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Mechanisms of Odor Discrimination in the Olfactory Bulb of Mice

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Olfaction, the sense of smell, was generally thought as a ‘slow’ sense compared to ‘fast’ senses such as vision or hearing. In this study the odor discrimination times (DTs) for different stimuli and the molecular and synaptic mechanisms of DTs in the olfactory bulb (OB) were investigated using mice as the model system. We have determined the DT using a go/no-go operant conditioning paradigm employing an automated olfactometer. Discrimination accuracy and time were studied for different simple monomolecular odors (e.g., 1% amyl acetate (AA) versus 1% ethyl butyrate (EB) and binary mixtures 0.6% AA + 0.4% EB versus 0.4% AA + 0.6% EB). Mice discriminated simple odors in as little as 200 ms with an accuracy exceeding 95%. Binary mixtures evoking highly overlapping spatio-temporal patterns of activity in the olfactory bulb (OB) were discriminated equally well. However, mice required more time to discriminate highly similar binary mixtures, suggesting that DTs are stimulus-dependent. DTs and stimulus-dependence was investigated for different odor pairs including cineol vs. eugenol and enantiomers (carvones and octanols). These experiments showed that the DT for different simple odor pairs was in the range of 200-340 ms, whereas DT for different binary mixtures was in the range of 300-380 ms. In all odor pairs tested, the DT was longer for binary mixtures, indicating that stimulus-dependency is likely to be a general property of the olfactory system. In summary, DT in mice is fast and stimulus-dependent. Thus, the underlying neuronal mechanisms contributing to odor discrimination act on a fast time scale, requiring only a brief moment of odor-specific spatio-temporal representations to achieve rapid discrimination of dissimilar odors. The fine discrimination of highly similar stimuli, however, requires temporal integration of activity, revealing a tradeoff between accuracy and speed.

After having established the timeframe and stimulus-dependent properties of odor discrimination, the molecular and synaptic mechanisms of fine odor discrimination contributed by the olfactory bulb were investigated. In the OB, the reciprocal dendro-dendritic synapse, connecting mitral (M) /tufted (T) cells and granule cells (GC), mediates reciprocal and lateral inhibition, mechanisms that may contribute to temporal processing and contrast enhancement during odor discrimination. To examine the role of glutamate receptors at the reciprocal synapse, the function of AMPA and NMDA receptors of GCs was specifically perturbed. Spatio-temporally controlled deletions of the GluR-B and NR1 subunits in the GC of the OB was achieved by stereotaxic delivery of adeno associated virus (AAV1/2) expressing the Cre recombinase in mice carrying gene-targeted loxP-flanked GluR-B or NR1 alleles. The behavioral consequences of OB-specific GluR deletions were assessed by determining the DT using the behavioral assay established in the first part of this thesis. DTs were determined for dissimilar (simple odors) and highly similar odors (binary mixtures). AAV-mediated Cre expression in the OB of mice with floxed GluR-B alleles resulted in GluR-B deletion in about 40% of the GC population. The DTs were reduced for similar odors while they remained unchanged for dissimilar odors. Hence, deleting the GluR-B subunit may

lead to an increased Ca^{2+} influx into the GC and thereby cause more GABA release. This may cause increased inhibition and better contrast enhancement, thereby allowing faster odor discrimination of similar stimuli. Cre expression in mice with floxed NR1 alleles resulted in deletion of NR1 in about 45% of the GC population. The DTs were increased for dissimilar odors more prominently than for similar odors compared to control animals. Thus, deleting the NR1 subunit may decrease Ca^{2+} influx into the GC and thereby reduce GABA release. In turn, this modification may decrease inhibition, and hence, contrast enhancement, resulting in slower odor discrimination. In summary, the results show that inhibitory interactions between M/T cells and GC play an essential role in the refinement of the odor stimuli and that processing time differences are mainly generated in the OB.