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Serotonin and Pancreatic Duct Function

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1. 5-HT inhibits spontaneous fluid secretion as well as stimulated secretion with secretin (cAMP mediated) or ACh (Ca^{2+} mediated) in the isolated guinea pig pancreatic ducts.
2. The inhibitory effect of 5-HT is reversible and is dependent on the concentration in the range 0.01-0.1 μM, which is much lower than those that affect intestinal motility and secretion.
3. The 5-HT_3 receptor in duct cells appears to mediate the inhibitory effect of 5-HT.
4. $[Ca^{2+}]_i$ is unlikely to mediate the inhibitory effect of 5-HT.

The gastrointestinal tract is the major source of serotonin, 5-hydroxytryptamine (5-HT), in our body. It is released from enterochromaffin cells as a paracrine hormone or from enteric neurons as a neurotransmitter in the gastrointestinal tract. In the guinea pig pancreas, serotonin-positive cells distribute mainly in the endocrine pancreas but they are also scattered in the exocrine pancreas. When their distribution in the exocrine part was carefully examined, enterochromaffin cell-like cells were present among the epithelial cells of the main and interlobular ducts. This observation led us to study the function of serotonin-positive cells in the regulation of the pancreatic duct.

Interlobular ducts were isolated from the guinea-pig pancreas as described previously (1). They were cultured for 3 hr, during which time both ends of the ducts sealed spontaneously. They were then superfused by HEPES- or bicarbonate-buffered solution (pH 7.4, 37℃) on an inverted microscope and bright-field images were acquired at 1 min intervals using a CCD camera. Fluid secretion was calculated from the increment of the luminal volume and expressed as secretory rate per unit area of epithelium (nL/min/mm^2) (2). Intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) was estimated by microfluorometry in duct cells loaded with fura-2 as described previously (3).

Key Words: *Pancreatic Duct; Serotonin (5-HT); Fluid Secretion; Secretin; Acethylcholine*

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Spontaneous secretion

The isolated pancreatic ducts secreted 0.01±0.13 (mean±SE, n=4) nL/min/mm^2 during a superfusion with a HEPES-buffered solution. Fluid secretion increased to 0.78±0.02 nL/min/mm^2 when the solution was switched to a bicarbonate-buffered solution. When 0.1 μM 5-HT was applied to the bath, spontaneous secretion decreased significantly ($p<0.01$) to 0.22±0.04 nL/min/mm^2. Fluid secretion after removal of 5-HT returned to control levels in 10 min.

Secretin-stimulated secretion

During superfusion with a bicarbonate-buffered solution, secretin (1 nM) stimulated ductal fluid secretion to 2.23±0.05 nL/min/mm^2 (n=24). 5-HT at 0.01 μM failed to affect secretin-stimulated fluid secretion but at doses of 0.03 and 0.1 μM it significantly ($p<0.01$) reduced secretion to 1.01±0.06 and 0.44±0.08 nL/min/mm^2, respectively, in a concentration dependent manner. As in spontaneous secretion, the secretory rate returned to controls levels after the removal of 5-HT. No further reduction in fluid secretion was obtained at doses of 1 and 10 μM but the inhibitory effect remained after stopping the application of 5-HT.

Acetylcholine (ACh)-stimulated secretion

Ductal fluid secretion in the presence of bicarbonate buffer was increased from 0.70±0.02 nL/min/mm^2 to 1.42±0.04 nL/min/mm^2 (n=4) by 1 μM Ach. 5-HT at 0.1 μM significantly ($p<0.01$) inhibited ACh-stimulated fluid secretion (0.37±0.02 nL/min/mm^2). Again, withdrawal of 5-HT from the bath returned fluid secretion to control levels.

2-methyl-5-HT and 5-methoxytryptamine

Secretin (0.1 nM)-stimulated fluid secretion was significantly ($p<0.01$) inhibited by 2-methyl-5-HT (1 μM),

a 5-HT_3 agonist to 0.44±0.07 nL/min/mm^2 (n=4) but was not affected by 5-methoxytryptamine, a 5-HT_4 agonist (2.03±0.07 nL/min/mm^2).

$[Ca^{2+}]_i$ in duct cells

5-HT at 0.1 μM had no effect on $[Ca^{2+}]_i$ in duct cells. As reported previously (3), 1 μM Ach increased $[Ca^{2+}]_i$. Addition of 0.1 μM 5-HT during stimulation with 1 μM Ach induced a small and transient elevation of $[Ca^{2+}]_i$.

Conclusion

Serotonin (5-HT) containing cells in the pancreatic duct can regulate ductal fluid secretion by locally releasing 5-HT and may function as a local intraductal pressure regulator.

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