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Different types of sympathomimetic α-receptors

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Sympathomimetic effects have been studied on the isolated vas deferens of the rat, in the isolated jejunum of the rabbit and on the cardiovascular system of the cat. (−)-Noradrenaline (1-*R* configuration), (+)-noradrenaline (1-*S* configuration) and dopamine as well as a number of homologues were used as agonists. The adrenergic blocking drugs piperoxan, phentolamine, yohimbine, aceperone and the tranquillising drugs chlorpromazine, (−)-mepromazine, haloperidol, droperidol and spiramide as well as bulbocapnine were used as antagonists. The results obtained with both agonists and antagonists provide evidence that the structural requirements for drugs to react with and to activate α-receptors in the vas deferens and the rabbit intestine are different; epinine and dopamine have an identical mechanism of action.

IT is now generally accepted that adrenaline exerts its physiological actions by reacting with two distinct types of sympathetic receptors, which are classified as α- and β-receptors (Ahlquist, 1948).

(−)-Noradrenaline is the physiological substance acting on α-receptors. The configuration of the (essential) hydroxyl group in the side chain of (−)-noradrenaline is D according to Pratesi, LaManna, Campiglia & Ghislandi (1958) and consequently 1-*R* in terms of the sequence rule of Cahn, Ingold & Prelog (1956). Dopamine differs in not having the hydroxyl group in the side chain. Evidence is available that it has a transmitter function of its own in the central nervous system (Carlsson, Lindquist, Magnusson & Waldeck, 1958; Bertler & Rosengren, 1959; Hornykiewicz, 1963; Everett & Wiegand, 1962). In addition it has been found that dopamine in the peripheral nervous system to some degree evokes a different type of effect, as e.g. fall in blood pressure in the dog, rabbit and guinea-pig (Holtz & Credner, 1942; Burn & Rand, 1958; Holtz, Stock & Westermann, 1963; McDonald & Goldberg, 1963). Recently, Eble (1964) proposed specific receptors for dopamine in the renal and mesenteric vessels in the dog.

It is uncertain whether the peripheral effects of dopamine are caused by an action on sympathetic receptors or on separate non-sympathetic dopamine receptors. If dopamine is acting on sympathetic α-receptors the question is raised whether there is a scale of α-receptors with at one end receptors which are best fitted by noradrenaline and at the other end receptors which are best fitted by dopamine. The present study on the sympathetic action of optical isomers with known configuration and of other drugs is an attempt to clarify this point, and is also an attempt to determine if α-receptors in the rabbit intestine or the rat vas deferens could form a model for dopamine receptors in the brain.

Methods and materials

(*a*) The isolated vas deferens of the rat was used for making cumulative dose-response curves of α-sympathomimetic drugs, both in the absence and the presence of their antagonists. See Figs 1, 2 and 4. It has been

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shown that β-sympathomimetic agents have no relaxing effect on the vas deferens except in very high doses when myotropic spasmolytic actions become involved, this suggesting an absence of β-receptors in this organ. From the dose-response curves obtained, the intrinsic activity constant (i.a.c.) and the affinity constant (pD_2 or pA_2) was calculated by using (−)-noradrenaline, (−)-NA, as a reference drug (Ariëns, van Rossum & Simonis, 1957; Schild, 1949; van Rossum, 1963). The affinity is also given relative to that of (−)-noradrenaline (rel. aff. = 100).

(*b*) The isolated rabbit intestine was used for studying the inhibitory effect on pendular movements by individual doses of the α-sympathomimetic drugs, as well as the prevention of inhibition by antagonists. See Figs 3 and 5. The rabbit intestine contains both α- and β-receptors, and activation of both kinds results in inhibition of pendular movements (Ahlquist & Levy, 1959). Recently, van Rossum & Mujíc, (1965) have demonstrated that the types of inhibition induced by α- and β- drugs are essentially different. α-Sympathomimetics cause an inhibition with a rapid onset of action, whereas the onset of action of β-drugs is very slow. The β-type effect is seen only at the same time as an α-type effect when both effects occur at the same concentration. This is so with α-methyl-noradrenaline (van Rossum & Mujíc, 1965). Furthermore the indirectly acting α-sympathomimetics do not cause an inhibition of peristalsis but behave as antagonists (van Rossum & Mujíc, 1965). This appears to be a general feature of indirectly-acting sympathomimetic drugs in the rabbit intestine. From dose-response curves obtained by plotting the percentage inhibition versus the logarithm of the molar concentration, the intrinsic activity constant and affinity constant were calculated in a manner analogous to that used for the curves obtained from the vas deferens. A β-receptor activation, which may occur with adrenaline and noradrenaline in addition to their predominantly α-receptor activation, might influence the estimates of pD_2 values and relative affinities. However, β-receptor activation does not influence our results to a significant degree since β-receptor blockade has no effect on the relative affinities.

(*c*) The pentobarbitone anaesthetised cat (30 mg/kg) was used for studying the antagonistic action of adrenergic blocking drugs and tranquillisers on the effects of (−)-noradrenaline and dopamine.

(*d*) Some experiments were made on the chloralose anaesthetised rabbit (70 mg/kg) to study the antagonistic action of yohimbine, droperidol and spiramide on the pressor effects of (−)-noradrenaline, dopamine, (−)-adrenaline and epinine.

(*e*) The adrenergic blocking drugs and tranquillisers were also studied as antagonists of dexamphetamine using as the parameter the increase in locomotor activity in mice as measured by a light-beam method with continuous cumulative registration (van Rossum, 1962) (see Fig. 6).

AGONISTS AND ANTAGONISTS

The sympathomimetic agents (−)-, (+)-noradrenaline and dopamine as well as the enantiomorphs and the corresponding desoxy compounds

of adrenaline, phenylephrine and oxedrine (parasympatol) were used as agonists. Phentolamine, piperoxan, droperidol, yohimbine, aceperone, (−)-mepromazine, chlorpromazine, spiramide and bulbocapnine were used as adrenergic blocking agents.

Results

SYMPATHOMIMETIC DRUGS AND RAT VAS DEFERENS

A difference in sympathomimetic activity of stereo- and optical isomers has been found for many compounds (Luduena & others, 1962; Ariëns, 1963). However, no systematic study in which the absolute configuration has been taken into account is available. The absolute configurations of the isomers and derivatives used in the present study are known.

Fig. 1 records a typical experiment on the isolated vas deferens of a rat using (−)-, (+)-noradrenaline (NA) and dopamine (DA). (−)-noradrenaline was used as a reference drug. This procedure was also adopted

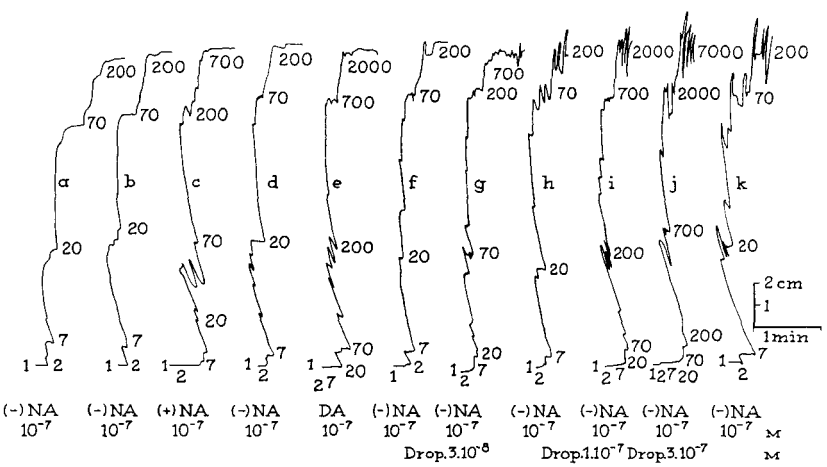

FIG. 1. Record of eleven cumulative dose-response curves obtained from a single vas deferens of a rat. The sympathomimetic stimulants (−)-noradrenaline, (−)NA, (reference drug) (+)-noradrenaline (+)NA, and dopamine, (DA), cause a similar type of response although different doses are required to produce 50% contraction. Curves were also made from results obtained in the presence of the antagonist droperidol. The doses correspond to molar concentration in the 10 ml bath. If, for instance, a dose of 20×10^{-7} M causes about 80% contraction, the concentration in the bath is actually 30×10^{-7} M (1 + 2 + 7 + 20). See curve a.

for the other drugs. Dose-response curves had a similar shape and equal height. From records such as that in Fig. 1, dose-response curves were calculated by using 100% contraction for the maximal effect obtained with (−)-noradrenaline (see Fig. 2a). From a number of such dose-response curves, usually more than 10 for each drug obtained on at least 5 preparations of the vas deferens, the average value of the negative logarithm of the molar concentration that produced a 50% effect was calculated (see Table 1). Dose-response curves were also made with

(−)-, (+)-adrenaline (A) and epinine (DAMe) showing similar results (Fig. 2b). Since the experiment in Fig. 2b was on a single isolated organ, the dose-response curve of the reference drug, (−)NA, is also given. The average values for the affinity constants and intrinsic activity constants are in Table 1.

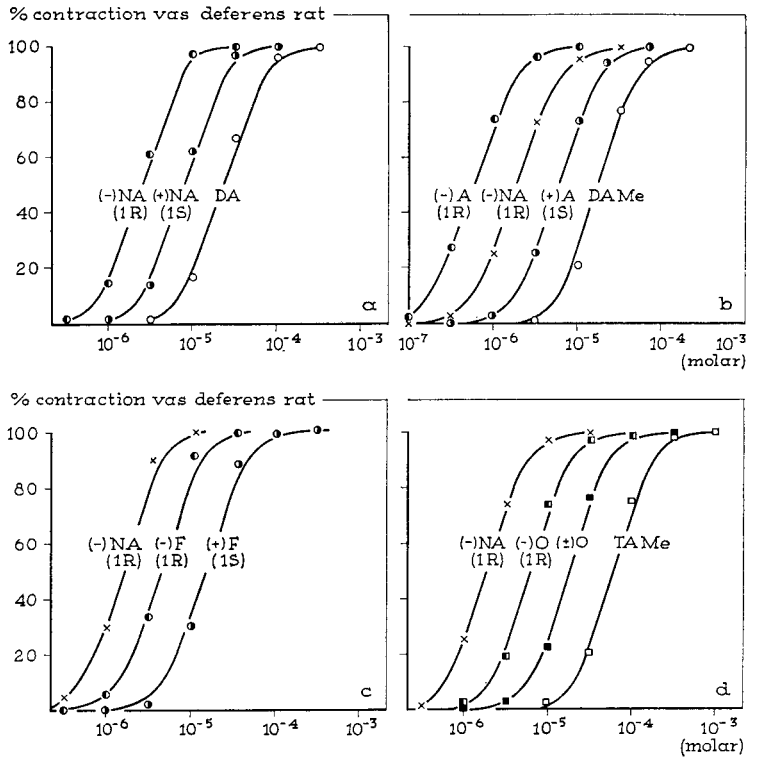

FIG. 2. Dose-response curves from several experiments given in the Fig. 1, left hand side, calculated by plotting the % contraction versus the concentration in the bath (logarithm scale). (*a*) (−)- and (+)-noradrenaline and dopamine; (*b*) (−)- and (+)-adrenaline and epinine (DAMe), reference drug (−)NA; (*c*) (−)- and (+)-phenylephrine and (−)NA; (*d*) (−)- and racemic oxedrine and *N*-methyltyramine. Note that the drugs with the OH-group in the *R*-configuration are the most potent of each group.

Dose-response curves of the enantiomorphs of phenylephrine, (−)F, and (+)F are in Fig. 2c. The corresponding desoxy derivative was not available. Curves for the (−)-isomer of oxedrine (parasympatol), (−)O, and the corresponding desoxy derivative *N*-methyltyramine, TAMe, as well as the racemic oxedrine, (±)O, are in Fig. 2d.

All drugs are agonists with equal intrinsic activity. From the average pD_2-values and the relative affinities given in Table 1 it may be seen that there is no great difference in affinity between the optical isomers and the corresponding desoxy derivatives. The 1-*R*/1-*S* affinity ratios for noradrenaline, adrenaline and phenylephrine are 4; 10 and 3 respectively.

The affinity ratios for 1-*R*-NA/DA and 1-*R*-A/epinine are 10 and 24 respectively.

TABLE 1. α-SYMPATHOMIMETIC DRUGS ON DIFFERENT TYPES OF α-RECEPTORS

	Rat vas deferens			Rabbit intestine				Affinity ratio vas/intestine
Drug	i.a.c.†	pD_2	rel. aff.‡	conf.§	i.a.c.	pD_2	rel. aff.	
(−)NA	1	5·7	100	1*R*	1	7·8	100	0·008
(+)NA	1	5·1	25	1*S*	1	6·0	6	0·13
DA	1	4·7	10	—	1	5·2	0·25	0·32
(−)A	1	6·0	200	1*R*	1	8·3	300	0·005
(+)A	1	5·0	20	1*S*	1	6·0	1·6	0·10
DAMe	1	4·6	8	—	1	5·4	0·4	0·16
(−)F	1	5·2	30	1*R*	1	7·2	22·5	0·01
(+)F	1	4·7	10	1*S*	1	4·1	0·02	4·0
(−)O	1	4·9	15	1*R*	1	4·6	0·06	2
(+)O	–	—	—	1*S*	0·8	4·4	0·04	—
(±)O	–	4·5	7	—	1	4·3	0·03	1·6
TAMe	1	4·1	2·5	—	0	4·4*	0·04	—

* antagonists so that pA_2 values were determined.
† Intrinsic activity constant.
‡ Relative affinity.
§ Configuration.

The sympathomimetic drugs containing a hydroxyl group on the side chain in the 1-*R* configuration are most potent and the desoxy derivatives, dopamine and epinine are the least potent drugs. With the aid of a competitive antagonist it could be ascertained that all the compounds in Table 1 react with common α-receptors in the isolated vas deferens of the rat.

SYMPATHOMIMETICS AND THE RABBIT INTESTINE

The various enantiomorphs and desoxy derivatives were tested as α-sympathomimetic drugs in the rabbit intestine. With the exception of *N*-methyltyramine, all compounds induced a rapid inhibition of pendular movements. This suggests a direct α-sympathomimetic action (van Rossum & Mujíc, 1965) (Fig. 3). The inhibitory action of (−)-noradrenaline and dopamine was antagonised by α-adrenergic blocking drugs, piperoxan for example, indicating a reaction with common α-receptors. Specific β-adrenergic blocking agents such as pronethalol and propranolol (inderal) did not influence the estimates of the pD_2 values of the various sympathomimetics. Only in very high concentrations ($>10^{-4}$M) did the β-adrenergic blocking drugs augment the response of the sympathomimetics and this was by a myotropic spasmolytic effect. In some experiments with (−)-noradrenaline and (−)-adrenaline a β-sympathomimetic effect was uncovered by giving an α-adrenergic blocking agent. However, no indications of β-effects were observed with the other drugs. Although the intestine contains both α- and β-receptors, the effects of the drugs were elicited only on α-receptors (Fig. 3).

The various sympathomimetics in sufficiently high concentrations cause complete inhibition of peristalsis as does (−)-noradrenaline. They have therefore an intrinsic activity constant equal to that of (−)-noradrenaline and differ only in affinity (Table 1). There are great differences

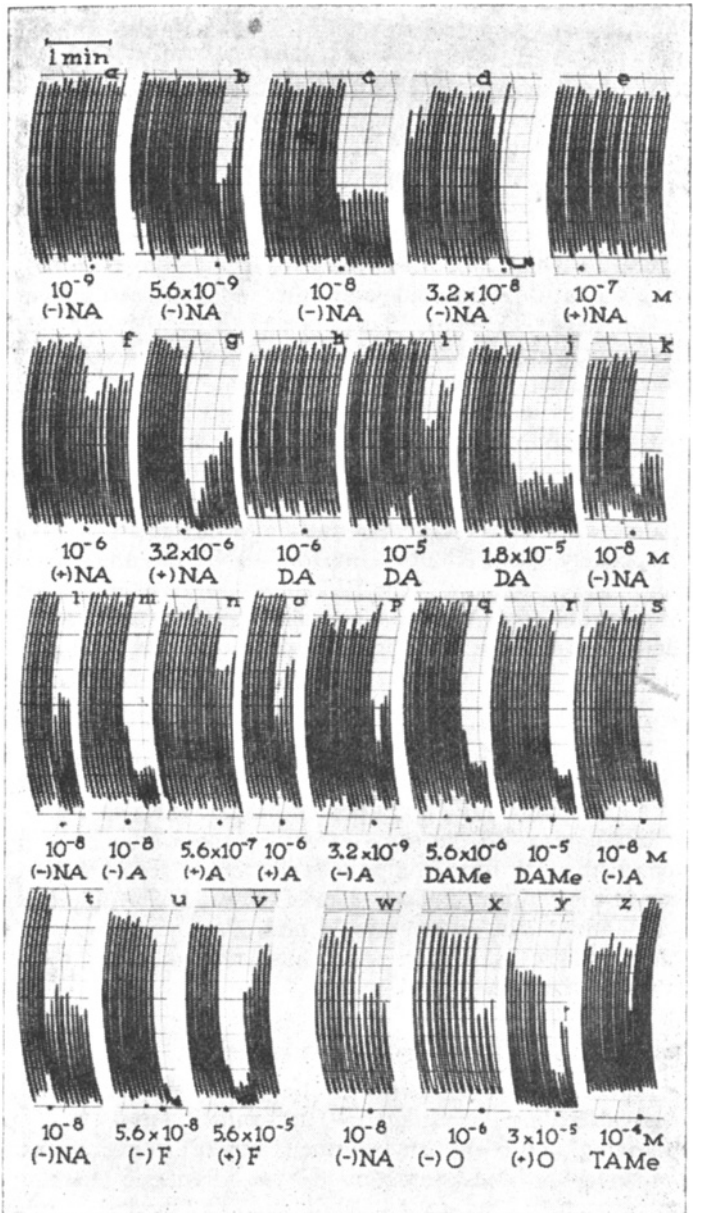

FIG. 3. Records of the inhibition of peristalsis on rabbit intestine by various α-sympathomimetic drugs related to noradrenaline and dopamines. Note the difference in potency between (−)-noradrenaline (exper. *a*, *b*, *c*, *d*, *k*) and dopamine (exper. *h*, *i*, *j*) between (−)-adrenaline (exper. *m*, *p*, *s*) and epinine, (DAMe), (exper. *q*, *r*) and between (−)-phenylephrine (exper. u) and (+)-phenylephrine (exper. *v*). Note also that *N*-methyltyramine (exper. *z*) does not cause inhibition and that the 1-*R* configuration of the OH-group in the side-chain is of great importance for α-sympathomimetic action.

between the optical isomers. (−)-Noradrenaline and (−)-adrenaline have a high affinity compared with their isomers and also with dopamine and epinine (Fig. 3; Table 1). (−)-Phenylephrine (1-*R* configuration) is almost 1,000 times more potent than its optical isomer.

The optical isomers of oxedrine differ slightly in action. The (−)-isomer is an α-sympathomimetic while the (+)-isomer is only a partial mimetic. This difference in potency is slight presumably because the affinity of (−)-oxedrine is low initially. The desoxy derivative, *N*-methyltyramine, does not inhibit but increases peristalsis (Fig. 3). At a concentration at which alone it is inactive, it antagonises noradrenaline in the same way as does tyramine and other indirectly-acting compounds (van Rossum & Mujíc, 1965). This appears to be a general feature of indirectly-acting sympathomimetics.

The potent isomers of the various series have the same absolute configuration (1-*R*) as natural noradrenaline (Table 1). The configuration of the hydroxyl group is therefore critical. The drugs in which the OH-group is lacking—dopamine, epinine and methyltyramine—are weak α-sympathomimetics or even antagonists. The 1-*R*/1-*S* affinity ratios for noradrenaline, adrenaline, phenylephrine and oxedrine are 16; 180; 1,000 and 1·5 respctively. The affinity ratios for (−)NA/DA and (−)A/epinine are 400 and 750 respectively. The *R*/*S* affinity ratios as well as the ratios of the affinity of the 1-*R* compounds and their desoxy derivatives are substantially greater in the rabbit intestine than in the vas deferens. These results indicate a difference in the α-receptor systems investigated.

SYMPATHOMIMETICS ON THE CAT BLOOD PRESSURE

(−)-Noradrenaline (1 μg/kg), dopamine (30 μg/kg), (−)-adrenaline (0·5 μg/kg) and epinine (20 μg/kg) have a pressor effect in the cat which could be antagonised to the same extent by the α-adrenergic blocking drug piperoxan. All four compounds therefore react with common α-receptors in the cardiovascular system of the cat. The affinity ratios of 1-*R*-NA/DA and 1-*R*-A/epinine are 30 and 50 respectively. Dopamine and epinine do not cause an increase in heart rate indicating that they do not activate β-receptors.

SYMPATHOMIMETICS ON THE RABBIT BLOOD PRESSURE

In the rabbit, (−)-noradrenaline (1 μg/kg), (+)-noradrenaline (10 μg/kg), (−)-adrenaline (0·7 μg/kg), (+)-adrenaline (8 μg/kg), (−)-phenylephrine (5 μg/kg) and (+)-phenylephrine (1 mg/kg) caused an increase in blood pressure, which was antagonised by α-adrenergic blocking agents such as piperoxan (0·2 mg/kg) and yohimbine (0·2 mg/kg). In contrast, dopamine (20–50 μg/kg) and epinine (10–20 μg/kg) induced a fall in blood pressure or a biphasic effect. With the fall in blood pressure there was often a fast and a slow component. We confirmed the results of Eble (1964) who found that the fall in blood pressure produced by dopamine was not antagonised by piperoxan and yohimbine. The same holds for epinine. Since no specific antagonists are yet available, it is not

possible to prove that dopamine and epinine react with common dopamine receptors. The similarity in the action of dopamine and epinine suggests that both drugs may react with common dopamine receptors.

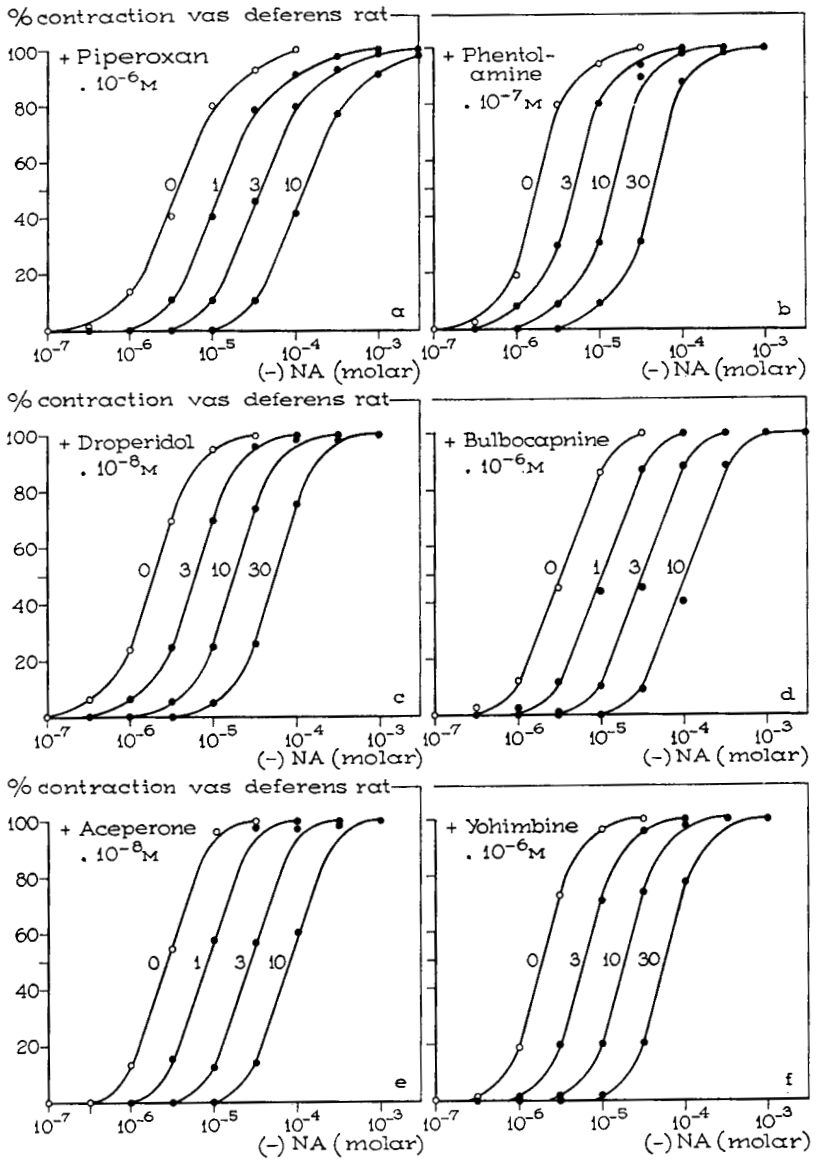

FIG. 4. Dose-response curves from experiments given in Fig. 1, at right hand side, calculated by plotting % contraction of (−)-noradrenaline versus the concentration in the bath (logarithm scale). (*a*) In combination with various concentrations of piperoxan; (*b*) with phentolamine; (*c*) with droperidol; (*d*) with bulbocapnine; (*e*) with aceperone and (*f*) with yohimbine. Note a parallel shift of the curves indicating competitive antagonism. The concentration to cause a given shift varies. The lowest concentration is required with the most potent drug, aceperone.

In a few experiments, droperidol (0·5–1 μmol/kg) and spiramide (1–10 μmol/kg) antagonised vasodepressor effects of dopamine and epinine. However, in some experiments these tranquillising drugs were ineffective themselves or caused prolonged vasodepression (see discussion).

ADRENERGIC BLOCKING DRUGS ON THE VAS DEFERENS OF THE RAT

By using (−)-noradrenaline and dopamine as agonists, cumulative dose-response curves were made on the vas deferens in the presence and in the absence of various concentrations of α-adrenergic blocking and tranquillising drugs. A typical record is given at the right-hand of Fig. 1 for droperidol. The adrenergic blocking drugs merely cause a shift of the dose-response curve to higher concentrations. From such experiments, dose-response curves were calculated as in Fig. 4. There are examples of experiments for each drug on a single organ. From a number of these experiments the affinity constants of the antagonists were calculated from the degree of antagonism and were given as pA_2-values. The average values are given in Table 2. Relative affinities are also given using piperoxan as a reference compound (rel. aff. = 1). It is interesting to see that yohimbine, which is a good adrenergic blocking agent, is the weakest of this group, while the tranquillisers droperidol and aceperone are potent α-adrenergic blocking agents.

All the compounds examined were competitive antagonists of noradrenaline and of dopamine. This can be seen from the parallel shift of the curves in Fig. 4. In some experiments, spiramide (10^{-7} M) sensitised the vas deferens to (−)-noradrenaline, but in most experiments there was a parallel shift at relatively high concentrations (Table 2). Since the isolated vas deferens contains only α-receptors, these results indicate that the tranquillisers, chlorpromazine, (−)-mepromazine, haloperidol, droperidol and spiramide, are also α-adrenergic blocking drugs like piperoxan, phentolamine, yohimbine and aceperone (see discussion).

ADRENERGIC BLOCKING DRUGS IN THE RABBIT INTESTINE

The adrenergic blocking drugs were also studied as antagonists of (−)-noradrenaline and dopamine on the rabbit intestine. A typical record of some experiments is given in Fig. 5. A dose of (−)-noradrenaline, causing about 50–80% inhibition is given first. After washing, a dose of an adrenergic blocking drug which alone does not influence the pendular movements, is given; 30 sec later noradrenaline is given in the same dose as before. The intestine is then washed and again an antagonist is given and after that a threefold higher dose of noradrenaline (Fig. 5). When the effect of this higher dose in the presence of an antagonist is equal to that of the previous dose in the absence of it, the negative logarithm of the molar concentration of the adrenergic blocking agent is equal to the pA_3 value. It is generally the custom to give the pA_2-value which is simply obtained by adding 0·3 to the pA_3-value. Due to variations in the sensitivity only a rough estimate of the pA_2-value may be obtained. On a single piece of intestine, differences in pA_2-value to the amount of 0·3 are significant.

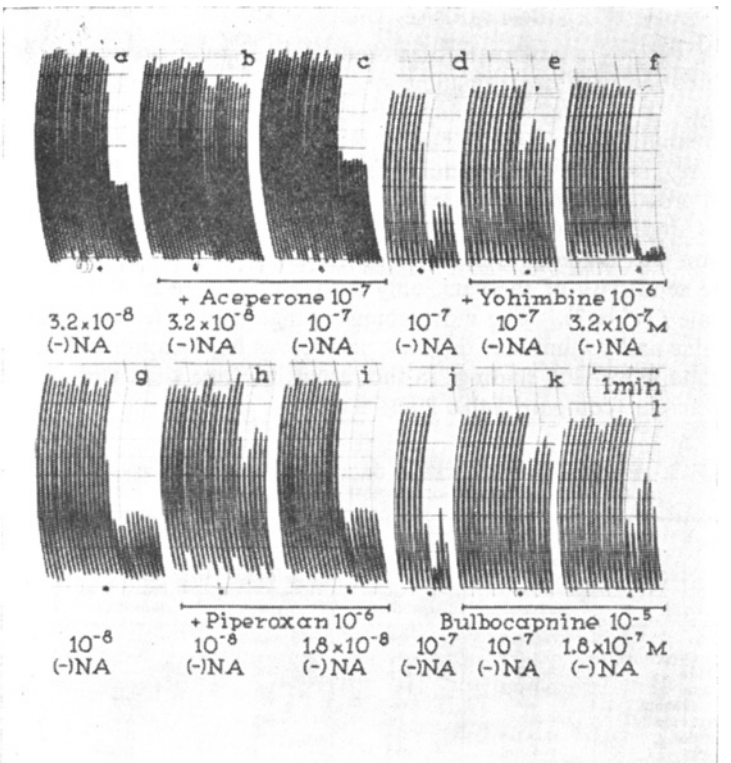

FIG. 5. Records of the inhibition of peristalsis of rabbit intestine by (−)-noradrenaline (−)NA alone and with some adrenergic blocking drugs and tranquillisers. Aceperone (exper. *a*, *b*, *c*) is the most potent antagonist of this series, yohimbine (exper. *d*, *e*, *f*) and piperoxan (exper. *g*, *h*, *i*) are relatively potent whereas bulbocapnine (exper. *j*, *k*, *l*) is a weak antagonist. Compare the order of potency with that found for the vas deferens. Note that the antagonists do not inhibit peristalsis on their own but antagonise the effect of noradrenaline, while a higher concentration of noradrenaline can break through (competition).

The affinity constants for the various antagonists (α-adrenergic blocking drugs) are given in Table 2. There is a different order of potency to that found in the vas deferens (see discussion).

TABLE 2. EFFECTS OF α-ADRENERGIC BLOCKING DRUGS AND TRANQUILLISERS ON DIFFERENT TYPES OF α-RECEPTORS

Drug	Rat vas deferens			Rabbit intestine			Affinity ratio vas/intestine
	i.a.c.*	pA_2	rel. aff.	i.a.c.	pA_2	rel. aff.	
Piperoxan	0	6·0	1	0	5·8	1	1·6
Phentolamine ..	0	6·9	8	0	6·3	3	4·0
Yohimbine	0	5·3	0·2	0	6·1	2	0·16
Aceperone	0	8·3	200	0	7·6	65	5·0
Chlorpromazine ..	0	6·8	6	0	6·1	2	5·0
Levomepromazine ..	0	7·3	20	0	6·0	1·6	20
Haloperidol	0	6·7	5	0	5·4	0·7	20
Droperidol	0	7·9	80	0	6·3	3	40
Spiramide	0	6·3	2	0	—	—	—
Bulbocapnine ..	0	6·4	2·5	0	5·2	0·2	16

* Intrinsic activity constant.

ADRENERGIC BLOCKING DRUGS ON THE BLOOD PRESSURE OF THE CAT

The various antagonists of noradrenaline were also investigated in combination with noradrenaline and dopamine on the blood pressure of the cat. Two doses of noradrenaline, 0·5 and 1 μg/cat, and 10 and 20 μg of dopamine were given. These produce the characteristic rise in blood pressure. A dose of an antagonist was then given which reduced the blood pressure response to the highest dose of agonist to about that of the lowest dose. The dose of the antagonist producing this degree of inhibition was taken as a measure of its potency. Because of a variation in the sensitivity of the cats, only a rough estimate of the potency was possible (Table 3). The most potent antagonists were aceperone, phentolamine and yohimbine; the least potent was bulbocapnine. The results correlate more with findings in the rabbit intestine than with those from vas deferens (compare Table 2 and 3 and see discussion).

TABLE 3. α-ADRENERGIC BLOCKING DRUGS AND TRANQUILLISERS AS ANTAGONISTS OF (−)-NORADRENALINE AND DEXAMPHETAMINE

Drug	Anti-NA blood pressure (cat)	Anti-amphetamine locomotive activity (mice)		Anti-amphetamine ED50*	Affinity ratio vas/anti-amphetamine
	μmoles/kg	μmoles/kg	pA_2	μmoles/kg	
Piperoxan	0·4–0·7	100†	—	—	—
Phentolamine ..	0·2–0·3	60†	—	—	—
Yohimbine	0·2–0·3	30†	—	—	—
Aceperone	0·1–0·2	18	5·1	>1500	1600
Chlorpromazine ..	—	6	5·5	3·5	20
Levomepromazine ..	0·8–1·5	1·6	6·2	6·0	12
Haloperidol	0·8–1·5	0·5	6·8	0·1	0·8
Droperidol	0·4–0·6	0·5	6·8	0·094	12
Spiramide	—	0·4	7·0	0·042	0·2
Bulbocapnine ..	2 –4	40	4·8	—	40

* Data from Janssen & others (1965).
† A competitive antagonism could not be determined.

ADRENERGIC BLOCKING DRUGS ON THE AMPHETAMINE-INDUCED LOCOMOTOR STIMULANT ACTION IN MICE

The various adrenergic blocking drugs and tranquillisers were studied as antagonists to dexamphetamine in mice. Dexamphetamine, 3·16 and 10 μmol/kg, caused a medium and a strong increase in locomotor activity. The same mice 3 or 4 days later, received the medium dose of dexamphetamine again and then a dose of antagonist. About 20 min after the antagonist a large dose of dexamphetamine was given. Doses of the antagonist were such that the effect of the larger dose of dexamphetamine was reduced to approximately that of the medium dose (Fig. 6). The average dose of antagonist in μmol/kg to produce this degree of antagonism is given in Table 3. The negative logarithm of this dose reflects a $pA_{3\cdot16}$ value when the concentration is taken in mol/kg instead of mol/litre. From the $pA_{3\cdot16}$ value, the pA_2 value is found by adding 0·34. The pA_2 values determined for the various antagonists are given in Table 3. In addition, the affinity ratio for (−)-noradrenaline antagonistic potency in the vas deferens and the anti-dexamphetamine potency is given.

Since the anti-dexamphetamine activities of a number of tranquillisers have been determined by Janssen, Niemegeers & Schellekens (1964), taking as an effect the amphetamine-induced compulsatory gnawing, these results after converting mg/kg into μmol/kg are also included in Table 3. As may be seen from Tables 2 and 3, the central anti-dexamphetamine activity does not correlate with a peripheral α-adrenergic blocking action of the various adrenergic blocking agents and tranquillisers. However, the results obtained on the vas deferens are more consistent with the central action than those obtained in the other tissues (see discussion).

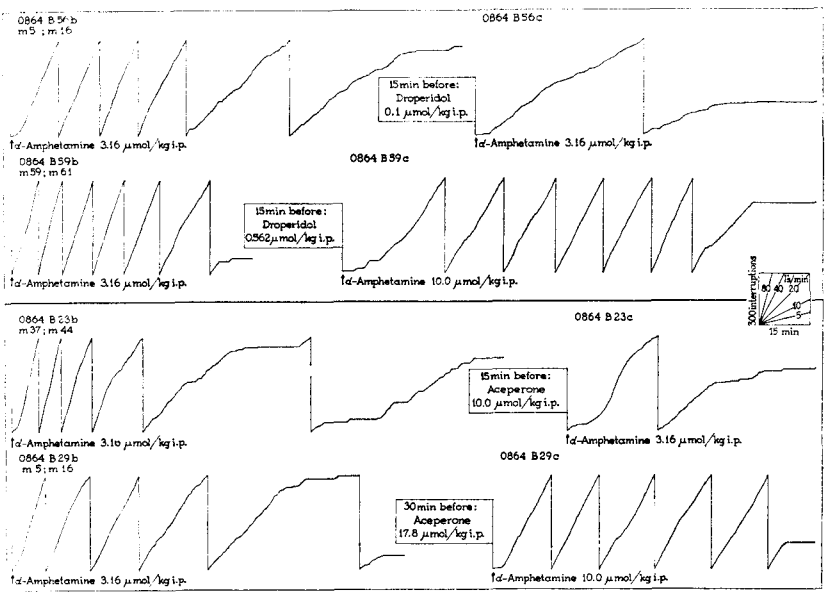

FIG. 6. Cumulative records of induction of locomotor activity by dexamphetamine, in control groups of two mice and in groups pre-treated with the tranquilliser droperidol or the adrenergic blocking drug aceperone. A higher dose of dexamphetamine can break through the inhibition, indicating a competition. Droperidol, 0·3 μmol/kg (100 μg/kg) causes the same degree of antagonism as aceperone 17·8 μmol/kg (6 mg/kg). See text. Droperidol is about 50 times more potent than aceperone in the CNS although it is about three times less potent as an antagonist of (−)-noradrenaline. Compare with Table 3.

Discussion

Dopamine like noradrenaline is known to act on sympathetic α-receptors, but there is also evidence for an action on separate dopamine receptors in peripheral tissues and in the peripheral and central nervous systems.

It has been shown that dopamine, in contrast to noradrenaline, causes a fall in blood pressure in the dog, guinea-pig and the rabbit (Holtz & Credner, 1942; Burn & Rand, 1958; Holtz & others, 1963). Dopamine causes an increase in the blood flow through the kidneys, the superior

mesenteric vessels and the coeliac vessels (Eble, 1964; McDonald, Goldberg, McNay & Tuttle, 1964). Also, in man, it differs from noradrenaline in increasing blood pressure without raising the diastolic pressure and by inducing pilo-erection (Horwitz, Fox & Goldberg, 1962; Allwood & Ginsberg, 1964). The specific dopamine effects in dogs and rabbits are not affected by specific α-blocking agents such as piperoxan, tolazoline, yohimbine and phenoxybenzamine (Holtz & others, 1963; McDonald & Goldberg, 1963; Eble, 1964; and present study) or by specific β-blocking agents (Holtz & others, 1963; Eble, 1964; Vanov, 1963). Also antihistamines and atropine-like drugs are ineffective (McDonald & Goldberg, 1963).

From the work of various authors it may be concluded that in the peripheral nervous system there are dopamine receptors and that there might be dopaminergic nerves innervating certain tissues. (Allwood & Ginsberg, 1964; Eble, 1964; Holtz & others, 1963). Dopamine on the other hand also fits sympathetic α-receptors so that depending on the relative amounts of these two types of receptors, dopamine may exert a blood pressure rise (in the cat) or a blood pressure fall (in the rabbit). Experiments on nerve transmission in lower animals also indicate specific dopamine receptors.

The rate of discharge of neurones in the stretch receptor organ in the abdominal segments of the crayfish, *Pacifastacus leniusculus*, is blocked by γ-aminobutyric acid (GABA), noradrenaline and dopamine (McGeer, McGeer & McLennan, 1961). Dopamine is 100 times more potent than noradrenaline. The inhibitory action of dopamine on the stretch receptor organ can be blocked selectively by chlorpromazine but not by picrotoxin, whereas the GABA action can be blocked by picrotoxin but not by chlorpromazine (McGeer & others, 1961). In a recent report, Gerschenfeld (1964), found receptive sites in inhibition neurones in the nervous system of the mollusc, *Cryptomphallus aspera*, which respond to dopamine in a concentration of 10^{-9} M but hardly at all to other inhibitory substances. This also points to the existence of specific dopamine receptors in nervous tissue.

It has been suggested that dopamine in the central nervous system is not only a precursor of (−)-noradrenaline, but has a "transmitter function" of its own (Carlsson & others, 1958). In reserpinised rats, the psychomotor stimulant action of dihydroxyphenylalanine (dopa) is correlated with brain dopamine levels but not with brain noradrenaline levels (Everett & Wiegand, 1961). Evidence has been provided that the central stimulant action of amphetamine may be mediated through reaction with dopamine receptors (van Rossum & Hurkmans, 1964).

These observations raise the question whether dopamine receptors are part of a range of α-receptors at one end of which are receptors best fitted by noradrenaline, and at the other end receptors which are best fitted by dopamine. This possibility has been challenged by comparing the relative activities of various α-sympathomimetic-, α-adrenergic blocking and tranquillising drugs on α-receptors in both the vas deferens of the rat and the rabbit intestine. It has been postulated by Holman & Jowett,

(1964) that there are β-receptors in the vas deferens of the guinea-pig, but in the isolated vas deferens of the rat they are absent or play an insignificant part in the study of α-sympathomimetics (Ariëns, 1963). The rabbit intestine does contain β-receptors, but the type of relaxation obtained by activation of α- or β-receptors differs substantially (van Rossum & Mujíc, 1964). In contrast to the responses obtained with β-sympathomimetics the sympathomimetics we used caused a rapid relaxation of the rabbit intestine. This is characteristic of α-sympathomimetics. Furthermore, sympathomimetics were competitively antagonised to the same degree by α-adrenergic blocking drugs. Specific β-receptor antagonists like pronethalol and propranolol did not influence the pD_2 estimates of the sympathomimetics as given in Table 1, unless used at concentrations causing myotropic spasmolytic effects.

The experiments have shown that the 1-*R* configuration of the hydroxy group in the side-chain of the various groups of mimetic drugs is essential for optimal affinity. This holds for an action on the α-receptors in the vas deferens and the rabbit intestine. Dopamine and epinine, which lacks the hydroxyl group, are relatively weak. The trend in the affinity change with alterations of the structure or configuration is the same in the vas deferens and rabbit intestine. However, there are large quantitative differences in the α-receptors of both tissues. For instance, the affinity ratios for 1-*R*-noradrenaline: dopamine and 1-*R*-adrenaline: epinine are 10 and 24, in the vas deferens but 400 and 150 respectively in the rabbit intestine (Table 1). The α-receptors of the rabbit intestine are more specific noradrenaline receptors than those in the vas deferens, but although the relative affinity of dopamine is greater for the receptors in the vas these receptors cannot be classed as dopamine receptors because they are more sensitive to noradrenaline or adrenaline.

The difference in properties of the α-receptors in the rabbit intestine and rat vas deferens is supported by a difference in the actions of antagonist drugs (Table 2). Yohimbine is about 6 times more potent as an α-adrenergic blocking agent in the rabbit intestine, whereas droperidol is 40 times more potent in the vas deferens.

Since yohimbine has a higher affinity for α-receptors best fitted by noradrenaline it may be a selective antagonist for noradrenaline receptors. Conversely it is tempting to speculate that the greater potency of droperidol on the vas deferens is related to the more pronounced affinity of the receptors in the vas for dopamine. The experiments reported here show differences between the properties of the α-receptors in the rabbit intestine and the rat vas deferens, but further work is necessary to find dopamine receptors in the peripheral tissues. A simple test organ reacting to activation of dopamine receptors would provide a valuable model and greatly facilitate the study of drugs which mimic or antagonise dopamine in the central nervous system.

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