

Artificial and natural firing of motoneurons

Antidromic and trans-membrane stimulation compared

If depolarizing current is injected into a motoneuron from the tip of an intracellular electrode, the cell fires repetitively from a strength of 1.4–1.5 times the absolute threshold of spiking. It can also be fired repetitively at modest frequencies by an antidromic tetanus and it is of some interest to compare the two modes of discharge at corresponding firing rates. This is done in Figure 18.

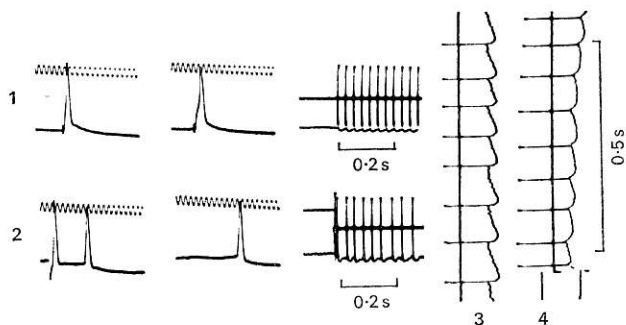


Fig. 18. Rat (1–3) and cat (4) motoneurons. Time in milliseconds unless otherwise marked. Trans-membrane stimulation through microelectrode in 2 to 4. 1 and 2, same spike of 75 mV stimulated antidromically in 1, singly and repetitively and by injected current of 11.4 nA in 2. Note gradually increasing after-hyperpolarization. 3, stimulation by injected current, maintained at 2.0 nA, of rat motoneuron, spike height 92 mV; 4, cat motoneuron of 54 mV starting discharge to 8.4 nA. Note characteristic firing with after-hyperpolarization (Granit, Kernell and Smith, *J. Physiol.*, 1963).

In the rat (Granit, Kernell and Smith 1963) and in some 60 per cent of cells with a spike amplitude exceeding 60 mV (in the cat, Kernell 1964) the spike is succeeded by delayed depolarization. This is a little hump (in the records 1, Fig. 18), which delays the onset of after-hyperpolarization and sometimes may be large enough almost to obliterate it, particularly in the rat motoneurons whose after-hyperpolarizations tend to be small and of short duration (Bradley and

Somjen 1961; Granit *et al.* 1963). After-hyperpolarization was illustrated in the inset of Figure 12. The delayed depolarization has been interpreted as a sign of invasion of the dendrites from the axon hillock (Granit *et al.* 1963; Nelson and Burke 1967). Even when the cell is fired repetitively from that end (record 1, on the right) there is delayed depolarization left.

When the same spike (in records 2, Fig. 18) is elicited by depolarization with trans-membrane stimulation, after-hyperpolarization develops over a few initial spikes and then remains stationary. The two vertical records show that the depolarized cat and rat motoneurons

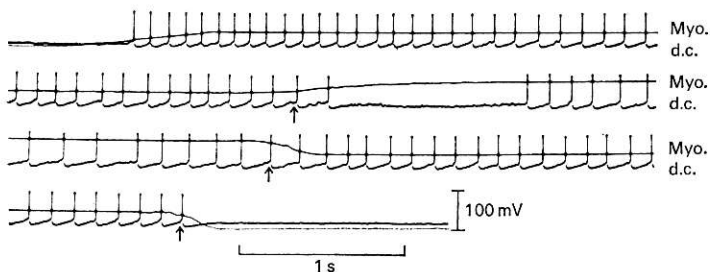


Fig. 19. Anaemically narcotized cat. Pentobarbitone 11 mg/kg. Popliteal motoneuron (75 mV spike height). Membrane potential around 65 mV. Pull on triceps (500 g) maintained till last arrow; between first and second arrow pull on tibialis anterior (400 g). Note excitatory and inhibitory stretch reflexes of the kind shown were present for a long time in this cell. Semitendinosus inhibition was more powerful than the tibialis anterior inhibition illustrated, otherwise similar (Granit, Kellerth and Williams, *J. Physiol.*, 1964a).

behave in the same way in the adapted state. This mode of firing in fact is characteristic of a large number of central neurons, e.g. of the Betz cells (Phillips 1956). The rhythmic discharge is similar with trans-membrane and natural stimulation (Fig. 19) and we shall see below that these two modes of firing actually are replaceable by very strict criteria of identity. Figure 19 shows natural firing in a stretch reflex. In the middle record inhibition by stretch of an antagonist is displayed.

There are various ways in which the spike of the axon hillock can be isolated—e.g. by trans-membrane hyperpolarization—and Coombs *et al.* (1955a, c) have shown that this spike is followed by negligible if any after-hyperpolarization. The axon hillock was found by Araki and Otani (1955) to be the firing zone. Taken in a wider sense as the region down to the initial segment of the motor axon it is responsible for the spike lacking after-hyperpolarization, the IS spike of Eccles (1957, 1964a). In his terminology, the normally recorded spike is the SD spike,

the lettering implying that it involves the soma together with the initial portion of the dendrites. Fuortes, Frank and Becker (1957) use the more neutral terms A (for IS) and B (for SD) spikes.

The SD spike is the more important one in 'natural' firing because frequency regulation has been shown (see p. 17) to depend upon after-hyperpolarization. Nevertheless, as we shall see, situations may occur in which motoneurons fire to both natural and artificial stimuli with spikes virtually lacking after-hyperpolarization or with irregularities in its time course. It seems likely that firing then is largely restricted to the IS zone. A case in point is the high-frequency beginning of the bottom discharge in Figure 8, produced by strong trans-membrane stimulation, the early spikes being displayed separately on the left in Figure 8.

The primary and secondary range of firing

The curves illustrating firing rate as a function of strength of the injected current in the cat differed from those obtained with the rat motoneurons (Fig. 9) in that they tended to turn upwards at high

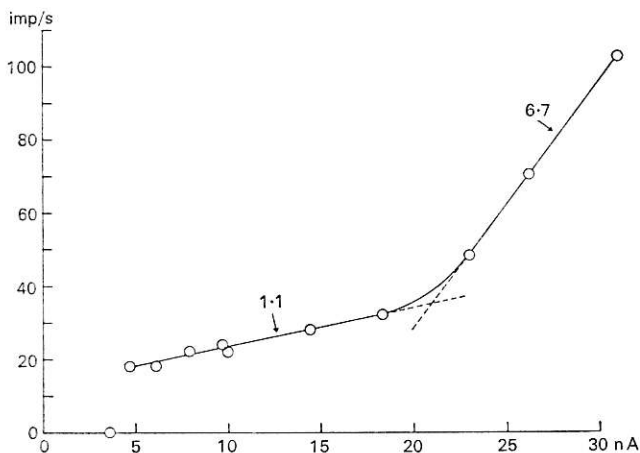


Fig. 20. Cat, motoneuron of spike size 63 mV at resting membrane potential. Trans-membrane stimulation. Steady discharge frequencies are plotted against current strength, and straight lines are fitted to the values as in Figure 9. A pause was allowed between each strength of stimulation and firing rates were measured at 1.0–1.5 s following the onset of each current strength (Kernell, *Acta physiol. scand.*, 1965b).

frequencies (Kernell 1965b). A typical result is illustrated in Figure 20. It proved possible to approximate the relation between current strength and firing rate by two straight lines as in Figure 20. Kernell has intro-

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duced the terms primary and secondary range respectively for the two branches with their different slope constants, in this experiment of 1.1 and 6.7 impulses $s^{-1} nA^{-1}$. The primary range is the one hitherto discussed and it alone is the one described in cortical pyramidal cells (Creutzfeldt, Lux and Nacimiento 1964) and in the Clarke cells of the dorsal spino-cerebellar path (Eide, Fedina, Jansen, Lundberg and

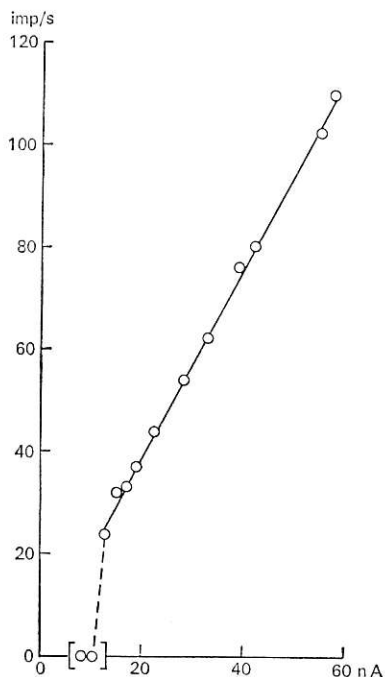


Fig. 21. Decerebrate cat. Hamstring motoneuron of spike height 85 mV, recorded by 2M potassium citrate (intracellular) electrode. The curve shows relation between steady discharge frequency (measured during first 0.5 s) and maintained transmembrane stimulation from tip of microelectrode. This cell fires repetitively in the 'primary range' from 22 impulses s^{-1} (minimal firing rate) up to at least 110 impulses s^{-1} . The slope of the straight line (by the method of least squares) is 1.84 impulses $s^{-1} nA^{-1}$. The precision of the rhythmic threshold is indicated by the two readings on zero ordinate (Granit, Kernell and Lamarre, *J. Physiol.*, 1966a).

Vyklický 1969). Barron and Matthews (1938), depolarizing motoneurons through the ventral root, suggested that spike frequency and current strength are linearly related; convincingly this result was demonstrated in a few motoneurons by Frank and Fuortes (personal communication) by the intracellular method and by Shapovalov (1964). The findings of Frank and Fuortes were briefly referred to in a study by Fuortes and Mantegazzini (1962) devoted to a similar analysis of the *Limulus* eccentric cell. It was pointed out above that the slope constants are much higher at the onset of the discharge, but our first concern is now the adapted state.

The upper limit of the primary range can be at some 100–20 impulses s^{-1} of which an instance is given in Figure 21. More commonly it is 30

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around 30–50 impulses s^{-1} . In the Clarke cells Eide *et al.* (1969) report values up to around 300 impulses s^{-1} plotting on a straight line through their data. The high values indicate high slope constants. Thus, in the Clarke cells they are of the order of 5–11 impulses $s^{-1} nA^{-1}$ while in most lumbo-sacral motoneurons in the cat (which are likely to be large cells) they ranged between 1 and 2 impulses $s^{-1} nA^{-1}$. Another important factor determining the limit of the primary range in impulses per

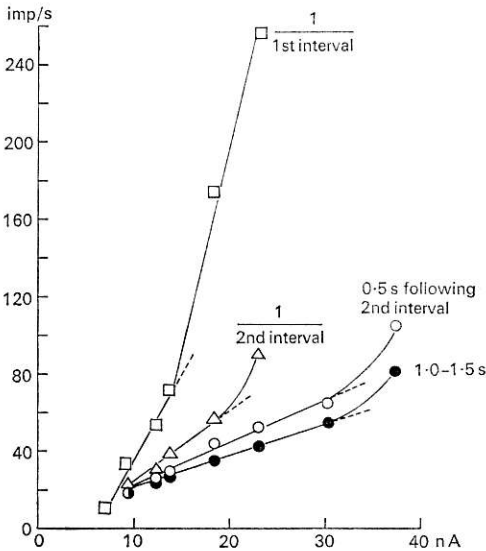


Fig. 22. Cat motoneuron of spike size 55 mV at resting membrane potential. As Figure 20. Diagram showing the relation between discharge frequency and current strength at the indicated times after onset of stimulation. A pause was allowed between each change of strength of stimulation. Steady firing rates were obtained at 1.0–1.5 s following the onset of each current strength. Straight lines fitted to the values obtained at weaker currents, and the slopes of these lines (the f - I slopes within the primary range) are 9.0, 3.6, 2.2 and 1.6 impulses $s^{-1} nA^{-1}$ respectively (Kernell, *Acta physiol. scand.*, 1965b).

second is inhibition but this question will have to be taken up separately below.

The time course of adaptation is shown in Figure 22. The striking feature of this diagram is that the turning point between the primary and the secondary range depends upon the actual firing rate reached at any one moment and not upon strength of current as such. Owing to the adaptation it is necessary, during maintained stimulation, to use increasingly stronger currents for reaching the turning point. This will

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cause technical difficulties such as large changes of electrode resistance and possibly also blocking of the cell membrane by the very strong currents around the tip itself. It is assumed that such factors made it difficult to reach the secondary range with the smaller rat motoneurons but the point has never been explicitly tested. Another striking fact is that it is almost always possible to reach the secondary range at the onset of a discharge, as is well illustrated by Figure 22. It was shown in Figure 8 that in this early phase of the discharge the mechanism of after-hyperpolarization is as yet underdeveloped.

The events at the turning point are better illustrated by the records of Figure 23. In the diagram (B) the upper curve (circles) is the analysis of

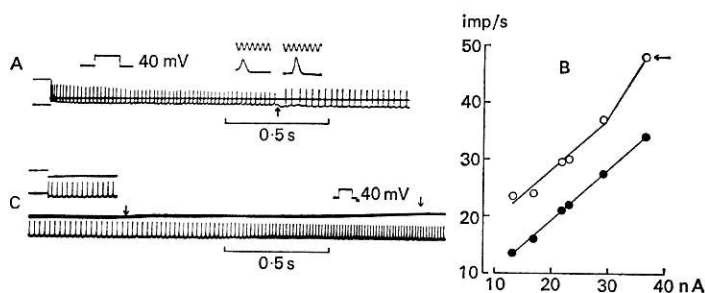


Fig. 23. A and B. Pentobarbitone cat (35 mg/kg). Popliteal motoneuron of spike height 87 mV (2M potassium citrate electrode) inhibited by high-frequency stimulation of the cut hamstring nerve. In B, control and inhibited curves measured for 0.5 s before and 0.5 s after onset of nerve stimulation respectively. In the primary range 'control' $k_A = 0.88$ impulses $s^{-1} nA^{-1}$, 'inhibited' $k_A = 0.89$ impulses $s^{-1} nA^{-1}$. Actual records at the current strength which is indicated by an arrow are shown in A. Repetitive discharge initiated by trans-membrane current at 36.5 nA, as indicated by downward deflexion of upper trace. High-frequency stimulation of hamstring nerve added about 1.0 s later, at arrow. Note increase of spike height during synaptic inhibition. Above, samples of spikes recorded simultaneously at faster sweep speeds (time, 1,000 c/s) before and after inhibition. C. Anaemically narcotized cat. Gastrocnemius-soleus motoneuron of spike height 78 mV (2M potassium citrate electrode) facilitated by a 10-mm stretch of the gastrocnemius-soleus muscle. Spikes recorded on upper beam together with current indicator (30 nA), on lower beam with myogram. Lower records begin 1.0 s after end of upper record. Stretch from 0 to 10 mm between arrows. Note disappearance of after-hyperpolarization when facilitation pushes cell into secondary range with inactivation reducing spike height (Granit, Kernell and Lamarre, *J. Physiol.*, 1966b).

an experiment on the effect of current strength on impulse frequency. At the reading marked by an arrow the curve has entered the secondary range. The lower curve (filled circles) repeats the same experiment with a constant synaptic inhibition added. The record A belongs to this experiment and refers to the discharge at strength just before and just

after insertion of the inhibitory stimulus. For the upper and lower curves in the plot (B) this is the strength reached with the last reading on the right. In record A the spike is seen to diminish and also to become broader during stimulation with the injected current. Insertion of synaptic inhibition at the arrow restores spike height and spike width. The conclusion is that in the secondary range a partial inactivation of the spike-generating mechanism has taken place. Inactivation has been thoroughly investigated in the vertebrate nerve fibre (Frankenhaeuser 1963; Vallbo 1964; Frankenhaeuser and Vallbo 1965) and been shown to increase strikingly at higher grades of depolarization such as would be required for the secondary range in the present case. Similarly, when inactivation was seen by Granit and Phillips (1956) in cerebellar Purkinje cells, it had the character of a high-frequency discharge riding upon a potential wave. The spikes decreased in amplitude until wholly lost. Inactivation has since been seen in many types of neurons.

The lowermost record (C) of Figure 23 illustrates a motoneuron running into a state of partial inactivation when (at the arrow) stretch is added to the injected current. The record serves to emphasize the virtual disappearance of after-hyperpolarization when, at high frequencies, the spikes begin to diminish.

From the theoretical point of view a good tentative explanation of firing within the secondary range is that IS firing gradually comes to involve less of the SD response. The hyper-depolarization of the cell limits the active region to the axon hillock.

The functional role of the secondary range

There is a definite functional role for the high initial frequencies in the secondary range at onset of stimulation. It has been shown by Buller and Lewis (1965) that the rate of tension development, in isometric maximal contractions, is critically dependent upon high firing rates in both fast and slow mammalian muscles. Thus, for instance, the slow soleus that in the steady state fuses at stimulus frequencies around 30 shocks per second to its muscle nerve, increases its maximum rate of rise of tension with frequencies up to approximately 300 impulses per second, the fast flexor hallucis longus does it up to rates of 600 per second. Clearly means of firing at very high initial rates is a useful property of the alpha executive.

The significance for the motor unit of firing within the secondary range in the adapted or steady state has been investigated by Kernell

in lumbo-sacral motoneurons. The intracellular technique was used in combination with a sensitive myograph. In Figure 24A, a motoneuron is stimulated by injected current and above this record is shown the isometric myogram of its motor unit. This record serves to introduce the

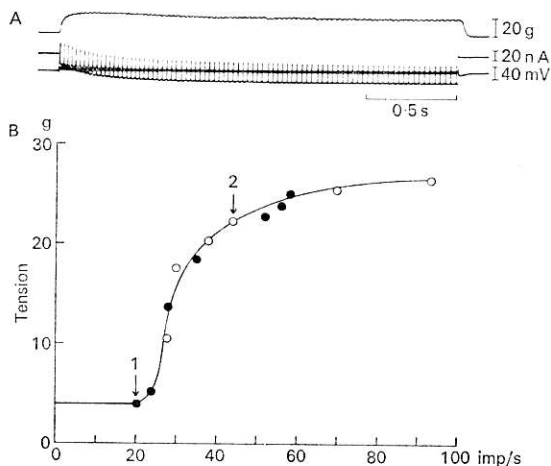


Fig. 24. Cat. A. Record showing the repetitive discharge to trans-membrane stimulation of a gastrocnemius motoneuron (lower beam) and, simultaneously, the isometric tension developed by its motor unit (upper beam). The whole gastrocnemius muscle was hooked up on a myograph, and variations in its isometric tension were recorded at high sensitivity. The motoneuron was stimulated by a steady current whose strength is indicated by the deflexion of the middle beam. B. From the same experiment. Diagram showing the relation between the firing rate of the motoneuron and the simultaneously recorded isometric tetanic tension of its motor unit. Tensions and firing rates were measured at 0.1-0.2 s (circles) and at 1.7-2.2 s (filled circles) after the onset of each current. The discharge of a single spike elicited a muscle twitch whose tension is indicated by the initial horizontal part of curve. Arrow 1 shows the minimal rate of steady firing of the motoneuron. The firing rates of the motoneuron were also plotted against current strength and from this diagram (not shown here) the maximal firing rate within the primary range could be determined. This firing rate is indicated by arrow 2. At higher discharge rates the cell fired within the secondary range. The temperature of the muscle was 37.7 °C. The recordings were taken at a muscle tension for which the single twitch of the whole gastrocnemius muscle had its optimal amplitude (Kernell, *Muscular Afferents and Motor Control*, Nobel Symp. I, Stockholm, 1966).

technical approach to the problem. The motoneuron can in such experiments be fired at all frequencies of which it is capable, and the amount of tension obtained directly correlated with firing rates within both the primary and the secondary ranges. The outcome of such an experiment is shown in graph B of Figure 24. Firing within the primary

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range takes place in the region within the arrows marked 1 and 2; values above arrow 2 fall within the secondary range. It is seen that most of the contraction is taken care of within the primary range. Only some 15 per cent is left over for the secondary range.

Thus the primary range of firing is the more important one, at least in action maintained beyond the time required for the rate of rise of the muscular contraction. The secondary range would seem to be intended for a more extreme display of force and for velocity control of the rate of rise of tension.

Algebraical addition within the primary range

The leading experiment of this and the next section is illustrated in Figure 25. It consists in superposing a constant synaptic stimulus on a discharge varied in firing rate by injected current. Thus, in Figure 25,

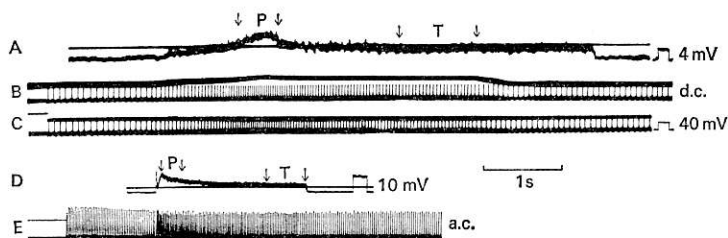


Fig. 25. Records of post synaptic potentials and of repetitive discharges set up in two different motoneurons by injected currents (2 M potassium citrate electrode) in two anaemically narcotized cats. A-C from a gastrocnemius-soleus motoneuron of spike height 78 mV. In A, excitatory postsynaptic potential produced by 10-mm stretch of the gastrocnemius-soleus muscle. B and C recorded simultaneously. Repetitive discharge initiated by depolarizing trans-membrane current of 14 nA (indicated by the downward deflexion of the upper trace in C). Stretch of the gastrocnemius-soleus muscle indicated by myograph record in upper trace of B beginning about 1.5 s after onset of trans-membrane stimulation. A illustrates the measured phasic and tonic component potentials of the synaptic test stimulus (labelled P and T respectively). D and E are from a hamstring motoneuron of spike height 84 mV. In this case, the synaptic effect elicited by high-frequency stimulation of cut hamstring nerve. D. Excitatory postsynaptic potential produced by nerve stimulation alone. In E, the cell is fired repetitively by trans-membrane current of 43 nA (downward deflexion of upper trace) and, after about 1 s, the synaptic test stimulus is added. Here again, two facilitated values of spike frequency were obtained; one phasic, the other tonic (P and T between arrows) (Granit, Kernell and Lamarre, *J. Physiol.*, 1966a).

A is the subliminal response of a gastrocnemius-soleus motoneuron to stretch of these muscles. The initial phase and part of the response to maintained stretch are illustrated in the upper record of B, the lower

one showing the discharge caused by the trans-membrane stimulation. The arrows on either side of P and T in record A serve to indicate the duration of the period for which the phasic or tonic discharge frequency was measured when the subliminal postsynaptic potential was superposed on the discharge in B. C repeats B merely in order to illustrate the stimulus marker by a simultaneous record on the oscillograph. What is obvious in these records is that the subliminal postsynaptic potential elicited by stretch has a powerful effect on the discharge frequency of a firing cell. The lower records D and E show a similar experiment in which the subliminal synaptic stimulus was produced by a hamstring tetanus.

Two questions are raised by these experiments: (i) what is the relation between amount of potential change and the increase in firing rate that it produces and (ii) what is the slope of the curve relating current strength to firing rate *with* and *without* the added constant synaptic stimulus?

(i) Realizing as we now do (from results mentioned above) that the amount of potential produced by a given stimulus depends upon the total membrane resistance, the first question makes sense only for a relatively homogeneous population of cells. Gain, as we have seen, is also dependent on cell size, at least within a set of closely related motoneurons such as the lumbo-sacral ones used in these experiments. The quantitative results required for answering these two questions exclude all but the very best impalements and these are likely to be obtained with the largest motoneurons. In these experiments the average duration of their after-hyperpolarizations was 63 ms (cf. Figs. 11 and 12). Using gain as a further test of homogeneity of the population, the average value for twenty-eight cells, 1.33 ± 0.54 impulses $s^{-1} nA^{-1}$ shows that we are justified in working out an average figure for the number of impulses per second per millivolt from data such as those illustrated in Figure 25.

The result is shown in Figure 26A in which both excitatory and inhibitory constant inputs have been used. These motoneurons thus deliver 2.28 impulses $s^{-1} mV^{-1}$. The same values are plotted in Figure 26B for current as abscissa. The slope constant for current is 1.06 impulses $s^{-1} nA^{-1}$. Assuming that it is possible to measure firing rates with an accuracy of one impulse per second, then changes of membrane potential of the order of 0.4 mV could be detected by measuring impulse frequencies. The frequency of 2.28 impulses mV should serve as a first approximation to firing rates in experiments producing subliminal postsynaptic potentials because often one wants to know what would have

happened had the cell been sufficiently depolarized. Unfortunately we do not yet possess comparable figures for motoneurons of different sizes.

Granit, Kellerth and Williams (1964a, b) studied a number of methods of measuring the excitability of motoneurons when the conditioning stimulus was autogenetic or antagonistic stretch. In Figures 3 and 4 we have seen how difficult interpretation can be with direct observation of activation noise or with monosynaptic testing. Nor was it always possible to judge about the change of excitability from the level of the

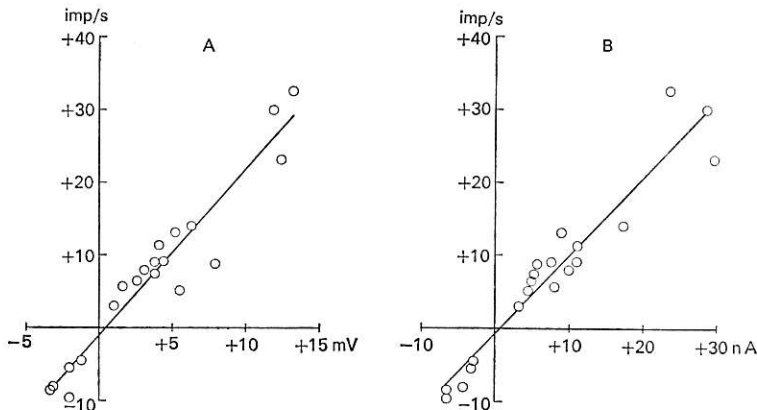


Fig. 26. A. Plot of constant increase or decrease in impulse frequency (ordinate) against the corresponding amount of postsynaptic potential required for it (abscissa). The slope constant $K_V = 2.28$ impulses $s^{-1} mV^{-1}$. B. Same ordinates as in A but plotted against current on the abscissa. The slope constant $K_A = 1.06$ impulses $s^{-1} nA^{-1}$. Five readings refer to experiments with inhibition, as in Figure 29 (Granit, Kernell and Lamarre, *J. Physiol.*, 1966a).

membrane potential. In firing cells these difficulties disappear. When stretching a muscle merely produced activation noise its effect on motoneurons fired by injected current generally was unequivocal, an excitation or an inhibition. Similarly, when as in Figure 4, the interpretation of the monosynaptic test required a great deal of arguing from uncontrollable assumptions, with firing cells autogenetic stretch generally increased the discharge frequency, antagonistic stretch reduced it. This is the kind of language motor units are used to interpret. The advantage of 'biasing' a motoneuron by injected current is that the process then is restricted to the membrane of the neuron that has been impaled. These cells can, of course, be biased in many other ways, but, by what route this is done, tends to remain unknown. Furthermore, when firing

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 motoneurons are used in intracellular work, measuring of gain, resistance, duration of after-hyperpolarization, etc., is available for penetrating all the problems that have been discussed above, not in the least that of how motor units are matched to their motoneurons.

(ii) A large number of experiments were performed (Granit, Kernell and Lamarre 1966a) in order to analyse the effect of a constant input on motoneurons kept firing within the primary range to injected currents.

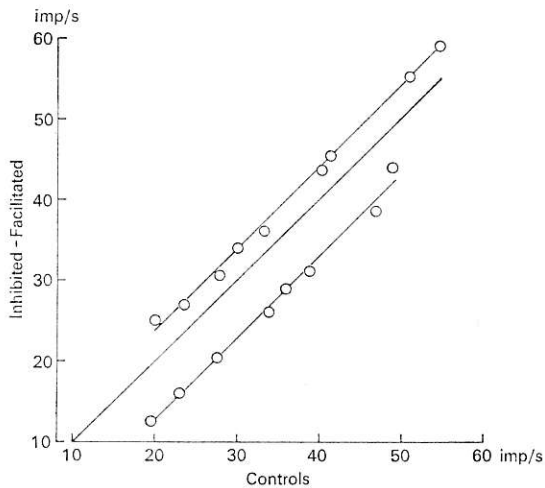


Fig. 27. Pentobarbitone cat (35 mg/kg). Hamstring motoneuron of spike height 75 mV (2M potassium citrate electrode). This neuron was studied for more than 3 h and values could be obtained for both excitation (tetanus of cut hamstring nerve) and inhibition (tetanus of deep peroneal nerve). In this graph, inhibited and facilitated values are plotted against their own corresponding control values. Thus the 'inhibited' curve is found below and the 'facilitated' one above the 45° line (for excitation = 0 and inhibition = 0) through origo, inserted for comparison. The perfect algebraical summation for both excitation and inhibition by the same motoneuron is shown by the regression coefficients of the two curves, which are 1.02 (excitation) and 1.01 (inhibition). The difference in impulse frequency is +3.7 impulses per second for excitation and -7.3 impulses per second for inhibition (Granit, Kernell and Lamarre, *J. Physiol.*, 1966a).

An experiment in which both constant inhibition and constant excitation were tried on the same cell is illustrated in Figure 27. On the abscissae are plotted impulses per second when no additional stimulus was added, i.e. the effect of trans-membrane stimulation as such. On the ordinates, the firing rates obtained when either a constant E or a constant I was superposed. The 45° line in the middle for which ordinates and abscissae coincide is drawn to show the case of $E = I = 0$.

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It is seen that the upper line for added excitation and the lower one for added inhibition run parallel with the one in the middle. Their slopes are 1.01 and 1.02 respectively or near enough to 1.0 to support the inference that the motoneuron adds E and I algebraically in terms of spike frequencies.

The result means that if the slope constants of control curves (without added synaptic stimuli) are plotted against those with added excitations, they should all fall on the same curve with a slope of 1.00. This is shown

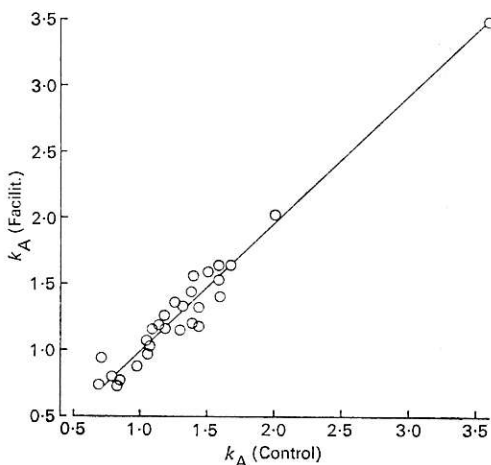


Fig. 28. Plot of slope constants of facilitated curves (ordinates) against slope constants of control curves (abscissae), for the 28 experiments in which linear curves were obtained. The regression coefficient is 0.96 ($S_{y,\bar{x}} = \pm 0.11$) and the linear correlation coefficient $r = 0.974$ (Granit, Kernell and Lamarre, *J. Physiol.*, 1966a).

to actually be the case for twenty-eight experiments on added excitations in Figure 28.

In some of these experiments quite large amounts of E or I were added. Figure 29 shows a case of an added inhibition plotted in a slightly different manner. The abscissae are current strength and the ordinates spike frequency. The upper curve is the control (injected current alone), the lower one the effect of added inhibition at these same current strengths. The result illustrates one of the largest inhibitions used. Inhibitions tend to be more difficult to measure than excitations because the motoneuron may easily be hyperpolarized to the level of its equilibrium potential for the IPSP. This may escape notice. Nevertheless, when the inhibitions were plotted in the manner of Figure 28, the regression coefficient came out reasonably good, at

MECHANISMS REGULATING THE DISCHARGE OF MOTONEURONS 1.06 (see caption) in Figure 30. In the experiments the mean difference between inhibited values and controls was -8.4 ± 1.20 (SD) impulses per second, the range from -2.8 to -21.8 impulses per second. The corresponding figures for added excitations were: mean 13.6 ± 1.95 (SD) impulses per second, the range being from 2.0 to 56.2 impulses per second.

Some idea about the precision with which these experiments could be done can be arrived at by regarding all thirty experiments on excitation

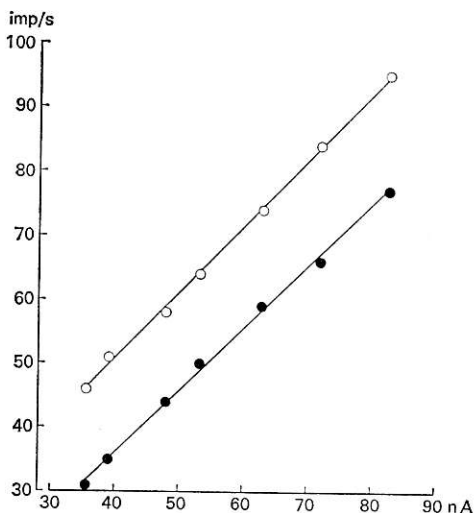


Fig. 29. Pentobarbitone cat (35 mg/kg). Hamstring motoneuron of spike height 67 mV and resting membrane potential -63 mV (2M potassium citrate electrode). Firing inhibited by high-frequency stimulation of deep peroneal nerve. Upper curve 'control', as measured for 0.5 s before onset of nerve stimulation. Lower curve (filled circles), same inhibited during the first 0.5 s of peroneal nerve stimulation. 'Control' $k_A = 1.03$ impulses $s^{-1} nA^{-1}$, 'inhibited' $k_A = 0.96$ impulses $s^{-1} nA^{-1}$. The difference between the two curves is 15.7 ± 1.6 (SD) impulses per second (Granit, Kernell and Lamarre, *J. Physiol.*, 1966a).

(twenty-eight with linear controls) as one single experiment, plotted as in Figure 27. The regression coefficient would then have to be 1.00. Weighted means should be used because of the varying number N of observations in each case. The value found was 0.985 ± 0.157 (SD). For the experiments on inhibition (seventeen motoneurons) the corresponding figure was 0.973 ± 0.073 (SD). Similar experiments with extra-cellular recording had been performed by Granit and Renkin (1961) using a constant recurrent inhibition to diminish the firing rate of tonic

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motoneurons (see below, p. 56). Their value of the average slope constant of all experiments was 0.996. Very likely the precision with which motoneurons add and subtract synaptic stimuli algebraically exceeds that obtainable by experimentation.

Clearly artificial stimulation by injected currents reproduces synaptic stimulation to the extent of making the two replaceable with respect to the firing mechanism, generally held to be located in the 'axon hillock-initial segment' region of the motoneuron. All kinds of synaptic stimuli

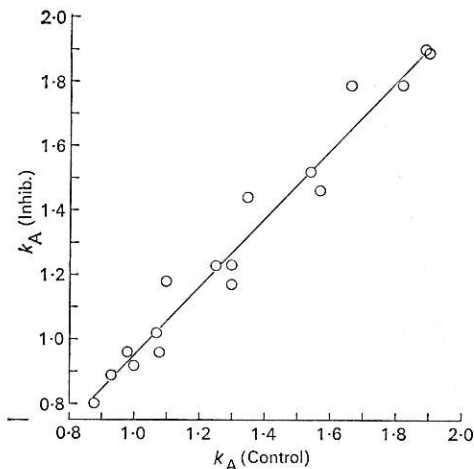


Fig. 30. Plot of slope constants of 'inhibited' curves (ordinates) against slope constants of control curves (abscissae) for 17 experiments. The regression coefficient is 1.06 ($S_{y \cdot x} = 0.09$) and the linear correlation coefficient $r = 0.982$. The slope constant of one experiment on inhibition was left out as being based on two readings only (Granit, Kernell and Lamarre, *J. Physiol.*, 1966a).

were used in these experiments, mono- and polysynaptic ones, electrical stimulation of bared afferents, stretch or contraction of a muscle. The boutons of the terminals cannot have been restricted to any special part of the motoneuron. It was therefore concluded that the 'conductance changes induced by peripheral impulses have released currents from synaptic batteries lying in parallel along the cell membrane. All of them contribute their own share to the activation of the common spike generator engaged in summing up their net value' (Granit *et al.* 1966a, p. 396). In fact, all these findings would be very difficult to explain without assuming a firing zone responding to the total depolarizing pressure.

Similar experiments have since been performed with cortical pyra-

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 midal cells (Brooks, Kameda and Nagel 1968) and with the Clarke
 neurons in the spinal cord (Eide *et al.* 1969). In both cases algebraical
 summation was reported.

Synaptic stimuli superposed within the secondary range

Within this range the characteristic finding—when unwanted blocking
 around the electrodes can be excluded—is shown in Figure 31. Owing
 to the higher slope constant of the added curve (filled circles) the two

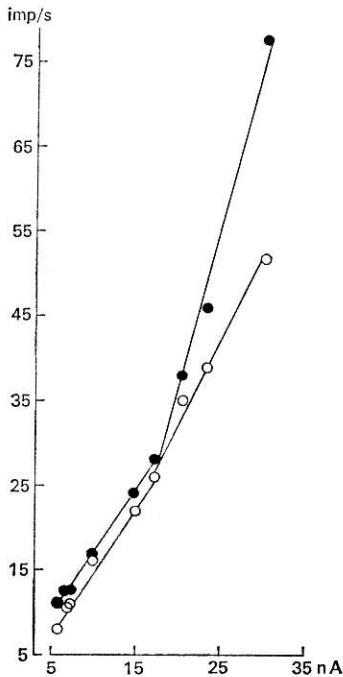


Fig. 31. Pentobarbitone-chloralose cat. Hamstring motoneuron of spike height 62 mV (2M potassium citrate electrode) facilitated by steady tetanic contraction of gastrocnemius-soleus muscle as elicited from peripheral stump of cut ventral root. Maximal discharge frequency within the primary range at about 30 impulses per second. In the primary range 'control' $k_A = 1.51$ impulses $s^{-1} nA^{-1}$, 'facilitated' $k_A = 1.59$ impulses $s^{-1} nA^{-1}$; difference, 2.0 impulses per second. In the secondary range 'facilitated' $k_A = 3.79$ impulses $s^{-1} nA^{-1}$ ('control' $k_A = 1.9$) indicating increase of the synaptic excitatory effect (Granit, Kernell and Lamarre, *J. Physiol.*, 1966b).

curves diverge in that region. Figure 32 is inserted to show that synaptic stimulation may, on occasion, induce the secondary range at a slightly lower rate of discharge than the one provoking this response with injected current alone. Clearly, the rule of algebraical summation breaks down within the secondary range.

If the views set forth above as to the nature of the secondary range be correct, inactivation is induced more easily from the synapses, which are likely to be all over the motoneuron, than from the somatic region where the tip of the microelectrode is located. The excessive depolariza-

tion required for inactivation may well occupy the whole of the SD region but the spikes issued from the firing zone do not have access to the efficient mechanism of after-hyperpolarization which holds up the membrane potential. The consequence is increasing depolarization. This, however, is what inhibition should be able to prevent and so it is of

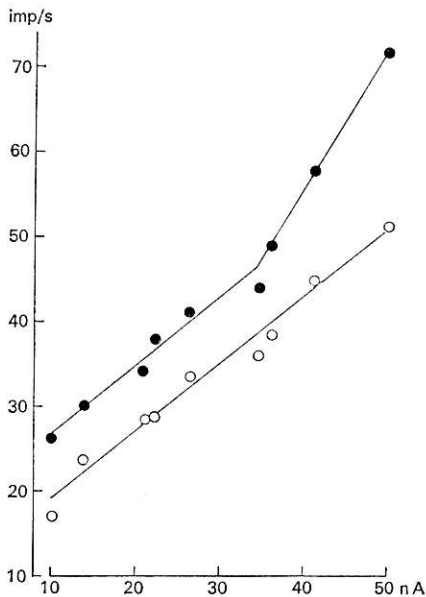


Fig. 32. Anaemically narcotized cat. Ankle extensor motoneuron of spike height 65 mV (2M potassium citrate electrode) facilitated by 10-mm stretch of the gastrocnemius-soleus muscle rising in 1.4 s. Control curve is the mean of values measured before and after stretch (1.0 s before onset of stretch and from 0.5 to 1.0 s after cessation of stretch). Facilitated curve measured from 0.5 to 2.5 s after onset of stretch. 'Control' stays within the primary range ($k_A = 0.74$ impulses s^{-1} nA^{-1}). Facilitated curve is parallel with 'control' in the primary range ($k_A = 0.80$ impulses s^{-1} nA^{-1}). Difference = 7.9 ± 1.35 (SD) impulses per second. Synaptic excitation pushed the cell into the secondary range where $k_A = 1.63$ impulses s^{-1} nA^{-1} . (Granit, Kernell and Lamarre, *J. Physiol.*, 1966b).

particular interest to see that it actually does it, as was shown above in Figure 23. The corollaries of this role of inhibition are extremely important for problems of regulation.

In the experiments of Figure 33 the controls again are given as circles, those with inhibition added as filled circles. The algebraical summation within the primary range is replaced by divergence of the curves in the secondary range. This means that with higher degrees of depolarization the inhibitions become more powerful in terms of hyperpolarizing potential (Coombs *et al.* 1955b). The final effect of this is a tendency toward linearizing the curves of spike frequency against current strength so that the primary range is extended to higher frequencies of discharge. The linearization is nearly perfect in Figure 33A. To put this differently, inhibition does not only reduce the firing rate but also extends the well-controlled primary range to higher values of discharge frequencies.

It was pointed out above that in different motoneurons the turning

MECHANISMS REGULATING THE DISCHARGE OF MOTONEURONS
 point of the curve from the primary into the secondary range is at different frequencies. This was partly ascribed to the variations of the gain constant (that is likely to depend on the time course of after-hyperpolarization, Kernell 1968), but the present findings suggest that

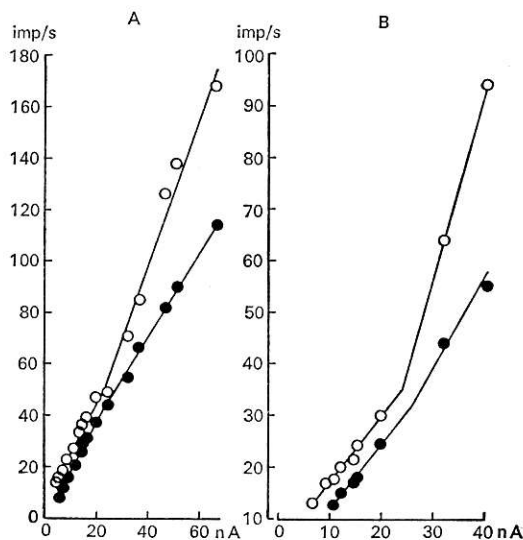


Fig. 33. A. Pentobarbitone cat (35 mg/kg). Hamstring motoneuron of spike height 75 mV (2M potassium citrate electrode), inhibited by high-frequency stimulation of the deep peroneal nerve. 'Control' and inhibited curves measured for 0.5 s before and 0.5 s after onset of nerve stimulation. In the primary range the two curves are parallel; 'control' $k_A = 1.89$ impulses $s^{-1} nA^{-1}$; 'inhibited' $k_A = 1.90$ impulses $s^{-1} nA^{-1}$ and the difference is -7.3 ± 0.94 (SD) impulses per second. In the secondary range, 'control' $k_A = 2.86$ impulses $s^{-1} nA^{-1}$ and 'inhibited' $k_A = 1.66$ impulses $s^{-1} nA^{-1}$. B. Pentobarbitone cat (35 mg/kg). Popliteal motoneuron of spike height 88 mV (2M potassium citrate electrode) inhibited by high-frequency stimulation of deep peroneal nerve. Control and inhibited curves measured for 1.0 s after and 1.0 s before cessation of nerve stimulation respectively. In the primary range, 'control' $k_A = 1.25$ impulses $s^{-1} nA^{-1}$ and 'inhibited' $k_A = 1.23$ impulses $s^{-1} nA^{-1}$. The difference is -5.1 ± 0.58 (SD) impulses per second. In the secondary range 'control' k_A about 3.5, the 'inhibited' k_A about 1.7 impulses $s^{-1} nA^{-1}$. (Granit, Kernell and Lamarre, *J. Physiol.*, 1966b).

the load of inhibition carried by a motoneuron probably is more important in the end. There are well-known tonic inhibitions on motoneurons, such as the Schiff-Sherrington inhibition from segments below the one recorded, the tonic cerebellar inhibition released by cooling the cerebellar cortex and the inhibition from dorsal roots on the opposite side revealed by cutting them (Moruzzi and Pompeiano 1957). These inhi-

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bitions have been admirably presented and discussed by Moruzzi in his section in Dow and Moruzzi (1958). It is assumed that variations in the amount of tonic inhibition may be large enough to cause corresponding variations in the boundaries of the primary range.

It is, of course, of prime importance for the executive of a power output not to run into inactivation at very slight provocations, as this would lead to uncontrollable violent contractions succeeded by pauses of recovery. Therefore, as usual in the central nervous system, when something needs to be held in check, there are several mechanisms available for the task. They may here as elsewhere have a number of

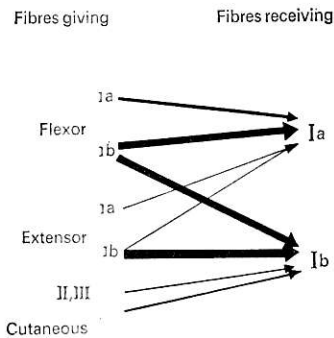


Fig. 34. Diagram showing types of afferent fibres which depolarize Group Ia and Ib fibres of flexor and extensor muscles. The afferent fibres which produce the depolarizations are listed in the left column. The relative amount of depolarization contributed by each is approximately indicated by the width of the arrows (Eccles, Schmidt and Willis, *J. Neurophysiol.*, 1963).

other things to do but they overlap with respect to the function now holding our attention. There is the adaptation of the cell membrane, the gain, the after-hyperpolarization, tonic and other inhibitions, among them the recurrent variety to which the last chapter will be devoted.

Even before an impulse reaches the knob at the end of the afferent terminal, it is supposed to be held in check by a special mechanism, that of primary afferent depolarization (Wall 1958, 1964) leading to so-called presynaptic inhibition. It is being assumed (Eccles 1964b) that depolarization of the terminals by special synapses upon them reduces the size of the spike and thereby its efficacy as an agent of transmitter release. If the P boutons that Conradi (1969a-d) has described on the monosynaptic terminals (see Introduction) are the substrate of presynaptic inhibition, one would expect a large number of them on the monosynaptic spindle afferents of flexors, the only motoneurons so far studied by him. Figure 34 is a summary of the distribution of the giving and receiving fibres in primary afferent depolarization which, as far as the flexor is concerned, agrees with that notion. Some of the difficulties encountered in trying to place presynaptic inhibition firmly into the

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sequence of events controlling discharge rate have been pointed out elsewhere (Granit 1970). So far, this process is not quantitative in terms of output, as is the postsynaptic inhibition discussed above; the presynaptic variety is universal and potent (Eccles 1964b) and thus one would like to know (in terms of output frequencies) how much of a reduction of firing rate is due to it and how much to postsynaptic inhibition which is equally universal. One would also need to know what proportion of any given input is curtailed by presynaptic inhibition. In this lecture the aim has been to look for the role of a given process in the control of movement by the alpha executive. With regard to presynaptic inhibition, the knowledge we possess is still very much at the phenomenological level. It is not even quite convincingly shown that presynaptic inhibition is one process only, i.e. that the various indicators used measure the same process. As stated, the process named primary afferent depolarization appears to be the most reliable event so far discovered. We are entitled to expect further information on it from the electron-microscopical approach of the anatomists.