Na/K pump mutations lead to hypertension by impairing Na+ and K+ transport

Aldosterone is a hormone that regulates blood pressure by increasing the amount of salt and water that your body retains as blood is filtered through the kidney. Aldosterone is produced by specific cells in the adrenal gland and its production is carefully controlled by the voltage (a difference of electrical charge) across the cell's membrane. Normally, aldosterone production is increased in response to the peptide Angiotensin II or to high blood potassium (K^+) levels, both of which decrease the membrane voltage (decrease the electrical charge difference). The change of membrane voltage then allows calcium ions (Ca^{2+}) to flow into the cell and stimulate the metabolic processes that synthesize aldosterone.

In some individuals, aldosterone production is uncontrolled, leading to abnormally high aldosterone levels. This leads to severe hypertension (high blood pressure) and increased risk for heart attack and stroke as well as electrolyte imbalances. Many of these cases are due to an adrenal tumor that produces aldosterone independently of normal physiological triggers. Genomic sequencing of the tumors has revealed mutations in many genes that regulate the adrenal cell's membrane voltage, including an ion transporting protein known as the sodium-potassium pump (Na/K pump).

The Na/K pump transports 3 Na^+ out of the cell and 2 K^+ into the cell by using ATP during each pump "cycle". In doing so, the Na/K pump creates gradients of Na^+ and K^+ across the cell membrane (outside the cell there is high Na^+ and low K^+, and inside the cell there is low Na^+ and high K^+). Since the Na/K pump transports more positive charge out of the cell than into the cell per "cycle", it produces net outward movement of electrical charge (i.e. an outward current), therefore making the membrane voltage larger. The contribution of the pump's outward current to the overall membrane voltage depends on the cell in question, but is normally small (~5% of the total). Phrased in another way, if the Na/K pump's current were suddenly stopped (with all else remaining the same), the electrical charge difference across the membrane would decrease by ~5%.

In contrast to the normal Na/K pump, the first four mutant Na/K pumps (from aldosterone-producing adenomas) were shown to produce current in the opposite direction (inward), making the membrane voltage smaller. Thus, it was thought that the abnormal inward current through the Na/K pump mutants elevate aldosterone production and lead to hypertension by decreasing the membrane voltage to a large extent and allowing more Ca^{2+} ions to flow into the cell. Meyer et al. looked at each Na/K pump mutant in detail and found that the size of inward current through several mutant Na/K pumps is very small (similar to the normal Na/K pump's outward current), which indicates that these inward currents would only decrease the membrane voltage to a very small extent. Meyer et al. also found that one of the mutant Na/K pumps completely lacks an inward current, which means that hypertension produced by this mutant must happen in a different way.

Despite not all Na/K pump mutants having inward currents, they have one commonality: each mutation damages the pump so it cannot transport Na^+ and K^+ efficiently. This means that the Na^+ and K^+ gradients across the cell's membrane will dissipate. There are important cellular functions that depend on these gradients, including the Na^+/Ca^{2+}-exchanger (NCX), a protein that uses the energy of the Na^+ gradient to regulate the cell's Ca^{2+} levels. Meyer et al. propose that Na/K pump mutations likely augment aldosterone production by impairing the pump's ability to maintain the Na^+ gradient, which subsequently impairs the cell's Ca^{2+} regulation by NCX.

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