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THE INHIBITION OF THE PERISTALTIC REFLEX BY SYMPATHOMIMETIC AMINES

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The peristaltic reflex initiated by raising the pressure in the lumen of the isolated intestine of rabbits and guinea-pigs (Trendelenburg's method) is inhibited by low concentrations of adrenaline and noradrenaline (McDougal and West, 1952). The nature of the mechanism by which this inhibition is produced is still somewhat uncertain. Adrenaline could either relax the muscle fibres directly, or interfere with transmission at various levels in the peristaltic reflex arc—at, for instance, the ganglionic synapse or the neuromuscular junction.

It seemed of interest to investigate the inhibition of the peristaltic reflex further, by determining the effect of various sympathomimetic amines upon it, and whether the effects of these are influenced by sympatholytic drugs. Such observations might be expected to throw light on the mechanism whereby the reflex is inhibited.

METHODS

Strips of guinea-pig ileum (2–3 cm. long) were suspended in aerated Tyrode's solution at 37° C. in a 50 ml. isolated organ bath. The intestinal volume was recorded by the method of Trendelenburg (1917) as modified by Feldberg and Solandt (1942). The peristaltic reflex was initiated by raising the pressure in the lumen by 2–3 cm. of Tyrode's solution.

In other experiments, similar strips of ileum were suspended in aerated Tyrode's solution at 37° C. in a 15 ml. bath, and the longitudinal muscle contractions were recorded with a frontal writing lever (magnification ×8). Preparations of strips of rabbit ileum and uterus were also tested.

The sympathomimetic amines used are listed in Table I, the sympatholytic drugs in Table III, and other drugs in Table IV.

RESULTS

Activities of Various Sympathomimetic Amines

Peristaltic Inhibitory Action.—Concentrations of 10^{-8} adrenaline regularly produce inhibition of the peristaltic reflex in the isolated guinea-pig gut (Fig. 1). The activities of the other amines relative to that of adrenaline are shown in Table I, each value being the geometric mean of at least three experiments. The most potent compounds are all dihydroxyphenylalkylamines. The dihydroxyphenyl compounds studied are shown in Table II, which gives their structures, and, for comparison, their relative activities in stimulating the isolated rabbit uterus and in inhibiting the pendular movements of the isolated rabbit ileum (geometric means of four experiments). It is evident that in the more potent amines a relationship exists between these three effects, though notable exceptions are isoprenaline (compound 10), α-ethylnoradrenaline (9), and adrenalone (7). Isoprenaline does not possess any excitor action on the rabbit uterus.

TABLE I

RATIO OF DOSES OF SYMPATHOMIMETIC AMINES AND AMINO-ACIDS TO EQUIACTIVE DOSE OF (−)-ADRENALINE ON GUINEA-PIG ILEUM

No.	Amine	Inhibition of Peristalsis	Inhibition of Nicotine Contraction	No. of Expts.
1	(−)-Adrenaline	1	1	30
2	(−)-Noradrenaline	4	2	20
3	(±)-Corbasil	10	5	3
4	Epinine	17	15	3
5	(±)-*N*-Ethylnoradrenaline	20	8	3
6	Lactyladrenaline	20	20	3
7	Adrenalone	28	20	3
8	Lactylnoradrenaline	40	35	3
9	(±)-α-Ethylnoradrenaline	86	30	3
10	(±)-Isoprenaline	200	200	20
11	Hydroxytyramine	250	100	3
12	Tyramine	1,200	1,000	3
13	Amphetamine	1,200	560	6
14	Ephedrine	1,300	540	6
15	Dihydroxyphenylalanine	1,500	1,500	3
16	Dihydroxyphenylserine	3,000	3,000	3
17	Propadrine	3,000	500	3
18	*m*-Sympatol	5,000	1,000	3
19	Sympatol	6,000	2,000	3
20	*m*-Norsynephrine	6,000	2,000	3
21	Paredrine	6,000	1,000	3
22	*p*-Norsynephrine	7,500	2,000	3

TABLE II

RELATIONSHIP BETWEEN STRUCTURE AND ACTIVITY OF DIHYDROXYPHENYL COMPOUNDS, THE ACTIONS OF WHICH ON THE GUINEA-PIG PERISTALTIC REFLEX AND ON RABBIT UTERUS (BUT NOT ON RABBIT ILEUM) ARE PREVENTED BY SYMPATHOLYTIC DRUGS

Amine No.	Formula	Ratio of Dose to Equiactive Dose of Adrenaline		
		Peristaltic Reflex (Guinea-pig)	Rabbit Uterus (Excitor)	Rabbit Ileum (Inhibitor)
2	OH H H	4	1	2
1	OH H CH_3	1	1	1
5	OH H C_2H_5	20	15	8
10	OH H $CH(CH_3)_2$	200	—	20
3	OH CH_3 H	10	30	10
9	OH C_2H_5 H	86	500	100
16	OH COOH H	3,000	>1,000	> 10,000
11	H H H	250	200	200
4	H H CH_3	17	30	25
15	H COOH H	1,500	>1,000	>10,000
7	—CH(—)— replaced by —C(=O)—	H CH_3	28	500	40

Interaction with Motor Drugs.—The results of experiments on the inhibition of the nicotine response of the longitudinal muscle of the guinea-pig ileum are also recorded in Table I. The concentrations of the amines and amino-acids required to reduce the nicotine response have little effect on equally strong contractions produced by ACh or by histamine (see Fig. 2A). An ACh, but not a nicotine, contraction is maintained, for example, in the presence of 1 in 50,000 adrenaline; relaxation of the nicotine contraction starts 5 sec. after adding the adrenaline to the bath.

Feldberg and Lin (1949) showed that, when the peristaltic reflex in the isolated rabbit gut is abolished by cocaine or hexamethonium, eserine (10^{-7} to 10^{-6}) elicits rhythmic contractions affecting the whole muscle simultaneously. They concluded that the circular muscle is still responsive to eserine although the nervous elements are depressed. We repeated this experiment with most of the sympathomimetic amines and obtained similar results on adding eserine in their presence. It is, however, easier to obtain this effect with dihydroxyphenylalkylamines than with the other amines.

These results show that the inhibitory action of the dihydroxyphenylalkylamines on peristalsis is not due to a diminution in the sensitivity of the muscle fibres to motor drugs in general, and, more specifically, to ACh. They suggest, rather, that this effect of adrenaline, and of its derivatives, is due to an interruption of the peristaltic reflex arc, either by virtue of the known ganglion-blocking action of the amines, or by their suppressing the release of ACh.

Sympatholytic Drugs

Effect on Peristaltic Inhibitory Action of Dihydroxyphenylalkylamines.—It is well known that

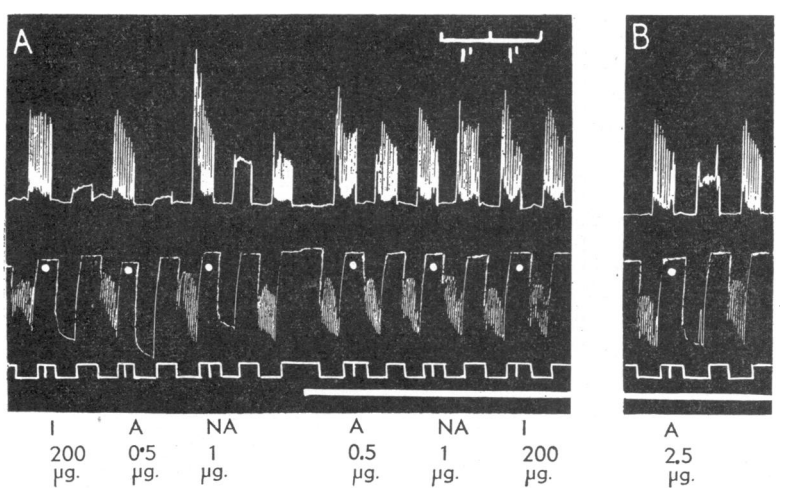

FIG. 1.—Isolated guinea-pig ileum. Bath volume 50 ml. Top tracing, contractions of longitudinal muscle; middle tracing, intestinal volume; lower tracing, marker indicating (downwards) rise of pressure in the lumen, and points of injection of drugs. Time in min. In A, Adrenaline (A, 0.5 μg.), noradrenaline (NA, 1 μg.) and isoprenaline (I, 200 μg.) inhibit the peristaltic reflex. These doses, however, are ineffective in the continuous presence of 933F (10^{-7}), indicated by the white line. In B, increasing the dose of adrenaline to 2.5 μg. overcomes this block.

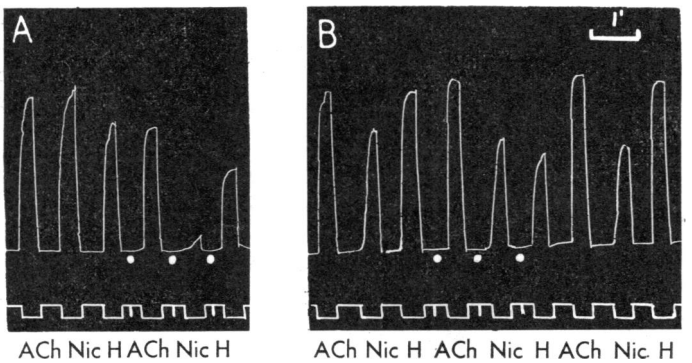

FIG. 2.—Isolated guinea-pig ileum. Bath volume 15 ml. Contractions of longitudinal muscle. Time in min. In A, effects of acetylcholine (ACh, 0.2 μg.), nicotine (Nic, 20 μg.) and histamine (H, 0.2 μg.) alone, and in the presence of adrenaline, 1 μg. (indicated by the dots). In B, the same drugs in the continuous presence of 933F (10^{-7}).

anti-adrenaline (sympatholytic) drugs block most excitatory actions of adrenaline (e.g., that on the rabbit uterus) but fail to suppress most of its inhibitory actions (e.g., that on the muscle fibres of the rabbit ileum). In the presence of sympatholytic drugs, however, the action of all the dihydroxyphenylalkylamines on the peristaltic reflex of the guinea-pig is prevented (Fig. 1). This result suggests that the anti-peristaltic action of these amines is exerted on nervous structures and not directly on the muscle fibres. Effective concentrations of the blocking drugs are recorded in Table III, together with their concentrations

TABLE III

CONCENTRATION OF SYMPATHOLYTIC DRUGS REQUIRED TO ANTAGONIZE THE ACTIONS OF DIHYDROXYPHENYLALKYLAMINES ON THE PERISTALTIC REFLEX OF THE GUINEA-PIG AND ON THE RABBIT UTERUS

Drug	Peristaltic Reflex	Rabbit Uterus	Type of Antagonism	Concn. of Sympatholytic Drug which Itself Inhibits Peristalsis
Tolazoline ..	5×10^{-7}	2×10^{-6}	Reversible	2×10^{-4}
933F ..	10^{-7}	5×10^{-7}	,,	4×10^{-5}
Dibenamine ..	2×10^{-7}	2×10^{-7}	Complete	2×10^{-6}
SKF 688A ..	5×10^{-8}	5×10^{-8}	,,	10^{-6}
SY 28 ..	2×10^{-8}	2×10^{-8}	,,	10^{-6}

needed to antagonize the amine response on the rabbit uterus (an excitor action). There appears to be a close similarity in the effective concentrations of the blocking drugs for these two effects. Whereas the action of tolazoline and 933F is reversible (the block is easily washed away or may be overcome by increasing the dose of the amine, as shown in Fig. 1), that of the other three related drugs is complete (the block is not removed by washing and cannot be overcome by increasing the dose, as shown in Fig. 3). High doses of the sympatholytic drugs themselves inhibit peristalsis (Table III), although this may be the result of some depressant action on the nervous or muscular elements.

Effect on Nicotine-stimulation.—On the longitudinal muscle of the guinea-pig ileum, the inhibition of the nicotine contraction by dihydroxyphenylalkylamines is removed when the blocking drugs are present (Fig. 2B).

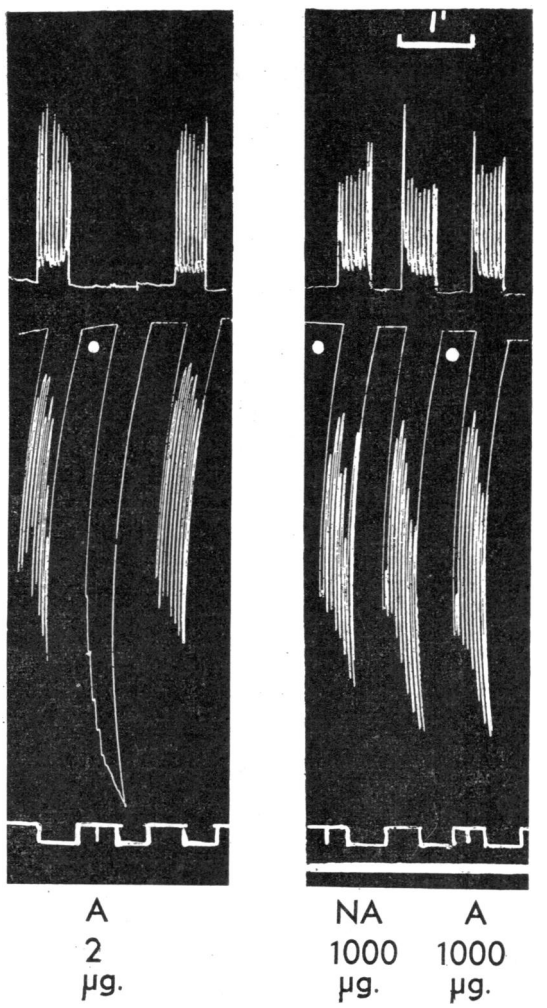

FIG. 3.—As Fig. 1. White line indicates continuous presence of dibenamine (2×10^{-7}). Note that the action of this sympatholytic agent in removing inhibition is complete, and cannot be overcome by increasing the dose of adrenaline (A) or noradrenaline (NA).

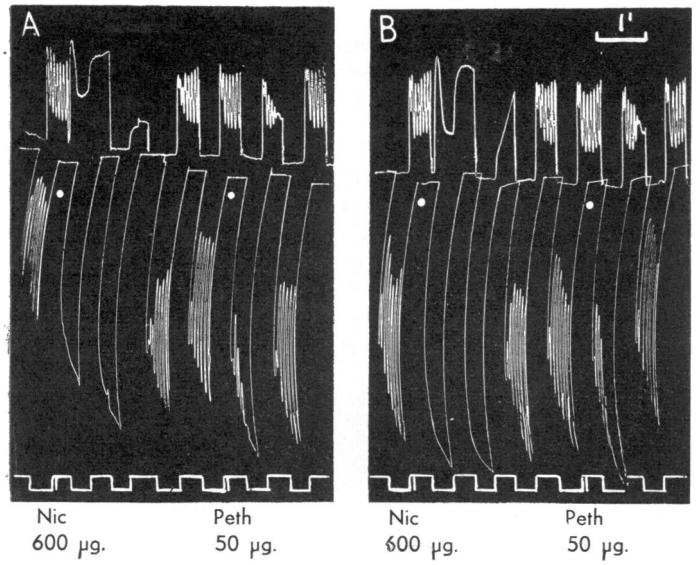

FIG. 4.—As Fig. 1. In A, the effect of nicotine (Nic, 600 μg.) and pethidine (Peth, 50 μg.) on the peristaltic reflex. In B, these effects in the continuous presence of 933F (10^{-7}).

This action is easier to obtain with 933F or tolazoline than with one of the other water-insoluble blocking drugs.

TABLE IV

CONCENTRATION OF DRUGS WHICH INHIBIT THE PERISTALTIC REFLEX OF THE GUINEA-PIG ILEUM AND ARE UNAFFECTED BY SYMPATHOLYTIC DRUGS

Drug	Concn.
Hexamethonium	10^{-5}
Nicotine	10^{-5}
(+)-Tubocurarine	10^{-5}
Cocaine	5×10^{-6}
Atropine	10^{-8}
Pethidine	10^{-6}
Mepyramine	2×10^{-5}

Effect on the Peristaltic Inhibition Produced by Other Drugs.— To see if sympatholytic agents can counteract other types of peristaltic inhibition, we have examined their effect on the inhibition produced by ganglion-blocking agents (hexamethonium, nicotine and (+)-tubocurarine), by drugs known to have little ganglionic blocking action (atropine, pethidine, and mepyramine), and by a local anaesthetic (cocaine). Table IV gives the concentrations of these drugs needed to inhibit the peristaltic reflex in the guinea-pig ileum. Sympatholytic agents do not affect the action of any of this varied group of drugs (Fig. 4).

These results show that the nature of the inhibitory action of the dihydroxyphenylalkylamines on peristalsis differs radically from that of the other substances enumerated, and that the antagonism by sympatholytic drugs is restricted specifically to the site of action of the sympathomimetic amines.

Monohydroxyphenyl- and Phenyl-alkylamines

These amines are listed in Table V. The importance of the *meta*-hydroxyphenyl group for stimulation of the rabbit uterus and relaxation of the rabbit ileum is shown (compare the activities of compounds 18 and 20 with those of compounds 19 and 22 respectively). Yet all of these compounds are almost inactive in suppressing the peristaltic reflex in the guinea-pig. Since there is no correlation with the other two effects, the inhibition of the reflex by the compounds shown in

TABLE V

RELATIONSHIP BETWEEN STRUCTURE AND ACTIVITY OF AMINES, THE ACTIONS OF WHICH ON THE PERISTALTIC REFLEX AND RABBIT ILEUM ARE NOT PREVENTED BY SYMPATHOLYTIC DRUGS

Amine No.	R^1	R^2	R^3	R^4	R^5	Ratio of Dose to Equiactive Dose of Adrenaline: Peristaltic Reflex (Guinea-pig)	Rabbit Uterus (Excitor)	Rabbit Ileum (Inhibitor)
12	OH	H	H	H	H	1,200	1,000	—
21	OH	H	H	CH_3	H	6,000	1,000	—
22	OH	H	OH	H	H	7,500	500	4,000
19	OH	H	OH	H	CH_3	6,000	100	2,000
20	H	OH	OH	H	H	6,000	20	50
18	H	OH	OH	H	CH_3	5,000	5	10
13	H	H	H	CH_3	H	1,200	>1,000	>10,000
17	H	H	OH	CH_3	H	3,000	200	>10,000
14	H	H	OH	CH_3	CH_3	1,300	1,000	>10,000

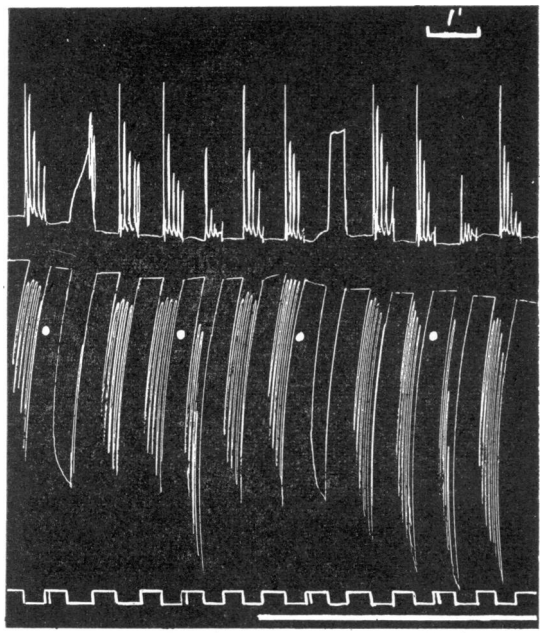

FIG. 5.—As Fig. 1. White line indicates continuous presence of 933F (10^{-7}). Note that the action of meta-sympatol (m-sym, 10.0 mg.), and of ephedrine (Eph, 2.5 mg.), is uninfluenced by this concn. of 933F.

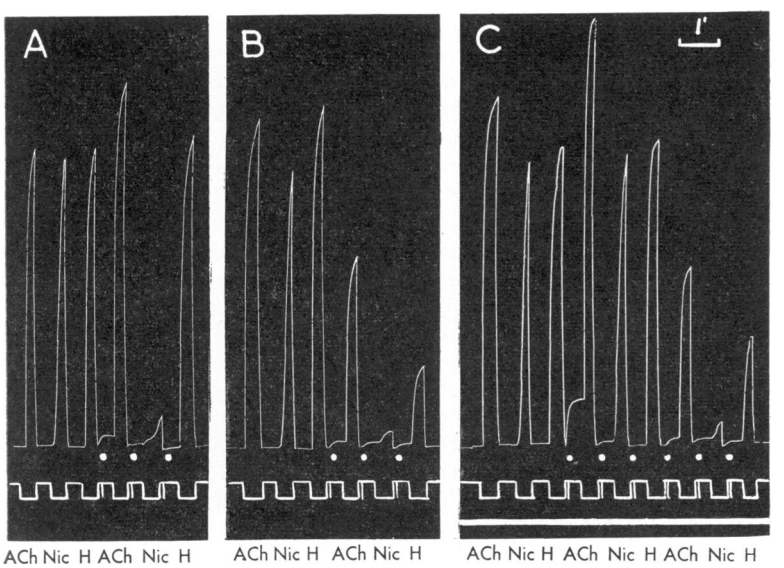

FIG. 6.—As Fig. 2. In A, the effects of acetylcholine (ACh, 0.4 μg.), nicotine (Nic, 40 μg.) and histamine (H, 0.4 μg.) alone and in the presence of adrenalone 10 μg. (indicated by the dots). In B, the same drugs alone and in the presence of amphetamine 500 μg. (indicated by the dots). In C, the white line indicates the continuous presence of 933F (10^{-7}); the first three dots indicate the presence of adrenalone (10 μg.); the second three, amphetamine (500 μg.). For further explanation, see text.

Table V may be of a non-specific nature. This is supported by the failure of sympatholytic drugs to suppress the effect of these compounds on the peristaltic reflex and on the nicotine response of the longitudinal muscle, although the excitation of the rabbit uterus by these amines is abolished. Fig. 5 illustrates this point on the peristaltic reflex, the actions of a monohydroxyphenyl compound (meta-sympatol) and an unsubstituted phenyl compound (ephedrine) being uninfluenced by the continuous presence of 933F. Fig. 6 illustrates the comparison on the longitudinal muscle for adrenalone on the one hand (inhibition of the nicotine response prevented), and for amphetamine on the other (inhibition not affected). It is noticeable in the tracing that both adrenalone and amphetamine exert a weak motor action which is not suppressed by the sympatholytic drugs.

DISCUSSION

We have shown that a series of 22 sympathomimetic amines inhibit the peristaltic reflex and reduce the nicotine contraction of the longitudinal muscle of the guinea-pig ileum without greatly affecting those of histamine and ACh. Among the more active members of the series there is some correlation between the relative ability to produce these two effects and some other well-known actions of the amines—such as stimulation of the rabbit uterus and relaxation of the rabbit ileum—but this is not so with the less active ones. When the peristaltic reflex is inhibited, eserine produces rhythmic contractions and an increase in tone of the circular muscle, as it does in the presence of ganglion-blocking concentrations of hexamethonium (Feldberg and Lin, 1949; Feldberg, 1951). Since the muscle is also still responsive to ACh, it is probable that these sympathomimetic amines block or depress ganglionic transmission.

A direct depressant action of adrenaline on the response of the superior cervical ganglion in the dog to repetitive stimulation of its preganglionic trunk has been reported by Marrazzi (1939).

It was then considered that adrenaline may block ACh by acting at the same site as the latter, since the action was found to be independent of the vasoconstriction produced. Bülbring and Burn (1942) also demonstrated this ganglion-blocking action by experiments in dogs in which the ganglia of the lumbar sympathetic chain and the vessels of the hind leg were separately perfused. Small concentrations of adrenaline, added to the blood perfusing the ganglia, increased the vasoconstrictor effect of preganglionic stimulation, but higher concentrations reduced the effect to zero. They also noted than in atropinized spinal cats the ganglionic stimulant action of ACh was augmented by small doses, but depressed by large doses, of adrenaline. Paton and Thompson (1953) have recently shown that in the superior cervical ganglion of the cat adrenaline not only diminishes the release of ACh in response to preganglionic stimulation but also depresses the action of ACh on ganglion cells.

Why should adrenaline and noradrenaline depress the activity of parasympathetic ganglia? Such a depression would reduce the excitor effects of preganglionic parasympathetic stimulation in the gut, thereby augmenting the relaxant action of these amines on the effector muscle cells at the postganglionic sympathetic nerve endings. Since there is now strong evidence that transmission at the parasympathetic ganglionic synapse is cholinergic (Perry and Talesnik, 1953), adrenaline must antagonize the action of ACh at this site. The antagonism, however, is not of the same type as that with hexamethonium or (+)-tubocurarine (competitive antagonism), which is unaffected by sympatholytic drugs. Nicotine block, which is said to result from depolarization of the ganglion cells, is also unchanged by sympatholytic drugs; thus the mechanism by which adrenaline and the related amines produce ganglionic blockade is not clear, although it appears to be related either to the phenomena described by Marrazzi (1939) and by Bülbring and Burn (1942), or to those of Paton and Thompson (1953) and of Ellis (1953).

We have found that sympatholytic drugs specifically prevent the inhibition of peristalsis by dihydroxyphenylalkylamines and that they fall into two groups—firstly, one where the block is reversible and easily removed by washing (tolazoline and 933F), and secondly, one where the block is complete (the β-chlorophenylethylamines). In both groups the concentrations required for this effect are very similar to those required to prevent stimulation of the rabbit uterus. Sympatholytic drugs, however, do not influence the action of the sympathomimetic amines on the isolated rabbit ileum. Thus there is evidence that the ganglionic blocking action of the dihydroxyphenylalkylamines may be classed with excitor effects. But there is the difference that both the *meta*- and *para*-hydroxy groups in the ring are most important for inhibition of peristalsis, whereas the *meta*-hydroxy group is the most important for stimulation of the excitor receptors in the rabbit uterus.

We have also found that many of the dihydroxyphenylalkylamines excite the lower third of the guinea-pig ileum (as reported by Munro, 1951). All the sympatholytic drugs used block this excitation in the same concentrations as are required to prevent the inhibition of the peristaltic reflex. This is of interest, since Munro (1952) has shown that this action of adrenaline is probably a direct one on the smooth muscle.

It is also interesting that the catechol ring has already been shown to be essential for various other ganglionic and neuromuscular effects; for example, augmentation of the response to ACh in the isolated perfused superior cervical ganglion of the cat (Konzett, 1950), potentiation of the twitch tension developed by the tibialis anterior muscle in the cat when stimulated indirectly (Huidobro, Cubillos, and Eyzaguirre, 1952), and decurarization in the nerve-muscle preparation of the dog (Maddock, Rankin, and Youmans, 1948).

When we turn to the monohydroxyphenylalkylamines and the phenylalkylamines, we find three important facts: (1) the doses needed to inhibit the reflex are large, since all are more than 1,000 times less active than adrenaline, (2) the relative activities do not correspond either with those on the rabbit uterus or on the rabbit ileum, and (3) sympatholytic drugs do not influence this action. These observations imply that the effects of the compounds on the reflex may be non-specific. However, other drugs which act specifically on the nervous components of the reflex are also unaffected by sympatholytic agents.

We consider the evidence sufficient to state that adrenaline, noradrenaline, and other dihydroxyphenylalkylamines have an action on the parasympathetic ganglia in the guinea-pig ileum. Adrenaline, noradrenaline, and other dihydroxyphenylalkylamines have what Ahlquist (1948) would have called an α-effect on the parasympathetic ganglia in the guinea-pig ileum. This response is altered by sympatholytic agents as specifically as the excitor actions of sympathomimetic amines (with the exception of that on the heart).

SUMMARY

1. Dihydroxyphenylalkylamines are potent inhibitors of the peristaltic reflex in the guinea-pig ileum. The mechanism by which this inhibition is produced is not clear, although it is probably a direct depressant action on transmission in the ganglionic synapses within the enteric plexus.

2. The contraction of the longitudinal muscle produced by nicotine is likewise reduced by doses of the amines which have little or no effect on the contractions produced by histamine and acetylcholine.

3. Sympatholytic agents prevent these two actions of the dihydroxyphenylalkylamines without influencing those of hexamethonium and of nicotine, but do not antagonize the block produced by hexamethonium and by paralytic doses of nicotine.

4. Monohydroxyphenylalkylamines and phenylalkylamines are feeble in these actions ; they are not affected by sympatholytic drugs.

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