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EDITORIAL

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Mechanism of gustatory flushing in Frey's syndrome

Injury to a branch of the mandibular nerve typically interrupts the sympathetic supply within the distribution of that nerve branch. The mandibular nerve supplies the tissues of the lower jaw (the teeth, part of the oral cavity, the lower lip, the temporomandibular joint, part of the external ear, and the skin above the jaw line extending in a band from the chin and lower lip to the temple) with sensory fibers [1]. Postganglionic sympathetic neurons originate in the superior cervical ganglion and project in a plexus around branches of the carotid artery. Bundles of fibers periodically leave this plexus to join branches of the mandibular nerve, ultimately to supply blood vessels, glands, and other tissue.

Parasympathetic fibers also target certain blood vessels and glands within the distribution of the mandibular nerve. Preganglionic fibers that originate in the inferior salivatory nucleus travel with the glossopharyngeal nerve, tympanic nerve and lesser petrosal nerve to the otic ganglion [1]. Postganglionic fibers join branches of the mandibular nerve (primarily the auriculotemporal and buccal nerves) to supply the parotid gland and nearby mucous glands with secretomotor fibers [2], and also supply the vasculature with vasodilator fibers [3]. Preganglionic fibers from the superior salivatory nucleus course along the facial and chorda tympani nerves to join the lingual nerve and synapse in the submandibular ganglion [1]. Postganglionic secretomotor and vasodilator fibers ultimately project along branches of the mandibular nerve to the submandibular and sublingual salivary glands, and blood vessels and glands of the oral cavity and lower lip [4]. Facial injuries usually spare these parasympathetic fibers because of their limited distal distribution. However, more proximal trauma, particularly to the auriculotemporal and lingual nerves, can simultaneously injure sympathetic and parasympathetic fibers.

Gustatory sweating and flushing within and surrounding the cutaneous distribution of the auriculotemporal nerve (Frey's syndrome) develops months or years after surgery on the parotid gland, and can also develop after other forms of trauma or parotid gland disease. The most widely accepted explanation for Frey's syndrome is misdirected regeneration or collateral sprouting of parasympathetic fibers into vacated sympathetic pathways in the auriculotemporal and nearby nerves. Over time, functional connections develop between parasympathetic secretomotor and vasodilator fibers and sympathetically-denervated sweat glands and cutaneous blood vessels. Consequently, salivation is accompanied by flushing and sweating in the sympathetically-denervated region of skin. As might be expected, sympathetic blockade does not affect this form of gustatory sweating and flushing [5]. However, blocking the otic ganglion or resectioning the glossopharyngeal nerve (which supplies the otic ganglion and hence the auriculotemporal and buccal nerves with parasympathetic fibers) abolishes the syndrome [5, 6]. A similar syndrome that involves parasympathetic fibers in the chorda tympani can develop after injury to the submandibular gland [7, 8].

In recent years, injection of botulinum toxin into the symptomatic skin has been shown to block pathological gustatory sweating [e. g., 9, 10]. This obviously is a major advance in treatment because it is far simpler and less invasive than sectioning parasympathetic nerves intracranially. Botulinum toxin enters cholinergic neuron terminals and prevents the exocytotic release of acetylcholine. Since parasympathetic secretomotor fibers use acetylcholine as a neurotransmitter, and sweat glands have cholinergic muscarinic receptors, botulinum toxin abolishes the cholinergic activation of sympathetically-

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denervated sweat glands during salivation. Tugnoli et al. [11] now report that botulinum toxin also inhibits gustatory flushing in Frey's syndrome. This finding is interesting, because it implies that cholinergic neurons mediate cutaneous vasodilatation in Frey's syndrome. However, the neurotransmitter responsible for pathological gustatory flushing is unlikely to be acetylcholine, because studies many years ago established that flushing persisted after sweating had been blocked by atropine [7, 8]. Incidentally, this observation also rules out mediation of flushing by a substance released from activated sweat glands. Thus, in addition to preventing the release of acetylcholine from cholinergic neurons, botulinum toxin appears to inhibit the release of another vasodilator substance.

There are close parallels between these new observations on pathological gustatory flushing and findings that have recently clarified the mechanism of thermoregulatory flushing. In particular a substance, probably co-released with acetylcholine from sympathetic sudomotor neurons, seems to be responsible for increases in cutaneous blood flow during body heating. Kellogg et al. [12] studied the mechanism of this thermoregulatory response in the forearm skin of healthy human subjects. Increases in cutaneous blood flow provoked by the local administration of acetylcholine were blocked by atropine pretreatment (indicating that the only functional vascular receptors for acetylcholine were muscarinic). However, the increase in blood flow during body heating persisted after sweating had been abolished with atropine (indicating that the vascular response did not involve muscarinic cholinergic receptors). Furthermore, botulinum toxin prevented increases in cutaneous blood flow during body heating (indicating that a substance released from cholinergic neurons mediated active cutaneous vasodilatation).

The nature of this vasodilating substance is uncertain [13]. Nitric oxide appears to contribute to active cutaneous vasodilatation, but does not account completely for the response. For example, Shastry et al. [14] reported recently that microdialysis of the nitric oxide synthesis inhibitor L-NAME blunted the increase in cutaneous forearm blood flow during body heating by 27 % to 47 % in different individuals. The nitric oxide component was not mediated by muscarinic receptor activation because the skin had been pretreated with atropine.

Some years ago, vasoactive intestinal polypeptide (VIP) was put forward as a likely candidate for mediating vasodilatation in exocrine glands such as the salivary and lacrimal glands [15], and possibly also the sweat glands [16]; in fact, dense networks of VIP-immunoreactive nerve fibers cluster around eccrine sweat glands in human skin [17]. Nitric oxide appears to regulate both the release of VIP from parasympathetic nerves and postjunctional vascular reactivity to VIP [18]. VIP co-exists with choline acetyltransferase in neurons in cranial parasympathetic ganglia [19], and nerve fibers containing VIP and nitric oxide synthase congregate around large proximal arteries that supply muscles, glands, the supraorbital skin, and the mucous membranes of the face [3]. Thus, the release of VIP or a similar neuropeptide from regenerating parasympathetic fibers could conceivably contribute to pathological gustatory flushing, perhaps by activating vascular receptors that previously mediated active sympathetic vasodilatation in the facial skin. Testing this hypothesis will have to wait until antagonists for VIP and related neuropeptides that are suitable for use in humans become available.

Frey's syndrome is harmless, but the aberrant gustatory flushing and sweating cause significant social distress in some patients. Thus, it is encouraging that botulinum toxin has emerged as a safe and effective treatment for pathological gustatory flushing as well as sweating [11].

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