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Review

Regulation of hemodynamics in major salivary glands by parasympathetic vasodilation

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ABSTRACT

Background: Since salivary fluid is created from blood plasma, hemodynamics in the salivary glands play an important role in the production of saliva. Trigeminal sensory input induces both salivary secretion and reflex parasympathetic vasodilation in salivary glands. This glandular vasodilation is thought to be important for the regulation of glandular hemodynamics due to the rapidity with which blood flow is increased. This review article summarizes recent research on the involvement of parasympathetic vasodilation in regulating hemodynamics in the salivary gland.

Highlight: Electrical stimulation of the lingual nerve, a branch of the trigeminal nerve, elicits parasympathetic vasodilation in the salivary glands. Parasympathetic vasodilation is mainly evoked by cholinergic fibers in the submandibular and parotid glands and by cholinergic and vasoactive intestinal peptide (VIP)-ergic fibers in the sublingual gland. The vasodilator mechanism changes from cholinergic to VIP-ergic when muscarinic receptors are deactivated.

Conclusion: Glandular hemodynamics in the submandibular, parotid, and sublingual glands are regulated by different parasympathetic vasodilator mechanisms, which may functionally contribute to the differences in secretion among the major salivary glands.

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1. Introduction

Hemodynamics in the salivary gland are largely regulated by both the sympathetic and parasympathetic nervous systems [1]. The importance of the autonomic nervous system in the regulation of glandular hemodynamics was established by Bernard in 1858 [2], who observed that stimulation of the sympathetic nerve caused vasoconstriction, whereas stimulation of the parasympathetic nerve led to marked vasodilation. The parasympathetic vasodilator response is due to both cholinergic and non-cholinergic neurotransmitters, such as vasoactive intestinal peptide (VIP) [3–15]. Conversely, the sympathetic

Abbreviations: Ach, acetylcholine; SABP, systemic arterial blood pressure; VC, vascular conductance; VIP, vasoactive intestinal peptide; Vsp, spinal trigeminal nucleus

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vasoconstrictor response is mainly due to α-adrenoceptor activation and neuropeptide Y, and only a small portion of the vasodilator response is attributable to β-adrenoceptor activation [16]. Taken together, these studies demonstrated that the autonomic nervous system is involved in regulating the secretion and hemodynamics of the salivary gland.

In addition to salivary secretion, trigeminal sensory input induces cholinergic as well as non-cholinergic parasympathetic reflex vasodilation in the salivary glands [3–5]. The sympathetic vasoconstrictive nerve fibers to the salivary glands, however, remain in a state of tonic control. Therefore, parasympathetic vasoactive nerve fibers predominantly contribute to vasodilation under reflex conditions, such as during feeding [1]. This glandular vasodilation is thought to be important in the regulation of glandular hemodynamics due to the rapidity with which blood flow increases. Parasympathetic reflex vasodilation in salivary glands, especially in the submandibular gland, has been previously examined [3–5]. It is thought that the mechanisms underlying glandular parasympathetic vasodilation differ among the major salivary glands, because of differences in the composition of serous and mucous acini and the type of secretion.

In this review, we focus on the differences in parasympathetic vasodilation among the major salivary glands, the interaction between cholinergic and non-cholinergic vasodilator mechanisms, and the physiological role of parasympathetic vasodilation in salivary glands.

2. Nerve-mediated vasodilation in the orofacial area

Until quite recently, it was believed that the regulation of blood flow in the orofacial area depended on vasoconstrictor fibers from the cervical sympathetic trunk, that is, an increase in sympathetic nerve activation induced vasoconstriction, while vasodilation was elicited by a decrease in sympathetic nerve activation. However, as we previously reported, parasympathetic vasodilator fibers exist in the orofacial area, and trigeminal sensory input elicits vasodilation mediated via trigeminal-parasympathetic reflex mechanisms in the lower lip [17–24], tongue [25], palate [22,24], masseter muscle [26–34], and submandibular gland [3–5]. Furthermore, recent research on blood vessels in cerebral, pulmonary, renal, mesenteric, hepatic, ocular, uterine, nasal, skeletal muscle, and cutaneous arteries provides evidence of the existence of parasympathetic vasodilator fibers [35]. These studies indicate the importance of parasympathetic vasodilator fibers in regulating hemodynamics.

The neural pathways mediating parasympathetic vasodilation, evoked by trigeminal nerve stimulation in salivary glands, are thought to be composed of the trigeminal afferent, spinal trigeminal nucleus (Vsp), superior and inferior salivary nucleus, submandibular, and otic postganglionic neurons (Fig. 1). The activation of neurons in the Vsp, elicited by trigeminal sensory input, has been previously observed in association with the immunohistochemical detection of c-Fos expression [36]. Parasympathetic preganglionic neurons in the salivary nucleus receive projections from the Vsp [37]; however, central neural connections between the salivary nucleus and other nuclei are still not well understood. The glossopharyngeal nerve contains efferent fibers from the inferior salivary nucleus, and connects with the parotid gland via the otic ganglion. Meanwhile, the facial nerve contains efferent fibers from the superior salivary nucleus, and connects with the submandibular and sublingual gland via the submandibular ganglion [38].

There are two different mechanisms that elicit parasympathetic vasodilation in the orofacial area; these are the reflex mechanism and direct stimulation of the parasympathetic efferent vasodilator fibers [17]. Electrical stimulation of the central cut end of the lingual nerve (Fig. 1), a branch of the trigeminal nerve, elicits reflex vasodilation, not only in the submandibular gland [3–5] but also in the lower lip [17–24], tongue [25], palate [22,24], and masseter muscle [26–34]. Conversely, direct electrical stimulation of the peripheral cut end of the parasympathetic vasodilator fibers, such as the chorda-lingual nerve innervation of the submandibular

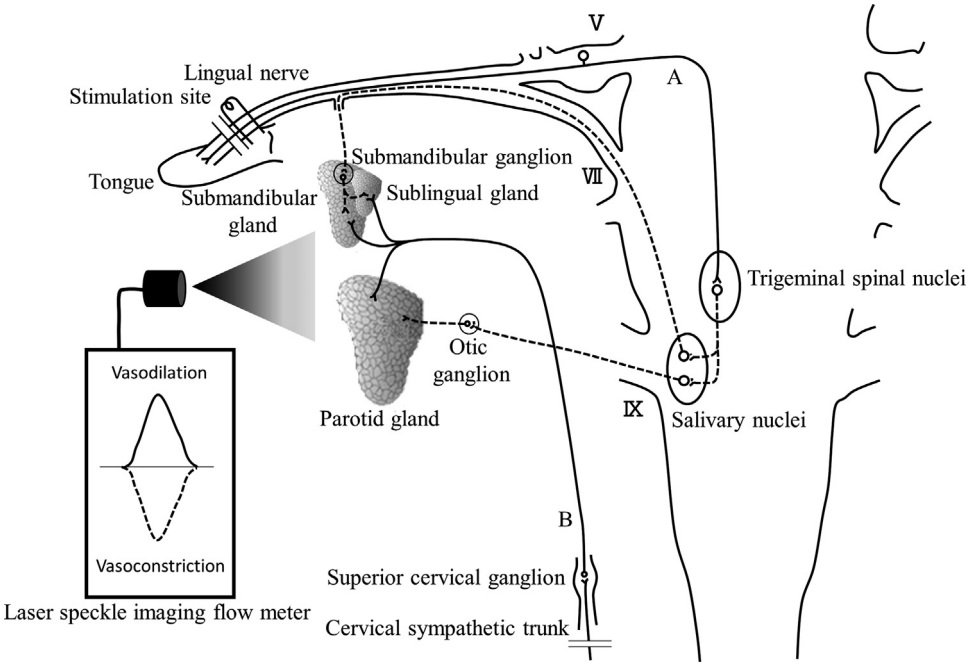

Fig. 1. Schematic representation of neural pathways mediating the parasympathetic vasodilation evoked by trigeminal nerve stimulation and blood flow measurements in salivary glands. Solid lines indicate trigeminal sensory inputs to the brain stem (A) and sympathetic vasoconstrictor fibers to the salivary glands from the cervical sympathetic trunk, which were cut on both sides of the neck before the experiments (B). Broken lines indicate the possible pathways by which nerve excitation may evoke vasodilation in the salivary glands in response to lingual nerve stimulation. The stimulation site was the central cut end of the lingual nerve. Blood flow was measured in the three major salivary glands by using a laser speckle imaging flow meter. V, trigeminal nerve root; VII, facial nerve root; IX, glossopharyngeal nerve root.