Pass the salt, please! Understanding how cells deal with high salt

Table salt, a molecule made up of the charged ions sodium and chloride, is an essential nutrient fundamental to life and once worth its weight in gold. Historically a precious commodity, salt also helped civilizations develop because it could preserve food over long winters and long voyages. Although all living organisms need salt to live, too much salt is toxic to bacteria and moulds that would otherwise spoil food. Today the price of salt has dropped dramatically but its dietary use has soared. High salt is toxic to humans too and has been associated with increased risk of developing high blood pressure, heart attack, stroke, stomach cancer and even osteosporosis.

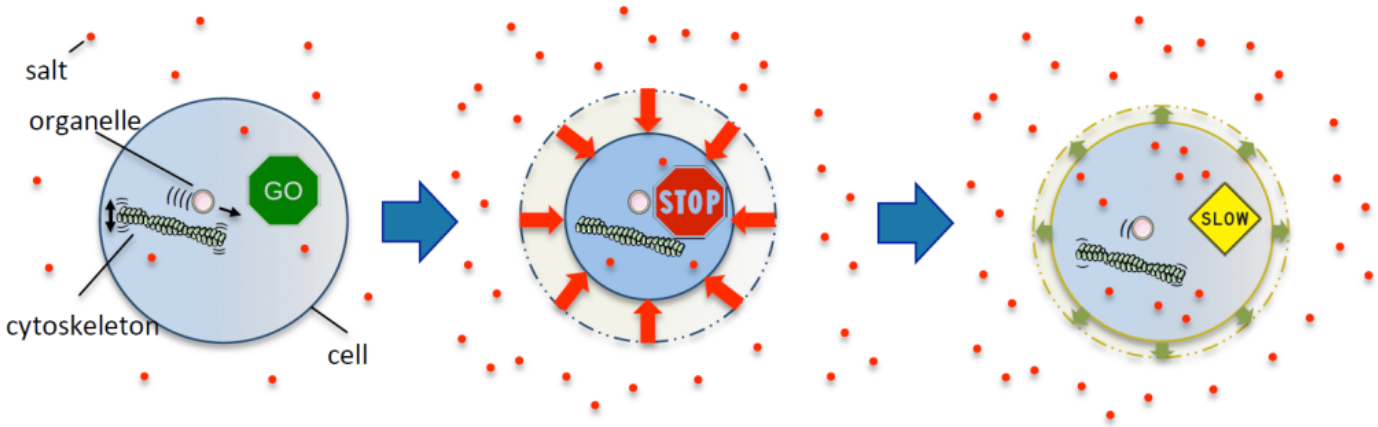

Fig. 1. When cells are exposed to high levels of salt (sodium chloride) they lose water by osmosis and shrink. The cytoplasm condenses and the movement of cellular components, such as the cytoskeleton and organelles, stops. Cells adapt to high salt by quickly importing salt in order to attract water and regain volume, at the expense of increased salt concentration. Unlike cell volume, the movements of cellular components are slow to recover and, depending on the dose of salt, may not recover fully. (Images made in part with Servier Medical Art.)

Why is too much salt toxic? When we eat salt, it enters the digestive tract and blood stream, drawing water out of all of cells in its vicinity through osmosis. As a consequence, blood volume swells, adding pressure to blood vessels. Although the kidneys restore blood salt to physiological levels, recent studies revealed that not all excess salt is effectively eliminated. For instance, one study showed that salt gradually accumulates within the skin of mice fed a high salt diet. This implies that many different types of cells in the body may actually be affected by increased dietary salt. Because high salt draws water out of cells, they shrink and critical components like DNA and protein are damaged. Recently, scientists showed that compression associated with cell shrinking condenses cellular contents into a glass-like gel, suggesting that compression itself may directly

damage components and slow intracellular signals and function.

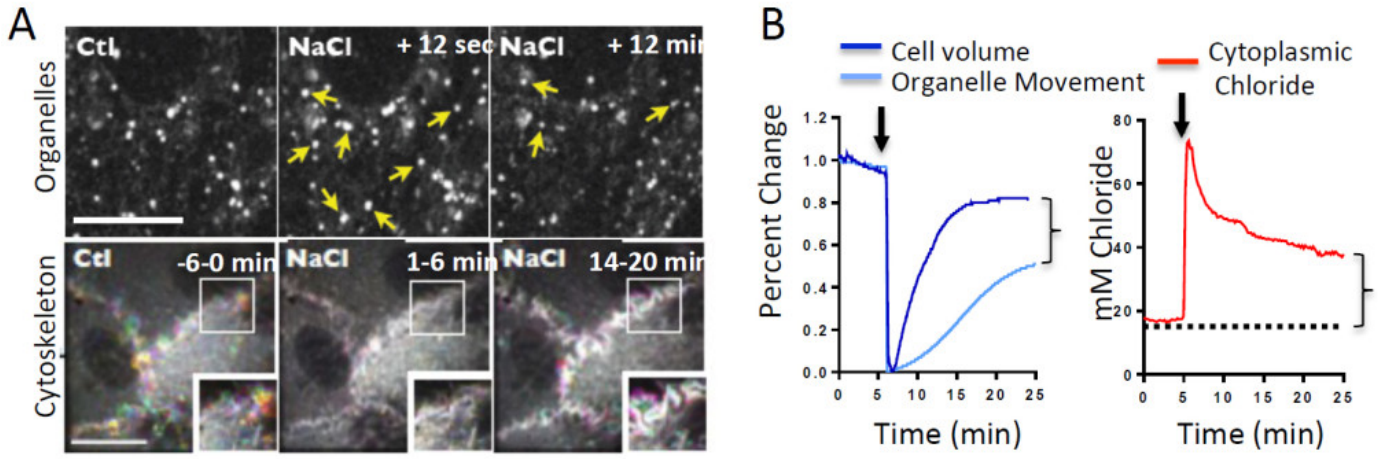

Fig. 2. A. The top panels show images of organelles called endosomes labelled with the fluorescent dye FITC-dextran, that immobilize (yellow arrows) and remain immobile after several minutes following addition of high salt (NaCl) to cells. The bottom panels show timelapse composite images of the cytoskeleton fluorescently labelled with GFP-actin. Time-lapse movies are color-coded so that the more movement, the more colourful the image. Observe how the middle panel, representing times shorty after exposure to high salt, is less colorful than before or after longer periods of adaptation to high salt. B. Left panel: Comparing relative changes of cell volume and organelle movement following the same dose of high salt (black arrow) illustrates how organelle movement recovers more slowly and to a smaller extent than cell volume, implying factors other than just relief of compression may be involved. Right panel: measurements of cytoplasmic levels of chloride following exposure to high salt (black arrow) using a fluorescent dye suggest that persistent higher levels of chloride may contribute to toxicity due to high salt. (Modified from Nunes et. al. Proc Natl Acad Sci U S A. 2015 Jun 16;112(24):E3104-13. doi: 10.1073)

Cells can adapt to high salt but how is this achieved? Upon exposure to salt, cells must immediately restore lost volume. They do this by importing salt, which draws water back into the cell. However, excess salt inside a cell hinders its function. This dilemma is resolved by energy-consuming mechanisms that slowly pump excess salt out of the cell. These are replaced by more compatible, uncharged substances called ‘osmolytes’. Our research group recently explored in detail intracellular changes induced by salt by live-cell microscopy using a variety of fluorescent dyes that label cellular components, such as the cytoskeleton, organelles, as well as chloride ions themselves. When we exposed cells to non-lethal doses of salt, the movement of the organelles and cytoskeleton froze and then slowly recovered. Surprisingly, the recovery of movement was not fast like cell volume recovery, but instead followed the slow removal of excess chloride. When we added a chemical that allowed chloride to enter the cells passively, a dramatic reduction in

movement was also observed. When higher doses of salt were used, cells could not remove all of the extra chloride, and movement remained persistently slower. We compared many cell types, including liver, pancreatic, and white blood cells, and found that recovery was fastest in kidney cells, which are very efficient at removing excess chloride. Together, these data imply that while loss of volume and compression certainly contribute to cellular damage, lingering excess chloride also contributes to the long-term toxicity of high salt.

Many questions still remain. For example, why exactly does chloride lead to decreased movement, what limits the cell's ability to remove excess chloride, and could a dietary supplement of osmolytes relieve some of these effects? Salt is such a basic and fundamental component of all living cells that understanding salt balance at the cellular and molecular levels will help scientists to better understand how cells work in general. Answers may also help us to better understand salt-related diseases, and to develop strategies to combat them.

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Publication

Ionic imbalance, in addition to molecular crowding, abates cytoskeletal dynamics and vesicle motility during hypertonic stress.
Nunes P, Roth I, Meda P, Féraille E, Brown D, Hasler U
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