EARLY AND LATE POST-TETANIC POTENTIATION, AND POST-TETANIC BLOCK IN A MONOSYNAPTIC REFLEX PATHWAY

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ABSTRACT

Observations have been made upon the nature of early and late post-tetanic potentiation and upon post-tetanic block of presynaptic collaterals with particular reference to behavior in circumstances of varied duration and frequency of conditioning stimulation. Early potentiation is most conspicuous following brief tetani at high frequency, late potentiation following long tetani, much lower frequencies being all that are needed. The two phenomena thus are distinguishable and separate. Dorsal root electrotonus produced by stimulations of varying duration and frequency is described, and the similarity between behavior of the D.R.IV R. electronic potential and early potentiation demonstrated. It is shown how early potentiation and post-tetanic block are due to the same process (hyperpolarization) at different intensities. The view that the agency for potentiation is associated with augmented presynaptic action due to hyperpolarization is confirmed. A diagram is constructed to indicate the probable temporal courses of early and late potentiation.

A complex group of changes in action and excitability follows the act of reflex transmission through a monosynaptic reflex pathway. The changes are in the direction both of enhancement and depression: certain of them may be prominent, others may not reveal themselves and, indeed, may be absent depending on the circumstances of prior engagement of the pathway. To catalogue them: there is the "early" potentiation described by Eccles and Rall (1951), the "late" potentiation described by Lloyd (1949), an "early" depression that is the subnormal period of Gasser, a "late" depression (or low-frequency depression) described by Brooks, Downman, and Eccles (1950) and by Jefferson and Schlapp (1953) and, finally, a depression of a different nature seen as an enduring failure of response anteceding the onset of late potentiation if the monosynaptic pathway has been active repetitively for some seconds prior to sampling of its ability to conduct.

The present study is concerned in the main with a differentiation between early and late potentiation and with the last aforementioned form of depression. Brief mention of these phenomena has been made in the course of an earlier discussion on electrotonus in dorsal nerve roots (Lloyd, 1952).
Decapitate cat preparations were used, the monosynaptic reflexes elicited by stimulation of a dorsal root, or of the gastrocnemius nerves, being recorded in the appropriate distally severed ventral root.

Fig. 1 illustrates the main features of the phenomena under discussion. If the afferent limb of a monosynaptic reflex pathway is tetanized briefly at a reasonably high frequency then the response to a subsequent test stimulation is enhanced in the manner described by Fig. 1, A and B. Response amplitude increments rapidly, as the test interval increases, to reach a peak at about 150 msec. following the close of the tetanus (Fig. 1 A). It declines fairly rapidly thereafter and control value is reached in about 0.5 min. (Fig. 1 B). This maximum is the “early” potentiation. If the conditioning tetanus is more enduring, response to ensuing test stimulation during the first few seconds far from being potentiated is suppressed (Fig. 1 C) and then only gradually potentiated (Fig. 1 D) with the peak of enhancement being reached only when some 12 to 15 sec. have elapsed following the close of tetanization. Post-tetanic potentiation in this circumstance endures for many minutes (Lloyd, 1949). This is the now so-called “late potentiation.” The depression that follows enduring tetanization and antecedes late potentiation for semantic purpose will be designated “post-tetanic block.”
The Transition from Late Depression to Early Potentiation.—As was shown by Beswick and Evanson (1955) the late depression that follows a single act of monosynaptic reflex transmission is intensified if several reflex volleys constitute the conditioning action and, if the conditioning train is further lengthened, it gives way to potentiation of the test response. Fig. 2 illustrates in detail the manner in which this reversal of effect takes place. The first curve reveals the test reflex depressed during the first 0.5 min. after 6 volleys at 590 per sec. There is, however, and this will be discussed further in connection with Fig. 3, a slight reversal thereafter into what clearly is a late potentiation. On lengthening the conditioning train to 23 volleys the amplitude plot of the test reflexes crosses from depression into potentiation at approximately 200 msec. After 36 volleys a well defined peak of potentiation is established at approximately 170 msec. With further increase in the number of volleys (to 71 and 157) the peak becomes more prominent, shifts a little to a shorter interval following the close of the conditioning train, and the onset of potentiation comes to what must be approximately the minimum latency of 50 msec. Obviously in the last curve potentiation ensues abruptly after the subnormal period.

The Transition from Late Depression to Late Potentiation.—If a lower frequency of stimulation is selected for the conditioning train the sequence of events occurring with increasing duration of stimulation is different from that illustrated in Fig. 2. Briefly put late depression leads into late potentiation without there being at any of the durations of stimulation a frank development of early potentiation. This is not, however, to say that the process underlying early potentiation may not be in operation. Fig. 3 exemplifies the argument.
In the first curve of Fig. 3 there is, following 3 volleys at 180 per sec., a well developed late depression, but no sign whatever of potentiated response. After 7 volleys the degree of late depression is less than it is after 3 volleys, and it continues to decrease in intensity as the train of conditioning volleys is further extended. This presumably means that the process underlying potentiation is operating to truncate the late depression without, in these circumstances of stimulation, producing overt potentiation within the interval at which the early potentiation is, in other circumstances, at its peak of intensity. At longer intervals following the conditioning stimulation there is a degree of late potentiation that increments approximately with duration of the conditioning train.

Transition from Late Depression to Potentiation as a Function of Frequency.—A particularly interesting series of observations can be made if the duration of stimulation is fixed at a value suitable for the display both of early and late potentiation and frequency varied over a wide range. Fig. 4 presents such a
series in which, at 120 per sec., late depression yields directly to late potentiation. At 150 per sec. there is a maximum in the location of the early potentiation peak that does not, however, reach control amplitude. With further increase in frequency to 220 and 312 per sec. there are clear cut peaks of early potentiation, but the over-all curve of potentiation is bimodal, there being also maxima of late potentiation. At 820 per sec. early potentiation has quite outstripped late potentiation in magnitude and the over-all curve of potentiation is again unimodal. The full plot of this last curve would resemble that in Fig. 1, A and B. Although late potentiation can appear without any overt (at least) expression of early potentiation the question arises as to whether the converse can be true. The observations of Fig. 1, A and B and in the last curve of Fig. 4 taken alone might lead to the supposition that it could and that Fig. 1, A and B describe the time course of early potentiation. However, in view of the other observations in Fig. 4 one must suppose that late potentiation contributes to the form of the curve in Fig. 1, A and B.

On the available evidence, then, it appears that early potentiation reflects a process, presynaptic in locus, that has a relatively fixed duration, but increases greatly in magnitude with increased stimulation. On the contrary late potentiation increases in duration with duration of stimulation, and much less so with frequency, from something less that 0.5 min. to many minutes. It is suggestive that these properties of the early and late potentiation are reminiscent of those of P1 and P2 respectively in the after-potential cycle of nerve (Gasser, 1935). The similarity in behavior of late potentiation and the P2 after-potential has already been commented upon (Lloyd, 1949). Discussion of the qualities of early potentiation will follow below.

**Transition from Early Potentiation to Post-Tetanic Block.**—Fig. 5 illustrates the manner in which early potentiation is replaced by a profound depression as the duration of conditioning stimulation is increased, frequency being maintained constant. One may suppose that the depression influences some of the pathways involved even at the peak of potentiation if the tetanic stimulation be prolonged. There would, for instance, seem to be no other simple explanation...
for the fact that the degree of potentiation achieved after 14.4 sec. tetanization fails to match that following 9.6 sec. tetanization (cf. Fig. 5).

Influence of Changed Duration and Frequency of Stimulation upon the Degree of Potentiation.—From the foregoing the fact emerges that there are clear dis-

Fig. 6. The relation between duration of conditioning tetanus and degree of resulting potentiation.

Fig. 7. The relation between frequency of conditioning tetanus and degree of resulting potentiation.

tinctions between early and late potentiation. Figs. 6 and 7 are so constructed as to permit a ready contrast between the two as they are influenced by variation either in duration of stimulation at fixed frequency or in frequency at fixed duration of stimulation. In each instance the unvaried parameter is fixed at a value near optimal for expression of the phenomenon, which optimal values were found in preliminary experiment of the sort exemplified in Figs. 1 to 5.
The information now presented with respect to late potentiation is not new (cf. Lloyd, 1949) and serves merely for facilitating contrast between the phenomena.

As duration of stimulation is increased the degree of early potentiation increments rapidly to become maximal at a duration of some 0.6 to 0.7 sec., whereas the late potentiation becomes maximal only after conditioning tetani of some 10 sec. duration. As the duration of tetanization exceeds approximately 0.7 sec. the degree of early potentiation declines and with the use of stimuli of sufficient duration to secure late potentiation of maximal intensity is no longer in evidence.

Fig. 7 presents the relation between frequency and degree of potentiation. Whereas, as earlier shown, the major increase in late potentiation occurs in the range of stimulation frequency between 100 and 300 per sec. it is only at frequencies considerably in excess of these that the maximal rate of increase with increasing frequency is realized with respect to early potentiation. One would expect the curve relating degree of early potentiation to frequency of stimulation to be sigmoid as is the comparable curve for late potentiation. The maximum frequency employed in the experiments, 850 per sec., was determined by the capabilities of the stimulator then in use.

Some Further Observations on Post-Tetanic Dorsal Root Potentials.—Much of the experimental material concerning the dorsal root electrotonus following tetani has been presented elsewhere (Lloyd, 1952). Yet there are observations on the influence of varied frequency and duration of stimulation, of import to the present considerations, that have not previously been published. Of particular concern is that deflection known as D.R.IV R., which is positive in sign in the stimulated dorsal root, and of considerable magnitude, and which is negative in sign and relatively small in amplitude in a neighboring root (Lloyd, 1952, Fig. 10). According to these facts the origin of the D.R.IV R. electrotonic deflection is in the terminal portions of the primary afferent fibers and not elsewhere (Lloyd and McIntyre, 1949). It denotes a flow of current in the direction from the terminals to the preterminal regions of the primary afferent fibers and is in effect a reversal of the D.R.IV deflection which results from a persisting sink of current flow in the terminals. According to Lloyd and McIntyre (1949) and Lloyd (1952) that sink of current flow is recordable by microelectrode within the spinal cord, and was first so recorded by Brooks and Eccles (1947), as the "focal synaptic potential." That the cause of the current flow giving rise to the D.R.IV reversal is hyperpolarization of the endings rather than depolarization of the preterminal collaterals follows from the fact that the latter too are hyperpolarized with respect to the resting condition, although less so than are the endings.

Fig. 8 presents two series of observations on the influence upon dorsal root electrotonus of variation in the duration of stimulation. One series was made
with frequency fixed at 240 per sec. (A to E), the other at 850 per sec. (F to K).
The potential level, referred to the electrode proximal to the cord, remains neg-

![Diagram of potential levels](Attachment)

**Fig. 8.** Dorsal root electrotonus as a function of duration of stimulation. The notation IP4EP34 denotes the intrapolar distance in millimeters between recording leads, one of which is at but not touching the cord junction, and the extrapolar distance, also in millimeters, from distal recording lead to severed peripheral end of dorsal root. With this disposition of leads dorsal root after-potentials are not recorded. A to E: frequency 240 per sec. F to K: frequency 850 per sec.

Pretive throughout the period of stimulation thereafter reversing to positivity that grows in amplitude with duration of stimulation.

Contained in Fig. 9 are recordings of dorsal root electrotonus resulting from bouts of stimulation at frequencies varying from 56 to 850 per sec. the duration being maintained constant at 630 msec. Again one sees the characteristic
manner in which the positive phase of dorsal root electrotonus increments with incrementing stimulation.

The purpose of Figs. 8 and 9 is to illustrate by comparison with Figs. 2 and 4 the remarkable parallelism between the form of the positive dorsal root electrotonus and the course of early potentiation which is maintained as frequency

![Diagram](image)

**Fig. 9.** As in Fig. 8 except that frequency of tetanic stimulation is varied between 56 and 850 per sec., duration being held constant.

or duration of stimulation is altered. Actually the correlation is not perfect for two reasons that have been discussed briefly in a preliminary account (Lloyd, 1952). Firstly the positive dorsal root electrotonus contains not one but two fractions, D.R.IV R. and D.R.VI. The latter, positive in both stimulated and neighboring roots, does not grow significantly in size, or duration, with increase either in duration or frequency stimulation. It provides, therefore, essentially a constant distortion of the correlation between early potentiation and the D.R.IV R. process. Secondly the electrotonus appears in a dorsal root only as current flows within the volume of the spinal cord. Thus D.R.IV R. is the
resultant of differences in the after-potentials of the several parts of the intramedullary projections of the primary afferent fibers rather than an exact expression of the after-polarization itself. Some 7 sec. after the close of tetanic stimulation the after-potentials of the intramedullary portions of the primary fibers come into phase which accounts for the fact that deflection D.R.IV R. regresses more rapidly than does potentiation as measured (cf. Lloyd, 1952, Fig. 15).

COMMENT

Discussion will center about the postulate that the terminal regions of the primary afferent collaterals are hyperpolarized following tetanic stimulation which causes subsequent impulses to be augmented by reason of which their terminal action upon the motoneurons is greater than in the resting state (Lloyd, 1949, 1952). A readily measurable aspect of impulse augmentation in the afferent fibers is the increment in spike amplitude (Lloyd, 1949), but it must not be assumed that this change merely because it is easily measured is the only aspect of the nerve impulse that is augmented. An exact statement would be that such features of the presynaptic impulses as are responsible for transmission (and facilitation and inhibition—Lloyd, 1949; Wilson 1958) are augmented in a manner that is precisely paralleled by augmentation of the terminal action potential due to after-hyperpolarization.

Eccles and Rall (1951) have presented a detailed criticism of the foregoing postulate based upon their assumption that the “focal synaptic potential” of Brooks and Eccles (1947) is postsynaptic rather than presynaptic in origin, and upon their observation that their “presynaptic spike,” which they assumed to represent activity in terminals, did not always vary pari passu with potentiation of the synaptic potentials or reflex discharge. Specifically they noted an increase in synaptic potential coupled with a (slight) decrease in the “presynaptic spike,” as measured, after brief tetani and, during the initial phase of post-tetanic block following more prolonged tetani, a depression of synaptic potential coupled with an increase in the measured “presynaptic spike.”

Unfortunately Eccles and Rall did not recognize an important proposition concerning the recording of responses in a volume conductor and did not enquire into the possible reasons for the discrepancies noted before rejecting the notion of relation between potentiation and after-polarization of the presynaptic structures.

The proposition in question concerns the recording of action currents at various points of neurons during the development of a block (Lloyd, 1953). As a conduction block develops the negative phase of action as recorded in volume increases at points immediately above the block whilst decreasing at points beyond the block. Thus change in opposite direction in the focal synaptic potential and the “presynaptic spike” means that the conduction properties
of the primary afferent collaterals are altered at a point between those points at which action is represented by the "presynaptic spike" and by the focal synaptic potential. For example, the observation that a diminished focal synaptic potential is coupled with an augmented "presynaptic spike" during a brief period following prolonged tetanization is a demonstration not of the lack of parallellism between action in the terminals and postsynaptic response as Eccles and Rall have supposed, but rather a demonstration that the depression preceding the onset of late potentiation following prolonged tetanization is due to block (anodal) occurring between the preterminal and terminal portions of the primary afferent projections. It appears then that the process underlying early post-tetanic potentiation when intensified beyond a certain level becomes the cause of post-tetanic block.

Recognizing that the focal synaptic potential is a presynaptic potential it is clear that the results of Eccles and Rall are in complete accord with the present results and with the postulate that post-tetanic potentiation is linked with augmented action due to concurrent hyperpolarization of the synaptic terminals.

Recently Wall and Johnson (1958) have explored the excitability of the primary afferent projections following tetanic stimulation and find them subnormal in degree that largely parallels the degree of potentiation. Of particular interest is their observation that potentiation of the reflex had a delay in reaching maximum, whereas the decrease in excitability of the fibers reached maximum almost immediately after the end of the tetanus. It is important to note that the durations of conditioning tetanization and frequency of testing (each 2.5 sec.) were such that their observations concerned post-tetanic block and late potentiation, and that early post-tetanic potentiation would not have occurred in the circumstances of experiment. Presumably the discrepancy noted by Wall and Johnson would not have appeared had they employed conditioning tetani of shorter duration, for the rise in early potentiation is certainly as rapid as is the post-tetanic rise in hyperpolarization revealed by their excitability measurements. Since the onset of presynaptic threshold rise remains abrupt as early potentiation disappears with increasing duration of conditioning tetanization, Wall and Johnson provide a direct indication that presynaptic hyperpolarization exists to account for the post-tetanic block in the terminal regions of the primary afferent projections. It should be noted that Wall and Johnson suggest that the existence of an anodal block would be consistent with their findings.

It is one matter to state that augmented impulses, the result of hyperpolarization, are cause for the augmented reflex response during potentiation, it is quite another to say what aspect of the impulses is concerned. To account for post-tetanic block one need look no further than to the hyperpolarization, but this would be the case with potentiation only if the presynaptic potential per
were the transmitting agent. This few, even of those committed to an electrical hypothesis of synaptic transmission, would be prepared to concede.

From the more popular "chemical" point of view one might suppose that synaptic vesicles discharge their content into the synaptic cleft for a time and in numbers that are functions of the duration and amplitude of the presynaptic potential. Or, since the ability of the transmitting agency to transmit is severely limited in time (Hunt, 1955) one might even suppose a jet-like discharge of mediator securing transmission, the mediator lingering in a waning concentration to depolarize not only the post-synaptic soma, thereby producing the post-synaptic potential and characteristic facilitation, but also the synaptic face of the presynaptic knobs, thereby producing the presynaptic potential. The possibilities are so numerous that the need would appear to be for information rather than speculation.

Differential behavior with respect to duration and frequency would seem sufficient reason for making the distinction between early and late potentiation. The problems then are: when does one end and when does the other begin? Fig. 10 presents one possible, reasonable, and not unlikely solution to the problems. The plotted curves describe the course of potentiation after a brief (d 0.27 sec.) and after a more enduring (d 9.6 sec.) tetanization. Experimentally obtained points for the early course of the former curve are not plotted; they are to be found in Figs. 1 A and 5. After tetani of short duration the curve of potentiation displays, shortly after its maximum, a discontinuity (cf. also Lloyd, 1952, Fig. 15), at which time the course of potentiation and the course of electrotonic potential D.R.IV R. begin to diverge. The broken line declining from

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Fig. 10. Experimental curves and extrapolations, as described in text, to illustrate hypothesis concerning the temporal courses of early and late potentiation.
the maximum of early potentiation plots the decay of D.R.IV R. (positivity in this case plotted upwards). It is now proposed that this broken line also plots the decay of early potentiation. By subtraction, then, one obtains a representation of the incrementing phase of late potentiation (also plotted as a broken line). It is proposed that the remainder of curve d 0.27 sec. plots the decay of late potentiation in the circumstance. The course of late potentiation so obtained is like that plotted in curve d 9.6 sec.—except in duration. In short the hypothesis is that early potentiation is related to that fraction of post-tetanic hyperpolarization of the terminals that gives rise to current flow and so to D.R.IV R., and that late potentiation is related to that fraction of post-tetanic hyperpolarization that can, because all parts of the projections are in phase, only be measured as a change in demarcation (cf. Woolsey and Larrabee, 1940). The former is of fixed duration, the latter increases in duration with duration of stimulation after the manner of P2 after-potentials generally (Gasser, 1935).

The implication now is that early potentiation and D.R.IV R. are manifestations of a P1 after-potential of the primary afferent terminals. These phenomena have some of the characteristics of P1 after-potentials except that duration is enormously greater: some 7 sec. as against 50 to 100 msec. in the parent fibers (cf. Lloyd, 1952, Fig. 11). This, however, is not so surprising when one considers that the negative phase of action in the terminals, the presynaptic potential, is enormously greater in duration than is the axon spike of the parent fibers.

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