DEFECTS IN A FAMILY OF SALT TRANSPORTING PROTEINS AND THEIR REGULATION LIE AT THE HEART OF MANY BLOOD PRESSURE PROBLEMS. OUR WORK ON THE BEHAVIOUR OF THESE TRANSPORTERS AND THEIR CONTROL BY A NETWORK OF REGULATORY PROTEINS SHOULD HELP DEVELOP MORE EFFECTIVE TREATMENTS FOR BLOOD PRESSURE PROBLEMS BY BEING TUNED TO A PATIENT’S SPECIFIC GENETIC PROFILE.

To reduce blood pressure and the risk of strokes and heart disease doctors advise us to reduce the salt (NaCl) in our diet. But what links salt and blood pressure? Opinions differ. Some believe a high salt diet sensitises blood vessels to over-contract so pressure increases. Others believe the problem lies in the kidney which retains too much salt which together with water, overfills the circulatory system causing pressure to rise. However, our bodies have strong self-regulating mechanisms that should excrete the salt and bring pressure back to normal. For high blood pressure to be maintained, something must go wrong with the salt-sensing mechanisms.

Members of my lab are interested in a family of proteins (the cation-chloride-cotransporters) that play major roles in reabsorbing salt in the kidney, helping regulate salt levels in vascular smooth muscle, and sensing body salt levels. Could problems with these proteins be responsible for the sustained blood pressure rise? If so, it may be possible to formulate a more unified explanation for high blood pressure, and devise more effective therapies. It may also help us identify those who would benefit most from a low-salt diet, and these may need to reduce their salt intake to a much greater extent than currently recommended.

Our current focus is on sodium potassium-

NKCC2 is key to reabsorption in the kidney’s TAL. 20% NaCl is reabsorbed in the kidney’s thick ascending limb (TAL). Basolateral Na-pumps reduce intracellular Na concentration favouring inward movement of Na with K and Cl through luminal NKCC2. Cl leaves through basolateral Cl channels (CLCKB) with their associated Barttin. K depletion in urine and accumulation in cytoplasm would stop further transport if it were not for K recycling through luminal ROMK channels. This generates a lumen positive potential which drives cations through the tight junctions. Loop diuretics inhibit NKCC2, stopping Na reabsorption and K recycling. Lumen potential then collapses and inhibits paracellular ion movement. Raised basolateral levels of Mg and Ca inhibit reabsorption (red arrow) by binding to CASR. Bartter’s disease is caused by failure of Na uptake in the TAL due to mutations in NKCC2 (Bartter’s type I), ROMK (type II), CLCKB (type III) or Barttin (type IV).
chloride cotransporters. There are two closely related forms, NKCC1, found in most cells where it helps regulate cell composition and volume and NKCC2, found only in the kidney where it reabsorbs substantial amounts of NaCl into the body. It also senses the amount of NaCl in the urine allowing the kidney to control the rate at which it filters blood. Too much NaCl in the urine slows filtration whereas too little increase it. Drugs that inhibit these cotransporters cause a dramatic loss of NaCl and water in the urine (they are powerful diuretics), and are used to treat high blood pressure.

Although it is easy to see how over-activity of NKCC2 causes high blood pressure by allowing the kidney to retain too much NaCl, it is not so easy to understand how NKCC1 dysfunction might cause similar problems. Currently, it is believed that over-activity of NKCC1 brings too much Na into smooth muscle which in turn causes the calcium concentration in these cells to rise. This then causes the muscle to contract – raising pressure in blood vessels.

Much of our work is on the behaviour and regulation of NKCC1. We use red cells from blood samples as an easily obtainable and flexible model, and also express the transporter in cultured cells. A clear picture is emerging. The transporter is sluggish under normal circumstances but can be stimulated many fold when cells become shrunken, deprived of oxygen or exposed to a variety of hormones. Activation is due to the addition of phosphate to several highly specific regions of the transporter. Some enzymes that add phosphate (kinases) have been identified, but little is known about the phosphatases that carry out the equally important task of removing it. As defects in these regulatory enzymes are associated with poor blood pressure control, a deeper understanding of these processes is an important future goal.

Understanding of NKCC2 is more rudimentary due to experimental limitations. NKCC2 is found in a poorly accessible part of the kidney, and so far has defied attempts to express it in appropriate cultured cells. Much of its behaviour has been inferred from studies on NKCC1 – which could be misleading. We are working on ways to express NKCC2 in cultured cells so its properties can be examined more readily. Preliminary results are promising and suggest that although NKCC2 behaves like NKCC1 in some respects there are major differences which could be exploited to develop better therapies for high blood pressure.

Selected References:

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