This Week in The Journal

Taste-Bud Responses to Chloride in Salts

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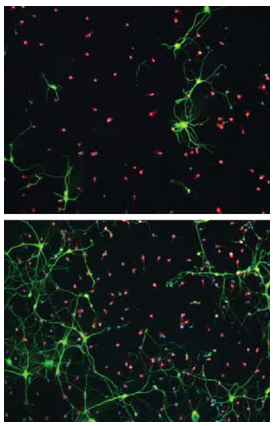
(see pages 6224 – 6232)

Taste perception begins with depolarization of neuroepithelial cells in taste buds. Sugars, amino acids, and bitter substances activate G-protein-coupled receptors in type II taste-bud cells. This leads to activation of phospholipase C (PLCβ2), release of calcium from intracellular stores, and opening of TRPM5 channels, which depolarize the cell. Organic acids, which taste sour, enter type III cells, where they induce depolarization by directly blocking resting potassium currents. In rodents, some responses to NaCl salt are mediated by amiloride-sensitive epithelial sodium channels, possibly expressed in type I cells; but a separate, amiloride-insensitive pathway involving type II and/or III cells appears to mediate responses to aversively high ($>$ 300 mM) salt concentrations. Furthermore, amiloride has minimal effects on salt perception in humans, suggesting that the unknown alternative pathway is the primary means for salt detection in people.

To elucidate the mechanisms of salt perception, Roebber et al. expressed a fluorescent calcium indicator selectively in type II and type III cells of fungiform taste buds in mouse lingual slices. Application of NaCl to taste pores evoked calcium increases in some cells. The response increased with NaCl concentration, but even the lowest concentration tested (80 mM) elicited a response. Importantly, the responses were insensitive to amiloride.

None of the cells that responded to NaCl responded to acid, and unlike acid responses, NaCl responses did not require extracellular calcium. In contrast, most cells that responded to NaCl also responded to saccharin, and some responded to bitter compounds. Consistent with this, most NaCl-responsive cells expressed PLCβ2, indicating that they were type II cells. Notably, all NaCl-responsive cells also responded to KCl and choline chloride, whereas none responded to sodium gluconate. Moreover, responses to choline chloride were undiminished in sodium-free medium. Finally—and surprisingly—most NaCl responses were unaffected by inhibition of PLCβ2, chloride channels, or chloride cotransporters.

These results suggest that amiloride-independent responses to salt are mediated by type II cells in fungiform taste buds, and these responses are driven by chloride rather than sodium. How chloride increases intracellular calcium levels remains unclear, given that it does not require PLCβ2, chloride channels, or cotransporters. Future work will be necessary to solve this mystery.



Inhibiting ATM induces degeneration of neurons (green) in cocultures of neurons and microglia (top). This effect was prevented by blocking IL-1β receptors (bottom). See Song et al. for details.

Microglial Role in Neurodegeneration in Ataxia-Telangiectasia

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(see pages 6378 – 6394)

The ataxia-telangiectasia mutated (ATM) kinase regulates several processes fundamental to cell survival, including repair of DNA double-strand breaks, glucose uptake, mitochondrial metabolism, and responses to oxidative stress. People with ATM mutations develop progressive motor impairment resulting from cerebellar neurodegeneration. Disruption of any of ATM's functions might contribute to neuronal death, but which is most important remains unknown. In fact, new work indicates that loss of ATM in microglia may be a major contributor to neurodegeneration in ataxia-telangiectasia.

Song et al. found that a greater percentage of cerebellar microglia exhibited an activated morphology in ATM-deficient mice than in controls. Furthermore, when wild-type microglia were treated with an ATM inhibitor *in vitro*, they acquired an activated morphology and secreted neurotoxic cytokines, including interleukin-1β (IL-1β), into their culture medium. When this conditioned medium was transferred to neuronal cultures, it caused dendritic and axonal damage, reduced synaptic density, and increased neuronal apoptosis. Notably, the ATM inhibitor had no effect on neuronal survival in the absence of microglia. Nonetheless, inhibiting ATM in cocultures of neurons and microglia increased neuronal apoptosis, and this effect was prevented by blocking IL-1β receptors.

Because ATM is required for repairing DNA double-strand breaks, loss of ATM function leads to an accumulation of damaged DNA in cells. Song et al. hypothesized that this would lead to accumulation of DNA fragments in the cytoplasm, which might induce an antiviral immune response in microglia. Indeed, both single and double strands of DNA accumulated in the cytoplasm not only in ATM-deficient microglia, but also in ATM-deficient Purkinje cells and fibroblasts, including fibroblasts from people with ataxia-telangiectasia. Cytoplasmic DNA levels also increased in cultured microglia treated with an ATM inhibitor. Moreover, the ATM inhibitor caused activation of a protein—stimulator of interferon genes (STING)—that initiates a microglial immune response when it detects cytosolic DNA. Inhibiting STING reduced the production and secretion of cytokines after ATM inhibition.

These results suggest that cerebellar degeneration in ataxia-telangiectasia stems partly from failure of DNA repair in microglia. This leads to an accumulation of DNA fragments in the cytoplasm, which activates an immune response culminating in the release of neurotoxic cytokines. Anti-inflammatory agents might therefore help to slow degeneration in people with ATM mutations.

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