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POST-TETANIC RESTORATION OF NEUROMUSCULAR TRANSMISSION BLOCKED BY D-TUBOCURARINE

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The changes in neuromuscular transmission, which result from repetitive stimulation of the motor nerve, in nerve-muscle preparations partly blocked by D-tubocurarine have been described repeatedly (Boehm, 1894; Boyd, 1932), but little is understood, so far, about their intimate nature. This is partly due to the difficulty of determining the site of the responsible mechanisms, for, so long as the changes in transmission can be detected only by recording from the post-junctional unit, we have no means of telling whether they are due to alterations in the amount of acetylcholine liberated by each nerve impulse, or to changes in the motor end-plates. The experiments here presented were designed to dissociate these variables, by comparing the effects of nerve volleys with those of injected acetylcholine. It will be shown that the early failure of transmission during repetitive stimulation and the subsequent restoration of transmission are both due to changes which take place at the nerve endings, i.e. proximal to the motor end-plates. A preliminary account of these findings has already appeared (Hutter, 1951).

METHODS

Cats, decerebrated or anaesthetized with chloralose, were used. Tension was recorded from the tibialis anterior muscle and, in a few experiments, from the soleus. The sciatic nerve was tied high in the thigh and stimulated through two pairs of shielded electrodes. The distal pair usually served for stimulation at a frequency of 6 shocks per min, the central pair for tetanic stimulation. The shocks were either short condenser discharges (*CR* 0·1 msec) or square pulses of voltage (80 μsec duration). The shocks were 4 to 6 times the minimum voltage required to give a maximal twitch. When it was desired to maintain a constant level of curarization accurately for a long period, the muscles of both legs were prepared. One side then served as a control, while the time course of the phenomena was studied on the other preparation. Close arterial injections into the tibialis muscle were made as described by Brown (1938*a*). When several injections were given in quick succession care was taken that the blood supply was restored after each injection. End-plate potentials were recorded from gracilis (Brown & Burns, 1949; Burns & Paton, 1951). When end-plate depolarization was also measured, non-polarizable silver–silver chloride electrodes were

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used, contact with the muscles being made through agar-soaked wicks. The electrical recording system was directly coupled throughout. Close arterial injections into gracilis were made through a cannula in the femoral artery below the branch to the muscle. Proximal to the branch, the artery was looped with a thick thread, whose ends were passed through a glass tube fixed vertically above. During injection the femoral artery was occluded by pulling the loop into the tube. Quantitative results could best be obtained in animals in which one large branch of the femoral artery supplied gracilis, as it was then easier to isolate the circulation to it. The infusion apparatus described by Burn & Dale (1924) proved suitable for intravenous administration of D-tubocurarine chloride. It consists of a burette whose delivery is controlled by the flow of oil through a capillary tube. For initial curarization a positive pressure was created in the oil reservoir until the desired degree of neuromuscular block was attained. Curarization was then maintained by suitably adjusting the height of the reservoir. The rate of infusion necessary to maintain block varied greatly between preparations, the range extending from 0·25 to 1·1 mg/kg/hr.

RESULTS

The after-effects of activity at the neuromuscular junction are best revealed in nerve muscle preparations partly blocked by D-tubocurarine, for such treatment, by reducing the sensitivity of the motor end-plates to acetylcholine (Cowan, 1936; Kuffler, 1943), permits detection of changes in the transmitting apparatus which may otherwise remain masked. In a muscle which has been treated with enough D-tubocurarine to reduce the twitch tension to, for instance, 10% its initial value, the junctions which continue to transmit do so with a reduced margin of safety so that they fail rapidly when conditions for transmission deteriorate; on the other hand, the idle muscle fibres constitute a subliminally excited fringe and thus provide for the detection of facilitation of transmission. The mechanical response of a partly curarized muscle reflects, therefore, any changes which occur in the neuromuscular apparatus. The results of junctional activity, in such preparations, are seen to best advantage when a period of rapid repetitive stimulation of the motor nerve is interpolated into a series of infrequently applied single shocks. At the onset of the motor nerve tetanus a transient contraction occurs which, if the frequency of stimulation is high enough, gives way rapidly to complete neuromuscular block for the remaining duration of the tetanus. On returning to infrequent stimulation a striking and long-lasting restoration of transmission is seen. These phenomena, which were first described by Boehm (1894) and rediscovered by Boyd (1932), are again illustrated in Fig. 1.

Time course of post-tetanic decurarization. A reduction of the single twitch to 5% or less of its initial value was sought in these experiments. At this level of neuromuscular block a constant degree of curarization could be readily maintained by suitable infusion of D-tubocurarine; moreover, the mechanical response of the muscle to the conditioning tetani was transient, so that the potentiation of twitches, which occurs after tetanic contractions (Feng, Lee, Meng & Weng, 1938; Brown & von Euler, 1938), was minimized. Fig. 2A shows the time-course of the decurarization with tetani of varying duration,

the frequency being kept constant at 250/sec. Three phases may be recognized: a rising phase to maximum decurarization, which was reached more slowly after the more severe tetani; a period of rapid decline from the crest; and a slow final decay to the pretetanic level, the duration of which was rather variable. The restoration of neuromuscular transmission, at maximum decurarization,

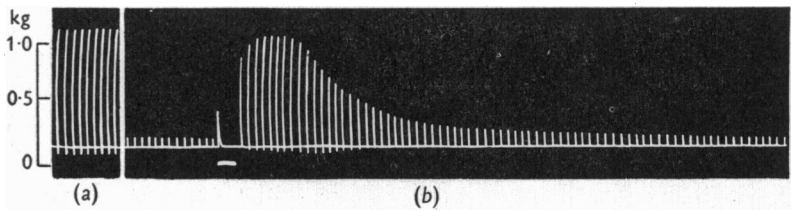

Fig. 1. Cat, 3·8 kg, chloralose. Contractions of tibialis excited by supramaximal shocks to sciatic nerve every 10 sec (*a*) untreated preparation; (*b*) 90% curarized; infusion of D-tubocurarine at 1·6 mg/hr. At signal, sciatic nerve stimulated for 20 sec at 80 per sec.

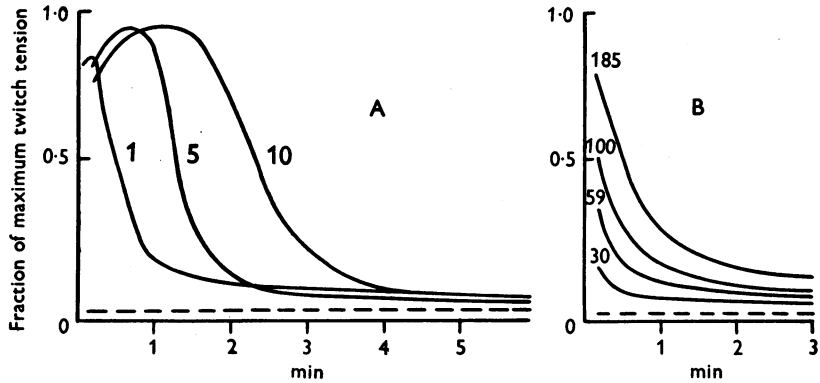

Fig. 2. Cat, decerebrate. Time course of post-tetanic decurarization in tibialis anterior. Supramaximal shocks to sciatic nerve every 10 sec. Twitch tension, expressed as fraction of maximum twitch in untreated preparation, plotted against time in minutes after end of tetanic stimulation of sciatic nerve. Broken line indicates level of block maintained by infusion of D-tubocurarine. A, after 1, 5 and 10 sec repetitive stimulation at constant frequency (250 per sec). B, after 1 sec repetitive stimulation at different frequencies (30, 59, 100 and 185 per sec).

was almost complete, and with longer tetani was maintained for a minute or more. In Fig. 2B the time-course of the decurarization after tetanic stimulation for 1 sec at different frequencies is plotted. In the case of these shorter tetani, the development of the decurarization was exceedingly rapid, and the phase between the end of the tetanus and maximum decurarization could not be explored with the infrequent test volleys here employed.

The rapid onset of decurarization after repetitive stimulation is noteworthy, since it stands in contrast to the long-lasting depression of transmission seen

after a single volley (Brown, 1938*b*; Brown & Harvey, 1941). At the level of neuromuscular block used in the experiments described above, for instance, the response to the second of a pair of maximal nerve volleys is reduced for about 10 sec. Yet, as is seen from Fig. 2B, 10 sec after the last of 185 shocks, the twitch tension is increased many times above the pretetanic level, and even after as few as 30 shocks some relief of block is seen at that time. Evidently, the long-lasting depression of transmission after a single volley has been replaced, after many volleys, by facilitation. In order to discover how this reversal was brought about, experiments with short trains of conditioning

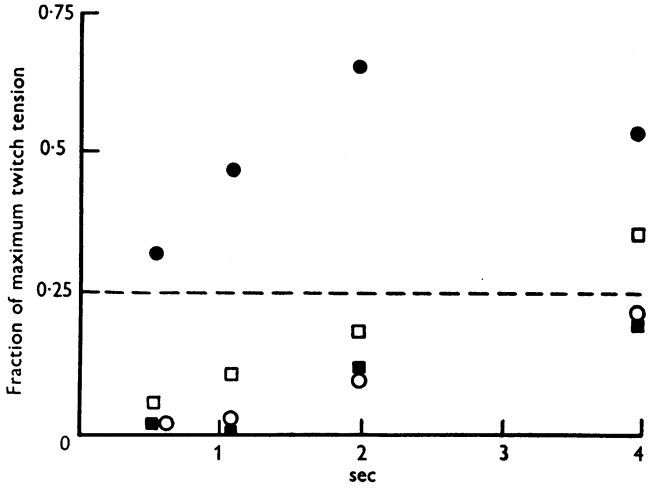

Fig. 3. Cat, chloralose. Contraction of tibialis excited by supramaximal shocks to sciatic nerve. Time course of changes in neuromuscular transmission after 1 (○), 4 (■), 9 (□), and 18 (●) conditioning volleys (at 100 per sec) to sciatic nerve. Twitch tension, expressed as fraction of maximum twitch in untreated preparation, plotted against time in sec after last conditioning volley. Broken line indicates level of neuromuscular block maintained throughout experiment by slow infusion of D-tubocurarine.

volleys were made. Preparations were used which had received enough D-tubocurarine to reduce the twitch tension to about 25%, so that both depression and restoration of transmission could be observed. To avoid summation of twitches, the shortest interval between the last conditioning shock and the test shock was 0·5 sec. Under these conditions there was still some evidence of depression 4 sec after a single volley (Fig. 3), and after four conditioning volleys the depression ran the same time-course. Recovery was considerably quicker after nine volleys, some decurarization being evident at 4 sec. When eighteen conditioning volleys were given, striking restoration of transmission was seen 1 sec after the last stimulus.

Changes in end-plate potential. Further information about the nature of post-tetanic decurarization may be obtained by recording end-plate potentials

in preparations which have been treated with enough D-tubocurarine to reduce their size to well below the level necessary for initiation of muscle action potentials. Feng (1941), using sartorius preparations of the toad, showed that repetitive stimulation of the motor nerve is followed by a large increase in the end-plate potential set up by subsequent test volleys, and Brown & Burns (1949, personal communication) have observed the same effect in the cat's gracilis. A few experiments were made to determine the time-course of this phenomenon. It was found that the increase in the end-plate potential in gracilis ran substantially the same course as the changes in twitch tension in tibialis after comparable conditioning tetani. At the peak of the effect the end-plate potential was 2–3 times the pretetanic size; no change of its time-course could be detected. During the tetanus the end-plate potential decreased rapidly and there was no evidence of long-lasting after-potentials.

To determine whether changes in the threshold voltage required for spike propagation played any part in the post-tetanic restoration of transmission, the following experiment was made. Potentials were recorded from the end-plate region of a gracilis preparation during the initial administration of D-tubocurarine, and the voltage of the end-plate potential at which spikes were last seen was noted. This height was taken as a measure of the propagation threshold of the junctions most resistant to block. D-Tubocurarine was then given until the size of the end-plate potentials was reduced to about a third of this 'threshold' value. After a tetanus the end-plate potentials recovered and the voltage necessary for initiation of spikes was again estimated. Comparison of the records (Fig. 4) shows that the threshold for spike initiation had not altered detectably in the course of the experiment.

Effects of injected acetylcholine. Electrical recording, although indicating that post-tetanic decurarization is brought about by an increase in the size of the end-plate potential, does not, by itself, throw any light on how this increase is achieved. Two explanations may be offered. Either the motor end-plates have become more sensitive to the depolarizing action of acetylcholine or more acetylcholine is released per nerve volley. The validity of the first hypothesis may be tested by injecting a constant dose of acetylcholine before and after a tetanus. Two types of experiment were made. In the first, the mechanical response of tibialis anterior to close arterial injection was taken as an index of the excitability of the motor end-plates; in the second, end-plate depolarization was directly recorded in gracilis preparations.

To produce a mechanical response in curarized preparations, doses of acetylcholine 10–20 times the dose required in untreated preparations had to be given. So long as the total number of injections made into any one tibialis preparation was limited to about 8, repeated injection of the same dose usually had remarkably constant effects, and graded responses to graded doses of acetylcholine could be obtained. The relationship between the peak tension

of the mechanical response and the dose of acetylcholine injected was determined in one experiment. Near the threshold an almost linear relationship was observed, but when larger amounts were given, the mechanical response increased more than in proportion to the dosage (Fig. 5); this was due, presumably, to more frequent firing of those fibres which had responded already to smaller doses. In Fig. 6 A an experiment is illustrated in which a near threshold dose of acetylcholine was injected into tibialis before a tetanus,

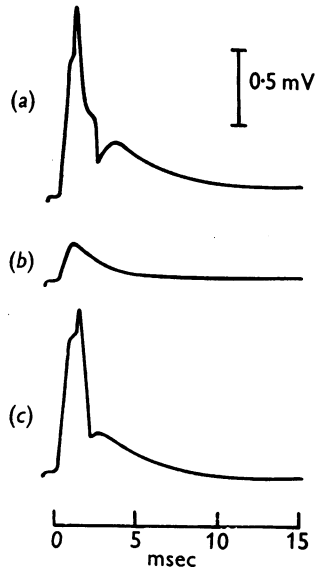

Fig. 4.

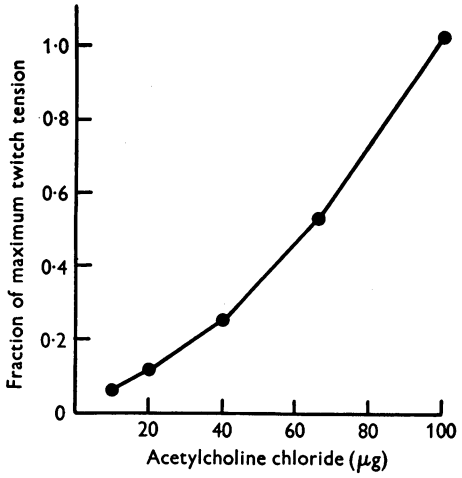

Fig. 5.

Fig. 4. Cat, 3·9 kg, chloralose. End-plate potentials recorded from gracilis. (*a*) after 6 mg D-tubocurarine chloride; (*b*) 110 min later, after a further 23 mg D-tubocurarine chloride; (*c*) 35 sec after (*b*). Between (*b*) and (*c*) the obturator nerve was stimulated repetitively for 5 sec at 200 per sec.

Fig. 5. Cat, decerebrate, 90% curarized. Relationship between dose of acetylcholine chloride injected into tibialis anterior and mechanical response of the muscle.

and afterwards, when the decurarization was at its peak. It can be seen that the mechanical responses were nearly the same and quite unrelated to the effects of nerve stimulation. Occasionally, as in Fig. 6 B, a slight potentiation in the response to acetylcholine was observed after the tetanus, but it was never of the same order as the increase in the transmitted response.

To verify the results obtained with mechanical responses experiments were made in which the end-plate depolarization (Burns & Paton, 1951) caused by subthreshold doses of acetylcholine was recorded together with changes of end-plate potentials. Fig. 7 B shows the depolarization produced by close arterial injection of 20 and 40 μg of acetylcholine into a gracilis preparation

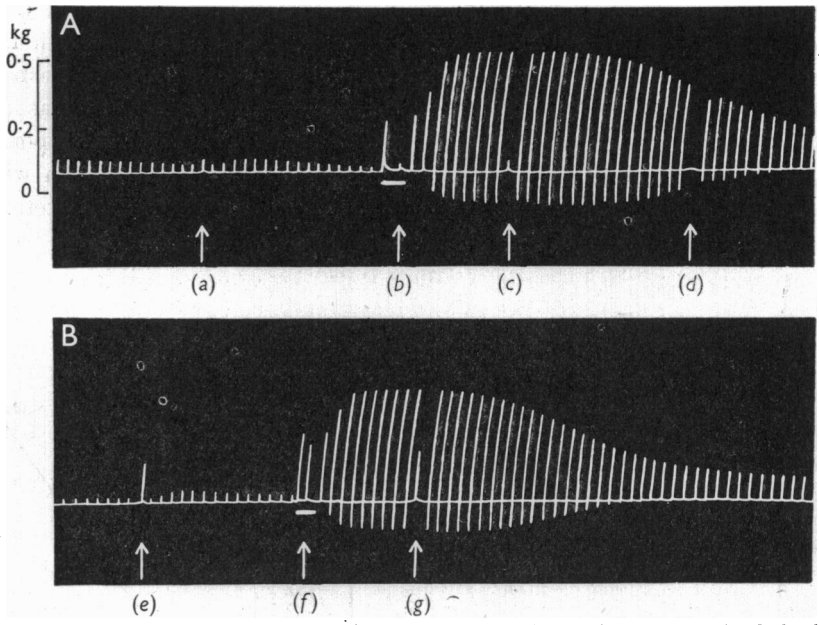

Fig. 6. Cat, decerebrate. Contraction of tibialis anterior elicited by supramaximal shocks to sciatic nerve every 10 sec, 90% curarized. A, effect of close arterial injection of 5 μg acetylcholine chloride interposed, (*a*) before, (*b*) during, tetanic stimulation of the sciatic nerve (20 sec at 100 per sec) and (*c*) 1½ min after end of motor nerve tetanus. At (*d*) 0·2 ml. saline. B, same preparation. At arrows (*e*), (*f*) and (*g*) close arterial injection of 10 μg acetylcholine chloride. At signal, motor nerve tetanus (15 sec at 200 per sec).

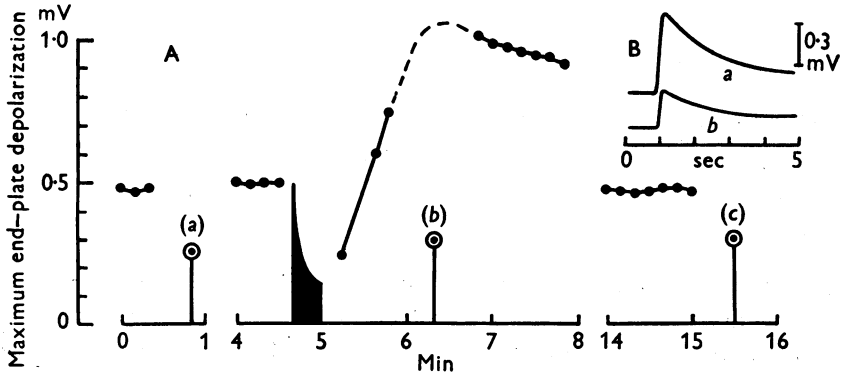

Fig. 7. Cat, chloralose. Gracilis preparation. Fully curarized. A, end-plate depolarization caused by close arterial injection of 20 μg acetylcholine chloride (⊙), (*a*) 4 min before, (*b*) 1 min 20 sec after and (*c*) 10 min after tetanic stimulation of obturator nerve (20 sec at 220 per sec). End-plate potential (●) set up by supramaximal shocks to obturator nerve recorded between injection. Broken line indicates conjectured time course of changes in end-plate potential during the interval that the oscillograph time base had to be stopped for registration of end-plate depolarization on moving film. Changes in end-plate potential during tetanus represented diagrammatically by solid curve. B, same preparation. Time course of end-plate depolarization caused by close arterial injection of (*a*) 40 μg, (*b*) 20 μg acetylcholine chloride.

which had received enough D-tubocurarine to reduce the size of the end-plate potentials to about half the 'threshold' value. Maximum depolarization was attained within 0·1 sec and was proportional to the dose of acetylcholine given. The depolarization decayed to half the maximum value within 1·5 sec. Injections of 20 μg were then made, 3 min before a severe conditioning tetanus, and at 1 min 20 sec and 10 min after the end of the tetanus. End-plate potentials were recorded throughout, except during the time that the oscillograph time-base had to be stopped for registration of end-plate depolarization on moving film. After the tetanus the end-plate potentials grew to twice the pretetanic size, but no corresponding changes in the responses to acetylcholine could be detected (Fig. 7A). From these experiments it was concluded that the sensitivity of the motor end-plates to acetylcholine is not increased as a result of repetitive stimulation of the motor nerve.

The failure of transmission during repetitive stimulation. In the course of the above experiments opportunity was taken to verify the suggestion (Brown 1937; Rosenblueth & Morison, 1937) that the early failure of transmission during tetanic stimulation of the motor nerve in partly curarized preparations is due to progressive diminution in the amount of acetylcholine released by each nerve impulse. If this is the only mechanism involved, then injection of acetylcholine should remain effective after transmission has failed. This was indeed found to be so. Fig. 6A and B shows that the mechanical response to acetylcholine was substantially the same during the tetanus as before or after it. The changes in transmission observed on altering the frequency of stimulation in either direction are thus of prejunctional origin.

DISCUSSION

The striking and long-lasting restoration of neuromuscular transmission observed in partly curarized preparations, after rapid repetitive stimulation of the motor nerve, is brought about by an increase in the size of the end-plate potential, set up by subsequent infrequent nerve volleys. The time-course of the end-plate potential and the threshold voltage for initiation of muscle impulses remain unaltered during the decurarization. These facts rule out the participation of two mechanisms which may cause long-lasting restoration of neuromuscular transmission after block by D-tubocurarine: an inhibition of cholinesterase and a subthreshold depolarization of the motor end-plate region (Katz, 1939). Inhibitors of cholinesterase increase the size of the end-plate potential, but the increase is invariably attended by a prolongation of its time-course (Eccles & MacFarlane, 1949). A subthreshold depolarization of the motor end-plate region, produced by administration of a specific depolarizing agent, such as decamethonium, causes a long-lasting restoration of transmission (Hutter & Pascoe, 1951), which, when muscle twitches alone are recorded, closely resembles the post-tetanic effect. Examination of end-plate

potentials reveals, however, that, with decamethonium, restoration of transmission is achieved without increase in their size, it being due, presumably, to summation between the depolarization caused by the drug and the nerve impulse. There is, moreover, no evidence that a motor nerve tetanus sets up a long-lasting depolarization of the end-plate region (Burns & Paton, 1951; Hutter, 1952).

Two possibilities remain then, which may account satisfactorily for the post-tetanic increase in the end-plate potential. Either the motor end-plate has become more sensitive to acetylcholine, that is, a true reversal of the action of D-tubocurarine has taken place, or more acetylcholine is released by the nerve endings per incident volley. The first hypothesis was put to the test by injection of acetylcholine at different times, and recording either the contraction of the muscle, or the local depolarization of the motor end-plate region. No significant change in the response to acetylcholine could be detected at a time when post-tetanic decurarization was at its peak. A change in the sensitivity of the motor end-plates to acetylcholine is not, therefore, the cause of the relief of neuromuscular block, and the effect can only be accounted for by assuming that more acetylcholine is released from the nerve ending per incident volley.

The early failure of neuromuscular transmission is also due to a change in the output of acetylcholine, for it could be shown, that the motor end-plates remained sensitive to acetylcholine when transmission had failed.

The experiments here presented localize the mechanisms responsible for the changes in transmission caused by altering the frequency of stimulation, to the motor nerve endings, but they give no indication of their nature. The complicated time-course of the phenomena strongly suggests that the variations of acetylcholine output are but the net result of a number of interacting processes. The spread of the nerve impulse into the motor nerve endings, the amount of preformed acetylcholine available there, and the rate of its resynthesis, may all be contributing factors. There is some indirect evidence that choline increases the output of acetylcholine from the motor nerve endings (Hutter, 1952). If choline accumulates at the neuromuscular junction during repetitive stimulation it may thus contribute to the decurarization. Similar facilitations which occur at non-cholinergic central synapses, cannot, however, be interpreted on this basis.

Potassium causes a long-lasting restoration in neuromuscular transmission in curarized preparations (Wilson & Wright, 1936), and it has been suggested on this basis (for references see Rosenblueth, 1951) that it may play a part in the post-tetanic decurarization. More work, however, is required to determine the mode of action of potassium, for its effect on muscle excitability could account for the decurarization it produces.

A striking similarity exists between the changes in transmission caused by

repetitive stimulation at the neuromuscular junction, and the phenomenon observed under analogous conditions at the synapse in the sympathetic ganglion and spinal cord. Larrabee & Bronk (1947) have found, in the stellate ganglion of the cat, that repetitive preganglionic stimulation causes a long-lasting facilitation of transmission of subsequent preganglionic volleys. From their analysis of this effect they concluded that it is due to some change resident in the presynaptic pathway which causes the nerve impulse arriving at the synapse to have a more effective excitatory action, probably as a result of release of an increased amount of acetylcholine. This explanation cannot be applied to the corresponding experiments on the spinal cord, for in this instance the presynaptic fibres concerned are non-cholinergic. Studying the long-lasting facilitation of transmission in the monosynaptic spinal reflex, which results from repetitive stimulation of the sensory nerve, Lloyd (1949) comes to the conclusion that this facilitation is of presynaptic origin. He relates the facilitation to the size of the nerve action potential, which, he showed, was increased as a result of the positive after potential set up by the rapidly repeating conditioning volleys. This attractive hypothesis has been challenged by Eccles & Rall (1951) who found that the potentiation of the presynaptic spike does not run, under all conditions, the same time-course as the facilitation of the reflex discharge. Eccles & Rall agree, however, with Lloyd that the facilitation is of presynaptic origin, and they show that it is brought about by a change in the synaptic potential, which increased during the facilitation, just as the end-plate potential increases during post-tetanic decurarization. In other respects, also, there is a striking analogy between the after-effects of activity in the non-cholinergic central synapse and at the neuromuscular junction where transmission is by acetylcholine. Brooks, Downman & Eccles (1950) have found, for instance, that the depression of the reflex response after a single test volley is of much longer duration on homosynaptic than heterosynaptic testing. In the former case the depression outlasts the positive after-potential at the neurone, and transmission through the activated pathway is not restored for several seconds. It seems likely, that this long-lasting depression is of presynaptic origin, comparable to the depression of neuromuscular transmission after a motor nerve volley (Brown, 1938*b*; Brown & Harvey, 1941). A detail of some interest is, that both at the neuromuscular junction and at the central synapse, a train of some twenty volleys is required before the depression of transmission is replaced by facilitation (cf. Fig. 3 with fig. 2 of Eccles & Rall, 1951). The progressive decrease in the size of the end-plate potentials in the curarized preparation during repetitive stimulation, and the decrease in the synaptic potentials under the same conditions, may thus also be analogous. Whatever else these striking similarities may mean, they at least illustrate that the changes of transmission on alteration of the frequency of stimulation in nerve-muscle preparations treated with D-tubocurarine have

their counterpart in other junctions not so treated, and this supports the view that D-tubocurarine acts solely by reducing the sensitivity of the motor end-plates to acetylcholine, thereby establishing the conditions necessary for detection of changes in the excitatory action of the nerve volley.

SUMMARY

1. Nerve-muscle preparations in decerebrate and anaesthetized cats have been used to study the restoration of transmission by repetitive stimulation of the motor nerve, when partial block has been produced with D-tubocurarine chloride.

2. A tetanus produces long-lasting restoration of transmission of subsequent single motor nerve impulses which is accounted for by increased motor end-plate potentials.

3. The time-course of the increased end-plate potentials is not detectably altered, nor is the threshold for the appearance of conducted muscle potentials.

4. The sensitivity of the muscle to acetylcholine has been determined by arterial injection and recording either muscle tension or end-plate depolarization. No significant change in the responsiveness of the muscle to acetylcholine occurs after tetanic stimulation of the motor nerve.

5. It is concluded that post-tetanic decurarization is a prejunctional phenomenon and is probably due to an increase in the amount of acetylcholine released per post-tetanic volley.

6. During the early failure of neuromuscular transmission which occurs on repetitive nerve stimulation, the response of the muscle to arterial injections of acetylcholine remains undiminished. This finding supports the view that the failure is due to progressive decrease in the amount of acetylcholine released per nerve volley.

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