Impact of Chronic Stimulation with Carbachol, Histamine and Serotonin on Ion Transport in a Novel, Chloride-Secreting Rabbit Lacrimal Acinar Cell Monolayer Model.

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Purpose: Ex vivo models make it possible to study how secretagogues, hormones, and inflammatory mediators influence the release of proteins by primary cultured lacrimal acini. Using our recently developed rabbit lacrimal acinar cell monolayer (RLACM) model we examined how lacrimal epithelial ion transport is influenced by chronic stimulation with carbachol (CCh), a surrogate for agonistic anti-M3 muscarinic receptor (MAChR) autoantibodies characteristic of Sjögren's syndrome, and by acute and chronic stimulation with histamine (H) and serotonin (5-HT), mediators released from mast cells, associated with chronic low grade dacryoadenitis. **Methods:** Purified RLACs were seeded onto polyester membrane inserts at a density of 5 x 10^5 cells/ml. The RLACMs were studied in Ussing chambers under short-circuit conditions (I_{sc}) to evaluate vectorial ion transport. **Results:** RLACMs spontaneously generated a small baseline I_{sc} in the BL→AP direction, presumably associated with either absorption or Na^+ secretion. As previously reported, acute CCh stimulation induced a large (50-70 $\mu A/cm^2$) I_{sc} in the AP→BL direction, reflecting a net, Na^+-dependent secretion of Cl^-. In contrast, RLACMs stimulated overnight with CCh generated only a small I_{sc} in the BL→AP direction. Acute stimulation with H at 1 μM and with 5-HT at 1 μM and 1 mM failed to alter the baseline I_{sc}. Acute stimulation with H at 10 mM induced a small I_{sc} in the BL→AP direction. Overnight stimulation with H and 5-HT at lower concentrations potentiated the response to acute CCh by extending the duration of the AP→BL I_{sc}. However, RLACMs chronically stimulated with higher concentrations of H and 5-HT generated significantly smaller (by 50% and 35%, respectively) AP→BL I_{sc} in response to acute CCh stimulation. **Conclusions:** Our data demonstrate that chronic M3AChR stimulation, which is thought to occur in patients with Sjögren's syndrome making anti-M3 MAChR autoantibodies, induces a functional quiescence that extends to the ion transport functions that drive lacrimal fluid production. Our observations also provide attractive potential mechanistic explanations for both the drying influence of antihistamines and impairment of lacrimal fluid production associated with chronic, low grade inflammation.

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