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.

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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.

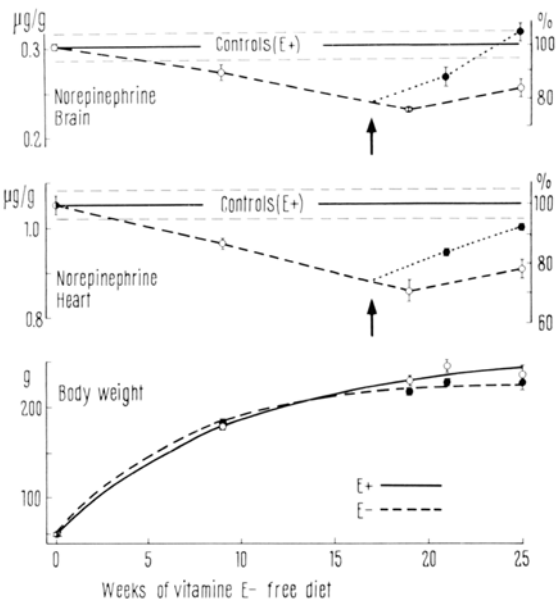
Female albino rats from a closed randomized colony (stock Füllinsdorf), 4 weeks of age, were fed a diet containing no vitamin E[10], ad libitum. Control animals (E+) were given per stomach tube 1 mg DL-α-tocopherol acetate dissolved in 0.2 ml of olive oil free of peroxides and vitamin E once weekly. 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).

Activity of tyrosine hydroxylase in brains and dopamine-β-hydroxylase in hearts of rats after 17–20 weeks of vitamin E deficient diet

Enzyme	E+	E−
Tyrosine hydroxylase	100 ± 2.0%	108 ± 6.3%
Dopamine-β-hydroxylase	100 ± 0.5%	98 ± 0.6%

The activity of tyrosine hydroxylase in rat brain was estimated in vivo by measuring the formation of ^{3}H-catechols from 0.2 mg/kg of 3,5-^{3}H-tyrosine injected s.c. 1 h prior to decapitation[13,14]. The activity of dopamine-β-hydroxylase was assayed in vivo in the heart of pheniprazine (10 mg/kg)-pretreated rats by the formation of ^{14}C-octopamine from 0.07 mg/kg of 1-^{14}C-tyramine injected s.c. 1 h before[15,16]. For technical reasons tyrosine hydroxylase can hardly be assayed in the rat heart, and the dopamine-β-hydroxylase method is restricted to extracerebral tissues. The figures represent mean ± S.E. of at least 6 determinations.

which have been considered rate-limiting in norepinephrine synthesis[8,9]. Therefore, the decrease of norepinephrine in vitamin E deficiency might have other reasons, such as reduced availability of tyrosine for norepinephrine formation (e.g. by enhanced protein synthesis[12]), decreased decarboxylation of dopa, diminished uptake of norepinephrine in storage organelles, enhanced release or increased catabolism of norepinephrine. These possibilities are at present under investigation.

Zusammenfassung. Viermonatiger Vitamin-E-Mangel bewirkt bei Ratten einen etwa 25 prozentigen Abfall des Noradrenalin-Gehaltes in Gehirn und Herz, der durch DL-α-Tokopherol rückgängig gemacht wird. Die Abnahme des Noradrenalins erfolgt ohne gleichzeitige Verminderung der Tyrosin-Hydroxylase- und Dopamin-β-Hydroxylase-Aktivität.

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Effects of Disodium EDTA on the Cardiovascular Responses to Prostaglandin E_1

Recently, Coceani and Wolfe[1] found that the effect of prostaglandin E_1 (PGE_1) on the contractility of the rat stomach fundus strip was significantly potentiated in high calcium Tyrode solution. Hence, they postulated that PGE_1 initiates the pharmacodynamic action by the release of bound Ca or by the facilitation of Ca influx[1,2]. It has been shown that PGE_1 exerts a positive inotropic action in propranolol-treated dogs[3]. The present study was undertaken to examine whether the Ca chelating agent, disodium EDTA, would influence the cardiovascular effects of PGE_1 in dogs.

Seven male dogs weighing 20–24 kg were anesthetized with sodium pentobarbital (30 mg/kg). The technique used in this study has been described previously[3,4]. In open-chest dogs under artificial respiration, heart rate, mean systemic arterial pressure, and myocardial contractile force were measured continuously with an Electronics for Medicine tachometer (Model TDC-1), a Statham pressure transducer (Model P23AA) and a Walton-Brodie strain gauge arch[5], respectively. Disodium of EDTA was administered continuously at constant rates (2 and 5 mg/kg/min) using a Harvard perfusion pump (Model 600-900). A single dose (1 μg/kg) of PGE_1 was given i.v. prior to and after 15 min infusion of 2 and 5 mg/kg/min of EDTA.

The results of the effects of PGE_1 on the cardiovascular parameters are summarized in the Figure. As shown previously[3], the i.v. administration of 1 μg/kg of PGE_1 decreased mean systemic arterial pressure, and increased

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