The effect of imipramine, cocaine and neostigmine on the hyperglycaemic response to noradrenaline and adrenaline

SIR,—There are reports of an increased glycogenolytic action of adrenaline and noradrenaline in animals treated with cocaine (Schmidt & Späth, 1963; Hardman & Mayer, 1965). We could find no data about such an effect for imipramine. We have compared the activity of some drugs causing hypersensitivity to catecholamines on the hyperglycaemia caused by the catecholamines.

Rabbits of either sex, 2–3 kg weight, were fasted for 24 hr. The concentration of glucose in blood withdrawn from the ear vein was measured at the time of administering a catecholamine subcutaneously, and at 1, 2 and 3 hr afterwards. One week later the experiment was repeated but imipramine, cocaine, or atropine and neostigmine were given beforehand (see Tables for time, route and dosage). Blood glucose was estimated by the method of Hagedorn & Jensen (1923).

The adrenergic sensitizers were used in doses which caused clear-cut enhancement of the blood pressure responses to catecholamines. At these doses they did not alter the resting blood glucose level. Atropine (3 mg/kg s.c.) was also without any effect in this respect.

Cocaine, in doses of either 2 or 5 mg/kg, did not influence the effect of noradrenaline. In a dose of 5 mg/kg intravenously, it enhanced the response to adrenaline. Similarly, imipramine (2 or 5 mg/kg) did not alter the sensitivity to noradrenaline, while in a dose of 5 mg/kg it enhanced the sensitivity of the animals to adrenaline-induced hyperglycaemia.

TABLE 1. THE EFFECT OF NEOSTIGMINE ON THE BLOOD GLUCOSE CHANGES CAUSED BY NORADRENALINE

Treatments*	No. of rabbits	Blood glucose level (mg/100ml) after, hr			
		0	1	2	3
Noradrenaline 500 μg/kg + atropine 3 mg/kg s.c.	5	87·0 ± 4·2	184·8 ± 17·1	225·2 ± 10·5	203·6 ± 24·0
Noradrenaline 500 μg/kg + atropine 3 mg/kg s.c. + neostigmine 10 μg/kg i.v.	5	89·0 ± 11·6	233·2† ± 12·3	234·0 ± 5·2	234·8 ± 27·3

* Neostigmine given 1 hr and atropine 3 hr before noradrenaline.
† $P < 0.05$.

TABLE 2. THE EFFECT OF IMIPRAMINE, COCAINE AND NEOSTIGMINE ON THE BLOOD GLUCOSE CHANGES CAUSED BY ADRENALINE

Treatments*	No. of rabbits	Blood glucose level (mg/100ml) after, hr				Significance to control
		0	1	2	3	
Adrenaline 200 μg/kg s.c.	45	85·73±2·0	200·38± 6·3	235·91± 7·1	222·2 ± 6·6	
Adrenaline 200 μg/kg + imipramine 5 mg/kg i.v.	5	98·6 ±4·1	232·8†±14·0	240·0 ±21·0	241·6 ±22·9	†P<0·01
Adrenaline 200 μg/kg + cocaine 5 mg/kg i.v. ..	10	114·0 ±3·5	262·6†± 7·8	259·3 ± 8·1	208·9 ±25·9	†P<0·001
Adrenaline 200 μg/kg + atropine 3 mg/kg s.c. ..	10	101·5 ±4·3	196·4 ± 9·2	232·8 ±15·3	220·0 ±10·4	
Adrenaline 200 μg/kg + atropine 3 mg/kg s.c. + neostigmine 10 μg/kg i.v.	10	104·0 ±5·0	243·0†±13·8	275·6 ±15·7	254·8†± 9·4	†P<0·02

* See the footnote to Table 1.

The animals given neostigmine showed a definite hypersensitivity. The hyperglycaemia seen 1 hr after 500 μg/kg noradrenaline was significantly greater than the control, so too were the differences between the control and neostigmine-treated groups during the 3 hr period of the experiment when adrenaline was administered in a dose of 200 μg/kg (Tables 1 and 2).

On the basis of our results cocaine and imipramine are relatively less effective than neostigmine in enhancing the hyperglycaemic action of catecholamines. It is possible that enzymes described as destroying tropine derivatives in rabbits (Werner, 1965) could be responsible for the weak activity of cocaine.

It has been shown that neostigmine potentiates the blood pressure response to noradrenaline (Fekete, 1966). The present experiments show that this effect of neostigmine can also be demonstrated on glucose mobilization caused by catecholamines in atropinized animals.

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The origin of epileptiform seizures caused by oil of *Artemisia caerulescens* L. (Correction)

SIR,—An error has arisen in the Letter to the Editor on the above topic (Srebočan & Stern, 1968). In all instances γ-aminobenzoic acid should be replaced by γ-aminobutyric acid.

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Reference

Srebočan, S. & Stern, P. (1968). *J. Pharm. Pharmac.*, **20**, 160–161.