

## Nerve–Target Interactions in the Gustatory System Following Unilateral Chorda Tympani Nerve Section

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Although much effort has been directed at examining the morphological characteristics of denervated and regenerated taste buds, relatively little is known about the physiology of reinnervated taste cells (Vintschgau and Hönigschmied, 1876; Guth, 1957; Fujimoto and Murray, 1970; Cheal and Oakley, 1977; Whitehead *et al.*, 1987). Over 25 years ago, Oakley (Cheal *et al.*, 1977) and colleagues found that some chorda tympani fibers reinnervated fungiform papillae on the gerbil's anterior tongue in <2 weeks post-sectioning. Studies that examined recovery of taste function following nerve damage (Cain *et al.*, 1996; Cheal *et al.*, 1977; Ninomiya, 1998; Yasumatsu *et al.*, 2003) indicate that regenerated taste nerves generally recover normal function after progressing through a transitional period. Only relatively recently has the impact of environment on the adult regenerating taste system been explored.

Regenerating taste receptor cells in adult rats are susceptible to dietary influences (Hill and Phillips, 1994). Sectioning the chorda tympani unilaterally in rats fed a sodium-restricted diet at adulthood resulted in a regenerated nerve that had attenuated responses to sodium salts. Responses to other stimuli were unaffected. In addition, there were other, novel effects. In the same rat, the contralateral, uncut nerve was supersensitive to sodium salts. The supersensitivity developed progressively following an initial subnormal response. Moreover, these remarkable changes happened in the absence of reinnervation. Although the mechanism underlying these large, dynamic functional changes are not clearly identified, increasing evidence suggests a novel and important interaction exists with the immune system (Phillips and Hill, 1996; Hendricks *et al.*, 2002; McCluskey and Hill, 2002; McCluskey, 2003). We hypothesize that the immune system may be activated during phagocytosis of neural and taste receptor cell debris following nerve section in sodium-replete rats. The activated immune cells may then play a role in maintaining normal function. We further hypothesized, from published reports (Chandra and Dayton, 1982; Pimentel and Cook, 1987; Latshaw, 1991), that sodium-restricted rats are immunocompromised and may fail to maintain normal taste function on the intact side of the tongue following unilateral nerve section. In summary, there is emerging evidence that the immune system has a significant role in the biology of adult taste buds and may be similar to roles demonstrated in other sensory receptors (Warchol, 1997; Warchol, 1999; Warchol *et al.*, 2001).

In addition to providing an excellent model for functional studies of taste receptor cell plasticity, the regenerating taste system provides an excellent model in which to study the plasticity of gustatory neuron/target matching. We explored the hypothesis that the altered taste function produced by combining unilateral chorda tympani nerve section with sodium restriction in adult rats also produces alterations in peripheral innervation (Shuler *et al.*, 2004). For both sodium-restricted and sodium-replete rats, section-induced morphological alterations occurred on both the regenerated and the intact side of the tongue. Namely, fewer than normal numbers of geniculate ganglion neurons per taste bud volume innervated single fungiform papillae on the regenerated side, and greater than normal numbers of

neurons per taste bud volume innervated single papillae on the intact, contralateral side. The effect on the regenerated side of the tongue was primarily due to a 20% decrease in geniculate ganglion cells available to innervate taste buds, while the effects on the intact side were due primarily to a decrease in taste bud volumes and not to a change in numbers of innervating neurons. The percentage of ganglion cells lost following chorda tympani section is similar to that found in other sensory systems (Aldskogius *et al.*, 1985; Arvidsson *et al.*, 1986). Unlike our functional data, there were no diet-dependent effects on the numbers of innervating neurons or on neuron/target relationships. Therefore, our hypothesis that altered function translates into altered patterns of innervation was not supported. Instead, unilateral nerve section produced alterations on both the regenerated and intact sides of the tongue, regardless of the diet.

The gustatory neurons sustaining profound structural and functional changes peripherally following nerve section also have a central limb. Previous work showed that changes in the nucleus of the solitary tract (NTS) following nerve damage include long-term transganglionic degeneration (Barry and Frank, 1992; Whitehead *et al.*, 1995; Barry, 1999), incomplete recovery of acetylcholinesterase staining (Barry and Frank, 1992), and relatively specific functional changes (Barry, 1999). The transganglionic degeneration occurred within 2 days after chorda tympani nerve section, peaked at 8 days and continued as long as 161 days post-section, without loss of cell soma of the chorda tympani nerve (i.e. ganglion cells; Whitehead *et al.*, 1995). Although these are pioneering studies, none examined (i) the amount of terminal field remaining after nerve section; (ii) the anatomical and functional plasticity of other gustatory nerves; (iii) the compensatory or aberrant synaptic changes induced by peripheral nerve damage; or (iv) the influence of environment on central plasticity. To address some of these questions, we examined the terminal field volume of the chorda tympani nerve in the NTS of rats sustaining unilateral chorda tympani nerve section and/or dietary sodium restriction (Cheon and Hill, 2003). The terminal field of the chorda tympani decreased dramatically after 7 days post nerve section. The total terminal field was ~33% of the control field volume at 14 days postsection and 25% of controls at 60+ days. Although there was a decrease in volume throughout the dorsal to ventral extent of the field, the largest effect occurred in the dorsal zone. This was also the zone that appeared most susceptible to environmental effects during development in rat (King and Hill, 1991; Krimm and Hill, 1997; Pittman and Contreras, 2002). Our early results also showed that there is no large-scale effect in the contralateral NTS and there were no diet-related effects.

In summary, there is a dramatic amount of plasticity in the peripheral and central gustatory system induced by unilateral chorda tympani nerve sectioning and/or dietary sodium restriction at adulthood. Neurobiological effects not only occur on the sectioned side of the gustatory system, but also occur on the intact side in some experimental conditions. These experimental procedures will be useful to uncover the underlying cellular/molecular mechanism

involved in matching neurons with their peripheral and central targets.

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