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THE CASE FOR PRESYNAPTIC INHIBITION BY SYNAPSES ON THE TERMINALS OF MOTONEURONS*

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IT IS my intention to keep strictly to the title and only consider the evidence for presynaptic inhibition upon the motoneurons by the mechanism proposed by Eccles in several papers (e.g. Eccles, 1964) to explain a correlation between a number of events interpreted by this theory. I willingly admit that I find the idea of synapses on the synapses of the motoneurons unattractive. The reasons will be set forth below. I would like to preserve in some form, the wealth of data and the interesting correlations that Eccles and his co-workers have unearthed, but tied together by a different kind of hypothesis. I am encouraged in this attitude also by the knowledge that Eccles always has been very open-minded about his own theories.

We know enough nowadays about axo-axonic synapses to realize that inhibitions need not be restricted to soma and dendrites. The passage of impulses may be blocked at such synapses. Any central block, located at an earlier site in the passage of afferent impulses to the motoneurons, can be called a "presynaptic inhibition", provided that it somehow and somewhere curtails the rate of afferent firing. An example is the one described by Howland, Lettvin, McCulloch, Pitts and Wall (1955). But the presynaptic inhibition to be discussed below is once and for all tied to the motoneurons by what Eccles (1964) has called the "particularly convincing evidence of presynaptic inhibition . . . reported by Frank and Fuortes (1957) and Frank (1959) implying that the size of a testing monosynaptic EPSP is diminished without any change of membrane potential or electrical excitability of the motoneuron." This inhibition is widely distributed and, according to Eccles (1964) "more powerful than postsynaptic inhibition in depressing the central excitatory actions of almost all primary afferent fibres". If it is so widely distributed and as powerful as this statement implies, it seems necessary to be particularly precise about correlations with other events because in response to a few high-frequency shocks many processes in the spinal cord are both initial, slowly rising and falling as well as favoured by brief tetani.

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With regard to the findings of Frank and Fuortes we are not prepared to give up the idea of "remote inhibition" altogether, having less confidence than perhaps is customary in the microelectrode as a detector of distant dendritic events, until the moment has arrived when the cell actually has started discharging in response to their pooled effects. I shall return to these points of view later.

It is not necessary for me to discuss the anatomical evidence for synapses on the synapses of motoneurons because it will be competently dealt with by others at this Symposium (Szentágothai, Conradi and Skoglund). Nevertheless let me point out that, in view of the power ful and omnipresent process we are discussing, the synapses on the synapses of motoneurons, if really present, ought to be commonly seen as well as generally agreed upon by electronmicroscopists of today. My impression is that this is one of the most hypothetical aspects of the hypothesis as a whole, in spite of the wealth of new information on central synaptic organizations unearthed by electronmicroscopists.

The excitability of the motoneuron membrane in relation to the size of its monosynaptic response and membrane potential seems a matter of straightforward measurements but there are some pitfalls. Recording intracellularly from ankle muscle motoneurons and plotting the size of its autogenetic monosynaptic test response during stretch (Granit, Kellerth and Williams, 1964b), one may obtain a graph of the kind shown in Fig. 1. The

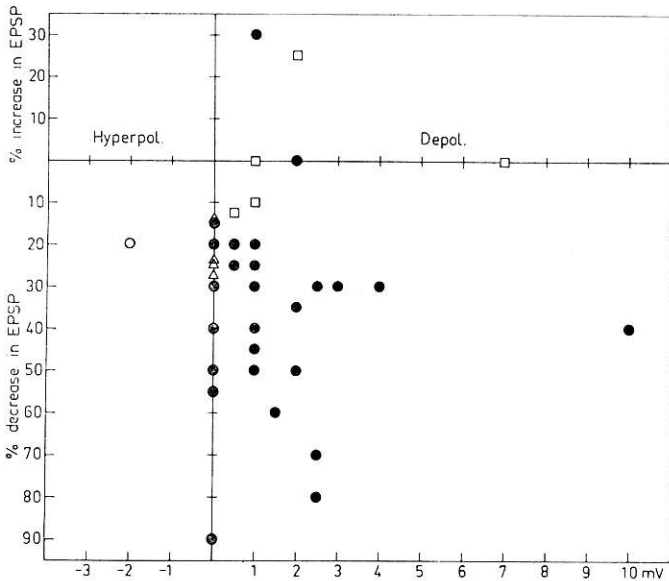


FIG. 1. Relation between percentage increase or decrease in the postsynaptic test response and the shift of average membrane potential during autogenetic stretch of triceps (circles), semitendinosus (squares) and tibialis anterior (triangles). (Granit, Kellerth and Williams, 1964b.)

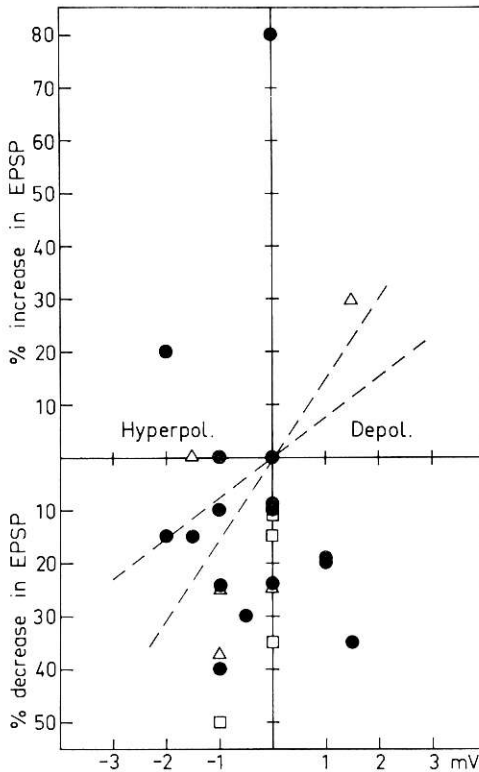


FIG. 2. Relation between percentage increase or decrease in the postsynaptic test response and the shift of average membrane potential during stretch of muscles antagonistic to popliteal (circles), hamstring (squares) and peroneal (triangles) motoneurons. (Granit, Kellerth and Williams, 1964b.)

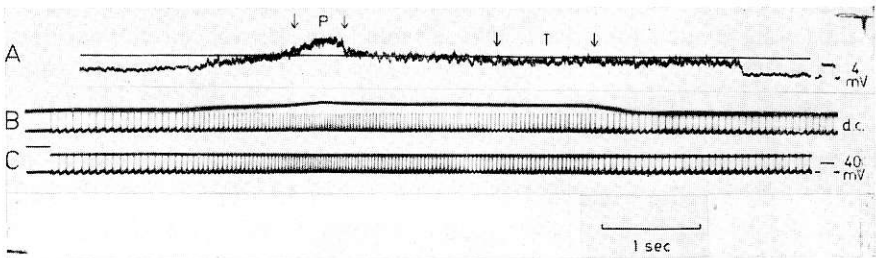


FIG. 3. *A-C* from a gastrocnemius-soleus motoneuron of spike height 78 mV. In *A*, excitatory postsynaptic potential produced by a 10 mm stretch of the gastrocnemius-soleus muscle. *B* and *C* recorded simultaneously. Repetitive discharge initiated by depolarizing transmembrane current of 14 nA (indicated 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 sec after onset of transmembrane stimulation. *A* illustrates the measured phasic and tonic component potentials of the synaptic test stimulus (labelled *P* and *T* respectively). Hence, two facilitated values were obtained, one referring to the phasic rise of impulse frequency, another to the semi-stationary state of firing, as measured between arrows. (Granit, Kernell and Lamarre, 1966.)

correlation between the percentage change of the EPSP and the equivalent change of membrane potential is not particularly good. Nor is it very much better when, as in Fig. 2, antagonistic combinations have been studied. In those papers we advocated change of firing rate of a firing cell as a more reliable index of inhibition. Our later experiments support this recommendation. It is often difficult by mere inspection of records to correlate firing rate

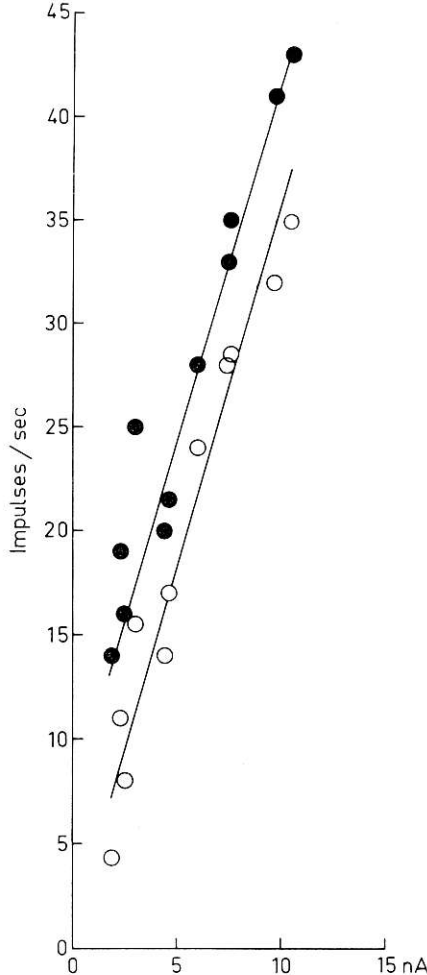


FIG. 4. Pentobarbitone-chloralose cat. Hamstring motoneurons of spike height 100 mV (2M potassium citrate electrode) facilitated by steady tetanic contraction of gastrocnemius-soleus muscle elicited from peripheral stump of cut ventral root. Lower curve, relation between steady discharge frequency and maintained transmembrane stimulation from tip of microelectrode. Slope constant $k_A = 3.59$ impulses $\text{sec}^{-1}\text{nA}^{-1}$. Upper curve (filled circles), same facilitated, $k_A = 3.48$ impulses $\text{sec}^{-1}\text{nA}^{-1}$. The difference between the two curves is 6.5 ± 2.03 (S.D.) impulses/sec. (Granit, Kernell and Lamarre, 1966.)

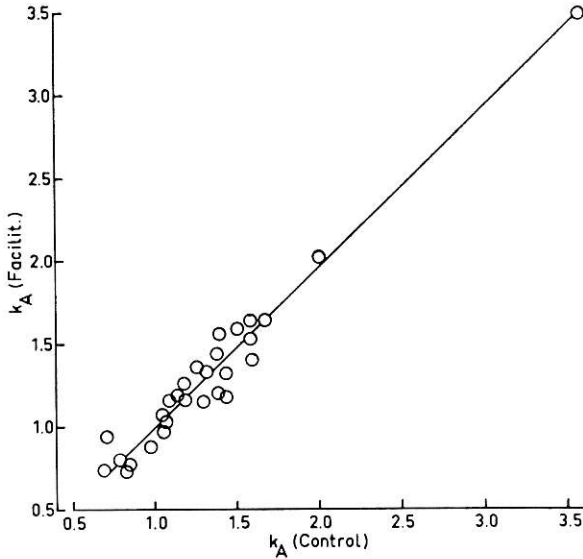


FIG. 5. Plot of slope constants of facilitated curves (ordinates) against slope constants of control curves (abscissae), for the twenty-eight experiments in which linear curves were obtained. The regression coefficient is 0.96 ($S_{y,x} = \pm 0.11$) and the linear correlation coefficient $r = 0.974$. (Granit, Kernell and Lamarre, 1966.)

and depolarization (see e.g. Purpura and Shofer, 1963 on thalamic neurons, and Granit *et al.*, 1964a on motoneurons). By transmembrane stimulation it is possible to analyze such problems.

Figure 3A shows the postsynaptic potential obtained by stretch at constant extension (Granit, Kernell and Lamarre, 1966). In the same figure (B, C) this natural stimulus is made to act upon a motoneuron fired from the inside at a given rate. Our (Granit *et al.*, 1966) experiments have shown that whatever the firing rate forced upon the cell by stimulating it from the tip of the intracellular microelectrode, the constant natural stimulus will always add the same number of impulses within the so-called primary range of firing (as defined by Kernell, 1966) of which an instance is given in Fig. 4. Clearly this means that the slope of the two curves plotted in Fig. 4, the control and the facilitated one, should be equal. Hence I can give a brief summary of our results by showing in Fig. 5 a plot of "facilitated" slopes against those obtained when impulse frequency is plotted against current strength alone. Both stretch, contractions and nerve tetani have been used as constant afferent stimuli in this graph. Algebraical summation at different firing rates is seen to be practically perfect.

From records of the kind shown in Fig. 3 it should be possible to obtain the number of impulses per second per mV change of membrane potential.

This is a measure of the sensitivity of the method. The restriction imposed is that one is obliged to work with large cells in order to carry out the elaborate programme involved in adding constant natural stimuli to variable discharge rates produced by transmembrane stimulation. For an assembly of motoneurons, some excited, some inhibited by the natural stimulus which is stretch or contraction of ankle muscles, the results turned out as in Fig. 6 in which the constant increase of frequency in impulses per second is plotted against the amount of postsynaptic de- or hyperpolarization needed for it. The slope of the regression line is 2.28 impulses/sec/mV. This is the sensitivity of the method based on a change in the firing rate. This can be measured to 1 impulse/sec meaning that one can record a response to about 0.4 mV of postsynaptic potential.

In view of the results which we (Granit *et al.*, 1966) obtained in studying algebraical summation by the method of firing the cell and adding natural stimuli to it, I think we are entitled to state that this method is reliable and sensitive enough as a basic test for postsynaptic inhibition; better than the EPSP-test because the perfect algebraical summation means that one is

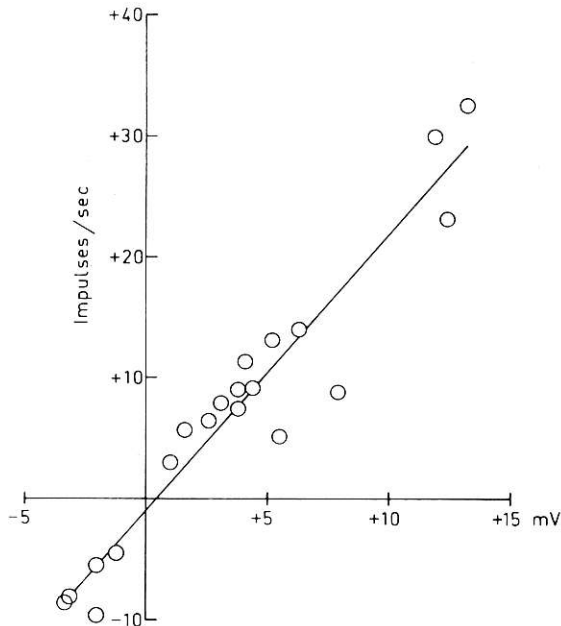


FIG. 6. In the manner, shown earlier in Fig. 3, the relation was obtained between amount of postsynaptic potential and the addition in impulse frequency it gave, when superimposed upon the firing rates produced by injected currents of different strengths. This, as shown in Fig. 4, is a constant. Similarly it is a constant when the postsynaptic potential is inhibitory. Such constant values are plotted for a number of motoneurons against the amounts of postsynaptic potential that produced them. The slope obtained is 2.28 impulses $\text{sec}^{-1} \text{mV}^{-1}$.

testing the summed effects of all relevant synaptic batteries on a single firing zone with which they are in parallel. If there be a distant dendritic effect it may well serve as a shunt for the EPSP and signify inhibition by this index while in reality excitability may be increased, diminished or unaltered. The firing cell, so to speak, extracts the information in terms of a parameter which has greater relevance than the EPSP showing, as it does, what the cell is supposed to do when activated by a given natural stimulus. One need not discuss what it means. This is why I hesitate to accept the notion that the evidence of Frank and Fuortes, referred to above, demonstrates the existence of presynaptic inhibition in a particularly convincing fashion. A remote effect, as originally suggested, could diminish the EPSP just as well and yet be localized to some portion of the motoneuron membrane (Granit *et al.*, 1964a, b). It is, in fact, recommended to use a number of tests for postsynaptic inhibition before excluding it as a possible cause of an observed effect.

The criticism directed against the monosynaptic EPSP as a test of excitability in single cells would seem to be equally valid when the test is a very brief electrical shock from the tip of the intracellular electrode, because, essentially, it centres around the highly localized nature of the recording of this effect. Possibly, if electrical stimulation were to be maintained for a longer time it would be a better criterion, because then its effect sums algebraically with synaptic excitation or inhibition in the perfect manner we have found it to do (Granit *et al.*, 1966). We cannot yet produce a complete theory of how the neuron achieves perfect algebraical summation regardless of localization of the synapses and uninfluenced by shunts capable of modifying a monosynaptic EPSP when the latter is used as a test of excitability. But for the moment it suffices to take it as an empirical fact, established, as far as our work is concerned, with a high margin of statistical validity for which the original paper must be consulted.

Our conclusion, which is that the Frank-Fuortes experiment can be interpreted also on the basis of remote postsynaptic action (Frank) within the neuron and hence cannot be an unequivocal sign of presynaptic inhibition, does not mean that it could not indicate that the input had been reduced at some stage before it arrived at the motoneuron terminals. But what has caused us some worry is the circumstance that in our experiments with natural stimuli, from muscular afferents, those mentioned and those to be mentioned by Kellerth at this Symposium, have all shown a wealth of postsynaptic effects, as determined by several criteria (cf. below), so that there is no difficulty in explaining the classical reflexes from these sources postsynaptically. I have now gone into one of our criteria with more detail, and will enumerate the others briefly; one of them is the hyperpolarizing noise caused by stretch or contraction which in a very definite manner localizes an inhibitory effect to the membrane of the penetrated motoneuron (Katz and Miledi, 1963). This is

quite interesting because hyperpolarizing noise may occur for some time after autogenetic extensor contractions and suppress excitability without this being reflected in a change of average membrane potential (Granit, Kellerth and Szumski, 1966). The inhibition during the rising contraction is also post-synaptic but is accompanied by a sharp increase of membrane potential. Both these events are shown in Fig. 7. The delayed inhibition, seen after extensor

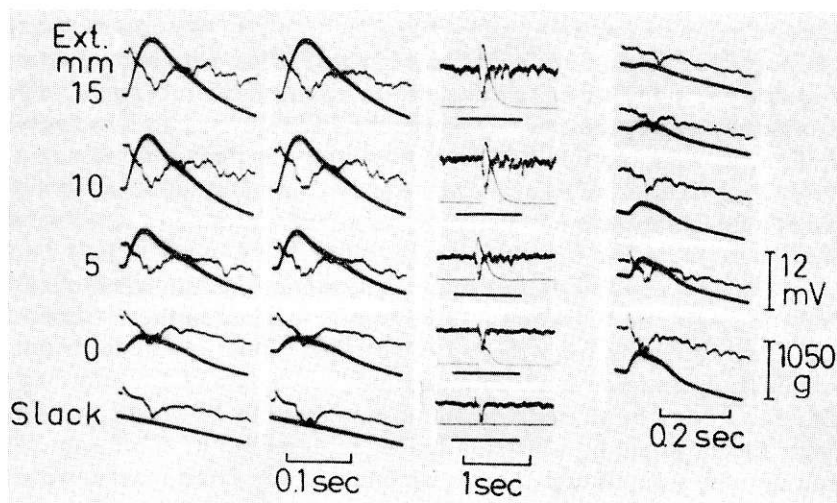


FIG. 7. Gastrocnemius-soleus motoneuron of 68 mV spike height stimulated by triple shock (except vertical right row) at 330/sec to peripheral portion of cut ventral root L7. The two vertical rows on the left (at threshold strength for full contraction) refer to different extensions of GS muscle, the third, same at slow speed. The fourth vertical row on the right illustrates effect of stimulus strength, for single shock and zero extension. Note in the third row hyperpolarizing noise after the larger contractions obtained at greater extensions of the muscle.

contractions, has been established by average monosynaptic testing (Granit 1950) and further analyzed in this manner by Bianconi, Granit and Rei (1964a). Since it does not occur in flexors (Bianconi *et al.*, 1964b) we would have been quite willing to attribute it to presynaptic inhibition, had it not in several cases been so obvious that there was inhibitory activation noise at the membrane (as in Fig. 7) when individual extensor motoneurons were analyzed intracellularly. This noise was not visible in all cases but we had good evidence to the effect that the microelectrode does not always succeed in picking up the noise that must be there. Inhibitory activation noise was very prominent also in the inhibition that stretch of semitendinosus exerted upon a motoneuron of the ankle extensors, as shown in Fig. 8 (Granit *et al.*, 1964a). This is inhibition across one joint and one expected it to be predominantly presynaptic (Eccles, Schmidt and Willis, 1963a, b; Eccles, 1964).

When our natural stimuli gave a definite hyperpolarization of the cell membrane the explanation could be withdrawal of excitation (dis-excitation) by any kind of internuncial or presynaptic mechanism or, alternatively, a true inhibition at the membrane penetrated. Coombs, Eccles and Fatt (1955) have devised a well-known test differentiating between these two possibilities, (a) by an injection of chloride from the microelectrode tip or (b) by hyperpolarizing the cell. This test was systematically applied and supported the evidence for true postsynaptic inhibitions. Then Kellerth (1965) alone and with Szumski (1966a, b) started a systematic study of the pharmacological argument in favour of presynaptic inhibition (Eccles *et al.*, 1963c) according

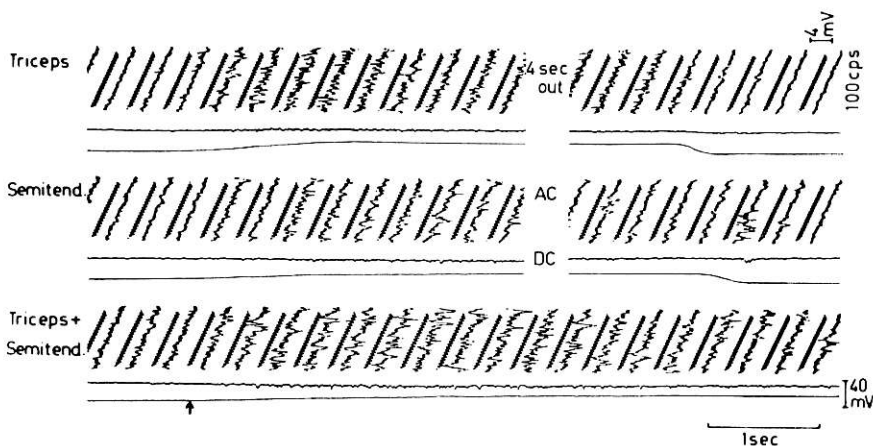


FIG. 8. Anaemically narcotized cat. Pentobarbitone 28 mg/kg. Popliteal motoneuron of about 75 mV spike height, membrane potential 65 mV. Activation noise recorded on sweep (a.c.) and standing spot (d.c.). The upper and middle records are controls with triceps (autogenetic) and semitendinosus (antagonistic). The lowermost record begins with the end of about 4 sec pull on triceps maintained throughout. At the arrow semitendinosus pull begins. Weight of 500 g used. *Note.* In this interference record hyperpolarizing activation noise of semitendinosus is more prominent than in the control. *Note* also "spiky noise" to triceps pull as well as wavelets. (Granit, Kellerth and Williams, 1964a.)

to which it can be differentiated by strychnine or picrotoxine from postsynaptic inhibition, adding to this study the criteria discussed above. Kellerth reported the results at last year's Nobel Symposium (Kellerth and Szumski, 1966c) and will add something today, but, briefly, the outcome was that strychnine and picrotoxin proved excellent also for differentiating two kinds of postsynaptic inhibitions from muscular afferents. All this work led us to the standpoint that the motoneuron aspect of the evidence for presynaptic inhibition, problems of membrane excitability, etc. still left something to be desired and that possibly our fault had been that we have used desynchronized natural stimuli such as stretch and contraction. But these are, of course, the

ones motoneurons handle in real life. To be sure, Devanandan, R. Eccles and Yokota (1965a, b) had used brief practically instant stretches but these also give synchronous effects and then Green and Kellerth (personal communication) detected signs of postsynaptic inhibition also in their records. The work of Nelson and Frank (1964), Nelson (1966) and that of Grinnell (1966) has recently taught us that there still is something to learn about the effect of synchronous stimuli on motoneurons. On that part of the evidence for presynaptic inhibition, which hitherto has been considered, the case for synapses on the synapses of the motoneurons does not seem to be convincingly supported, nor has this variety of inhibition as yet been found with natural desynchronized firing from muscular afferents.

Primary afferent depolarization, PAD for short, is the postulated effect at the terminals caused by the synapses on the synapses of motoneurons. To record PAD intracellularly "has been possible only in the dorsal region of the cord, where the fibres are rather coarse" (Eccles, 1964) and there it seems to average 0.50 mV in 34 experiments with the posterior biceps-semitendinosus nerve conditioning the large spindle afferents (Willis, Thesis, 1962). Other combinations gave lower averages. By hypothesis the PAD is supposed to arise at the site of the synapses upon the synapses and there to be large enough to make the spike undergo a really significant diminution decreasing its synaptic stimulus value. Wall (1962, 1964), on the other hand, suggests that the entrance region of the dorsal rootlets in the substantia gelatinosa is the site of the PAD. This location of the process makes some sense out of the correlation with the dorsal root potential of Barron and Matthews (1938), rather a diffuse multi-fibre event for comparing with the extreme variability of afferent effects upon single motoneurons. A serious argument against the idea of the PAD being generated at the motoneuron end seems to me that the initial depolarization of the terminal synapses should lead to an initial increase of excitability of the motoneuron. Such an effect has never been reported. The case for and against making the synaptic effect dependent on the size of the prespike could also be profitably discussed but hardly as long as there is complete absence of data from motoneuron experiments. Kuno's (1964a, b) results suggest complications which could be considered in the discussion.

An argument in favour of the notion that the PAD originates at the motoneuron end of the afferent fibres has been developed by Eccles *et al.* (1963a) by Wall's technique (1958). This consists in stimulating by a relatively coarse extracellular microelectrode at different depths in the spinal cord and recording the antidromic volley in the afferent fibres which is augmented by PAD. The size of the antidromic volley plotted against depth in the cord was found to be maximal at about 3.5 mm. Sometimes there was a second maximum at about 2.5 mm which is the intermediate nucleus where Eccles, Eccles and Lundberg (1960) also had found a projection of the large muscular afferents.

I refer to Wall's criticism of this argument on anatomical grounds (in Discussion of Eccles, 1964), based on the work of Szentágothai. It seems to me that fibre density, electrode distortion and degree of myelination should also influence the threshold and these factors are unknown. In addition field potentials may support electrical stimulation (Nelson, 1966).

There is finally the experiment of Green and Kellerth (1966) which I trust Dr. Kellerth will report at this Symposium. Briefly, theirs was a situation inviting presynaptic inhibition to play its role in that ankle extensor motoneurons were inhibited by stretch of semitendinosus. This inhibition was equally potent when the cell was fired from the tip of the intracellular microelectrode and when it was discharged by ankle muscle stretch producing the same original rates of firing. In the latter case only, had the impulses traversed supposedly depolarized terminals. The difference between the two situations was non-existent. In both cases there was precisely the same amount of postsynaptic inhibition. One is of course free to assume that, in establishing the original firing rate by stretch of the ankle extensor presynaptic inhibition had done its work and that, accordingly, the semitendinosus-impulses were transmitted through fibres partially recovered and thus leaving for attack only postsynaptic inhibitions at the membrane. This explanation means that presynaptic inhibition is negligible in maintained afferent firing. Alternatively one may assume that semitendinosus stretch does not produce presynaptic inhibition, only the postsynaptic variety demonstrable by a large number of criteria, as pointed out above. The second explanation cannot be refuted and means that a considerable amount of work needs to be done before we have discovered the natural stimuli capable of imitating the specific effects which muscular afferents produce when synchronous shocks are applied in the manner used for elucidation of presynaptic inhibition on the motoneurons.

To sum up, my criticism has followed two lines. One has been concerned with the difficulties encountered in measuring motoneuron excitability by its intracellularly recorded EPSP or response to brief electric shocks, the other more directly with the notion of synapses upon the synapses of the motoneuron. With regard to the sum total of the evidence and the correlations established with dorsal root and cord potentials making use of synchronous stimuli I definitely feel the need for an explanation. The discussion that has given me the greatest satisfaction up till now is that of Wall (1964a) making use of a common system but placing it at the zone of entry of the dorsal root afferents. But I hope that participants at this meeting will put forth alternative and, perhaps even better, suggestions.

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