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Research Interests

The regulation of cell volume is of critical importance to the CNS due to the restrictions of the skull. Brain swelling, which may occur in response to a lowering of plasma osmolarity (hyponatremia) or during cytotoxic edema, is associated with a number of clinical conditions, including congestive heart failure, hepatic encephalopathy, ischemic stroke, or head trauma. To counteract the increased volume, cells release K^+ , Cl^- , and non-perturbing organic osmolytes, the quantitatively major ones being myo-inositol, taurine and glutamate. Efflux of the osmolytes occurs via a volume-sensitive organic anion channel (VSOAC), which primarily gates Cl^- . Although most attention has been focused on the role played by glia in the process of volume regulation, cultured neuronal cells have also been recently shown to exhibit similar properties. Although the electrophysiological and pharmacological characteristics of VSOAC have been well documented, relatively little is known of the cell signaling pathways that regulate osmolyte efflux through this channel.

The major hypothesis that we examine is that, in the face of hypoosmotic challenge, the capacity of neural cells to restore their volume via the efflux of osmolytes (such as inositol, taurine and aspartate) can be regulated by extracellular agonists operating via pharmacologically specific cell-surface receptors. Our results indicate that, in response to hypotonic stress, human SH-SY5Y neuroblastoma and 1321N1 astrocytoma cells release inositol, taurine and D-aspartate. Moreover, this release can be significantly enhanced following agonist occupancy of muscarinic cholinergic receptors, lysophospholipid receptors and also PAR-1 (thrombin) receptors. Receptor activation facilitates osmolyte release under conditions of very limited changes in



osmolarity- conditions under which little or no release of osmolytes can be detected in the absence of receptor activation. Stimulation of osmolyte efflux is mediated by a rise in cytoplasmic Ca²⁺ concentrations and also by activation of protein kinase C. An ability to manipulate osmolyte efflux could be of potential benefit for a number of clinically relevant conditions. Accordingly, knowledge of the signal transduction pathways that regulate VSOAC is an essential prerequisite for the rational design of therapeutic agents.

Selected References

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