INHIBITION OF PERISTALTIC REFLEX BY SYMPATHOMIMETIC DRUGS

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The Action of sympathomimetic amines has been studied on peristaltic reflex in guinea-pig ileum by Trendelenburg's method with slight modification. It has been shown that all the sympathomimetic amines used, cause inhibition of peristalsis and this action is blocked by priscol. The inhibitory action of dihydroxyphenyl-alkylamines on peristaltic reflex can be blocked by smaller doses of phenyl-alkylamines. The inhibition of peristalsis caused by sympathomimetic amines can be revived by neostigmine. Sympathomimetic amines block the action of acetylcholine, but do not block that of nicotine on longitudinal movements of guineapig ileum. These observations suggest that all the sympathomimetic drugs used in this work cause inhibition of peristalsis by blocking the intestinal ganglia.

During our work on the mechanism of action of parasympathomimetic drugs on peristalsis, we observed that neostigmine could restart peristalsis in the isolated guineapig ileum which had been inhibited by ephedrine. This observation did not seem to fit in with the conclusions arrived at by Mc Dougal and West (1954), who had studied the mechanism of action of sympathomimetic amines in producing inhibition of the peristaltic reflex. According to them, the dihydroxyphenylalkylamines produced inhibition of peristalsis by blocking the ganglia in the intestine, and their action was blocked by sympatholytic drugs. The phenylalkylamines, according to them, produced inhibition of peristalsis in a nonspecific manner, and their action was not blocked by sympatholytic agents.

Sharma and Grewal have shown (1962) that neostigmine restarts peristalsis which has been inhibited by ganglionic blocking agents, by stimulating the ganglia in the intastinal wall. Since ephedrine-inhibited peristalsis could be restarted by neostigmine, therefore, it seemed to us that ephedrine should be producing inhibition of peristalsis by blocking the ganglia. It was thus thought to be of interest to restudy the mechanism of action of various sympathomimetic amines, and the results are described in this paper.

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METHODS

Peristalsis in guinea-pig ileum.—Trendelenburg's method was followed for recording peristaltic activity in the guinea-pig ileum with slight modifications as described by Sharma and Grewal (1963). Peristalsis was allowed to continue for two min by raising the reservoir to a critical height. The intestine was given two min rest periods by lowering the reservoir. The drugs were kept in the bath for two min before eliciting their effects on peristalsis. Neostigmine was added to the bath to revive peristalsis after it had been inhibited by the sympathomimetic amines.

Longitudinal movements of guinea-pig ileum.—A piece of guinea-pig ileum was mounted in an isolated organ bath for recording longitudinal movements of the intestine according to the method described by Burn (1952). Action of acetylcholine (1 μg/ml), nicotine (5 μg/ml) and neostigmine (5 μg/ml) was seen with and without sympathomimetic amines. All the drugs used with their doses are shown in Table 1.

TABLE I
Showing the drugs with their doses

Drugs	Doses
Adrenaline	0.1 μg/ml
Noradrenaline	0.1 μg/ml
Isopropylnoradrenaline	25 μg/ml
Ephedrine	100 μg/ml & 200 μg/ml
Amphetamine	100 μg/ml & 200 μg/ml
Methylamphetamine	100 μg/ml & 200 μg/ml
Acetylcholine	1 μg/ml
Nicotine	5 μg/ml
Neostigmine	5 μg/ml
Priscol	50 μg/ml & 400 μg/ml

RESULTS

Peristalsis in guinea-pig ileum.—All the sympathomimetic amines produced inhibition of peristalsis in the doses shown in Table I. In this respect adrenaline and noradrenaline are the most potent, followed by isoprenaline, which has moderate potency, while ephedrine, amphetamine and methylamphetamine are least potent, and relatively large doses of these drugs are required to produce inhibition of paristalsis (Fig. 1, 2 and 3).
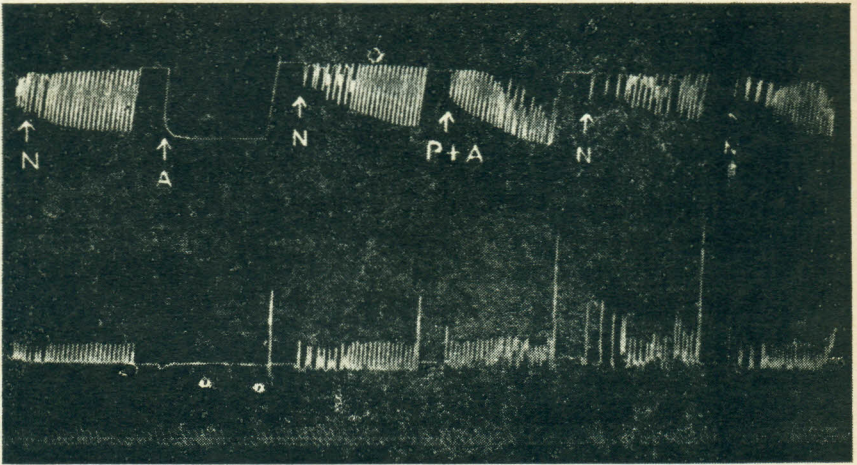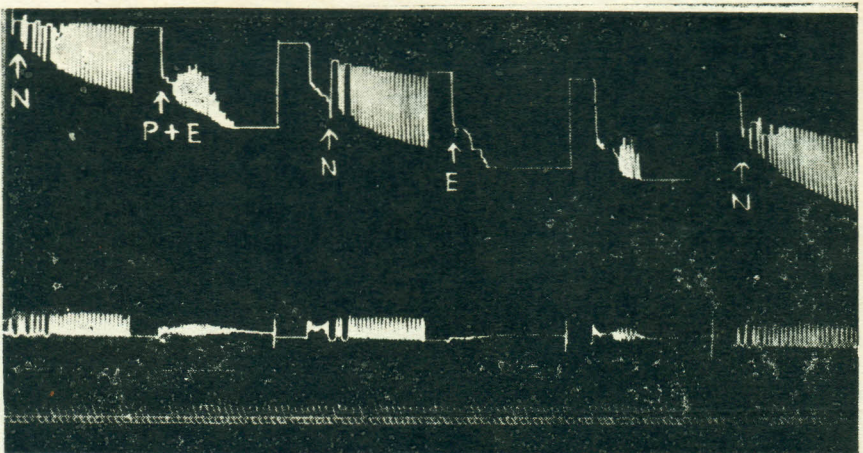
Fig. 1. Effect of adrenaline on the peristalsis in guinea-pig ileum and its blockade by priscol.
Upper tracing, peristalsis.   Lower tracing, longitudinal movements.   N, normal peris-
talsis.   A, adrenaline 0·1 μg/ml, P+A, adrenaline 0·1 μg/ml, in presence of priscol
50 μg/ml.
Time marking every ten seconds.
Note the complete blockade of the effect of adrenaline hy priscol.

Fig. 2.   Effect of ephedrine on the peristalsis in guineapig ileum and its blockade by priscol.
Upper tracing, peristalsis.   Lower tracing, longitudinal movements.   N, normal peris-
talsis.   E, ephedrine 200 μg/ml, P+E, ephedrine 200 μg/ml in presence of priscol
400 μg/ml.
Time marking every ten seconds.
Note the complete inhibition of persistalsis by ephedrine and recovery after 4 min.
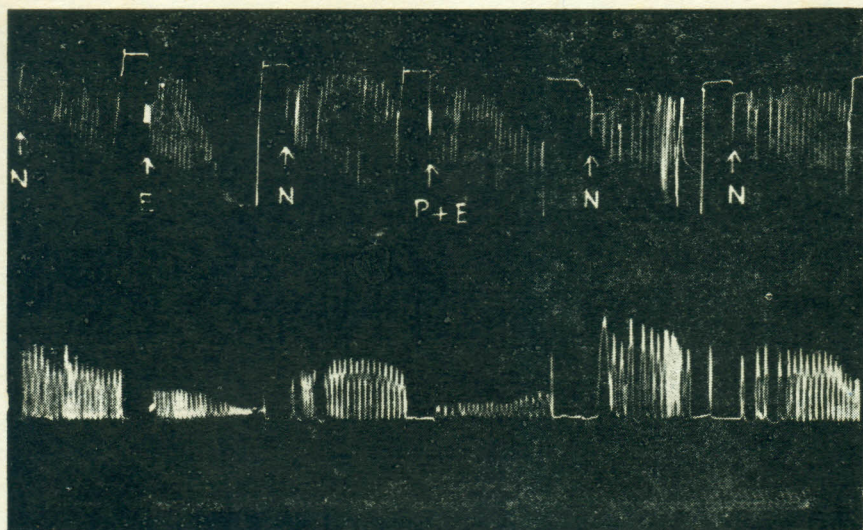Priscol has partially blocked the effect of ephedrine and recovery has come after 2 min.

Fig. 3. Effect of ephedsine on the peristalsis in guinea-pig ileum and its blockade by priscol.
Upper tracing, peristalsis. Lower tracing, longitudinal movements. N, Normal peristalsis. E, ephedrine 100 μg/ml P+E, ephedrine 100 μg/ml in presence of priscol 400 μg/ml
Time marking every ten seconds.
Note the partial inhibition of peristalsis by ephidrine and its complete blockade by priscol.

The action of adrenaline, noradrenaline and isopropylnoradrenaline was completely blocked by priscol in doses of 25—50 μg/ml In the cases of ephedrine, amphetamine and methylamphetamine, if the inhibition of peristalsis was complete, then priscol in doses of 400 μg/ml partially blocked their action, but if the inhibition was partial, then priscol in the above dose completely blocked their effect in producing inhibition of peristalsis. Priscol by itself, in doses of 400 μg/ml, did not modify peristalsis, but with larger doses it caused a depression of peristalsis, eventually producing complete inhibition (Fig. 4).

Neostigmine produced revival of peristalsis inhibited by the sympathomimetic drugs used in this study (Fig. 5 and 6).

Ephedrine, amphetamine and methylamphetamine in doses of 5 μg/ml completely blocked the action of adrenaline, noradrenaline and isopropylnoradrenaline (Fig. 7).

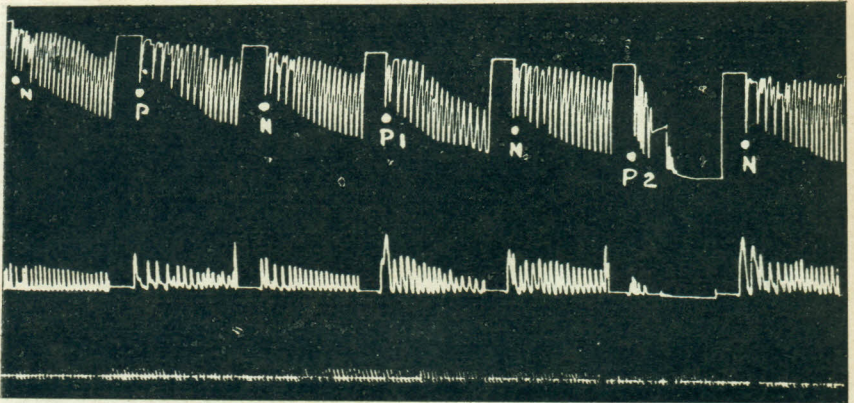Fig. 4. Effect of priscol on peristalsis.
Upper tracing, peristalsis. Lower tracing, longitudinal movements. N, normal. P, 200 μg/ml, P1, 400 μg/ml, P2, – 800 μg./ml.
Time marking every 20 seconds.
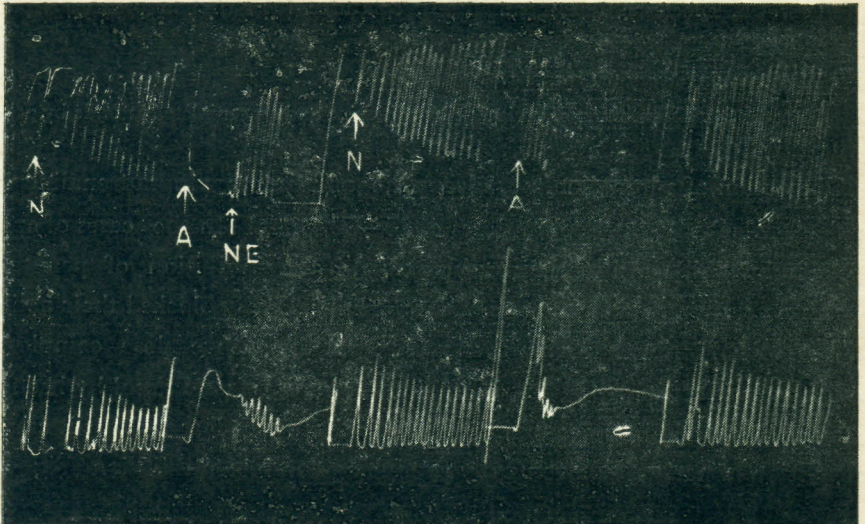Note the inhibition of peristalsis by priscol 800 μg/ml.

Fig. 5. Effect of neostigmine on the inhibition of peristalsis caused by adrenaline in guinea-pig ileum.
Upper tracing, peristalsis. Lower tracing, longitudinal movements. N, Normal. A, Adrenaline 0·1 μg/ml, NE, Neostigmine 5 μg/ml.
Time marking every ten seconds.
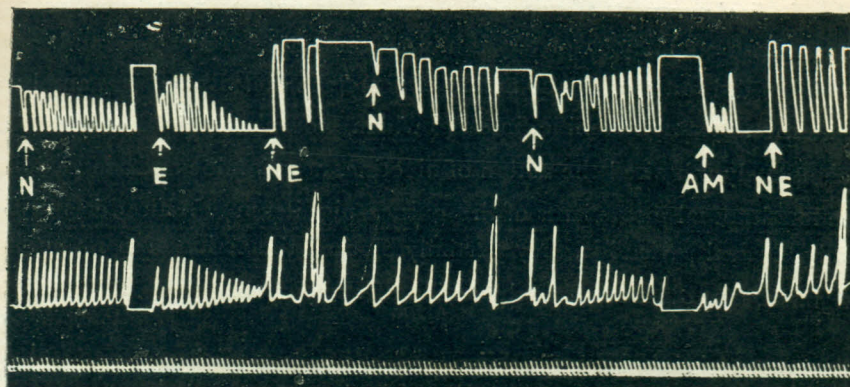Note the revival of peristalsis by neostigmine.

Fig. 6.   Effect of neostigmine on the inhibition of peristalsis caused by ephedrine and amphetamine.

Upper tracing, peristalsis. Lower tracing, longitudinal movements. N,—Normal peristalsis. E,—Ephedrine 100 μg/ml, NE,—Neostigmine 5 μg/ml, AM, 'Amphetamine' 100 μg/ml.

Time marking every 10 seconds.

Note the action of neostigmine in reviving peristalsis inhibited by ephedrine and amphetamine.
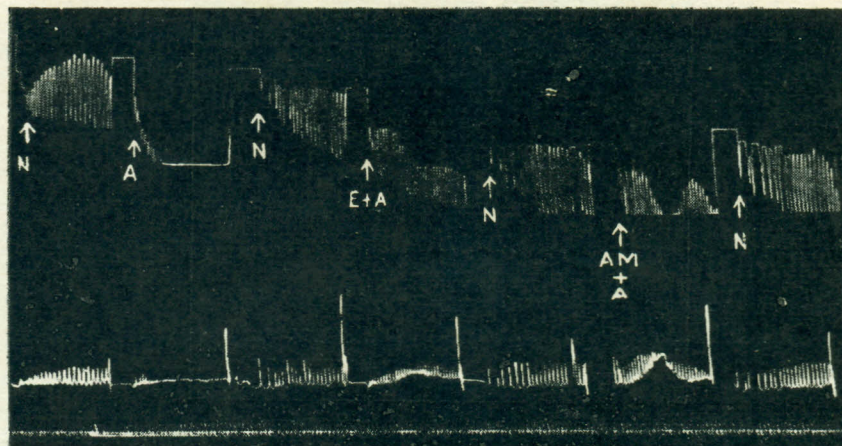

Fig. 7.   Effect of ephedrine and amphetamine in blocking the action of adrenaline on peristalsis in guinea-pig ileum.

Upper tracing, peristalsis.

Lower tracing, longitudinal movements. N, normal peristalsis. A, adrenaline 0·1 μg/ml, E+A, adrenaline 0·1 μg/ml, in presence of ephedrine 5 μg / ml, AM + A, adrenaline 0·1 μg/ml, in presence of amphetamine 5 μg/ml.

Time marking every 10 seconds.

Note the blockade of adrenaline response by ephedrine as well as amphetamine.

Longitudinal movements of guinea-pig ileum.—Adrenaline, noradrenaline and isopropylnoradrenaline completely inhibited the action of nicotine and neostigmine, but did not modify the action of acetylcholine. Ephedrine, amphetamine and methylamphetamine, in doses which completely inhibit peristalsis, also completely inhibited the action of nicotine, neostigmine and acetylcholine on the longitudinal movements of the guinea-pig ileum. With doses which partially blocked peristalsis, they partially blocked the action of nicotine and neostigmine, but did not affect the action of acetylcholine (Figs. 8, 9 and 10).

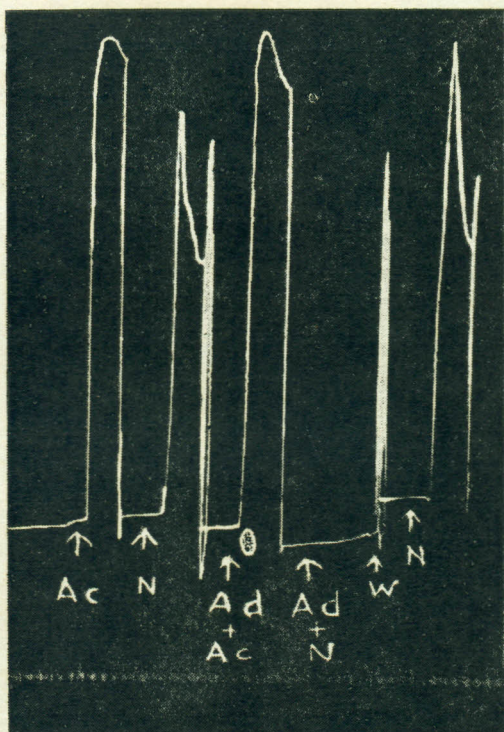
Fig. 8.   Effect of acetylcholine and nicotine in presence of adrenaline on longitudinal movements of the guinea-pig ileum.

Ac, acetylcholine 1 µg / ml, N, nicotine 5 µg/ml, Ad, adrenaline 0·1 µg/ml, W, wash.

Time marking every 10 seconds.

Note the absence of nicotine response in the presence of adrenaline. Nicotine is producing its usual effect after the wash.
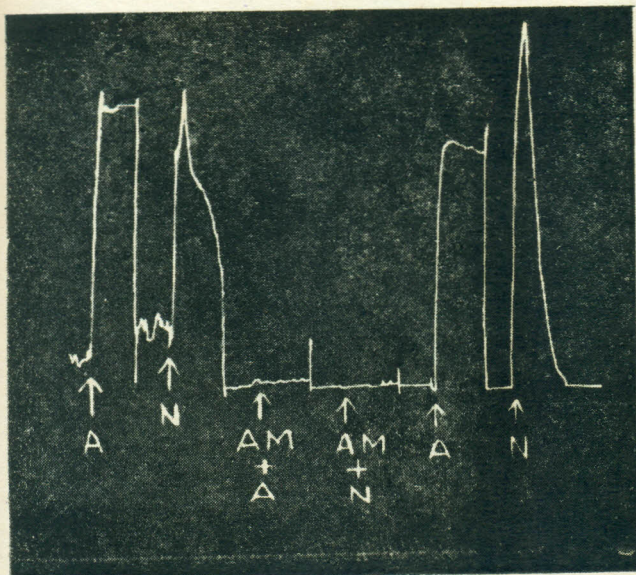
Fig. 9. Effect of acetylcholine and nicotine in the presence of amphetamine.

A, acetylcholine 1 μg/ml. N, nicotine 5 μg/ml. AM, amphetamine 200 μg/ml. Time marking every 10 seconds.

Note the absence of response of acetylcholine and nicotine in presence of amphetamine

Fig. 10, Effect of acetylcholine and nicotine in presence of ephedrine. N, nicotine 5 μg/ml. A, acetylcholine 1 μg/ml. E, ephedrine 100 μg/ml.

Time marking every 10 seconds.

Note the significant partial inhibition of the response of nicotine in presence of ephedrine. There is insignificant lsight inhibition of the response of acetylcholine also.

DISCUSSION

All the sympathomimetic drugs used in this study inhibit peristalsis in the isolated guinea-pig ileum. However, they differ in their potency to a considerable extent. In this respect, adrenaline and noradrenaline are most potent, followed by isopropylnoradrenaline, which has moderate potency, while ephedrine, amphetamine and methylamphetamine are least potent, and relatively large doses of these drugs are required to produce inhibition of peristalsis.

The inhibition of peristalsis produced by these drugs is blocked by priscol. In the case of dihydroxyphenylalkylamine, relatively small doses of priscol (25-50 μg/ml) are needed to completely block their inhibitory effect, while larger doses of priscol (400 μg/ml) are required to complete'y block the effect of those doses of phenylethylamine which produced partial inhibition of peristalsis. The doses of phenylethylamine which produced complete inhibition of peristalsis could only be partially blocked by priscol. This is contrary to the observation of McDougal and West (1954), who did not observe any antagonism between sympatholytics and phenylalkylamines. The reason for this discrepancy might lie in the ratio of the sympathomimetic to the sympatholytic drug used by the two workers. Since priscol blocks the effect of sympathomimetic drugs by competitive antagonism, therefore, the ratio of the dose of sympathomimetic to sympatholytic would determine how good the antagonism is going to be. In their experiments the dose of phenylalkylamine seems to be higher than that of priscol, whereas in our experiments the dose of priscol was four times more than that of phenylethylamines. In order to completely block the inhibitory action of dihydroxyphenylalkylamines, the dose of priscol needed is 50-250 times that of dihydroxyphenylalkylamine. Bigger doses of priscol against phenylalkylamines could not be used as it produced inhibition of peristalsis by itself.

It was observed that priscol could only partially block the effect or larger doses of phenylethylamines. In addition to the above-mentioned difficulty in obtaining the proper ratio of the two antagonistic drugs, there seemed to be the possibility that diphenylalkylamines might be depressing the plain muscle of the intestine directly by what has been referred to by McDougal and West (1954) as "nonspecific" action. In order to test this possibility, the Feldberg's method (1949) was used. He has shown that drugs that block the action of nicotine on the longitudinal muscle of the isolated ileum, but do not modify the action of acetylcholine are acting by blocking the ganglia in the intestine. Sharma & Grewal (1962) have shown that neostigmine can be used in place of nicotine with advantage for this purpose. Dihydroxyphenylalkylamines have been shown to block the action of nicotine and neostigmine,

but not that of acetylcholine, thus confirming their locus of action being the ganglia in the intestine.

It is interesting to note that phenylalkylamines markedly inhibit the nicotine and neostigmine action, but do not affect the acetylcholine response in doses in which they partially inhibit peristalsis. However, phenylalkyalamines in doses which completely inhibit peristalsis, also completely block the action of nicotine and neostigmine as well as acetylcholine. This indicates that in larger doses phenylalkylamines, in addition to their action on the intestinal ganglia, exhibit a direct depressant action on the smooth muscle of the intestine.

Ephedrine has been shown to block the action of adrenaline on the blood sugar of rabbits (Grewal and Deshpande, 1961) and on the isolated rabbit intestine (Burn, 1952). This has been interpreted as being due to the blocking of the receptors by a weaker drug, thus leaving fewer receptors available for adrenaline with consequent diminution of its effect. It was, therefore, of interest to note that ephedrine and other phenylalkylamines blocked the action of adrenaline on peristalsis. It has been shown by McDougal and West (1954), and also in our experiments, that adrenaline produces inhibition of peristalsis by blocking the intestinal ganglia. The inhibition of adrenaline effect by phenylalkylamines would indicate that the two drugs are competing for the same receptors and the site of their action is at the level of intestinal ganglia.

It was also interesting to observe that neostigmine restarted peristalsis in the guineapig ileum after it had been inhibited by sympathomimetic amines. Sharma and Grewal (1962) have shown that neostigmine restarts peristalsis, which has been inhibited by ganglion blocking agents, by stimulating the ganglia in the intestinal wall. The fact that neostigmine restarted peristalsis inhibited by phenylalkylamines would indicate that these drugs inhibit peristalsis by causing the depression of ganglia in the intestinal wall.

It seems to us that phenylalkylamines produce inhibition of peristalsis in the guineapig ileum mainly by acting on the intestinal ganglia in a manner similar to that of dihydroxyphenylalkylamines. This conclusion is based on the following observations, (i) Priscol blocks the action of phenylethylamines, (ii) Neostigmine can restart peristalsis after it has been inhibited by phenylalkylamines, (iii) The action of dihydroxyphenylalkylamines is blocked by phenylalkylamines, (iv) Phenylethylamines block the action of nicotine and neostigmine without affecting that of acetylcholine.

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