Muscarinic receptors and salivary secretion

The release of acetylcholine from parasympathetic nerves and its interaction with muscarinic acetylcholine receptors (mACHRs) regulates many fundamental functions in the periphery (smooth muscle contraction, glandular secretion, modulation of cardiac output) and central nervous system (motor control, thermoregulation, memory). Five subtypes of mACHR, M1–M5, have been designated on the basis of cDNA cloning, and the interactions of agonists and antagonists with these receptors, along with their intracellular coupling through different G proteins, continue to be characterized (2). Given the range of important functions regulated by mACHRs, they are frequently therapeutic targets in treatment of a number of pathologies. Muscarinic agonists continue to be developed for use in treating Alzheimer’s disease, nociceptive pain, schizophrenia, and xerostomia, whereas muscarinic antagonists have been developed to treat Parkinson’s disease, urinary incontinence, irritable bowel syndrome, gastric ulceration, and chronic obstructive pulmonary disease (4). Progress in therapeutics has been hindered by a lack of resolution of the roles that the different mACHRs play in physiology. Muscarinic agonists and antagonists currently used therapeutically lack the necessary selectivity to prevent unwanted side effects. A frequent side effect of the use of muscarinic antagonists is inhibition of salivary secretion, leading to xerostomia or chronic dry mouth (4).

Salivary gland secretion is a reflex, the effector arm of which is mediated by both branches of the autonomic nervous system. Stimuli mediated by sympathetic secretomotor nerves modify the protein composition of saliva and evoke a modest fluid secretory response. However, salivary secretion is almost completely abolished by atropine, and it is clear that release of acetylcholine from parasympathetic nerves plays the main role in evoking fluid secretion, acting via mACHRs on salivary secretory cells. The three pairs of major salivary glands (parotid, submandibular, and sublingual) differ in the details of how autonomic control is exerted and in the types of saliva secreted, both within and between species. However, despite this variety, there has been a tendency to base most of our understanding of salivary secretion on the most frequently employed animal model, the rat parotid gland (1). There has been a widespread acceptance, based on studies of the rat parotid gland, that salivary secretion is mediated entirely by M3 receptors.

To develop more selective muscarinic antagonists without the xerostomic side effect, we need to gain an understanding of how different muscarinic receptor subtypes are involved in the physiological control of salivary secretion. The paper by Tobin and colleagues, including the late Tony Edwards, in the current issue of the Journal of Applied Physiology, examines the effects of muscarinic antagonists on electrical stimulation of parasympathetic (chorda lingual) nerve-mediated secretion of saliva by the ovine submandibular gland (13). Antisera directed against the different mACHRs were also used immuno-cytocytochemically and on tissue homogenates to provide further evidence for the presence of particular subtypes. The results indicate a role for M1 receptors in addition to M3 receptors in mediating salivary fluid secretion and a possible role for M4 receptors in regulating salivary protein secretion. Previous studies by Tobin and coworkers (11, 12) and others (3) indicate that secretion by the rabbit and rat submandibular and rat sublingual salivary glands is also partially mediated by M1 and other non-M3 receptors.

Further progress in resolving the contributions made by different mACHRs to the control of salivary secretion has followed from the generation of mutant mice with single or double knockouts of different mACHRs (e.g., Refs. 5, 10). These studies indicate that both M1 and M3 receptors make a contribution to the secretion of whole mouth saliva (the combined secretion of all of the salivary glands) evoked by pilocarpine and other muscarinic agonists. The M1 receptor appears to make more of a contribution at higher doses of pilocarpine, whereas the M3 receptor appears to be important in mediating secretion in response to lower doses of agonist. In the present study by Tobin et al. (13), nerve stimulation can be regarded as a “more physiological” form of stimulation, and the contribution of the M1 receptor appeared to be greater at lower frequencies of stimulation. Interestingly, there was reduced fluid but not protein secretion in response to stimulation in the presence of M1 receptor blocker. This might suggest a difference between the M1 and M3 receptors in intracellular coupling of stimulation to secretion, although Culp’s group (8) found no evidence of different G protein coupling for these receptors in the rat sublingual gland. Studies of carbacol-induced calcium signaling in mACHR knockout mice suggest that, unlike M3 receptors, M1 receptors are not ubiquitously expressed on submandibular acinar cells (10). Similar studies on the parotid gland do not appear to have been undertaken. Given the earlier demonstration of a relatively greater contribution of M3 receptors to parotid gland secretion, it may be that the saliva secreted in M3 knockout mice is predominantly from submandibular and sublingual glands. Radioligand binding studies on human submandibular and labial minor salivary glands indicate the presence of both M1 and M3 receptors (7, 9).

It is generally accepted that the parotid glands in humans make a greater contribution to the whole mouth saliva secreted in response to overt stimulation during the tasting and chewing of food. The nonparotid glands make a greater contribution to the resting or “background” whole mouth saliva that coats the oral surfaces for most of the day and night between episodes of stronger stimulation. We can speculate that the development of more selective M3 receptor antagonists might affect parotid function but allow sufficient function of other salivary glands to reduce the most severe dry mouth side effects. Although the expression of other mACHRs may increase in pathology, leading to a more complex picture (6), more selective M3 antagonists may have therapeutic applications in the treatment of urinary incontinence and other pathologies.

REFERENCES


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