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Phosphodiesterase 1C: leveling the playing field for olfactory receptor neuron sensitivity and targeting?

Michele Dibattista, Johannes Reisert*

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In mammalian olfactory receptor neurons (ORNs) signal transduction begins with the binding of an odor molecule to odorant receptors (ORs), which in turn, via a G protein-coupled cascade, activates adenylyl cyclase III (ACIII) and increase intracellular cAMP. cAMP opens the cyclic nucleotide-gated (CNG) channel to initiate odorant-induced depolarization. In the absence of stimulation, basal activity of odorant receptors (ORs) drives basal fluctuations of cAMP, which is observed as baseline current noise that leads to basal action potential firing. Two phosphodiesterases (PDEs) are expressed in ORNs, one located in the cilia (PDE1C) and one restricted to the dendrite and cell body (PDE4A) to lower increased cAMP levels. Perplexingly, neither PDE alone seems to play a significant role in termination of the odorant-induced response, raising the question what their roles might be, not only in signal transduction, but also in cAMP controlled axonal targeting.

We investigated the role of PDE1C in ORN transduction by recording from ORNs dissociated from PDE1C knockout mice that had been crossed with odorant receptor-tagged mice (mice expressing GFP in ORNs expressing the highly basally active I7 OR or the mEG-OR with low basal activity). We found little difference in peak amplitude and time course in eugenol responses in the mOR-EG ORNs regardless of whether PDE1C was present or not. In contrast, in I7 ORNs the response magnitude to heptanal was greatly reduced and the time for the response to reach its peak magnitude was prolonged once PDE1C was knocked out. Interestingly, PDE1C does not seem to control the overall sensitivity of ORNs since no shift in the dose-response relation was observed in I7 and mOR-EG ORNs.

Comparison of I7 and mOR-EG ORN axonal targeting to the bulb in wild-type and PDE1C knockout mice showed that PDE1C did not influence the overall number of main glomeruli innervated by I7 or mOR-EG ORN axons. But in the absence of PDE1C I7 ORNs substantially mis-targeted to a large number of glomeruli neighboring the main glomerulus, which was not observed in mOR-EG ORNs.

Together our results suggest that PDE1C is important to retain response magnitude and kinetics across ORNs expressing ORs with different basal activity as well as insuring proper glomerular targeting.

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Monell Chemical Senses Center, Philadelphia, USA