CADMIUM BLOCKS THE INHIBITORY RESPONSE TO SOMATOSTATIN IN THE PERFUSED SHARK RECTAL GLAND

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We reported in 1986 that cadmium (28 ppm) reversibly blocked A_1 adenosine receptor-mediated inhibition of chloride secretion in the isolated perfused rectal gland. (Forrest, et al. CMTS Annual Report, 1986). We recently reported that cadmium (250 μM) also blocks the effects of peptide YY to inhibit forskolin (1μM) stimulated chloride secretion (Grasso, et al Bull. MDIBL 29:57, 1990). In contrast, the effect of forskolin to stimulate chloride secretion was entirely unaffected by cadmium. Thus, cadmium appears to block receptor-mediated inhibition (but not stimulation) of chloride transport, indicating that this metal selectively interferes with inhibitory signal transduction. Somatostatin (SRIF) is a potent, receptor mediated inhibitor of chloride secretion (Silva, et al.Am. J. Physiol. 249:R329-R334, 1985) and adenylate cyclase and cyclic AMP accumulation (Kelley et al.J. Clin. Invest. 85:1629-1636. 1990) in the perfused gland. Therefore, the present experiments were performed to determine whether cadmium blocks the inhibitory response to somatostatin.

We also sought to determine if cadmium will block inhibitory signals when chloride secretion is stimulated to near maximal rates by higher concentrations of forskolin (10μM). A four part experiment in perfused rectal glands was performed with 5-8 glands in each experimental group. All glands were perfused for 30 min in the basal state and then forskolin (10μM) was added to the perfusion for the next 30 min in the presence and absence of SRIF and/or cadmium. In the control group, chloride transport was stimulated to near maximal value (2000-2400 μEq chloride/hour/gram) with 10μM forskolin only (Figure 1). In group 2, glands were perfused with forskolin (10μM) in the presence of SRIF, 100 nM. In group 3, cadmium (25μM) was present in addition to forskolin and SRIF. To determine if cadmium alone had an effect on forskolin stimulated transport, a final group of glands were perfused with forskolin (10μM) and cadmium (25μM). The results are shown in Figure 1.

In the presence of SRIF, the chloride secretory response to 10μM forskolin was markedly inhibited (Figure 1). In the presence of cadmium and SRIF, the inhibitory response to SRIF was present at the 40 min. time point (10 min. after the addition of SRIF and cadmium). However, at 50 min the inhibitory effect of SRIF was partially reversed and at 60 min. of perfusion, the inhibitory response to SRIF was entirely abolished by the presence of cadmium.

In separate experiments, we determined that at concentrations as low as 5 and 10μM, cadmium completely reversed the ability of somatostatin to inhibit chloride transport. This reversal of the effect of SRIF always occurred after a 10 minute delay. Cadmium was without effect on the ability of forskolin to stimulate chloride transport to near maximal values (Figure 1). Cadmium also blocked the effect of neuropeptide Y (NPY) to inhibit forskolin stimulated chloride secretion (results not shown).

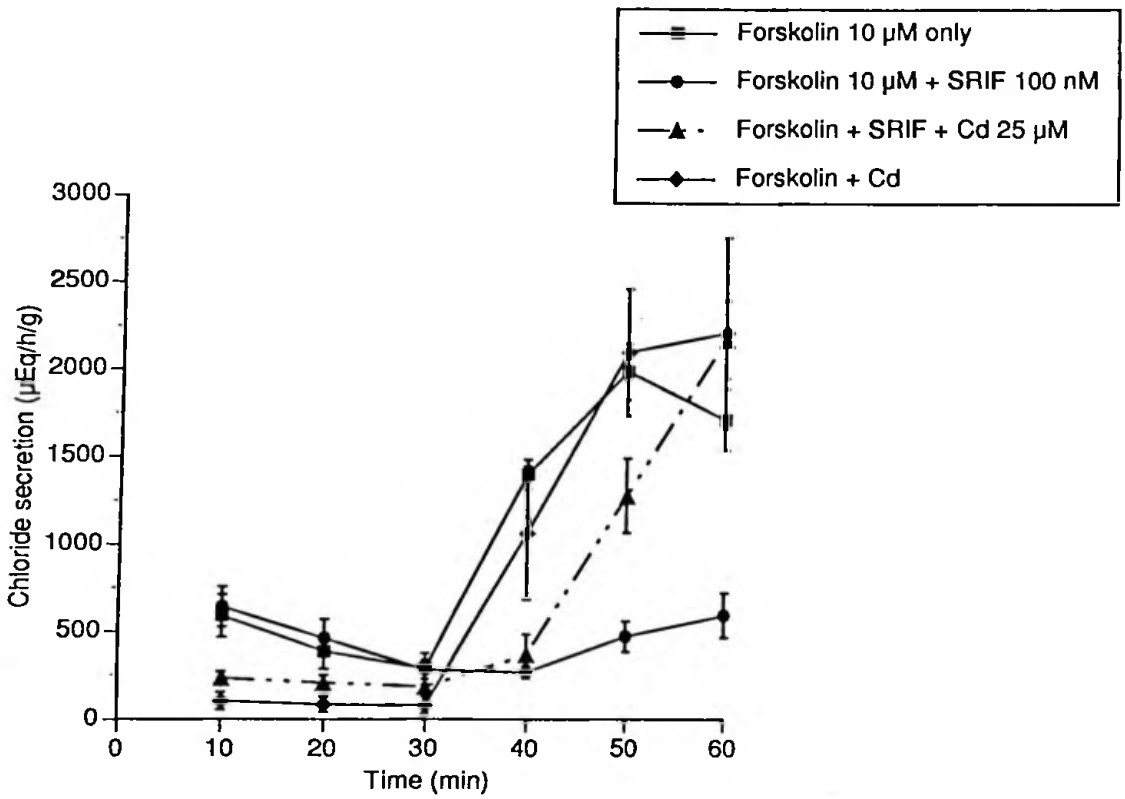

Figure 1. Effects of cadmium on somatostatin (SRIF) mediated inhibition of forskolin stimulated chloride secretion in the perfused rectal gland.

The ability of low concentrations of cadmium to block multiple receptor-mediated hormone and autacoid inhibitors of chloride transport (adenosine, peptide YY, NPY and SRIF) suggests that cadmium is acting on a common pathway in signal transduction of inhibitory receptors. This site of action could be a direct effect on inhibitory G proteins, an effect on receptor-G protein interaction or at other distal sites (K^+ channel or Cl-channel) in receptor regulated secretion of chloride.

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