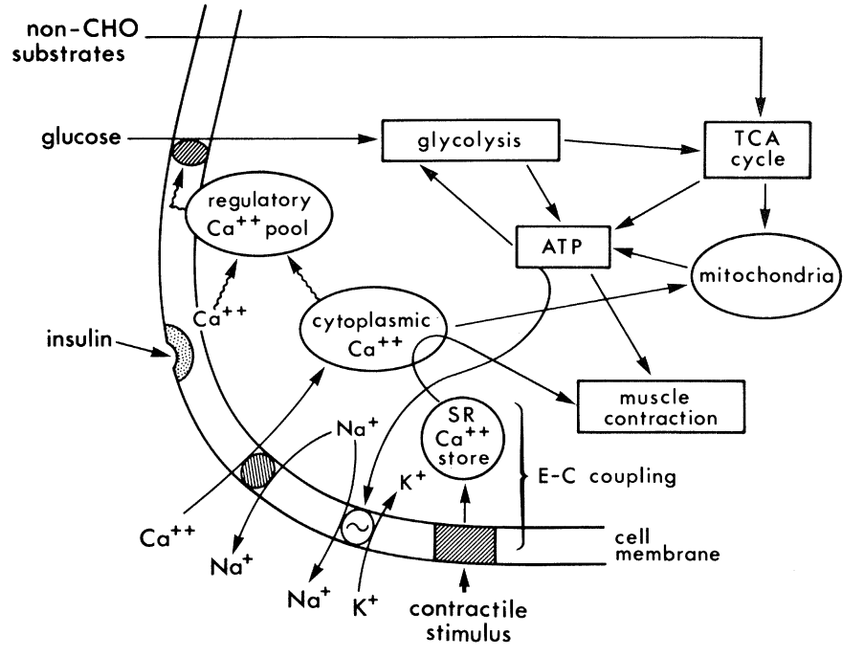

Fig. 2. Interactions between glucose transport and modulating factors. The full arrows indicate metabolic pathways and ion fluxes. The wavy arrows show the proposed modulating effects via the hypothetical regulatory Ca^{2+} pool. The binding of Ca^{2+} to specific sites at the internal face of the membrane is thought to alter the conformation of some membrane constituents and thereby to control the "mobility" of the sugar carrier. The extent of this binding is shown to be influenced by the binding of insulin to its receptor and by the cytoplasmic Ca^{2+} level which is affected by Ca^{2+}-Na^+ exchange and by excitation-contraction coupling (*E-C*); the coupling mechanism acts by releasing Ca^{2+} from storage in the sarcoplasmic reticulum (*SR*) or in some more direct manner (not shown). Ca^{2+}-Na^+ exchange depends, in turn, on the activity of the energy-dependent Na^+ pump. Rapid mitochondrial oxidation may decrease the size of the regulatory Ca^{2+} pool by inducing a shift of cellular Ca^{2+} to the mitochondria. This mechanism acting in reverse, as well as decreased activity of the Na^+ pump, may also mediate the increase in sugar transport evoked by anoxia. The metabolic effects of insulin and the regulatory feedbacks between various metabolic steps have been omitted for clarity.

It may be more than a coincidence that three cellular functions involving major changes in membrane permeability (in a wider sense), that is, excitation-contraction coupling, stimulus-secretion coupling, and what may be called stimulus-metabolite permeation coupling show so many similarities in the nature of the factors controlling them. Could a primitive mechanism for control of membrane permeability have evolved into specialized processes for adjusting the membrane permeability to particular ions, nonelectrolyte metabolites, and proteins, depending on cellular function?

We have classified the regulatory effects on sugar transport according to their linkage to cellular metabolism. In activity or demand regulation the modulating factors are associated with cellular activity itself or with the energy charge of the cells. Thus, contractile activity provides the signal for stimulation of sugar transport, enhancing the supply of substrate required for the increase in energy metabolism. Similarly, the metabolic changes in anoxia provide a stimulatory signal to the sugar transport system which is essential for the operation of the Pasteur effect. Conversely, oxidation of fatty acids in muscle generates a signal for decreased transport resulting in the sparing of glucose. In supply or storage regulation transport is controlled by the availability of nutrients. Thus, high blood sugar levels stimulate the pancreatic secretion of insulin, serving as messenger and signal for increased sugar transport and glycogen and triglyceride synthesis. This effect is additional to the change in transport rate resulting directly from alterations in substrate concentrations.

Some of the proposed mechanisms for activity and storage regulation are outlined in Fig. 2.

Summary

The regulation of sugar transport in several animal tissues is correlated with the metabolic requirements of each tissue. As a general rule, in tissues where glucose utilization is stable, free intracellular glucose is present and the transport system has a more than sufficient capacity to supply the required substrate. In this category are the mature mammalian erythrocyte and the lens of the eye. Transport is also not rate limiting in the liver although its metabolic rate is variable; this may be related to the

very large capacity of its transport system, suited to rapid release as well as rapid uptake of glucose. As for the brain, although the rate of glucose metabolism in this organ appears to be variable under certain conditions, whether or not the transport step itself is also regulated has not yet been determined.

In tissues where glucose utilization is variable, its penetration across the cell membrane is rate limiting, providing an additional means of controlling metabolism through a number of feedback systems. This is the case in various types of muscle, in adipose tissue, and perhaps in some other tissues. Cellular activities which result in greater energy consumption, and other changes in the tissue's pattern of metabolism, modulate sugar transport in a manner consistent with the concomitant changes in its metabolism; this has been called activity or demand regulation. The effect of insulin in increasing sugar transport in coordination with its stimulatory effect on the synthesis on energy reserves is an example of storage or supply regulation.

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92. This work was supported by grants from the Medical Research Council of Canada and the Manitoba Heart Foundation. I.B. is an Associate of the Medical Research Council.

What Next in Health Policy?

Eli Ginzberg

Little is to be gained by playing the game of guessing whether legislation for a National Health Insurance (NHI) bill will be passed this year. The new chairman of the House of Representatives Committee on Ways and Means has been quoted as saying that a bill will be passed and that it will have such widespread public support that the President will not dare veto it (a threat implied in his State of the Union message in which he stated that he was opposed to any new legislation involving new expenditures this year).

The chairman's remark can be interpreted as a gambit in the psychological warfare that often takes place when the differences between the executive and the legislative, between Democrats and Republicans, and among interest groups do not appear easily reconcilable. The last attempt to write an NHI bill (1974) foundered just because of unreconcilable differences. Although the new Congress is more to the Left, there is a new chairman of the Ways and Means Committee, and the election of 1976 is nearer; it is still not clear that even these three potent factors will provide the solvent required to reduce the combined barriers of philosophy and money. In any case, what could a new NHI act possibly accomplish?

Even if it were passed, NHI would not involve basic changes in the health infrastructure; that is, it would not modify seriously the stakes of commercial insurance and the Blue Cross–Blue Shield or the autonomy of physicians to practice and hospitals to operate as they do. Any NHI law passed would address primarily two issues: financial coverage for catastrophic illness and some broadening of entitlements for ambulatory care.

The next question is how the health services that are provided to the American people are likely to change, particularly services available to those people who have inadequate access at the present time. My tentative reply is very little. Services are provided only if people seek them and only if additional outputs become available. Currently most physicians are busy, and although they could cut down on the time that they allocate to each patient and thus increase the number they treat, those with a middle-class clientele are unlikely to do so. Consequently, a significant expansion in ambulatory services, particularly for the poor and the aged, particularly in the large urban centers, is likely to replicate the Medicaid experience: additional services will be produced by avaricious groups that have earned the nickname "mills," or by the expansion of ambulatory services at community and teaching hospitals. Neither prospect is encouraging if the past is any guide, and there is little reason to disregard it.

Current Health Needs

It is widely believed that tens of millions of citizens are handicapped by their lack of access to health services. The forms of evidence usually adduced are the statistical data which record higher utilization rates among those in the higher income brackets. No informed observer of the changing health scene would question that the poor, especially in the rural South, do not have easy access to medical care. But except for the rural South, lack of access per se is not the critical factor in obtaining medical care in urban centers, where there is a high concentration of health facilities and practitioners. The issue is not access to medical services, but the quality of care that the poor receive. Moreover, we must differentiate between surgical and medical interventions. As early as 1948, the poor, both urban and rural, were able to obtain access to hospitals when they required surgery, but they were not readily admitted to hospitals for medical conditions at that time (*1*). This problem has been substantially alleviated by the Medicaid and Medicare programs. The remaining issues of access to medical services involve access to ambulatory care.

It would be desirable for the protagonists of major health reforms to identify the health conditions of the underserved populations which are currently not diagnosed and treated and to relate this neglect to problems of access. It is important to keep problems of access to medical care separate from conditions important for health. Many poor people require improved housing, more income, new jobs, and other adjustments to better their health, adjustments which no medical care system can provide. I suspect that much of the pulling and hauling in health policy derives from the confusion between access to medical services and access to effective therapies. I suspect that the public is more aware of this than the health policy-makers since the public puts health reform low on its list of priorities.

How Much Money Is Needed for Effective Reform?

When the possibility of NHI first emerged a few years ago as a political reality, the costs of several bills introduced varied from under $10 billion to over $80 billion. Part of the difference was explainable by the range of services that were to be covered and the extent to which the consumer would carry part of the cost. Another explanation for the wide spread was the difference in the national total as com-

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