This Week in The Journal

Type II Taste Cells Activate Type I Taste Cells

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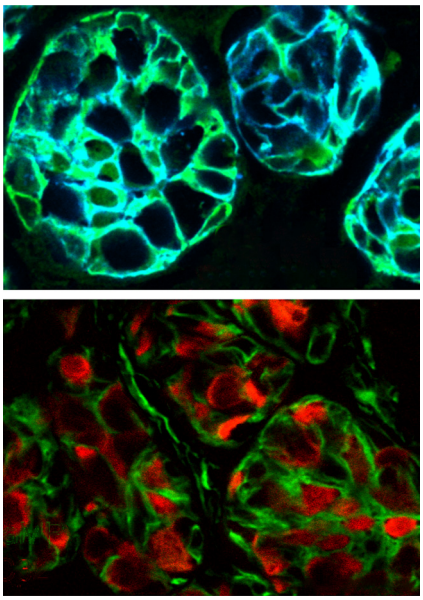
(see pages 9860–9871)

Taste buds contain three types of taste cells. Type III cells express proton-selective ion channels that sense sour tastes. Type II cells express G-protein-coupled receptors that sense sweet, bitter, and/or umami tastes. And Type I cells, the most numerous taste-cell type, are thought to have glia-like functions, ensheathing other taste cells, limiting the spread of neurotransmitters, and regulating ionic balance in the taste bud. Type I cells may also contribute to the perception of sodium, however (Baumer-Harrison et al., 2020, J Neurosci 40:7795), and Rodriguez et al. show that Type I cells respond to ATP, the neurotransmitter released by Type II cells, which may allow them to modulate perception of other tastes as well.

Type I cells strongly express the GABA-synthesizing enzyme Gad2. Therefore, the authors used the *Gad2* promoter to drive expression of a fluorescent calcium sensor predominantly in Type I cells. Treating dissociated taste bud cells with ATP increased intracellular calcium levels in 50–75% of Type I cells by stimulating release from intracellular stores. In contrast, treating cells with 5-HT, the neurotransmitter released by Type III cells, had no effect. ATP also increased calcium levels in Type I cells in intact taste buds in lingual slices. More importantly, whereas dissociated taste cells did not respond to bitter tastants, those in taste buds did. These responses were significantly reduced by pretreating slices with an ATPase, an ATP analog that desensitizes ATP-sensitive purinoceptors, or purinoceptor antagonists. Similarly, blocking ATP release from Type II cells reduced Type I cell responses to tastants.

These data suggest that ATP released by Type II taste cells in response to bitter tastants activates purinoceptors on Type I cells, leading to calcium release from intracellular stores. The effect of this calcium elevation is unclear, but one possibility is that it triggers the release of GABA, which is synthesized in Type I cells. Future work should determine whether sweet and umami tastants also lead to indirect stimulation of calcium elevation in Type I cells and investigate how such responses affect taste perception.



The *Gad2* promoter drives expression of GFP (green) in Type I taste cells (cyan, top) but not in Type II cells (red, bottom). See Rodriguez et al. for details.

Hyperactivation of ErbB Signaling Kills Oligodendrocytes

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(see pages 9872–9890)

Multiple lines of evidence suggest that improper myelination contributes to the pathophysiology of schizophrenia. First, symptoms of schizophrenia typically emerge late in adolescence, when myelination of fiber tracts connecting frontal and temporal lobes is underway. Second, the integrity of white matter tracts is lower than normal starting at the time of symptom onset in people with schizophrenia. Third, the number of oligodendrocytes—the glial cells that produce myelin in the CNS—is significantly lower in people with schizophrenia than in controls. Finally, several candidate risk genes for schizophrenia, including those encoding neuregulin and its ErbB receptors, regulate oligodendrocyte proliferation and gene expression (Bennett, 2011, Prog Neurobiol 95:275). Adding to this, Hu, Xiao, He, et al. show that excessive activation of ErbB signaling disrupts myelination in mice.

The authors increased activation of ErbB3, ErbB4, and downstream effectors in oligodendrocytes of adolescent mice by inducing expression of a mutant form of ErbB2, which dimerizes with ErbB3 and ErbB4. Hyperactivation of ErbB signaling led to deficient myelination and consequently to ataxia. Notably, however, different cellular and molecular mechanisms produced these outcomes when ErbB signaling was increased at different stages of oligodendrocyte differentiation. Activating ErbB signaling predominantly in oligodendrocyte precursor cells (OPCs) led to apoptosis of these cells. This resulted in reduced numbers of postmitotic oligodendrocytes and hypomyelination of white matter tracts. There was no sign of myelin fragmentation or degeneration, and no gliosis in white matter tracts in these mice, however. In contrast, activating ErbB signaling predominantly in mature (my elinating) oligodendrocytes led to pronounced gliosis, suggestive of an inflammatory response, and to the death of mature oligodendrocytes by programmed necrosis. This resulted in the fragmentation of myelin sheaths and an increase in the number of OPCs—consistent with previous work showing that demyelination triggers OPC proliferation. Importantly, regardless of where ErbB signaling was induced, ceasing transgene expression after 6 d led to a reversal of pathology; if transgene expression was continued for just a few more days, however, pathology continued to progress after expression was suppressed.

These results indicate that excessive signaling mediated by ErbB disrupts myelination by inducing apoptosis in OPCs and inducing necroptosis in mature oligodendrocytes. If this occurs in people with schizophrenia, it may disrupt communication between frontal and temporal lobes and thus contribute to multiple symptoms. Early intervention may be able to restore normal function, however.

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