INTESTINAL ABSORPTION OF GLUCOSE AND SODIUM: EFFECTS OF EPINEPHRINE AND NOREPINEPHRINE.

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Catecholamines influence transmembrane potentials in cardiac muscle and carbohydrate metabolism in liver and skeletal muscle (Sutherland and Rall, 1960), and more recently it has been reported that epinephrine infusion increased renal glucose T_m in dogs (Blake, 1962) and reduced renal sodium excretion in humans (Baldwin et al., 1963). The small intestine, like the nephron, exhibits active transport mechanisms for both sodium and glucose (Wilson, 1962). Therefore, it seemed of interest to study effects of catecholamines on absorption of these substances by everted segments of rat small intestine in vitro, a preparation which permits investigation of direct influences on sugar and ion transport.

Sutherland and his associates (Davoren and Sutherland, 1963) have shown that adenyl cyclase, an enzyme which catalyzes the conversion of ATP to cyclic AMP, is stimulated by epinephrine. Effects of epinephrine on cyclic AMP formation are blocked by dichloroisoproterenol (DCI) and by ergotamine. Since the cyclizing enzyme is present in the mucosa of the intestine (Sutherland and Rall, 1960), it seemed that effects of epinephrine on glucose and ion absorption might be related to increases in tissue levels of cyclic AMP. If so, these effects should be inhibited by DCI and ergotamine. The results reported here show that epinephrine and norepinephrine stimulate glucose and sodium absorption, and that these effects are reduced when the tissue is pre-incubated with DCI or ergotamine.

Methods and materials. Male Sprague rats weighing 270-300 grams were used. One segment of upper jejunum about 15 cm in length and a

second of lower jejunum and upper ileum of the same size were taken from each animal and incubated for 90 minutes in a Dubnoff shaker. The buffer was a Ringer-bicarbonate with 137 mM of Na, 5 of K, 1 of Ca, and glucose 3 mg/ml. Details of preparing and incubating the segments appear elsewhere (Aulsebrook, 1961). Sodium in the serosal (absorbed) fluid was determined by flame photometry and glucose by the Somogyi modification of the Nelson method (Somogyi, 1945). Drugs were added to the mucosal (outer bathing) fluid at the start of incubation unless otherwise noted.

Results and discussion. Effects of several catecholamines and glucagon on absorption appear in table 1. Both epinephrine and norepinephrine stimulated absorption of glucose and sodium, and the effect of epinephrine on sodium transport persisted when buffer glucose was replaced by mannitol. Dopamine and glucagon were without effect on absorption. Because epinephrine and norepinephrine are unstable at alkaline pH, it appeared that their effects on absorption might have been produced by oxidation products rather than the added amines, although the incubation medium did not become pink. Therefore, epinephrine was pre-incubated for one hour prior to addition of segments to the medium. This abolished the effects of epinephrine, and thus it appears likely that the increases in absorption observed in earlier experiments were produced by the added catecholamines *per se*. Persistence of the effect of epinephrine on sodium absorption when glucose was replaced by mannitol is of interest in connection with the observation of Davoren (Davoren and Sutherland, 1963) that withholding glucose from buffer did not impair the activity of epinephrine in increasing intracellular levels of cyclic AMP.

Table 2 presents results of a series of experiments concerned with testing the hypothesis that epinephrine stimulated glucose and sodium absorption by increasing adenyl cyclase activity and thus raising tissue levels of cyclic AMP. In studies with blocking agents, segments were incubated with DCI or ergotamine for 20 minutes prior to addition of epinephrine, and the incubation then continued for an additional 90 minutes. DCI and ergotamine in the absence of epinephrine were also tested for possible effects on absorption. The data show that DCI at twice the molar concentration of epinephrine produced sig-

Table 1. Effects of Catecholamines and Glucagon on Glucose and Sodium Absorption

Drug	No. segments	Absorption, μg/mg/hr Glucose	Na
None	13	80 ± 8	16.2 ± 1.3
L-norepinephrine	13	121 ± 9*	24.5 ± 1.5*
None	9	51 ± 8	12.5 ± 1.3
L-epinephrine	12	87 ± 9*	20.1 ± 1.5*
None	12	-----	12.9 ± 0.8
L-epinephrine+	12	-----	16.0 ± 0.8*
None	7	44 ± 8	10.4 ± 1.0
L-epinephrine**	7	46 ± 7	9.7 ± 0.6
None	8	50 ± 15	14.3 ± 1.3
Dopamine	8	44 ± 8	12.2 ± 1.0
None	6	57 ± 10	17.2 ± 1.9
Glucagon	6	68 ± 11	15.0 ± 1.5

Means ± S.E. * $P < 0.05$. ** Drug preincubated for one hour.
+ = Buffer glucose replaced by mannitol.
Mucosal fluid epinephrine concentration 5×10^{-5}M, other amines 10^{-4}M, and glucagon 10 μg/ml.

nificant blocking of the effects of epinephrine on both sodium and glucose absorption, while DCI alone was without effect. Ergotamine also demonstrated blocking ability, but considerably higher concentrations of the drug were required. Like DCI, ergotamine alone had no effect on absorption. These results suggest that the effects of epinephrine and norepinephrine on glucose and sodium absorption are in some way dependent on production of increased tissue levels of cyclic AMP by the catecholamines.

Attempts to show an effect of added cyclic AMP were negative.

Table 2. Effects of Dichloroisoproterenol, Ergotamine, and Cyclic Adenylic Acid on Absorption.

Drug	No. segments	Absorption, μg/mg/hr Glucose	Na
L-epinephrine	8	104 ± 6	24.5 ± 1.3
DCI, L-epinephrine	8	74 ± 6*	21.5 ± 1.2*
None	8	84 ± 7	16.8 ± 0.9
DCI	8	70 ± 3	18.8 ± 1.0
L-epinephrine	7	96 ± 5	26.0 ± 1.4
Ergotamine (1), L-epinephrine	7	90 ± 5	24.2 ± 1.2
L-epinephrine	8	109 ± 7	22.7 ± 0.9
Ergotamine (2), L-epinephrine	7	82 ± 5*	16.9 ± 1.2*
None	8	67 ± 6	15.0 ± 1.5
Ergotamine (2)	8	72 ± 4	15.9 ± 1.3
None	4	72 ± 9	15.7 ± 1.2
Cyclic AMP (1)	4	57 ± 10	14.7 ± 0.8
None	4	52 ± 8	12.7 ± 1.1
Cyclic AMP (2)	4	62 ± 8	10.0 ± 1.3

Means ± S.E. * $P < 0.05$.
Epinephrine concentration 5×10^{-5} M, DCI 6×10^{-5}M. Ergotamine (1) 6×10^{-5}M, (2) 10^{-4}M. Cyclic AMP (1) 10^{-4}M, (2) 2×10^{-3}M serosal fluid only.

In one experiment, the metabolite was present in the buffer at a concentration of 10^{-4}M; in another, it was present in the serosal fluid only at the high concentration of 2×10^{-3}M. These results are probably accountable to at least two factors: Purine nucleotides are rapidly hydrolysed by enxymes produced by the intestinal mucosa (Wilson,

1962), and cyclic AMP apparently enters intact cells very poorly (Sutherland and Rall, 1960; Davoren and Sutherland, 1963).

In summary, epinephrine and norepinephrine stimulated absorption of glucose and sodium by everted segments of rat small intestine. These effects were not produced by dopamine or glucagon, indicating a certain specificity for epinephrine and norepinephrine. Effects of epinephrine were blocked by dichloroisoproterenol and ergotamine, suggesting that cyclic AMP in some way mediates the effects of these catecholamines on glucose and sodium absorption.

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