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THE RELATIONSHIP BETWEEN DEPOLARIZATION AND BLOCK IN THE CAT'S SUPERIOR CERVICAL GANGLION

By W. D. M. PATON* and W. L. M. PERRY
From the National Institute for Medical Research, Mill Hill, London, N.W. 7

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It is now generally accepted that synaptic transmission in the superior cervical ganglion and at the neuromuscular junction is chemically mediated, and that acetylcholine is the transmitter responsible. The neuromuscular junction has been the more closely studied, and direct evidence has been obtained (Kuffler, 1943) that acetylcholine, applied directly, will produce a local electrical change at the end-plate sufficient to initiate a propagated impulse in the muscle fibre. Moreover, Burns & Paton (1951) showed that acetylcholine's ability to depolarize the end-plate was shared by certain of the neuromuscular blocking agents (e.g. decamethonium) but not by others (e.g. D-tubocurarine).

Direct evidence of this type has not hitherto been available for the ganglionic synapse and, although Brink, Bronk & Larrabee (1946) have shown that intra-arterial perfusion with acetylcholine will produce a train of impulses in the postganglionic fibres, there has been no evidence of a local electrical response of the ganglion cell to injected acetylcholine comparable to that described by Kuffler at the end-plate. Eccles (1935) described slow potential waves localized to the ganglion in response to preganglionic nerve volleys: he showed that nicotine affected these slow waves, but did not apply any such tests to acetylcholine.

Emmelin, MacIntosh & Perry (1949) attempted to show depolarization of the ganglion cell membrane, using the exchange of radio-potassium (^{42}K) across the cell membrane as a measure of depolarization. They found that preganglionic stimulation significantly increased the uptake of radio-potassium by the perfused ganglion. They were unable, however, to show that antidromic stimulation of the postganglionic fibres produced the same effect, so that their experiments were inconclusive, since the effect observed might conceivably

* Present address: University College Hospital Medical School.

have been due to the stimulation of short postganglionic fibres supplying the blood vessels of the ganglion, or to potassium exchange in the stimulated preganglionic nerve terminations.

For these reasons the present experiments were undertaken. They show a local response of the ganglion to injected acetylcholine, and have made possible classification of ganglion blocking drugs according to whether they act like acetylcholine or by preventing its action. Moreover, these experiments have shown that remarkable changes in the shape of the action potential complex are caused by acetylcholine-like drugs, and led to an investigation of the relation between the action potential complex and the cell membrane depolarization. Brief accounts of both of these series of experiments have already appeared (Paton & Perry, 1951*a*, *b*).

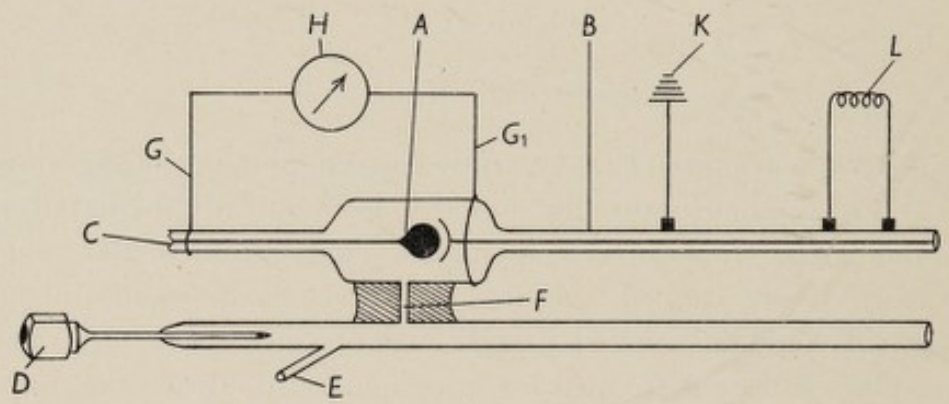

Fig. 1. Recording and injection technique for cat's superior cervical ganglion. *A*, superior cervical ganglion cell; *B*, preganglionic cervical sympathetic trunk; *C*, cut tied end of postganglionic trunk; *D*, needle cannula in distal end of external carotid artery; all other branches of the common carotid are tied except *E*, occipital artery, and *F*, arterial branches supplying the ganglion; *G*, recording electrodes; *H*, d.c. amplifier; *K*, earth lead; *L*, stimulating electrodes.

METHODS

Cats were anaesthetized with ethyl chloride and ether, followed by intravenous chloralose (80 mg/kg). The superior cervical ganglion, usually the right, was prepared as for ganglion perfusion by the method suggested by Kibjakow (1933), but the blood supply was left intact. In order to minimize the mass of inert tissue under the recording leads, the last stage of the preparation consisted of the dissection of the vagus nerve and nodose ganglion away from the cervical sympathetic trunk and superior cervical ganglion. Bleeding at this point is inevitable, since the blood supply to the nodose ganglion passes through the capsule of the superior cervical ganglion; but if care is taken, the bleeding is transient and the preparation does not suffer, and can be used for many hours.

Platinum wire stimulating electrodes were placed on the cut preganglionic cervical sympathetic trunk, and square wave stimuli of 0·5 msec duration were applied at varying frequencies. Non-polarizable (Ag–AgCl) recording electrodes were used, and contact with the ganglion itself and with the cut postganglionic trunk was made by thin silk threads soaked in agar–0·9% NaCl. The arrangement of the electrodes is illustrated diagrammatically in Fig. 1. One lead was looped round the body of the ganglion, the other placed at the point where the postganglionic trunk had been tied and cut.

Retrograde intra-arterial injections were generally used, to avoid the systemic effects of ganglion stimulating drugs, since the vigorous carotid pulsation resulting from intravenous injections interfered seriously with the electrical recording. All the branches of the common carotid artery were tied, except those supplying the ganglion, and a needle cannula was tied into the cut stump of the external carotid artery which was occluded proximal to the cannula by a 'bulldog' clamp operated by remote control. In most experiments the occipital artery was left intact, to permit a free flow of blood past the ganglion, which otherwise lay at the end of a cul-de-sac in the arterial circulation. This procedure appeared to prolong the life of the ganglion, although rather larger doses of drugs were required.

Action potentials from the recording leads in response to single maximal preganglionic volleys were fed into cathode followers, passed through a d.c. amplifier and recorded on one beam of a cathode-ray oscillograph, the second beam being used solely as the marker of an arbitrary base-line. Thus the distance between the two beams provided a measure of the steady potential difference between the ganglion and the cut postganglionic trunk, and slow changes of potential could be recorded as an increase or decrease in this distance. In all our records a negativity of the ganglion relative to the cut postganglionic trunk is recorded as an upward deflexion, whether transiently due to an action potential, or as a relatively prolonged rise in base-line due to a steady depolarization.

Doses of D-tubocurarine chloride, toxiferine I chloride, penta-, hexa-, and decamethonium iodide, nicotine tartrate, tetraethylammonium and tetramethylammonium iodides, and eserine sulphate are given in terms of these salts. Doses of acetylcholine are of the base. Doses of all drugs were usually given in a volume of 0·2 ml. when inspected intra-arterially.

In two experiments the spatial distribution of potential along the ganglion and its postganglionic trunk relative to the cut end of the postganglionic trunk was recorded, using the 'space-base' described by Burns & Paton (1951). With this technique, one electrode is made to traverse the ganglion and its postganglionic trunk, this movement being recorded horizontally on the cathode-ray screen; the other electrode is fixed at the cut end of the trunk, and the potential difference between these electrodes is recorded as a vertical deflexion. In one experiment, the superior cervical ganglion with both its preganglionic and postganglionic trunks was dissected free and immersed in oxygenated Locke's solution at a temperature of 37° C; in the other experiment, the stellate ganglion was isolated in the same way, since it offers a longer postganglionic nerve from which to record. In order to make a recording, the saline bath was removed from round the ganglion for a few seconds.

RESULTS

Effects of injected acetylcholine

Small doses of acetylcholine (1–10 μg intra-arterially; 200 μg intravenously) have as their only apparent effect a transient depolarization of the ganglion. The action potential is not greatly affected, although there are actually definite changes, if not in the spike height of the action potential at least in the accompanying slow waves. Larger doses of acetylcholine (200 μg/i.a.) increase both the extent and the duration of the depolarization, and this is then accompanied by a partial or complete abolition of the action potential (Fig. 2). Where the action potential is only partially abolished there is, in addition to a reduction of the spike height, an obvious distortion in shape, which seems to be due mainly to an effect on the after-positivity. Both the depolarization and the reduction of the action potential may be slightly potentiated by eserine in doses of approximately 200 μg intravenously. These actions are illustrated graphically in Fig. 3. It will be seen that 0·2 mg of acetylcholine

intravenously produced a slight depolarization but no reduction in spike height; in the presence of eserine the same dose produces a larger depolarization accompanied, in this case, by a reduction in spike height. When a dose

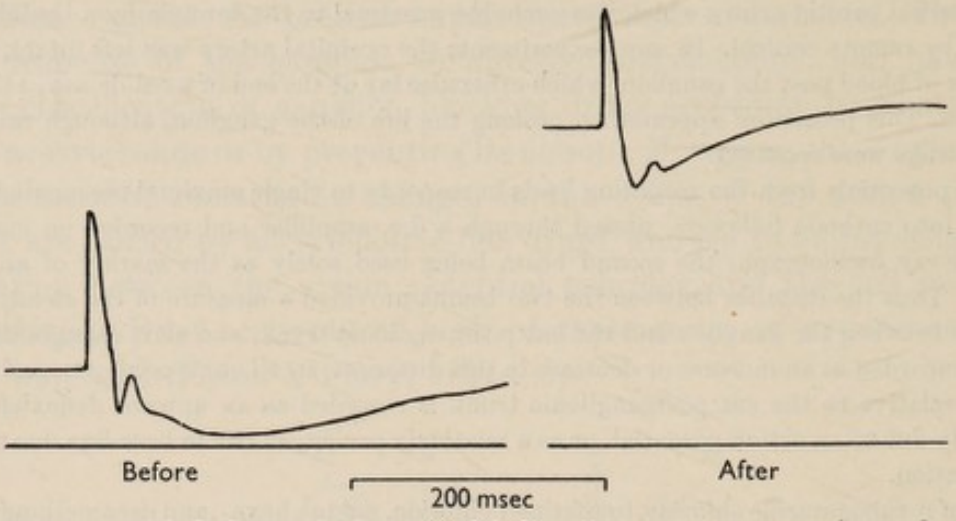

Fig. 2. Action potentials before and after acetylcholine (200 μg i.a.) (traced from photographic records). Cat, chloralose. Upper records—ganglionic action potentials. Lower records—arbitrary base-line. Time scale 200 msec. In this and subsequent figures, an increase in the distance between the arbitrary base-line and the action potential record represents the degree of depolarization of the ganglion.

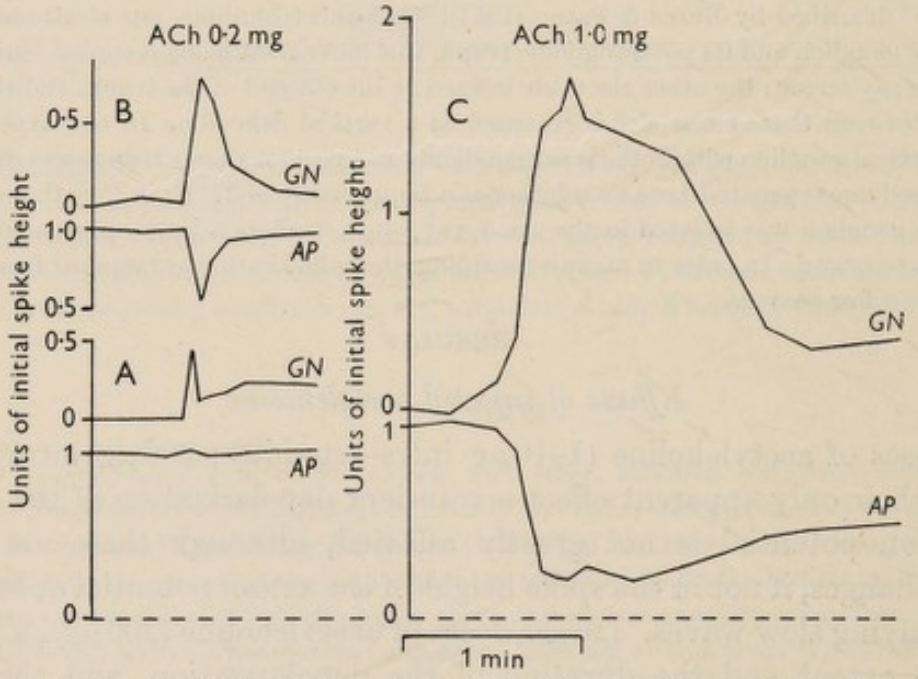

Fig. 3. The effect of acetylcholine on the spike height of the ganglionic action and the depolarization of the ganglion cells. *GN*, ganglionic negativity in terms of initial spike height; *AP*, spike height of action potential. *A*, effect of 200 μg acetylcholine i.v; *B*, effect of same dose of acetylcholine after 200 μg eserine i.v; *C*, effect of 1·0 mg acetylcholine i.v.

of 1·0 mg acetylcholine is injected intravenously, even in the absence of eserine, there is almost complete abolition of the spike with slow recovery during 3–5 min (Fig. 3). Simultaneously there is a depolarization of more than twice the initial spike height.

A study of the onset of, and recovery from, depolarization and block of the spike height following acetylcholine (Fig. 4) shows no simple relationship between the two phenomena. The degree of depolarization for a given degree of reduction of the spike potential is much greater during the onset of the effect than during the recovery from acetylcholine. This may be put in another way; the reduction of spike height is greater for a given degree of depolarization the longer the depolarization has been present.

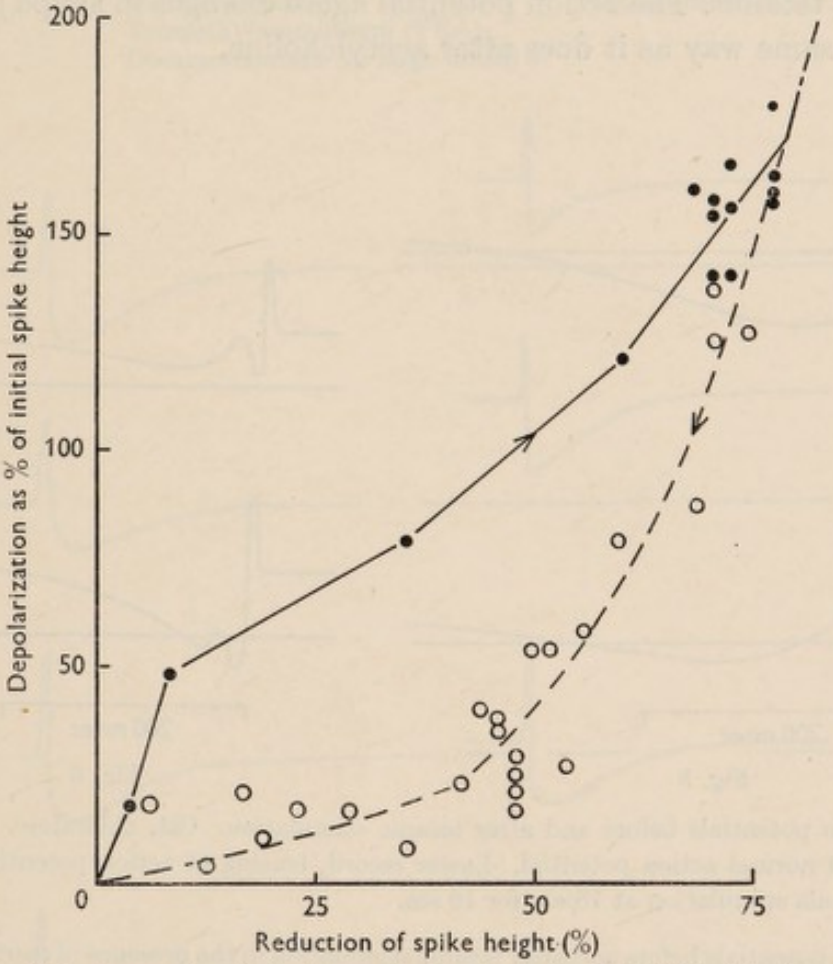

Fig. 4. Relationship between depolarization and reduction of spike height of action potential after acetylcholine. Abscissa: depolarization of the ganglion as percentage of initial spike height. Ordinate: percentage reduction of spike height. Closed circles, during onset of block; open circles, during recovery from block.

Larger doses of eserine, without the administration of acetylcholine, will abolish the action potential without producing any depolarization of the ganglion. This type of eserine block is seen only after single shocks, since in these circumstances tetani release sufficient acetylcholine to produce a depolarization.

The effects of a tetanus

If a tetanus at a frequency of 76 per sec is applied to the preganglionic trunk, a depolarization of the ganglion occurs which outlasts the period of tetanization and of post-tetanic increase of the spike height by 5–10 min. This de-

polarization is slower in development of its peak size than that observed after intra-arterial injections of acetylcholine, possibly because of a concurrent but shorter-lasting after-positivity resulting from the tetanus. At the same time, the shape of the action potential is greatly altered, although in a way quite different from the change produced by acetylcholine (Fig. 5).

The depolarization evoked by a tetanus is still observed in the presence of eserine, and with sufficient eserine the spike height may be reduced considerably by the tetanus. The action potential again changes in shape (Fig. 6), but now in the same way as it does after acetylcholine.

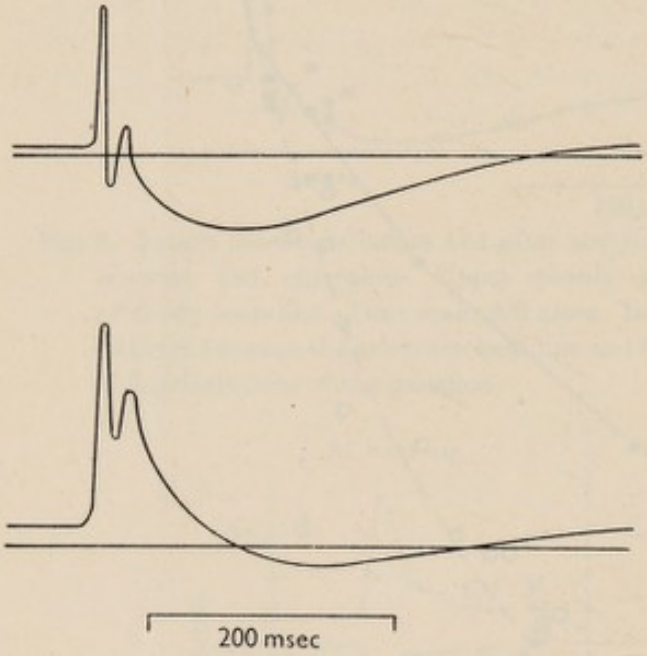

Fig. 5

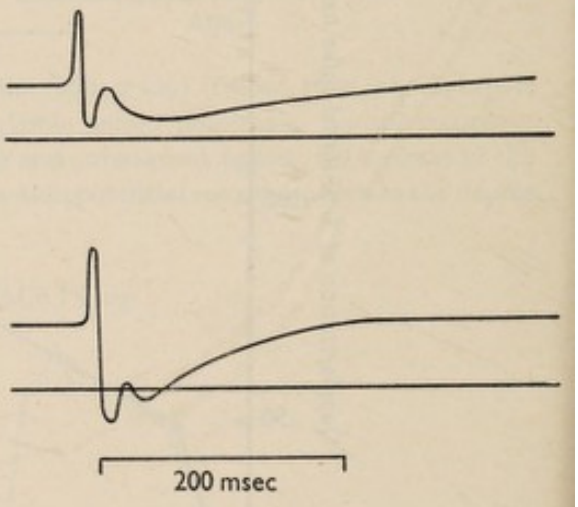

Fig. 6

Fig. 5. Action potentials before and after tetanic stimulation. Cat, chloralose. Upper record, tracing of normal action potential. Lower record, tracing of action potential immediately after tetanic stimulation at 76/sec for 10 sec.

Fig. 6. Action potentials before and after tetanic stimulation in the presence of eserine (200 μg i.v.). Cat, chloralose. Upper record, tracing of action potential before tetanic stimulation. Lower record, tracing of action potential after tetanic stimulation at 76/sec for 10 sec. Time scale 200 msec.

The effects of ganglionic blocking drugs

The effect of a number of ganglionic blocking drugs was investigated and the results, summarized in Table 1, show that these drugs can be clearly differentiated into those which depolarize the ganglion and those which do not.

In Fig. 7 some tracings from these experiments are shown. In this figure all the doses given were such that the depression of the action potential is small; nevertheless, the depolarization produced by acetylcholine, nicotine and tetramethylammonium is, in all cases, about 1–1½ times the initial spike height. It is apparent, too, that these substances produce the same typical distortion in the shape of the action potential complex, a distortion quite absent with

TABLE 1. Modes of action of various drugs blocking transmission at ganglion synapse and motor end-plate

Action	Ganglion	Motor end-plate
Depolarization	Acetylcholine Nicotine Tetramethylammonium (TMA)	Acetylcholine Nicotine Tetramethylammonium (TMA) Decamethonium
Competition with acetylcholine	D-Tubocurarine Pentamethonium Hexamethonium Tetraethylammonium (TEA) Decamethonium (in large doses)	D-Tubocurarine Pentamethonium } (in large Hexamethonium } doses)

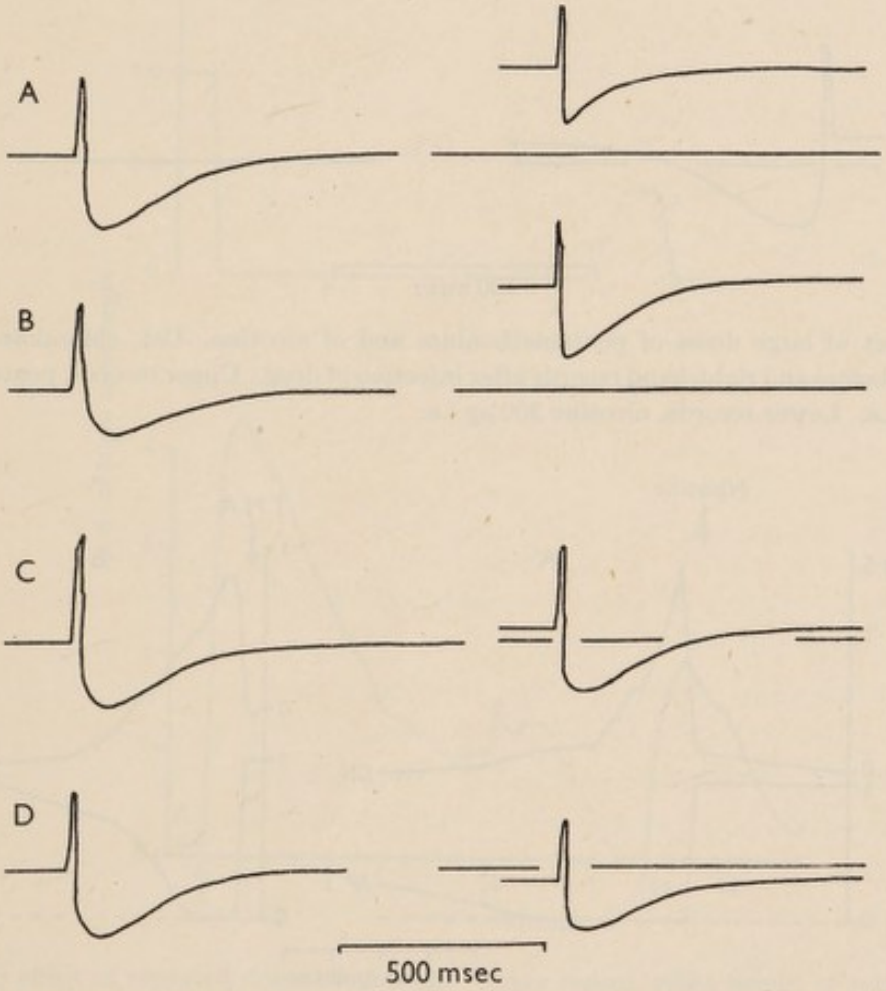

Fig. 7. Effect of ganglionic blocking drugs on action potential. Cat, chloralose. Tracings in left-hand column were obtained before and those in right-hand column after the injection of drugs. *A*, nicotine 50 μg; B, tetramethylammonium 50 μg; C, tetraethylammonium 50 μg; D, pentamethonium 50 μg.

the non-depolarizing drugs. The effect of larger doses of nicotine and pentamethonium is shown in Fig. 8. In this case the abolition of the action potential is almost complete; with pentamethonium there is no evidence at all of depolarization, whereas with nicotine the degree of depolarization is nearly three times the initial spike height.

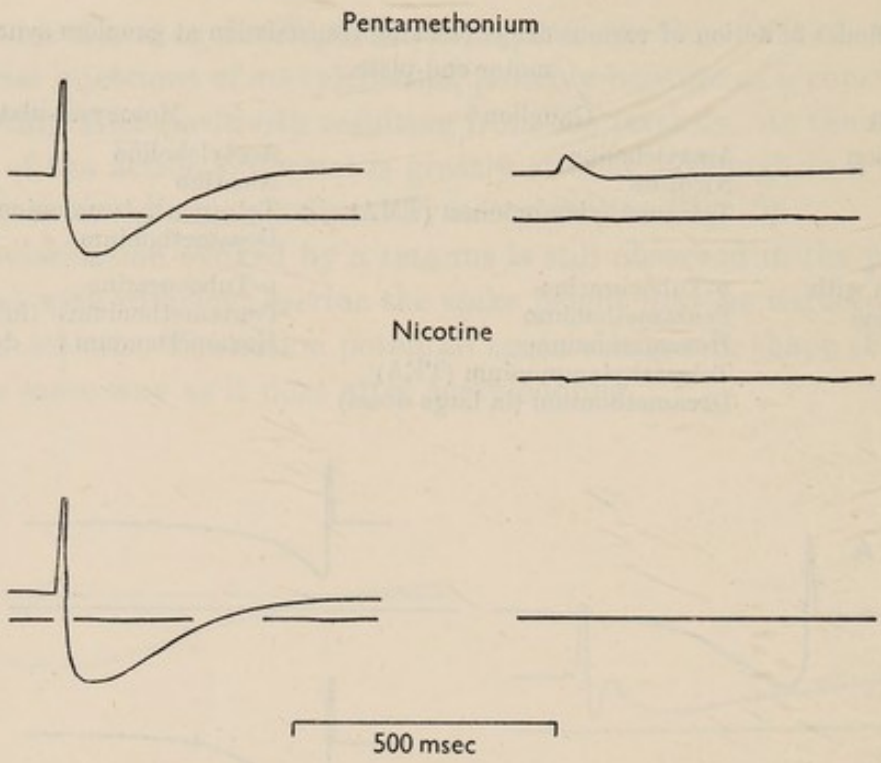

Fig. 8. Effect of large doses of pentamethonium and of nicotine. Cat, chloralose. Left-hand records before and right-hand records after injection of drug. Upper records, pentamethonium 300 μg i.a. Lower records, nicotine 300 μg i.a.

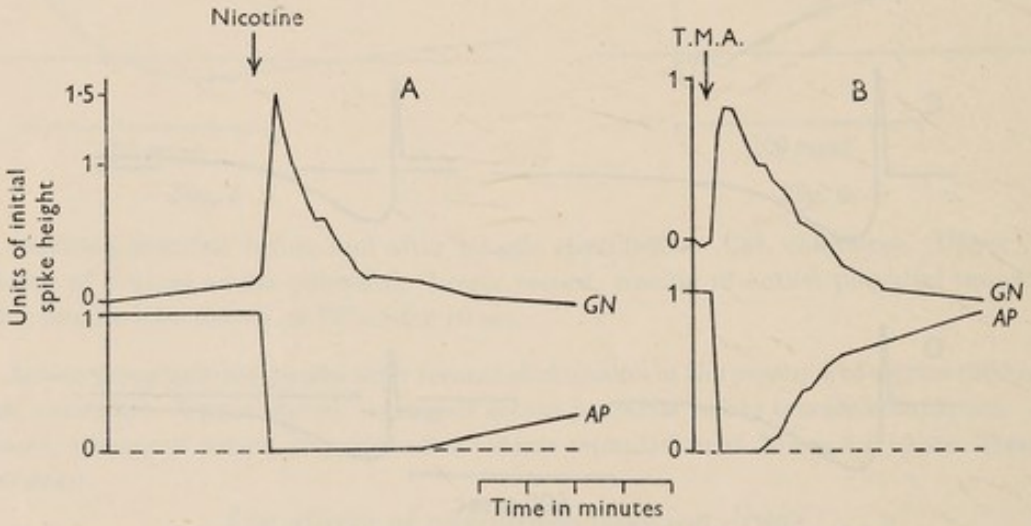

Fig. 9. The effect of nicotine and of tetramethylammonium. (Conventions as in Fig. 3.) A, effect of nicotine 300 μg i.a.; B, effect of tetramethylammonium 300 μg i.a.

Further analysis of the effects of nicotine

The depolarization produced by nicotine was always much more transient than that with acetylcholine or tetramethylammonium, compared with the duration of reduction of spike height produced by it. In the experiment illustrated in Fig. 9*a*, the ganglion negativity had disappeared 3 min after the injection, although the spike did not reappear for 10 min, nor return to normal

for 30 min. Fig. 9*b* shows a comparable experiment with tetramethyl ammonium, in which the recovery from depolarization is much slower and almost parallels that of the spike height.

These observations suggested that nicotine might possess a mixed action, partly acetylcholine-like, and partly by antagonizing the effects of acetylcholine. If this were the case, one would expect that a subsequent identical dose of nicotine, given soon after the disappearance of the ganglion depolarization but before full recovery of the spike potential, would produce a smaller depolarization than normally. Fig. 10 shows that this is true. The second dose

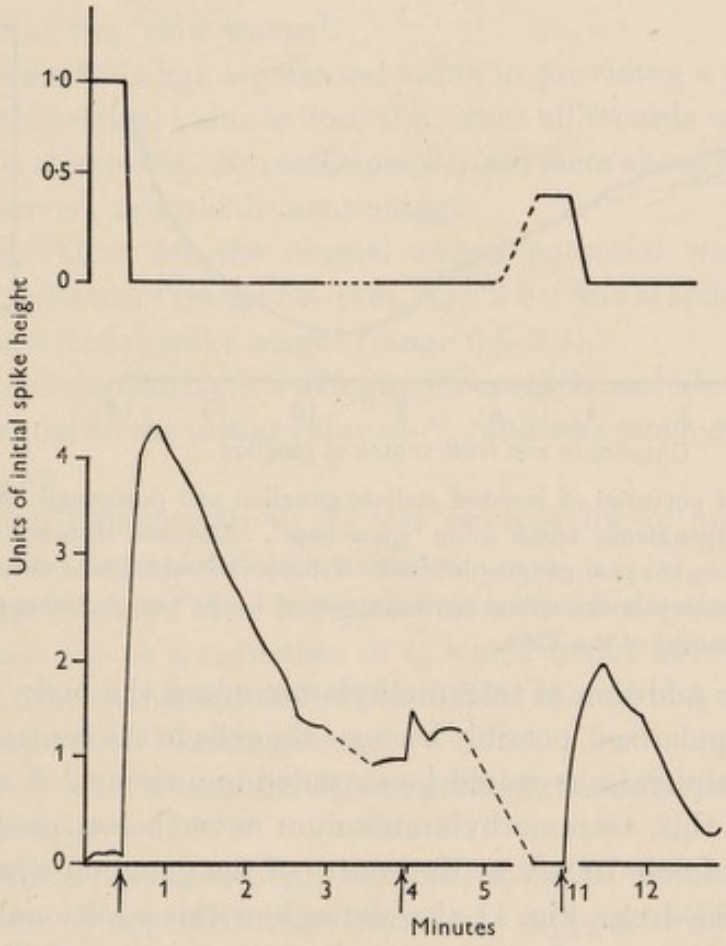

Fig. 10. The effect of repeated doses of nicotine. Upper record, spike height of action potential in terms of initial spike height. Lower record, depolarization in terms of initial spike height. At arrows 200 μg nicotine i.a. Continuous lines represent continuous recording with stimuli once every 3 sec; dotted lines represent absence of recording. Time scale in minutes.

of nicotine produced only one-eighth or less of the original depolarization, which had almost completely passed off. As the spike potential returned towards its normal height, the depolarization produced by a third identical dose of nicotine also increased; in Fig. 10, where the spike had returned to 50% of normal, the depolarization was 50% of its original magnitude.

Decremental spread of ganglion negativity

The fact that the ganglionic body becomes negative to the postganglionic trunk after treatment with the depolarizing drugs, suggests that the depolarization is a local response of the ganglion cells.

Depolarization of the ganglion cells was produced by acetylcholine (10^{-5}) in one superior cervical ganglion and by tetramethylammonium iodide (10^{-4}) in one stellate ganglion. Space base records were taken before the addition of these drugs to the bath, during their action, and after washing the ganglion, and Fig. 11 shows tracings of the results obtained on the stellate ganglion.

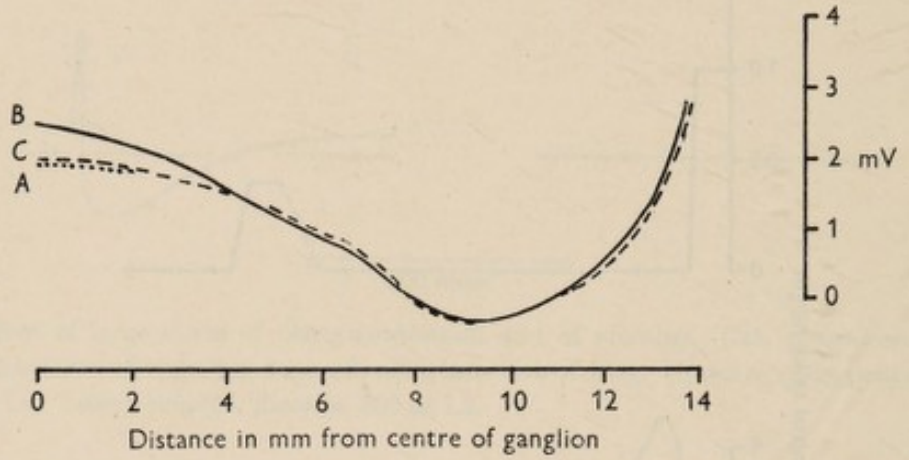

Fig. 11. Records of potential of isolated stellate ganglion and postganglionic trunk relative to cut end of postganglionic trunk using 'space-base'. Abscissa: distance from the centre of the ganglion along the post-ganglionic trunk. *A*, before the addition of tetramethylammonium (TMA) to the bath to make a final concentration of 1×10^{-4} in *B*, during the action of TMA. *C*, after the removal of the TMA.

Even before the addition of tetramethylammonium the body of the ganglion was partially depolarized, possibly because the cells in the centre of the ganglion had died from asphyxia as would be expected in a tissue 2–3 mm thick (Hill, 1929). Despite this, tetramethylammonium nevertheless produced a further depolarization of 600–700 μV at the centre of the ganglion which disappeared on removal of the drug. Fig. 11 also shows how this additional depolarization diminishes with distance from the centre of the ganglion, falling to one-third of its maximum value approximately 1·8 mm from the centre of the ganglion. Acetylcholine produced on the superior cervical ganglion a similar but smaller localized ganglion depolarization. The ganglion negativity, therefore, which results from the action of the depolarizing drugs, is a local depolarization of the ganglion cell spreading decrementally a short distance along the postganglionic trunk.

Changes in shape of the action potential complex

Eccles (1935) suggested that the latter part of the action potential complex consisted of two separate components, a negative wave (*N*) and a positive wave (*P*), both decaying approximately exponentially, the *P* wave more slowly

than the *N* wave. In order to express the changes in the shape of the action potential in a quantitative way, we have analysed our records graphically as previously described (Paton & Perry, 1951*b*), and have found that the complex can be satisfactorily fitted by the sum of two such exponential curves, although, no doubt, other mathematical functions fitting equally well could be devised. This analysis provides a short and convenient description of the shape of a given action potential in terms of four parameters (two initial magnitudes, N_0 and P_0; and two time constants t_n and t_p). Although only the latter part of the action potential (later than the S_3 and S_4 spikes) was used for this analysis, it was noted that summing the two waves obtained back to zero time reproduced a 'spike' as well as the 'slow waves'.

Although this analysis has a potential value in providing a short means of description, its theoretical value is doubtful, since all records were taken with external ganglion electrodes. Nevertheless, certain facts about the parameters, consistently observed, are worth mentioning:

(1) The mean values for the normal action potential were $t_n = 33$ msec (range 26–38), $t_p = 86$ msec (range 62–112), $N_0 = 2{\cdot}8 \times$ initial spike height (range 1·3–3·7), $P_0 = 1{\cdot}6 \times$ initial spike height (range 0·6–2·4).

(2) The maximal depolarization of a ganglion which could be produced, was approximately equal to the initial value of N_0, and was much greater than the initial spike height.

(3) With partial depolarization, N_0 was reduced by an amount approximately equal to the degree of depolarization.

(4) The change in shape after acetylcholine and the depolarizing blocking drugs was largely due to a reduction of t_n which might become vanishingly small. t_p on the other hand was not affected. This change in t_n was completely absent after competitive blocking drugs.

(5) Immediately after a tetanus, P_0 was greatly reduced, without change in the other parameters.

The fact that these parameters can, to some extent, be varied independently, e.g. by a tetanus or by depolarization, lends some support to the idea originally put forward by Eccles (1935), that there are at least two independent processes taking place during the action potential.

DISCUSSION

The observation that injected acetylcholine will produce a depolarization of the cells of the superior cervical ganglion fills one of the main remaining gaps in our picture of the mechanism whereby acetylcholine mediates the transmission of the nervous impulse from the preganglionic to the postganglionic trunk.

It has been shown that the depolarization is localized to the ganglion and spreads only decrementally down the postganglionic trunk. In this respect it

resembles the slow after-potentials described and analysed by Eccles (1935). Thus, acetylcholine at the ganglion, as at the neuromuscular junction, can cause a localized depolarization of the cell membrane, which is then capable of exciting the discharge in the postsynaptic fibre already described (for the ganglion) by Brink *et al.* (1946).

The electrical effects of an injection of acetylcholine are considerably more prolonged than is the response to a single preganglionic volley, where the acetylcholine is released locally at the nerve terminals and does not flood the whole ganglion. As Brink *et al.* showed, perfusion with acetylcholine does not cause a single propagated postganglionic spike, but rather a train of such impulses; this corresponds well with the depolarization which we have observed. But even with injected acetylcholine, the transience of the depolarization compared with that produced by other drugs, and the considerable prolongation by eserine, show that the cholinesterase activity of the ganglion is considerable.

With large doses of acetylcholine, or smaller doses in the presence of a little eserine, the spike potential to preganglionic shocks dwindles or disappears entirely. Although the exact relationship between the height of the spike potential and the degree of block (as defined by contraction of the nictitating membrane), has not been established there is presumably some continuous relation between the two, and obviously complete absence of spike implies complete block. In general, the depression of the spike parallels the depolarization in its active course; but a closer comparison shows that the reduction in spike is greater, for a given degree of depolarization, the longer the depolarization has lasted. There are at least two possible explanations for this observation. First, it may be that prolonged depolarization of the ganglion cell membrane leads to a change in its electrical response to acetylcholine, due (one might imagine) to an alteration in the distribution of ions on either side of the membrane. Alternatively, the situation may be comparable to that of the neuromuscular junction, for which it has been shown (Burns & Paton, 1951) that persistence of the localized depolarization of the end-plate region by specific depolarizing drugs leads to a spread of the depolarization by discharge of the adjacent membrane. At this site, therefore, the *area* depolarized some time after the injection of decamethonium may be considerably wider than that immediately after the injection, although the peak height of depolarization is smaller, and the resulting inexcitability of the adjacent membrane leads to a rise of the propagation threshold with lapse of time. If such an explanation is to be applied to the ganglion, it implies that there is a differentiation of the structures within the ganglion as a whole into specifically reactive membrane (the site of a local depolarization) and adjacent membrane excited by electrotonic spread; and that even under the propagated ganglion spike there is a considerable element of local slow non-propagated response. This conclusion

had already been reached by Eccles (1935) who states that 'the *N* wave is considerably developed under the S_2 summit'.

Ganglion blocking drugs

The classification of ganglion blocking drugs according to whether or not they depolarize the ganglion (Table 1) corresponds to their pharmacological properties, in that those which depolarize also have as their first action a stimulation of the ganglion, whereas those lacking such stimulant action uniformly fail to depolarize. The first group will be referred to as depolarizing, and the second group as competitive blocking agents. (We are not here concerned with drugs such as local anaesthetics which interfere with ganglionic transmission by preventing the release of acetylcholine). It follows that depolarization of the ganglion (of any origin) may give rise to a train of impulses in the postganglionic trunk, before block supervenes due to the persistence or spread of the depolarization. This classification is precisely analogous to that at the neuromuscular junction (Burns & Paton, 1951; Zaimis, 1951), where the depolarizing drugs are also those causing signs of stimulation (twitch), contracture and repetitive discharge.

Apart from acetylcholine, the only two drugs amongst those tested which depolarized were tetramethylammonium and nicotine, of which tetramethylammonium appeared to resemble acetylcholine in everything except its speed of destruction. With nicotine, however, the depolarization was always transient, although the reduction in spike and indeed the block might be prolonged. During the period of block, in the absence of depolarization, a further identical dose of nicotine produced only a small fraction of the original depolarization. This association of block without depolarization with resistance to a depolarizing drug during the block probably implies a blocking action by nicotine of the competitive type. It appears, therefore, that nicotine has two distinct actions, an initial depolarization accompanied by excitation and then block, which passes over into a typical competitive block. This may explain why it is traditionally recommended that to produce block with nicotine the doses should be divided and slowly worked up, thereby securing the competitive block with a minimum of stimulation.

Among the competitive blocking drugs investigated were decamethonium and eserine. A particularly interesting comparison is afforded by the actions of decamethonium at the two synapses. That the cell membranes at these two sites are closely related physiologically follows from the fact that at both the normal transmitter, acetylcholine, produces as its first effect a local depolarization. Yet whereas at one site, the neuromuscular junction, decamethonium almost rivals acetylcholine in its depolarizing activity, at the ganglion synapse it is not only almost inactive but, when given in relatively large doses it actually produces block not by depolarizing the membrane but by the alter-

native method of competition with acetylcholine. This illustrates the fact that, in spite of the similarity in the two membranes in respect of their reaction to acetylcholine, there must be distinct physical differences between them; a fact which might well go undiscovered but for pharmacological distinctions of this sort. This appears to be the only known case where a drug will produce block at both synapses, but by different mechanisms.

The effects of eserine are usually overshadowed by its powerful anti-esterase activity. But other actions have been described, such as the non-specific increased excitability it produces in the ganglion (Feldberg & Vartiainen 1934), its blocking action in relatively small doses on antidromic vasodilatation (Holton & Perry, 1951), its curare-like action at the end-plate and in very large doses (Eccles & MacFarlane, 1949; Fatt 1950), its depressant action on nerve conduction (Bullock, Nachmansohn & Rothenberg, 1946). To these actions can now be added ganglionic block which (in the absence of preganglionic excitation) is not accompanied by depolarization. This is probably a true competitive block and not, like procaine, a block of the preganglionic nerve terminals, since Feldberg & Vartiainen (1934) showed that during perfusion with high concentrations of eserine the ganglion was not responsive to injected acetylcholine.

There is usually little practical difficulty at present in allotting a given compound to one or the other class of blocking agents, since injection of any depolarizing blocking agent causes (by ganglionic excitation) a vigorous contracture of the unexcited nictitating membrane, whereas none of the competitive blocking agents do this. But the action of nicotine, in which a depolarizing is succeeded by a competing action, already indicates that this simple test may not reveal the complete picture. It is, further, possible that a drug might produce a depolarization of such slow onset that excitatory effects were trivial, although the block was due to this depolarization. For the time being, therefore, it appears that an electrical record of the type described is essential to the complete study of the mode of any paralysis of ganglionic transmission.

SUMMARY

1. Acetylcholine, given in small doses by intra-arterial injection, causes a transient depolarization of the ganglion relative to the postganglionic trunk.

2. In large doses acetylcholine causes further depolarization which is accompanied by reduction or abolition of the spike of the ganglionic action potential in response to single preganglionic volleys.

3. These effects are potentiated by eserine.

4. Tetanic, preganglionic stimulation will produce a depolarization of the ganglion, which outlasts the period of tetanization.

5. A new classification of ganglionic blocking drugs is introduced. Those drugs which cause initial stimulation of the ganglion and block by depolarizing

the ganglion are referred to as depolarizing blocking drugs; those which cause no initial stimulation and block in the absence of any depolarization are referred to as competitive blocking drugs.

6. Nicotine appears to have a dual action, being initially a depolarizing and later a competitive blocking drug.

7. Depolarizing blocking agents cause a distortion in the shape of the ganglionic action potential.

8. Eserine, in the absence of preganglionic stimulation, can, in large doses, itself produce competitive block.

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