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Effects of PGE_1 Alone and on Sympathetically Mediated Na, K Transport in the Perfused Main Submandibular Duct of Rat (42644)

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Abstract. PGE_1 was administered in 5 μg/kg doses every 5 min over a period of 70 min and Na and K transport in the perfused main duct of rat submandibular gland was examined during a period without stimulation of the sympathetic nerve as well as during stimulation of the sympathetic nerve. A 25% decrease in the amount of Na absorbed and a 42% decrease in the amount of K secreted occurred when PGE_1 alone was administered; the same change occurred when the sympathetic nerve was stimulated in the presence of PGE_1. These data show, for the first time, an effect of PGE_1 alone on electrolyte transport, and suggest that specific PGE_1 receptors are activated.

Prostaglandin, especially PGE_1, has been shown to have a modulating effect on nerve-elicited salivary flow rate (1–3), although PGE_1 itself does not cause secretion. With parasympathetic nerve stimulation, e.g., it caused a reduction in flow rate, the magnitude of which was related to the dosage of PGE_1 (2). It has been postulated that PGE_1 modulates such nerve-induced secretion by causing a reduction in acetylcholine release (2–4). However, preliminary results from our lab show that PGE_1 also causes a reduction in sympathetically elicited secretion and, therefore, diminished acetylcholine release may not be the cause of the PGE_1-induced modulation of nerve-induced secretion. Determination of the mechanism of the PGE_1-induced modulation of nerve-induced salivary function is complicated by the fact that PGE_1 itself does not induce secretion (3). PGE_1 may nonetheless exert specific effects on cell membranes and modulation of nerve-evoked changes by PGE_1 may be a reflection of effects induced by the prostaglandin itself. Thus, for clarification of the modulating role of PGE_1 it is necessary to see if effects of the PGE_1 itself on some aspects of secretory activity of the gland can be disclosed. It appeared possible that the study of its effects on electrolyte transport in the perfused main duct of submandibular gland might yield important information about the PGE_1 effects on this basic aspect of secretory function. In addition, the relation between effects of PGE_1 alone and the modulating effects of PGE_1 on nerve-induced changes in regulation of transport kinetics was also examined. For this study, we employed stimulation of the sympathetic nerve, since stimulation of the parasympathetic nerve and perfusion of the main duct simultaneously is extremely difficult and has only been accomplished at the hands of a single investigator (5). The fact that stimulation of either nerve led to equally great reductions in flow rate when PGE_1 was administered further justified use of this nerve (unpublished data, and 2).

Materials and Methods. Male Long-Evans rats, 4–5 months of age, were used as the experimental animals. They were fasted overnight but allowed water *ad libitum*. The rats were anesthetized with sodium pentobarbital (50 mg/kg body wt, ip) and tracheotomized. Th carotid sheath was carefully dissected, and the cervical sympathetic trunk was isolated from the common carotid artery and vagus nerve. Biopolar platinum electrodes were mounted on a micromanipulator and the tips of the electrodes were placed under and around the sympathetic trunk. The sympathetic nerve was stimulated by a stimulator (Grass Instruments Co., Model SD5) which delivered square wave pulses (5-msec duration) at 4–5 V and 20 Hz. The appearance of saliva from the cut end of the main excretory duct of the parotid gland of the ipsilateral side was used as a criterion of

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successful stimulation of the sympathetic nerve.

The main excretory duct of one submandibular gland was cannulated at its oral opening by insertion of a fine beveled end of polyethylene tubing (PE 10) approximately 3 cm long to a depth of about 3 mm. For cannulation of the hilar end of the duct, the submandibular and sublingual gland complex was exposed and cleared. The sublingual gland and duct were separated from the submandibular gland and duct to expose the hilar end of the submandibular gland. An incision was made in the wall of the submandibular duct close to the hilar end, the polyethylene tubing (PE 10), pulled to a tip diameter of 70 to 100 μm, was inserted and ligated in place. The other end of the cannula was connected to a 0.5-ml glass syringe. The syringe was mounted on a microperfusion pump (Harvard Model 940) and set to deliver fluid at the rate of 980 nl/min. The perfusion solution contained 145 m*M* Na, 5 m*M* K, 125 m*M* Cl, and 25 m*M* HCO_3. Trace amounts of ^{14}C-inulin were incorporated into the perfusion fluid to serve as an indicator of net water movement across the duct epithelium. Three microliter samples of perfusate were collected from the free end of the oral cannula by disposable micropipets (Drummond Scientific Co.) for analysis of Na and K by flame photometry (Instrumentation Laboratories, Inc., Model 143).

A jugular vein was cannulated by PE 50 tubing for the administration of PGE_1 (Upjohn Diagnostics) at a dose of 5 μg/kg body wt; this amount was administered every 5 min for 70 min, since the effects of the PGE_1 are very transient.

After the preparation of the animals, 30 min was allowed for stabilization. Three to four samples were collected for analysis of Na and K. These samples served as controls. The PGE_1 was administered, the first 20-min sample was discarded, and 3–4 samples were collected thereafter. Then the sympathetic nerve to the submandibular gland was stimulated in the presence of PGE_1, and again the first 20-min sample was discarded and another 3–4 samples of perfusate was collected for electrolyte analysis.

Net water transport across the ductal epithelium was also determined. Time for collection of the perfusates for each maneuver was carefully determined. It was observed that there was no significant change in the flow rate during each maneuver. Thus, the data suggested that neither PGE_1 nor sympathetic nerve stimulation in the presence of PGE_1 caused any change in net transductal flux of water.

Analysis of Data. All data in text, table, and figures are expressed as means ± SE. Control data were compared with experimental data within the same animals by paired Student's *t* test. Values were considered to be statistically significant if *P* values were less than 0.05.

Results. The data in Table I show the effects of iv administration of repeated 5 μg/kg doses of PGE_1 on Na reabsorption and K secretion in perfused main duct of rat submandibular gland. In the presence of PGE_1, the amount of Na absorbed was decreased from controls by 25%, and the amount of K secreted was reduced by 42%. When the sympathetic nerve was stimulated, PGE_1 administration did not cause a statistically significant ($P > 0.05$) change in either Na or K, and values were indistinguishable from those obtained for PGE_1 in the absence of nerve stimulation.

Discussion. Present data show that PGE_1 itself can affect Na and K transport in the main duct of rat submandibular gland. Furthermore, the modifications in Na reabsorption and K secretion are considerable. These findings thus suggest that PGE_1 receptors are

TABLE I. EFFECTS OF PGE_1 AND PGE_1 PLUS STIMULATION OF SYMPATHETIC NERVE ON TRANSDUCTAL ELECTROLYTE TRANSPORT

Condition	Na absorption	K secretion
	neq/min duct	
Control	28.0 ± 2.7	22.3 ± 2.0
PGE_1	20.9 ± 2.3*	13.0 ± 1.5*
PGE_1 + Sym N Stim	22.8 ± 2.0*	12.9 ± 1.3*

Note. Values are means ± SE, number of rats = 6. PGE_1 was given at a dose of 5 μg/kg body wt, iv, and repeated every 5 min throughout the experiment (70 min). Sym N Stim = sympathetic nerve stimulation, 4 V, 5 msec, 20 Hz. Control = transport values prior to administration of PGE_1 and/or nerve stimulation.

* Value differs significantly from control ($P < .001$).

activated. Since the changes observed when the sympathetic nerve is stimulated in the presence of the prostaglandin do not differ from those observed when only the prostaglandin is perfused and no nerve stimulation is induced, a modulating effect of the PGE_1 on nerve-elicited responses is thus not implied from present data, although such an effect also is not excluded. The amount of Na absorbed with sympathetic nerve stimulation alone (6, and present data) is even less than that absorbed with nerve stimulation in the presence of PGE_1 (46% reduction in Na efflux), but the amount of K secreted is nearly the same (42% compared with 45% reduction in net influx of K) (6). In fact, in view of the present data and the fact that PGE_1 itself does not elicit salivary secretion from the whole gland (2), the modulation of nerve-evoked salivary flow rate by PGE_1 may be a reflection of changes induced in the membrane by PGE_1 itself, and these effects only become evident when the nerve-induced secretory response is superimposed on them. From previous work on prostaglandin-induced modulation of nerve-elicited secretory flow, it was only possible to suggest that the PGE_1 had selective effects on acinar and duct cells (7, 8). Thus, it was not heretofore possible to assess the effects of PGE_1 itself, and by the present work, such effects now become demonstrable.

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