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New Mechanism of Regulation of K+-Cl- Cotransport

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Nitrovasodilators, through a CAMP-dependent pathway involving the inositol phosphate (IP) cycle decrease intracellular Ca++ and induce vasodilation by activation of ion channels. K+-Cl cotransport (COT) promotes the electroneutral cotransport of K+ and Cl− ions and plays an important role in regulating cellular Na+. The volume of K+-Cl− cotransport is reduced in thiol (SH) reagents, and by lowering cellular Mg++ and H+ concentrations. Our results indicate that Li+ stimulates K+-Cl− cotransport with involvement of the IP cycle and that in low K+ sheep red blood cells (LRK SRBCs), nitrite (a nitric oxide derivative) and other vasodilators stimulate the transporter from two- to 10-fold. To test our hypothesis that the new mechanism of regulation of K+-Cl− cotransport involves CAMP-dependent pathway, we further characterized the effects of the vasodilators studied before. LRK SRBCs and cultured vascular smooth muscle cells (CVSMCs) K+-Cl− cotransport was measured at different osmolalities, drug concentrations and in the presence or absence of inhibitors for K(+) or Na(+) transport. Hyaluronic acid-stimulated K+-Cl− cotransport by 5-fold in LRK SRBCs and by 20-fold in CVSMCs, and was the most potent activator in LRK SRBCs where it decreased glutathione by 100%. Protein/threonine phosphatase 1 and tyrosine kinase regulate K+-Cl− cotransport via a metabolic cascade. Inhibition of the phosphatase and kinase by calyculin and genistein, respectively, suggest an upstream site for the action of hyaluronic acid and osmoregulate mononucleotide. Further testing of our hypothesis include the study of specific activators and inhibitors of the CAMP pathway on K+-Cl− cotransport activity. Our findings suggest a role for K+-Cl− cotransport in vasodilation. (Supported by NIH, NADA, AHA/HH and the WSU BMS Program)