TRANSMISSION AND BLOCK IN AUTONOMIC GANGLIA

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The modern conception of transmission in the autonomic ganglion as being mediated by a specific chemical substance, acetylcholine, derived in its earlier stages from experiments in which a close analogy was drawn or implied between the ganglion and the nerve muscle preparation. Thus Langley used a single drug —nicotine—to map out ganglia and to study the muscle receptor substance; and as early as 1914, Dale remarked on "the biochemical similarity between the ganglion cells of the whole involuntary system and the terminations of voluntary nerve fibres in striated muscle" (10). A review of the advances in our knowledge since those early experiments is a task better suited for a military historian than for a contributor to this Symposium. But it is still of interest to go back to this original analogy and to ask how far, in the light of our newer knowledge, the two synapses can still be regarded as closely analogous.

The point of this question is sharpened if one looks at the histological structures involved. The usual diagrammatic representation of a motor endplate is already over-simplified, but the usual diagram of a ganglionic synapse is an almost ridiculous idealisation of the true state of affairs. To a naive observer it would seem nearly incredible that there should be many or even a few features in common between the compact motor endplate activating a muscle fibre, and the elaborate basket-work of fibrils which shrouds a neurone specialised to transmit signals and to release at its far end a neuro-humor.

We can conveniently begin, therefore, by discussing first those characteristics of transmission which are common to the two synapses, and then the differences between them.

Characteristics Shared by Neuromuscular and Ganglionic Synapses. At both sites acetylcholine produces a non-propagated depolarization of the receptor membrane. It had, of course, been well established during the *anni mirabiles* of chemical transmission from 1934 onwards that acetylcholine could stimulate both muscle and ganglion cell; and depolarization by acetylcholine of the motor endplate has also been known for a considerable time for the frog (19), although only directly demonstrated for the mammal quite recently (5). Definite evidence has now been obtained that a comparable state of affairs exists at the ganglion (22). It could not lightly be assumed that this would be the case, in view of Gaskell's (15) old observation (recently reinvestigated and confirmed by Burgen and Terroux (4)) that acetylcholine can increase the membrane potential of the auricle.

At both sites it also appears that acetylcholine in producing its depolarization does so by some process which can be described as producing a "short circuit" of the limiting membrane (normally of a high specific resistance). This was demonstrated unequivocally in Fatt and Katz's elegant experiments (13) on the motor endplate, and they were even able to quantitate the change in resistance produced

by acetylcholine during normal transmission. The evidence is of a different character at the ganglion, and much less direct; it will no doubt remain so until microelectrodes are more successful in penetrating ganglion cells. It rests on the characteristic change in shape of the ganglion action potential after depolarization (22). This change in shape is due to a great acceleration of the time course of the slow negative wave of the ganglionic after-potential. This negative wave bears a close relationship to the primary excitatory process. Thus depolarization of the ganglion produces a change, at the membrane at which the excitation takes place, such that a charge set up across it disappears more quickly than usual. From this one can infer that resistance to ionic movement at this point has greatly decreased, an analogous state of affairs with that at the motor endplate.

At both synapses, when they are paralysed by a competitive blocking agent, the block is considerably intensified by increase in the rate of stimulation. From this derives the waning of the response of a muscle to repetitive stimulation of its motor nerve, or of the contraction of a nictitating membrane to preganglionic stimulation. It can be so marked at the ganglion as to bring into vigorous operation the "law of diminishing returns" (one form of Wedensky inhibition) at excitation rates as low as 1 shock/sec, so that more rapid excitation than this will lead only to a progressively feebler postganglionic response. This is obviously an important fact, not only in determining the sensitivity of a particular ganglionic system, but in limiting the responses possible in a partly paralysed organism. It implies, for instance, that any attempt at an autonomic response to the effects of partial ganglion blockade may only be effective if the new activity is relatively slow; acceleration of pre-existing discharges may merely increase the block. The autonomic system is hamstrung, as it were, reduced to the same type of impotence as (at the neuromuscular level) is the patient with myasthenia gravis.

After sustained activity there is at both synapses a considerable facilitation. In the normal muscle this is to a large extent a muscular phenomenon (3) and any synaptic events are swamped by the much more extensive processes taking place in the fibres as a whole. But if the muscle is completely paralysed with curare then a considerable facilitation of the endplate potential after repeated excitation is easily demonstrated. In the normal ganglion a similar facilitation can be shown quite easily. Alternatively with a paralysed ganglion an increase in the synaptic potential can be recognised.

The two synapses are also alike in the general character of their behaviour to drugs. There are a number of types of action on the ganglion that can be clearly identified and differentiated in their relationship to the natural transmitter, of which I would like to mention six: (a) Mimicry of the transmitter; for instance by tetramethylammonium at the ganglion, or by decamethonium and succinylcholine at the motor end plate. (b) Competitive block, exemplified by specific drugs such as the methyl ether of *d*-tubocurarine at the endplate, or hexamethonium at the ganglion. (c) Block which passes from depolarization mimicry to competition, such as that of nicotine at the ganglion (22) or, at the endplate of C10 in the monkey and C13 in the cat (24). (d) Preservation of the transmitter

from enzymic destruction, whence arise those effects which eserine and neostigmine can produce both at the ganglion and the neuromuscular junction. (There are, as a matter of fact, differences between the two synapses here, to be discussed later.) (e) Sensitization by certain drugs of the receptor area to the transmitter in some way independent of anti-cholinesterase activity. Particularly interesting in this connection are the phenyl-alkylammonium compounds which possess this activity quite notably. (f) Interference with transmitter release at the presynaptic nerve terminals by agents such as calcium deficiency (7, 17): or magnesium excess (6, 18).

Besides there being a general similarity in the pattern of pharmacological behaviour, in that one can identify drugs related to acetylcholine that act in analogous ways at both synapses, there is also a significant number of compounds which in fact have a considerable potency at both sites. We shall come later to mention the large number of drugs which discriminate between the two synapses. But their multiplication of recent years should not blind us to the fact that the two drugs on which almost the whole of synaptic pharmacology and a great deal of synaptic physiology rest, i.e. nicotine and curare, are both potent at both sites, as well of course as their somewhat more junior but still more important cousin, acetylcholine itself.

We find, therefore, that among the common properties shared by the two synapses are (a) a non-propagated depolarization by acetylcholine, which is (b) accompanied by evidence of a short-circuiting of the synaptic membrane; (c) repetitive stimulation increases synaptic block during the period of excitation; (d) after repetitive excitation considerable facilitation occurs; (e) both synapses can show the same characteristic *types* of interference by drugs related to the transmitter; and (f) there are in fact particular drugs which are highly active at both synapses.

This is a remarkably extensive analogy between the two junctional regions. It is, of course, what one would expect in terms of cholinergic transmission. But if there were any other important factor in ganglionic transmission, such as the histological differences might suggest, for instance another chemical transmitter, or the intervention of some more purely electrical process, one would surely expect some gross discrepancy, some unexpected effect by a drug. It can only mean that in major respects, the transmissions are fundamentally alike; and that despite the anatomical differences, suggesting other or additional mechanisms in the ganglion, recent as well as older work leads to the belief that there is at both synapses a single common process of acetylcholine release at presynaptic nerve-endings, arousing a response in the specialised postsynaptic membrane.

Characteristics not shared by neuromuscular and ganglionic synapses. The action potential of the blocked ganglion and the endplate potential differ considerably in general form, in part simply by time scale (which is about one hundred times slower in the ganglion) but principally by the large positive after-potential which can be recorded at the ganglion. Eccles (11) has shown that with the stellate ganglion curarization will eventually produce a synaptic potential in which there is no propagated spike and which has no positive after-potential; but it is some-

times difficult to show this on other ganglia. Recent work using ganglia removed *in toto* either from the turtle or from the rabbit (12, 20) and studied thus deprived of natural circulation, has revealed that in the curarized ganglion pre-ganglionic stimulation can under some circumstances produce a potential wave which is almost entirely in a positive direction. Deep curarization combined with repeated stimulation or with anticholinesterases appear to be the main factors required.

It may be dangerous to assume that the observations on isolated ganglia are comparable with those in the intact animal. But they represent striking phenomena, which remain to be explained on the chemical theory of transmission, and which seem to have no obvious analogue at the endplate.

While it is true that repeated stimulation of a motor nerve to a muscle may occasionally produce repetitive firing of synaptic origin when the stimulation is remitted, this is in general an unusual phenomenon. Normally the last stimulus shock is immediately followed by the last muscle action potential. In the ganglion however, repeated stimulation at fairly rapid rates can give rise quite easily to a repetitive discharge which may last for as long as half a minute. Bronk and his colleagues (1) point out that this response may not be of particular biological importance, since the rates of excitation required are probably outside the normal range, but they are still prepared to regard it as a significant characteristic of ganglionic behaviour. Corresponding to this after-discharge is the prolonged facilitation, short of that required for actual ganglionic discharge, which can be observed after sustained excitation of a ganglion, lasting up to five minutes or more beyond the end of stimulation. Such facilitation occurs also at the neuromuscular synapse, but it is a more brief affair. Thus we can say that after repetitive stimulation of the presynaptic nerve facilitation is greater and more prolonged in the ganglion than in the endplate. Bronk *et al.* concluded that the facilitation was due to some change produced in the active presynaptic endings.

At the neuromuscular junction, it has proved relatively easy to produce depolarization block, and it follows rapidly after the injection of agents such as decamethonium or succinylcholine. Indeed it is not possible to maintain a prolonged stimulant action by such drugs without block ensuing. A dose which is sufficient to initiate a fairly vigorous effector discharge passes on rapidly into block; a smaller dose either produces block more slowly, or its action disappears altogether. At the ganglion on the other hand, it is possible, to produce a vigorous post-ganglionic discharge by means of a continuous infusion of acetylcholine through the stellate ganglion in concentration as high as 100 micrograms per cc., and for these discharges to persist as long as the infusion is maintained (1). Similarly in a cat anaesthetised with chloralose it is quite hard to obtain a relaxation of the nictitating membrane preganglionically excited, with a drug such as tetramethylammonium. One could perhaps express the difference by saying that the end-result of the action of a persisting depolarizing drug at the mammalian endplate appears as paralysis complicated by some vestiges of stimulant action; but at the ganglion as persistent excitation behind which some blocking action can be detected.

It also appears that the ganglion is less readily influenced by anticholin-

esterases. Thus Feldberg and Vartiainen (14) required special conditions of submaximal stimulation before they could demonstrate, with eserine, an effect on normal transmission. Chou and Elio (9) were able to show a moderate antagonism to d-tubocurarine by carefully chosen doses of eserine, provided brief periods of stimulation were used, but none with neostigmine. Grob and Harvey (16), in man, could not antagonise the hypotension produced by C6 with neostigmine. In my own experience, an antagonism to hexamethonium in animals can sometimes be shown, but not invariably. It cannot be argued that this is because anticholinesterases themselves readily produce a block which 'neutralises', as it were, the looked-for augmentor or antagonistic action. For this too is quite hard to produce, and is, indeed, only well seen in the perfused ganglion. All this is in considerable contrast to the neuromuscular junction at which anticholinesterases produce a wealth of effects: such as vigorous repetitive discharge to single shocks with potentiation of the twitch, an antagonism to curare-like drugs which the veriest tyro can be sure to demonstrate, and a block with repetitive stimulation so considerable as to lead, in early work, to the belief that they were preimarily depressant to transmission. The usefulness of the anti-curare effect of antiesterases at the neuromuscular junction receives almost its strongest testimony in its widespread employment clinically; but these agents have no corresponding use against ganglionic block, a striking fact even when allowance is made for the other drugs available as antidotes which act directly on effector cells. While it is by no means true to say, therefore, that anticholinesterases are active on the neuromuscular junction and not at the ganglion, it does appear that their actions are much more prominent at the former than at the latter.

Using a drug such as *d*-tubocurarine, there is a certain variation in the sensitivity of different muscles. But this variation is not great; from the account of experiments such as that by Smith et al (23) it seems that a four-fold increase in dose in the human will carry you from the early stages of block of the most sensitive muscles to virtually complete paralysis. With ganglia on the other hand this does not seem to be the case. Even within a single ganglion, the superior cervical ganglion of the cat, one needs about ten times as much hexamethonium to paralyse the contraction of the nictitating membrane as to paralyse dilatation of the pupil. Salivary secretion in the cat is particularly sensitive and begins to be affected by a dose one-five hundredth of that needed completely to paralyse the the superior cervical ganglion. Similarly in man, some subjects will respond by a fall of blood pressure to as little as 1 to 5 mg. hexamethonium, although in others receiving amounts of 1 gm. or more per day, evidence of incomplete ganglionic block can be obtained.

Until interest arose in synthetic curarizing compounds and later in ganglion blocking substances, the fact that the blocking agents normally used were active at both synapses, obscured differences between them in their specific affinities. But now that the synthetic chemists have irrupted into pharmacology, destroying old ideas and bringing a wealth of new ones, there are countless examples of drugs significantly more active on one synapse or the other, among derivatives of natural alkaloids as well as in wholly synthetic products. A particularly

striking example of this remains the methonium series, with C6 almost devoid of neuromuscular action, and C10 of ganglionic potency. The series is remarkable, too, for the rate of change of activity within it; thus for chain lengths between 6 and 8 carbon atoms, the compounds lose ganglionic activity by a factor of 10 and gain endplate activity by a factor of 20 per carbon atom.

We have to set, therefore, against the striking analogies between the two junctional regions the following differences: that the ganglionic synapses tend to show (a) post-tetanic facilitation more readily, (b) depolarization block less readily, (c) less effect with anticholinesterases, (d) a wider range of sensitivity to competitive block, (e) more complex electrical phenomena (after-positivities) compared to neuromuscular junctions, and (f) wide differences in sensitivity to particular drugs.

The structure of the ganglion. One immediately wonders how far differences in the anatomy of the two synapses may contribute to the differences in behaviour I have mentioned. It is probably too early to ask this question, since histology is still not able to bear the burden of questions which physiologists put. But one may comment on the three possible points. First, the ganglion rests within a framework of glial material enclosed within a connective tissue sheath (8). This cellular and connective tissue cloak around the neurone might well act as a barrier in two respects, by preventing the access of drugs from outside into the ganglion, and by delaying the removal of substances produced by the cell, for instance during activity. The histologists seem to regard this sheath as comparable to the bloodbrain barrier (although this is not proved), so that there is a real possibility of a barrier existing at the ganglion which is not present at the neuromuscular junction. This could have two consequences: first, to cause a resistance to quaternary blocking salts in those ganglia in which the barrier is well developed, and so provide a factor in the large difference of sensitivity among ganglia. (For this theory of course it is necessary to postulate a variability in sheath structure or thickness, but this is not at all unreasonable.) Secondly, the sheath could retain products of activity, such as potassium, choline, acetic acid, or unhydrolysed acetylcholine, which at the endplate could escape relatively easily; indeed one might even wonder whether there might not be some delay in the equilibration of sodium concentrations across this barrier, so that there could be sodium deprivation in the spaces immediately outside the neurone. If retention of products of activity is of importance, then it might account for some of the prolonged after-discharge obtained, and possibly for the exaggerated after-positivities. It is perhaps more than a coincidence that the after-positivities are best developed in isolated ganglia, in which removal of metabolites would be still more difficult.

A second anatomical feature is, of course, the long and elaborate course of the pre-ganglionic terminals. Clearly it would be only too easy for conduction to fail along these fine nerve endings, and it is not at all improbable that in fact normally a number of these do not conduct. Given a process whereby passage of an impulse in adjacent fibrils, or down part of one fibril, favours discharge down the rest of it, then one would have a mechanism by which post-tetanic facilitation

would be greater the more elaborate the pre-terminal network. Another consequence would be an exaggerated sensitivity to drugs acting on nerve terminals; probably the reason why it appears easier to paralyse the ganglion with local anaesthetics than the neuromuscular synapse.

Third, we have a difference in the localization of the cholinesterases, which at the motor endplate is, so to say, sitting there at the post-synaptic membrane waiting for the acetylcholine, whereas in the ganglion it seems to exist mostly in the presynaptic terminals themselves from where the acetylcholine has just come. Obviously it is much more likely to modify the postsynaptic effects of the drug in the former case and, correspondingly, anticholinesterases will there have the more vigorous action. Indeed at the ganglion it is not impossible that diffusion plays an appreciable part in removing acetylcholine from the immediate site of release. If one applies a diffusion equation one can calculate that 90 per cent of the acetylcholine released at a point source could have diffused away from a cube 2μ x 2μ x 2μ round that source, within 1.2 msec., a sufficiently short period to conform to the facts of transmission.

Fourthly, one might suggest that there is also an anatomical basis for the resistance to cathodal block. In the analysis of the action of depolarizing agents at the endplate, the onset of inexcitability appeared to be closely associated with the spread of the depolarization into the adjacent muscle fibre. Now this is, at the endplate region, a relatively easy process, since the endplate is a small depolarized area, forming a sink in the middle of a relatively wide reservoir; a considerable current could therefore be expected to flow. At the ganglion, however, the sink is big, but the reservoir is very narrow and extended. And it may well be that there the injury current cannot be so great and hence the inexcitability cannot develop so rapidly.

We reach, therefore, the following final position. Although ganglionic and neuromuscular transmission have many striking similarities, there are also some important differences. But these differences, on examination, and on comparing the structures of the two synapses, may well arise, not from any fundamental difference in transmission processes, but as consequences of the varying anatomy. One might say that the language of both synapses is the same, modified only by certain local idiom.

Central nervous synapse. From this sort of analysis the suggestion obviously follows that at a central nervous synapse, there should be observed those features which are common to the ganglionic and neuromuscular synapse, and that where these differ there might be a closer resemblance to the ganglion. Such a harmless generalization has no tactical value, but might have some strategic use. For instance, it would be expected that drugs acting on central nervous structures could have one of at least five actions, in relation to a hypothetical transmitter: that is they might imitate it, compete with it, (or have both these actions in series), inactivate the enzyme destroying it, sensitize to it by some non-enzymatic means, or prevent the release of the transmitter. This is not, heuristically, a very helpful conclusion, at present anyway, but at least it may prevent an over-simple approach to the problem. A second point to be borne in mind is that there is no

reason to suppose that inactivity of a neurone by excess of a transmitter would be an easy phenomenon to produce in the central nervous system; and even if it were produced, there should be fairly prominent signs of initial stimulation. If one observed a purely depressant action, one's first guess would be that the agent concerned was interfering with transmission or release in the finer nerve endings, or competing with some transmitter.

Physiological and pathological significance of the autonomic nervous system. So far we have been discussing, chiefly, the analytic side of ganglionic physiology and pharmacology. But an equally interesting aspect of it is the knowledge we are gaining about the functions of the whole autonomic system in health and disease. Not much attention is paid to this as a general problem. Indeed it is remarkable to consider how many chronically sympathectomized individuals are walking about, without there having been yet any proper analysis of the effects of this on their everyday life. Clinically attention is concentrated rather on whether the sought-for effect is obtained than on the aetiological implications of the effects seen. To quote a simple illustration, it now seems that the most effective treatment of raised blood pressure is to interrupt the efferent autonomic pathways surgically or (at present better) by drugs. The obvious implication is that the disease is, to an important degree, a disease in or above the autonomic nervous system. But this implication has passed hardly noticed among the bulk of experimental work now focussed on the discovery of pressor substances.

It is not only in disease that interesting information could be obtained. Suppose one enquires whether a particular autonomic pathway is normally in use, in ordinary life: this is a question perhaps almost impossible for the neurophysiologist to answer. But one can, by ganglion block, get some idea about it. To illustrate my meaning and to end this discussion, I would like to quote from a resumé of the effects of hexamethonium that have been seen in patients and in normal young students, to make a slightly artificial and distinctly frivolous "hexamethonium man" (21).

He is a pink complexioned person, except when he has stood for a long time, when he may get pale and faint. His handshake is warm and dry. He is a placid and relaxed companion; for instance he may laugh, but he can't cry because the tears cannot come. Your rudest story will not make him blush, and the most unpleasant circumstances will fail to make him turn pale. His collars and socks stay very clean and sweet. He wears corsets and may, if you meet him out, be rather fidgety (corsets to compress his splanchnic vascular pool, fidgety to keep the venous return going from his legs). He dislikes speaking much unless helped with something to moisten his dry mouth and throat. He is long-sighted and easily blinded by bright light. The redness of his eye-balls may suggest irregular habits and in fact his head is rather weak. But he always behaves like a gentleman and never belches nor hiccups. He tends to get cold and keeps well wrapped up. But his health is good; he does not have chilblains and those diseases of modern civilization, hypertension and peptic ulcer, pass him by. He is thin because his appetite is modest; he never feels hunger pains and his stomach never rumbles. He gets rather constipated so that his intake of liquid paraffin is high. As old age

comes on he will suffer from retention of urine and impotence, but frequency, precipitancy, and strangury will not worry him. One is uncertain how he will end, but perhaps if he is not careful, by eating less and less and getting colder and colder, he will sink into a symptomless, hypoglycaemic coma and die, as was proposed for the universe, a sort of entropy death.

This is rather a caricature, but I hope it may serve to make the point that the study of ganglion transmission and block may lead one not only into the world of after potentials and microelectrodes but also into the wider aspects of the functioning of a whole man.

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