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INTERACTIONS OF SYMPATHOMIMETIC DRUGS AND THEIR ANTAGONISTS ON THE ISOLATED ATRIUM

BY

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In the isolated guinea-pig atrium, phenoxybenzamine and other antagonists of sympathomimetic drugs and the adrenergic nerve blocking agent guanethidine inhibited the action of butyrylcholine and tyramine and potentiated the action of noradrenaline. Also in the isolated guinea-pig atrium, phenoxybenzamine and cocaine abolished the parasympathetic, and potentiated the sympathetic, effects of vagus stimulation.

In the isolated atrium phenoxybenzamine appears to mimic cocaine. Huković (1959) found that both phenoxybenzamine and cocaine potentiate the effect of sympathetic nervous stimulation in rabbit atria. Since Holtz (1959) showed that cocaine inhibits the nicotinic action of butyrylcholine, it appeared to be of interest to investigate the effect of phenoxybenzamine in this respect. It has now been found that phenoxybenzamine and other antagonists of sympathomimetic agents inhibit the action of butyrylcholine and tyramine like cocaine and potentiate the action of noradrenaline. On the other hand, McEwen (1956) found that cocaine potentiates the sympathetic effects of vagus stimulation, and a similar action of phenoxybenzamine has now been found.

The adrenergic nerve blocking drug bretylium inhibits the nicotinic action of acetylcholine but potentiates the action of tyramine (Huković, 1960). However, it has now been found that a similar agent, guanethidine, inhibits the effects of both butyrylcholine and tyramine while potentiating the effect of noradrenaline.

METHODS

The isolated guinea-pig atrium preparation has been described before (Greeff, Benfey & Bokelmann, 1959). For the vagus stimulation the right vagus nerve was fixed on a Perspex rod electrode in the bath.

The following drugs, kindly donated by the manufacturers, were used: phenoxybenzamine (Dibenzyline hydrochloride), dibenamine hydrochloride and chlorpromazine sulphoxide (S.K.F. 4260-A) from Smith, Kline & French; phentolamine (Regitine methanesulphonate) and guanethidine (Ismelin) from Ciba; piperoxane (Benzodioxane hydrochloride) from Poulenc; chlorpromazine (Megaphen) from Bayer; yohimbine from Kali Chemie; dihydroergotamine from Sandoz; opilon (acetoxythymoxyethyldimethylamine) and butyrylcholine bromide from Diwag; and noradrenaline (Arterenol) from Farbwerke Hoechst.

RESULTS

Seven minutes after a dose of phentolamine (17 μg/ml.) the action of butyrylcholine (3 μg/ml.) was prevented, the action of tyramine (3 μg/ml.) was inhibited,

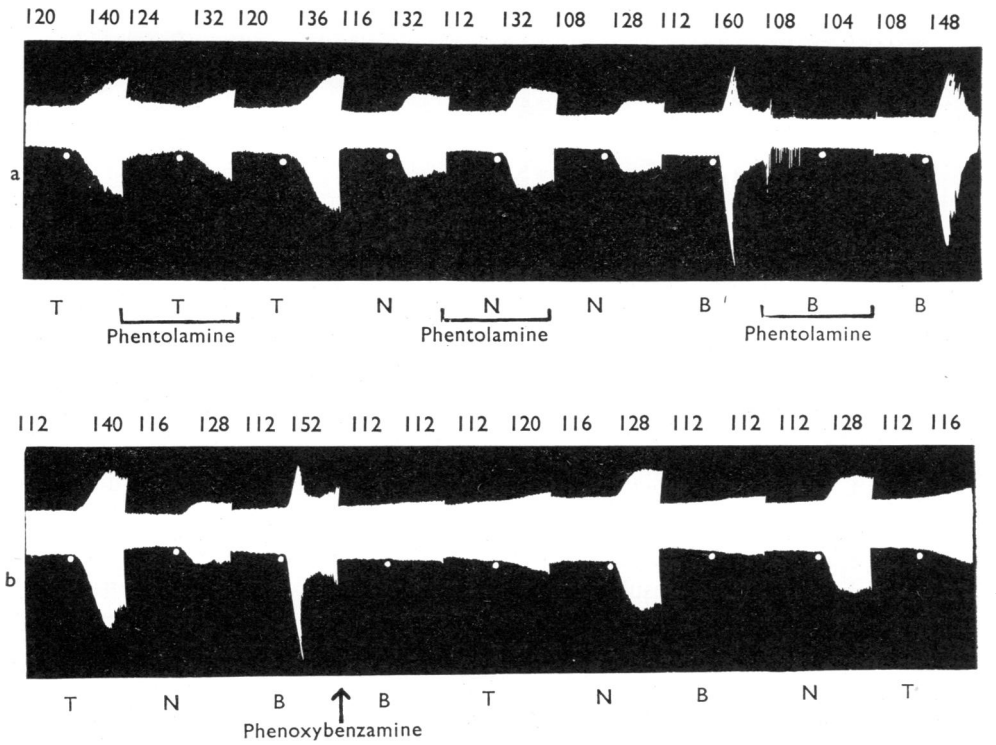

Fig. 1. Isolated guinea-pig atrium. Kymograph record taken from 3 min before until 3 min after the administration of each drug. Not recorded again until 4 min after washing out the bath. The numerals at the top of the record show the atrial rate. T=tyramine (3 μg/ml. in *a* and 7 μg/ml. in *b*); B=butyrylcholine (3 μg/ml.); N=noradrenaline (0.05 μg/ml.). During the periods marked by bars phentolamine (17 μg/ml.) was added (immediately after washing out the previous dose). In *b*, at the arrow phenoxybenzamine 25 μg/ml. was added. The bath was washed out 15 min later and the kymograph was started after an additional 4 min.

and the action of noradrenaline (0.05 μg/ml.) was potentiated (Fig. 1 A). Washing restored the activity of the drugs. The same preparation was then exposed to phenoxybenzamine (25 μg/ml.) for 15 min and the bath washed out (Fig. 1 B). The effects now were irreversible, and there was a prolonged depression of the actions of butyrylcholine and tyramine and a potentiation of that of noradrenaline.

Other antagonists of sympathomimetic drugs inhibited the response to tyramine while potentiating or not affecting that to noradrenaline. Dibenamine (25 μg/ml.) had a prolonged effect, whereas the effects of the other agents were more or less readily reversible by washing out the bath. These were: piperoxane (5 μg/ml.), chlorpromazine (3 μg/ml.), chlorpromazine sulphoxide (3 μg/ml.), dihydroergotamine (8 μg/ml.), yohimbine (5 μg/ml.), and opilon (17 μg/ml.).

Depression of the action of butyrylcholine was mostly obtained with smaller doses than were needed to inhibit the action of tyramine, for example, phentolamine

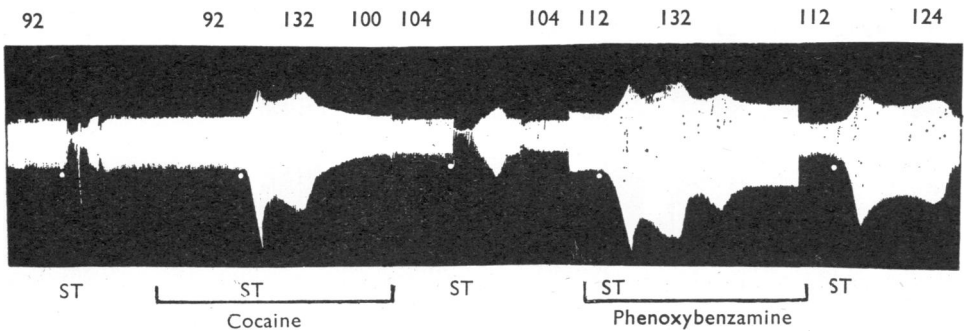

Fig. 2. Isolated guinea-pig atrium. The numerals at the top of the record show the atrial rate. At ST, the vagus was stimulated for 1.5 min with pulses of 4 mA, 1 msec duration and a frequency of 10/sec. During the period marked by the first bar cocaine 5 μg/ml. was present in the bath, and during the second bar phenoxybenzamine 25 μg/ml. was present.

(4 μg/ml.), piperoxane (3 μg/ml.), chlorpromazine (1 μg/ml.), and dihydroergotamine (4 μg/ml.).

An exposure of 5 to 10 min to 2 μg/ml. of guanethidine reversed the stimulant action of butyrylcholine, resulting in a transient depression of atrial contractions. To inhibit the action of tyramine the dose of guanethidine was increased threefold; the response to noradrenaline was potentiated under these conditions.

Fig. 2 shows that both cocaine (5 μg/ml.) and phenoxybenzamine (25 μg/ml.) converted the inhibitory effect of vagus stimulation to an excitatory one. The action of cocaine was readily reversible by washing out the bath; however, that of phenoxybenzamine persisted for a prolonged period of time.

DISCUSSION

It is puzzling that cocaine and phenoxybenzamine potentiate the effect of sympathetic stimulation (Huković, 1959) but inhibit the action of butyrylcholine. Therefore, although prevented by hexamethonium (Holtz & Westermann, 1955), the action of butyrylcholine cannot be simply a stimulation of sympathetic ganglia.

The indirectly acting sympathomimetic agents butyrylcholine and tyramine are presumably antagonized by prevention of the release of endogenous catecholamine. However, it has been found that some antagonists of sympathomimetic drugs, for example, phenoxybenzamine (Benfey, 1961), and dibenamine, phentolamine and chlorpromazine (Benfey & Varma, 1961), stimulate the heart of the spinal dog and cat, an effect prevented by reserpine or guanethidine pretreatment and apparently due to a release of endogenous catecholamine.

The sympathomimetic drug antagonists and cocaine did not convert the excitatory effect of butyrylcholine to an inhibitory one, as did reserpine (Greeff *et al.*, 1959), bretylium (Huković, 1960) and guanethidine. Furchgott (1954) found that dibenamine prevented the inhibitory action of acetylcholine in the isolated rabbit auricle. He concluded that dibenamine is an antagonist of parasympathomimetic drugs. This may also account for the prevention by phenoxybenzamine of the initial depressant effect of vagal stimulation.

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