CARDIOVASCULAR AND SMOOTH MUSCLE ACTIONS OF SOME INDOLEALKYLAMINES

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Summary: The effects of three indole derivatives, U-7582, U-5092 and U-13625 were compared with those of 5-HT on the cardiovascular system and smooth muscle. Biphasic pressor responses were observed with 5-HT and U-7582 in normotensive dogs. The three indole derivatives and 5-HT potentiated the pressor response to adrenaline, reversed that to amphetamine but had no effect on that to carotid occlusion and noradrenaline. The depressor response to dopamine was potentiated by 5-HT.

5-HT and U-7582 decreased ventricular contractility in anaesthetised dogs. Both increased the amplitude of contraction and coronary flow in the isolated rabbit heart. The stimulant action of 5-HT on rat fundus was potentiated by U-7582 and U-5092. 5-HT potentiated and U-5092 and U-13625 blocked the responses of isolated rabbit ileum to acetylcholine.

Key words : 5-Hydroxytryptamine, adrenaline dopamine, amphetamine, biphasic pressor action, rat fundus, rabbit ileum

INTRODUCTION

The effects of a well known indole derivative, 5-hydroxytryptamine (5-HT) on the cardiovascular system are quite complex and ill understood (1, 8, 16, 20). However, the stimulant actions of 5-HT on a variety of smooth muscles are well recognized (4, 9, 12). Various explanations have been given for the agonistic action of 5-HT on smooth muscle (2, 11, 13).

In view of the importance of indole nucleus, certain aspects of the pharmacological profiles of three indole derivatives were examined on the cardiovascular and smooth muscle with particular attention to their relative potency and over toxicity.

MATERIALS AND METHODS

The structural formulae of the three indole derivatives and of 5-HT are given in Fig. 1. All the compunds were soluble in distilled water except U-13625 which dissolved in 1 part of propylene glycol and 2 parts of distilled water on heating.

STRUCTURAL FORMULAE OF THE FOUR INDOLE DERIVATIVES

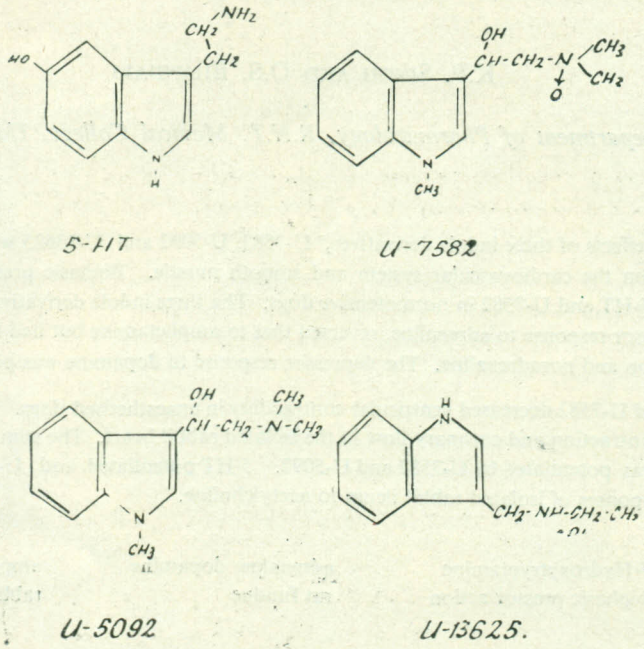

Fig. 1: Structural formulae of the indole derivatives:

(i) 5-HT.
(ii) 3-Indole methanol, alpha, (dimethylaminomethyl)-1-methyl, N-oxide; U-7582.
(iii) 3-Indole methanol, alpha-(dimethylaminomethyl)-1-methyl; U-5092.
(iv) 2-[(Indole-3-ylmethyl) amino]—ethanol); U-13625.

Cardiovascular system:

Intact dogs: Mongrel dogs of both sexes (10 to 20 *kg*) anaesthetised with pentobarbitone sodium (30 *mg/kg* iv) were used. Carotid blood pressure was recorded with mercurry manometer. Ventricular contractility was recorded according to the method of Boxill (3). The chest was opened by a midline thoracotomy, pericardium was cut and sutured to the chest wall. An entomological hook was hooked through maximally contracting portion of the ventricle and contractions were recorded on kymograph. Right atrial pressure was measured in an open chest dog by means of Statham pressure transducer (Model P 23) connected to an electromanometer (Hellige; Model Ma—88 G+K). The transducer was introduced directly by cutting the atrium and then tying a suture around the transducer needle. Electrocardiographic records were obtained on convention bipolar lead II, at fast speed (50 mm/sec) with Gallileo double channel ECG machine (Model R 8_{ss}). Drug effects were studied on blood

pressure responses to carotid occlusion (30 sec), adrenaline (5 $\mu g/kg$) noradrenaline (5 $\mu g/kg$), amphetamine (1 mg/kg) and dopamine (10 $\mu g/kg$). All drugs were administered through a cannulated femoral vein. The doses of drugs refer to their bases.

Rabbit heart perfusion: Modified Langendorff's method as described by Burn (5) was employed. Ascending doses of drugs were injected into the side arm keeping the volume of each injection constant (0.25 *ml*). The effects on heart rate, force of contraction and coronary flow were noted.

Smooth muscles :

Isolated pieces of *rabbit ileum* were set up according to Burn (6) and isolated *rat fundus* preparations were set up according to Vane (22).

Toxicity :

Acute intraperitoneal LD_{50} was determined in male albino mice (15-20 *g* weight) according to the method of Karber as described by Turner (21).

RESULTS

Cardiovascular system:

The typical effects of drugs on blood pressure, ventricular contractility, atrial pressure and electrocardiogram are shown in Fig. 2.

The three test indole derivatives were used in doses of 1,3 and 5 mg/kg and 5-HT was used in doses of 0.05 and 0.1 mg/kg. Biphasic effects *i.e.* rise followed by a fall in blood pressure was observed with 5-HT (0.1 mg/kg) and U-7582 (5 mg/kg). 0.05 mg/kg of 5-HT produced only a sharp fall in blood pressure which was prolonged (Fig. 2). On the contrary U-5092 and U-13625 always produced a dose dependent fall in blood pressure. Ventricular contractility was decreased by 5-HT and U-7582, whereas U-5092 and U-13625 increased it. Atrial pressure was slightly raised with U-5092 only. 5-HT slightly increased heart rate and had no appreciable effect on other components of the ECG. U-5092 and U-13625 only with the higher dose (5 mg/kg) produced bradycardia and prolonged P-R and Q-T intervals.

The effects of drugs on pressor responses to various procedures are presented in Table I. 5-HT (0.1 mg/kg) had no significant effect on pressor responses to carotid occlusion but potentiated those to adrenaline and decreased those to amphetamine. The depressor response to dopamine was significantly potentiated. The only significant effect with U-7582 (5 mg/kg) was the potentiation of pressor response to adrenaline. U-5092 (5 mg/kg) potentiated the pressor response to adrenaline, and reversed that to amphetamine. U-13625 decreased the response to pressor adrenaline, and reversed that to amphetamine.

Rabbit heart: The results are summarised in Table II. 5-HT and U-7582 increased the amplitude of contractions and coronary flow. 5-HT increased the heart rate but U-7582

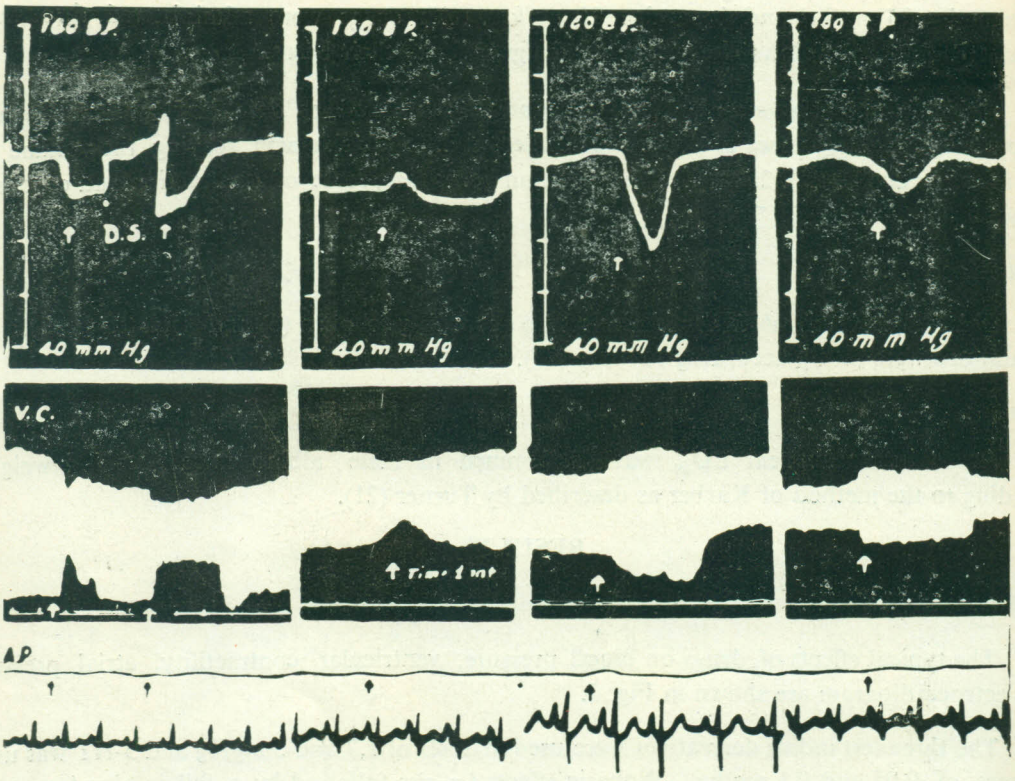

Fig. 2: Effect of drugs on dog B. P. ventricular contractility (V. C.) atrial pressure (A. P.) and electrocardiogram (ECG). Arrow heads indicate administration of 5-HT (0.05 and 0.1 *mg*/kg), U-7582 (5 *mg*/*kg*), U-5092 (5 *mg*/*kg*) and U-13625 (5 *mg*/*kg*)in the pannels from left to right respectively. D. S. indicates the stoppage of drum.

decreased it. On the other hand, U-5092 and U-13625 decreased the amplitude of contractions and coronary flow and slightly increased the heart rate at 200 μg dose.

Smooth Muscles:

Rat fundus: In five experiments the stimulating action of 5-HT (10 *ng*/*ml*) was potentiated by U-7582 and U-5092 (40 μg/*ml*). U-13625 in the same concentration exerted an antagonistic effect (Fig. 3).

Isolated rabbit ileum: In six experments the compounds in final concentrations of (1:25,000) and (1:12,500) elicited two types of effects on normal intestinal movements. 5-HT contracted the muscle, while U-5092 and U-13625 relaxed it. U-7582 on the other hand had no effect. Typical effects (1:12,500) on acetylocholine induced contractions are illustrated in Fig. 4. 5-HT potentiated, U-5092 and U-13625 antagonised while U-7582 had no effect on acetylcho-

TABLE I: Effect of indole compounds on dog blood pressure responses to carotid occlusion, noradrenaline, amphetamine and dopamine. Data of mean blood pressure responses (mm Hg ± S.E.) from 5 experiments in each category is given.

Compound and dosage	*Carotid occlusion (60 sec)*		*Adrenaline 5 μg/kg*		*Noradrenaline 5 μg/kg*		*Amphetamine 1 mg/kg*		*Dopamiine 10 μg/kg*	
	before	*after*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*
5-HT 0.1 *mg/kg*	25.6 ± 0.94	25.6 ± 0.94	44.0 ± 2.45	55.6 ± 2.48(a)	70.0 ± 5.48	70.0 ± 5.48	38.4 ± 1.12	24.8 ± 1.49	—26.0 ± 0.89	—37.8 ± 1.28(b)
U-7582 5 *mg/kg*	19.6 ± 1.94	18.4 ± 1.94	50.8 ± 1.20	61.4 ± 1.16(b)	43.6 ± 0.61	44.8 ± 0.47	39.8 ± 3.56	31.8 ± 3.98	—23.2 ± 0.48	—22.8 ± 0.48
U-5092 5 *mg/kg*	18.4 ± 0.74	19.2 ± 1.20	48.4 ± 2.77	60.6 ± 3.004(a)	72.4 ± 0.61	74.0 ± 0.502	37.2 ± 0.48	—32.0 ± 1.08(b)	—22.4 ± 1.83	—20.8 ± 1.96
U-13625 5 *mg/kg*	34.8 ± 0.93	34.0 ± 2.45	68.2 ± 0.91	50.4 ± 1.94(b)	69.2 ± 0.48	67.4 ± 0.86	36.4 ± 0.74	—25.2 ± 2.24(	—22.8 ± 1.35	—1.90 ± 1.00

Negative sign preceeding the response indicates fall in blood pressure. Absence of any sign preceeding the response indicates ries in blood pressure.

(a) indicates $P < 0.02$

(b) indicates $P < 0.001$

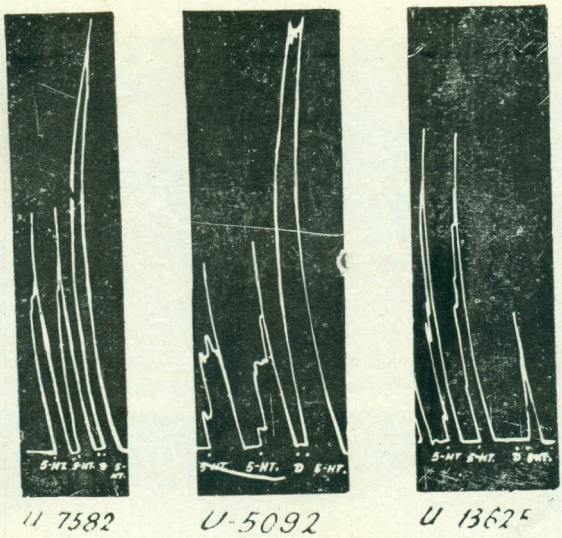

Fig. 3: Effect of compounds U-7582, U-5092 and U-13625 (40 *ug/ml* each) on 5-HT (10 *ng/ml*)-induced contractions of isolated rat fundus. D indicates addition of the coumpound.

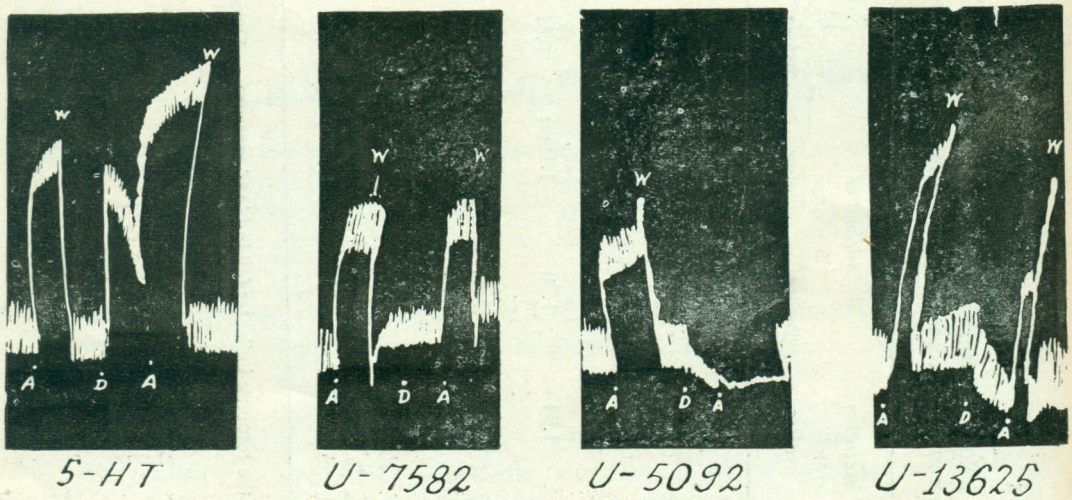

Fig. 4: Effect of 5-HT and compounds U-7482, U-5092 and U-13625 (1:12,500 of each) on acetylcholine-induced contractions of isolated rabbit ileum. A indicates acetylcholine (0,25 $\mu g/ml$). D indicates the addition of the indole compound to the bath. W. indicates wash.

line-induced contractions. The data on acute intraperitoneal LD_{50} in mice are summarised in Table III. U-7582 was the least toxic compound followed by U-5092, 5-HT and U-13625 in that order.

TABLE II: Effects of indole compounds on the isolated rabit heart.

Compound	*Dose (μg)*	*No. of observations*	*Average percentage change*		
			Amplitude	*Heart rate*	*Coronary flow*
5-HT	50.0	5	+20.8	+22.0	+9.7
	100.0	5	+26.0	+24.0	+11.3
	200.0	5	+34.0	+30.0	+16.2
U-7582	50.0	5	+ 5.5	0.0	0.0
	100.0	5	+10.0	—2.0	±3.0
	200.0	5	+18.2	—5.6	+4.4
U-5092	50.0	5	—5.0	0.0	0.0
	100.0	5	—8.5	0.0	—1.5
	200.0	5	—11.1	+ 4.2	—2.0
U-13625	50.0	5	—5.0	0.0	—1.7
	100.0	5	—9.8	0.0	—2.0
	200.0	5	—22.0	+2.1	—5.0

+ indicates increase. — indicates decrease.

TABLE III: LD_{50} of the indole compounds in albino mice.

Compound	LD_{50} *(mg/kg)*
5-HT	160.00
U-7582	1000.00
U-5092	744.00
U-13625	133.00

DISCUSSION

The changes in circulation following injection of 5-HT elicits biphasic effects on blood pressure (16, 17). U-7582 like 5-HT exerted biphasic effects on blood pressure. On the contrary, U-5092 and U-13625 induced only hypotensive effect and an increase in ventricular contractility.

5-HT produced coronary vasodilation which was dose related. The positive inotropic and chronotropic effects observed, seem to mask the direct effects on coronary flow in high doses. Thus our findings are supported by literature reports (14, 18). U-7582 like 5-HT increased coronary flow and myocardial contractility but decreased heart rate. However, 5-HT increased the heart rate. U-5092 and U-13625 were found to have opposite effects.

The effects of drugs on responses of B.P. to carotid occlusion and injection of adrenaline, noradrenaline, amphetamine and dopamine revealed some interesting features. 5-HT potentiated the asopressor effect of adrenaline (Table I). This could be explained on the basis of release of adrenaline from adrenal medulla by 5-HT which might supplement the effect of injected adrenaline (10). Had this rise been due to its direct vasoconstrictor effect, it should have modified the effect of noradrenaline as well. The inability of all the compounds of modify the noradrenaline response would indicate that they do not exert any excitatory or inhibitory effect on alpha-adrenergic receptors in the vessel wall; this is substantiated by their failure to increase or decrease the pressor responses to carotid occlusion thought to be mediated by the release of catecholamines (23). The vasopressor effects of indirectly acting amines like tyramine and amphetamine are generally attributed to their capacity to release noradrenaline from tissue stores (7). 5-HT decreased the vasopressor effect of amphetamine whereas U-5092 and U-13625 reversed it. Possibly stimulation of tryptamine receptors (23) in the myocardium leading to reflex vasodilatation may be responsible for this effect. This needs further investigation.

Nelson (15) reported that blood pressure response of anaesthetised dogs to dopamine is largely the result of a balance between increased resistance in the femoral and carotid beds and a decreased resistance in the coeliac, renal and mesentric beds, the latter being the most important with smaller doses of dopamine; the balance usually favours a fall in systemic pressure. With larger doses of dopamine the constrictor effect compensates more than the dilator effect and systemic pressor response results. In our study, the more commonly observed effect was a depressor one. In all the experiments, 5-HT increased the vasodepressor effect of dopamine which is in accord with the observation of others (19).

Because of the selective sensitivity of 5-HT of rat fundus, rat uterus and bronchi (22), it is believed that rat fundus also contains D-type of 5-HT receptors (23).

In our experiments, U-7582 potentiated the agonistic action 5-HT on rat fundus which would possibly suggest that these compounds are acting like 5-HT on D-type of receptors in the rat fundus. However, they did not show any agonistic activity of their own. Therefore, other possibilities for their potentiation like inhibition of uptake or action on other receptors (silent or spare) cannot be ruled out. On the other hand, U-13625 inhibited the 5-HT induced contraction of the rat fundus strip. This effect may be considered an example of cross tachyphylaxis, in which occupation by U-13625 of the receptors sensitive to 5-HT could explain the antagonism observed. Faddum (12) suggested the existance of two types of receptors in the intestine; D-receptors sensitive to 5-HT and blocked by phenoxybenzamine and lysergic acid diethylamide and M-receptors blocked by atropine, morphine and cocaine. M-receptors are blocked by drugs which act on nervous tissue through their precise site of action is unknown. The anti-acetylcholine effect of U-5092 and U-13625 on the rabbit ileum could be explained on the basis of their action on the M-receptors which are blocked by anticholinergic drug atropine. 5-HT-induced potentiation of accetylcholine response of rabbit ileum could be the result of different sites of agonistic actions of 5-HT and acetylcholine in

the same tissue. According to Gaddum's (12) concept of dual receptors in the intestine, 5-HT could act on D-receptors and acetylcholine on M-receptors. Thus the agonistic action of acetylcholine might be potentiated by 5-HT.

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