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RELATIVE ACTIONS OF QUATERNARY METHYL DERIVATIVES OF TYRAMINE, DOPAMINE AND NORADRENALINE

BY

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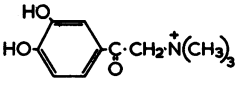
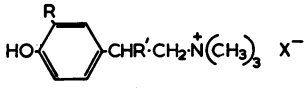
Tyramine methiodide and dopamine methobromide have greater pressor effect (three- to five-times) in the spinal cat than the parent amines. Noradrenaline methochloride has little pressor effect. Dopamine methobromide is about four times as potent as nicotine; tyramine methiodide is about equiactive to nicotine; and noradrenaline methochloride has only one-tenth the potency of nicotine. Their pressor effects are usually abolished by hexamethonium but in some experiments the effect of noradrenaline methochloride persisted and was then abolished by tolazoline. Injected intravenously into the cat anaesthetized with chloralose, each of the three quaternary derivatives contracts the nictitating membrane; dopamine methobromide is again the most active, having more than six times the potency of nicotine. When the contractions of the nictitating membrane are induced by continuous stimulation of the preganglionic fibres of the cervical sympathetic nerve, intravenous injection of the quaternary derivatives of tyramine and dopamine has a biphasic effect; there is a block on which a contraction of the membrane appears to be superimposed. Noradrenaline methochloride produces only a further contraction of the membrane. On the isolated rectus abdominis muscle preparation of the frog, dopamine methobromide is the most active in contracting the muscle, being about twelve times as active as nicotine; noradrenaline methochloride is weakest, having only one-hundredth the activity of nicotine. These effects are antagonized by hexamethonium. On the isolated phrenic nerve-diaphragm preparation of the rat, the quaternary derivatives of tyramine and dopamine each have neuromuscular blocking properties, 0.7- and 3-times respectively that of nicotine. Noradrenaline methochloride has no effect. In the sciatic nerve-tibialis preparation of the cat, the quaternary derivatives of tyramine and dopamine are approximately equipotent in producing neuromuscular paralysis, having about three times the activity of nicotine and one-fifth that of suxamethonium. These effects are not antagonized either by neostigmine or by edrophonium. Noradrenaline methochloride has no neuromuscular blocking effect. The nicotine-like properties of these quaternized sympathomimetic amines are discussed. It is of interest that the presence of an hydroxyl group attached to the β-carbon atom of the side-chain greatly reduces nicotine-like activity. By comparison, choline had about one forty-fifth the pressor activity of ethyltrimethylammonium.

The elucidation of the chemical structure of adrenaline, at the end of the last century, stimulated the synthesis of a number of related compounds. Dakin (1905), in examining the activity of a series of these compounds, noted that the quaternary compound (1)



(1)

had greater pressor activity than had the corresponding primary amine. Barger & Dale (1910) then studied the effect of quaternization on certain amines. They found that hordenine methiodide, for example, the quaternary derivative of tyramine (2 ; R=R′=H),



(2)

(X^-=chloride, bromide or iodide)

had nicotine-like properties, whereas hordenine itself (the *NN*-dimethyl derivative of tyramine) was sympathomimetic. They also found that the quaternary derivative of dopamine (2 ; R=OH, R′=H) had a more powerful nicotine-like action than hordenine methiodide, "approximating closely to nicotine itself." Feldberg & Vartiainen (1935) have reported that hordenine methiodide has both a stimulant and a paralysing action on the superior cervical ganglion of the cat.

It was therefore considered of interest to investigate more closely the relative nicotine-like properties of the quaternary derivatives of tyramine and dopamine and of the quaternary derivative of noradrenaline (2 ; R=R′=OH), which has recently been reported to be practically free from adrenergic effects (Pratesi, 1962). Some experiments with ethyltrimethylammonium and choline were also included for comparison.

A preliminary account of this work has been given by Burn, Cuthbert & Wien (1963).

METHODS

Blood pressure of the spinal cat. Cats weighing 2 to 3.8 kg were anaesthetized with ether and spinal preparations were made by cutting the spinal cord at the level of the second cervical vertebra and destroying the brain. Blood pressure was recorded from the left carotid artery with a mercury manometer.

Nictitating membrane preparation of the cat anaesthetized with chloralose. Cats weighing 1.8 to 3.7 kg were anaesthetized with chloralose (60 to 80 mg/kg, intravenously). The contractions of the membrane were recorded by a frontal writing lever with a magnification of approximately seven. The severed right cervical sympathetic nerve was stimulated continuously with supramaximal shocks, 0.5 msec duration, at 10 shocks/sec. In some experiments the contractions of both nictitating membranes were recorded, intermittent stimulation (20 shocks/sec for 20 sec every 3 min) being applied to the preganglionic fibres of one side and to the postganglionic fibres of the other side.

Frog rectus abdominis muscle preparation. The preparation was that described by Burn (1952) ; a 12 ml. organ-bath was used.

Rat phrenic nerve-diaphragm preparation. The preparation was that described by Bülbring (1946) ; a 60 ml. organ-bath was used.

Sciatic nerve-tibialis preparation of the cat. Cats weighing 2.25 to 3.4 kg were anaesthetized with chloralose. The contractions of the tibialis anterior muscle in response to supramaximal shocks applied to the sciatic nerve (7 shocks/min, 0.5 msec duration) were recorded as described by Paton & Zaimis (1951).

Rabbit isolated atria preparation. The isolated atria of a rabbit were suspended in a 60 ml. organ-bath containing Locke solution (Burn, 1952).

Thin-layer chromatography. As a test of purity of noradrenaline methochloride, 15 μg samples of adrenaline, noradrenaline and noradrenaline methochloride were spotted on a

cellulose thin-layer plate (thickness 0.25 mm) and the chromatogram was developed with saturated aqueous phenol solution. The plate was dried and sprayed with 0.44% potassium ferricyanide solution, phosphate buffered at *p*H 7.8. The method was a modification of that of James (1948). The three samples each showed up as a single reddish spot of the following R_F values: adrenaline 0.36, noradrenaline 0.2 and noradrenaline methochloride 0.68. The spots of adrenaline and noradrenaline fluoresced very brightly under ultra-violet light but noradrenaline methochloride gave no fluorescence. The presence of the single spot from noradrenaline methochloride showed it to be a pure compound uncontaminated by adrenaline or noradrenaline.

Drugs. The following substances were used: the quaternary derivative of tyramine, tyramine methiodide {[2-(4-hydroxyphenyl)ethyl]trimethylammonium iodide; m.p. 232–233° C}; the quaternary derivative of dopamine, dopamine methobromide {[2-(3,4-dihydroxyphenyl)ethyl]-trimethylammonium bromide; m.p. 241–243° C}; the quaternary derivative of noradrenaline, noradrenaline methochloride {(±)-[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]trimethyl-ammonium chloride; m.p. 171–172° C}; adrenaline B.P., noradrenaline bitartrate, tyramine hydrochloride, dopamine hydrochloride, nicotine acid tartrate, hexamethonium bromide, 1,1-dimethyl-4-phenylpiperazinium iodide, tolazoline chloride, atropine sulphate, suxamethonium bromide, neostigmine methylsulphate, edrophonium chloride, ethyltrimethylammonium iodide and choline chloride. All doses are given in terms of active base unless otherwise stated.

RESULTS

Pressor effects in the spinal cat

Experiments were performed to determine the effect of quaternization on the pressor activity of tyramine, dopamine and noradrenaline. Suitable doses of each amine and its quaternary derivative were injected intravenously to give points below and above a 60 mm Hg rise of pressure. This was done because the log dose/response curves for each amine and its quaternary derivative were not parallel and in addition a degree of tachyphylaxis was encountered even when an interval of 10 to 15 min was allowed between injections. Three experiments were carried out for each compound. Tyramine methiodide was 3.4-times, and dopamine methobromide 5-times, as active as their parent amines, but noradrenaline methochloride had only 0.002-times the pressor activity of noradrenaline (Table 1).

TABLE 1

PRESSOR ACTIVITIES OF TYRAMINE, DOPAMINE AND NORADRENALINE RELATIVE TO THOSE OF THEIR QUATERNARY DERIVATIVES IN THE SPINAL CAT

All drugs are expressed in terms of active base. Values for quaternary derivatives are mean and standard errors. There were three experiments for each derivative.

	Pressor activity of	
	Amine	Quaternary derivative
Tyramine	1·0	3·35 ±0·48
Dopamine	1·0	4·97 ±1·64
Noradrenaline	1·0	0·0016±0·0004

Effect of hexamethonium on pressor action. In a total of five experiments hexamethonium bromide (4 mg/kg), which blocked the pressor effect of nicotine (200 to 350 μg) and dimethylphenylpiperazinium (50 μg), completely blocked the pressor

effect of the quaternary derivatives of tyramine and dopamine (Fig. 1). In two experiments the pressor effect of noradrenaline methochloride was abolished by hexamethonium bromide; in two other experiments the pressor effect was only reduced (by 54% and 41% respectively), but was subsequently abolished by tolazoline (Fig. 1,*d*).

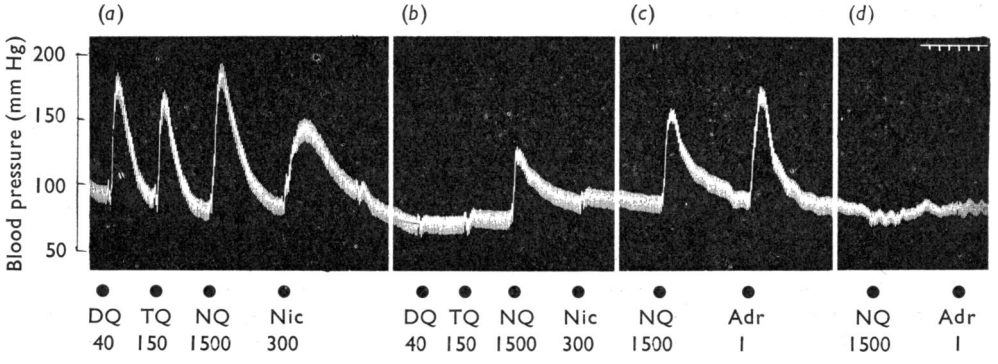


Fig. 1. Record of blood pressure of spinal cat. DQ, dopamine methobromide; TQ, tyramine methiodide; NQ, noradrenaline methochloride; Nic, nicotine; Adr, adrenaline. Doses (given in μg) refer to intravenous injections. Between (*a*) and (*b*), 4 mg/kg of hexamethonium bromide were injected intravenously; between (*b*) and (*c*) 10 mg/kg of hexamethonium; between (*c*) and (*d*), 5 mg/kg of tolazoline hydrochloride. Time marks, 30 sec. Note that the pressor effect of noradrenaline methochloride persisted in the presence of hexamethonium but was abolished by tolazoline.

Comparison with pressor effects of nicotine. Doses of each quaternary compound were injected intravenously into spinal cats and the pressor effects were compared with those of standard doses of nicotine. Four experiments were carried out for each compound. The log dose/response curves for the quaternary compounds were approximately parallel, suggesting a similar mode of action. In each experi-

TABLE 2

RELATIVE ACTIVITIES OF NICOTINE AND THE QUATERNARY DERIVATIVES OF TYRAMINE, DOPAMINE AND NORADRENALINE

All drugs are expressed in terms of active base. Values are means with standard errors. *Approximate value. The numbers in parentheses indicate the number of experiments with each quaternary compound. The headings refer to the pressor effect in the spinal cat; the direct response of the relaxed nictitating membrane; contracture of the frog isolated rectus abdominis muscle; neuromuscular block of the rat phrenic nerve-diaphragm and the cat sciatic nerve-tibialis preparation; and increase in rate of the rabbit isolated atria in the presence of atropine.

	Cat blood pressure (4)	Cat nictitating membrane (3)	Frog rectus abdominis (7)	Rat phrenic nerve-diaphragm (5)	Cat sciatic nerve-tibialis	Rabbit atria
Nicotine	1·0	1·0	1·0	1·0	1·0	1·0
Tyramine methiodide	1·01±0·26	2·5±0·53	0·6±0·17	0·72±0·07	3·3*	—
Dopamine methobromide	3·91±1·21	6·5±1·12	12·2±3·5	3·26±0·53	3·0*	4·0*
Noradrenaline methochloride	0·12±0·04	0·65±0·02	0·01±0·002	0	0	—

ment corrected values were calculated by applying the formula: $y=mx+c$($y=$ corrected value; $m=$slope; $x=$logarithm of dose; $c=$intercept). The relative potencies were calculated from the parallel log dose/response curves drawn on the corrected values. Tyramine methiodide was approximately equipotent to nicotine; dopamine methobromide was approximately four times as active as nicotine; but noradrenaline methochloride was only one-tenth as active as nicotine (Table 2).

Effects on the nictitating membrane

Intravenous injection of each of the three quaternary derivatives in the cat anaesthetized with chloralose caused a contraction of the nictitating membrane. In three experiments, comparable effects were obtained by nicotine, 175 to 325 μg, tyramine methiodide, 75 to 100 μg, dopamine methobromide, 20 to 40 μg, and noradrenaline methochloride, 0.5 to 1.25 mg. The relative potencies are shown in Table 2. Hexamethonium bromide (4 mg/kg) completely abolished the contractions produced by the quaternary derivatives.

When the severed preganglionic fibres of the cervical sympathetic nerve were stimulated continuously, intravenous injection of the quaternary derivatives of tyramine and dopamine caused a small initial contraction of the membrane, then a transient block, followed by a more pronounced block of longer duration (six experiments). On the other hand, only a superimposed contraction was observed with up to 2 mg/kg of noradrenaline methochloride (Fig. 2). In four experiments,

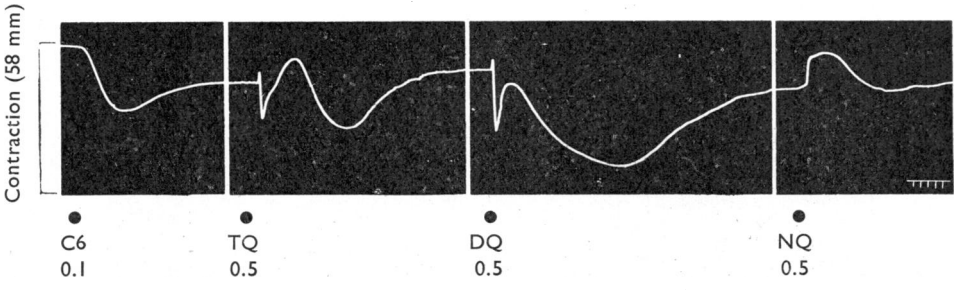


Fig. 2. Cat, anaesthetized with chloralose. Record of the responses of the nictitating membrane during continuous stimulation of the preganglionic cervical sympathetic nerve (supramaximal) 10 shocks/sec, pulse duration 0·5 msec). Initial height of contraction of membrane, 58 mm. C6, hexamethonium bromide; TQ, tyramine methiodide; DQ, dopamine methobromide; NQ, noradrenaline methochloride. All drugs were injected intravenously in the doses (mg/kg) shown. Time marks, 30 sec. Note the biphasic responses with the quaternary derivatives of tyramine and dopamine; noradrenaline methochloride produced only a superimposed contraction.

the ability of the quaternary derivatives to block continuous stimulation of the preganglionic cervical sympathetic nerve was compared with that of hexamethonium. The quaternary derivatives of tyramine and dopamine had, respectively, 0.12 ± 0.04 and 0.4 ± 0.15 (means and standard errors) the potency of hexamethonium; noradrenaline methochloride was inactive. In two experiments where both the preganglionic and postganglionic fibres of the cervical sympathetic nerve were stimulated intermittently, doses of the quaternary derivatives of tyramine and

dopamine (1.5 mg/kg and 0.25 to 0.5 mg/kg respectively) sufficient to block the effect of preganglionic stimulation, had no significant effect on the contractions caused by postganglionic stimulation. The observed effects must, therefore, have been at the ganglion. In one experiment the most active compound, dopamine methobromide, was injected directly to the superior cervical ganglion through the lingual artery, the external carotid artery being temporarily occluded (Fig. 3). The quaternary compound was approximately 3.5-times as active as nicotine under these conditions.

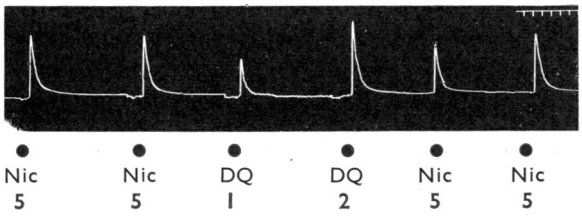


Fig. 3. Cat, anaesthetized with chloralose. Record of the contractions of the unstimulated nictitating membrane. Injections (doses in μg) were into the lingual artery with the external carotid artery temporarily occluded. Nic, nicotine ; DQ dopamine methobromide. Time marks, 30 sec. Dopamine methobromide has approximately 3·5-times the activity of nicotine.

Effects on skeletal muscle and on neuromuscular transmission

The quaternary derivatives were tested (*a*) on the frog isolated rectus abdominis muscle, (*b*) on the rat isolated phrenic nerve-diaphragm, and (*c*) on the sciatic nerve-tibialis muscle preparation of the cat anaesthetized with chloralose.

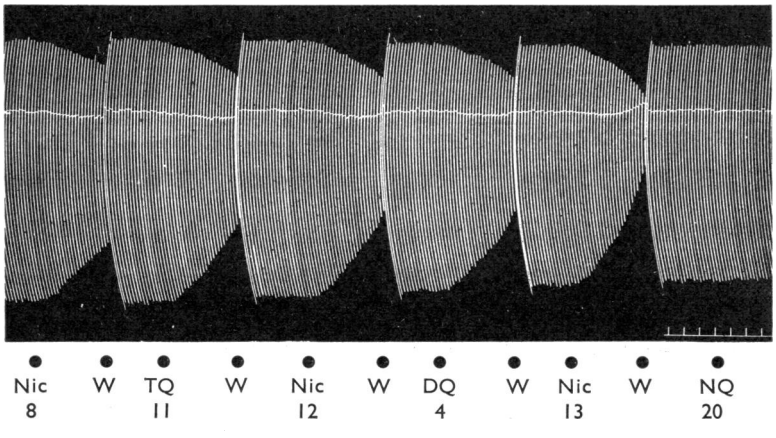


Fig. 4. Record of the contractions of a rat isolated diaphragm preparation stimulated electrically through the phrenic nerve (supramaximal shocks at 9 shocks/min, pulse duration 0·5 msec). Krebs solution at 25° C in a 60 ml. organ-bath. Nic, nicotine ; TQ, tyramine methiodide ; DQ, dopamine methobromide ; NQ, noradrenaline methochloride ; W, wash. Doses in mg. Time marks, 30 sec. Tyramine methiodide was approximately equipotent with nicotine ; dopamine methobromide had approximately three-times the activity of nicotine; noradrenaline methochloride had no effect.

(*a*) Each of the three compounds produced a contracture of the frog rectus muscle. Log dose/response curves of the quaternary derivatives were compared with that of nicotine. The quaternary derivatives of tyramine, dopamine and noradrenaline had 0.6-, 12- and 0.01-times respectively the activity of nicotine (mean of seven experiments, Table 2). These effects could be antagonized by hexamethonium.

(*b*) The quaternary derivatives both of tyramine and of dopamine had neuromuscular blocking properties on the rat phrenic nerve-diaphragm preparation. Noradrenaline methochloride, up to 330 μg/ml., had no effect (Fig. 4). In five experiments the mean relative potencies to nicotine (=1.0) were tyramine methiodide 0.7, and dopamine methobromide 3.3 (Table 2).

(*c*) In the cat sciatic nerve-tibialis preparation, the effects of intravenous injection of the quaternary derivatives were compared with those of suxamethonium (two experiments) and nicotine (two experiments). Tyramine methiodide was slightly more active than dopamine methobromide ; each produce a neuromuscular block of similar intensity and duration as did suxamethonium, but at about five-times the dosage (Fig. 5). Nicotine (0.75 to 1 mg/kg) caused a neuromuscular block

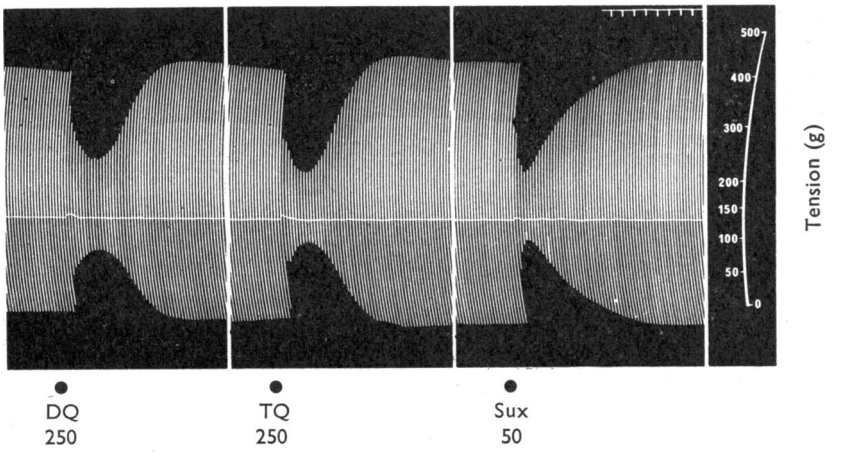


Fig. 5. Cat, anaesthetized with chloralose. Record of the contractions of the tibialis anterior muscle stimulated electrically through the sciatic nerve (supramaximal shocks at 7 shocks/min, pulse duration 0·5 msec.). Sux, suxamethonium ; TQ, tyramine methiodide ; DQ, dopamine methobromide. Drugs injected intravenously (doses in μg/kg). Time marks, 30 sec. Note that the quaternary derivatives of tyramine and dopamine are approximately equipotent and have about one-fifth the activity of suxamethonium.

of long duration. The approximate relative potencies to nicotine (=1.0) were tyramine methiodide 3.3, and dopamine methobromide 3.0. Noradrenaline methochloride had no blocking effect in doses up to 5 mg/kg. Edrophonium chloride (1 mg/kg, intravenously) and neostigmine methylsulphate (50 μg/kg, by retrograde injection into the opposite external iliac artery) did not antagonize the neuromuscular paralysis produced by the quaternary derivatives of either tyramine or dopamine.

Effect on the rabbit isolated atria preparation

In the absence of atropine, both nicotine and dopamine methobromide gave variable responses on the rate and amplitude of the beat of the atria. Nicotine caused either stimulation or a mixture of stimulation and inhibition; dopamine methobromide usually caused a moderate increase in the rate and amplitude of the contractions. In the presence of atropine (1 μg/ml.) both compounds increased the rate and and amplitude of the contractions. In four experiments an increase of between 20 and 40 beats/min over control level was produced by 2 to 20 μg/ml. of nicotine and 0.5 to 5 μg/ml. of dopamine methobromide, giving a ratio of approximately 4:1. Hexamethonium bromide (100 to 200 μg/ml.) diminished but did not obliterate the stimulant effect of dopamine methobromide (Fig. 6).

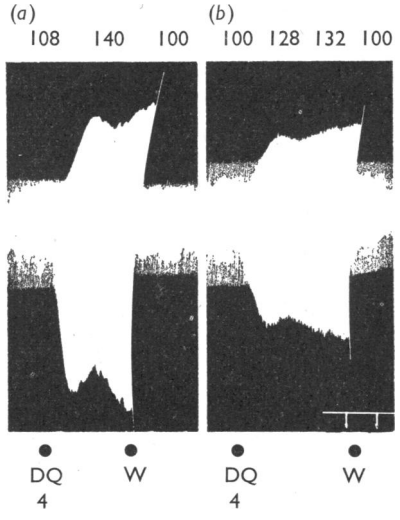


Fig. 6. Record of the contractions of a rabbit isolated atrial preparation in Locke solution at 30° C. DQ, dopamine methobromide ; W, wash. (*a*), in the presence of 1 μg/ml. of atropine sulphate ; (*b*), in the presence of 1 μg/ml. of atropine sulphate and 200 μg/ml. of hexamethonium bromide. The numbers above the tracings refer to the rate of beat of the atria per minute. Doses in μg/ml. Time marks, 30 sec. Hexamethonium reduces but does not obliterate the stimulant effect of dopamine methobromide on the atria.

Ethyltrimethylammonium and choline

In four experiments in the spinal cat the pressor effects of ethyltrimethylammonium bromide and choline chloride were compared. Approximate relative values were obtained by matching the rises of pressure obtained with different doses. The approximate potency of ethyltrimethylammonium and choline on the blood pressure was in the ratio of 46:1 expressed in terms of active base. The pressor effects were completely abolished by hexamethonium bromide (2 mg/kg).

DISCUSSION

Quaternization of the terminal amino-group of both tyramine and dopamine enhanced pressor activity; this is in contrast to the greatly diminished pressor

activity of noradrenaline methochloride. The pressor responses of the quaternary derivatives both of tyramine and of dopamine could be completely blocked by hexamethonium, which indicates that the sympathomimetic action of the parent amines was converted to one of a purely nicotine-like nature, as suggested by Barger & Dale (1910). On the other hand noradrenaline methochloride had only a weak pressor action and did not possess exclusively nicotine-like properties but retained some of its sympathomimetic activity ; in some experiments a component of its pressor action persisted in the presence of hexamethonium, but this effect could be abolished by tolazoline. Since these latter results could have been produced by contamination of the noradrenaline methochloride by noradrenaline or adrenaline, this compound was examined chromatographically. This showed the noradrenaline methochloride to be a pure single substance containing no adrenaline or noradrenaline.

In the nictitating membrane preparation of the cat, the ability of hexamethonium to block the contractions induced by the intravenous injection of the quaternary derivatives indicated a stimulant action on the superior cervical ganglion. Larger doses of the quaternary derivatives of tyramine and dopamine had a blocking action on the membrane. That this action was essentially ganglionic was confirmed by experiments in which the effects of preganglionic stimulation of the cervical sympathetic nerve were selectively blocked, in contrast to those produced by post-ganglionic stimulation. These results may be compared with those obtained by Leach (1957) with dimethylphenylpiperazinium, which possesses both ganglion-stimulant and blocking properties and is thought to act by depolarization. It is interesting to note that noradrenaline methochloride had no demonstrable blocking effect on the nictitating membrane.

Nicotine and the depolarizing type of neuromuscular blocking agent, for example, suxamethonium and decamethonium, are among the compounds capable of producing a contracture of the frog isolated rectus abdominis muscle preparation. All quaternary derivatives studied produced a contracture of this preparation, dopamine methobromide being the most potent ; that their effects were antagonized by hexamethonium suggests a depolarizing mode of action. This suggestion is further supported by the inability of neostigmine or edrophonium to reverse the neuromuscular blocking activity of the quaternary derivatives of tyramine and dopamine on the sciatic nerve-tibialis preparation of the cat. No neuromuscular blocking activity was detected with noradrenaline methochloride, a result which accords with the weak action of this compound on the frog isolated rectus preparation.

An interesting observation was the biphasic nature of the block produced by the quaternary derivatives of tyramine and dopamine on the nictitating membrane previously excited to contract by electrical stimulation of the preganglionic cervical sympathetic nerve. A probable explanation of these effects is that these substances produced a ganglionic block like that due to hexamethonium, but that superimposed on the block was a contraction due to their sympathomimetic action, which corresponded to the effect of noradrenaline methochloride. Noradrenaline methochloride produced only a superimposed contraction, slower in onset, probably caused by its sympathomimetic and weak nicotine-like properties.

If we compare the results at the ganglion and at the neuromuscular junction, dopamine methobromide was the most active at both sites. The ratio of activity of the quaternary derivatives of tyramine and dopamine was different on rat and cat muscle. On the rat phrenic nerve-diaphragm preparation the quaternary derivatives of tyramine and dopamine had 0.7- and 3.3-times the activity of nicotine; in the cat sciatic nerve-tibialis preparation the two quaternary derivatives were approximately equipotent and were both about three times as active as nicotine. Various responses in different species to neuromuscular blocking drugs have previously been noted by Wien (1948).

Dimethylphenylpiperazinium, which has marked ganglion-stimulant properties, has also neuromuscular blocking properties (Riker, 1953; Ling, 1959). On the other hand, some quaternary compounds which have a paralysing action on sympathetic ganglia may have little effect on neuromuscular transmission. For example, Bülbring & Depierre (1949) found that, in the cat, triethyl(2-phenoxyethyl) ammonium iodide, which had a potent action in blocking transmission in the superior cervical ganglion, had a very weak action on the sciatic nerve-tibialis preparation. With the corresponding triquaternary compound, gallamine, the ratio of activity was reversed.

It is interesting to note that the most active compound, dopamine methobromide, had two hydroxyl groups in the nucleus and an unsubstituted side-chain of two carbon atoms. When an hydroxyl group was introduced, attached to the β-carbon atom of the chain (noradrenaline methochloride) the nicotine-like stimulant properties were greatly reduced and paralysing effects at the superior cervical ganglion and at the neuromuscular junction were absent. The same comparison can be made between ethyltrimethylammonium and choline. In the spinal cat ethyltrimethylammonium was approximately 45-times as active as choline on the blood pressure; thus in this pair of compounds also, the presence of an hydroxyl group on the β-carbon atom greatly reduces nicotine-like activity.

Dopamine methobromide had the same order of nicotine-like pressor activity as some of the halogenated phenyl ethers of choline described by Hey (1952).

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