REPETITIVE DISCHARGES IN HUMAN MOTOR NERVE FIBRES DURING THE POST-ISCHAEMIC STATE

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A number of motor and sensory changes follow the release of a human limb from ischaemia. The sensory changes are necessarily subjective but the motor changes lend themselves readily to delimitation by modern recording methods; it is a little surprising, therefore, to find as great a disagreement between observations in the latter field as in the former. Among these phenomena are bursts of repetitive muscle action-potentials, found mainly in the more distal muscles. They occur in the first phase of recovery from ischaemia and may be spontaneous, but are also induced by voluntary contractions of the muscle and by electrical stimulation of its nerve.

It was considered by Kugelberg (1946a) and by Denny-Brown and Foley (1948) that the repetitive action-potentials were initiated in the nerve, and it seemed necessary for large segments to be in the post-ischaemic state for the response to occur. Magladery, McDougal, and Stoll (1950), on the contrary, have little doubt that repetitive firing takes place distally, most probably at the myoneural junction. Whether this is so is of some importance for its own sake, and also because of the light it throws on the parallel sensory disturbances, so far inaccessible to objective analysis. The following work, therefore, describes experiments which have been made to establish the site of origin of spontaneous and induced repetitive discharges.

Method

For experimental convenience, and standardization, the ulnar nerve and first dorsal interosseous muscle of the hand were used in all experiments; the subjects (including the authors) were all healthy young adults, to some small extent selected for the ease with which their repetitive responses were obtained.

Action potentials were picked up from the muscle by coaxial needle electrodes, amplified by a differential amplifier with an adequate range of frequency response, and displayed on one beam of a Cossor double-beam cathode ray oscilloscope. The other beam was fed

with a sinusoidal time-scale at 500 or 100 c/s (intervals of 2 or 10 msec.).

Bipolar stimulation of the ulnar nerve, by electric shocks of 0.5 msec. duration, was applied above the elbow or at the wrist, through surface electrodes with a diameter of about 1 cm. and separated by 2-3 cm. Current strength was adjusted, before ischaemia began, to give the maximal amplitude of recorded muscle action-potential. The shock repetition rate was usually 1/sec., and the stimulating pulse triggered the sweep of the C.R.O. In some experiments a slowly rising current was used as stimulus, with the active cathode over the nerve (Kugelberg and Skoglund, 1946).

Ischaemia was produced by means of pneumatic cuffs, 10 cm. in width. On the upper arm the pressure was 200 mm. Hg., and on the forearm 250 to 300 mm. Hg.

Results

Stimulation by Brief Shocks.—It was unnecessary in these experiments, and in fact a disadvantage, to maintain ischaemia until blocking of the ulnar nerve, indicated by loss of voluntary contraction, had occurred; it usually begins after about 20 minutes and may be complete in 30. In the subject illustrated (Fig. 1) lively repetitive responses occurred on release from ischaemia which had lasted only 14 minutes.

To decide from which part of the neuro-muscular apparatus the repetitive action-potentials arise one of the experiments of Magladery and others (1950) was repeated, whereby, with two occluding cuffs, the blood flow could be restored to the proximal part of the upper arm, while the more peripheral stretch of nerve and the muscle remained ischaemic. One cuff (A) was placed as high as possible on the arm and the second cuff (B) just above the elbow, with the stimulating electrodes between them, over the ulnar nerve. Shock stimulation, before ischaemia began, gave rise to a direct volley in the first interosseous muscle with a latency of 12 msec. followed by a smaller discharge with an approximate latency of 26 msec.

(The latter is the F wave of Magladery and others, and is evidently a central response set up by the ascending nerve volley; whether it is a reflex, as they hold, or the secondary discharge in antidromically excited motor neurones described by Renshaw (1941), is immaterial to the present study, and we shall use Magladery's uncontroversial term.)

The circulation in the whole arm was stopped by the inflation of cuff A; just before its release, after 14 minutes, cuff B was inflated so that the forearm and hand should remain ischaemic. At about this time the nerve was stimulated again, with a similar result, except that the latencies were somewhat increased, probably due to cooling. On stimulating three minutes later, however, the direct volley was followed by a long-lasting, repetitive discharge, detectable after a latency of 21 msec. (Fig. 1B and C). Thus it began before the expected time of the F wave and could not have been a spinal cord reflex. Since the muscle, neuromuscular junctions, and distal stretch of nerve were still ischaemic this experiment indicates clearly that the post-ischaemic nerve can give rise to repetitive action-potentials.

The above conditions, with both cuffs on the upper arm, are not ideal for the experiment as different subjects show considerable variation in the readiness with which a repetitive discharge is produced. In some ischaemia for 14 minutes is insufficient, while with longer periods nerve-block may develop below cuff B, so that little of the evoked direct response and subsequent repetitive discharge may pass through. Since blocking is more pronounced in the proximal part of the nerve (Lewis, Pickering, and Rothschild,

FIG. 1.—A. Single shock stimulation caused a large biphasic response with a latency of 12 msec. followed by a smaller (F) wave at 26 msec. B and C. Cuff A, high on the upper arm, has been inflated; just before its release cuff B, immediately above the elbow, has been inflated. The direct response to shock stimulation, three minutes after release of A, is followed by a repetitive response.

1931), it is more easily avoided if the lower cuff is placed more distally, on the forearm. Objections, to be discussed later, have been made to the use of forearm cuffs, for which reason we have described first the results obtained with both cuffs on the upper arm. Placing the second cuff on the forearm, however, enables repetitive responses to be obtained more readily and consistently. The following experiment of this type confirms the previous findings and also demonstrates a characteristic of the repetitive response, previously described as a pseudo-reflex (Kugelberg, 1946a).

One cuff was placed on the upper arm and inflated for 20 minutes, a second cuff on the forearm being inflated just before the release of the first. On stimulating the ulnar nerve at the elbow before ischaemia the direct response occurred after 8.5 msec. followed by a small F wave at 26 msec. (Fig. 2A), while when the nerve was stimulated at the wrist the latencies were 3 and 31 msec. respectively (Fig. 2B). From one half to seven minutes after the release of the upper cuff stimulation at the elbow evoked a prolonged repetitive response which immediately followed the direct volley (Fig. 2C). With stimulation at the wrist the repetitive discharge was delayed and followed the direct volley after a free interval in the case illustrated, with a latent period about the same as that of the F wave (Fig. 2D), though in other cases it appeared somewhat earlier, evidently unrelated to the F response. The lower cuff was released when, seven minutes after release of the upper, the repetitive discharge had subsided (Figs. 2E and F); shortly afterwards it began again, but without a free interval between it and the primary response,

FIG. 2.—A. Stimulation of the ulnar nerve at the elbow causes a direct response from first dorsal interosseus with a latency of 8.5 msec., followed by a small F wave at 26 msec.

B. With stimulation at the wrist the latencies are 3 msec. and 31 msec.

C. Cuff A has been inflated on the upper arm for 20 minutes; just before its release cuff B on the forearm has been inflated. From half to seven minutes later each direct response to a shock at the elbow is followed immediately by a repetitive discharge.

D. On stimulation at the wrist the direct response is followed by a repetitive discharge with a latency of 27 msec., leaving a silent interval between them.

E. Seven minutes after release of cuff A there is no longer an after-discharge when stimulating at the elbow or, F, at the wrist.

G. Shortly after release of cuff B, 27. minutes from the beginning of the experiment, repetitive after-discharge returns on stimulating at the elbow, and H, also at the wrist, but now without a silent interval.

I. After a further five minutes the repetitive discharge still follows the direct response to a stimulus at the elbow, but at the wrist, J, the silent interval has returned.

whether stimulation was at the elbow (Fig. 2G) or at the wrist (Fig. 2H). After a further five minutes, before it finally subsided, although there was no free interval between direct and repetitive responses when stimulating at the elbow (Fig. 2I), an increasingly long interval occurred when stimulating at the wrist (Fig. 2J).

This sequence of events again shows that it is motor nerve fibres in the post-ischaemic state which respond rhythmically, since the distal structures were still ischaemic when the repetitive discharge was evoked by proximal stimulation after release of the upper cuff. The free interval before the repetitive discharge evoked by distal stimulation

FIG. 4.—Cuff A has been inflated on the upper arm for 20 minutes ; just before its release cuff B on the forearm has been inflated.

A. Cathodal stimulation of the ulnar nerve at the elbow by a slowly rising current causes double or treble responses, or B, more prolonged bursts.

C. Sudden reduction of the current strength causes fresh repetitive outbursts.

FIG. 5.—With two cuffs on the upper arm, after release only of the more proximal, many of the action potentials of a voluntary contraction are followed by a repetitive after-discharge.

FIG. 6.—From the same experiment as Fig. 5. Repetitive action potentials occur spontaneously accompanying fascicular twitching of the muscle.

can be accounted for by the time taken for the antidromic volley, inevitably evoked by stimulation, to reach the post-ischæmic stretch of nerve, and there start a repetitive discharge, sent back as a pseudo-reflex (Kugelberg, 1946a). After release of the lower cuff the distal structures became post-ischæmic, and the repetitive discharge then followed the direct volley with little or no free interval. The reappearance of the pseudo-reflex, however, when repetition began to subside, indicates that a proximal stretch of nerve retains its property of rhythmic response longer than a more distal one.

Stimulation by Slowly Rising Current and Voluntary Contraction.—Stimulation of the ulnar nerve in the post-ischæmic state by a slowly rising current gave rise to rapidly repeated responses from single motor units. With both cuffs above the elbow, or better, for the reasons given above, with one cuff on the forearm, after release of the upper cuff stimulation at the elbow gave rise to

double or treble responses (Fig. 4A), or to longer bursts of responses (Fig. 4B). On sharply decreasing the current a further repetitive discharge was evoked (Fig. 4C).

With the same arrangement of cuffs a slight voluntary effort also gave rise to rapid rhythmic outbursts (Fig. 5) ; they were most pronounced at the beginning of the contraction, doubtless due to later fatigue of the trigger mechanism.

Spontaneous Repetitive Discharges.—Complete release of a limb from ischaemia regularly results in spontaneous repetitive discharges ; Magladery and others, however, did not find this to be the case when only 12 cm. of nerve in the upper arm were released after 30 minutes or after the abolition of voluntary movement. Even so, with a suitable choice of subject, repetitive discharges may occur under these conditions, as illustrated in Fig. 6. The bursts of repetitive action potentials were accompanied by rather slow fascicular twitches of

the muscle; these were also observed by Reid (1931), who assumed that they were caused by direct stimulation of the muscle. Their relationship to the return of circulation to the nerve rather than to the muscle was shown earlier (Kugelberg, 1944) and is illustrated again by the experiments described above.

Magladery and others (1950) state that the action potentials which accompany spontaneous contractions of the muscle in the post-ischaemic state are the result of spinal cord reflexes elicited by afferent discharges arising in distal structures. The pattern of discharge, in the records published by these authors, has not the same appearance as that accompanying the fasciculations studied here, and further, we found that blocking the ulnar nerve at the elbow, performed in one instance, did not abolish them. An injection of 10 c.cm. of 2% xylocain with adrenaline was given intraneurally, and the block proved effective in that 10 minutes before and after release of the cuff no action-potentials appeared either on maximal voluntary contraction, or on shock stimulation of the nerve proximal to the elbow. In this case the interosseous

muscle had no supplementary innervation from the median nerve, tested by stimulating the nerve and recording from the muscle. The cuff on the upper arm, just above the elbow, was released after 25 minutes' inflation and this release was followed by spontaneous repetitive activity which could not, in the circumstances, be of reflex causation.

The Use of Cuffs on the Forearm.—The results obtained by Lewis and others (1931) and Merrington and Nathan (1949) on post-ischaemic sensory disturbances after compression of the forearm, have been criticized by Weddell and Sinclair (1947) and Magladery and others (1950) on the ground that there is a risk of leakage past the cuff. The latter workers observed at surgical operations on the hand that a cuff-pressure of 140–150 mm. Hg. on the upper arm was sufficient to prevent oozing, whereas a pressure of 60–70 mm. Hg. greater was required on the forearm for the same purpose. They went so far as to say "that any interpretation of the results of cuff pressure in the forearm which assume complete arrest of circulation must be discounted". It is a simple matter to use, as we

FIG. 3.—A. A single shock to the ulnar nerve at the elbow causes a direct response from the first dorsal interosseous muscle with a latency of 8.5 msec.

B. A cuff has been inflated on the upper arm and after 17 minutes the pressure has been lowered sufficiently for the pulse to become perceptible at the ante-cubital fossa and at the wrist. On stimulation the direct response has an increased latency but there is no repetitive after-discharge.

C and D. After complete release of the cuff six minutes later a repetitive after-discharge follows each direct response.

did, a pressure of 250–300 mm. Hg. in all forearm cuffs, though it can be shown that, at least for the repetitive response, this is an unnecessary precaution, as the following experiment illustrates.

A cuff was placed proximally on the upper arm and inflated to 200 mm. Hg. Stimulation of the ulnar nerve at the elbow before the beginning of ischaemia evoked a direct response with a latency of 8.5 msec. (Fig. 3A). After compression for 17 minutes the pressure was lowered sufficiently for the pulse to be clearly perceptible in the ante-cubital fossa (on auscultation), and at the wrist. During the following six minutes, though no appreciable block had developed, no repetitive response could be elicited on stimulation (Fig 3B). Thirty seconds after the pressure had been fully released, however, the muscle responded with synchronized repetitive discharges, at intervals of about 7 msec. (Figs. 3C and D). Stimulation of the ulnar nerve of the other arm, used for reference, after the total release of pressure following compression for 17 minutes, evoked a lively repetitive response. Thus, much greater leakage than that which might occur past a forearm cuff at a pressure of 250–300 mm. Hg. did not give rise to repetitive discharges. We consider that our experiments cannot be considered invalid because of the use of forearm cuffs.

Discussion

Both induced and spontaneous repetitive discharges in the first phase of the post-ischaemic state evidently have their origin in motor nerve fibres, though not necessarily in these alone. If the period of ischaemia has been sufficiently long the whole stretch of nerve responds in this manner. No attempt was made to investigate quantitative differences between distal and proximal stretches of nerve, although the frequent occurrence of a pseudo-reflex on stimulating at the wrist does not point to an excess of repetitive tendency in distal nerve fibres, but rather to the contrary.

Repetitive firing during the post-ischaemic state is correlated with large changes in the excitability of motor nerve fibres; that is, with hyperexcitability (lowered rheobase), and the breakdown of accommodation (Kugelberg, 1944). These changes in both repetitive tendency and excitability are greatly augmented by hyperventilation and hypocalcaemia, and diminished by hypercapnia and hypercalcaemia (Kugelberg, 1944; 1946 a and b; 1948; Gernandt and Zotterman, 1946). This relationship to changes in the ionic environment of nerve may explain the rather large variations in the reaction to ischaemia and post-ischaemia among normal individuals, which complicate the experimental conditions, and may account for some of the discrepant opinions of different authors regarding the mechanisms concerned.

On the sensory side the rhythmic high-frequency

(100–200 p.s.) discharge in motor nerve fibres, occurring spontaneously or induced by action potentials which enter the hyperexcitable stretch of nerve, has its counterpart in the post-ischaemic paraesthesiae, which are intensified by touch or other stimulation of the skin. The results obtained on the motor side are in agreement with the opinions of Lewis and others (1931), Zotterman (1933), Gordon (1948), and Merrington and Nathan (1949), that the pins and needles have their origin in sensory nerve fibres and not at the nerve endings, as suggested by Weddell and Sinclair (1947), and by Magladery and others (1950).

Summary

The repetitive discharges in muscle which occur after the release of a limb from ischaemia have been variously considered as arising in proximal nerve or in distal structures, particularly the myoneural junctions.

When two pneumatic cuffs were inflated on the upper arm and, after a suitable interval, only the upper cuff was released, a repetitive discharge occurred in the first dorsal interosseous muscle following shock stimulation of the ulnar nerve. The distal stretch of nerve and the muscle were still ischaemic, so that the repetitive tendency must have developed in that stretch of nerve which had been released from ischaemia.

With the same arrangement of cuffs repetitive discharges occurred in response to a slowly increasing electrical stimulus or to voluntary contraction of the muscle, and also spontaneously.

Owing to individual variations in the onset of ischaemic nerve block and post-ischaemic repetition, as well as to the fact that nerve block occurs more readily in proximal nerve, more consistent results are obtained when one cuff of the pair is on the forearm. Objections to this arrangement are discussed and countered by experimental evidence.

The possibility of spontaneous repetitive discharges being of reflex causation is discounted by blocking the ulnar nerve in the ischaemic area with xylocain.

The bearing of these observations on the parallel post-ischaemic sensory phenomena is discussed.

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REFERENCES

- Denny-Brown, D., and Foley, J. M. (1948). *Trans. Ass. Amer. Phys.*, **61**, 88.
Gernandt, B., and Zotterman, Y. (1946). *Acta physiol. scand.*, **16**, 248.

- Gordon, G. (1948). *Nature, Lond.*, **162**, 742.
Kugelberg, E. (1944). *Acta physiol. scand.*, **8**, Suppl. 24.
— (1946a). *Brain*, **69**, 310.
— (1946b). *Arch. Neurol. Psychiat., Chicago*, **56**, 507.
— (1948). *Ibid.*, **60**, 140, 153.
—, and Skoglund, C. R. (1946). *J. Neurophysiol.*, **9**, 391.
Lewis, T., Pickering, G. W., and Rothschild, P. (1931). *Heart*, **16**, 1.
Magladery, J. W., McDougal, D. B. Jr., and Stoll, J. (1950). *Bull. Johns Hopk. Hosp.*, **86**, 313.
Merrington, W. R., and Nathan, P. W. (1949). *Journal of Neurology, Neurosurgery, and Psychiatry*, **12**, 1.
Reid, C. (1931). *Quart. J. exp. Physiol.*, **21**, 243.
Renshaw, B. (1941). *J. Neurophysiol.*, **4**, 167.
Weddell, G., and Sinclair, D. C. (1947). *Journal of Neurology, Neurosurgery, and Psychiatry*, **10**, 26.
Zotterman, Y. (1933). *Acta med. scand.*, **80**, 185.