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GRANIT, R.: **Circuit analysis of postural reflexes and the relative significance of alpha and gamma motoneurones.** — *(Nobel Institute for Neurophysiology, Karolinska Institutet, Stockholm 60, Sweden.)*

Recent work (summarized, Granit, 1955, 1957) has led to some conceptual advance in a field that, broadly speaking, might be specified by the general heading "motor control" and, more particularly, may be said to deal with the way in which the muscle sense organs are governed and themselves, in their turn, control movement. The experiments aim at visualizing certain neural circuits, intercepting them at various points and thus analyzing them in detail. Much of this research has centered on the classical circuit of Sherrington's stretch reflex. The hope sustaining these efforts is that the principles which emerge will be found useful elsewhere in the central nervous system where the experimenter is at greater disadvantage. In the stretch reflex he can sample the input in its dependence upon sense organs activated by natural means, he can study the output in both ventral roots and muscle whose reflex contraction must be a consequence of the sensory input, modified by commands from higher centres. There is also an interesting system of efferent feedback, the recurrent collaterals of Golgi (Renshaw, 1941, 1946), by no means unique –since Cajal described recurrent collaterals in most nervous centres– but the opportunity for analysis has proved unique and has been utilized to extract first principles. Furthermore, the muscle spindles are sense organs controlled by the central nervous system including the brain. Their level of excitability can be raised or lowered at will and so we have an opportunity of studying principles of central selection guided by input in terms of spike frequency and output in terms of movement and spike frequency.

Let us begin by recalling that it now has been definitely proved that the mammalian alpha motoneurones are of two kinds, phasic and tonic ones (Granit, 1956; Granit, Henatsch & Steg, 1956; Eccles, Eccles & Lundberg, 1957 *a*, *b*, 1957; Granit, Phillips, Skoglund & Steg, 1957), an organization reminiscent of the one seen in amphibians (Bremer, Bonnet & Moldaver, 1942). This subdivision refers to ordinary or extrafusal muscle. Until recently we used to think of the motoneurones for the muscle spindles' intrafusal muscles as being of one kind only, the small gamma motoneurones maintaining a tonic intrafusal contraction by repetitive firing in their thin efferent fibres. We have now completed experiments (to be reviewed below) which show that there is also a phasic mechanism of spindle activation, clearly based on alpha neurones (Granit, Pompeiano & Waltman, 1959 *a*, *b*). Thus we have to consider four principal pathways of control of movement from the spinal cord and higher stations, two destined for the extrafusal fibres and two for the intrafusal fibres of muscle. Since the fibres for intrafusal muscle exercise their control across a loop through the sense organs (the muscle spindles), which are in parallel with the ordinary or extrafusal motor fibres, great flexibility is ensured and much experimentation is required to find out how the organism utilizes the degrees of freedom allowed by the circuits layed out as described.

By now a basic structure of knowledge exists which may be said to have accounted reasonably well for the tonic stretch reflex though many details remain to be worked out. Phasic movement and phasic spindle control present a challenge that just has been taken up. It is therefore best to begin with a brief synthetic presentation of tonic control and to end by giving the evidence for phasic control and, finally, to discuss its implications.

All previous theories trying to explain decerebrate rigidity on the basis of release of the alpha motoneurones from cerebral inhibition failed in one fundamental respect: they could not account for the simple fact found by Sherrington that rigidity disappeared upon de-afferentiation of the limb. Why should the released alpha neurones require support from the stretch receptors? The modern work has solved this dilemma (Eldred, Granit & Merton, 1953; Granit, 1955; Henatsch & Ingvar, 1956; Matthews & Rushworth, 1957; Matthews, 1958). By interrupting the afferent input one also interrupts the gamma loop. This is tonically activated from the centre and thereby maintains a likewise tonic state of contraction of the spindle's intrafusal fibres which pull on the sense organ in the equatorial region and keep it discharging impulses up to the ventral horn cells of the same and synergist muscles. The spindles are a device for measuring muscle length and governing it at the same time. The gamma hyperactivity of the decerebrate preparation shortens the spindle by intrafusal contraction. The impulses discharged from it to the alpha ventral horn cells force the muscle to contract until the extrafusal component has adjusted itself to the length of the intrafusal component of the spindles. By this extrafusal contraction the spindle is unloaded, pull on the equatorial bag diminishes and the sense organ's firing frequency runs down. This new state of balance of intra — and extrafusal muscle outwardly takes the shape of increased tension or rigidity.

In sum, the decerebrate preparation of Sherrington has a strong component of gamma release. A good case can be made out for the localization of the most important point of release to the facilitatory motor region of Magoun & Rhines (1947) within the reticular formation (Granit & Kaada, 1952; Eldred & Fujimori, 1958). Theoretically we could imagine the case in which only the alpha system and not the gamma system is subject to release. The nearest approximation towards this state of affairs are the cerebellar rigidities (Granit, Holmgren & Merton, 1955; Matthews, 1958) which are well summarized in the important work of Dow & Moruzzi (1958). There is also in decerebrate rigidity a suppression of the inhibitory inflow from muscle receptors to interneurones (Job, 1953) discussed by Lundberg in his contribution to this symposium.

Considering next the stretch reflex of the decerebrate preparation as a typical specimen of a reflex run by the small tonic alpha motoneurones, mentioned above (cf. Liddell & Sherrington, 1924; Denny-Brown, 1929), it has proved possible to define a simple relationship between extension in mm and gram reflex tension (Granit, 1958; Matthews, 1958). The general rule is that reflex tension in gram is directly proportional to mm extension, or, in other words, the myotatic loop gain across the spinal cord is constant. With but a few alpha neurones activated by stretch the loop gain (the said constant) is small, again, with many motoneurones available (owing to sufficient cord excitability) loop gain is large. Values in different preparations may run from 20 to over a 100 gr/mm for this constant. It is not the first time in biology that the net result of a number of complex governed processes emerges in relatively simple terms.

Let us next assume that in any particular decerebrate animal one has plotted the straight line of the tension/extension diagram whose slope is the myotatic gain constant. One then proceeds (Matthews, 1958) to remove the tonic activity in the small gamma fibres by cocainization according to the method of Gasser & Erlanger (1929) who first showed that small fibres are attacked by cocaine in advance of large ones. By applying this method Matthews found that the slope of the curve relating tension to extension did not alter significantly. What happened was that the curve shifted to the right in the tension/extension plot, meaning that one had to pull the muscle further out to obtain the same amount of reflex tension. In many animals the reflex altogether disappears. This means that removal of gamma activity, with consequent slackening of the spindles, alters merely the threshold of the stretch reflex, not the fundamental property of the spinal cord to act on the principle of constant loop gain, a property in which it reminds one of an amplifier, provided one has a taste for electrical analogies.

Now, why does the stretch reflex as a

function of extension of muscle behave in this relatively simple fashion? Let us first consider what happens to muscle itself as it lengthens. Tension, as should be well known, is a function of length. The experiment (Granit, 1958) showed that a tonic fairly parallel-fibred muscle such as soleus responds to an unfused tetanus by producing static tension in direct proportion to its length. Thus, if the natural tonic stimulus in the stretch reflex were an unfused tetanus at constant strength and frequency (whereby 'strength' has its reflex counterpart in number of motoneurones), one would obtain the very result briefly referred to as constant loop gain. Of course, if the stretch reflex made use of a mechanism of frequency, meaning that, as the muscle is extended, each motoneurone discharged at higher frequency, then this rule would not hold, because changes of tetanic stimulus frequency have very strong non-linear effects on the amount of tension developed. However, Denny-Brown (1929) long ago showed that it is characteristic of the individual motoneurones in the stretch reflex to fire at constant frequency independently of muscle length and this has been confirmed (Granit, 1958).

Thus, with a constant number of motoneurones activated in static stretch the theoretical result would be the one actually obtained, i.e. constant gain. Or to put it into practical terms, we could stand and counteract gravity merely by maintaining a constant number of alpha motoneurones mobilized, provided that we kept the muscle spindles of these antigravity muscles well excited. This need not mean that we normally do stand that way utilizing merely gamma motoneurones and a constant group of alpha neurones leaving the rest to the mechanical properties of muscle. But we may. Thus Ralston & Libet (1953) conclude that standing in man merely consists in minor tonic adjustments of the forces around joints which are needed to set the supporting bony structures correctly. Joseph, Nightingale & Williams (1955 with references) have found tonic activity by electromyography. The research on animals, does not, in the first instance, feel itself under an obligation of doing more than demonstrating degrees of freedom obtainable with certain circuits when they are tested from definite points of view. The work can only proceed in steps and this is one such step. Also, unless allowed some scope for use of simplification (with a measure of common sense), research cannot proceed at all.

Before going on to demonstrate that the same net result, i.e. constant loop gain, may be obtained also with the process known as Sherrington's recruitment, let us consider the curious fact that many, if not all motoneurones in the stretch reflex fire at constant frequencies. Anyone who has seen a textbook in physiology knows that stretch receptors such as muscle spindles fire the faster, the more the muscle is stretched. In static stretch, with which we now are concerned, the discharge frequency is actually proportional to extension (Eldred, Granit & Merton, 1953; Granit, 1958; Whitteridge, 1958; Granit & Homma, 1959), again a simple linear relationship, not badly obeyed either. So why should not the greater input at greater muscle length drive the individual motoneurones in the spinal cord at greater frequencies?

Two answers have been provided to this question which is of fundamental importance because many of those who theorize about the central nervous system are inclined to assume implicitly that high input frequency to a cell automatically leads to high output frequency. One answer comes from the experiments of Eccles, Eccles & Lundberg (1957 *a*, 1958) who have shown with the intracellular technique of recording that the tonic ventral horn cells of soleus have especially long after-hyperpolarizations during which excitability is depressed. This will force them to discharge at slow frequency. Another comes from the experiments of Granit, Pascoe & Steg (1957) who found that the recurrent collaterals exercise their inhibitory effect especially upon the tonic alpha motoneurones and that this inhibition is cumulative in nature signifying that the greater the output frequency, the more inhibition mounts up. Consequently a cumulative process of self-strangulation of output frequency is constantly at work. The long after-hyperpolarization is counteracted by the membrane depolarization caused by the discharge following pull on the muscle, but the recurrent inhibition is independent and can never be counteracted by such means provided the activity lasts long enough to give the cumulative properties of this inhibitory circuit a chance. Thus the static stretch reflex is a state of balance between the gamma-controlled input from the muscle spindles and recurrent inhibition on the output line. This can be maintained only if the recurrent inhibition working through the Renshaw cells, as elucidated by Eccles, Fatt & Koketsu (1954), steers clear of the small gamma motoneurones. Granit, Pascoe & Steg (1957) tested this point and found that recurrent inhibition had no effect whatever on the gamma motoneurones. The Renshaw cells have recently in a skilful piece of anatomical research been localized to the ventral horns by Szentagothai (1958).

The heavy stabilization of output frequency of individual motoneurones in static stretch forces them to fire at such low frequencies that the muscle all the time oscillates, as is easily demonstrated with stretch reflexes in decerebrate rigidity. The tense spindles respond to this by irregular oscillations which probably makes them more efficient in stimulating the ventral horn cells, to judge by the fact that, whenever one supplants steady pull by oscillatory stretch, the motoneurones become more active (Granit, Phillips, Skoglund & Steg, 1957). The reason for this is not fully understood. It has been suggested that the spindles produce higher average frequencies when they are stimulated by irregular oscillations (Granit, 1958).

Hitherto we have assumed that the frequency of discharge of the muscle spindles is a linear function of extension, also when the spindles are under gamma control. This function actually is known for soleus. For the animals used in the study of reflex tension as a function of extension an average curve for impulse frequency (20 soleus spindles) against extension was plotted and found to give a slope of only 3.5 impulses per mm. The increase in frequency of discharge is therefore of a modest order and the main effect of the tonic gamma activity in soleus is not on slope, but on level of the curve for spike frequency against extension, i.e. there is a considerable basic discharge at zero extension so that this curve starts from a high level. When extensions reach 10 mm or thereabout the average curve approaches a constant level and in individual spindles frequency even may fall at high extensions (Granit, 1958). Now it is known that the activity of the gamma motoneurones is modified by inhibition from tension-sensitive receptors inside the muscle (Hunt, 1951; Eldred, Granit & Merton, 1953; Buller & Dornhorst, 1955). This effect is held to explain why soleus spindle frequencies refuse to rise higher at great extensions. When tension rises high enough to activate inhibition it overcomes excitation.

It was stated above that if the output in the stretch reflex were constant, the latter would increase linearly with extension and that would be a simple way of balancing out antigravity forces on the basis of properties of muscle with no more nervous effort than would be required to keep the tonic gamma activity going. The work by C. von Euler & Söderberg (1957) shows that the activity in the gamma system closely reflects variations of wakefulness in an animal kept by light anaesthesia on the margin between sleep and wakefulness. Thus the condition that the gamma system should be kept going is automatically fulfilled in the normal active state of an experimental animal.

However, it is well known (Denny-Brown, 1929) that in the decerebrate animal the stretch reflex recruits new neurones, the more the muscle is pulled upon. Even if, as we have seen, present evidence suggests that each of these neurones is held down to a low, reasonably constant frequency, the augmentation in number of activated neurones will make the slope of the curve in the tension/extension diagram rise the more, the greater the pull. The state of decerebrate rigidity is, as Sherrigton used to emphasize, an exaggerated posture. Most of the animals that are used in work on the stretch reflex are likely to be of the recruiting type. Yet in them, too, the reflex tension is proportional to extension.

Recent work by Matthews (1958 and 1959 in course of publication) demonstrates that, as found by Denny-Brown (1929, confirmed by Granit, 1958), there is considerable recruitment in the stretch reflex of an active decerebrate cat. In his, as well as in my own work, a linear relation between tension and extension again proved to be a reasonably adequate summary of the findings. Whereas in my opinion this suggests that some of his and my animals recruit fresh motoneurones linearly on account of the linear input from the spindle afferents, discussed above, Matthews is inclined to explain the linear relation in this particular case as a state of balance largely determined by inhibition from the Golgi tendon organs as a counter-force. This may be so, but it is necessary to remember that in the decerebrate animals the afferent input from these organs is suppressed (Job, 1953). Indeed, the work of R. M. Eccles & Lundberg (1957) as well as later work by Lundberg (reviewed by Lundberg in this symposium) shows that all kinds of inhibition from muscle afferents are suppressed in the decerebrate state, (in which the recurrent inhibition is at full play).

The constant loop gain may be regarded as a landmark from which further research can set out to investigate the two degrees of freedom defined by present data, constant *versus* recruiting output. The third possibility, increase of frequency in individual neurones, was as we saw prohibited. As stated, the essential point of my approach has been to try to fix the degrees of freedom on the output line while investigating the factors that determine them. Finally, it is necessary to realize that reflex work is not strict enough for precise calculations of mathematical formulas. Often the reflex tension/extension curve at small extensions rises at one slope and beyond a certain degree of extension at another much steeper slope as if a constant output had been replaced by a recruiting one (cf. also Matthews, 1958, 1959).

So far we have only dealt with tonic motoneurones of the gamma and alpha variety and the static stretch reflex which is a slow oscillatory contraction run at low, stable frequencies. One, who like myself, has followed this field for a long time cannot suppress a feeling of satisfaction when seeing how the later additions to the solid basic structure, erected by Sherrington, Liddell and Denny-Brown, have revealed more of the architectural design. Much has come from the deeper understanding of gamma control, experimental as well as conceptual. Let us hope that tension/extension diagrams can promote further advancement.

Now, early in contraction, is the intrafusal control doomed to silence? Is it too slow to be of any significance? In some experiments (Granit, 1950) I stimulated cut ventral roots to set up contraction and by monosynaptic testing studied the effect of the afferent input from the contracting extensor muscle. It was found that its motoneurones first were facilitated and then suppressed at the height of contraction. It was concluded that afferent control was organized so as first to facilitate and then to exercise a damping effect on contraction. We need not now consider the later suppression which I have discussed at some length elsewhere (Granit, 1955). The early facilitation, however, was so fast as to have to be caused by the large spindle afferents. Hunt & Kuffler (1951 *b*) studied this early inflow from muscle spindles to the ventral horn cells and arrived at the conclusion that in this phase of contraction the spindles responded to the rise of tension before a tension rise is seen in the myogram, a surprising conclusion, if generally true, since spindles are defined as organs unloaded by contraction and hence silenced. Only with rare freakish insertions could they be expected to discharge to extrafusal tension. Hunt & Kuffler felt, however, that they had excluded the alternative explanation, namely that some spindle efferents were fast enough to produce an intrafusal cocontraction, a kind of 'positive feedback' in the now so popular terminology. There were other factors to consider; Lloyd (1941, 1942) and Leksell (1945) had shown that there was an early 'back-response' from synchronously stimulated muscle and Lloyd, in particular, had convincingly demonstrated that ephaptic stimulation by the muscle action potential does occur. However, some of my experiments (Granit, 1950) were carried out with slowly rising currents so as to exclude synchronous stimulation (e.g. Fig. 9, p. 359). Yet the early facilitation remained.

At the moment, therefore, we have three major theories that need to be considered: 1) the ephaptic theory of Lloyd, 2) the tension theory of Hunt & Kuffler and 3) the innervation theory which assumes that there is fast enough activation of intrafusal muscle fibres to make the spindle discharge early in contraction. There is a considerable amount of anatomical support for the innervation theory in observations that suggest the existence of intrafusal efferent fibres larger than the gamma fibres (Cilimbaris, 1910; Garven, 1925; Barker, 1948; Cooper & Daniel, 1956). There are also observations by Boyd (1959), as yet only in preliminary form, in which he postulates the existence of special intrafusal twitch fibres. Two different types of motor ending have been described by Cooper & Daniel (1956), confirmed by Boyd (1959) in degeneration experiments. Finally, Pascoe (1958) has differentiated two types of spindle efferents only one of which definitely falls within the gamma range. The other one is differentiated by not being inhibited in stretch (Hunt, 1951).

To investigate this problem it seemed a sensible beginning to stimulate central stations by long shocks (2 msec) setting up non-synchronous bursts in the ventral root fibres and to measure the time of arrival of the first spike from the isolated ankle muscle to a thin dorsal root filament. In describing the results I shall quote two papers by Granit, Pompeiano & Waltman (at the moment in the press). It was soon found that with a considerable number of isolated spindle afferents an early discharge occurred at the foot of the small muscle contraction that it proved possible to elicit from the medullary pyramids by such means. There were other places from which the same result was obtained, places in the reticular formation, the medial longitudinal fasciculus and Deiters' nucleus, in the latter instance with quite a large contraction of hind leg ankle extensors. It is well known that the gamma system can be stimulated from sites in the same general regions. This, however, occurs without activation of the ordinary or extrafusal muscle fibres (Granit & Kaada, 1952; Granit & Holmgren, 1955; Eldred & Fujimori, 1958), in fact it has been a major ambition of the workers quoted to create conditions in which selective gamma stimulation could be demonstrated.

The gamma activation of the spindles from the brain stem generally has required times from a minimum of 18 msec to more common values between 20 and 24 msec, counted to the moment when the spike appears in the dorsal root afferent that was isolated. The corresponding values in the fast activation just described range from 11 to 16 msec. These short times are remarkable because they are of the order necessary for activation of the gamma circuit directly, from the very much shorter distance of the ventral root (Hunt & Kuffler, 1951 *a*; Kuffler, Hunt & Quilliam, 1951; Granit & Holmgren, 1955). Also gamma activation, as hitherto studied, is slow. Boyd (1959) observing spindles in the cat's tenuissimus muscle under a microscope has seen the slow intrafusal contraction. Thus, disregarding for the moment the nature of the nerve fibres concerned, it is clear that fast activation is a mechanism in its own right, capable of starting at the time when extrafusal contraction begins.

We thus arrive at the conclusion that there exists a fast mechanism of spindle activation behaving in every respect as if it were a co-contraction of intrafusal fibres timed to operate with the extrafusal ones. This conclusion makes it imperative to analyze the early discharge from spindle afferents, as elicited by shocks to the muscle nerve or a ventral root. Was the tension theory really as firmly established as to exclude both ephaptic activation and an innervation theory? Was the phenomenon of "early discharge" really homogeneous? Our results soon showed that the ephaptic theory of Lloyd held good for the earliest spikes arriving at the dorsal root but gave no evidence whatever in support of a tension theory to explain the slightly later spikes that occurred, as in the previous experiments, at the foot of the contraction. We shall now consider the nature of this evidence.

Hunt & Kuffler (1951 *b*) treated the early discharge as a homogeneous event. By comparing flexors, such as tibialis anterior and extensor longus digitorum with the two extensors, gastrocnemius and soleus, it proved possible in our work to distinguish the early ephaptic spike from the genuine physiological burst at the foot of the contraction. The ephaptic spike which is started by the muscle action potential —like the latter— occurs before contraction has become visible in the myogram. This spike was rare in the flexors and common in the extensors, the reason probably being that the motor fibres enter the two flexors spreading fan-like over a large distance while in soleus and gastrocnemius, especially in the former, there is a definite region in which the motor end plates are concentrated, as pointed out by Eccles & O'Connor (1939) who for this very reason used soleus for their studies of the muscle action potential. This muscle, too, has the greatest proportion of ephaptic spikes. Furthermore, the ephaptic spike can be differentiated by using high frequencies of stimulation. It then follows stimulus frequencies from 130 to 200 per sec, occasionally more (Lloyd, 1942), while the genuine early spike, so easily separable from the ephaptic spike in the flexors, could not, as a rule, be made to repeat itself at frequencies above 25 per sec. The ephaptic spike often wholly dissappears in the extended muscle while the physiological early spike, if influenced at all by extension, tends to be slightly favoured, in agreement with the notion that extended spindles are more sensitive to phasic changes than slack ones. The ephaptic spikes could always be elicited in slack muscle (unhooked from the isometric myograph), provided that sufficiently strong shocks were used.

The case of slack muscle proved particularly interesting to analyze because the early spikes in flexors generally failed to turn up under such circumstances (unless they were ephaptic and these were very rare). Our conclusion that this was because of insufficient gamma bias proved correct. By a variety of stimuli known to influence the gamma system selectively, slack flexor spindles could be made to fire an early spike, clearly therefore without requiring any extrafusal tension. An intrafusal contraction produced by gamma stimulation pulls up the muscular poles of the spindle and so sensitizes it for phasic activity by extending the equatorial region containing the nuclear bag with its sense organ (Granit & Henatsch, 1956). In other words, it produces the same effect as extension of the muscle which alternatively could be applied to produce an early spike when none was visible in the slack state.

Spindles are in series with intrafusal muscle just as Golgi tendon organs are in series with extrafusal ones. Accordingly both organs, on the innervation theory, should behave similarly, and this is what they do, provided one has excluded the ephaptic spike which also with tendon organ afferents (isolated in the root) can be made to disappear when the muscle is sufficiently extended. Times of activation are of the same order for the two tension recorders, and, when we now call the spindle a tension recorder, it should be observed that this is relative to its own intrafusal muscle. Relative to extrafusal muscle with which it is in parallel, the spindle is a length recorder, that measures the difference between intra-and extrafusal length.

It is not necessary to deal with Hunt & Kuffler's experiments on root division because they did not distinguish between the ephaptic spike and genuine fast activation. They apply their tension theory to a spike in advance of visible contraction. This, in our experience, is practically always an ephaptic spike and therefore of little functional interest. The ephaptic spike requires a good synchronous shock and so it disappears in subdivided roots and reappears when the subdivisions are put together. For a detailed analysis of root division the papers referred to should be consulted.

Finally, an analysis was carried out with the aid of Flaxedil which paralyzes extrafusal muscle long before the gamma end plates are paralyzed (Granit, Matthews & Homma, 1959). Fast activation, however, is very sensitive to Flaxedil and so must be based on a different mechanism. It can be reactivated by post-tetanic potentiation and then lingers on for a while in considerable independence from extrafusal tension but favoured by extension.

Thus it is concluded that both in extensors and flexors there is a genuine mechanism for fast activation of muscle spindles —seen in some 40 % of the flexors— which to all appearance behaves as if extra- and intrafusal muscles were cocontracted. This is the "positive feedback" described in the early paper referred to (Granit, 1950). This mechanism does behave as if it were an intrafusal twitch but comparisons with the observations of Boyd (1959) and Pascoe (1958) will have to be postponed till their results have appeared in full. Measurements of conduction velocity based on comparisons of root and nerve stimulation show that the fibres concerned are faster than the gamma fibres of Leksell (1945). Further study of various reflexes from the point of view of fast spindle activation is required before we are ready to discuss its role in motor control. It is now only possible to state that this mechanism definitely is put in operation from central stations capable of exciting extrafusal muscle.

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