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ACTION OF DEXAMPHETAMINE ON 5-HYDROXYTRYPTAMINE RECEPTORS

BY

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Dexamphetamine contracted isolated preparations of rat stomach, dog retractor penis, rabbit aorta, rabbit uterus and all sections of guinea-pig ileum. Adrenaline inhibited rat stomach and all but the terminal 10 cm of guinea-pig ileum, but contracted dog retractor penis, rabbit aorta, rabbit uterus and the terminal portion of the guinea-pig ileum. 5-Hydroxytryptamine contracted all five preparations. Responses to dexamphetamine and 5-hydroxytryptamine were not blocked in preparations protected by a high concentration of either drug during exposure to phenoxybenzamine in a dose which usually caused block. Responses to dexamphetamine and 5-hydroxytryptamine were blocked in preparations protected by adrenaline. Responses to dexamphetamine in dog retractor penis, rabbit aorta and rabbit uterus were not reduced in preparations from animals treated with reserpine or after cocaine, indicating that the contraction is not mediated by released noradrenaline. It is concluded that dexamphetamine acts directly on 5-hydroxytryptamine receptors in these smooth muscles and therefore cannot be regarded as a true sympathomimetic amine.

Amphetamine has been generally regarded as a sympathomimetic drug since its actions were first described by Piness, Miller & Alles (1930) and by Hartung & Munch (1931) and compared with those of adrenaline (Alles, 1933). However, Vane (1960) showed that, although adrenaline relaxed rat stomach and rabbit duodenum, amphetamine caused contraction by acting on 5-hydroxytryptamine receptors. He found that antagonists such as bromolysergic acid diethylamide and phenoxybenzamine reduced equally well the actions of 5-hydroxytryptamine and of amphetamine on isolated strips of rat stomach. An action on the same receptors was likely because desensitization to the actions of both 5-hydroxytryptamine and amphetamine followed prolonged exposure of the preparation to either of these drugs. Vane believed that amphetamine acted on the 5-hydroxytryptamine receptors of guinea-pig ileum also, but found this more difficult to establish on the sections of guinea-pig ileum he used because of the inherent difficulty of distinguishing between actions on 5-hydroxytryptamine receptors and on adrenaline receptors when both drugs caused contraction. This difficulty can be overcome in most parts of the guinea-pig ileum, for adrenaline is inhibitory in all but the terminal 10 cm where its action is usually excitatory (Munro, 1952). However, a more decisive technique is required to determine the receptors on which amphetamine acts in tissues where 5-hydroxytryptamine, amphetamine and adrenaline each cause contraction. Either 5-hydroxytryptamine or adrenaline

receptors can be selectively protected against block by dibenamine (Furchgott, 1954) or by phenoxybenzamine (Innes, 1962a). This receptor protection technique was applied in the experiments described here to a variety of smooth muscle tissues which contract in response to amphetamine. Adrenaline and 5-hydroxytryptamine have opposing actions in some of these muscles; in others both drugs cause contraction. The experiments were done with dexamphetamine since it is the more active of the isomers forming (±)-amphetamine. Some of the results were reported briefly at the 22nd International Physiological Congress (Innes, 1962b).

METHODS

Segments of guinea-pig ileum and rabbit uterus and strips of rat stomach, rabbit aorta and dog retractor penis were suspended in Krebs-Henseleit solution bubbled with 95% oxygen and 5% carbon dioxide. Dog retractor penis preparations were kept at 26° C to reduce spontaneous activity. Other preparations were kept at 38° C. Isotonic contractions at 1 g tension and at 5.5-times amplification were recorded on a kymograph. Receptor protection experiments were done as described earlier (Innes, 1962c). Preliminary experiments established for each kind of tissue the dose of phenoxybenzamine (Dibenzyline) needed to inhibit the excitatory actions of dexamphetamine, 5-hydroxytryptamine, adrenaline, acetylcholine and histamine when the organ was exposed to the antagonist for 5 min. Two sections of the same organ were used in each receptor protection experiment. One section, which was used as control, was exposed to the dose of phenoxybenzamine with no agonist present and therefore without receptor protection. The second section was exposed for 5 min to the blocking concentration of phenoxybenzamine only in the presence of a high concentration of one of the agonists which had been added to the bath 5 min earlier. The drugs were then washed out together. Protected preparations respond subsequently to compounds which act on the same receptors as the protecting agonist but do not respond to the other agonists whose actions are blocked by phenoxybenzamine. Responses to dexamphetamine, 5-hydroxytryptamine and, where applicable, adrenaline were tested before and 90 min after exposure to phenoxybenzamine, when the intensity of block had become stable. The drug concentrations used for each tissue are given in Table 1. The effect of phenoxybenzamine is shown by expressing the response to a single dose of agonist after phenoxybenzamine as a percentage of the control response obtained before adding the antagonist. The dose of agonist was always submaximal and usually one which caused a contraction of 20 to 70 mm on the kymograph before phenoxybenzamine.

Drugs. 5-Hydroxytryptamine creatinine sulphate, (+)-amphetamine (dexamphetamine) sulphate, (−)-adrenaline bitartrate, histamine diphosphate and acetylcholine chloride were added in amounts to give the indicated final concentrations of free bases. The drugs were added at 10 min intervals for guinea-pig ileum and at 15 min intervals for all other preparations. Each drug remained in the bath until the full contraction for that dose was attained, usually less than 2 min after the drug was added. The bath was then emptied and the fluid replaced. The fluid was exchanged at 5 min intervals between drug additions.

Other drugs used were phenoxybenzamine hydrochloride (Dibenzyline), morphine sulphate and reserpine phosphate (lyophilized, Serpasil). Phenoxybenzamine hydrochloride was kept as a 2.5% stock solution in acidified propylene glycol and a suitable dilution in 0.9% saline was made up freshly on the morning of use. Reserpine (1 mg/kg) was injected intraperitoneally 24 hr before the experiment in animals where noradrenaline stores were to be depleted.

RESULTS

Receptor protection against phenoxybenzamine block in rat stomach

Vane (1960) showed that rat stomach superfused with blood relaxed in response to dexamphetamine, while contraction occurred in preparations suspended in Krebs

TABLE 1

CONCENTRATIONS (G/ML.) OF DRUGS USED IN PROTECTION EXPERIMENTS

* In experiments with morphine (10^{-7} g/ml.) present throughout

	Rat stomach	Guinea-pig ileum	Rabbit uterus	Rabbit aorta	Dog retractor penis
Protecting dose of					
Adrenaline		10^{-4}	10^{-4}	10^{-4}	10^{-4}
Dexamphetamine	10^{-3}	10^{-3}	10^{-4} or 10^{-3}	10^{-3}	$2{\cdot}5\times10^{-3}$
5-Hydroxytryptamine	10^{-4}	10^{-3}	10^{-4} or 10^{-3}	10^{-3}	$2{\cdot}5\times10^{-3}$
Blocking dose of					
Phenoxybenzamine	10^{-5}	10^{-6}	5×10^{-9}	5×10^{-8}	10^{-7}
Test dose of					
Adrenaline		5×10^{-7}	10^{-7} or 10^{-6}	5×10^{-8}	$2{\cdot}5$ or 5×10^{-8}
Dexamphetamine	10^{-8}	10^{-6}	10^{-6} or 10^{-5}	10^{-3}	1 or $2{\cdot}5\times10^{-5}$
5-Hydroxytryptamine	5×10^{-9}	10^{-8} or $*5\times10^{-8}$	10^{-7} or 10^{-6}	5×10^{-8}	$2{\cdot}5$ or 5×10^{-8}

solution. The inhibitory effects of dexamphetamine were attributed to release of noradrenaline which masked the direct excitatory action of dexamphetamine. The direct excitatory action of dexamphetamine uncomplicated by release of noradrenaline was therefore the action observed in the present study with rat stomach strips suspended in Krebs solution.

Eight experiments were done with paired strips of rat stomach. 5-Hydroxytryptamine and dexamphetamine were used in four experiments each to protect against block by phenoxybenzamine. The results are shown in Table 2. The actions both

TABLE 2

EFFECT OF PROTECTION OF RECEPTORS AGAINST BLOCK BY PHENOXYBENZAMINE IN RAT STOMACH

During exposure to phenoxybenzamine (10^{-5} g/ml.) receptors were protected in one of two strips from the same stomach. Each line represents a single experiment with paired strips. Contractions after phenoxybenzamine are expressed as a percentage of the contraction before phenoxybenzamine. Drug concentrations are in g/ml.

	Residual response to agonist after phenoxybenzamine (% of control)			
	5-Hydroxytryptamine (5×10^{-9})		Dexamphetamine (10^{-8})	
	Unprotected strip	Protected strip	Unprotected strip	Protected strip
Protection with 5-hydroxytryptamine (10^{-8})	22	60	20	60
	30	40	0	25
	28	41	0	33
	0	35	0	40
Protection with dexamphetamine (10^{-4})	38	58	0	61
	29	64	0	29
	17	48	0	55
	7	84	0	60

of 5-hydroxytryptamine and of dexamphetamine were less effectively blocked in strips protected with either drug than in control strips without protection. The responses to acetylcholine (10^{-8} g/ml.) also were tested to ensure that the protection from 5-hydroxytryptamine and dexamphetamine was not unspecific. Contractions from acetylcholine were equally depressed in control and protected strips.

The cross-protection between 5-hydroxytryptamine and dexampetamine indicates that these drugs react with the same receptor sites.

Receptor protection against phenoxybenzamine block in guinea-pig ileum

The effect of receptor protection against phenoxybenzamine (10^{-6} g/ml.) was tested in eleven experiments on segments of guinea-pig ileum. Five were protected with 5-hydroxytryptamine, four with dexamphetamine and two with adrenaline (Table 3). Four of these experiments were done on segments taken from the aboral end of the ileum within 6 cm of the caecum; these segments contracted in response to adrenaline. The results were similar to those from segments from other regions of the ileum where adrenaline had an inhibitory action (Table 3). Responses to

TABLE 3

EFFECT OF PROTECTION OF RECEPTORS AGAINST BLOCK BY PHENOXYBENZAMINE IN GUINEA-PIG ILEUM

During exposure to phenoxybenzamine (10^{-6} g/ml.) receptors were protected in one of two segments from the same ileum. Contractions after phenoxybenzamine are expressed as a percentage of the contraction before phenoxybenzamine. Each line represents a single experiment with paired segments. Drug concentrations are in g/ml. * Experiments with segments from the terminal 6 cm of the ileum. † Experiments with morphine (10^{-7}) present throughout. The test concentration of 5-hydroxytryptamine was 5×10^{-8}

	Residual response of agonist after phenoxybenzamine (% of control)			
	5-Hydroxytryptamine (10^{-8})		Dexamphetamine (10^{-6})	
Protecting drug	Unprotected	Protected	Unprotected	Protected
5-Hydroxytryptamine (10^{-3})	8	67	0	53
	7	29	4	26
	* 0	20	11	35
	* 12	28	25	100
	† 15	48	17	75
Dexamphetamine (10^{-3})	19	100	4	60
	17	75	12	75
	* 0	60	0	30
	† 6	100	16	100
Adrenaline (10^{-4})	20	28	40	40
	* 43	31	50	22

5-hydroxytryptamine and dexamphetamine were greater in preparations which had been protected by either 5-hydroxytryptamine or dexamphetamine than in the corresponding unprotected control preparations. Adrenaline gave no protection towards 5-hydroxytryptamine or dexamphetamine. Block of the actions of acetylcholine and histamine by phenoxybenzamine was not reduced by protection with 5-hydroxytryptamine, dexamphetamine or adrenaline. The actions of dexamphetamine and 5-hydroxytryptamine were not preserved in four preparations in which the histamine or acetylcholine receptors were successfully protected with either histamine or acetylcholine. These experiments indicate that dexamphetamine and 5-hydroxytryptamine act on the same receptors in guinea-pig ileum.

Two protection experiments were done with morphine (10^{-7} g/ml.) present in the fluid bathing both control and test preparations throughout the entire experiment

in order to inactivate the "M" type of 5-hydroxytryptamine receptor (Gaddum & Picarelli, 1957). As expected, morphine reduced the responses to 5-hydroxytryptamine, and the test dose was accordingly increased from 1 to 5×10^{-8} g/ml. However, the protection experiments gave similar results whether morphine was present or not (Table 3). The effects of morphine on the responses of twelve preparations to dexamphetamine varied. The response to dexamphetamine was unchanged in eight preparations while the response to 5-hydroxytryptamine was reduced by 50 to 90%. In four preparations the response to dexamphetamine was reduced by 30 to 40% while the response to 5-hydroxytryptamine was reduced by 70 to 80%.

Receptor protection against phenoxybenzamine block in rabbit uterus

Table 4 shows the results of twelve receptor protection experiments with paired segments of rabbit uterus. Four were protected with adrenaline, four with 5-hydroxytryptamine and four with dexamphetamine. There was no cross-protection against phenoxybenzamine block between adrenaline and 5-hydroxytryptamine, showing that these agonists do not act on the same receptors. The results indicate that dexamphetamine acts on 5-hydroxytryptamine receptors, since preparations protected by 5-hydroxytryptamine showed greater responses to dexamphetamine than unprotected preparations. Responses to 5-hydroxytryptamine were much greater in preparations protected by dexamphetamine than in unprotected preparations. Adrenaline did not protect the dexamphetamine action in three of four experiments. In the fourth experiment the residual response to dexamphetamine after phenoxybenzamine was a contraction of only 3 mm on the kymograph, but this represented 33% of the control, since the response to dexamphetamine before phenoxybenzamine

TABLE 4

EFFECT OF PROTECTION OF RECEPTORS AGAINST BLOCK BY PHENOXYBENZAMINE IN RABBIT UTERUS

During exposure to phenoxybenzamine (5×10^{-9} g/ml.) receptors were protected in one of two preparations from the same uterus. Each line represents a single experiment with paired preparations. Contractions after phenoxybenzamine are expressed as a percentage of the contraction before phenoxybenzamine. Drug concentrations are in g/ml.

	Residual response to agonist after phenoxybenzamine (% of control)					
	Adrenaline (10^{-7} or 10^{-6})		5-Hydroxytryptamine (1 or 5×10^{-6})		Dexamphetamine (10^{-6} or 10^{-5})	
Protecting drug	Unprotected	Protected	Unprotected	Protected	Unprotected	Protected
Adrenaline (10^{-4})	36	80	0	0	0	0
	0	24	0	0	0	33
	0	35	8	0	25	29
	0	27	0	0	0	0
5-Hydroxytryptamine (10^{-4} or 10^{-3})	0	0	5	65	14	56
	0	0	0	43	0	67
	0	3	8	27	15	28
	0	0	0	29	0	29
Dexamphetamine (10^{-4} or 10^{-3})	0	0	0	60	0	38
	9	10	10	58	25	47
	0	9	5	29	15	95
	0	10	0	40	0	100

was unusually small. Responses to adrenaline were the same in protected and unprotected segments of uterus in two of the four experiments with protection by dexamphetamine. In the other two experiments the unprotected preparations showed small residual responses representing 9 and 10% of the control responses. This is a difference within the range of biological variation between preparations.

Receptor protection against phenoxybenzamine block in rabbit aorta and in dog retractor penis

Simpler protection experiments could be done with rabbit aorta and dog retractor penis preparations since four strips could be prepared for each experiment from a single animal. Three preparations were protected, one each by adrenaline, 5-hydroxytryptamine and dexamphetamine; the fourth preparation was the unprotected control. The results are given in Tables 5 and 6. The actions of both 5-hydroxytryptamine and dexamphetamine were preserved in both tissues by protection with either 5-hydroxytryptamine or dexamphetamine but not with adrenaline. Adrenaline action was preserved only by protection with adrenaline.

Action of dexamphetamine on dog retractor penis, rabbit aorta and rabbit uterus

Vane (1960) presented evidence that dexamphetamine released noradrenaline locally, which in turn caused relaxation of blood-bathed rat stomach. It was therefore necessary to find out if dexamphetamine owed a part of its excitatory action on the smooth muscles studied here to release of noradrenaline. Experiments of two kinds were done to test this possibility in dog retractor penis, rabbit aorta and rabbit uterus.

Preparations of these tissues were made from animals which had been depleted of noradrenaline by injection of reserpine (1 mg/kg) 24 hr before the experiment.

TABLE 5

EFFECT OF PROTECTION OF RECEPTORS AGAINST BLOCK BY PHENOXYBENZAMINE IN RABBIT AORTA STRIPS

During exposure to phenoxybenzamine (5×10^{-8} g/ml.) receptors are protected by adrenaline, 5-hydroxytryptamine or dexamphetamine in three of four strips from the same aorta. Contractions after phenoxybenzamine are expressed as a percentage of the contraction before phenoxybenzamine. Drug concentrations are in g/ml.

		Protecting agent			
Responses to	No. of experiment	None	Adrenaline (10^{-4})	5-Hydroxy-tryptamine (10^{-3})	Dex-amphetamine (10^{-3})
Adrenaline (5×10^{-8})	1	39	91	33	40
	2	0	26	0	0
	3	0	23	0	0
	4	10	37	12	15
5-Hydroxytrypt-amine (5×10^{-7})	1	27	28	56	62
	2	27	24	112	109
	3	14	4	57	56
	4	33	33	73	78
Dexamphetamine (10^{-3})	1	13	16	45	39
	2	8	3	100	90
	3	11	9	79	75
	4	25	10	58	74

TABLE 6

EFFECT OF PROTECTION OF RECEPTORS AGAINST BLOCK BY PHENOXYBENZAMINE IN DOG RETRACTOR PENIS

During exposure to phenoxybenzamine (10^{-7} g/ml.) receptors are protected by adrenaline, 5-hydroxytryptamine or dexamphetamine in three of four strips from the same retractor penis muscle. Contractions after phenoxybenzamine are expressed as a percentage of the contraction before phenoxybenzamine. Drug concentrations are in g/ml.

Responses to	No. of experiment	Protecting agent: None	Adrenaline (10^{-4})	5-Hydroxytryptamine ($2{\cdot}5\times10^{-3}$)	Dexamphetamine ($2{\cdot}5\times10^{-3}$)
Adrenaline ($2{\cdot}5$ or 5×10^{-8})	1	3	45	10	11
	2	6	28	0	14
	3	0	26	0	0
	4	0	55	0	3
5-Hydroxytryptamine (1 or $2{\cdot}5\times10^{-5}$)	1	0	0	67	38
	2	0	0	15	33
	3	0	0	50	55
	4	0	0	38	36
Dexamphetamine (1 or $2{\cdot}5\times10^{-5}$)	1	0	0	56	40
	2	0	0	32	55
	3	5	0	30	20
	4	6	0	59	40

Dexamphetamine was given in the same doses as had been used in similar preparations from normal animals. There was no appreciable difference in sensitivity to dexamphetamine between strips from normal and reserpine treated animals.

Cocaine depresses the action of amphetamine on some tissues. This effect is believed to be due to prevention of release of stored noradrenaline by amphetamine (Burn & Rand, 1958). Responses to dexamphetamine were therefore tested before and after cocaine (10^{-6} g/ml.). Cocaine did not reduce the responses to dexamphetamine in any of the three tissues.

DISCUSSION

The commonly held idea that dexamphetamine is a sympathomimetic drug acting on adrenaline receptors in the periphery appears to be no longer tenable. The results in all five types of preparation studied here indicate that adrenaline and 5-hydroxytryptamine act on different receptors and that dexamphetamine acts on the same receptors as 5-hydroxytryptamine. A high concentration of adrenaline protected adrenaline receptors against block by phenoxybenzamine in all preparations where adrenaline has an excitatory action; these protected preparations did not contract in response to dexamphetamine or 5-hydroxytryptamine. In contrast, either dexamphetamine or 5-hydroxytryptamine protected all preparations so that they subsequently contracted in response to both dexamphetamine and 5-hydroxytryptamine. The results therefore confirm the conclusion of Vane (1960) that dexamphetamine acts on the 5-hydroxytryptamine receptors of rat stomach and extend this conclusion to include guinea-pig ileum, dog retractor penis, rabbit aorta and rabbit uterus. It is possible that reaction with 5-hydroxytryptamine receptors may be the basis for a more exact classification of other smooth muscle stimulants which have previously been regarded as sympathomimetic amines.

The results from protection of rabbit uterus by adrenaline or dexamphetamine were not so clear cut as those from similar experiments in the other tissues. The possibility cannot be excluded that there may be in addition some cross-protection between adrenaline and dexamphetamine. This would indicate some reaction of dexamphetamine with adrenaline receptors in addition to the reaction with receptors for 5-hydroxytryptamine for which the evidence is much more striking.

Burn & Rand (1958) and Vane (1960) indicated that amphetamine and dexamphetamine may act in the whole animal by releasing stored noradrenaline locally within the tissues. This mechanism of action does not apply to isolated dog retractor penis, rabbit aorta or rabbit uterus, since respones to dexamphetamine were no less in preparations taken from animals depleted of noradrenaline by reserpine than in preparations from normal animals. Moreover, cocaine did not reduce responses of these tissues to dexamphetamine, although there is evidence that cocaine depresses the responses of a number of tissues to some sympathomimetic amines by preventing them from releasing noradrenaline (Burn & Rand, 1958 ; Lockett & Eakins, 1960).

The action of dexamphetamine on guinea-pig ileum is of special interest since this is the only organ where two kinds of receptor for 5-hydroxytryptamine have been demonstrated. Gaddum & Picarelli (1957) showed that 5-hydroxytryptamine "D" receptors were blocked by phenoxybenzamine while the "M" receptors were blocked by morphine. However, the high concentrations of phenoxybenzamine used in the present experiments completely abolished the action of 5-hydroxytryptamine in some instances and therefore blocked "M" as well as "D" receptors. Blocking "M" receptors with morphine appeared to have little effect on the responses of the ileum to dexamphetamine. The response to dexamphetamine was reduced in only one third of the experiments and in those experiments the response to 5-hydroxytryptamine was reduced less than in many experiments where dexamphetamine action was unchanged. Dexamphetamine therefore appears to act only on the "D" type of 5-hydroxytryptamine receptor of guinea-pig ileum.

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