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Muscular Afferents
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Effects of stretch and contraction on the membrane of motoneurones

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The natural modes of firing to stretch and contraction and quantitative aspects of convergence have been in the centre of interest of a team at the Nobel Institute consisting of Kellerth, Kernell, Shortess, Smith, Szumski, Williams and myself working in different combinations. This means that we have been chiefly concerned with such properties of motoneurones as relate to the repetitive discharge.

No sooner has one adjusted one's focus in this manner than questions announce themselves all of which concern the establishing of suitable parameters for the study of repetitive activity and of the concepts these parameters are supposed to substantiate. The basic parameter without which little can be achieved is the relation between generator current and impulse frequency. Knowing this for any one cell one can proceed to a quantitative study of convergence of excitation (E) and inhibition (I). Do E and I add algebraically or can convergence onto a single cell also lead to multiplication and division? This is but one instance of a problem which requires knowledge of a kind that so far has not been available. Many other examples will be mentioned as this Symposium develops. Thus, for instance, the nature of the subliminal state of excitation and inhibition is open to interpretation in different terms depending upon whether attention is centered on the average level of membrane potential or on the quantal nature of synaptic excitation demonstrated by Katz and his co-workers (Katz, 1962). The function of interneurones as biasing instruments, for which the gamma-loop provides a most interesting paradigm, is a third example of questions to which this Symposium will be devoted. Many of our problems are the very ones which the makers of neurone and circuit models ought to have raised but, on the whole, the imagination of the model-makers appears to be directed towards different goals, respectable in themselves, but incapable of providing substitutes for the lengthy experiments we have to face in this field, as always in physiology.

Beginning with the relation between impulse frequency and strength of the current injected through the tip of a micro-electrode inserted into a rat moto-

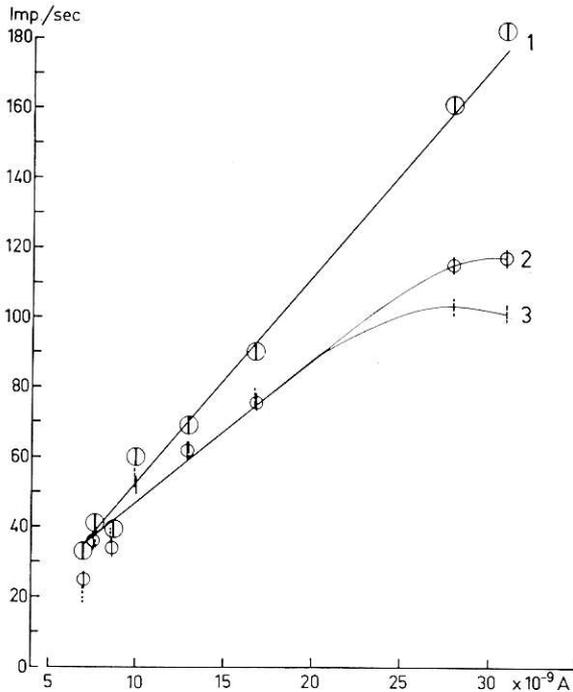


Fig. 1. Frequency of discharge plotted against current strength for motoneurone of 81 mV spike size. Curve 1, slope constant 5.9 (imp/sec)/nA derives from 1/3 sec following first interval; curve 2, same after 1.3 sec; curve 3, same after 2.6 sec, measuring time extended to 1/2 sec. Slope constant of 2 and 3 is 4.1 (imp/sec)/nA. The rectilinear portion of these curves was calculated by the method of least squares. (Granit, Kernell & Shortess, 1963a.)

neurone, Fig. 1 summarizes the result of a typical experiment (Granit, Kernell & Shortess, 1963a). A straight line is a fair approximation over a considerable range of current strengths. The same result is suggested by Shapovalov's (1964) similar experiments and by those of Creutzfeldt, Lux & Nacimiento (1964) on cortical cells.

The fast initial adaptation of discharge frequency which in Fig. 1 emerges as a decreasing slope of the curve is very characteristic and, from the point of view of muscular afferents, important because the spindle primaries initially fire at fast rates before they, too, settle down by adaptation to a steady rate of discharge (Matthews, 1933). The steady state of firing of the motoneurone (Fig. 1) has the interesting property of maintaining a fixed slope constant for as long as the continuously stimulated motoneurone can be held penetrated and active, in spite of the slow decrease that takes place in the absolute value of the discharge frequency (Granit, Kernell & Shortess, 1963b). The *initial* and the *late adaptation* of the firing rate are therefore different events. The former is over in a few hundred milliseconds or less. Kernell (1965a) has recently confirmed these conclusions with cat motoneurones. Kernell (1965b) has also added the important finding—to be reported by himself—that in many cat motoneurones the curve of Fig. 1 takes an upward turn at higher discharge frequencies. In this so-called secondary range of firing it is likewise possible to use a straight line at a steeper angle as a fair approximation to the findings. There are thus two

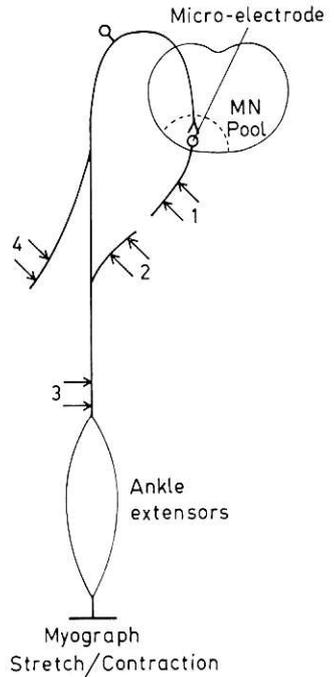


Fig. 2. Diagram of preparation used in experiments to be described below. Cross section of spinal cord. Ventral root is divided into a central stump with electrodes (1) for antidromic stimulation and a peripheral stump with electrodes (2) for producing contractions of alpha and gamma motoneurons. Electrodes (3) on the GS nerve serve to identify motoneurons. Electrode (4) is on the popliteal nerve. Electrodes (not shown) are also placed on the cut hamstring and peroneal nerves. When stretch alone was used the tibialis anterior and ext. digit. longus muscles together, as well as the semitendinosus by itself, were also isolated. These electrodes not included.

slope constants, representing, as it were, two amplifiers of different gain built into the same cell.

For the rest of the experiments to be considered in this paper the standard arrangement illustrated in Fig. 2 will be used. It is fully described in the legend. Cats under pentobarbitone were used and—practically always—potassium citrate micro-electrodes for intracellular recording. For stretch, three muscles, triceps surae, tibialis anterior *plus* ext. digitorum longus as well as semitendinosus, were freed and could be loaded with weights. For contraction we have so far only used gastrocnemius-soleus. In these de-efferented animals, effects of contraction always refer to stimulation of the muscle from the peripheral stump of the cut ventral root.

We shall now begin with a little piece of intracellular algebra (Granit & Kernell, unpublished). In the experiment of Fig. 3 the hamstring motoneurone was fired by injected currents of different strengths. The gastrocnemius-soleus was tetanized from the root and this contraction led to an increase of the discharge rate of the hamstring cell. Repeating stimulation by constant contractile tension, while the motoneurone was fired at increasingly faster rates, involves the following question: if there be algebraical summation, the constant convergent facilitation from the muscular source should always add the same number of impulses, independently of the firing rate of the cell. The experiment of Fig. 3 showed that the question was answered in the affirmative. The slopes

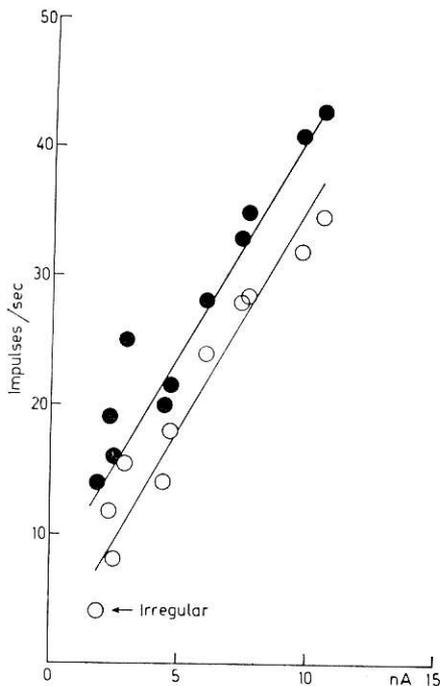


Fig. 3. Hamstring motoneurone of spike size 100 mV (recorded by 2 M potassium citrate intracellular electrode) and facilitated by steady tetanic contraction of gastrocnemius muscle elicited from peripheral stump of cut ventral root (cf. Fig. 2). *Lower curve*, relation between steady discharge frequency and maintained transmembrane stimulation from tip of micro-electrode. Reading marked 'irregular' is at a rate of discharge just below rhythmic threshold at which firing irregular. Equation by method of least squares, $F = 3.6 \text{ nA} + 0.3$. *Upper curve*, same facilitated by the superimposed contraction from ventral root. Equation, $F = 3.5 \text{ nA} + 6.75$. (Granit & Kernell, unpublished).

of the two curves, calculated by the method of least squares, do not differ by more than 0.1 (impulses/sec)/nA, which clearly is within the limits of error.

Lest algebraical summation of the kind shown be regarded as an artifact produced by the combination of transmembrane with synaptic depolarization, let us briefly recall our earlier experiments (Granit & Renkin, 1961) which were extracellular throughout and consisted in pitting a constant recurrent inhibition against a variable discharge rate (F_n) of a single cell whose axon had been isolated in the ventral root. Calling the inhibited rate of discharge F_i it is seen that the experimental curve (Fig. 4) during recurrent inhibition (F_i against F_n) differs from the curve without inhibition, $F_i = F_n$, by a constant amount. In this particular plot the slope constants of the two curves should be 1.00. With 18 cells and 470 observations the experimentally obtained value averaged out at 0.996 for an average inhibition of -5.5 impulses/sec. The latter value varied a great deal from case to case depending, of course, upon the relative inhibitory power of the recurrent projections. Thus there is no doubt but that the cell could do the piece of algebra that it was called upon to accomplish. The findings of Fig. 1, obtained with transmembrane depolarization, confirm the basic idea behind this experiment, a concept launched, as you all know, by Sherrington and substantiated in important papers by Eccles and his co-workers (e.g. Eccles, 1957), namely that E and I are represented by opposite currents, often also recordable as opposite potentials.

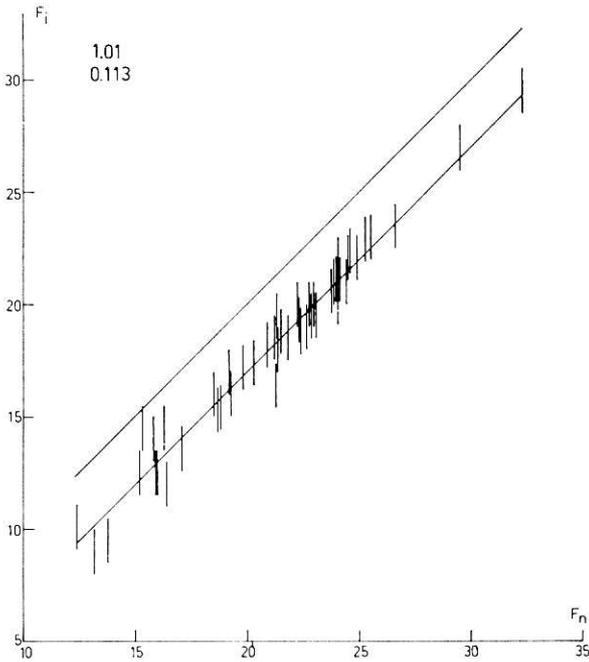


Fig. 4. Quantitative analysis of recurrent inhibition according to earlier work by Granit & Renkin. In this work a single fibre from cut ventral root was kept firing at different rates (F_n) by tetanization of the cut gastrocnemius nerves. This discharge was reduced in frequency to a value (F_i) when the rest of the same ventral root was tetanized antidromically at constant strength and high frequency. Upper vertical line in plot of F_i against F_n shows absence of recurrent inhibition or $F_i = F_n$. The line drawn through the experimental observations illustrates F_i during recurrent inhibition. In left upper corner, regression coefficient (above) and standard error (below). (Granit & Renkin, 1961.)

On the other hand, our experiments should not be taken to mean that algebraical summation inevitably follows whenever synaptic currents from convergent sources interact at the membrane of a firing cell, as if this mode of behaviour constituted a final limit to the mathematical talent of motoneurons.

Let us, for instance, look at Fig. 5 (Granit & Kernell, unpublished) which differs from Fig. 3 merely in that the same experiment is performed with another hamstring cell from a different animal. Up to about 26–28 impulses/sec the motoneurone goes on adding a constant amount of excitation derived from the constant tetanic contraction but from there onwards something else happens. The effect in impulses/sec of the constant contraction increases out of proportion to the increase caused by the injected current alone. Apparently the motoneurone at higher frequencies fires within Kernell's so-called secondary range but fundamentally, if the machinery were the same, there is no reason why the slopes in that range shouldn't be the same for the two curves compared. A constant synaptic current should add a constant amount to the

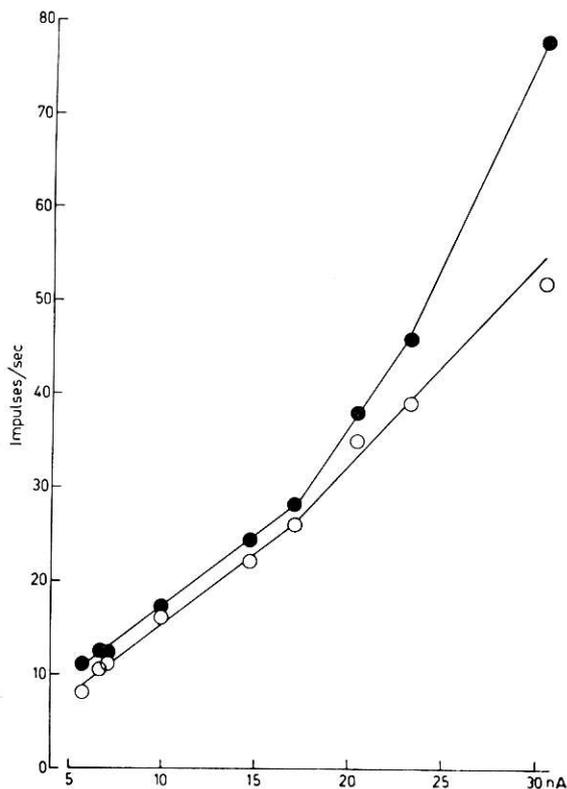


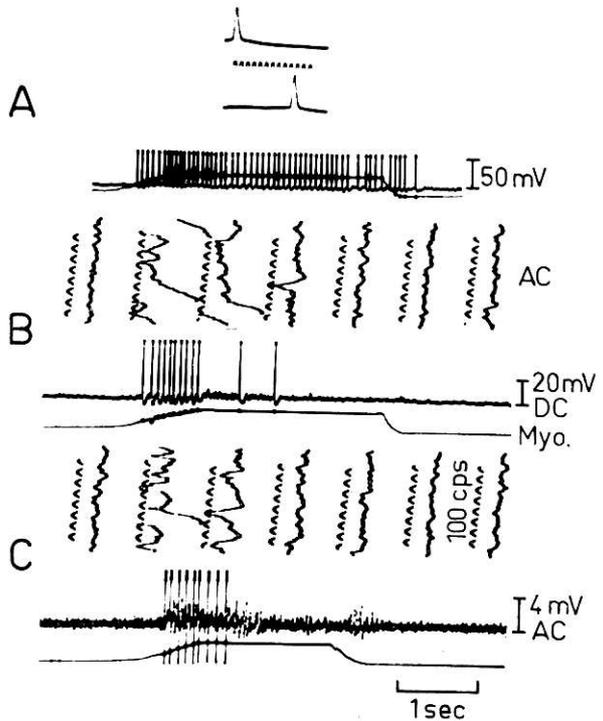
Fig. 5. Experiment identical with that of Fig. 3 but with another hamstring motoneurone whose spike height was 62 mV. Lower curve, relation between steady discharge frequency and maintained transmembrane stimulation by current from tip of microelectrode. Upper curve, same with facilitation by steady contraction of gastrocnemius muscle. (Granit & Kernell, unpublished.)

prevailing depolarizing current up to the saturation point. This particular experiment was repeated twice with a very stable penetration and in both cases with the same outcome. Why now with this cell is there something that in the upper range of activity looks more like a multiplication?

At the moment we cannot do more than postulate another form of activity as an explanation of 'multiplication' and proceed to show that other forms of activity actually do exist. An alternative hypothesis would be that the secondary range invokes a new firing zone, say, further out in the dendrites. While this to-day would remain a hypothesis, it is a definite experimental finding that firing in motoneurones can take place without the background of a steady depolarization. It is our next task to consider the evidence for this conclusion (which,—I find—will also be taken up by Shapovalov at this Symposium, below).

The other mode of firing that we have seen is caused by irregular wavelets of synaptic activation noise with peaks rising over and above the steady level of an average generator current. Firing on activation noise is shown in Fig. 6 which illustrates the effect of stretch of the muscle tibialis anterior on a popliteal motoneurone. In Fig. 6B there is little if any shift of average level of baseline

Fig. 6. Cat anaesthetized with pentobarbitone. Popliteal motoneurone which stayed at a spike height of 60 mV for a considerable time with same overshoot. It also fired to pull of tibialis anterior (insufficient mechanical isolation?), used in these records. Weight 500 g. Firing, initially tonic (A), then phasic (B, C). Activation noise (a.c.) recorded on sweep and also (d.c.) in B on standing spot at sensitivity cutting out upper part of spikes. Note, off-discharge of activation noise in C and just visible in B also. Uppermost records, samples on sweep and time msec. (Granit, Kellerth & Williams, 1964a.)



during stretch. The same experiment is repeated in Fig. 6C with a.c. recording. The sampling sweeps demonstrate the wavelets of activation noise.

It is instructive to compare this mode of firing with that of an ordinary stretch reflex, illustrated in Fig. 7. The latter is from a popliteal motoneurone activated by pull on the triceps surae starting at the beginning of the record and lasting to the final arrow. The cell is inhibited between the two arrows in the middle by pull on an antagonist muscle, tibialis anterior. The typical stretch reflex of a motoneurone responding tonically is characterized by a slight steady depolarization which the spikes interrupt in a regular fashion by afterhyperpolarization supported by the recurrent inhibition which, as we know, is so characteristic of those extensor motoneurones that respond in this beautifully steady manner to stretch (Granit, Pascoe & Steg, 1957; Kuno, 1959; Eccles, Eccles, Iggo & Ito, 1961). The records of Fig. 7 are a good example of a stabilization of the response of the membrane by the double negative feedback mechanisms of afterhyperpolarization and recurrent inhibition. In the secondary range Kernell (1965*b, c*) finds afterhyperpolarization to be changed in appearance. As to the antagonist inhibition, it is, as we shall see, postsynaptic (Granit, Kellerth & Williams, 1964*a, b*; Kellerth & Szumski, below).

Returning now to Fig. 5 in which for higher current strengths algebraical summation was replaced by 'multiplication' of the synaptic effect of stimulation

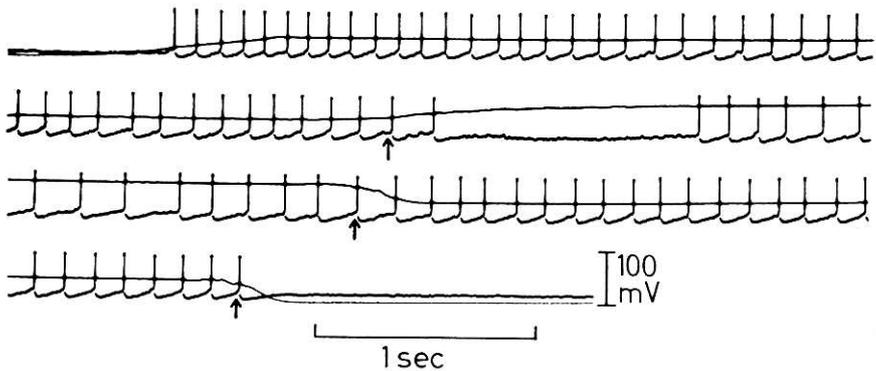


Fig. 7. Cat with external and internal carotids tied so as to sleep on smaller dose of anaesthetic. Pentobarbitone 11 mg/kg. Popliteal motoneurone (75 mV spike height). Membrane potential around 65 mV. Pull on triceps (500 g) maintained till last arrow; between first and second arrow pull on tibialis 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 & Williams, 1964a.)

caused by a constant contraction, we could assume that the confluent quantal effects producing wavelets of excitatory activation noise might be favoured by the strong depolarizing currents injected from the micro-electrode.

The existence of activation noise emphasizes Katz's (1962) work on the quantal nature of synaptic excitation and necessarily raises the question of how to define a state of subliminal excitation correctly. Long before the advent of intracellular recording I believe that most physiologists would have been satisfied—as was I—with the assumption that subliminal excitation always is a state of subliminal depolarization. This view must still be considered to be highly relevant and may often contain the whole truth. But since there is random noise (Katz & Miledi, 1963) as well as activation noise consisting of wavelets of depolarization, this form of activity represents another aspect of subliminal excitation and we have to consider both the site, the direction, frequency and amount of activation noise in addition to the question of whether the micro-electrode tip relative to the distance of distant synapses is a good enough measuring instrument for displaying subliminal states of activation further out in the dendrites. What I have said now refers *mutatis mutandis* also to inhibitory activation noise. We (Granit *et al.*, 1964b) have discussed these problems at some length in our paper on the intracellular effects of stretch.

Synchronized stimulation of bared afferents, so useful for many purposes, has come to rely largely on the size and direction of the postsynaptic potentials of which this mode of stimulation provides an exaggerated version. A natural event which is fairly well synchronized is respiration. In accordance with this the respiratory motoneurons produce rhythmic waves of depolarization of

the order of 5–6 mV, especially well demonstrated in a paper by Sears (1964) who speaks of “central respiratory drive potentials”.

Occasionally even larger depolarizing potentials are seen when using stretch of ankle muscles for driving their own motoneurons. These depolarizations may come and go, in spite of constant stretch, and even change sign, if the state of the animal is altered (Granit *et al.*, 1964*a*), suggesting commutation of sign by interneurons, as has been described with actual records from interneurons, by Lundberg and his co-workers (Jankowska, Jukes, Lund & Lundberg, 1965). Assume a motoneurone lacking recurrent inhibition (as many of them do) and assume it being fired at rates which do not permit enough time for afterhyperpolarization to develop. In such cases large generator potentials may arise, provided the interneurons are biased to deliver the necessary synaptic current strengths. Activation noise with stretch as a natural stimulus contains E and I components which may cancel out afterhyperpolarization. Then there is delayed depolarization after a spike which like afterhyperpolarization is influenced by synaptic currents in a complex fashion, as Kernell will discuss below (cf. also Granit, Kernell & Smith, 1963). Small wonder therefore that with muscle stretch de- and hyperpolarization often fail to be as reliable indicators of E and I respectively as the observations with synchronous stimuli make one expect. Inhibition is an especially interesting case because sometimes hyperpolarizing activation noise is absent, sometimes too mixed with depolarizing noise for interpretation and at times the average hyperpolarization may be absent.

What is then to be done in order to find out whether the applied stretch was excitatory or inhibitory in character? There is, of course monosynaptic testing, extracellular, or by an EPSP, if the intracellular approach is used. The EPSP represents a constant synaptic current. The barrage of impulses from the extended muscle will produce a leaky cell membrane and so the monosynaptic testing current may be shunted down without activating inhibitory synapses at all. How is one then to know whether the inhibition was real or not? The test that we have used in such cases consists in firing the motoneurone by injected current. Inhibition and excitation then appear as a suppression or augmentation of the discharge rate. Applying this test to the autogenetic inhibition, caused by stretch of extensor muscles, which is so easily demonstrated by extra- or intracellular monosynaptic testing (Bianconi, Granit & Reis, 1964*a, b*, with references), we (Granit *et al.*, 1964*b*) always find excitation, meaning that the firing rate is augmented and not inhibited.

On the other hand, the corresponding autogenetic effect of contraction (Granit, Kellerth & Szumski, 1965) which is a better synchronized stimulus than stretch we find accompanied by a trough of hyperpolarization and a reduction in firing rate, corresponding to the silent period of Hoffmann (1922).

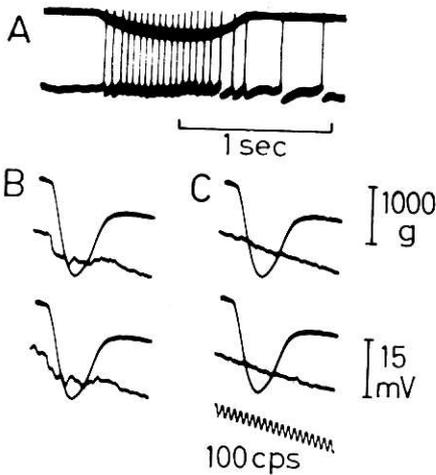


Fig. 8. Intracellular record from ankle extensor motoneurone of 61 mV spike height. *A*, cell fired by manual stretch re-recorded by myograph (above). *B*, contraction from peripheral stump of cut ventral root, twice repeated (d.c. recording). Note, trough of hyperpolarization initiated by contraction. *C*, same experiment repeated immediately after cessation of Cl⁻ injection for 8 sec by current of 40 nA from intracellular tip of KCl-micro-electrode. (Granit, Kellerth & Szumski, unpublished.)

When KCl-electrodes are then used to inject chloride into the cell, which is the well-known procedure of Coombs, Eccles & Fatt (1955), there is temporary disappearance of the hyperpolarization, as shown in Fig. 8. This inhibition which is sensitive to the amount of contractile tension at constant extension clearly mimicks the properties of the Golgi tendon organs, recently studied by Jansen & Rudjord (1964). These are far better activated by contractile tension than by passive tension in stretch, as the earlier work on autogenetic inhibition (Granit, 1950; Hagbarth & Naess, 1950) had suggested. There may be in the inhibition a component of spindle silence but with constant extension of the muscle this must be constant because the pause in de-efferented preparations is virtually independent of the size of the contraction, at least in its rising phase when hyperpolarization occurs. In the falling phase hyperpolarization is gone but may be replaced by hyperpolarizing activation noise which we have every reason to attribute to the action of spindle secondaries (Bianconi *et al.*, 1964*a, b*). It should be emphasized that the existence of hyperpolarizing activation noise is a criterion of postsynaptic inhibition second to none in reliability (Katz & Miledi, 1963; Granit *et al.*, 1964*a, b*).

I shall give but one example (Fig. 9) of inhibitions to stretch demonstrated by the criterion of suppression of the firing of a cell. It refers to a peroneal motoneurone stimulated by injected current. These two inhibitions by stretch of the muscles triceps surae and semitendinosus in Fig. 9 failed to show up by the other criteria that we have been discussing.

Inhibitions of this type are postsynaptic because they have acted upon the firing membrane but they may be dis-facilitations at this membrane. Most of them, however, display hyperpolarizing activation noise and so cannot be disfacilitations. Kellerth & Szumski (below) will return to this problem and present experiments with chloride injections, strychnine and picrotoxin, all

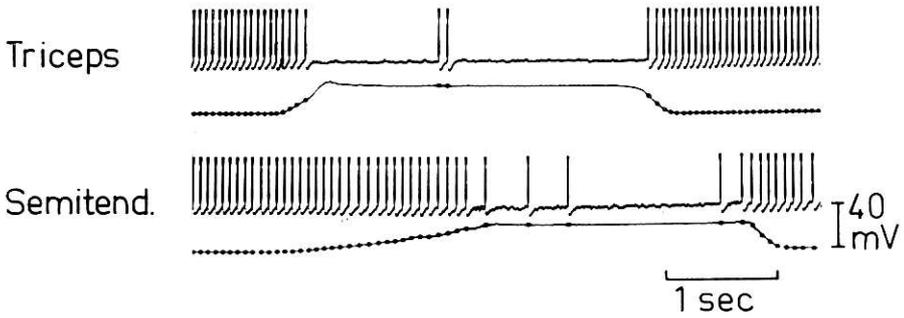


Fig. 9. Cat with external and internal carotids tied so as to sleep on smaller dose of anaesthetic. Pentobarbitone 15 mg/kg. Ventral roots L7 and S1 cut. Peroneal motoneurone (antidromic spike height over 70 mV). Motoneurone fired by injected current and discharge inhibited by muscle stretch. Weight 500 g in both cases. (Granit, Kellerth & Williams, 1964b.)

of which substantiate the thesis of Granit *et al.* (1964a, b) that the relevant inhibitions in antagonistic stretch, known from the classical literature, are genuine postsynaptic events. Autogenetic stretch, as we saw, causes a pseudo-inhibition which transmembrane stimulation shows to be excitation.

It seems to us singularly interesting that firing a cell by injected current should reveal postsynaptic inhibitions which without depolarization would have been subthreshold. Depolarization by transmembrane stimulation behaves as if it always extracted the final information of the message in terms of the net effect of opposing currents, otherwise uninterpretable, unless the cell somehow interprets mixed activation noise alone. Imagine what this fact means for our understanding of, for instance, the role of the non-specific afferents. Inasmuch as the latter produce general depolarization at any cortical site, this process need not be further elaborated in order to be useful for the interpretation of a message coded by specific afferents at a cell in terms of opposing currents. The general non-specific depolarization will emphasize the specific one by bringing out the net effect of the latter's synaptic activation noise.

I shall now leave to Kernell and Kellerth to develop many of the points which have been raised above. For the sake of the many muscle spindle problems to be reviewed at this Symposium let me just briefly refer to one more experiment of general interest. This consists in stimulating the gastrocnemius-soleus gamma motoneurons (and whatever spindle alphas that occur in the same preparation) by a tetanus to the peripheral stump of the cut ventral root and record the effect by an intracellular electrode in motoneurons belonging to the self-same extensors. Figure 10 illustrates the outcome.

The two uppermost records are at 10 (in A) and 2 mm (in B) extension respectively. Stimulation of the ventral root (as in Fig. 2) which was at greater strength in B caused a contraction of the ankle extensors and also fired their spindles across the gamma-loop which thereby activated the motoneurone

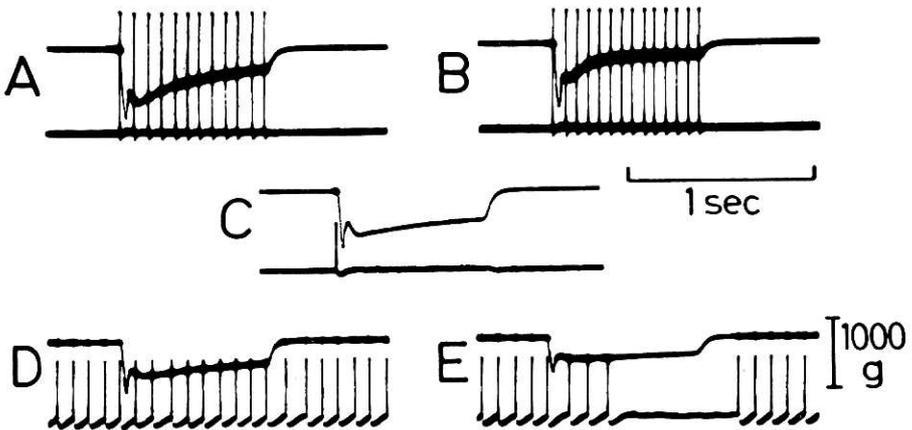


Fig. 10. Experimental arrangement as in Fig. 2 for stimulation of the peripheral stump of the cut ventral root. Myogram of ankle extensors and intracellular recording of spike of 82 mV from a motoneurone belonging to them. *A*, muscle at 10 mm extension, tetanus at 250/sec causing just maximal contraction; a.c. recording of intracellular spike as also in *B*, with muscle at 2 mm extension but stimulus strength increased to 2.0 times beyond max. needed for full contraction. This serves as control for the Xylocaine experiment. Then shift to d.c. recording and 2%. Xylocaine applied to the gastrocnemius nerves. *C*, 14 sec later; now contraction virtually the same but stimulation of ventral root only elicits single spike. In order to study effect of contraction on cell membrane, the motoneurone was fired by injected current in *D*, at 30 sec, and in *E*, at 56 sec after Xylocaine. Note that removal of small fibres (which at this stage may have included also inhibitory afferents from spindle secondaries) revealed the inhibition dependent on contractile tension from Golgi tendon organs. (Granit, Kellerth & Szumski, unpublished.)

(gastrocnemius-soleus). A wad of cotton wool soaked in 2 p.c. Xylocaine (cf. Matthews & Rushworth, 1957, 1958) was then applied to the gastrocnemius nerves, record *B* serving as the control. Within 14 sec the gamma-loop was silenced (record *C*) while the alpha contraction still was virtually uninfluenced. Then the motoneurone was fired by injected current (*D*, *E*) and the gradually diminishing contraction gave the expected inhibitory effect from the tension receptors whose activity before Xylocaine had been overruled by the primary afferents stimulated by their fusimotor fibres.

In a recent valuable review Peter Matthews (1964) stated that "the idea that movements are ever normally initiated solely by means of the γ route is not yet established" (p. 277). I do not agree with him there because I think the idea very well established,—in this particular laboratory in the paper by Granit & Kaada (1952)—not to mention many other well-known papers from Rossi onwards. If, however, Matthews intended to convey the notion that nobody so-far has discharged a single motoneurone across the γ -loop then I think the experiment of Fig. 10 provides the wanted evidence. If, however, the emphasis of his statement was meant to be on the word 'normally' I find it difficult to accept the evidence of Fig. 10 as in any way involving an abnormal efficiency

of the γ -loop. On the contrary, the motoneurone was fired against an extrafusal contraction. It is not at all difficult to excite motoneurons across the loop. In spite of using pentobarbitone animals we had no failures (35 cells), provided the cell gave activation noise or depolarization to stretch. But this, after all, is merely a criterion for the existence of the appropriate projections from spindle primaries. Thus I conclude, as many times before, that the γ -loop is an important, alternative motor route in its own right.

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