Demonstration of axon reflexes in human motor nerve fibres¹

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SUMMARY Responses of single muscle fibres to electrical stimulation of the tibial nerve trunk or of the intramuscular nerve twigs were detected in young volunteers without evidence of neurological disease. With suitably adjusted amplitude of the stimulus, clear-cut double distribution of the response latencies was obtained in some fibres. Experiments with two stimulating cathodes and with recordings from more than one muscle fibre in the same motor unit suggest that axon reflexes were involved. The results indicate that axonal branching normally occurs not only in the intramuscular course of the nerve but also outside the muscle, in some cases even rather high in the nerve trunk. The possibility is discussed that axon reflexes may underlie fasciculations evoked by neostigmine and those seen in some other conditions, such as amyotrophic lateral sclerosis, as well as muscle cramps in normal subjects.

The axon reflex has been described as the mechanism on which flare as a part of the 'triple response' to scratching the skin is based. Impulses pass up the afferent nerve fibres and along their branches down to local arterioles to dilate them. Blocking the nerve higher up does not abolish the reaction, while neuronal degeneration does. Only 'pain' afferent fibres were found to be provided with such special axon reflex arrangement (Celander and Folkow, 1953). Nevertheless, it appears to be a rule in other sensory nerve fibres that impulses initiated and orthodromically propagated in a single branch antidromically invade collateral branches (Cattell and Hoagland, 1931; Lindblom, 1958).

A similar mechanism in motor nerve fibres was suggested by Masland (1964) to underlie fasciculations evoked by neostigmine (Prostigmin) and possibly also fasciculations due to other causes—for example, in amyotrophic lateral sclerosis. Fullerton and Gilliatt (1965) were able to demonstrate axon reflexes in motor nerve fibres of patients with radicular or peripheral nerve lesions. By electrical stimulation of the median or ulnar nerve they evoked responses in hand muscles with latencies intermediate between those of the M and F waves. The suggestion that axon reflexes were involved was supported by the

fact that their latency shortened when the stimulating cathode was moved in a proximal direction and by the fact that they could be converted into M responses by increasing the intensity of the stimulus. The interesting finding in these pathological cases was axonal branching occurring unusually high above the muscles, but below the level of lesion. By this method no axon reflexes could be found in normal subjects, however.

In our own studies of direct responses of single muscle fibres to electrical stimulation of the tibial nerve trunk and of intramuscular nerve twigs in normal subjects we have observed responses which we believe to be based on axon reflexes. In fact, when we started to look actively for such responses we were able to detect them in almost every subject.

MATERIAL AND METHODS

Young adults aged 20 to 25 years, without signs and symptoms of neurological disorders, were used in all experiments. Electrical stimulation of motor nerve fibres was performed either in the nerve trunk (in nine subjects) or in their intramuscular course (in four subjects).

A. STIMULATION OF THE NERVE TRUNK Disa 13K23 stimulating electrode was introduced close to the tibial nerve in the popliteal fossa. Square stimulus pulses, 50 μ sec in duration, were delivered monopolarly, with the indifferent surface electrode placed over the patella. The rate of stimulation was 0.5, 1 or 2 per second.

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Stimulus amplitude (2 to 20 V) was adjusted so that a direct response was obtained in a portion of the medial head of the gastrocnemius muscle (which was usually the first to respond). Surface detection of the EMG was made from this muscle by means of silver cup electrodes 3 cm apart. Single muscle fibre action potentials were detected with a special needle electrode (Ekstedt, Häggqvist, and Stålberg, 1969), displayed on a Tektronix 565 oscilloscope with a 2A61 or 3A9 amplifier and recorded on magnetic tape. The criterion used to identify action potentials of single fibres was that, under recording conditions in which it was possible to detect time differences of at least 10 μ sec, consecutive potentials were of identical shape (Ekstedt, 1964; Ekstedt and Stålberg, 1969). Latencies of the responses were analysed on a computer of average transients (TMC CAT 1000).

B. STIMULATION OF INTRAMUSCULAR NERVE TWIGS A bipolar stimulating electrode was used (Disa 13K14) in which the distance between the anode and cathode was 500 μ . It was introduced in the extensor digitorum communis muscle near the endplate zone. Square stimulus pulses with a duration of 50 μ sec were used in all cases and the stimulation rate was one, two, or five impulses per second (Table). Recording was made as described above. A needle electrode of the same type was inserted in the extensor digitorum communis muscle some centimetres distally to the stimulating electrode, maximally 7 cm (in case 30, Table). For the analysis a storage oscilloscope (Tektronix 549 with a 1A7 amplifier) was also used.

Different muscles were studied because the authors started the experiments independently, each using one of these muscles.

RESULTS

In the following only recordings with needle electrodes will be discussed.

A. STIMULATION OF THE NERVE TRUNK The latencies between stimulus artefact and muscle response were nearly constant from discharge to discharge. They were 4 to 15 msec, which was within the range of the surface-detected M wave. The slight random variation observed was between 15 and 60 μ sec (SD) in more than 90% of the cases when the stimulus amplitude was more than 10% above the threshold. The greatest part of this variation, up to 40 μ sec (Broman, Ekstedt, and Stålberg, 1970), can be accounted for by the variability in neuromuscular transmission time—that is, by the neuromuscular jitter (Ekstedt, 1964). The comparatively small remaining part may be due to a possible inconstancy in conduction velocity along the nerve and muscle fibre. To minimize the influence of these factors the rate of stimulation was low and regular (Stålberg, 1966; Ekstedt and Stålberg, 1969). Another factor contributing to latency variation could be uncertainty of the point on the nerve fibre at which the action

potential starts. With constant stimulus strength this variation was probably small, as even gross changes in stimulation strength did not change the mean latency by more than 200 μ sec. With threshold stimulus the variation from discharge to discharge in latency was slightly increased.

A small proportion of fibres, however, showed a clear-cut double distribution of the latencies, the interval between the two mean values being 350 to 2,150 μ sec for different fibres (Table). The responses with long and short latencies could be clearly identified as being from one and the same fibre because the action potentials were of identical shape, amplitude, and duration. Whether the muscle fibre responded with a short or with a long latency depended on stimulus amplitude: when this had been brought up to a certain level, a small increment (of the order of 5 to 10%) could increase the proportion of the early responses to 100%, while with a slight decrease in the amplitude only late responses were obtained. The amplitude could be adjusted so that the early and the late responses alternated almost regularly.

Four recordings of this type were from pairs of muscle fibres which obviously belonged to the same motor unit, because they always appeared and disappeared together on changing stimulation strength. The potentials in such a pair invariably responded either both with a short or both with a long latency. In two recordings four muscle fibres behaved in the same way. Figure 1 is an illustration of the former example, showing also how slight increments in stimulus amplitude shortened the latencies of both fibres.

Another test was performed on one of these pairs of muscle fibres. The stimulating cathode was moved about 15 mm along the nerve in the distal direction. This resulted in shortening of the latency of the early response and in prolongation of the latency of the late response (Fig. 2). A similar test was made when recording from a single fibre. Here the cathode was moved approximately 2 cm distally. The procedure resulted in loss of the late response, but the early response appeared with 2.5 msec shorter latency.

In four cases, the responses appeared at three distinct latencies (nos. 12 to 15 in the Table). All of these were responses with largest latency changes; in one case (15) the total of both changes was 3,300 μ sec. The three latencies appeared at slightly different stimulus strengths, whereby a stronger stimulus was required for the intermediate, and the strongest for the short latency. Only exceptionally could the stimulus be adjusted so that all three latencies were obtained without changing it.

B. STIMULATION OF INTRAMUSCULAR NERVE TWIGS

TABLE
MUSCLE FIBRES RESPONDING WITH TWO OR THREE LATENCIES

Nerve trunk stimulation				Intramuscular stimulation			
No.	Short latency (msec)	Change in latency (μsec)	Stim. freq. (imp./sec)	No.	Short latency (msec)	Change in latency (μsec)	Stim. freq. (imp./sec)
1	7.0	350	0.5	16	6.2	200	1
2	7.2	400	1	17	6.0	200	2
3	10.0	400	1	18	7.8	280	1
4	6.0	600	1	19	7.1	330	1
(pair)							
5	8.3	620	1	20	4.5	420	1
6	7.0	650	0.5	21	1.9	470	5
(4 fibres)							
7	10.5	880	0.5	22	4.0	510	5
8	7.1	880	1	23	3.4	560	2
9	10.5	900	1	24	2.1	600	5
(pair)							
10	13.6	1,050	1	25	1.7	740	5
11	12.8	630 and 2,100*	0.5	26	9.4	800	2
(2 or more fibres)				(pair)			
12	7.0	500 + 1,120	0.5	27	7.5	1,850	1
13	6.4	550 + 1,250	0.5	28	4.5	8,900	5
(pair)							
14	7.6	1,040 + 1,440	2	29	8.0	350 + 370	1
15	13.5	1,150 + 2,150	0.5	30	13.1	330 + 760	2
(4 fibres)							

*Different stimulating cathode position.

When looking for the described phenomenon of dual latencies during intramuscular electrical stimulation, this could be found in every subject, although it was not quite easily obtainable. Fifteen such recordings were obtained. In all these cases the latency for one and the same potential varied a little from discharge to discharge, the jitter being of the order of 10 to 20 μsec (SD). When the stimulus strength was

gradually increased from threshold, the latency abruptly became shorter at a certain value of strength but the jitter was still the same and the shape of the action potential was unchanged. When the stimulation strength was decreased again the action potential reappeared with its first latency value. The differences between the mean values of the latencies were 200 to 8,900 μsec (Table, Fig. 3). The reverse

FIG. 1. Action potentials of two muscle fibres (no. 9 in Table) responding always both with a short latency or both with a long latency. The stimulus amplitude in consecutive sweeps is alternately varied by 10%. The stronger stimulus invariably produced short and the weaker one long latency. Sweep delay after the stimulus: 9 msec. Action potential amplitude was about 1.5 mV.

FIG. 2. Action potentials of fibres from a motor unit (no. 11 in Table) showing the jump in latency from A to D. In the lower traces, stimulation was applied through another stimulating cathode positioned approximately 15 mm distally from the first cathode, with which the upper traces were obtained. Sweep delay 12.1 msec. Action potential amplitude was about 2 mV.

phenomenon was seen when on lowering the stimulation strength the latency increased.

In most of the experiments many fibres were recorded from at the same time, but they presumably did not belong to the same motor unit, as they appeared in the response at different stimulation

strengths. It was, however, sometimes seen that more than one of the single muscle fibre action potentials in the complex showed the phenomenon with two mean latency values and jumped between them independently (Fig. 4).

In one of the recordings two action potentials

FIG. 3. Action potentials from the muscle fibre (no. 28 in Table) showing the largest change in latency. Action potential amplitude was about 2 mV.

FIG. 4. Two muscle fibres (no. 25 and 24 in Table) belonging to different motor units. The latency of both action potentials abruptly lengthened at two different values of decreasing stimulus strength. Both responses also show small continuous prolongation of the latency before the actual jump. Action potential amplitude was about 2 mV.

were linked (Fig. 5); they appeared at the same time, disappeared together, and jumped together between a short and a long latency value.

In two of the 15 cases a third mean value (shorter) could be obtained by increasing the stimulus strength. Here the differences in latencies were 350 and 370 μ sec (Fig. 6) and 330 and 760 μ sec, respectively.

Both with intramuscular and nerve trunk stimulation the continuous increase and reduction of stimulus strength resulted in continuous shortening and lengthening of the latencies, respectively. This was up to 200 μ sec and was also seen in recordings where jumps in the latencies did not occur (cf. Fig. 6, later action potential in B-D).

If the stimulation rate was more than 5/sec, there sometimes appeared continuous changes in latencies which were much beyond this range and measured 1 msec or more. These changes were not seen when the stimulation rate was 5/sec or below, the values actually used in this study.

DISCUSSION

Figure 7 is an attempt to interpret the recordings in Figs. 1 and 6 on the basis of an axon reflex: the responding pair of muscle fibres, part of a single motor unit, can be activated by stimulation of the axon either directly, at point D, or at point A, which lies on another axonal branch. In the latter case the nerve impulse must first pass antidromically to the

branching point and thus has to travel over a longer distance than in the former case.

The two-fibre example illustrated in Figs. 1 and 5, as well as the other six examples involving more than one muscle fibre, shows that the phenomenon must have occurred proximally to the branching point for these muscle fibres, because they invariably responded either all early or all late. Thus it seems unnecessary to consider any events taking place at the terminal or ultraterminal nerve endings, motor end-plates, and muscle fibres, including double motor end-plates.

A finding speaking in favour of an axon reflex is the dependence of the latency upon the amplitude of the stimulus. In the situation drawn in Fig. 7, the point A is closer to the electrode than D; when the stimulus is near the threshold for D, it is well above threshold for A. Evidently, slight increase in stimulus amplitude will tend to increase the proportion of the responses starting at D, and a decrease in the amplitude will decrease this proportion.

The experiment where the stimulating cathode was moved in the distal direction (Fig. 2) seems to confirm the hypothesis that the phenomenon of dual latencies is based on an axon reflex. As can be seen from Fig. 7, moving the stimulating electrode towards the muscle will result in shortening of the latency for the direct response and in its lengthening for the axon reflex response.

From this experiment, a rough estimation of

FIG. 5. A complex response of action potentials from at least five muscle fibres, two of which (no. 26 in Table) respond with two latencies, whereby they are always linked together. Note different time calibration in A and B-C. In C, 7 discharges were superimposed with each of the two latencies, to show the relative constancy of both latencies. Action potential amplitudes were about 3 and 1.5 mV.

conduction velocities along the afferent and the efferent limb of the axon reflex can be made. The former was, in the actual experiment, approximately 25 and the latter 13 m/sec. Both values were considerably lower than those of the fastest conducting motor fibres at that level of the nerve trunk. This is in agreement with the observation that almost none of the muscle fibres showing the phenomenon had a direct response corresponding to an early part of the surface detected M wave. They usually coincided

FIG. 6. One muscle fibre (no. 29 in Table) showing three different mean latencies on increasing stimulus strength (A-C). The picture reversed on decreasing stimulus strength (D-E). In B-D a new muscle fibre response appeared which did not jump but showed small continuous change of the latency. Action potential amplitude was about 2.5 mV.

with late deflections of the M wave and had latencies from 6.0 to 13.6 msec on 10 to 17 cm distance between stimulating and detecting electrode (Table).

FIG. 7. Suggested interpretation of dual latencies based on an axon reflex. The weaker stimulus depolarizes the adjacent axonal branch at point A. The nerve action potential propagates antidromically to the branching point and then orthodromically to the muscle fibre pair (cf. Figs. 1 and 5). The stronger stimulus gives a direct response starting at D.

This is in agreement with the explanation based on the axon reflex; as branching fibres always have smaller diameter than the parent fibre (Kashef, 1966), they should conduct at a slower velocity, and the more proximal the branching the longer will be the latency of the direct response.

The relatively low conduction velocity for both afferent and efferent limbs of the axon reflex has also been found by Fullerton and Gilliatt (1965, Table II), except for one case in which the afferent velocity was 50.0 m/sec, and the direct response of the fibres showing the axon reflex phenomenon appeared in the late deflections of the M wave (cf. Fullerton and Gilliatt, 1965, Fig. 6b and c).

A possible argument against the interpretation shown in Fig. 7 would be that responses appearing at the shorter latency actually belong to a part of another motor unit recruited by increasing stimulus strength. However, this cannot be the case as the action potentials of different muscle fibres differ in amplitude, shape, and duration, and can be relatively easily identified according to these parameters. Besides, there never appeared both an early and a late response to a single stimulus. This argument is further refuted by the two- and four-fibre examples; identical combination of identical action potentials belonging to different motor units cannot possibly be expected at one and the same recording site.

It might also be argued that the early latencies could be due to the nerve action potential starting at a more distal node of Ranvier. Indeed there is slight

fluctuation of the membrane potential of the axon (Verveen and Derksen, 1968), which could well bring into play such a mechanism. However, taking 13 and 50 m/sec (estimations made in two experiments by moving the stimulating cathode) as extreme values of conduction velocity along the axon branches, the shortening of the latency due to jumps of the stimulating point to a more distant node, 1 to 2 mm away, should fall between 20 to 140 μ sec. This is clearly outside the range of latency changes obtained on stimulation of the nerve trunk. These figures are not valid for the situation of intramuscular stimulation. So, the possibility that the shortest observed change in the latency—that is, 200 μ sec, and perhaps up to 500 μ sec (Table)—might be due to a jump of the starting point of the nerve action potential to the next node of Ranvier cannot be excluded with certainty. However, if such jumps were responsible for the phenomenon then we should expect it to be demonstrable with any nerve fibre activated in the described way. From several hundreds of recordings it occurred only in three cases on nerve stimulation and in six cases on intramuscular stimulation. It should also occur in several steps, but from six cases with triple latencies such short steps were seen in only one case (no. 29 in the Table).

If these short latency changes really are based on axon reflexes, in that case with very short reflex arcs, one might ask why they were obtained so often in relation to the long latency changes—that is, in about one third of the cases. A simple reason for this might be that the phenomenon is easier to demonstrate when the branches lie close to each other, and this is in the proximity of the branching point. When the branches are more separated the stimulus has to be so strong as to depolarize many neighbouring nerve fibres, and this tends to obscure the phenomenon.

Physical spread of the increasing stimulating current along the axon cannot be responsible for the jump in latencies (although it could account for the small continuous changes, which measured less than 200 μ sec) because it was possible in every case to adjust the stimulus strength to such a value that both early and late responses were obtained. Moreover, the jump of the response from the long to the short latency was produced by an increase in stimulus amplitude of the order of 10%, while with a further increment by 100% or more significant further shortening of the latency was not obtainable, except in six cases.

In these six cases the responses showed three distinct latencies occurring at different stimulus strengths. Here the explanation may be that three branches were involved. The anatomical details

underlying this phenomenon cannot be settled. One possibility may be trichotomous branching at one node of Ranvier and the other two dichotomous branchings at different nodes of Ranvier. Trichotomous branching, however, is much less common in histological preparations than dichotomous (Kashef, 1966). The explanation with trichotomous branching would theoretically be possible if the descendant fibres were unequal in diameter and conducted at different velocities giving rise to three latencies. This, in fact, is the most common situation in such branching (Kashef, 1966). Nevertheless, dichotomous branching at different levels remains the likeliest explanation.

In most of the experiments, recording was made from only one muscle fibre. It must be pointed out that this is not an indication that the axon reflex involved only a restricted number of muscle fibres in the motor unit. Also in the voluntarily activated muscle, where the whole motor unit is known to participate, it is our experience that with this type of detecting electrode ($25\ \mu$ in diameter) we record mainly from one muscle fibre of a motor unit in about 75% of random insertions. In this investigation 23 out of 30 recordings were from single fibres, which does not seem to differ from the proportion in recordings during voluntary activation.

The finding of axon reflexes in the tibial nerve trunk indicates that branching might occur in that nerve as high as about 100 to 150 mm above the point of entry into the muscle.

Eccles and Sherrington (1930) in their study of fibre branching in the nerve to the medial gastrocnemius muscle in normal cat reported only 4% increase in the total myelinated fibre count between sections taken at 60 and 30 mm from the muscle. In a similar study and in deafferented nerve to the same muscle in the baboon, Wray (1969) found an increase of 5.8% between sections at 52 and 42 mm above the muscle. At more distal levels, the rate of branching increased greatly, so that close to the muscle up to 37 to 67% of the efferent fibres branched. This percentage was found to approach 100 in rhesus monkeys and rats (Kashef, 1966).

Fullerton and Gilliatt (1965) and Gilliatt (1966) in their experiments on median and ulnar nerve were unable to detect axon reflexes in normal subjects and concluded therefore that normally, in the case of hand muscles, all branching may occur below the wrist. They collected evidence that the branches in their pathological cases were formed by the tips of regenerating axons.

Although in the present study axon branching was found somewhat closer to the muscle than in Fullerton's and Gilliatt's cases, it was nevertheless considerably higher than one would expect from the

negative results of these authors when looking for axon reflexes in normals.

The findings reported in this paper seem to suggest that an axon reflex will occur whenever a nerve impulse is set up in an axonal branch. Perhaps it may even be impossible to depolarize only one terminal nerve twig without activating other parts of the motor unit at the same time (cf. Stålberg, 1966, p. 39).

From the present experiments it is not possible to conclude whether or not the whole motor unit was activated. The fact that multiple potentials were seen in these recordings as often as in the voluntarily activated muscle, might support the possibility that all parts of the motor unit were involved. An indication that at least a great part of the motor unit must be activated by stimulation of terminal nerve twigs is provided by an unpublished observation made by one of us. The experiment was performed in the tibialis anterior muscle of a rabbit. A microscope slide was introduced distally in the exposed muscle *in situ*, parallel to the muscle fibres (Fig. 8). A bipolar stimulating electrode was inserted into the muscle on one side of the slide and recordings were made on both sides with multielectrodes. When stimulating with threshold stimulus strength for fibres nearest to the stimulating electrode, responses could also be obtained on the other side of the slide, indicating the activation of an axon reflex. Under the microscope, contractions were seen which presumably resulted from activation of many muscle fibres.

The axon reflex ought to be elicited by any kind of stimulus depolarizing a nerve twig. Thus it does not seem unlikely that fasciculations evoked by neostigmine and in some pathological conditions, such as amyotrophic lateral sclerosis, may represent the activation of motor units by axon reflexes initiated

FIG. 8. A microscope slide pushed through the muscle. STIM, stimulating electrode, REC, recording electrodes.

in single nerve endings (Masland, 1946). The same mechanism might be involved in peripheral painful muscular cramps sometimes experienced by healthy people. The peripheral triggering of such cramps has been demonstrated by Elmqvist (1970). They could be elicited in full strength by intramuscular electrical stimulation, were unaffected after nerve block outside the muscle, and disappeared after curarization.

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