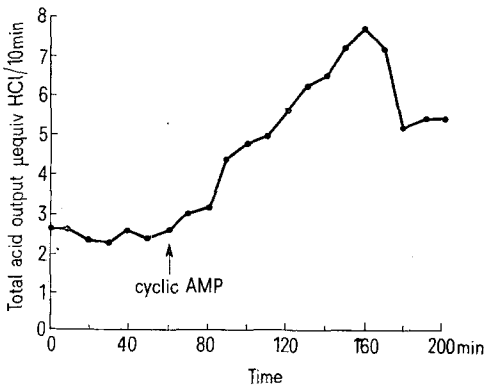

Fig. 1. The secretion of HCl by the rat stomach after injection of cyclic AMP. Each point on the curve represents the mean 10 min acid output for 20 consecutive collection periods for 4 rats.

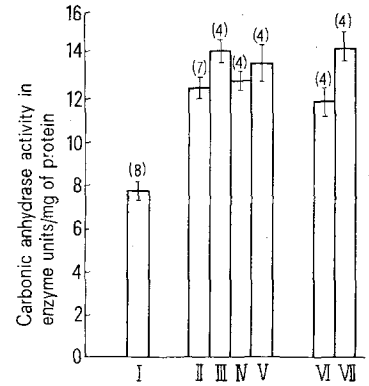

Fig. 2. Effect of cyclic AMP and dibutyryl cyclic AMP injection on carbonic anhydrase activity in rat gastric mucosa. Mean values ± standard deviation are presented. Number of experiments in parentheses. I, control; II, cyclic AMP; III, cyclic AMP + theophylline; IV, cyclic AMP + actinomycin D; V, cyclic AMP + cycloheximide; VI, dibutyryl cyclic AMP; VII, dibutyryl cyclic AMP + theophylline.

may be inhibited by actionomycin D and cycloheximide (Table II).

These results are compatible with our earlier findings indicating that the stimulating action of histamine on gastric acid secretion does not depend on DNA-directed synthesis of RNA and proteins while the effect of gastrin pentapeptide is concerned with induction of transcription[1–3].

The data obtained support the previously suggested scheme of regulation of gastric acid secretion[3,16] according to which gastrin (or gastrin pentapeptide in experiments) evokes transcription of DNA regions responsible for the synthesis of histidine decarboxylase, and the enzyme provides a supply of histamine in target cells of stomach mucosa. Histamine, in turn, activates adenyl cyclase and the cyclic AMP which is formed enhances carbonic anhydrase activity.

It is well known that cyclic AMP mediates the action of a number of hormones by activation of protein kinases of target cells[17,18]. The protein kinases, in turn, phosphorylate definite enzymes[19,20] or other proteins[21,22] providing physiological effects of these hormones. It is likely that changes in carbonic anhydrase activity produced by cyclic AMP may also arise as a result of the enzymic protein phosphorylation.

Выводы. Введение крысам пентапептида гастрина, гистамина и 3′,5′-АМФ усиливают активность карбоангидразы в слизистой желудка крыс. Установлено, что актиномицин Д и циклогексимид тормозят только активацию карбоангидразы, вызываемую пентапептидом гастрина, и не влияют на этот процесс, если он был стимулирован гистамином или 3′,5′-АМФ.

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Effect of Local Anaesthetics on the Accumulation of [^{3}H]-Metaraminol by Rabbit Atria and Vasa Deferentia

The potentiation of responses of peripheral tissues to noradrenaline produced by cocaine is most generally thought to result from the inhibition by cocaine of the uptake of noradrenaline into adrenergic nerves, with a consequent increase in the concentration of amine at the adrenergic receptors[1,2]. Procaine[3,4], lidocaine and prilocaine[5] have also been reported to either potentiate or prolong responses of peripheral tissues to noradrenaline and related amines. In view of these reports, the effect of these agents on the accumulation of [^{3}H]-metaraminol by isolated rabbit atria and vasa deferentia has been examined.

Methods and materials. Pieces of rabbit atria and vasa deferentia were prepared as described previously[6] and preincubated at 37°C for 30 min in a physiological salt solution[6]. [^{3}H]-metaraminol (1×10^{-8} *M*) was then added to the media and the incubation continued for a further 30 min. At the end of this period, the total [^{3}H] content

Effect of local anaesthetics on the accumulation of [^{3}H]-metaraminol

Tissue	Concentration (M)	Distribution ratio of [^{3}H]-metaraminol (mean ± S.E.)			
		Cocaine	Procaine	Licocaine	Prilocaine
Atria	—	8.31 ± 0.41	7.92 ± 0.43	7.92 ± 0.43	11.06 ± 0.38
	1×10^{-6}	3.82 ± 0.14[a]	7.30 ± 0.53	7.34 ± 0.48	7.73 ± 0.66[a]
	1×10^{-5}	1.68 ± 0.09[a]	5.89 ± 0.47[a]	8.06 ± 0.65	7.29 ± 0.52[a]
	1×10^{-4}	1.05 ± 0.05[a]	4.14 ± 0.37[a]	6.64 ± 0.47	5.39 ± 0.29[a]
	1×10^{-3}	1.00 ± 0.04[a]	1.81 ± 0.13[a]	4.24 ± 0.58[a]	3.39 ± 0.21[a]
Vasa deferentia	—	15.99 ± 0.84	12.05 ± 0.98	12.05 ± 0.98	21.60 ± 1.90
	1×10^{-6}	5.65 ± 0.48[a]	12.29 ± 1.17	13.72 ± 1.12	14.18 ± 1.16[a]
	1×10^{-5}	2.60 ± 0.16[a]	8.99 ± 0.92	13.99 ± 1.33	13.17 ± 2.06[a]
	1×10^{-4}	1.42 ± 0.05[a]	6.87 ± 0.36[a]	10.24 ± 1.68	12.80 ± 1.90[a]
	1×10^{-3}	1.20 ± 0.03[a]	2.74 ± 0.15[a]	8.47 ± 0.71[a]	5.65 ± 0.21[a]

Values represent the mean ± S.E. of 6–15 observations. [a] Indicates a value significantly different from that obtained in the absence of drug ($p < 0.05$).

of media and tissues was determined by liquid scintillation spectrometry as described previously[6]. The accumulation of [^{3}H]-metaraminol was expressed as a distribution ratio, calculated from (dpm/g tissue)/(dpm/ml incubation medium).

Chromatographically pure (±)-7-[^{3}H]-metaraminol with a specific activity of 8.23 Ci/mmole was obtained from the New England Nuclear Corporation. The following drugs (cocaine hydrochloride; procaine hydrochloride; lidocaine hydrochloride; and prilocaine hydrochloride) were present in the media at concentrations from 1×10^{-6} M to 1×10^{-3} M throughout both the preincubation and the subsequent incubation with [^{3}H]-metaraminol.

Results. The effect of the agents on the accumulation of [^{3}H]-metaraminol is shown in the Table. For comparative purposes, the effect of cocaine was also examined. As reported previously[1,7], cocaine was a very potent inhibitor of amine accumulation, 50% inhibition being produced by less than 1×10^{-6} M. By contrast, procaine, lidocaine and prilocaine were considerably less potent inhibitors of [^{3}H]-metaraminol accumulation, 50% inhibition being only produced by about 1×10^{-4} M or more.

Discussion. Procaine markedly slowed the relaxation after oil immersion of rabbit aortic strips contracted by either phenylephrine or noradrenaline[4]. It did not, however, potentiate responses to sympathomimetic amines and, at the highest concentrations used, caused a slight decrease in the contraction amplitude[4,5]. Brief exposure to prilocaine caused potentiation of rabbit aortic strips to adrenaline[5]. Other local anaesthetics (e.g. α-cocaine, tetracaine) have been reported to have little or no effect on the uptake of and responsiveness to nordrenaline[7,8].

The mechanism by which tetracaine and procaine block adrenergic transmission has recently been examined in detail[9]. Nearly identical concentrations of tetracaine inhibited both frog sciatic nerve conduction and adrenergic transmission to rabbit heart. Similarly, procaine inhibited both processes but was considerably less potent than tetracaine. In lower concentrations, procaine, but not tetracaine, potentiated and prolonged the chromotropic response to adrenergic nerve stimulation and increased the nordrenaline output resulting from such stimulation. Both agents also inhibited noradrenaline transport into adrenergic nerves, the agents being equipotent in this regard. These workers concluded that the ability of a local anaesthetic to potentiate adrenergic transmission depends on its potency to block nerve conduction on one hand and uptake of amine on the other. Local anaesthetics have also been shown to depress the contractile responses of certain smooth muscles to agonists, possibly by an action on Ca^{++} fluxes, but also may themselves cause contractures[10].

It is clear that a number of local anaesthetics, in addition to cocaine, inhibit the transport of noradrenaline into adrenergic nerves. Whether this inhibition results in potentiation of responses to exogenously administered or endogenously released noradrenaline, will be determined by the other effects of these agents on nerve conduction and on muscle excitability and contractility.

Zusammenfassung. Es wurde die Wirkung von Lokalanästhetika auf die Anhäufung von [^{3}H]-Metaraminol im Vorhofmuskel und Vas deferens des Kaninchens untersucht. Die von Kokain hervorgerufene Hemmung der [^{3}H]-Metaraminol-Akkumulation ist mindestens hundertmal stärker als diejenige nach Procain, Prilocain und Lidocain.

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