Brit. J. Pharmacol. (1965), **24**, 76–88.

CENTRALLY ACTIVE DRUGS AND TRANSMISSION THROUGH THE ISOLATED SUPERIOR CERVICAL GANGLION PREPARATION OF THE RABBIT WHEN STIMULATED REPETITIVELY

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(*Received May* 18, 1964)

The action of some centrally active compounds on transmission of single impulses through the isolated superior cervical ganglion of the rabbit has been reported by Elliott & Quilliam (1964). Since the sympathetic nerve fibres may transmit 6 to 8 impulses/sec (Folkow, 1952) and investigations of the action of compounds on transmission through the superior cervical ganglion using the nictitating membrane method (Brown & Quilliam, 1964) rely on repetitive stimulation of the preganglionic trunk, the action of centrally active drugs on the repetitively stimulated ganglion is of special interest.

METHODS

The method of recording action potentials from the rabbit isolated superior cervical ganglion preparation and the drugs used were those described by Elliott (1963) and Elliott & Quilliam (1964). Ganglionic potentials, elicited by repetitive supramaximal stimulation of the preganglionic trunk, were recorded with one electrode placed on the ganglion and the other on the postganglionic trunk (Fig. 1). Recordings were made in a moist chamber which could be flooded with Krebs solution equilibrated with 95% oxygen and 5% carbon dioxide between recording periods. Drugs were added to the chamber fluid and allowed to act for 10 min.

A stimulator control apparatus (Bell, 1962) delivered trains of stimuli at a selected frequency. The duration of the train of stimuli was usually 3 sec. A switch, operated by the shutter release mechanism of the oscilloscope camera, triggered the oscilloscope sweep and, after a suitable delay, triggered the train of impulses. The frequency of stimulation lay between 1.4 and 61 shocks/sec.

For most of the experiments, the ganglion was stimulated by 3-sec trains of stimuli at 30-sec intervals in ascending order of frequency at the following rates: 3.3, 9.2, 16.5, 28 and 36 shocks/sec.

Under the experimental conditions described, posttetanic potentiation following single stimuli may last up to 3 min and probably lasts considerably longer after a train of stimuli. A 30-sec interval between trains of stimuli was chosen as a compromise to avoid the necessity for re-immersion in the drug solution between trains of stimuli and yet not to leave the preparation out of the bath fluid for the long period which would elapse if time were allowed for full recovery of the ganglion after each train of stimuli before applying the next train.

As posttetanic potentiation lasted for more than 30 sec in the isolated ganglion, the first two or three stimuli in a train elicited larger responses than the initial response in the preceding train due to potentiation carried over from the preceding train of stimuli. For example, the 16.5-shocks/sec train of impulses potentiated the first few action potentials in the subsequent 28-shocks/sec train even though this train was 30 sec

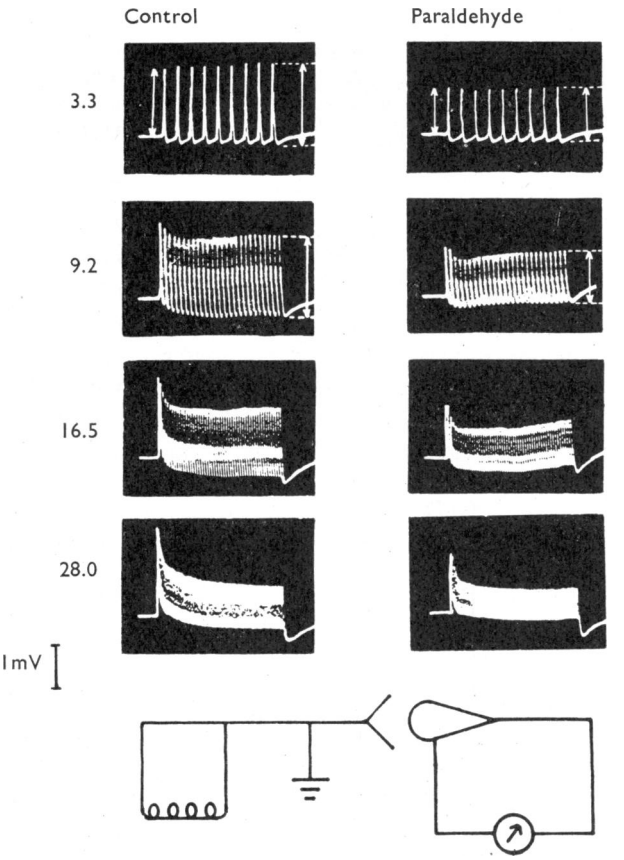


Fig. 1. The effects of paraldehyde (4 mg/ml.) on the response of the ganglion to repetitive stimulation. The first ganglionic potential in the control train at 3.3 shocks/sec is compared with the amplitude of the ganglionic response during the subsequent trains; this measurement is shown by the arrows and dotted lines. Similarly the first ganglionic potential of the 3.3-shocks/sec train of the paraldehyde-treated ganglion is compared with the amplitudes of the repetitive response during subsequent trains in the paraldehyde-treated ganglion. The diagram shows the stimulating and recording arrangement. The effect of paraldehyde is shown graphically in Fig. 2*a*. The ganglion was stimulated for 3 sec at 30-sec intervals. Stimulus frequencies are given on the left in shocks/sec.

later. Measurement of the degree of depression of the ganglionic potential produced by rapid stimulation must be related, therefore, to the first action potential of the first train of the series of trains of stimuli (usually the 3.3-shocks/sec train) as in Fig. 1. Failure to use this form of control results in exaggerated estimates of depression of transmission at the higher rates of stimulation.

The amplitude of the first (control) action potential, against which all comparisons in the control series were made, was measured from the baseline to the peak of the deflection and the amplitude of the response to repetitive stimulation was measured as the total excursion of the potential, namely from the peak of the potential to the lowest point of the P wave (Fig. 1, 3.3 shocks/sec). This latter measurement was made at a point in the train at which the ganglionic responses were of constant amplitude. At rates above about 10 shocks/sec, action potentials succeeded each other at such short intervals that it was impossible to be certain of the origin of each action potential, whereas it was possible to measure the total excursion of the potential at all rates. Clearly the higher the rate of stimulation, the more nearly does this measure correspond to the true amplitude of the spike potential since the individual P waves disappear as the spike

potentials get sufficiently close together to fall on succeeding N waves. There will usually be some apparent facilitation at low rates of stimulation since the amplitude of the control spike potential measured from the baseline is then being compared with the spike potential plus the P wave. Experience showed that P waves in excess of 20% of the spike amplitude were unusual, so that the test response would have to be in excess of 120% of the control before genuine facilitation could be said to have occurred. No adjustments have been made in this respect.

RESULTS

Typical control curves relating stimulus frequency to the amplitude of the ganglionic potential are shown in Fig. 2*a*, *b* and *c* (filled circles). As the stimulus frequency was increased, there was initially a small facilitation of the ganglionic response which declined above about 10 shocks/sec. At higher frequencies the relation between the stimulus frequency and the reduction of the ganglionic potential was almost linear. The broken lines in Fig. 2 show the effect of paraldehyde, hydroxyzine, and methylpentynol carbamate on these responses. The effect of drugs on the relationship between frequency and ganglionic potential is often more clearly seen if the potentials are expressed as a percentage

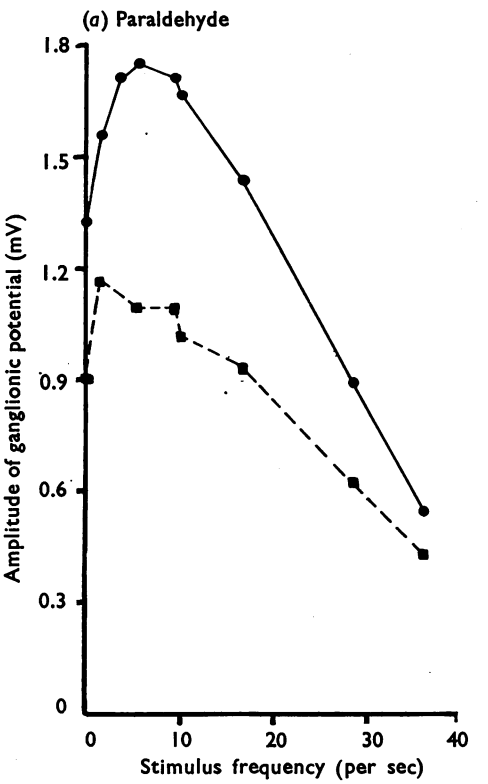
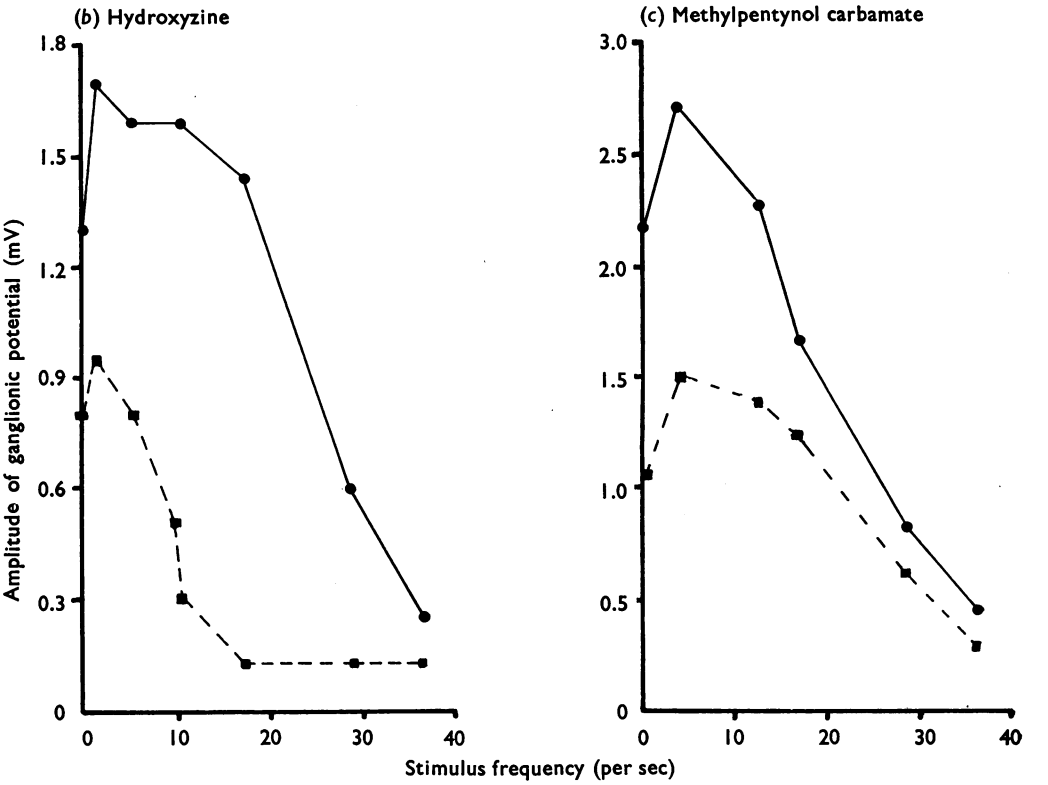


Fig. 2. The relation between the rate of stimulation of the preganglionic nerve trunk and the amplitude of the ganglionic potential. The ganglionic potential was measured as the total excursion of the potential, namely from the peak of the potential to the lowest point of the P wave. This measurement was made at a point in the train at which the ganglionic responses were of constant amplitude. These results are shown as percentage responses in Fig. 3. Solid lines and circles, relation in the absence of drugs; squares and broken lines, relation in the presence of paraldehyde (4 mg/ml., *a*), hydroxyzine (24 μg/ml., *b*) and methylpentynol carbamate (0.8 mg/ml., *c*).

Fig. 2 (*cont.*)



of that to a single volley. Fig. 3*a*, *b* and *c* show corresponding graphs in which the ganglionic potential at various stimulus frequencies has been expressed in this way. This method of presentation has been used in the remainder of the results which will be described.

The relation between the stimulus frequency and the percentage response was essentially unchanged after immersing the ganglion for 10 min in paraldehyde solution (4 mg/ml.) (Fig. 3*a*, broken line) although the amplitude of the response to a single stimulus was reduced to 67% of the control.

On the other hand, a concentration of hydroxyzine (24 μg/ml.) which reduced the response to a single stimulus to 62% of the control decreased considerably the ability of the ganglion to follow repetitive stimulation (Figs. 3*b* and 4).

Methylpentynol carbamate (0.8 mg/ml.) differed from both paraldehyde and hydroxyzine in that it increased the ability of the ganglion to respond to repetitive stimulation. In the experiment analysed in Fig. 3*c*, the ganglionic potential in response to a single stimulus had been reduced to 49% of the control.

Two numerical indices were estimated, firstly I_1 the stimulus frequency necessary to produce a 50% reduction of the ganglionic response to a single stimulus and, secondly, I_2 the response at a rate of 15 shocks/sec expressed as a percentage of the response to a single shock, given in the presence of the same concentration of drug. Fig. 3*a*, *b* and *c* show the method of estimating these indices. Generally speaking, effects on both indices

were qualitatively the same, that is a drug which reduced the rate of stimulation necessary to produce 50% block also reduced the value of the percentage response at 15 shocks/sec. Table 1 summarizes the results. Most of the drugs tested fell into one or other of two groups exemplified by hydroxyzine (Group A) and paraldehyde (Group B) respectively, that is the block was intensified or unaffected by the higher stimulus frequencies. However, a small group of drugs (Group C) increased the percentage response to repetitive stimulation, an action best developed with adrenaline particularly with the higher concentrations and higher rates of stimulation (Figs. 5 and 6).

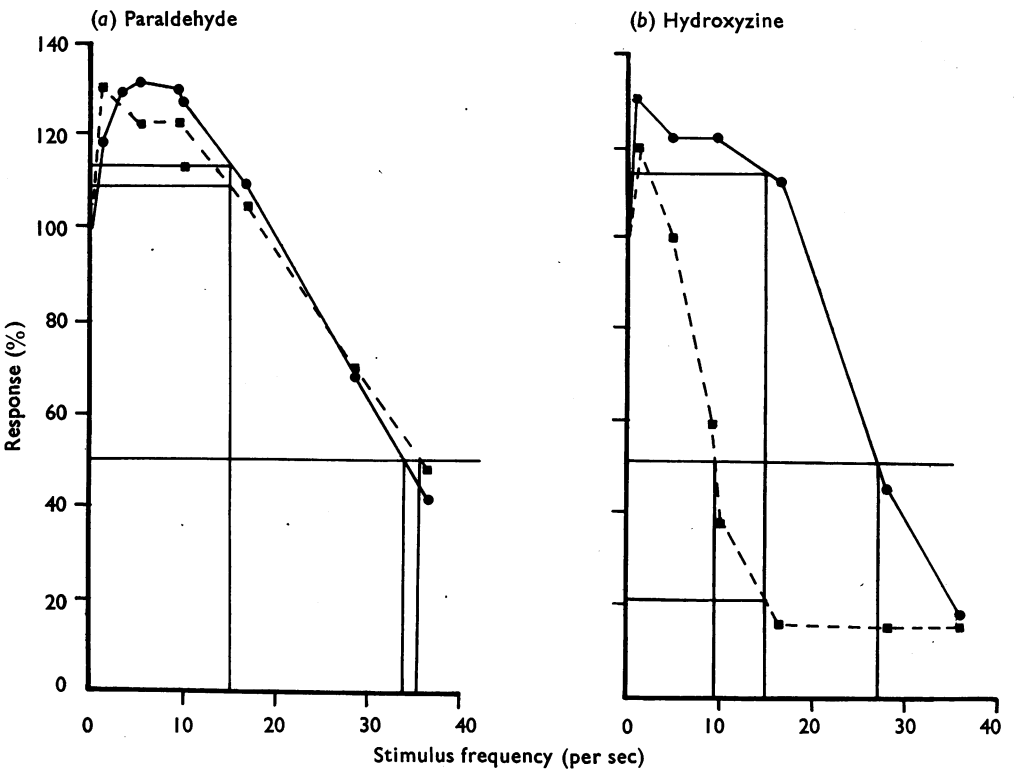
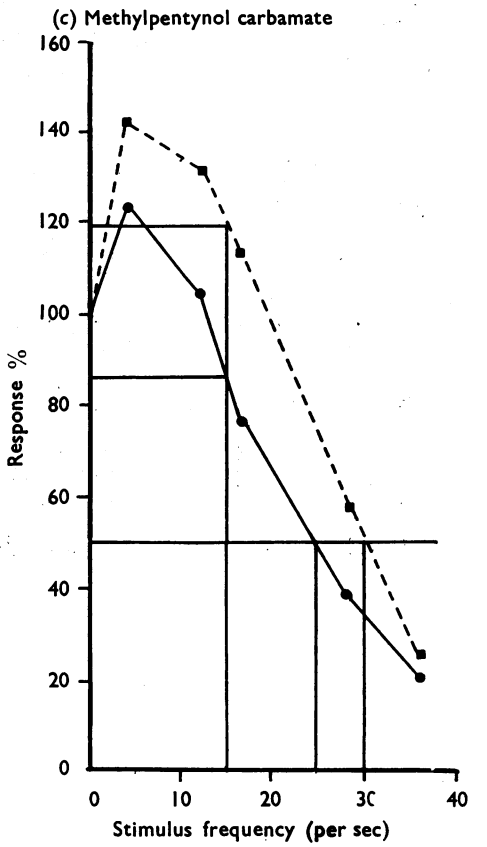


Fig. 3. The relation between stimulus frequency of the preganglionic nerve trunk and the amplitude of the ganglionic potential expressed as a percentage of the first (control) response in the first of a series of 30-sec trains of stimuli calculated as explained in the text. Solid lines and circles, relation in absence of drugs; squares and broken lines, relation in presence of paraldehyde (4 mg/ml., *a*), hydroxyzine (24 μg/ml., *b*) and methylpentynol carbamate (0.8 mg/ml., *c*).

Two methods of numerical expression of the effects of these drugs are shown. I_1, the stimulus frequency giving 50% response for paraldehyde was 35 shocks/sec (control 33.5), for hydroxyzine 9.5 shocks/sec (control 27.5) and for methylpentynol carbamate 30 shocks/sec (control 24.5). I_2, the percentage response at 15 shocks/sec for paraldehyde was 106% (control 113%), for hydroxyzine 21% (control 113%) and for methylpentynol carbamate 118% (control 86%). The ratios $R=I_2$ control/I_2 drug (Table 1) derived from these figures are for paraldehyde 1.07, for hydroxyzine 5.38 and for methylpentynol carbamate 0.73.

Fig. 3 (*cont.*)



A striking example of the action of adrenaline is shown in Fig. 7, in which concentrations of hexamethonium (100 μg/ml.) and adrenaline (2 μg/ml.) were selected which gave approximately the same degree of block of single impulses when tested successively on the same ganglion. Repetitive stimulation at 30 shocks/sec for 3 sec in the presence of hexamethonium resulted in complete block, which stood in marked contrast to the response to repetitive stimulation in the adrenaline-treated ganglion. The ganglionic response to repetitive stimulation was not only increased relative to the amplitude of the response to single stimuli in the adrenaline-treated ganglion (Fig. 7), but at certain stimulus frequencies (for example 16.5 to 28 shocks/sec in Fig. 6) the ganglionic potentials in the adrenaline-treated preparation were larger than those in the control untreated ganglion at the same frequency.

DISCUSSION

The effects of repetitive stimulation on drug-induced ganglion blockade have been reported by Paton & Zaimis (1951) for methonium compounds, Exley (1954) for barbiturate drugs and Matthews (1956) for adrenaline. However, no attempt seems to have been made previously to assess such effects quantitatively. The findings in the present study have been amenable to quantitative assessment. The drugs have been divided into

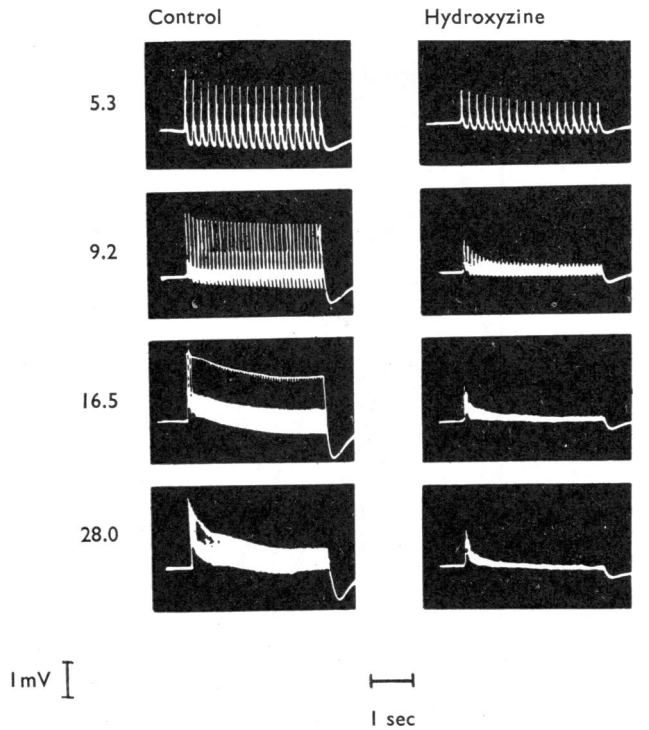


Fig. 4. Recording as in Fig. 1 showing the effects of 24 μg/ml. of hydroxyzine on the ganglionic response to repetitive stimulation. The effect of hydroxyzine is expressed graphically in Fig. 2*b*. Numbers on the left give stimulus frequencies in shocks/sec.

three groups and the position of each drug within its group is determined by the ratio (R) of I_2 (before) to I_2 (after) treatment with the drug, the order being in descending ratio (Table 1). The groups are as follows:

Group A: those drugs, the ganglion-blocking action of which was intensified by repetitive stimulation: hydroxyzine, azacyclonal, benactyzine, promazine, tetraethylammonium, pipradrol, tubocurarine, meprobamate and hexamethonium.

Group B: those drugs, the ganglion-blocking action of which was relatively unaffected by repetitive stimulation: paraldehyde, amylobarbitone and methylpentynol.

Group C: those drugs, the ganglion-blocking action of which tended to be reversed by repetitive stimulation: mescaline, nicotine, methylpentynol carbamate and adrenaline.

Interpretation of these results presents difficulties because the reason for the fall off of ganglionic responses in the absence of drugs during repetitive preganglionic stimulation is still the subject of speculation. Birks & MacIntosh (1961), who measured the acetylcholine release from the perfused superior cervical ganglion of the cat during repetitive stimulation, state that " if prolonged high-frequency stimulation leads to block, the block must be due to lowered sensitivity of the postsynaptic structures to acetylcholine, or to an excess of free acetylcholine, or to an asynchronous release of acetylcholine rather than to a reduction of volley output." However, they pointed out that it is impossible with present methods of assay to measure the output of acetylcholine during the first seconds of stimulation and it is

TABLE 1

THE EFFECT OF CENTRALLY ACTIVE DRUGS ON THE RESPONSE OF THE ISOLATED SUPERIOR CERVICAL GANGLION OF THE RABBIT TO REPETITIVE STIMULATION

The third column shows how the given concentration of the drug affected the transmission of single impulses through the ganglion. The next four columns give the effects of repetitive stimulation on transmission before and after application of the drug. The two numerical indices of transmission block, I_1 and I_2, are given; see text for definitions. The last column gives the ratio R. The drugs have been arranged in order of descending ratio. Where several concentrations of the drug are given, that producing the highest ratio has determined the position of the drug in the table. The table has been divided into three parts corresponding to the three arbitrary groups described in the text

Drug	Concentration (μg/ml.)	Effect of drug on single impulse (% of control)	Stimuli/sec for 50% reduction ($=I_1$)		Effect of 15 stimuli/sec ($=I_2$)		$\frac{I_2 \text{ Control}}{I_2 \text{ Drug}}$
			No drug	Drug	No drug (%)	Drug (%)	(=R)
Group A							
Hydroxyzine	12	103	27·5	23·5	113	95	1·19
Hydroxyzine	18	103	27·5	17·0	113	46	2·46
Hydroxyzine	24	62	27·5	9·5	113	21	5·38
Azacyclonal	100	79	26·5	5·0	110	21	5·24
Benactyzine	12	87·5	26·0	10·0	105	32	3·28
Benactyzine	18	54	26·0	9·5	105	29	3·62
Promazine	1·5	74	26·5	18·5	86	62	1·39
Promazine	3	62	26·5	10·0	97	34	2·85
Tetraethylammonium	75	58	31·0	16·5	120	59	2·03
Tetraethylammonium	75	55	25·5	—	100	57	1·75
Tetraethylammonium	75	37	33·5	20·5	148	68	2·18
Tetraethylammonium	100	62	27·5	13·5	113	46	2·46
Pipradrol	20	31	22·5	9·5	82	40	2·05
Tubocurarine	8	75	25·0	16·0	86	52	1·65
Tubocurarine	15	39	24·0	13·5	94	46	2·04
Meprobamate	800	65	26·0	16·5	100	55	1·82
Hexamethonium	25	83	24·5	21·0	81	72	1·13
Hexamethonium	50	61	24·5	15·0	81	50	1·62
Group B							
Paraldehyde	2,000	78	33·5	34·5	113	111	1·02
Paraldehyde	4,000	67	33·5	35·0	113	106	1·07
Amylobarbitone	50	49	27·5	31·0	94	91	1·03
Amylobarbitone	100	31	27·5	27·5	94	94	1·00
Methylpentynol	3,000	36	33·5	32·5	101	101	1·00
Group C							
Mescaline sulphate	100	76·5	24	25	86	80	1·08
Mescaline sulphate	500	50	24	30·5	86	95	0·91
Mescaline sulphate	800	29	24	31·5	86	100	0·86
Nicotine	1	65	27·5	32·5	94	112	0·84
Nicotine	2	42	27·5	32·0	94	112	0·84
Methylpentynol carbamate	600	62	24·5	32·0	86	118	0·73
Methylpentynol carbamate	800	49	24·5	30·0	86	118	0·73
Adrenaline acid tartrate	1	106	29·0	31·0	116	134	0·87
Adrenaline acid tartrate	10	69	29·0	35·0	116	230	0·50
Adrenaline acid tartrate	100	50	29·0	37·0	116	324	0·36

possible that there may be a rapid decline of acetylcholine output per volley during this period. It seems unlikely that excessive release of acetylcholine could be a factor since the block produced by competitive blocking agents such as hexamethonium was intensified by repetitive stimulation.

The most probable explanation seems to be that there is a diminishing acetylcholine output during the first seconds of fast repetitive stimulation which cannot be examined by the current method of measuring outputs from the perfused ganglion preparation. This might result from the acetylcholine release mechanism functioning less efficiently at high rates of stimulation. If this view is correct, then one would expect the competitive blocking agents (Group A; Table 1) to be more effective at high stimulus frequencies, as indeed they are.

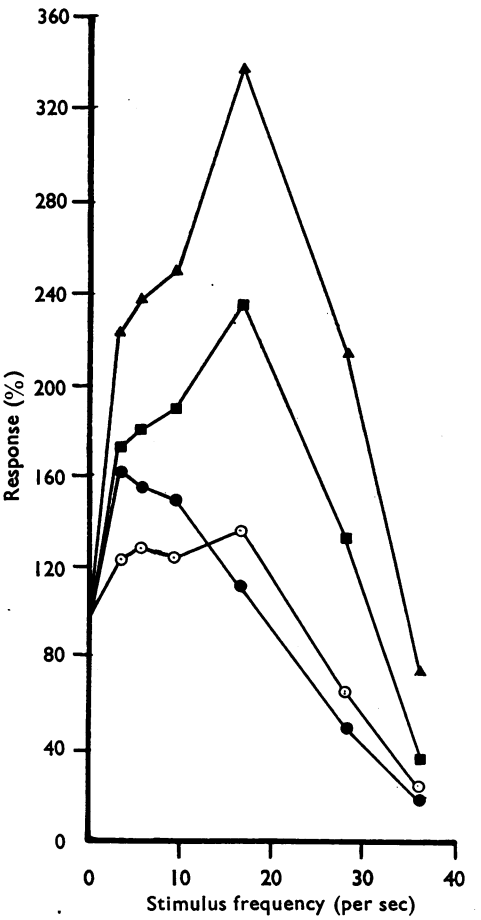


Fig. 5. Graphs illustrating the effect of three concentrations of adrenaline acid tartrate on the response of the ganglion to repetitive preganglionic stimulation. Filled circles, control; empty circles, in the presence of 1 μg/ml.; squares, 10 μg/ml.; and triangles, 100 μg/ml. of adrenaline acid tartrate.

Birks & MacIntosh (1961) have shown that the effect of adrenaline on the acetylcholine output of the ganglion is variable. When the repetitively stimulated ganglion was perfused with plasma instead of Locke solution, adrenaline facilitated the acetylcholine release mechanism. Thus in my experiments adrenaline may have blocked single impulses by its antiacetylcholine action at the postganglionic membrane (Paton & Thompson, 1953), whilst it facilitated the response to repetitive stimulation by its action on the preganglionic terminals.

The suggested mode of action of drugs on transmission through the repetitively stimulated ganglion may be summarized as follows:

Group A. It has been postulated above that the response of the repetitively stimulated ganglion diminished because of a diminished acetylcholine output during the first second or so of fast repetitive stimulation. These drugs could increase synaptic block because (1) they were competitive blocking agents such as tubocurarine, hexamethonium and tetraethyl-

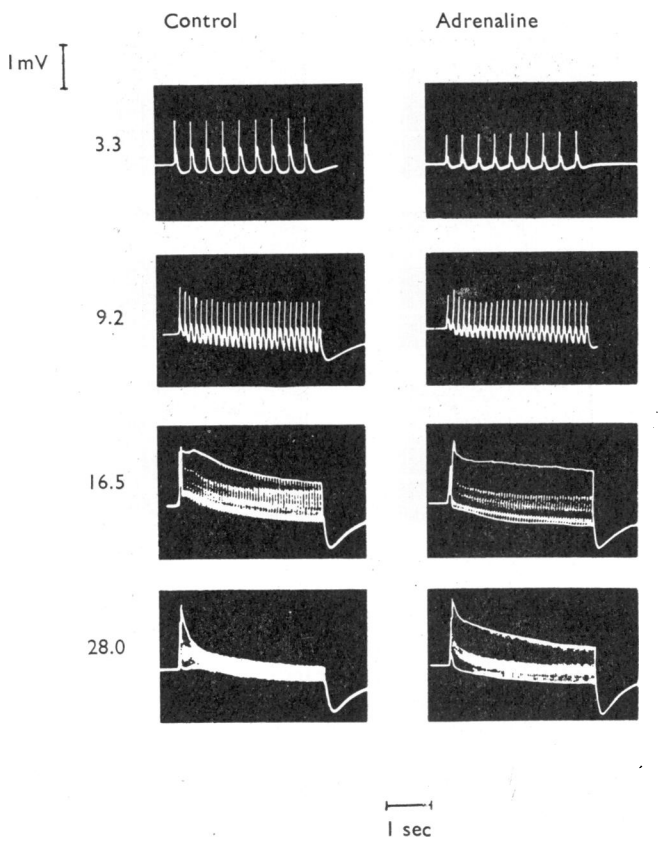


Fig. 6. Recording as in Fig. 1. The effect of 100 μg/ml. of adrenaline acid tartrate on the response of the ganglion to repetitive preganglionic stimulation. The ganglion was stimulated for 3 sec at 30-sec intervals. Note that the train of 3.3 shocks/sec was preceded by a 1.4-shock/sec train and that the first potential of this train (not shown) was taken as the control value for calculating the percentage response. Numbers on the left are stimulus frequencies in shocks/sec.

ammonium; (2) they had an atropine-like antiacetylcholine action, blocking the release of adrenaline (Eccles & Libet, 1961), as, for instance, has benactyzine; or (3) they were antiadrenaline compounds like azacyclonal, promazine, meprobamate and hydroxyzine, and therefore diminished the facilitatory action of naturally released sympathomimetic amines on the repetitively stimulated ganglion. Although Bülbring (1944) and Reinert (1963) have demonstrated the release of sympathomimetic amines from the cat ganglion,

Elliott & Quilliam (1964), in their experiments on the isolated superior cervical ganglion of the rabbit, found no evidence to support a physiological role for adrenaline in ganglionic transmission.

Group B. These compounds shared none of the three properties of the Group A drugs and therefore repetitive stimulation would be expected to have no effect on the degree of block.

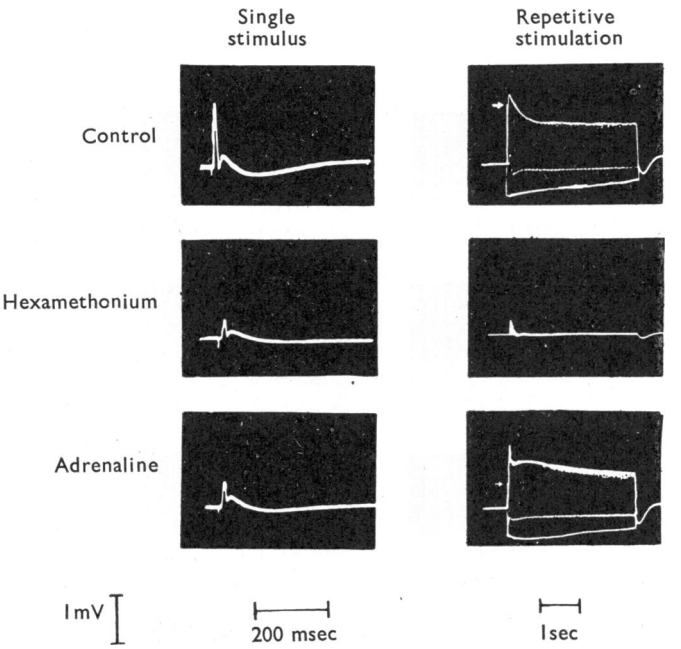


Fig. 7. The effects of 100 μg/ml. of hexamethonium and 2 μg/ml. of adrenaline on the response of the same ganglion to repetitive stimulation. The arrows show the height of the first impulse in each train. In the untreated ganglion the response to repetitive stimulation at 30 shocks/sec declined slightly, after a brief phase of facilitation at the beginning of the train. In the presence of adrenaline the same stimulus frequency approximately doubled the amplitude of later potentials compared with the initial one, whilst it abolished the ganglionic potential in the same preparation treated with hexamethonium. The responses of the ganglion to single supramaximal stimuli are shown in the left-hand column.

Group C. These compounds might supplement a deficient acetylcholine release in the repetitively stimulated ganglion in two ways. They might act as depolarizing agents, as do nicotine and mescaline, or they might facilitate acetylcholine release, as does adrenaline and possibly mescaline.

Methylpentynol carbamate appears in Group C and it is interesting to note that Marley & Paton (1959) have reported that it has a ganglion-stimulant action in the perfused ganglion of the cat, a finding confirmed by Matthews & Quilliam (1964). The reversal by repetitive stimulation of the block of transmission of single impulses produced by adrenaline (Fig. 7) confirms the findings of Eccles & Libet (1961) on the superior cervical ganglion of the rabbit anaesthetized with paraldehyde. Whether adrenaline can facilitate transmission through the ganglion has long been the subject of disagreement (Marrazzi, 1939; Bülbring,

1944; Marrazzi & Marrazzi, 1947; Matthews, 1956; Pardo, Cato, Gijón & Alonso-de Florida, 1963). It is clear that adrenaline may either facilitate or inhibit transmission through the ganglion depending on the stimulus frequency used. Thus in Fig. 6, adrenaline acid tartrate (100 μg/ml.) produced inhibition of transmission when the preganglionic trunk was stimulated at 3.3 shocks/sec but facilitation when the ganglion was stimulated at 16.5 or 28.0 shocks/sec.

The effect of altering the stimulus frequency on the ganglion-block produced by adrenaline is but a particular instance of the general conclusion derived from my findings, namely the importance of selecting a suitable stimulus frequency when testing drugs for their ganglion-blocking properties. This is of especial importance when two drugs are being compared. When a Group A drug, such as tetraethylammonium or hydroxyzine (Fig. 3*b*), is compared with a Group C drug, such as methylpentynol carbamate (Fig. 3*c*), then as the stimulus frequency is raised the block produced by hydroxyzine increases whilst that produced by the carbamate decreases. Consequently the ganglion-blocking activity of the carbamate relative to that of hydroxyzine will decrease as the stimulus frequency increases.

It follows that physiological stimulus frequencies should be used in studies comparing the ganglion-blocking activities of drugs. If high rates of stimulation have to be used, as in the experiments of Brown & Quilliam (1964) with the nictitating membrane method of measuring ganglion block, then both the drugs to be tested and the standard blocking agent with which they are compared should belong to the same group of compounds as defined in this paper.

SUMMARY

1. The action of some centrally active drugs on transmission by the isolated superior cervical sympathetic ganglion of trains of impulses at rates between 1.4 and 61/sec has been studied in the rabbit.

2. Drugs could be divided into three groups according to their action on transmission. Group A (hydroxyzine, azacyclonal, benactyzine, promazine, tetraethylammonium, pipradrol, tubocurarine, meprobamate and hexamethonium) were drugs the blocking action of which was increased by repetitive stimulation. Group B (paraldehyde, amylobarbitone and methylpentynol) were drugs the blocking action of which was unaffected by repetitive stimulation. Group C (mescaline, nicotine, methylpentynol carbamate and adrenaline) were drugs the blocking action of which was partially or completely reversed by repetitive stimulation.

3. Possible modes of action of drugs on the repetitively stimulated ganglion and factors underlying selection of stimulation frequency in experiments designed to assess drug effects on ganglionic transmission are discussed.

This work was undertaken in partial fulfilment of the requirements for the degree of Ph.D. in the University of London and was supported by a grant (No. AF 61(052)-25) from the United States Air Force Office of Scientific Research (OAR) to whom I am most grateful. It is a pleasure to thank Professor J. P. Quilliam and his colleagues for their unfailing help and advice and Mr K. A. H. Didcock and Miss A. Cattermole for technical assistance.

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