

J. Physiol. (1956) 131, 32-51

REFLEX REBOUND BY POST-TETANIC POTENTIATION.
TEMPORAL SUMMATION—SPASTICITY

BY RAGNAR GRANIT

From the Nobel Institute for Neurophysiology, Stockholm 60, Sweden

(Received 25 April 1955)

The two phenomena of post-tetanic potentiation and reflex rebound are in this paper brought to a common focus created by the general working hypothesis that under certain circumstances they would have a common denominator in temporal summation. It is assumed that post-tetanic potentiation is a basic, if not the basic, process in temporal summation. If this be true, it should be possible to design an experiment in which rebound is produced by post-tetanic potentiation. The paper reports such an experiment.

Before stating the problem it is necessary to recall briefly what is meant by post-tetanic potentiation and by reflex rebound.

Post-tetanic potentiation is a state of residual presynaptic facilitation which is common to most synaptic junctions so far examined. In muscle, facilitatory after-effects of a single shock or a tetanus have been known from the early days of electrophysiology, and this problem was one of the main themes of Lucas's classical monograph (1917). In 1937-41 Feng and his collaborators (Feng, 1937, 1941; Feng, Lee, Meng & Wang, 1938) gave a particularly lucid account of the neuro-myal potentiation, and separated it from purely muscular effects (cf. Brown & v. Euler, 1938). Larrabee & Bronk (1947) described post-tetanic facilitation in the sympathetic neuro-neural junction in terms similar to those of Feng, and Lloyd (1949) found it in the monosynaptic path to the ventral horn cells. Eccles (1953) has summarized later developments. Potentiation in the neuro-myal junction has since been studied in the motor end-plate by Castillo & Katz (1954*a, b*). There, just as in sympathetic ganglia (Larrabee & Bronk, 1947; Job & Lundberg, 1953), it is seen even after a single impulse, which need not set up any change in the end-plate potential (Castillo & Katz, 1954*a*), so that the process probably operates preterminally above the site of release of acetylcholine (cf. also Lloyd, 1949; discussion by Eccles, 1953; and a recent summary by Fatt, 1954).

With the neuro-neural junctions it has been established that the residual facilitation following a tetanus is restricted to the synapses tetanized (Larrabee & Bronk, 1947; Lloyd, 1949; Ström, 1951; Eccles, 1953) and rigorous tests described in recent papers (Jefferson & Benson, 1953; Job & Lundberg, 1953; and particularly Beswick & Evanson, 1955) have supported this view. The potentiation is also present in polysynaptic pathways (Lloyd, 1949; Hagbarth & Naess, 1950; Eccles, 1953), but all workers find it far more potent in the monosynaptic, a fact which may be partly a matter of accessibility to testing. In complex pathways a multitude of factors may also combine to obscure it. Within limits post-tetanic potentiation is favoured by a high frequency and a long duration of stimulation.

Reflex rebound is a technical term for a centrally determined rise of excitability after cessation of stimulation and need not be a single homogeneous process. Sherrington (1913) pointed out that electrical stimulation of a mixed nerve with a dominant inhibitory effect often led to rebound and, on the whole, seems to have been inclined to regard this post-inhibitory rebound as a neurological entity in its own right. The diagram of Fig. 1*a* illustrates one widely accepted explanation of post-inhibitory rebound (see, for example, Forbes, 1922). It is seen that, because of the assumed properties of excitation *E* and inhibition *I*, algebraical summation will lead to inhibition during stimulation followed by post-inhibitory rebound of excitation afterwards. This raises the question of how and where excitation was concealed during stimulation and presupposes excitatory after-discharge stored in specific neurones or 'delay paths' (Forbes, 1922) for delivery at the appropriate moment. For the retinal off-effect different views have been proposed (Granit, 1955).

On the hypothesis to be examined below, residual facilitation stored pre-synaptically in the junctions tetanized should also lead to rebound. An attractive consequence is that, with the site of 'storage' defined, one of the complex phenomena of rebound would have been reduced to a well-known process accessible to analysis in precise terms. As stated above, rebound is merely a descriptive term which may cover a variety of phenomena. It will therefore be necessary to select specific cases and test them with the aid of reasonable working hypotheses, such as the one suggested.

In the case to be examined, stretch of a leg extensor provides the mixed input of impulses causing inhibition and excitation of the muscle itself. All the sensory endings causing inhibition have polysynaptic connexions, but among those causing excitation are the muscle spindle's nuclear bag endings (annulospiral, primary endings, or A2) whose monosynaptic arcs can so easily be potentiated by tetanization of the muscle nerve (for a review, see Granit, 1955). Cessation of stretch should therefore lead to post-tetanic residual facilitation of the monosynaptic excitatory pathway, rising and falling along

a characteristic curve, measurable by monosynaptic testing. This effect should be enhanced after a tetanus to the muscle nerve.

Excited spindle afferents may respond to stretch by frequencies as high as 300 per sec (Eldred, Granit & Merton, 1953). Post-tetanic potentiation is obtained at very much lower frequencies. By electrical stimulation the optimum potentiation requires 10–12 sec of tetanization at a rate of 280–300 per sec (Lloyd, 1949).

METHODS

The commonest preparation was the decerebrate cat,* but decerebrate-low spinal cats and some cats under pentobarbitone were also used. In the de-efferented preparations all ventral roots from L5 or L6 to the end of the cord were cut. When some γ efferent excitation of the spindle was desired, L6 and L7 were left intact, the monosynaptic test response being recorded from S1. The spinal cord was covered by warm paraffin in the customary way. Often a muscle spindle afferent fibre was isolated in a root to serve as frequency indicator for the spindle discharge. Fig. 1*b* illustrates the arrangement for monosynaptic testing. In the hind-leg, which was denervated

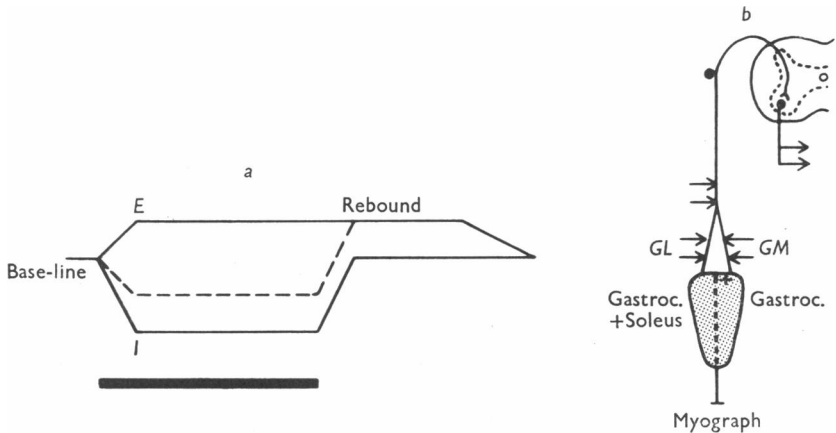


Fig. 1. *a*, diagram illustrating algebraical summation of excitation *E* and inhibition *I* leading to rebound of *E* after cessation of repetitive stimulation as indicated in the text. *b*, afferent path from gastrocnemius lateralis, *GL*, innervating soleus and lateral head of gastrocnemius muscle, and from gastrocnemius medialis, *GM*, innervating medial head. Pairs of arrows pointing outwards and placed on cut ventral root show site of recording of monosynaptic test response. Sites of stimulation: arrows point inwards.

except for the nerve to the ankle extensors, stimulating electrodes were placed on this nerve (*GL* + *GM*) and the muscle was attached to a strain gauge isometric myograph. Alternatively, stimulating electrodes could be placed on either branch (*GL* or *GM* in the diagram). If either or both branches were cut, this will be specifically mentioned in the text. The diagram illustrates the de-efferented preparation with recording electrodes on the cut ventral root. In a considerable number of experiments the soleus muscle was separated from the gastrocnemius.

The equipment used in this work was the same as that used by Eldred *et al.* (1953). New features were circuits for selecting predetermined periods of stimulation at desired frequencies. For tetanization the standard frequency was 420 shocks/sec. Testing was generally carried out at 2.7 sec intervals. By means of a switchboard any one of the four cathode-ray beams could be

* Decerebration generally took place in *thiogenal* anaesthesia which is short-lasting. This substance was kindly placed at my disposal by the makers (Merck, Darmstadt.)

selected to display any of the following events: monosynaptic test response, discharge from indicator muscle spindle, isometric myogram, time. Generally two beams were run alongside the film and two swept across it at the 2.7 sec interval (see Fig. 7).

The monosynaptic test for facilitation is based on the activation of neurones from the subliminal fringe; if many neurones are active, so that the fringe is small, there can be but a small increase of the number of recruited neurones above that of the control. For this reason it is necessary to supplement monosynaptic testing by other methods. The one used consisted in isolation of single fibres from the cut ventral roots in order to study their reflex activity under the conditions chosen. All experiments with single-fibre reflexes in the manner of Granit & Ström (1951) were carried out in de-efferented limbs.

The indicator spindle need not be representative of all the spindles in the muscle, but it does show whether the muscle receptors are in good condition during the whole experiment; it gives an indication of how and when the spindles come in after a tetanus to the muscle nerve (but antidromic for the spindles), and how this moment relates to the curve for post-tetanic potentiation. Also, if L6 and L7 are left intact, the existence of γ efferent excitation to the spindle and its disappearance after de-efferentation can be demonstrated in qualitative terms. Since S1 had to be used for monosynaptic testing and so much of the important ventral root supply for the ankle extensors is represented in this root (Sherrington, 1892; Jefferson, 1954) really high spindle excitation could never be contrasted with the state of no excitation. For tetanization, stimuli just above the threshold of the large muscular afferent fibres (and the α motor fibres) have to be used. Too strong shocks will stimulate the γ fibres and complicate the issue. In experiments with tense muscles, the muscle was generally released during tetanization so as to avoid excessive stretch of the elastic components.

RESULTS

Potentiation before and after cutting the muscle nerve

It has been established that, with optimal frequencies, tetanization times beyond 10–12 sec chiefly extend the duration of the facilitatory after-effect (Lloyd, 1949); these results were obtained with severed muscle nerves. In the present work the gastrocnemius-soleus muscle remained attached to its nerve which was tetanized. Typical results before and after severance of the muscle nerve are illustrated in Fig. 2. It is seen that the presence of active muscle has curtailed the duration of the potentiation (cf. Ström, 1951) even though, as in this case, the muscle was slack while the experiment was carried out. There was often a rise in the control monosynaptic response after section of the muscle nerves, but the particular experiment illustrated was chosen because this rise happened to be negligible. Potentiation times of the order described by previous workers were but rarely obtained before the nerve was severed.

Almost a corollary of this fact is that, without exception, potentiation has been found to last longer with slack muscles than with muscles under some initial tension (see Fig. 6). An increase of muscle tension augments the inhibitory inflow from muscle end-organs (Granit, 1950, since repeatedly confirmed), and so it seems reasonable to ascribe the curtailment of the potentiation period by impulses from muscular sensory endings to suppression of the number of subliminal-fringe neurones which by tetanization can be brought to liminal values. There are also inhibitory impulses from muscle

spindles (Hunt, 1953) which in a slack muscle, in good preparations, maintain a spontaneous discharge, particularly in the soleus. Thus, since post-tetanic potentiation is a *presynaptic* effect, which is tested with the aid of a *post-synaptic* reflex volley, part of the effect may well be concealed for purely experimental reasons (cf. below).

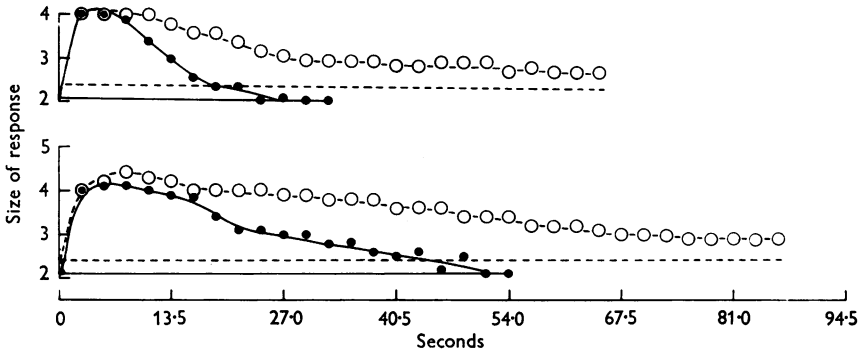


Fig. 2. Decerebrate cat, de-efferented hind-limb. Upper set of curves refer to tetanization for 2.1 sec, lower to tetanization for 10 sec, both at a rate of 420 shocks/sec. In this and successive figures zero time is at cessation of tetanization and ordinates show relative size of monosynaptic test reflex with control before tetanization marked by horizontal line. Ordinates in all figures are mm deflexion on film. The lines drawn in full (filled circles) show the course of post-tetanic potentiation from control line drawn in full and refer to stimulation of intact gastrocnemius-soleus nerves (muscle slack). The set of curves (open circles) in broken lines were obtained 15-30 min after severance of the muscle nerves which led to rise of control level to that of broken horizontals.

Tetanizing the nerve with its muscle attached made it possible to observe simultaneously the potentiation in both muscle and spinal cord. In Fig. 3 the myographic and monosynaptic responses are illustrated together. Both are potentiated in a roughly parallel manner and this, in fact, is very often observed. The arrangement is convenient for the analysis of agents which remove or emphasize potentiation and has been used to demonstrate (Granit, unpublished) that both neuro-myal and neuro-neural potentiation are depressed, e.g. by the anti-spastic drug myanesin (Berger & Bradley, 1946), tried because of the general theory that post-tetanic potentiation is an essential factor in temporal summation.

Addition and facilitation of potentiations

Since, in these experiments, afferent impulses set up by muscle stretch followed tetanization of the nerve, it was an important preliminary to find out what happened when brief potentiations were added by themselves, the muscle being kept slack. The control potentiation curve of Fig. 4 (extreme left) is an average of the four curves, obtained after 2.1 sec tetanizations, which were interposed between the individual experiments illustrated in the figure. This

control curve serves as a base-line for three additional 2.1 sec tetanizations (black oblongs) superimposed, one at a time, upon the potentiation due to the first one. As was expected, there is a further rise in the early portion of each potentiation curve which diminishes with distance from the first tetanization.

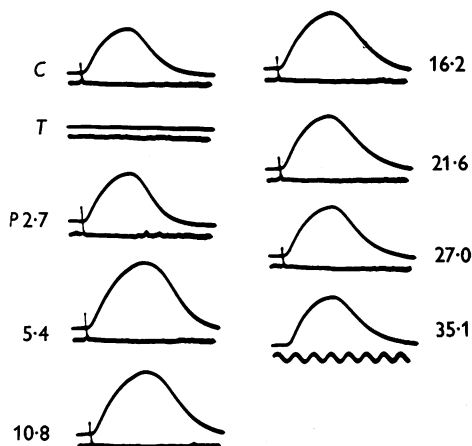


Fig. 3. Decerebrate cat. Gastrocnemius-soleus together at 175 g initial tension. Myogram on upper beam and monosynaptic test response on lower beam. *C*, control twitch before tetanization giving 656 g tension. *T*, tetanization at a rate of 420 shocks/sec for 2.1 sec during which time the muscle was released. *P*, post-tetanic period. Tests at intervals indicated in sec alongside records. In the last record root response exchanged for time in 100 c/s. Note roughly parallel behaviour of potentiation in neuro-myal and neuro-neural junction.

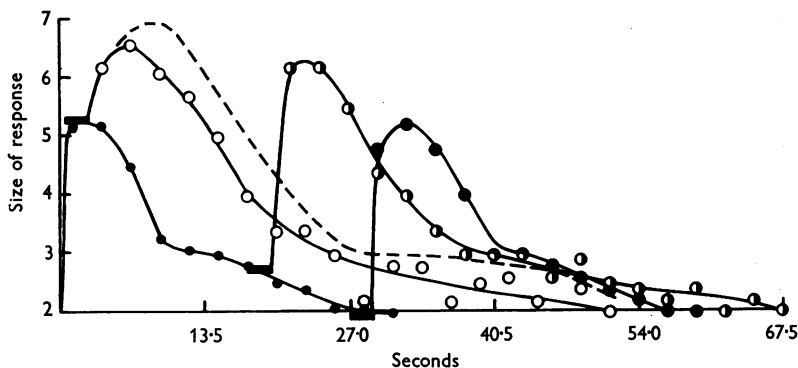


Fig. 4. Decerebrate cat. All sacral ventral roots and L6 severed. Some spindle excitation from L7. Test response from S1, control being zero. Gastrocnemius-soleus together. Muscle slack. Tetanic stimulations for 2.1 sec at a rate of 420 shocks/sec. Small filled circles (curve, extreme left): averages of four post-tetanic potentiations, serving as control for three later experiments (open circles, half-filled, and large filled circles), identical, but with tetanization periods placed as indicated by black oblongs from which the three curves are rising. The broken line represents the potentiation curve for a 10 sec tetanus at same rate of stimulation.

More striking, however, is the prolongation of the state of potentiation. The second test tetanization occupies an optimum position. Two 2·1 sec tetanizations 16·6 sec apart thus produced an effect lasting roughly as long as the effect of one single, uninterrupted 10 sec tetanus (broken line). This experiment is therefore a demonstration of temporal summation of two states of presynaptic residual facilitation. (The advantage of using brief tetanizations is that the experiment can be repeated several times under a variety of conditions.)

It is concluded from the experiments of these two sections that in tetanization with the muscle-nerve intact there may be a considerable margin of concealed post-tetanic residual facilitation, the course of which is not deducible from the curve obtained. At least some of it can be revealed by an additional tetanization. In 'natural potentiations' this state of affairs would be the normal one. Tetanization of cut nerves is an artificial situation. It does, however, give a good indication of the range of the residual effect, particularly with regard to its duration.

The facilitation of potentiation, demonstrated above, is of considerable interest. Facilitations are generally regarded as effects of 'convergence' leading to spatial summation maintained by brief synaptic detonations. Clearly, however, presynaptic temporal summation is equally important, and much work remains to be done in order to separate the two.

Stretch during potentiation

The experiment of Fig. 5 is directly connected with that of Fig. 4. Both show the 'base-line' potentiation to a 2·1 sec tetanus and in Fig. 5 there is the curve illustrating the effect of one additional 2·1 sec tetanus. The experiment was then repeated, but this time the muscle was stretched to a tension of 105 g for the period marked by the oblong. There was inhibition during the stretch and potentiation afterwards rising as a rebound to coincide with the curve for the additional 2·1 sec potentiation. The monosynaptic control was around zero and muscle stretch by itself did not succeed in causing rebound above that value. An indicator spindle was used (see legend). As to the inhibition during stretch, see below (Fig. 10).

The question of whether release of a tense muscle leads to a rebound exceeding the value obtained with it slack is answered by Fig. 6. The potentiation control of the slack muscle is lying above the one for 135 g tension, a very regular finding. Two experiments on release of this tension, at the moments marked by arrows, showed rebound of the potentiation to values greatly exceeding those obtained with zero tension throughout. Thus release does not merely lead to readjustment of motoneurone excitability to the level characteristic of zero tension but to a true rebound, probably based on concealed residual facilitation. In this case, too, stretch by itself did not elicit rebound.

Some of the first experiments were carried out with animals under pentobarbitone and good rebound was found in them also, though, by comparison with decerebrate preparations, more tension seemed to be needed for the effect. The records of Fig. 7 are from such an experiment. At that time tension was adjusted by shifting the myograph stand and not, as later, by pulling up the myograph against a stopper. Fig. 7 shows the three records, myographic, monosynaptic response and indicator spindle discharge. The latter, for frequency counts, was switched over to the stationary beam run alongside the

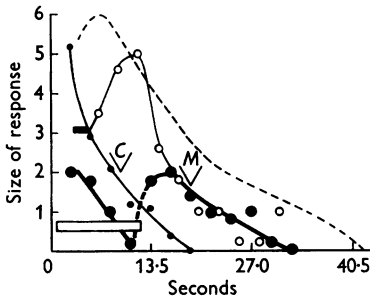


Fig. 5.

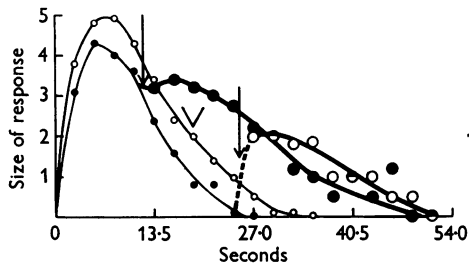


Fig. 6.

Fig. 5. Decerebrate cat. Sacral ventral roots cut, thus spindle bias from L6 and L7, test response from S1, control being zero. Tetanization at a rate of 420 shocks/sec for 2.1 sec. Gastrocnemius-soleus together. Small filled circles: averages of three potentiations with muscle slack. Small open circles: effect of superimposed tetanization for 2.1 sec during black oblong. Large filled circles: muscle at 105 g tension during time marked by white oblong. Curve in thick line also traces rebound of monosynaptic test response after release of tension. Broken line: course of post-tetanic potentiation after a 10 sec stimulation at a rate of 420 shocks/sec. First V, marked C, at moment when indicator spindle, silenced by tetanization, gradually begins to respond; second V, marked M, same for spindle silenced at release of muscle tension. Basic rhythm of indicator spindle: 33 spikes per second.

Fig. 6. Decerebrate cat. De-efferented from ventral root L6 to end of cord. L7 used for monosynaptic testing, the control being at practically zero. Gastrocnemius-soleus together. Tetanization for 10 sec at a rate of 420 shocks/sec. Small open circles: muscle slack throughout. Small filled circles: muscle at 135 g tension. Base-line frequency of indicator spindle at 37 spikes per sec in the slack muscle; after potentiation it is at zero frequency and begins gradually to discharge at mark V. Both curves based on averages of two experiments. The curves in thick lines show two single experiments on release of muscle tension (135 g) at arrow; note rebound of monosynaptic test response.

film, but in this case it is on the sweep to display tetanization (*T*). The test reflex was recorded at a sensitivity higher than usual. By 37.8 sec the potentiation had sunk to the level indicated (lower left record). Pull on the muscle from post-tetanic time 40.5 to about 50 sec led to very good rebound, though short-lasting compared with the effects seen in the best decerebrate animals. By itself the same amount of stretch did not cause any rebound.

The amount of rebound shown by monosynaptic testing depends largely

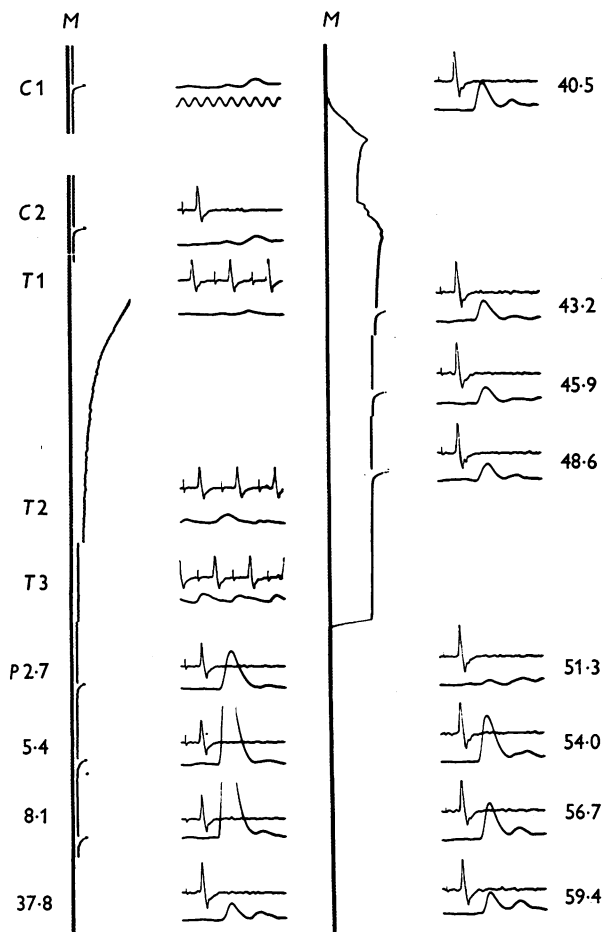


Fig. 7. Cat under pentobarbitone. Only S1 cut for monosynaptic test response. Gastrocnemius-soleus together. *C1*: slack muscle so that only top of contraction visible on myograph line *M*; time 1000 c/s and small monosynaptic response succeeded by secondary volley caused by muscle contraction. *C2*: indicator spindle and monosynaptic control as above. *T1*: tetanus, indicated by spindle firing to shock (note artifacts) and transitory muscle contraction; interval *T1-T2* is 2.7 sec, maintained during testing, *T3*, later. First test after 10 sec of tetanization (*P*, potentiation period) is at time 2.7 sec, the following ones are also marked by their post-tetanic times in sec. When at time 37.8 sec the monosynaptic control had diminished to value shown, tension was adjusted manually between sweeps at 40.5 sec (which fell on the rising phase) and 43.2 sec; the record is uncut here to show the tension change. Final tension value is 550 g, the animal failing to give rebound with lower tensions. The record is also uncut between sweeps at 48.6 and 51.3 sec to show cessation of stretch. Note gradually rising rebound after release, not visible immediately (51.3).

upon the number of subliminal-fringe neurones which are near enough threshold to make up a mobile and sensitive indicator. Thus, for instance, anaemic decerebration with its characteristic pillar-like rigidity maintains most of the would-be indicator motor neurones above threshold and so, by this index, there cannot be significant rebound to post-tetanic stretch. One such animal was afterwards spinalized. The monosynaptic control fell to one-tenth of its pre-spinalization size and a large rebound was recorded to a 12 sec post-tetanic pull of 175 g. This effect was still present after de-efferentation. (Only two such animals were studied.)

The standard type of experiment by means of which comparisons of effects of tension, de-efferentation, etc., were made is reproduced in Fig. 8. The experiment consisted of (I) control potentiation following a 2.1 sec tetanus, (II) the same tetanization with stretch superimposed after 4-6 sweeps, and (III) stretch by itself. It is fully explained in the legend.

In the best preparations 75-100 g tension gave a good rebound tending to outlast the potentiation control by roughly 0.5-1 min. This was often followed by an asymptotic fall that made it necessary to wait for 2-3 more minutes before exposing the nerve to a fresh 2.1 sec tetanus. A stronger pull did not augment this effect very much, but tended to prolong it. Even when the amount of rebound was small, the prolongation could always be demonstrated. It was sometimes definitely visible for 3-4 min. During the onset of stretch to a predetermined tension-value, a suitably placed early test response was enhanced (cf. Granit, 1950); but, later in stretch, more often than not, test reflexes were depressed below the value of the post-tetanic control by autogenetic inhibition from the muscle (Figs. 5, 6, 8 and 9).

Above 200 g tension there was usually some rebound after muscle stretch by itself (without previous tetanization). As tension was further increased the effect of 'muscle by itself' became relatively more prominent and led to monosynaptic facilitations lasting for 3-4 min. Figs. 9 and 10 show two cases in which there was rebound to stretch by itself, an effect augmented by previous tetanization. Fig. 10 also demonstrates that depression of the test response during stretch is not necessary for the effect (see Discussion).

The behaviour of the indicator spindle shows that tetanization of the muscle nerve for 2.1 sec is regularly followed by a pause in the spindle discharge, due to various factors such as antidromic stimulation, sudden decrease of a load and length (Matthews, 1933), etc. This, with different spindles, lasted from 8 to 20 sec. The beginning of gradual recovery has been marked by a V in Figs. 5 and 6. In Fig. 10, from a very active preparation with a small tendon jerk despite severance of S1, the recovery was fast, as is to be expected from excited spindles. There was always a striking difference in spindle behaviour to stretch by itself as compared with stretch after tetanization. The (antidromically) tetanized spindle was not capable of delivering as high frequencies to stretch as it did with stretch by itself (see legend of Fig. 9). In both cases stretch was followed by a silent period, prolonged in the tetanized spindle which also recovered more slowly. The pause was often longer than in Fig. 10. Thus potentiation has nothing whatever to do with re-stimulation of the motoneurone by muscular afferents and may, indeed, be improved by spindle silence.

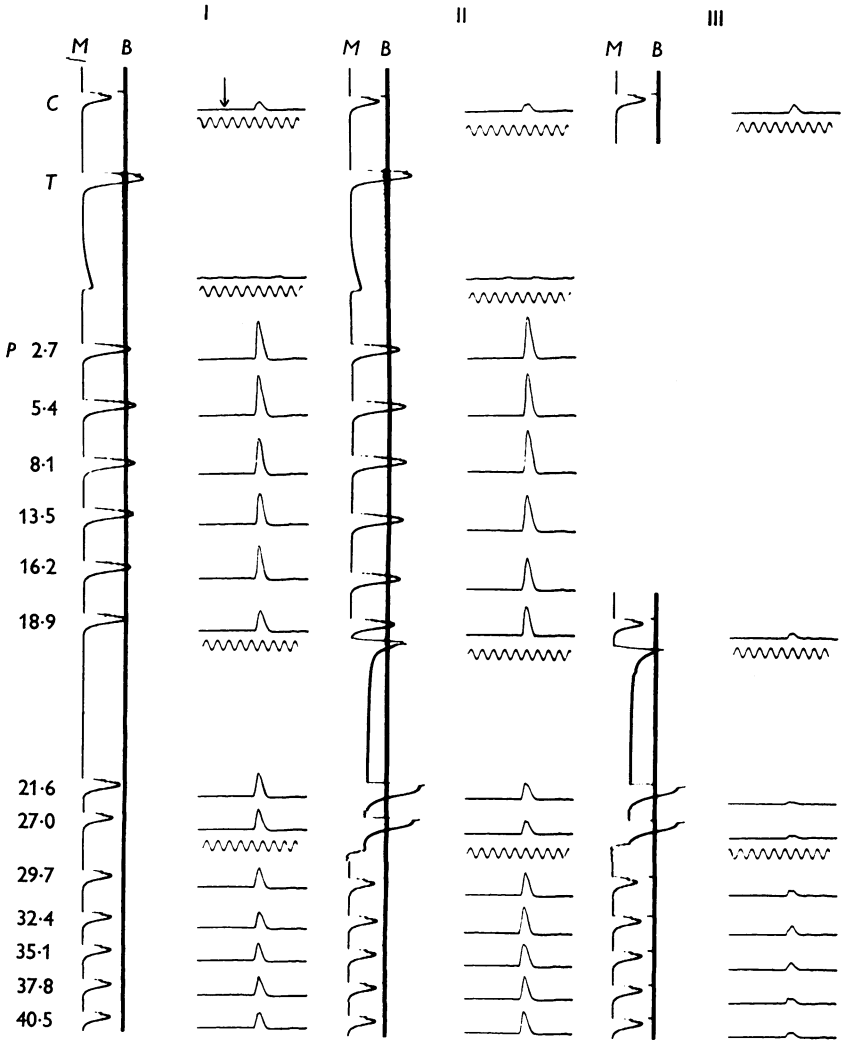


Fig. 8. Decerebrate cat with some spindle excitation from L6 and L7, the sacral roots having been cut. Gastrocnemius-soleus together. *M*, myographic response of muscle at zero tension. Film speed too slow to show (in reproduction) records on *B*. The monosynaptic test response is swept across the film at 2.7 sec intervals, two of which (*C-T* and 18.9–21.6) are shown at original film distance. The rest of the records cut out at the times after tetanization (*T*) marked in sec during *P*, the potentiation period. I, control (*C*) followed by tetanization (*T*) at a rate of 500 shocks/sec for 2.1 sec, succeeded by tests showing potentiation. II, same, but with stretch of 210 g put in at time 18.9 sec and released at 27.0 sec. Note rebound of monosynaptic facilitation. III, control muscle stretch alone without previous potentiation. Time in 1000 c/s occasionally left in the records and position of shock marked by arrow in first control *C*. Note also potentiation of muscular response alongside records.

Many experiments began with ventral roots L6 and L7 intact so that some excitation of γ fibres was present, generally modest because the main supply of the ankle extensors is from S1. Section of the two remaining roots followed later. Sometimes this led to a slight decrease of rebound, in other cases a definite effect of de-efferentation could not be demonstrated.

Section of S1 for the monosynaptic test presupposes a considerable reduction of γ activity, but it does not explain the relatively insignificant effect of γ fibres on the amount of rebound. Enough γ activity remains to be clearly reflected in the behaviour of an indicator spindle before and after root section. However, the muscle afferents give complex effects. Their activity, as shown above, leads to curtailment of potentiation. Yet, on the other hand, their activity *during* stretch sets up the state of *residual facilitation* that is so easily demonstrated by raising muscle tension by the necessary amount (Figs. 9, 10). The sum total of these opposing influences, in the present type of experiment, cannot be predicted. Similar considerations apply to the effect of muscle tension in a preparation under some γ excitation. The final rate of spindle discharge in a 10–12 sec period of pull need not then differ very much at different lengths (tensions), a fact which explains what Sherrington (1909) called 'plasticity' in the decerebrate preparation. From the point of view of tetanization, spindle discharge frequencies will be in the lower range and so, for the residual facilitation, duration of pull, within limits, will be relatively more important than amount of tension.

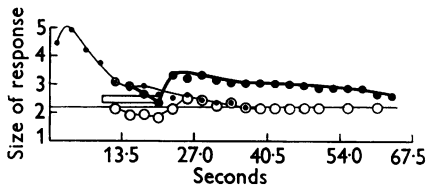


Fig. 9

Fig. 9. Decerebrate cat. All sacral ventral roots and L6 severed. Some spindle excitation from L7. Test response from S1. Gastrocnemius-soleus together. Tetanic stimulation for 2.1 sec at a rate of 420 shocks/sec. Small filled circles: potentiation control with slack muscle. Large filled circles: potentiation with muscle tension raised to 210 g for period marked by oblong. Large open circles: muscle raised to same amount of tension for same period but without previous tetanization. Spindle indicator at an average basic frequency of 16 spikes/sec. In stretch during potentiation it stabilized to an adapted value around 28 spikes/sec. When muscle was pulled without previous tetanization the spindle discharge stabilized to an adapted value around 40 spikes/sec.

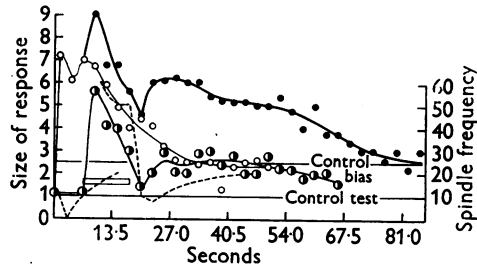


Fig. 10

Fig. 10. Decerebrate cat with some spindle excitation from L7 and L6 and small tendon jerk left in gastrocnemius-soleus. All sacral roots cut. Monosynaptic test response from S1 (curves drawn in full) and spindle discharge frequency (in broken lines). Small open circles: control potentiation curve after 2.1 sec tetanus at a rate of 420 spikes/sec. Small filled circles: potentiation curve after similar tetanization, but this time a stretch of 350 g was applied during time marked by oblong. Note initial facilitation and rebound. Half-filled circles: control stretch alone without potentiation by tetanus. Note initial facilitation and rebound. Ordinates on the right show frequency of indicator spindle in spikes per sec, the basic frequency being around 25 spikes/sec. Broken line on extreme left traces frequency of indicator spindle after tetanization. The curve in broken lines starting with very high spindle discharge frequencies during stretch, stabilizing around 50 spikes/sec, shows rapid fall in early potentiation period after stretch and characteristic slow recovery. Spindle discharge frequencies belong to experiment presented by filled circles.

Synergist tetanization

So far it has been shown that cessation of muscle stretch restitutes a concealed potentiation or, vice versa, that potentiation revives a long-lasting residual facilitation to pull, which without it would have been subthreshold or concealed. There has not been any rebound exceeding that amount and that duration of potentiation which were to be expected from the observations with severed nerves. These, as it were, set the technically measurable limit for the residual presynaptic effect. On account of the slow progressive changes in the level of the monosynaptic control and in the potentiation curve itself, it is not possible to reach greater precision in comparing results before and after nerve section (see Fig. 2) than is implied in the preceding statement. The assumption that cessation of stretch does something to the motoneurone that cannot be fully accounted for by post-tetanic residual facilitation is at the moment superfluous. There is also a characteristic property of post-tetanic potentiation that can be brought to bear upon this argument. This is its limitation to the synapses of the nerve fibres which are tetanized, mentioned in the introduction.

In Fig. 11 the nerve to the lateral head of gastrocnemius + soleus (*GL* of Fig. 1) was cut and control potentiations established both for it and the medial intact head (*GM*), each tested individually. In both cases stretch of the muscle (gastrocnemius medialis) has been superimposed on potentiation in precisely the same way. The experiment (upper) with the intact muscle-nerve is thus comparable to the previous ones and differs from them merely by the use of about half the afferent and efferent supply. The result was a rebound of the familiar type. When stretch was superimposed upon the potentiation induced by the cut synergist (lower), it caused a considerable immediate facilitation but no subsequent rebound. Afterwards the curve dropped along the values of the potentiation curve which served as control. This experiment was carried out on three animals, all of which behaved in the same way. The good synergist facilitation to stretch (Granit, 1950), seen in Fig. 11 (lower), showed that impulses in *GM* actually had a strong influence on the neurone pool tested from the severed *GL*. Nevertheless, there was little if anything to be seen of this facilitation in the period after stretch. Thus rebound of this particular type behaved like post-tetanic potentiation in that it was only seen in the central pathway of the fibres tetanized.

It is concluded that the excitatory rebound to stretch described in this paper has shown close enough agreement with the presynaptic residual facilitation to be explicable on this basis. It sums with post-tetanic potentiation as if it were another post-tetanic potentiation, it rises and decays in the manner of such potentiations and, like the latter, is restricted to the terminals of the tetanized fibres. Furthermore, there is a sound experimental basis for such

effects in the well-known behaviour of monosynaptic potentiations from the large nuclear bag sensory endings of the muscle spindles which are excitatory on the motoneurone.

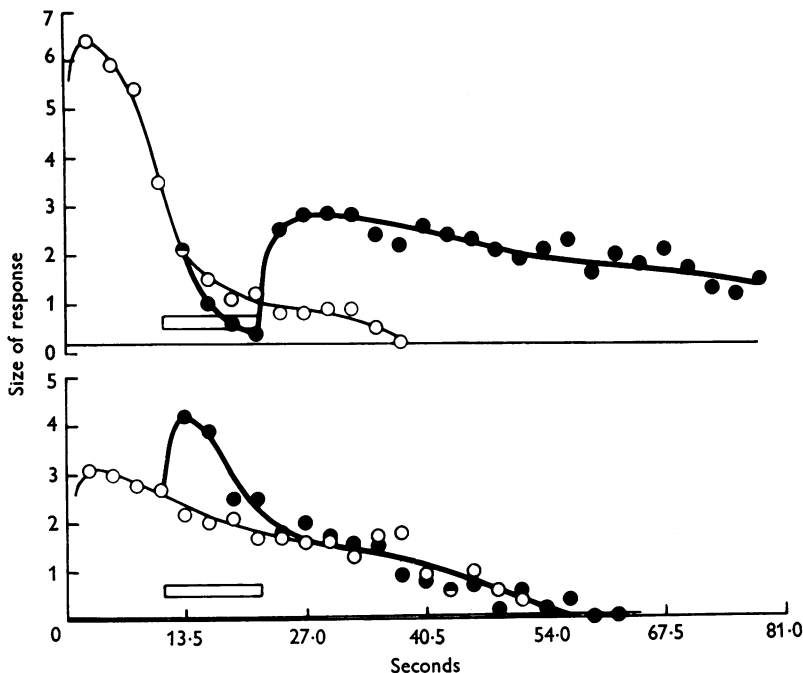


Fig. 11. Decerebrate cat. De-efferented from L5 to end of spinal cord. Nerve to soleus and lateral head of gastrocnemius (*GL*) cut. Medial head of gastrocnemius (*GM*) at initial tension 50 g. Double line in lower record indicates that control test response was just above zero. Comparison of the effect of 105 g stretch inserted after tetanization of intact *GM* (upper) with similar tetanization of cut *GL* (lower). Tetanization at 420 shocks/sec for 2.1 sec. Note that control potentiation (circles) from cut nerve lasted for a longer time than same from intact nerve. Only when the intact nerve of the stretched muscle itself was stimulated (filled circles, upper) was there the characteristic rebound after stretch (oblong). The cut synergist (filled circles, lower) gave good facilitation during stretch but no definite rebound above value of the post-tetanic control curve.

Potentiated single-fibre reflexes

After selecting a suitable neurone from the pool of the ankle extensors it is possible to repeat the experiment by monosynaptic testing, despite loss of the statistical advantages of the method. It is not difficult, by splitting ventral-root filaments, to find a motoneurone which is just below threshold for the test shock, yet responds to it for some time after stretch; it also responds after tetanization, and, for a considerably longer time, when tetanization and stretch are added in the manner described above. It is, however, of greater interest to use this type of experiment for testing by repeated brief stretches. This

proposition may also be put in the following form: is it possible to make an individual neurone 'spastic' by such means? Spasticity by definition is ultimately based on tests which depend on muscular end organs, and in the last instance is always an exaggerated facilitatory stretch reflex.

In Fig. 12 soleus has been used since it is known to give a better stretch reflex than gastrocnemius (Denny-Brown, 1929). A ventral-root fibre was selected which was silent to single stretches of the muscle at sufficiently long intervals (record *C*) but could be made to discharge a few reflex spikes to stretches repeated at intervals of 5–10 sec. However, the experiment began with the fibre silent. *GL* (see Fig. 1) was then tetanized for 2.1 sec (*T*), and during

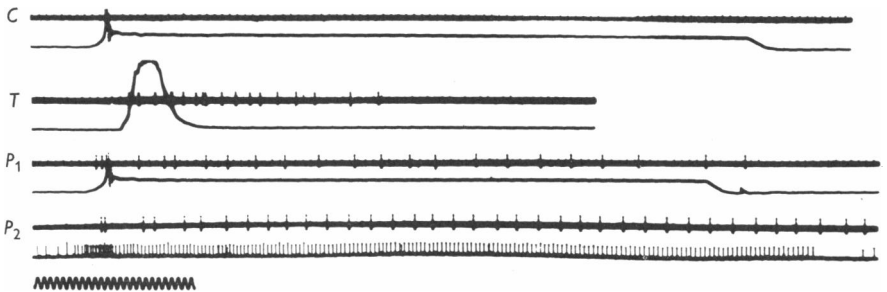


Fig. 12. Decerebrate cat. Ventral roots from L5 to end of spinal cord severed. Soleus muscle alone. Single fibre in filament of ventral horn cell responding to stretch of soleus alone but only after potentiation. Zero initial tension. *C*: control stretch before tetanization. Stopper placed to give tension of 175 g under pull. No reflex response in filament. *T*: tetanization of *GL* for 2.1 sec at rate of 500 shocks/sec with rise of myographic response and reflex firing of isolated ventral horn cell efferent. *P*₁: same stretch as above, but this time after tetanization. *P*₂: same somewhat later, but myograph record now replaced by that of indicator spindle (lower curve, in which spikes retouched). Time, $\frac{1}{2}$ sec at 50 c/s.

tetanization a good reflex response appeared. After this brief tetanization the fibre again became silent, but some 10 sec later (in the potentiation period) it gave a good reflex to muscle stretch, shown as *P*₁. At the moment of stretch, potentiation was still in the increasing phase but the spindle afferents were depressed for a while after the tetanus. The myograph recording was then exchanged for the recording of discharges from the indicator spindle. This record (*P*₂) represents a period combining optimally spindle recovery and post-tetanic potentiation, the one rising, the other falling. Stretch yields the two single fibre records, spindle (below) and ventral horn cell (above). Acceleration and cessation of spindle activity serve to indicate onset and cessation of stretch respectively. With longer tetanization periods high degrees of 'spasticity' could be produced in this neurone and 5–6 min of rest were a minimum time for restitution of the original state. It was, of course, a sensitive neurone selected to behave in this manner, but no selection was

needed for demonstrating the general principle on a smaller scale with other neurones from the same pool (*GL*).

Stretch is a slow method of testing and presupposes recovery of the spindle afferents after the (for them antidromic) tetanization. It is therefore better to use a 10 sec tetanization instead in order to have a post-tetanic effect of longer duration. This was done in the experiment illustrated in Fig. 13, with brief stretches repeated at intervals of 5 sec. Some of the ventral root filament

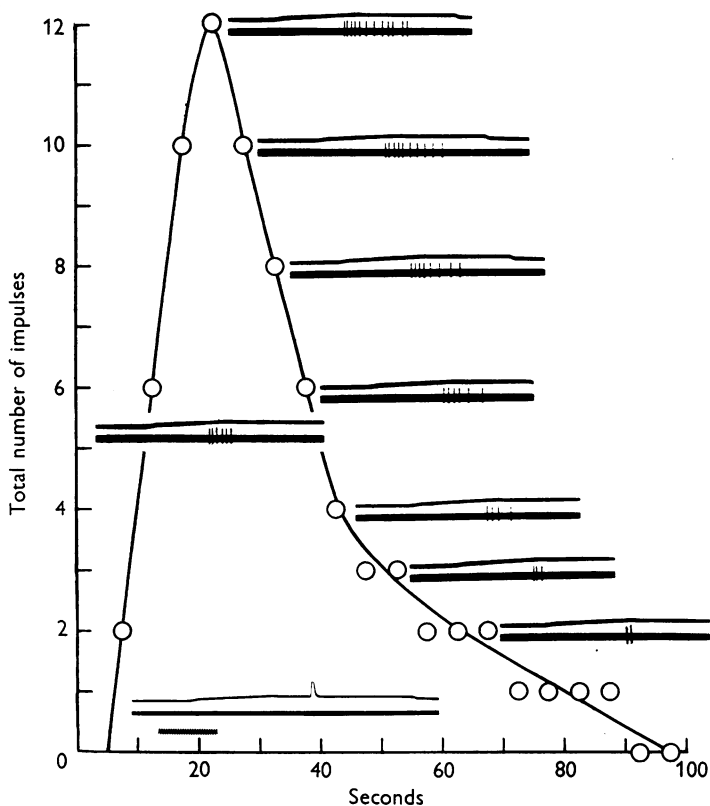


Fig. 13. Decerebrate cat. De-efferented from L5 to end of spinal cord. Potentiation of single fibre stretch reflex. This fibre (ventral root filament) responded to stretch of medial head of gastrocnemius muscle (lateral denervated) after tetanization of the muscle nerve. No response to stimulation of cut *GL*. Stretch of 105 g, below in diagram, did not elicit reflex response in filament either by itself or when repeated at intervals of 5 sec, nor did an interpolated test shock on top of it do so. Stretches were then given at 5 sec intervals after tetanization for 10 sec at a rate of 420 shocks/sec. Graph illustrates rise and decay of the single-fibre stretch reflex in the post-tetanic period with some of the ventral root filament records inserted (retouched). Reflex discharge, stabilizing around 44 spikes per sec, was maintained to the end of the tetanization period, but afterwards and in between the stretches the cell was silent all through the potentiation period. No potentiation obtained from the cut *GL*. Time below control: $\frac{1}{2}$ sec.

records are inserted in the graph against the readings, which give total number of impulses obtained. This is one way of plotting the result. A slightly different curve would have been obtained by taking the maximal motoneurone frequencies. For the same total number these were somewhat higher on the rising than on the falling phase of the curve.

Later, in the same experiment, the motoneurone whose responses are shown in Fig. 13 became more sensitive and changed to another category of ventral horn cell, one which could be potentiated by stretch alone. A single stretch did not elicit a reflex response but left behind it a state of residual facilitation during which a test stretch was effective. The response rose slowly to a maximum of three spikes per stretch and the reflex could be repeated (apparently indefinitely) if brief stretches were given at suitably chosen intervals (5–10 sec).

It is concluded from these experiments that states of spasticity can be produced by residual facilitation. Thus the connexion between spasticity, rebound, residual facilitation and temporal summation can be established using natural stimuli.

DISCUSSION

The general and basic notion behind the experiments reported has been the postulate that a junctional phenomenon as common, potent, and striking as the post-tetanic residual facilitation must play a major role in the physiology of the central nervous system. This view was by no means foreign to Larrabee & Bronk (1947) and to Lloyd (1949), and led Eccles and his collaborators (Eccles, 1953) to experiments showing that the effects of disuse could be counteracted by tetanization. On the other hand, Ström (1951) did not succeed in demonstrating a significant physiological role for potentiation. Clearly, therefore, some crucial tests for the analysis of normal situations had to be developed, and such considerations led to the work presented above. From this it can be safely concluded that presynaptic residual facilitation is a singularly important process in temporal summation. Incidentally, by reducing one specific case of rebound to a known process, it has removed something of the enigma that has prevented study of these complex reflex events. These experiments do not exclude the possibility that other types of rebound may actually require inhibition as a causal factor, as has been suggested for the retinal off-effect (cf. Granit, 1955).

The successful analysis of brief synaptic processes in so much important work within the last twenty years has perhaps led to some overemphasis on spatial summation. The concept arrived at, correct as far it goes, has been that cells are depolarized and kept active by brief detonations due to the impulse barrage from different sources (cf. particularly Brock, Coombs & Eccles, 1952). This, it has been assumed, requires constant renewal and so, in order to explain drawn-out states of excitation, such as those studied earlier in the spinal cord, e.g. by Eccles & Granit (1929), it has been found necessary to

re-voke Forbes's (1922) old concept of 'delay paths' (or reverberation circuits) which he used to explain rebound. The present experiments show that muscle stretch by itself, as well as afferent nerve tetanizations by synchronous shocks at high frequencies, 'deposits' a long-lasting state of presynaptic facilitation, the well-known post-tetanic potentiation, part of which is concealed or silent unless brought to light by suitable modes of testing. This residual facilitation provides an alternative to reverberation or, inasmuch as reverberation actually has been demonstrated, a supplementary factor.

The number of impulses necessary for presynaptic residual facilitation may vary from junction to junction. In sympathetic ganglia a definite effect can be demonstrated after a single impulse (Larrabee & Bronk, 1947; Job & Lundberg, 1953). Thus post-tetanic potentiation is not the best possible term. It merely expresses the fact that several impulses leave a greater change than one single impulse. Residual facilitation is more to the point.

New light is thrown on spasticity in the decerebrate state when these results are related to the work on efferent γ control of the muscle spindles, recently reviewed in detail by Granit (1955). In the present preparations γ activity is high to begin with and is strongly facilitated by a variety of stimuli. The γ system is, as it were, subject to Jacksonian release, apparently in parallel with the motor or α system. Thus the spindle afferents are thrown into violent activity on fairly slight provocation and so a physiological condition arises which is the very situation analysed in the present experiments. There will be periods of intense spindle firing leaving protracted states of residual facilitation and thus aggravating a condition to which concomitant α -release has also contributed.

It should be realized that the analytical conditions developed in this paper were decided upon merely because their relative simplicity proved attractive. The principles, however, are general. Thus intense repetitive activation of any single common path receiving polysynaptic influences from different sources is likely to be a focal point of residual facilitation capable of mobilizing the neurone upon which it impinges. In the present experiments some mutual cancellation of polysynaptic residual inhibition and excitation has probably occurred. The polysynaptic residual effects will prove a more baffling problem.

SUMMARY

1. When the nerve to an ankle extensor (cat) is tetanized, a state of post-tetanic potentiation to a test shock develops in both muscle and monosynaptic reflex response. After severance of the muscle nerve the duration of reflex post-tetanic potentiation is greatly prolonged. Impulses from muscle afferents thus curtail the state of potentiation. In this work the effects of muscle tension and stretch on the potentiated monosynaptic reflexes have been studied.

2. Two brief tetani 10–20 sec apart cause a greater and more prolonged effect than the same two tetani given with no interval between. There is thus facilitation of one post-tetanic effect by a previous or conditioning tetanus, demonstrating a concealed component in potentiation.

3. If muscle stretch, which by itself does not have any after-effect on the monosynaptic test response, is superimposed on a period of post-tetanic potentiation, rebound of monosynaptic facilitation occurs when the muscle is released. This rebound is limited to the monosynaptic pathway of the nerve tetanized and so is a re-activation of the concealed remainder of post-tetanic potentiation.

4. Muscle stretch by itself also creates rebound, provided that a high enough tension is used. Thus post-tetanic potentiation reveals a rebound of facilitation after stretch or, vice versa, stretch reveals a concealed remainder of post-tetanic potentiation. The basis for this is that in both cases long trains of impulses have been set up in the large afferent fibres which excite the motoneurones monosynaptically.

5. By using reflexes in single-fibre pathways of the ankle extensors, recorded in ventral root filaments, it is possible to prove that tetanization and/or stretch create a long-lasting state of post-tetanic potentiation or hypersensitivity to subsequent stretch reflexes. This means that single ventral horn cells have been made spastic by post-tetanic potentiation.

6. The natural frequencies of the large spindle endings, particularly when they are excited by γ efferents, are high enough to set up this state of residual temporal facilitation (or post-tetanic potentiation). Rebound to stretch is one of its consequences.

7. The paper thus traces the known and measurable factor of post-tetanic potentiation in a number of protracted events, different aspects of which are known under descriptive terms such as temporal summation, rebound, etc.

The expenses of this work have in part been defrayed by a grant from the Swedish Medical Research Council.

REFERENCES

- BERGER, F. M. & BRADLEY, W. (1946). The pharmacological properties of α : β -dihydroxy- γ -(2-methylphenoxy)-propane (myanesin). *Brit. J. Pharmacol.* **1**, 265–272.
- BESWICK, F. B. & EVANSON, J. M. (1955). The heterosynaptic activation of motoneurones during post-tetanic potentiation. *J. Physiol.* **128**, 89–98.
- BROCK, L. G., COOMBS, J. S. & ECCLES, J. C. (1952). The recording of potentials from motoneurones with an intracellular electrode. *J. Physiol.* **117**, 431–460.
- BROWN, G. L. & v. EULER, U. S. (1938). The after effects of a tetanus on mammalian muscle. *J. Physiol.* **93**, 39–60.
- CASTILLO, J. DEL & KATZ, B. (1954a). Statistical factors involved in neuromuscular facilitation and depression. *J. Physiol.* **124**, 574–585.
- CASTILLO, J. DEL & KATZ, B. (1954b). Changes in end-plate activity produced by pre-synaptic polarization. *J. Physiol.* **124**, 586–604.
- DENNY-BROWN, D. B. (1929). On the nature of postural reflexes. *Proc. Roy. Soc. B*, **104**, 252–301.

- ECCLES, J. C. (1953). *The Neurophysiological Basis of Mind. The Principles of Neurophysiology.* Oxford: Clarendon Press.
- ECCLES, J. C. & GRANIT, R. (1929). Crossed extensor reflexes and their interaction. *J. Physiol.* **67**, 97-118.
- ELDRED, E., GRANIT, R. & MERTON, P. A. (1953). Supraspinal control of the muscle spindles and its significance. *J. Physiol.* **122**, 498-523.
- FATT, P. (1954). Biophysics of junctional transmission. *Physiol. Rev.* **34**, 674-710.
- FENG, T. P. (1937). The eserine-like effects of barium on motor nerve-endings. *Chin. J. Physiol.* **12**, 177-196.
- FENG, T. P. (1941). The changes in the end-plate potential during and after prolonged stimulation. *Chin. J. Physiol.* **16**, 341-372.
- FENG, T. P., LEE, L.-Y., MENG, C.-W. & WANG, S.-C. (1938). The after effects of tetanization on *n-m* transmission in cat. *Chin. J. Physiol.* **13**, 79-108.
- FORBES, A. (1922). The interpretation of spinal reflexes in terms of present knowledge of nerve conduction. *Physiol. Rev.* **2**, 361-414.
- GRANIT, R. (1950). Reflex self-regulation of muscle contraction and autogenetic inhibition. *J. Neurophysiol.* **13**, 351-372.
- GRANIT, R. (1955). *Receptors and Sensory Perception. A Discussion of Results, Aims and Means of Electrophysiological Research into the Process of Reception.* New Haven: Yale University Press.
- GRANIT, R. & STRÖM, G. (1951). Autogenetic modulation of excitability of single ventral horn cells. *J. Neurophysiol.* **14**, 113-132.
- HAGBARTH, K.-E. & NAESS, K. (1950). Reflex effects of tetanic stimulation of different afferent fibre-systems in the hind limb of the cat. *Acta physiol. scand.* **21**, 336-361.
- HUNT, C. C. (1953). Diameter and function of afferent fibres from muscle. *Abstr. XIX int. physiol. Congr.* pp. 485-486.
- JEFFERSON, A. (1954). Aspects of the segmental innervation of the cat's hind limb. *J. comp. Neurol.* **100**, 569-596.
- JEFFERSON, A. & BENSON, A. (1953). Some effects of post-tetanic potentiation of monosynaptic response of spinal cord of cat. *J. Neurophysiol.* **16**, 381-396.
- JOB, C. & LUNDBERG, A. (1953). On the significance of post- and pre-synaptic events for facilitation and inhibition in the sympathetic ganglion of the cat. *Acta physiol. scand.* **28**, 14-28.
- LARRABEE, M. G. & BRONK, D. W. (1947). Prolonged facilitation of synaptic excitation in sympathetic ganglia. *J. Neurophysiol.* **10**, 139-154.
- LLOYD, D. P. C. (1949). Post-tetanic potentiation of response in monosynaptic reflex pathways of the spinal cord. *J. gen. Physiol.* **33**, 147-170.
- LUCAS, K. (1917). *The Conduction of the Nervous Impulse.* London: Longmans, Green.
- MATTHEWS, B. H. C. (1933). Nerve endings in mammalian muscle. *J. Physiol.* **78**, 1-53.
- SHERREINGTON, C. S. (1892). Notes on the arrangement of some motor fibres in the lumbo-sacral plexus. *J. Physiol.* **13**, 621-772.
- SHERREINGTON, C. S. (1909). On plastic tonus and proprioceptive reflexes. *Quart. J. exp. Physiol.* **2**, 109-156.
- SHERREINGTON, C. S. (1913). Reflex inhibition as a factor in the co-ordination of movements and postures. *Quart. J. exp. Physiol.* **6**, 251-310.
- STRÖM, G. (1951). Physiological significance of post-tetanic potentiation of the spinal monosynaptic reflex. *Acta physiol. scand.* **24**, 61-83.