

AUTOGENETIC INHIBITION

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Recent work at this Institute has been devoted to a study of autogenetic inhibition as part of the wider problem of reflex self-regulation of muscular contraction (Granit and Suursoet 1949, Granit 1950, Naess and Hagbarth 1950, Granit and Strøm 1950, 1951). The results have already been presented but with relatively meagre discussions. The present paper, by considering general points of view and theoretical aspects of the work, serves to remedy this deficiency with regard to inhibition. References absent from this work may be referred to in the experimental papers.

My interest in reopening this field arose from two sources: (a) an experimental observation, confirming Sherrington, that nerves stimulated to elicit reflex responses often failed to produce their full effect as long as they were unsevered below the electrodes and thus connected with their muscles, (b) the facts that the monosynaptic reflex of Eccles and Pritchard had been shown by Lloyd to run in the largest and fastest muscle afferents and to be responsible for the stretch reflex. The latter facts seemed to suggest an elegant method of studying this and related phenomena by testing motoneurone excitability directly.

If a gastrocnemius muscle in a cat under Dial is stretched or made to contract by a conditioning shock to the peripheral stump of a ventral root (commonly S1) its motoneurone pool will be influenced by the muscle end organs in a certain fashion. We want to know in what state of excitability the gastrocnemius ventral horn cells have been thrown by the afferent impulses set up by stretch or contraction. To this end the muscle's own nerve is stimulated by a test shock and its monosynaptic response picked up from the central stump of the ventral root. S1 is a long

root and can easily be cut across in the middle to provide a peripheral stump for the conditioning stimulus setting up the contraction and a central stump for recording the monosynaptic volley. The latter is so fast that the second contraction, caused by the test shock to the muscle nerve, has not yet had time to influence the state of excitability of the motoneurone pool at the moment when the monosynaptic response traverses it. Hence the size of the monosynaptic volley measures the state of excitability of the ventral horn cells in any phase of the contraction. The equivalent experiment with stretch is still simpler because no conditioning shock is needed in order to condition by stretch impulses. The general arrangement may be studied in figure 1, left. It should be added that the limb of the animal has been denervated, except for the nerve used, and that the motor roots L5 — S2 have been severed. Antidromic effects, which were an unattractive complication of the earlier work on the so-called silent period of Paul Hoffmann, have thus been removed. The extreme complexity of antidromic effects is well known nowadays, mainly thanks to the work of Renshaw, Lloyd and Eccles.

On the right in figure 1 is shown the typical result of an experiment in which the motoneurones have been conditioned by a muscle contraction. The isometric myogram appears below each neurogram. The effect of the conditioning shock alone is found in the first record C. The next one T illustrates the monosynaptic control in response to the test shock; 1, 2, 3, and 4 are combined responses at different shock intervals taken with the fast time base shown below no. 4. At short intervals the response, during contraction, is facilitated, at longer intervals depressed. Finally a slow time base was switched on for

record 5 showing full inhibition; a final control of the monosynaptic response alone is found in T (lower) for the slow time base of record 5. A complete analysis of this experiment is found in figure 2 the shock intervals being plotted logarithmically.

Essentially the same result is obtained by merely stretching the muscle and testing by

the tensile stress, the more effective the inhibition. In stretch more inhibition may be obtained by increasing the length of pull. Pure facilitation may be obtained by light stretch. On the whole, contraction seems more prone to set up the late depression than stretch. The variations are considerable from animal to animal.

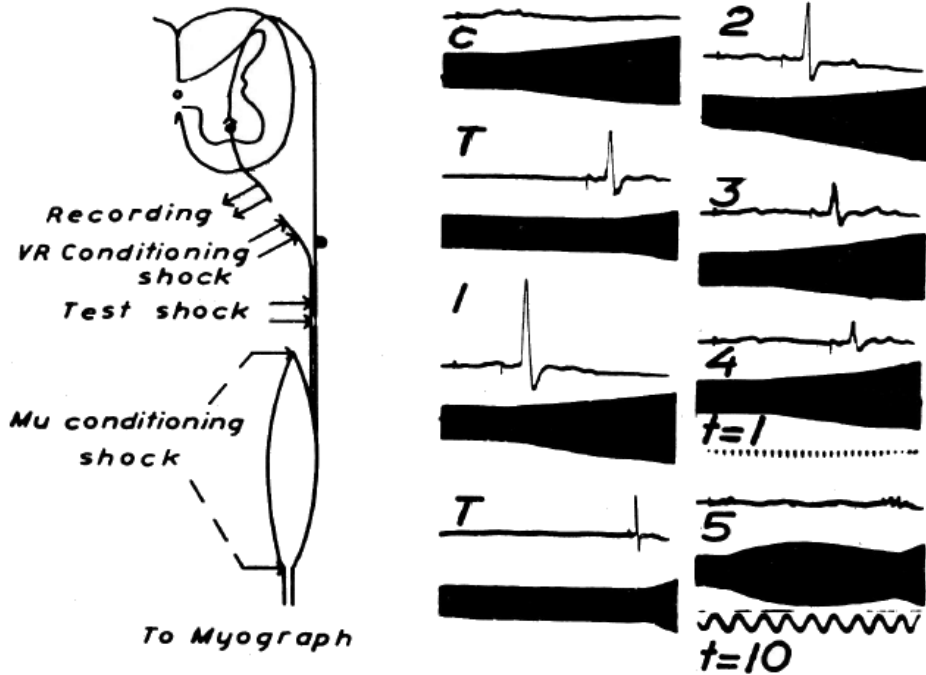


Fig. 1

Excitability of gastrocnemius motoneurons during contraction of gastrocnemius. Left. Diagram illustrating experimental arrangement. Right. C, conditioning shock alone, its discharge above, its myogram below; T (upper) test shock with its myogram; 1-4, both together at different time intervals ($t = 1$ msec.). T (lower) test shock alone at $t = 10$ msec.; 5, together with conditioning shock at $t = 10$ msec.

the monosynaptic response during stretch. Figure 3 is instructive inasmuch as the test shock is on the severed lateral gastrocnemius nerve whilst the conditioning impulses during stretch are coming from the medial component of the muscle through its intact nerve. Again, there is facilitation followed by inhibition. Indeed, even by stretching a more distant synergist such as the quadriceps, there is an initial facilitation followed by inhibition though in this case facilitation is less prominent and inhibition stronger.

In the complex motoneurone response the depression at the moment is in the centre of our interest. It is strongly influenced by the initial tension of the muscle. The greater

It seems that we are dealing with a true physiological mechanism of integration. "In the normal mode of operation of the muscle machine the contraction is first speeded up by facilitation, then damped by inhibition. The greater the initial tension or the more (in stretch) the muscle is stretched, the more important become the inhibitory brakes." (Granit 1950). In a journal devoted to clinical aspects of neurophysiology it is perhaps not out of place to emphasize that this particular type of inhibition stands in need of some attention from pathology and clinical neurology.

The "silent period" of the knee jerk neurogram (Hoffmann, Denny-Brown) is part of

this integration. It was explained by Gasser as a typical subnormal phase of excitability, consequent upon the discharge of the ventral horn cell. By this explanation Gasser applied his theory of inhibition to a specific case. Events have proved this theory to contain an essential element of truth. It implies that, just as in peripheral nerve a transmitted volley is succeeded by a supernormal and a subnormal phase each associated with respectively negative and positive afterpotential, so

excitability change, Lloyd's confirmation of this work ending up in a complete analogy with the behaviour of peripheral nerve. Lorente de N6 and Graham's work on the oculomotor motoneurons of the rabbit in which evidence for the existence of a subnormal phase in these cells was obtained. Among later contributions should be men-

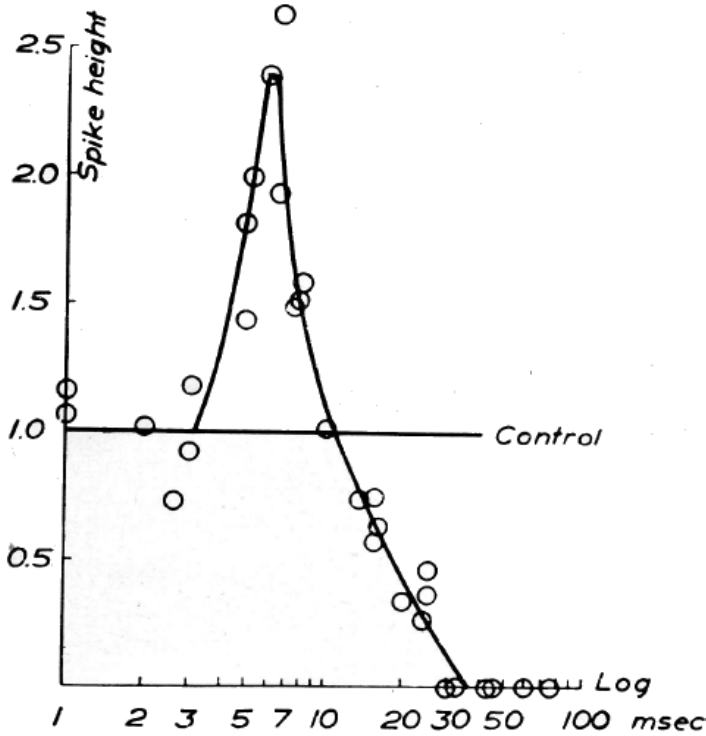


Fig. 2

Variation of spike height relative to monosynaptic control = 1.0 plotted against interval between conditioning and test shock in experiment such as that of figure 1. Conditioning shock in ventral root L7, test shock on med. and lat. gastroc. nerves. Initial tension 250 g. Conditioning shock elicits contraction of 550 g.

also in the central nervous system supernormality and subnormality will succeed the passage of an impulse. On this view proper timing of impulses within the central nervous system assumes fundamental importance as a physiological mechanism of regulation. The work supporting Gasser's theory is well known and need not be reviewed. I shall but briefly recall Eccles' analysis of slow negative and positive potentials in the sympathetic ganglions, both associated with their proper

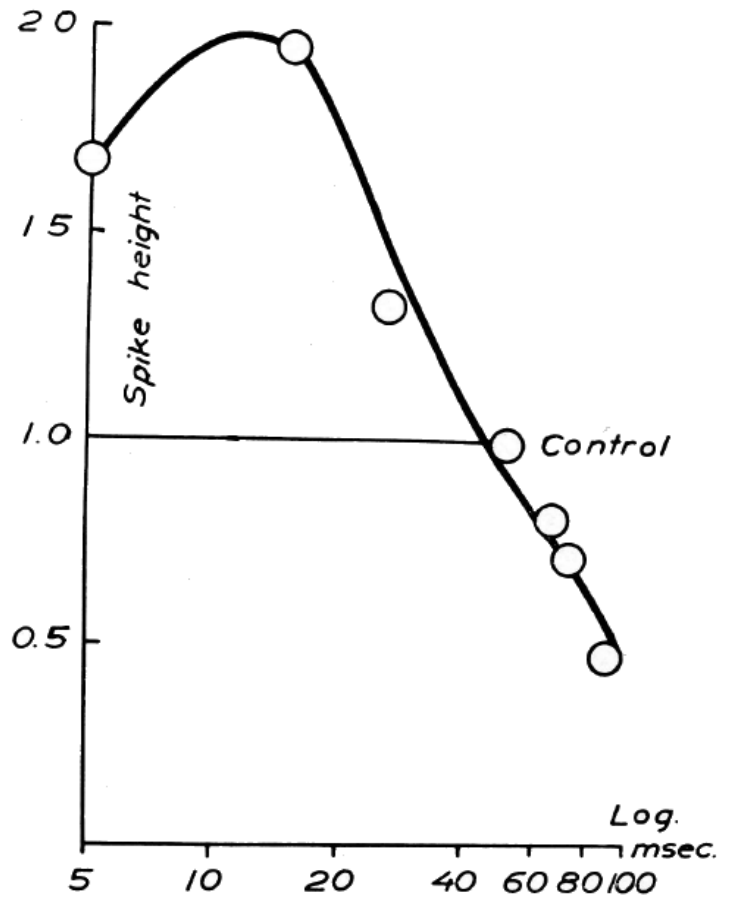


Fig. 3

Spinal cat. Analysis of effect of stretch of gastrocnemius muscle on its monosynaptic response. Ordinates, spike height in terms of control 1.0; abscissae, time from beginning of visible stretch of, in all, 4 mm at modest initial tension: Note: stretch increasing during the time shown. Lateral and medial components of gastrocnemius muscle separated. Test shock for monosynaptic response to severed lat. nerve, medial component in good initial tension stretched 4-5 mm.

tioned papers by Bremer and Bonnet, Eccles and his collaborators, Bernhard. On the whole the evidence for a real subnormal phase in the ventral horn cells or their axons seems impressive. Hence no specific inhibitory end organs are needed to explain the silent period. Demonstration of a real supernormal phase has offered difficulties. The best recent contribution with full discussion is to be found

in a paper by Brooks, Downman and Eccles (1950).

Gasser's explanation of the silent period suggests that the inhibition, described above as a component in a physiological mechanism of integration, possibly might be fully accounted for by refractoriness succeeded by a subnormal phase in motoneurons which have fired an impulse. On this idea all sense organs in the muscle would be of equal importance as potential inhibitors. They could all excite and all inhibit the motoneurone depending merely upon whether they succeeded in firing it or not. As a matter of fact I had come to the conclusion (1950) that the Golgi tendon organs were likely to be more potent inhibitors than others. Accordingly it became important for us to find out what firing really is doing to a ventral horn cell, whether or not the impulse always is succeeded by a long period of inexcitability. For this purpose it was necessary to isolate the discharge of a single ventral horn cell. Otherwise we would never know with certainty whether the cell had fired or not and what sort of depressions follow upon the motor impulse. With the monosynaptic mass discharge (as in figs. 2 and 3) it had already been possible to show that the facilitation could be removed by pressure upon or by local cooling of the nerve responsible for the conditioning impulses without any effect whatever on the inhibition. This result did not agree with an explanation of our inhibition merely as subnormality. One would surely have expected more firing from facilitated motoneurons than from those with the facilitation removed, in the manner indicated, and so, if firing had been the main cause of the inhibition, there should have been some reduction of inhibition after removal of facilitation. Actually the two processes appeared to be wholly independent.

Strøm and myself (1950, 1951) were pursuing the analysis with monosynaptic responses from single ventral horn cells when through the Editorial office of the *Journal of Neurophysiology* we became aware of a most interesting contribution by McCouch, Deering and Stewart (1950), kindly placed at our

disposal in manuscript by Dr. McCouch who had sent their paper to the same *Journal*. They had found that electrical stimulation of the crureus tendon inhibited the knee jerk, that the locus of stimulation had to be carefully chosen (suggesting specific end organs or nerves) and that the effect could be seen without the electrical stimulus causing any measurable muscle contraction. They concluded that there were specific inhibitory receptors between muscle and tendon and suggested that these were the Golgi tendon organs. Evidence from two independent sources had thus led to the same conclusion. Matthews had previously suggested that the Golgi tendon organs were responsible for the silent period-inhibition but we have seen that all work on the silent period could be satisfactorily explained by subnormality after firing, particularly since Denny-Brown had shown that a good efferent volley was necessary for a silent period to appear at all.

We are thus thrown back upon the necessity of completing our analysis by isolating a single ventral root fibre in order to test by the monosynaptic response the excitability of one particular horn cell. For this Strøm and I (1950, 1951) used stretch at different initial tensions as our physiological conditioning stimulus.

The monosynaptic response, uppermost in figure 4, actually consists of two fibres. It was an animal with good inhibition and so it was merely necessary to press on the string joining muscle and myograph to set up enough inhibition to block the monosynaptic response altogether. This effect is shown in the middle record. The bottom record illustrates that removal of the high tension immediately made the ventral horn cell accessible to the monosynaptic test shock. Thus, by merely increasing the initial tension of the gastrocnemius muscle one obtained full inhibition of long duration without any previous firing of the motoneurone.

The early experiments (Granit, 1950) with the mass response could easily be made quantitative. In them facilitation was measured in the usual fashion by the number of

fresh neurones added from the subliminal fringe. During stretch of the gastrocnemius muscle, the individual horn cell, be it facilitated or inhibited, either fires or refuses to fire in response to the test shock? How then is the level of excitability to be gauged? (It should be noted that a change of concepts has taken place: we measure level of excitability directly and not the number of neurones.)

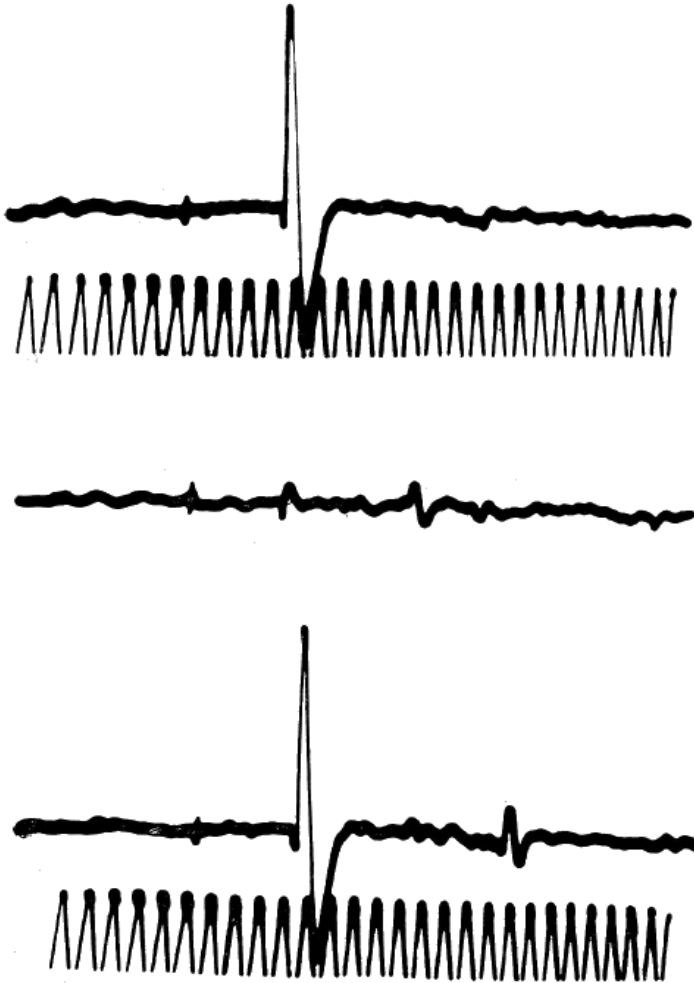


Fig. 4

2-fibre preparation of A-neurones (Pr 10/10) giving two spikes which mostly (without stretch) were well synchronized. Uppermost record: Muscle at rest in light tension. Permanent pressure then exerted by hand on string joining muscle and myograph before record in the middle was taken. Lowermost record: after release of pressure. No phasic stretch.

Assume that the ventral horn cell is in the subliminal fringe. Ten trials are made to make certain that every time the test shock fails to excite the motoneurone so that the probability of response (= Pr) is 0/10. If then the gastrocnemius muscle is slightly stretched

and the test shock properly adjusted with respect to phase of stretch, the facilitation by stretch impulses suffices to make a monosynaptic test response suprathreshold in some trials. Assuming ten trials with stretch, the Pr may be 7/10, perhaps even 10/10. Thus, by measuring Pr in ten trials for each interval tested we can plot a curve showing the level of excitability of a single ventral horn cell as a function of time from beginning of stretch. To gauge inhibition we begin by adjusting the test shock to give a control Pr of 10/10 and measure the reduction of this value by inhibition.

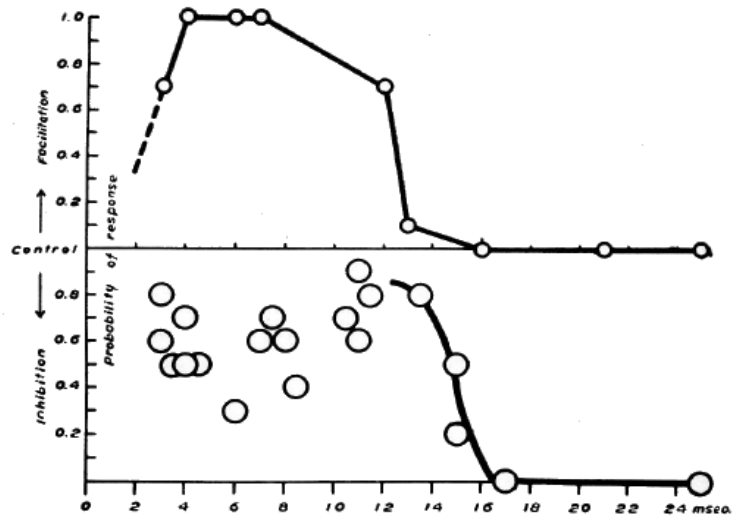


Fig. 5

Active neurone tested during stretch by shock from med. gastroc. nerve. *Upper curve.* Light tension and stretch. Test shock (Pr = 0/10 at rest) subliminal so as to show up level of excitability during facilitation by stretch. *Lower curve.* Med. gastroc. nerve now tied below electrodes, and muscle at high initial tension. Pr put at 10/10. The afferent discharge (through lat. gastroc. nerve), as shown by the large number of observations taken (200), now gave inhibition from the very beginning.

Of the many cases presented in the original paper (Granit and Strøm 1951) I shall select two of particular interest for the problem of autogenetic inhibition. In case 1, figure 5, we happened to strike a ventral horn cell for which excitation and inhibition were different for the two components of the gastrocnemius nerve. The test shock was elicited from the medial gastroc. nerve. The lateral gastroc. nerve could neither by itself, nor supported by afferent stretch impulses from both nerves, elicit a monosynaptic response to a supra-

maximal test shock. The upper curve of figure 5 illustrates that, with light tension and 2 mm. stretch, there was facilitation as long as the medial gastroc. nerve was intact. The Pr of the control had originally been adjusted to 0/10. Then the medial gastroc. nerve was severed below the test shock electrodes and, at the same time, the muscle put under high initial tension to increase inhibition. By increasing stimulus strength the Pr of the control was adjusted to 10/10. The lower curve shows that the sole and immediate effect of stretch was inhibition, a long lasting inhibitory state that became complete around 17 msec. after the beginning of stretch. Now stretch is difficult to time but, by comparison with the upper curve, inhibition is just as fast as facilitation. There were no impulses fired during stretch, despite the high initial tension. The reason for this is apparently that the lat. gastroc. nerve had chiefly inhibitory fibres for the neurone isolated.

In view of the results presented in figures 4 and 5 it has become extremely difficult to maintain that the sense organs for autogenetic excitation and inhibition are identical. Likewise it is impossible to believe that autogenetic inhibition can be fully accounted for by a silent period in consequence of a subnormal excitability due to firing on the part of the horn cell. The neurones investigated have not fired. The autogenetic inhibition is favoured by high initial tension in such an obvious fashion that it seems more reasonable to look for high tension recorders among the muscle sense organs. At the moment the Golgi tendon organs are the most likely candidates for this role. In terms of Matthews' classification the B end organs are the ones best fitted for the same task. He believed that they were the Golgi tendon organs.

Eccles and his collaborators want to extend the concept of the subnormal state (to be identified with positive afterpotential) to the case when the neurone merely has been subliminally excited because they have evidence to the effect that subliminal excitation also causes the sequence of negative and positive afterpotential noted in supraliminally excited

motor horn cells. I am in favour of the accepted terminology established by Gasser's work. One reason for this standpoint is that the fibres of the B end organs of Matthews were found to be as large as those of the annulo-spiral organs. On the view that the B organs are inhibitory we must count with threshold stimuli setting up central equivalents of true inhibition and so we cannot affirm that ventral horn cells have been stimulated by purely excitatory shocks, however weak they are made. Brooks, Downman and Eccles (1950), however, find similar potential changes with antidromic stimuli.

Let us assume that autogenetic inhibition had to be explained by the findings of Eccles. This means that, by increasing muscle tension, we have suddenly made all, most or many of the end organs fire in such a fashion that all neurones have become subliminally excited. For this reason they have become refractory to the test shock. But, during stretch, firing will go on all the time and so may inhibition. It seems as if one needed a second theory to explain how the machinery of subliminal excitation could be so nicely balanced and maintained as to give the neurones no chance of ever becoming facilitated. After all, both the negative and the positive phase of the synaptic potential is capable of subliminal activation. Why have all the facilitations disappeared? I have no doubt whatever that the facts are as stated by Eccles and his collaborators but I do not see how these facts could be used to explain autogenetic inhibition. To prevent misunderstanding it should be added that Eccles has not attempted to do so, it is merely from the point of view of a silent period as a possible consequence of subliminal excitation that it has become necessary to discuss his important results.

The real reason for going into this question so thoroughly is that refractoriness and subnormality after firing cannot be neglected in the discussion of such problems (see Hagbarth and Naess, 1950). Just what this means is shown by the following experiment with a single ventral horn cell. For the

upper curve of figure 6 the test shock was made just subliminal to give a Pr of 0/10 for the control with the resting muscle at low initial tension. Stretch (1.5 mm) was applied and facilitation ensued as shown by the state of increased excitability in the upper curve. The test shock was next made supramaximal to obtain a regular and reliable Pr of 10/10. The muscle was placed at very high initial tension so that each time a stretch impulse followed in the early phase of the adequate stimulus set up by

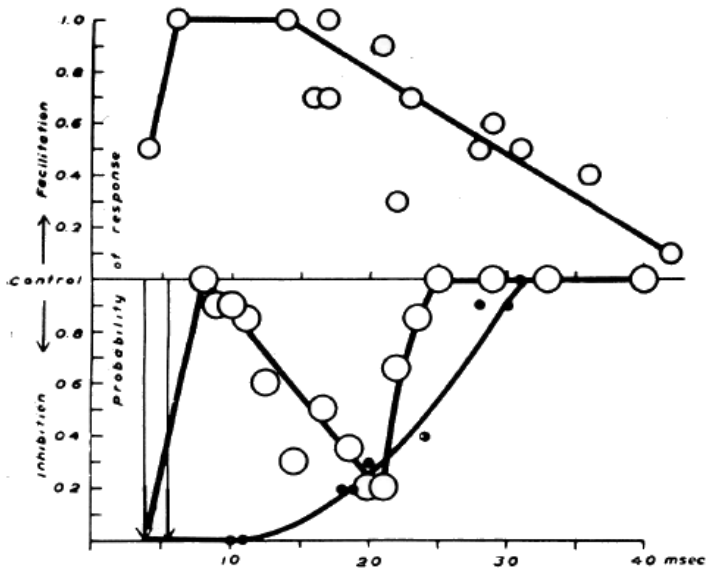


Fig. 6

Active neurone. In upper curve tested with test shock at strength 1.3, subliminal without stretch, in order to measure course of excitability during light 1.5 mm. stretch at light initial tension. Lower curves. Test shock increased in strength to 3.9 in order to obtain a regular Pr = 10/10. Dots, high tension and 1.5 mm. stretch. Circles, tension diminished and stretch increased to 3 mm. Both lower curves obtained while one initial natural impulse arose in response to stretch. "Stretch responses" inside region marked by arrows on the abscissa.

pull. This adequate impulse followed within the region marked by two arrows in the lower half of the figure. The curve between black dots illustrates the depression after the impulse. Pr began to rise for an interval around 6 - 8 msec., counted from the natural or adequate impulse to stretch, and reached 50 per cent around 20 msec. Next tension was decreased to a modest value but the degree of stretch augmented to 3 mm, these adjustments being made to reduce the in-

hibition due to high tension and increase the facilitatory component from the muscle afferents. Tension was kept just high enough to make the neurone still discharge a stretch impulse. Now, as shown by lower curve drawn between open circles, the neurone was capable of delivering a response to the test shock with a Pr 10/10 already 3.5 msec. after the stretch impulse. The state of excitability then fell slowly towards 20 msec. and rose again quickly to reach Pr = 10/10.

This experiment thus shows that whether or not a silent period is obtained depends wholly upon the balance between excitation and inhibition that determines the level of excitability of the ventral horn cells. This concept, i.e. level of excitability as determined by excitatory and inhibitory afferents, is the essential one. If we choose a neurone, "deep" in the subliminal fringe, which only can be made to fire by a great deal of stretch, the stretch impulse will exert the horn cell and make it silent for 50 - 100 msec. Refractoriness and subnormal states are thus of paramount importance. But active neurones can fire in response to the test shock already 2.5 msec. after the stretch impulse. These neurones, however, can be thrown into the fringe and be inactivated by increasing the amount of initial tension of the muscle. The concept "subnormal state", as far as ventral horn cells are concerned, is devoid of precise meaning except in combination with the concept "level of excitability".

Thus there is real autogenetic inhibition in the original sense of Sherrington and this inhibition is probably responsible for the lengthening reaction that he described long ago (1911). As to the central nature of this inhibition we are ignorant. It may be a direct inhibition in the sense of Lloyd and Renshaw, at an earlier synapse than the ventral horn cell, or any other kind of inhibition. It is best to admit our ignorance. The fact that it can be gauged by means of the monosynaptic reflex seems, however, significant. It means that the ventral horn cell itself is suffering from the depressed state of excitability. This can only be because the

inhibitory impulses ultimately attack the ventral horn cell or because they have succeeded in blocking facilitatory impulses that are assumed to be necessary in order to maintain the excitability of the horn cell. This block may well be established by a combination of refractoriness and subnormality in the sense of the "théorie interneuronique". It may also be a direct inhibition.

In his original paper with Bronk on the discharge from ventral horn cells Adrian pointed out the slow rate of firing characterising these cells. The reason for this is probably the extreme complexity of the afferent supply of the motoneurons. Reid (1949) has recently found firing frequencies as high as 175 per sec. in single oculomotor motoneurons whereas 50 per sec. would be a good value for ventral horn cells. Retinal ganglion cells, as examples of sensory neurons, have widely different firing frequencies, from 300 to a few impulses per second, and in this case we have every reason to believe that the variations are due to the particular state of balance between excitation and inhibition which happens to prevail in the unit isolated. The low firing frequencies of ventral horn cells suggest that they always work with the inhibitory brakes applied.

SUMMARY

A brief summary has been given of the results of experiments which have made it necessary to reconsider current views on autogenetic inhibition and have given a func-

tional explanation of the role of autogenetic inhibition co-operating with the so-called subnormal phase in reflex self-regulation of the muscle contraction.

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