Sodium / Potassium pump

Na^+/K^+-ATPase (sodium–potassium adenosine triphosphatase, also known as the Na^+/K^+ pump or sodium–potassium pump) is an enzyme (an electrogenic transmembrane ATPase) found in the membrane of all animal cells. It performs several functions in cell physiology.

The Na^+/K^+-ATPase enzyme is active (i.e. it uses energy from ATP). For every ATP molecule that the pump uses, three sodium ions are exported and two potassium ions are imported; there is hence a net export of a single positive charge per pump cycle.

The sodium–potassium pump was discovered in 1957 by the Danish scientist Jens Christian Skou, who was awarded a Nobel Prize for his work in 1997. Its discovery marked an important step forward in the understanding of how ions get into and out of cells, and it has particular significance for excitable cells such as nerve cells, which depend on this pump to respond to stimuli and transmit impulses.

All mammals have four different sodium pump sub-types, or isoforms. Each has unique properties and tissue expression patterns. This enzyme belongs to the family of P-type ATPases.

Function

The Na^+/K^+-ATPase helps maintain resting potential, affects transport, and regulates cellular volume. It also functions as a signal transducer/integrator to regulate the MAPK pathway, reactive oxygen species (ROS), as well as intracellular calcium. In fact, all cells expend a large fraction of the ATP they produce (typically 30% and up to 70% in nerve cells) to maintain their required cytosolic Na and K concentrations.[3] For neurons, the Na^+/K^+-ATPase can be responsible for up to 3/4 of the cell's energy expenditure.[4] In many types of tissue, ATP consumption by the Na^+/K^+-ATPases have been related to glycolysis. This was first discovered in red blood cells (Schrier, 1966), but has later been evidenced in renal cells,[5] smooth muscles surrounding the blood vessels,[6] and cardiac purkinje cells.[7] Recently, glycolysis has also been shown to be of particular importance for Na^+/K^+-ATPases in skeletal muscles, where inhibition of glycogen breakdown (a substrate for glycolysis) leads to reduced Na^+/K^+-ATPase activity and lower force production.

Resting potential

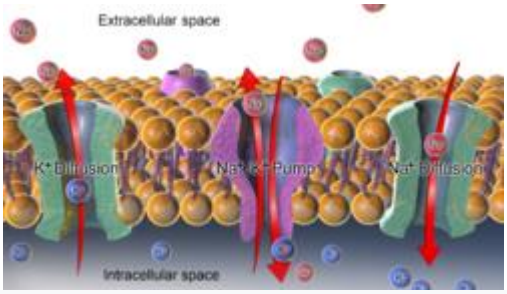

Figure : The Na^+/K^+-ATPase, as well as effects of diffusion of the involved ions maintain the resting potential across the membranes.

Resting potential

In order to maintain the cell membrane potential, cells keep a low concentration of sodium ions and high levels of potassium ions within the cell (intracellular). The sodium–potassium pump mechanism moves 3 sodium ions out and moves 2 potassium ions in, thus, in total, removing one positive charge carrier from the intracellular space (please see Mechanism for details). In addition, there is a short-circuit channel (i.e. a highly K-permeable ion channel) for potassium in the membrane, thus the voltage across the plasma membrane is close to the Nernst potential of potassium.

Reversal potential

Even if both K^+ and Na^+ ions have the same charge, they can still have very different equilibrium potentials for both outside and/or inside concentrations. The sodium-potassium pump moves toward an equilibrium state with the relative concentrations of Na^+ and K^+ for both inside and outside of cell. For instance, the concentration of K^+ in cytosol is 100mM, whereas the concentration of Na^+ is 10mM. On the other hand, in extracellular space, the concentration of K^+ is 5mM, whereas the concentration of Na^+ is 150mM.

Transport

Export of sodium from the cell provides the driving force for several secondary active transporters membrane transport proteins, which import glucose, amino acids, and other nutrients into the cell by use of the sodium gradient.

Another important task of the Na^+-K^+ pump is to provide a Na^+ gradient that is used by certain carrier processes. In the gut, for example, sodium is transported out of the reabsorbing cell on the blood (interstitial fluid) side via the Na^+-K^+ pump, whereas, on the reabsorbing

(lumenal) side, the Na^+-glucose symporter uses the created Na^+ gradient as a source of energy to import both Na^+ and glucose, which is far more efficient than simple diffusion. Similar processes are located in the renal tubular system.

Controlling cell volume

Failure of the Na^+-K^+ pumps can result in swelling of the cell. A cell's osmolarity is the sum of the concentrations of the various ion species and many proteins and other organic compounds inside the cell. When this is higher than the osmolarity outside of the cell, water flows into the cell through osmosis. This can cause the cell to swell up and lyse. The Na^+-K^+ pump helps to maintain the right concentrations of ions. Furthermore, when the cell begins to swell, this automatically activates the Na^+-K^+ pump because it changes the internal concentrations of Na^+-K^+ to which the pump is sensitive.

Functioning as signal transducer

Within the last decade many independent labs have demonstrated that, in addition to the classical ion transporting, this membrane protein can also relay extracellular ouabain-binding signalling into the cell through regulation of protein tyrosine phosphorylation. For example in Ramnanan CJ. 2006, the study investigates the function of Na+/K+ATPase in foot muscle and hepatopancreas in land snail *O.Lactea* comparing the active and estivating states. They concluded that reversible phosphorylation can control the same means of coordinating ATP use by this ion pump with the rates of the ATP generation by catabolic pathways in estivating *O. Lactea*.The downstream signals through ouabain-triggered protein phosphorylation events include activation of the mitogen-activated protein kinase (MAPK) signal cascades, mitochondrial reactive oxygen species (ROS) production, as well as activation of phospholipase C (PLC) and inositol triphosphate (IP3) receptor (IP3R) in different intracellular compartments.

Protein-protein interactions play a very important role in Na^+-K^+ pump-mediated signal transduction. For example, Na^+-K^+ pump interacts directly with Src, a non-receptor tyrosine kinase, to form a signaling receptor complex.[14] Src kinase is inhibited by Na^+-K^+ pump, while, upon ouabain binding, the Src kinase domain will be released and then activated. Based on this scenario, NaKtide, a peptide Src inhibitor derived from Na^+-K^+ pump, was developed as a functional ouabain–Na^+-K^+ pump-mediated signal transduction. Na^+-K^+ pump also interacts with ankyrin, IP3R, PI3K, PLC-gamma and cofilin.

Controlling neuron activity states

The Na^+-K^+ pump has been shown to control and set the intrinsic activity mode of cerebellar Purkinje neurons, accessory olfactory bulb mitral cells and probably other neuron types. This suggests that the pump might not simply be a homeostatic, "housekeeping" molecule for ionic gradients, but could be a computation element in the cerebellum and the brain. Indeed, a mutation in the Na^+-K^+ pump causes rapid onset dystonia-parkinsonism, which has symptoms to indicate that it is a pathology of cerebellar computation. Furthermore, an ouabain block of Na^+-K^+ pumps in the cerebellum of a live mouse results in it displaying ataxia and dystonia. Alcohol inhibits sodium–potassium pumps in the cerebellum and this is likely how it corrupts cerebellar computation and body coordination. The distribution of the Na^+-K^+ pump on myelinated axons, in human brain, was demonstrated to be along the internodal axolemma, and not within the nodal axolemma as previously thought.