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EDITORIAL

Sodium-dependent transporters in health and disease—a special issue

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Sodium-dependent transporters utilize the energy stored in the transmembrane sodium gradient to move ions or other solutes against their concentration gradient across the plasma membrane. This sodium gradient is established and maintained by the sodium pump or Na^+–K^+ ATPase that directly hydrolysis ATP. The Na^+–K^+ ATPase pumps three sodium ions out of the cell in concert with pumping two potassium ions into the cell, thus maintaining an intracellular environment that has low sodium and high potassium (the opposite of extracellular fluid). In most cells, 50 % of the total energy expended is used to run these ion pumps. In neurons, which repeatedly gain sodium during action potentials, two thirds of the ATP usage goes toward fueling this single pump.

Sodium-dependent transporters belong to the class of cotransporters including symporters and antiporters. Some of which carry both solutes in the same direction (symport), while others transport sodium into the cell and an ion or solute out of the cell (antiport). In general, cotransporters are one of three main classes of integral membrane proteins known as transporters that move solutes and ions across the plasma membrane. The cotransporters belong the solute carrier (SLC) group of membrane transport with nearly 400 members organized into 52 families [2, http://slc.bioparadigms.org/]. The SLC gene nomenclature system was originally proposed by the HUGO Gene Nomenclature Committee (HGNC) and is the basis for the official HGNC names of the genes that encode these transporters.

Sodium-dependent transporters can be found in various tissues. In epithelial cells located along the intestine or renal nephrons, these cotransporters can be present in the apical and basolateral membrane. For instance, the sodium-dependent glucose transporters (SGLT) use the energy from the downhill sodium ion gradient to transport glucose across the apical membrane of the proximal tubule against an uphill glucose gradient [4]. Actually, one or two sodium ions are transported along with each sugar. SGLTs are known as symporters since both sodium ions and glucose are transported in the same direction across the plasma membrane. The sodium-dependent transporters can also be found in excitable tissues. For example, the sodium-calcium exchanger (NCX) is an antiporter that extrudes calcium ions from cells. It allows sodium to flow down its gradient across the plasma membrane in exchange for the counter transport of calcium ions. The NCX removes a single calcium ion in exchange for the import of three sodium ions [1]. The exchanger exists not only in the heart muscle but also in the basolateral membrane of the distal convoluted tubule in the kidney and is considered one of the most important cellular mechanisms for removing calcium ions [1].

The importance of this class of cotransporters is further illustrated by genetic disorders in which mutations in a sodium-dependent transporter result in serious disorders. A well-studied example is glucose–galactose malabsorption (GGM, MIM 182380) that is due to mutations in the gene coding for the intestinal brush-border sodium-glucose cotransporter (SGLT1). Consequently, the young patients fail to absorb glucose and galactose causing diarrhea that leads to severe dehydration and death if left untreated [4].

These membrane proteins are frequently used as drug targets as illustrated [3]. L-glutamate is an excitatory amino acid neurotransmitter in the mammalian central nervous

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system. Sodium-dependent glutamate transporters play not only a key role in mechanisms associated with synaptic plasticity such as learning and memory but also participate in the pathology of different neuropsychiatric disorders [3]. Many compounds targeted to these transporters have been developed and tested as potential therapeutic targets for different neurodegenerative and neuropsychiatric disorders. Similarly, sodium-dependent transporters in the kidney are major targets for diuretics such as loop and thiazide diuretics.

Over the last decades, ample researchers have studied several aspects of the sodium-dependent transporters including the molecular structure, genetics, kinetics, localization, and regulation. In this special issue, a selection of sodium-dependent transporters are discussed by illustrating the typical hallmarks of the particular SLC transporters, their up- and downstream signaling cascades, their physiological functions, and relation to diseases.

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