Comparative Effects of Caerulein, Pancreozymin and Secretin on Pancreatic Blood Flow

Caerulein, the natural decapeptide from *Hyla caerulea* skin, induces, like pancreozymin, an increase in volume flow and enzymatic content of pancreatic juice as shown by ERSPAMER et al.[1].

We showed in a previous investigation[2] that caerulein increases blood flow through the pancreaticoduodenal artery and through its branch supplying the pancreas. The vasodilating effect of caerulein on the pancreatic vascular district was present at doses which stimulate pancreatic external secretion and was not accompanied by other important cardiovascular alterations. Also another pancreatic stimulating agent[3], the gastrin-like pentapeptide ICI 50,123, was active on both pancreatic external secretion and on pancreatic blood flow, being however 25 times less active than caerulein.

Highly purified samples of pancreozymin and secretin kindly supplied by Prof. JORPES, permitted a comparative investigation of the effects of these 2 hormones and caerulein on pancreatic vascular beds.

While there is no doubt that secretin increases blood flow to the pancreas[4–6], pancreozymin was found to increase the blood content of the gland[7] but to be inactive when isotope clearance techniques were used[6].

Pancreatic blood flow of 5 beagle dogs fasted overnight and anaesthetized with urethane-chloralose, was measured. This was accomplished by placing an electromagnetic flow probe around the caudal pancreaticoduodenal artery[8]. In this way a mixture of undetermined proportions of pancreatic and duodenal flow was measured. On the other hand, a nearly pure pancreatic blood flow was recorded when the main duodenal branches of the artery were ligated or when the vessel just before its entry into the pancreas was big enough to allow the placement of a flow probe. In these cases, post mortem injections of indian-ink stained mainly the right portion of the pancreas but the nearby duodenum very slightly. When vessels to the pancreas were ligated, indian-ink stained only the duodenum. Total femoral blood flow was measured at the femoral triangle. All blood flows (mean and phasic) were measured by Nycotron 372 S electromagnetic flowmeter, and blood pressure by a Statham P 23 Db transducer. Heart rate was counted from the tracings. All parameters were recorded simultaneously by a Honeywell 1508 Visicorder. The substances were administered i.v. by rapid injections and doses expressed as ng for caerulein, as Ivy dog units (IDU) for pancreozymin and as clinical units (CU) for secretin.

Some of our results are reported in Figures 1 and 2. In accordance with previous results, caerulein caused a blood flow increase through the pancreaticoduodenal artery. This effect was satisfactory dose-related, at least in the dose range of 2–30 ng/kg i.v. used in these experiments.

After a latency of 20–30 sec, blood flow started to increase and reached its peak effect in about 40–60 sec after the injection. Even at the highest dose the action lasted no more than 6 min. Also pancreozymin caused a dose-related increase of blood flow from 0.1–1.5 IDU. The

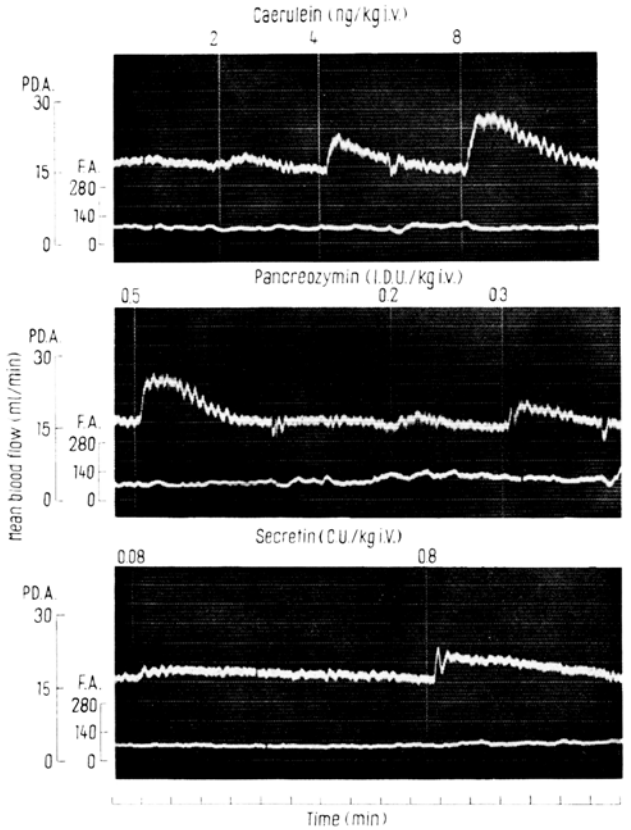

Fig. 1. Effects of graded i.v. doses of caerulein, pancreozymin, and secretin on pancreaticuduodenal (PD.A) and on total femoral blood flow (F.A.).

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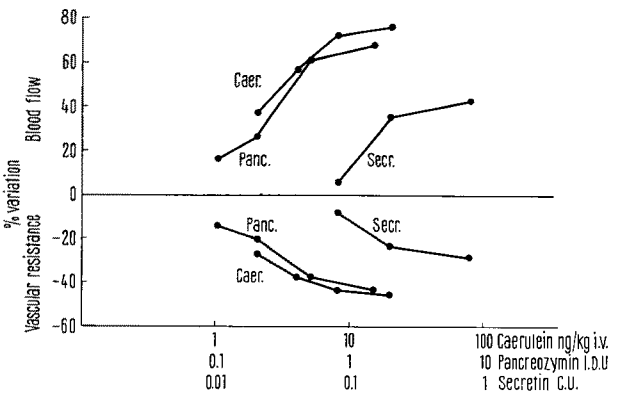

Fig. 2. % variations of pancreaticoduodenal blood flow and vascular resistance against increasing doses of caerulein, pancreozymin and secretin.

responses were similar to those of caerulein with respect to latency, peak effect, duration of action, and absence of tackyphylaxis.

Secretin in the range of 0.08–0.8 CU behaved similarly except for a flatter dose-response curve. Both caerulein and pancreozymin were tested on the nearly pure pancreatic blood flow. In this case too, the peptides showed even more pronounced vasodilating action. Neither caerulein nor pancreozymin and secretin modified arterial blood pressure, heart rate or total femoral flow in the range of doses active on pancreatic blood flow.

In conclusion, all the agents, caerulein, pancreozymin, secretin and ICI 50,123, known to stimulate pancreatic external secretion, are able to increase arterial blood inflow to the gland by reducing locally vascular resistances. This may be due to a functional hyperaemia in the activated gland.

However, a comparison between our data on blood flow with those of ERSPAMER et al.[1] on the volume of pancreatic secretion shows that pancreozymin and caerulein, over a wide range of doses, from the threshold one upwards, produce both an increase in secretory rate and in arterial blood inflow to the gland; secretin, on the contrary, increases secretion at doses by far lower than those active on blood flow. Therefore, secretin stimulation of pancreatic secretion may occur independently of a corresponding increase in blood flow to the gland.

Riassunto. La registrazione del flusso ematico dell'arteria pancreaticoduodenale caudale con flussimetro elettromagnetico ha messo in evidenza una potente azione vasodilatatrice della ceruleina, della pancreozimina e della secretina, a livello del pancreas, in assenza di modificazioni della pressione arteriosa, della frequenza cardiaca e del flusso ematico femorale.

L. DORIGOTTI and A. H. GLÄSSER

Farmitalia, Istituto Ricerche, 20146 Milano (Italy),
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Decrease of Norepinephrine in Brain and Heart of Vitamin E Deficient Rats

In rats, vitamin E is required for the normal development of the foetus and the normal function of tissues such as testis, muscle, hypophysis and thyroid as well as the central nervous system[1–5]. Vitamin E has antioxidative properties[6,7] and might thus be involved in the synthesis and/or catabolism of norepinephrine. Although norepinephrine is highly sensitive to oxygen, its formation includes 2 mixed-function oxidations, i.e. the hydroxylation of tyrosine[8] and of dopamine[9].

In the present study, the level of norepinephrine and the activity of tyrosine hydroxylase and dopamine-β-hydroxylase was measured in the brains and hearts of vitamin E deficient rats.

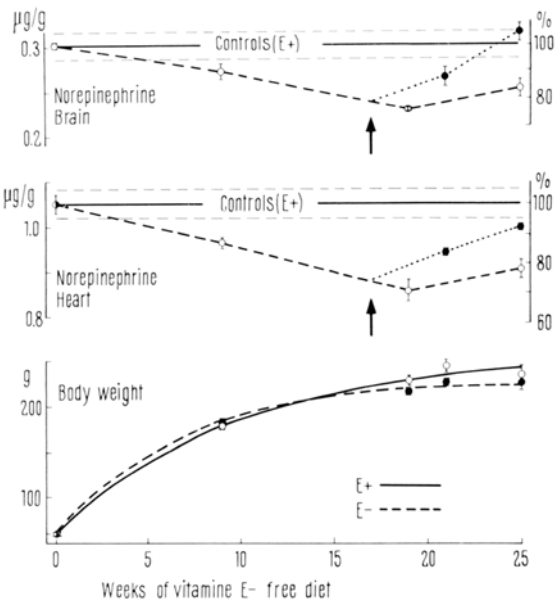
Female albino rats from a closed randomized colony (stock Füllinsdorf), 4 weeks of age, were fed a diet containing no vitamin E[10], ad libitum. Control animals (E+) were given per stomach tube 1 mg DL-α-tocopherol acetate dissolved in 0.2 ml of olive oil free of peroxides and vitamin E once weekly. Vitamin E deficient rats (E−) received olive oil lacking tocopherol. After 13 and 17 weeks the animals of group E− were almost depleted of vitamin E since 92 $\pm$ 4% of these animals showed dialuric acid-induced hemolysis[10,11], whereas erythrocytes of controls remained unaffected.

In the brains and hearts of the rat group E−, the norepinephrine level decreased slowly to about 75% of that of controls in 17 weeks ($p < 0.01$) and 25 weeks (< 0.001) respectively. This effect seems to be due to vitamin E deficiency only, since the decrease of norepinephrine was completely reversed by subsequent administration of DL-α-tocopherol for about 2 months (Figure).

The drop of norepinephrine in brain and heart seems to be relatively specific since in the group E− the weight curve (Figure), the survival rate (no spontaneous deaths) as well as the wet weight of the organs ($p > 0.05$ of E− as compared to E+) were the same as in controls.

The reported experiment was performed from February to August 1967. It was repeated twice with corresponding results, i.e. from May to December 1967 and from September 1967 to January 1968. In consequence, the drop of norepinephrine cannot be related to seasonal variations.

The decrease of norepinephrine in the brains and hearts of the E− group was not reflected by any change in the activity of tyrosine hydroxylase in the brain nor of dopamine-β-hydroxylase in the heart (Table), enzymes



Level of norepinephrine in the brains and hearts as well as body weight in vitamin E deficient rats. Norepinephrine was measured spectrophotofluorimetrically[17]. By internal standards it was excluded that the assay of norepinephrine was affected in E−. Each point represents mean $\pm$ S.E. of 3 determinations. The arrow indicates the replacement of diet E− by E+. The mean body weight $\pm$ S.E. was calculated from 70 rats (0 time) down to 9 rats (23 weeks).