rate of mesenteric artery was paralleled by its high endogenous amine content (Table).

These data focus attention on the unexpectedly high catecholamine biosynthetic capacity of the superior mesenteric artery. In addition, our results point to the potential value of this blood vessel for further study of adrenergic transmitter biosynthesis in vascular tissue[6].

Catecholamine-$C^{14}$ biosynthesis and noradrenaline content of vascular tissue

| Tissue | Catecholamine-$C^{14}$ synthesis[a] (ng/g per h ± S.E.M.) | | Endogenous noradrenaline (µg/g ± S.E.M.) | |
|---|---|---|---|---|
| Aorta | 67.5 ± 7.3 | (10)[b] | 0.51 ± 0.12 | (4)[b] |
| Femoral artery | 106.1 ± 26.2 | (6) | 0.64 ± 0.14 | (3) |
| Pulmonary artery | 208.5 ± 14.7 | (6) | 0.52 ± 0.10 | (4) |
| Mesenteric artery | 629.8 ± 55.3 | (7) | 2.02 ± 0.24 | (3) |
| Portal vein | 261.9 ± 39.6 | (7) | 0.72 ± 0.16 | (4) |

[a] Values extrapolated from synthesis rates determined during 15 min incubation periods. [b] Number of samples.

*Zusammenfassung.* Die Umwandlung von Tyrosin in Katecholamin wurde in verschiedenen Blutgefässen untersucht. Die Katecholamin-Biosynthese erfolgte am schnellsten in der Arteria mesenterica sup. (0,6 µg/g/h), was zehnmal höher liegt als diejenige in der Aorta oder in der Arteria pulmonalis.

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## The Effect of Theophylline on the Actions of Pancreozymin and Secretin

In recent years, cyclic AMP has been implicated as an intracellular mediator of hormonal action[1]. Administration of theophylline, a methyl xanthine which inhibits the breakdown of cyclic AMP[2], has been shown to augment or mimic the action of several hormones[3–5]. The possibility that the hormones of the G.I. tract exert their actions by means of this cyclic AMP mechanism has received scant attention. It was reported in 1968[6] that theophylline enhanced the action of histolog on gastric secretion in man, but the mechanism involved was not explored. Case et al.[7] in 1969, using an isolated perfused cat pancreas, demonstrated that a flow of pancreatic juice which contained enzymes, could be stimulated by the introduction of N6-2′-*O*-dibutyryl-adenosine 3′ 5′-monophosphate (dibutyryl cyclic AMP) and theophylline into their perfusate. This group states that although dibutyryl cyclic AMP and theophylline can mimic the action of secretin on the flow rate of pancreatic juice, these agents do not mimic the effects of pancreozymin. They attributed the apparent stimulation of pancreatic enzymes to a washout phenomenon secondary to the increased flow of juice.

The purpose of the present study was to determine whether the administration of theophylline could augment the flow rate, and enzyme output of pancreatic juice secreted in response to exogenous secretin and pancreozymin. Because of the known pepsin stimulatory action of secretin[8], this parameter was also monitored.

*Materials and methods.* Experiments were performed on unfed cats, anaesthetized with chloralose (80 mg/kg, i.v.). Splanchnic nerves were cut extraperitoneally, and the vagus nerves sectioned in the neck. The pancreatic duct was cannulated as it passed through the duodenal wall, and the pylorus was ligated. Gastric secretions were collected by means of a rubber tube inserted through an oesophageal incision in the neck.

Isosmolar glycine (pH 6.4) was used as a gastric washout fluid and the pepsin content of the washout was determined by the method of Anson[9], the output of pepsin being expressed as mg of tyrosine/15 min. The volume and protein output of pancreatic juice were measured in 15 min periods, protein output being determined spectrophotometrically assuming a standard of O.D. 1.8 = 10 mg free protein/ml of pancreatic juice.

Secretin (SN) and Pancreozymin (PZ) were obtained from GIH Laboratory Sweden (Secretin batch No. 16931; Pancreozymin batch No. 26841). These hormones were administered as constant i.v. infusions in doses of: PZ: 24 Crick Harper Raper U/kg/h; SN: 11.6 clinical U/h, irrespective of body weight. Infusion of both hormones continued for the duration of the experiment. When the flow rate and protein output of pancreatic juice had reached relatively constant levels (2–2.5 ml/15 min, 1.0 – 1.5 mg protein/15 min), theophylline (Schwarz Bioresearch Inc.) was administered as a constant i.v. infusion (6 mg/kg over 20 min).

*Results and discussion.* Infusion of theophylline resulted in a significant increase in pancreatic protein output ($p < 0.001$), which was not accompanied by a significant augmentation of flow rate ($p > 0.05$) (Figure 1). The latter result appears to disagree with the observations of Case et al.[7] who reported that their isolated pancreas preparation which produced no basal secretion, could be stimulated to secrete by administration of dibutyryl cyclic AMP and theophylline. A possible explanation for our

[1] G. A. Robison, R. W. Butcher and E. W. Sutherland, Ann. Rev. Biochem. *37*, 149 (1968).
[2] R. W. Butcher and E. W. Sutherland, J. biol. Chem. *237*, 1244 (1962).
[3] J. Orloff and J. S. Handler, J. clin. Invest. *41*, 702 (1962).
[4] J. M. Ensor and D. S. Munro, J. Endocrin. *38*, 28 (1967).
[5] J. R. Turtle, G. K. Littleton and D. M. Kipnis, Nature *213*, 727 (1967).
[6] D. P. Mertz, Experientia *25*, 269 (1969).
[7] R. M. Case, T. J. Laundy and T. Scratcherd, J. Physiol., London *204*, 45P (1969).
[8] E. L. Blair, A. A. Harper, J. A. Pearson and J. D. Reed, J. Physiol., London *175*, 60P (1964).
[9] M. L. Anson, J. gen. Physiol. *22*, 79 (1938).

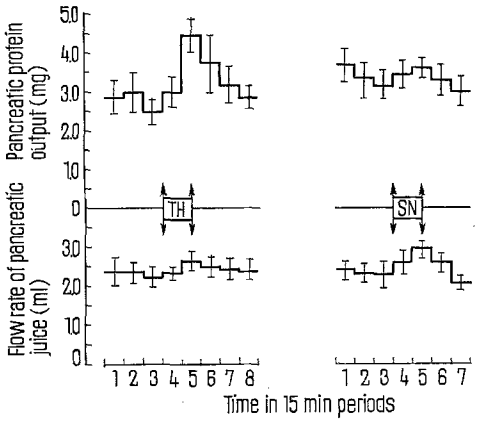


Fig. 1. The effect of an i.v. infusion of theophylline (TH) (6 mg/kg over 20 min) and supplementary dose of secretin (SN) (4 U/20 min) on output of protein (above) and flow rate (below) of pancreatic juice (± S. E.). Throughout each experiment, background pancreatic secretion was maintained by continuous i.v. infusion of secretin (11.6 U/h) and PZ (24 U/kg/h). For statistical evaluation of the effects of theophylline and the supplementary dose of SN, values obtained in the 15 min period preceeding the infusions were compared (*t*-test for paired values) with the values obtained in the second period after the beginning of the infusion.

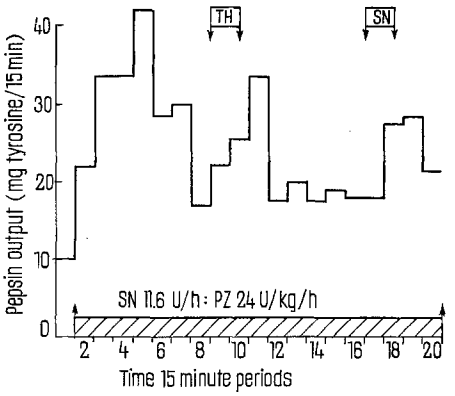


Fig. 2. The effect of an i.v. infusion of theophylline (TH) (6 mg/kg over 20 min) and a supplementary dose of secretin (SN) (4 U/20 min) on the output of pepsin. Throughout the experiment continuous i.v. infusions of secretin (11.6 U/h) and PZ (24 U/kg/h) were maintained.

finding that theophylline did not cause any significant change in the flow rate of pancreatic juice may be that flow rates stimulated by a continuous dose of SN, were already at maximal levels. To determine if the flow rate of pancreatic juice was indeed maximal, the dose of SN was doubled for a period of 20 min, 2–3 h after the injection of theophylline. This supplementary dose of SN did not result in any significant change in either flow rate ($p > 0.05$) or protein output ($p > 0.1$) of pancreatic juice (Figure 1). This suggests that the flow rate, prior to the administration of theophylline was maximal. Under the experimental conditions described in this paper, it would appear that i.v. administration of theophylline enhances the pancreatic protein stimulating effect of PZ, and that this effect is not dependent on increased flow rate.

In 5 out of 6 experiments, pepsin output was increased in response to theophylline, and in all experiments in response to the supplementary dose of SN. The results of one experiment are shown in Figure 2.

On the basis of the known action of theophylline on the cyclic AMP system[2], the above evidence suggests that cyclic AMP may be involved in mediating the pancreatic action of PZ and the pepsin stimulating action of SN.

*Résumé.* Chez le chat, l'injection intravéneuse de théophylline qui, comme on sait, produit une accumulation de l'AMP cyclique, augmente aussi l'effet de la pancréozymine sur la production des protéines pancréatiques et de la sécrétine sur celle de la pepsine.

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## Disposition of the Portal Vessels of the Avian Pituitary in Relation to the Median Eminence and the Pars Distalis

The existence of distinct anterior and posterior groups of hypophysial portal vessels has recently been demonstrated in the white-crowned sparrow, *Zonotrichia leucophrys gambelii*[1]. The anterior group of portal vessels originates from the primary capillary plexus in the anterior division of the median eminence and the posterior group of portal vessels originates from the primary capillary plexus in the posterior division of the median eminence. The anterior and posterior groups of portal vessels branch into the sinusoids of the cephalic and caudal lobes of the pars distalis respectively. It is postulated that this regional distribution of portal vessels in the white-crowned sparrow provides the anatomic basis for individual neuroendocrine controls by the anterior and posterior divisions of the median eminence over the cephalic and caudal lobes of the pars distalis[2]. In a recent study, we have demonstrated the presence of distinct anterior and posterior groups of portal vessels supplying respectively the cephalic and caudal lobes of the pars distalis in 15 species of birds and suggested that this type of arrangement may be widespread among birds[3].

[1] A. VITUMS, S. MIKAMI, A. OKSCHE and D. S. FARNER, Z. Zellforsch. *64*, 541 (1964).

[2] D. S. FARNER, F. E. WILSON and A. OKSCHE, in *Neuroendocrinology* (Ed. L. MARTINI and W. F. GANONG; Academic Press, New York 1967), vol. 2, p. 529.

[3] C. J. DOMINIC and R. M. SINGH, Gen. comp. Endocr. *13*, 22 (1969).