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Inhibition of mitral cells determines odor discrimination time in mice

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Granule cells are the dominant inhibitory interneurons in the olfactory bulb network mediating inhibition of mitral/tufted cells. The activation pattern of these cells reflects the spatio-temporal representation of odorant stimuli at the glomerular level. The olfactory inhibitory circuitry established by dendrodendritic synapses between mitral/tufted cells and granule cells has been implicated in mediating competitive interactions between active units enhancing the contrast of the spatial activity patterns of an odor, sharpen activity onset in the olfactory bulb network and also synchronization mechanisms with slow temporal latencies of mitral/tufted cells. As a whole, the olfactory bulb network is the first structure processing olfactory information before sending it to higher olfactory centers. Changes in the granule cell inhibitory abilities have been shown to influence odor discrimination times, but sparing odor discrimination learning.

This work provides evidence that granule cells express only the $Na_v1.2$ subunit of the voltage-gated sodium channel family α-subunits. Using identified granule cells, 3D-immunohistochemistry showed that this subunit is strongly expressed in the soma, dendrites and spines. Granule cell selective and specific deletion of the $Na_v1.2$ subunit using shRNA technology revealed that upon somatic current injections granule cells did not fire action potentials, as expected due to the strong abrogation of the Na^+-currents observed in infected cells. As a consequence of this manipulation, it was observed that inhibition of the mitral cells was strongly reduced. This result indicates that GABA release from granule cell gemmules requires activation of voltage-gated sodium channels, being an all-or-none event. At the behavioral level, the lack of the inhibitory drive onto mitral cells increased the discrimination time of highly similar odorant mixtures, but the discrimination time of monomolecular stimuli as well as discrimination learning were unaffected. Therefore, the inhibition of mitral cells relies on fast and synchronous release of GABA activation of a P/Q-type Ca^{2+}-current that requires sodium channel activation, as known for axonic nerve terminals.

Additionally, factors that regulate the strength of the inhibitory output of granule cells and its impact on odor discrimination were examined. The inhibitory drive onto granule cells is $GABA_A$-receptors-mediated and requires the obligatory β3-subunit. This subunit revealed to be distributed in a somato-dendritic pattern sparing the granule cell gemmules or dendritic spines. Moreover, I show that β3-contaning $GABA_A$-receptors in granule cells are synaptic because their clusters co-localize with gephyrin and are positioned opposite to presynaptic VIAAT clusters. These data argue for a phasic inhibitory drive onto granule cells that is disrupted by granule cell selective deletion of the β3-subunit, because such manipulation nearly abolished spontaneous and muscimol-stimulated currents mediated by $GABA_A$-receptors in granule cells. As a consequence, inhibition of the mitral cells was strongly enhanced. Mice with disinhibited granule cells require less time to discriminate both dissimilar

as well as highly similar odorants, while discrimination learning remained unaffected. Hence, granule cells are controlled by an inhibitory drive that in turn tunes mitral cell inhibition. As a consequence, the olfactory bulb inhibitory network adjusts the speed of early sensory processing.

Besides, I observed a strong correlation between the odor discrimination time and the amount of inhibition that mitral cells receive. Hence, the extent of mitral cell inhibition directly controls odor discrimination time.