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MEETING ABSTRACT

A3.5

Nogo receptor (NgR) – signalling is required for the maintenance of the structural integrity of mouse fungiform and circumvallate taste buds

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Background: Taste bud (TB) cells are constantly renewed and therefore require continuous re-establishment of connections between existing ganglion processes and newly born taste cells in order to maintain proper taste cell–neuron connectivity and taste homeostasis. How this re-wiring system is precisely established is unknown, but first lines of evidence suggest that attractive and repulsive molecules within the TB may play important roles. We recently discovered that the Nogo66 receptors (NgRs), which restrict axonal arborization and structural plasticity are expressed by geniculate and trigeminal neurons during the period of chemosensory innervation. Additionally, we found NgRs and their corresponding ligands being expressed in lingual proliferative active keratinocytes (K14), which are crucial in taste cell replenishment. Here, we attempt to expand upon these findings by investigating the role of NgR signaling in the maintenance of taste buds.

Methods: *In situ* hybridization (ISH) was performed to determine NgR1/2 mRNA expression in the geniculate ganglion and TBs. Furthermore, characterization of geniculate ganglion morphology, neuronal quantification, TB volume and taste papillae innervation pattern was analysed by immunohistochemistry (IHC) on age-matched wild-type and NgR1/2-DKO animals. Terminal deoxynucleotidyl transferase dUTP nick end labeling (Tunel) was performed to determine apoptotic rates in the tongue epithelia. Normally distributed data were analysed using the parametric unpaired Student's *t*-test. The non-parametric Mann–Whitney *U* test was used if the data did not fit a normal distribution. Significance was taken as $p < 0.05$ with a confidence interval of 95%. Data are presented as mean ± standard deviation.

Results: Genetic elimination of NgR1/2 caused severe progressive changes of TB structure. While total number of TBs were unchanged, TB volume and taste cell number of mutant p5–p21 fungiform (FF) and circumvallate (CV) papillae in the anterior and posterior tongue were significantly reduced by ~30%. NgR1 and NgR2 ablation lead to significantly reduced number of FF 35% and CV 23% type-I TB cells. Furthermore, we could show significantly diminished FF and CV TB innervation at p5 by ~15%, whereas p21 FF and CV TBs did show reduced TB innervation by 17% and 9%, respectively. No apparent changes of apoptotic rates (Tunel+) in the tongue epithelia were detectable in p21 FF papillae. However, the proliferation marker Ki67 did show a significant proliferation reduction in p21 NgR1/2$^{-/-}$ mutants in FF 20% and filiform papillae 23% and the number of sonic hedgehog-expressing (Shh+) cells, being important for taste cell renewal and differentiation in the TBs, was significantly decreased by 23%.

Discussion: These data suggest that NgR signaling is important for taste bud development and/or maintenance. Downregulated basal cell proliferation in the perigemmal area affects the replenishment of intermediate Shh+ basal cells in TBs and further results in a loss of taste cell numbers and subsequently in smaller TBs. In addition, reduced innervation and proliferation rates play a synergistic effect in NgR1/2 double mutants leading to a smaller TB size. Further *in vitro* studies are necessary to investigate the underlying molecular mechanisms of how NgR signaling affects cell proliferation rate of tongue keratinocytes.

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Keywords: chemosensory innervation – Nogo receptors – taste transduction – taste bud – taste papillae – sonic hedgehog – keratinocytes

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