Cellular hydration state: an important determinant of protein catabolism in health and disease.

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There is evidence that cellular hydration state is an important factor controlling cellular protein turnover; protein synthesis and protein degradation are affected in opposite directions by cell swelling and shrinking. An increase in cellular hydration (swelling) acts as an anabolic proliferative signal, whereas cell shrinkage is catabolic and antiproliferative. The cellular hydration state is mainly determined by the activity of ion and substrate transport systems in the plasma membrane. Hormones, substrates, and oxidative stress can change the cellular hydration state within minutes, thereby affecting protein turnover. We postulate that a decrease in cellular hydration in liver and skeletal muscle triggers the protein catabolic states that accompany various diseases. Lancet 1993; 341: 1330-32.

Changes in cellular hydration state may affect protein metabolism. Increased protein degradation, or catabolism, plays an important role in the development and progression of many diseases. Cellular hydration state is the amount of water inside a cell. A large volume of water inside a cell causes swelling, which may stimulate protein synthesis. A reduced volume of water inside the cell causes shrinkage, which may stimulate protein catabolism. Changes in cellular hydration state can occur within a matter of minutes. They are caused by alterations in the activity of ion and substrate transport systems in the cell membrane. Hormones, substrates and oxidative stress can all affect this type of activity. Protein wasting that occurs in critically ill patients may be caused by reduced hydration of liver and skeletal muscle cells.

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Background

Severe nitrogen wasting is commonly encountered in the management of patients with trauma, sepsis, and chronic illness. Increased production of catabolic hormones, low muscle glutamine concentrations, and changes in aminoacid metabolism have been implicated.[1-5] Most studies have concentrated on skeletal muscle and liver, the organs that contribute most to whole-body protein turnover, and have found that both synthesis and breakdown of proteins are controlled by aminoacids and hormones. However, the underlying mechanisms remained unclear.[6] Lately, studies have shown that the cellular hydration state can change within minutes in response to various signals and that changes in hydration state are an important means of regulating various cellular functions, including protein turnover.[7]

Physiological modulation of cellular hydration state

Many aminoacids are taken up into cells by sodium-ion-dependent transport systems, which convert the energy of the electrochemical sodium gradient across the plasma membrane into osmotically active aminoacid gradients with intracellular/extracellular concentration ratios of up to 30. Such gradients cause water to move into the cell and lead to cell swelling. Liver cells swell by as much as 12% within 2 min under the influence of glutamine, in physiological concentrations, and the increased cellular hydration is maintained as long as the aminoacid is present.[8] Hormones, again in physiological concentrations, also change the cellular hydration state (cell volume) rapidly by modulating the activity of ion-transport systems in the plasma membrane.[9,10] Insulin increases cellular hydration by causing Na+, K+ and Cl- to accumulate within the cell due to activation of the Na+/K+ antiporter, NA-K-2Cl cotransport, and the Na+/K+ ATPase.[7,9] Glucagon induces cell shrinkage by opening Ba2+ -sensitive K+ channels, which allows loss of K+ from the cell. Other hormones, such as adenosine, [Alpha]-adrenergic agonists, vasopressin, bradykinin, and serotonin also change cell volume.[10] Experimentally induced oxidative stress decreases cellular hydration by opening K+ channels in the plasma membrane, possibly by oxidation of important thiol groups or by raising intracellular Ca2+ concentration.[11]

Cell swelling/shrinkage and regulation of cellular metabolism

In liver, cell swelling inhibits breakdown of glycogen, glucose, RNA, and protein and simultaneously stimulates synthesis of glycogen, RNA, DNA, and protein. The opposite metabolic pattern is triggered within minutes by cell shrinkage. Apparently, cell swelling is a proliferative anabolic signal, whereas cell shrinkage is antiproliferative and catabolic. Hormone-induced changes in cellular hydration are now seen as another "second messenger" of hormone action.[9] Metabolic control by way of changes in cellular hydration suggests that the concentrative
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Aminoacid transport systems in the plasma membrane may not act simply as transporters of aminoacids across the plasma membrane but also as a signal transduction system modifying cellular function by changing the hydration state.

Evidence for the hypothesis

The antiproteolytic effects of some aminoacids and insulin and the proteolytic action of glucagon can be explained by the influence of these substances on cellular hydration.[12] In liver cells the extent of a change in hydration state, rather than the mechanism underlying the change, is what determines the size of the proteolytic response. The proteolytic effects of insulin, glycine, and glutamine can be quantitatively mimicked by swelling of cells in hypotonic environments to an extent as insulin and the aminoacids do. Pharmacological blockade of insulin-induced cell swelling abolishes the antiproteolytic effect of the hormone.[7,12] The opposing actions of glucagon and insulin on proteolysis are explained by their opposing effects on cellular hydration. The effects of cell shrinkage and swelling on protein synthesis are opposite to those on proteolysis (shrinkage inhibits and swelling stimulates protein synthesis).[13] Regulation of protein turnover by the cellular hydration state has been shown in rat liver cells and rat and human hepatoma cell lines, but it may also occur in skeletal muscle.

Skeletal muscle cells have a highly concentrative transport system for L-glutamine in the plasma membrane.[14] in human beings this system maintains an intracellular glutamine concentration of about 20 mmol/L whereas the extracellular concentration is about 0.6 mmol/L. The extent of nitrogen wasting correlates closely with muscle glutamine content, and severe depletion of muscle glutamine can predict death irrespective of the underlying disease.[5,15] These observations led to the idea that the intracellular glutamine concentration in skeletal muscle, which may depend on the activity of the glutamine-transporting system N, is somehow linked to muscle protein breakdown.[14] This notion was supported by the findings that glutamine stimulates protein synthesis and inhibits proteolysis in rat skeletal muscle preparations.[16-18] Changes in cellular hydration state might be the variable linking muscle glutamine content with protein turnover in skeletal muscle and, because of the large mass of skeletal muscle, to whole-body nitrogen balance. Data from our previous studies of the relation between intramuscular glutamine content and catabolism in patients with various underlying disorders[19-21] allowed us to look at the relation between muscle-cell water content and whole-body nitrogen balance; there is an inverse relation (figure).

Hypothesis

From in-vitro studies[7,9,12,13] and our findings in human beings (figure) we postulate that protein wasting in critically ill patients is due, at least partly, to decreased cellular hydration in skeletal muscle and liver. Although the hypothesis implies that the extent of cellular dehydration determines the extent of nitrogen wasting irrespective of the underlying disease, the pathogenetic mechanisms leading to cell shrinkage may well be multifactorial and heterogeneous and could involve disease-specific components. Low activities of aminoacid transporters, Na+/H+ antiport or NA-K-2Cl cotransport, dissipation of transmembrane substrate gradients, and opening of K+ channels under the influence of altered nutrition, hormones, cytokines, oxygen radicals, and other mediators of inflammation can all contribute to cellular shrinkage, which acts as the common end path triggering net protein breakdown. Sepsis[22] and tumour necrosis factor[23] lower muscle-cell-membrane potential and the transmembrane Na+ gradient.[24] Depolarisation favours cellular accumulation of chloride and thus cell swelling, but it also impairs the driving force for concentrative substrate uptake into the cells, which favours cell shrinkage. There have been reports of sepsis-induced inhibition of aminoacid transport system A activity[25] and decreased intracellular water content in severe disease.[24,26]

Clinical perspectives

The findings discussed above suggest that attention should be paid to the cellular hydration state, which is governed primarily by the activity of ion and substrate transport systems in the plasma membrane and probably only to a minor extent by the hydration state of the extracellular space. Most physicians pay careful attention to the hydration state of the extracellular space, whereas that of the intracellular space is largely ignored, probably because there are no routinely applicable techniques to assess cellular hydration and no potent therapeutic measures to interfere with cellular volume. However, clinicians may already interfere with cellular hydration when they try to overcome or to avert protein catabolism by administron of aminoacid mixtures. The concentrative uptake of some aminoacids (ie, those transported by Na+-dependent mechanisms into muscle and liver cells) would be expected to increase cellular hydration, thereby triggering a protein-anabolic signal. Few available aminoacid solutions contain glutamine, because of the instability of this aminoacid, and it is apparently the most potent with respect to cell swelling. Stability problems can be circumvented by use of glutamine dipeptides, which are rapidly hydrolysed in the circulation. Furst et al[27] have suggested that preparations containing glutamine...
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dipeptides have better anticatabolic action than other preparations, but further studies are needed. On the other hand, aminoacid infusion may not effectively overcome protein-catabolic states in every patient, because the cellular hydration state is governed not only by the transmembrane aminoacid gradient but also by the activity of diverse ion transport systems in the plasma membrane.

REFERENCES