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Afferent Modulation of the Excitability of Pyramidal Tract Fibers

M. D. MANN, W. S. HOLT, AND A. L. TOWE[1]

Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle, Washington 98195

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Recordings were taken extracellularly of the activity of single pyramidal tract (PT) neurons in the forepaw area of the cat's postcruciate cerebral cortex. The activity was evoked antidromically by near-threshold stimulation of the ipsilateral medullary pyramid, and orthodromically by shocks to each of the four paws and by light and sound. The excitability of the PT axons at the medullary pyramid was tested by measuring their threshold to antidromic activation in conditioning-testing interactions. PT,*s*a axons showed no change in excitability following stimulation of any of the four paws. In contrast, both PT,*s*b and PT,*m* axons showed increases in their excitability evokable from any where within their excitatory receptive fields, i.e., from both forepaws in *s*b neurons, and from all four paws and from auditory and visual receptors in *m* neurons. The *s*b axons showed no change in excitability following stimulation of either hindpaw. When tested with single medullary pyramidal tract shocks, the increased excitability began 9 to 25 ms after a contralateral forepaw shock, reached a maximum (decreased threshold of 20 to 45% of resting threshold) at 25 to 35 ms, and then decreased to normal by 100 ms. When tested with trains of shocks at 312/s to the pyramid, the increased excitability lasted about 2.5 times longer than when tested with single shocks. This increased excitability most likely results from depolarizainexcitability followed and, in fact, shortened the period of increased excitation of nearby terminals of the PT axons. In some cells, a period of apparent

Abbreviations: PT—pyramidal tract; *s*a—responds only to stimulation of the contralateral forepaw; *s*b—responds to stimulation of each forepaw; *m*—responds to stimulation of each of the four paws; 3U—unusual, unclassifiable, or untestable category of neurons.

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bility. During the inexcitable period, lasting 130 to 300 ms, the antidromic spike could not be evoked even by shocks 40 times resting threshold strength. This effect probably is not due to hyperpolarization of the same synaptic terminals that are apparently depolarized to produce the initial increased excitability. Rather, it must involve a process rostral to the site of antidromic stimulation, effectively blocking antidromic invasion of the soma and hillock region.

INTRODUCTION

The pyramidal tract (PT) has long been viewed as the major pathway by which the cerebral cortex influences distant subcortical structures. Implicit in this view is the idea that cerebral output, when formed, is not subject to modification; messages sent from the cerebral cortex arrive intact at each subcortical receiving site. A hint that this idea might require modification was published by Dubner *et al.*, (9) in 1969, when they reported having detected a transient increase in the excitability of some corticotrigeminal projection fibers in the cat. Using the method described by Wall (43), they found that the threshold to antidromic activation of those fibers, when stimulated within the main sensory trigeminal nucleus, decreased briefly after stimulation of the infraorbital nerve. About the same time, Towe (unpublished observations) found transient changes in the threshold of some pyramidal tract fibers to antidromic activation from the medullary pyramid after stimulation of the skin. Gugino *et al.* (13) followed this lead, measuring the changes in excitability of corticospinal fibers after peripheral nerve and cerebral cortex stimulation. Both cutaneous and muscle nerve stimulation, even at group I strength, were effective in modifying the threshold of corticospinal fibers to antidromic activation at the cervical enlargement of the spinal cord. An early decrease in excitability was followed by a prolonged increase, the latter being ascribed to a depolarizing action of the conditioning inputs onto the synaptic terminals of PT fibers near the site of testing (10). One possible consequence of such an action, presynaptic inhibition, has been studied extensively in other systems (28). Another possible consequence, resulting from the increased rate of spontaneous release of transmitter when the terminal is partially depolarized (20), has received no experimental attention. Perhaps the animal has found a convenient way to increase transiently the excitability of many postsynaptic neurons without seriously compromising the efficacy of the affected presynaptic terminals. The relative roles of these two possible consequences of any presynaptic depolarization in the behaving animal have not been assessed. Whatever they may turn out to be, it is evident that some corticobulbar and corticospinal fibers can be influenced via diverse sensory inputs. It is the aim of the present paper to

describe the time course and magnitude of the excitability changes produced on PT fibers by cutaneous stimulation, and to determine on what functional sets of pyramidal tract fibers these excitability changes occur.

METHODS

Domestic cats weighing 2.5 to 4.0 kg were anesthetized with α-chloralose (50 to 60 mg/kg, intraperitoneally), placed on artificial respiration, and paralyzed with decamethonium bromide as needed throughout the experiment. Surgical procedures included tracheal and venous cannulation, exposure of the medullary pyramids through the standard ventral approach, exposure of the right anterior cerebral hemisphere, and production of bilateral pneumothorax. Upon reflection of the dura mater, the cerebral cortex was covered with a protective polyethylene sheet. Respiration was adjusted to the weight of the animal, ranging from 20 to 50 ml/stroke at 17 to 20 strokes/min. Rectal temperature was maintained at 37.5°C via a servocontrolled dc heating pad placed under the animal.

A small hole was made in the polyethylene sheet to allow placement of a silver ball electrode and a glass micropipet, filled with 2.5 M NaCl, onto the standard postcruciate recording site described elsewhere (39). Signals were led through Grass P5 preamplifiers, with the low-frequency half-amplitude set at 1.5 Hz for the gross electrode channel and at 35 Hz for the microelectrode channel, to a Tektronix 565 oscilloscope (Type 2A63 differential amplifiers) for photographic recording. Two pairs of stimulating electrodes were placed along the long axis of the medullary pyramid, ipsilateral to the site of cerebral recording. Each pair of electrodes had a 2-mm tip separation, the two pairs being placed 6 to 8 mm apart, with the caudal pair at midolivary and the rostral pair at rostral trapezoid levels. Bipolar needle electrodes were inserted into the central footpad of each limb for cutaneous stimulation. Auditory and visual stimuli were produced by hand-claps and by quick and silent, on-and-off exposures of a mechanically interrupted light beam directed into the right eye. Cutaneous stimuli were 0.1-ms pulses of 14 V (supramaximal strength). PT stimuli were 0.5-ms pulses of various strengths, depending on the neuron and the experimental maneuver.

RESULTS

The basic maneuver consisted of testing the excitability of the axon of an individual PT neuron, as indicated by the presence or absence of an antidromic spike, recorded extracellularly in the cerebral cortex, after a shock to the medullary pyramid. This technique requires an adequate working definition of the resting or unconditioned threshold. Two forms

of medullary PT stimulation were used: (a) single shocks, applied once per second, and (b) a gated train of shocks applied once per two seconds. The gated train was a 500-ms series of shocks at 200/s or 312/s. In the former case, a satisfactory resting threshold value was sometimes difficult to obtain, for threshold drifted during the experimental procedures and sometimes appeared to fluctuate erratically. This made the single-shock condition-test procedure unsatisfactory, in some instances. Resting threshold was usually estimated by means of a gated train of shocks, although this method could not be used with high-threshold axons, due to activation of nearby medial lemniscus axons. Even with weaker shocks, some difficulty arose, presumably due to transsynaptic PT effects that ultimately affected the neuron under study. To obtain a relatively accurate estimate of resting threshold, the method of limits was used; threshold was taken as the midpoint between the two values at which the neuron just responded to each shock in the train, as the shock strength was gradually increased from below threshold and reduced from above threshold.

Many PT neurons discharged short bursts of antidromic spikes during near-threshold gated trains, as though membrane excitability fluctuated rapidly. In most instances, the bursts were not sufficiently regular to be ascribed to some direct consequence of the gated train, such as axon collateral action or activation of nearby medial lemniscus fibers, collaterals of which might affect PT axon terminals. In all units showing an A–B break in the spike, both the A and the B components appeared and disappeared together, suggesting that the silent periods between the bursts were not due to failure of antidromic invasion from a faithfully responding axon. The source of these effects must be sought distal to the cell body of the neuron.

Cutaneous Modulation of Axon Excitability. The basic observation in this study was a transient responsiveness of a PT neuron to a previously ineffective (subthreshold) stimulus to the ipsilateral medullary pyramid after a cutaneous conditioning stimulus. The interpretation is that the excitability of the axon of the PT neuron is increased as a consequence of the cutaneous stimulation. The mechanism underlying this transient increase in excitability is probably a presynaptic depolarization of PT axon terminals consequent to the cutaneous input. Stimulation anywhere within the excitatory receptive field of the neuron produced this excitability change, even when that receptive field included auditory and visual receptors. Stimulation outside the excitatory receptive field of the neuron was without effect. No clear excitability change was found on the axons of PT,*sa* (responds only to stimulation of contralateral forepaw) neurons.

The transient excitability change on non-*sa*, PT axons was readily seen when the contralateral forepaw was stimulated during a gated train of

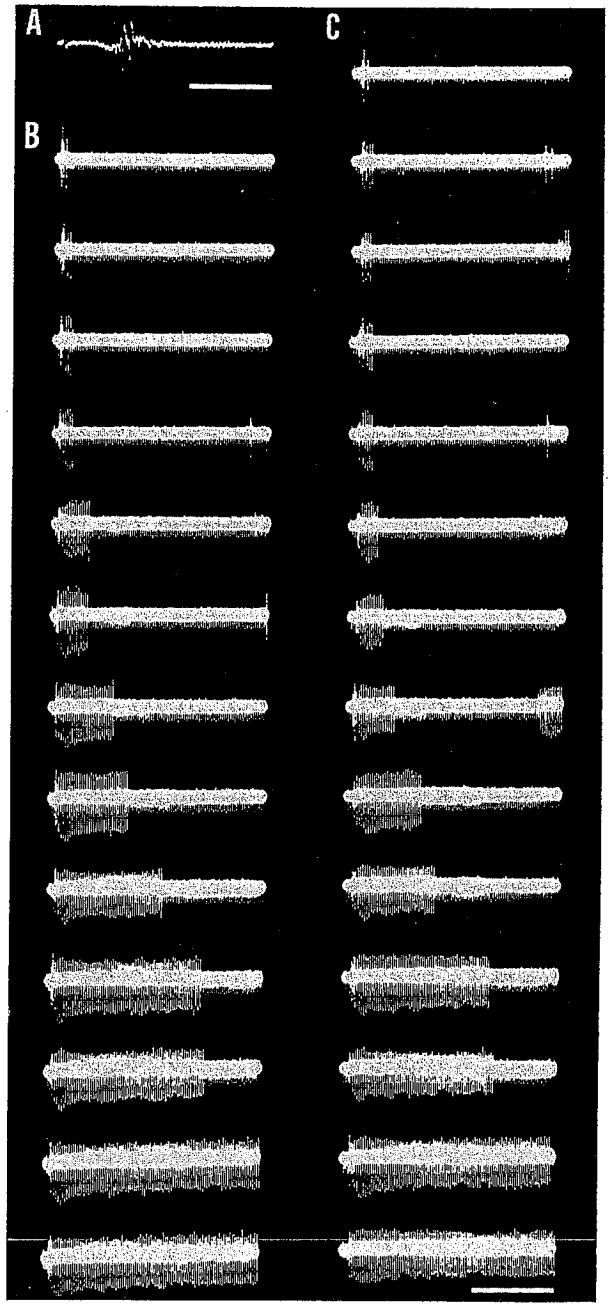


FIG. 1. Period of increased excitability for a PT,*m* axon after paw stimulation as tested with 500-ms, 312/s, gated trains of shocks at near-threshold strength. The antidromic spike was recorded at a depth of 2600 μm. A—Response of the neuron to

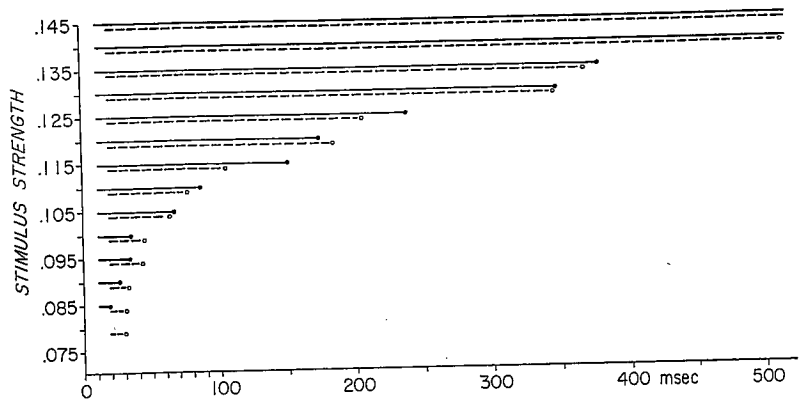
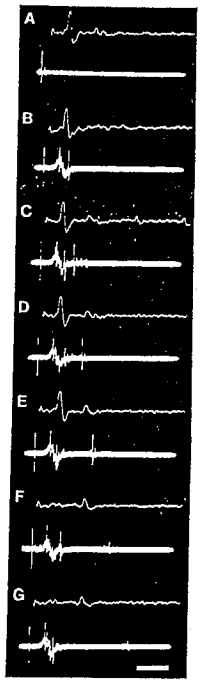


FIG. 2. Excitability curves plotted from responses shown in Fig. 1. Plots of the duration of one-to-one antidromic discharge after conditioning stimulation of contralateral (solid lines) and ipsilateral (dashed lines) forepaws at supramaximal strength. Duration of the discharge (abscissa) is plotted for different strengths of shocks to ipsilateral medullary pyramid (ordinate).

medullary PT shocks at subthreshold strengths for the axon. The neuron would first respond in a normal manner to the contralateral forepaw shock, and would then start responding to each PT shock for a period of time dependent on shock strength. Figure 1 illustrates this phenomenon for a PT,*m* (responds to stimulation of each of the four paws) neuron following both contralateral and ipsilateral forepaw stimulation. The increasing period of antidromic responsiveness with increasing strength of the subthreshold medullary PT shock is evident. At any shock strength, the period of antidromic responsiveness varied on repeated trials. Figure 2 shows the average duration of each period of antidromic responsiveness for the neuron illustrated in Fig. 1, as a function of time after stimulation of each forepaw. The time of onset of the effect could not be accurately measured in this set of data; it seemed to be about 11 ms for contralateral input and about 18 ms for ipsilateral input. The time course of the effect is consistent with the idea of presynaptic depolarization, though the magnitude of the effect is large with respect to the probable distance of the affected terminals from the site of excitability testing. The average peak

stimulation of contralateral forepaw at supramaximal strength. B—Effect of this same stimulus on the responsiveness of the PT axon to trains of shocks at gradually increasing strength. Medullary pyramidal shock strength in upper trace is 0.085, in arbitrary units, with the strength incremented by 0.005 for each succeeding trace, to a maximal strength of 0.145 in bottom trace. Threshold for one-to-one following by the axon is shown in the next-to-bottom trace ($I = 0.140$). C—Effect of a supramaximal shock to ipsilateral forepaw. Top trace in C taken at medullary shock strength of 0.80; adjacent traces in B and C were taken at same shock strengths. Time scales: A, 20 ms; B, 200 ms.



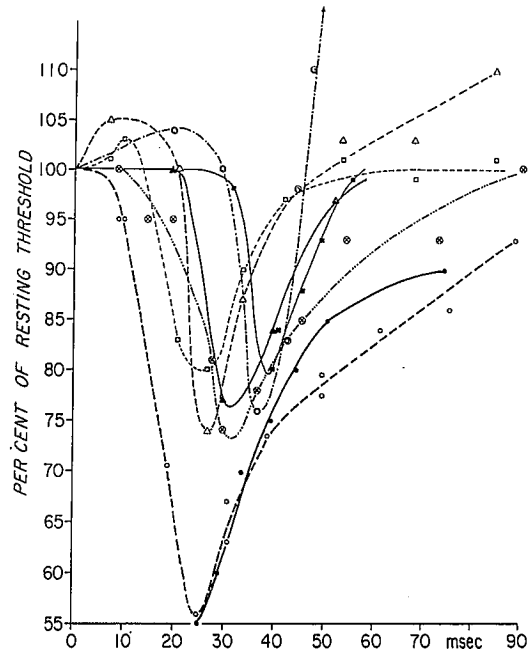


FIG. 3. (Left) Single-shock test of the excitability of a PT,*m* axon. A—Antidromic response to suprathreshold medullary pyramidal tract shock ($I = 0.33$) at two sweep speeds. B through G—Effect of a supramaximal shock to the contralateral forepaw on the responsiveness of the axon to a subthreshold ($I = 0.27$) shock applied to ipsilateral medullary pyramid at various times afterwards. The antidromic spike can be seen in traces B—E, but not in F and G. Time bar: upper traces, 2 ms; lower traces, 20 ms.

FIG. 4. (Right) Excitability curves for eight pyramidal tract neurons as measured with single-shock procedure. Threshold shock strength for antidromic spike is plotted on the ordinate as percentage of the resting threshold for each neuron against the time after supramaximal shock to contralateral forepaw on the abscissa.

magnitude of the effect for all neurons adequately studied was 32% of the unconditioned threshold for antidromic activation (threshold decreased to 68% of its unconditioned value); it ranged from 20 to 50%. The distal pair of PT stimulating electrodes was usually more effective (average magnitude of 34%) than the proximal pair (average magnitude of 29%), though the relative effectiveness was reversed on two of every five neurons that were adequately tested.

When the antidromic threshold was tested with single shocks instead of a 312/s train of shocks, the apparent time course of the effect was much reduced. This is illustrated by the PT,*m* neuron of Fig. 3 (trace F), where

a single shock at 85% of resting threshold strength failed to excite the axon when applied 50 ms after a supramaximal contralateral forepaw stimulus. A similar shock applied at 312/s to the medullary pyramid would be expected to evoke antidromic spikes regularly for at least 200 ms. By determining threshold strength for antidromic activation at successively longer intervals after a cutaneous conditioning stimulus, the time course of excitability change on the axon could be traced. This method yielded an average peak magnitude for the effect of 29% of the unconditioned threshold, with a range from 20 to 45%— values similar to those obtained using 312/s trains of shocks. The effect began 8 to 25 ms after the contralateral forepaw shock, reached a maximum 25 to 35 ms after the forepaw shock, and was generally over within 100 ms. The time courses for a number of neurons are shown in Fig. 4; it is evident that the effect may include an initial decrease in excitability on some axons (13). In those neurons held long enough for a direct comparison to be made, the time to "half-amplitude" recovery in the single-shock test procedure averaged 40% of that in the gated-train shock procedure. Figure 5 illustrates this relationship for a PT,*m* neuron. In this case, the time to half-amplitude recovery in the single-shock procedure was about 30% of that in the gated-train shock procedure. It is clear that the two testing procedures yield markedly different estimates of the time course of the effect, for the single-shock curve falls more than one standard deviation short of the mean gated-train shock curve, diverging by as much as three standard deviations. The difference in time course estimates by the two methods varied with the resting

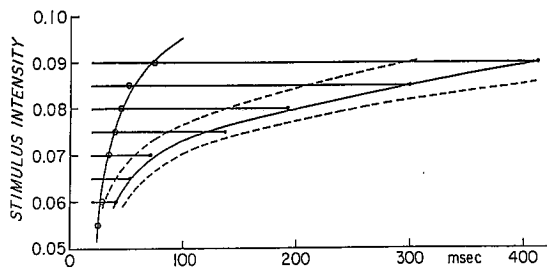


FIG. 5. Time course of increased excitability of a PT,*m* axon after supramaximal shock to contralateral forepaw as measured with single-shock (open circles) and gated-train-shock (filled circles) test procedures. The ordinate represents threshold stimulus strengths for single-shock procedure and strength of shock, below threshold ($I = 0.10$) for one-to-one firing at 312/s for 500 ms for the gated-train-shock procedure. Antidromic threshold for single shocks was $I = 0.10$. Horizontal line segments indicate duration of the one-to-one response at different pyramidal shock strengths; dots at their end-points are plotted at the mean termination time of the response; dashed lines are drawn one standard deviation from the mean.

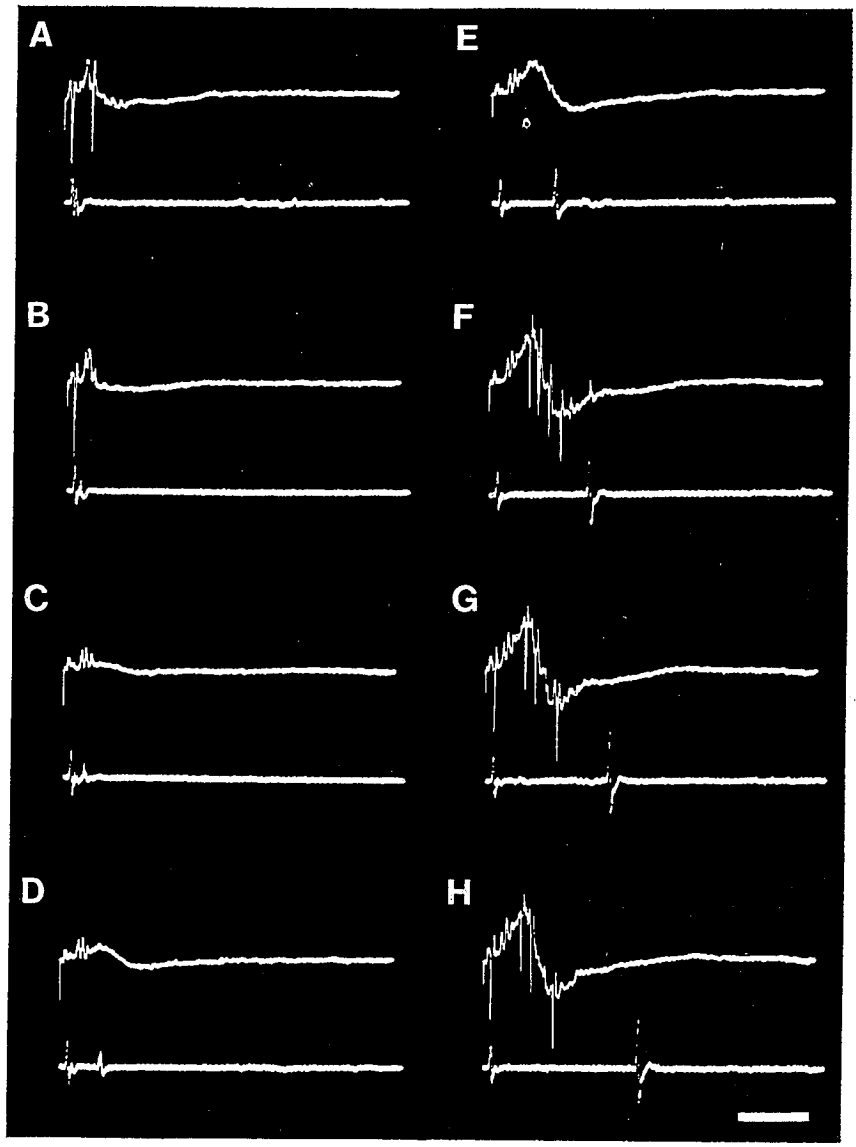


FIG. 6. Single-shock test of the excitability of a PT,*m* axon. The effect of a supramaximal shock to contralateral forepaw on responsiveness of the axon to a suprathreshold ($I = 2.0$; threshold, $I = 0.15$) shock applied to ipsilateral medullary pyramid at various times afterwards. The antidromic spike, clearly visible at the shorter intervals in A and B, was not elicited at longer intervals up to 130 ms, C through F. At longer intervals, the antidromic spike appears in response to the 13-times-threshold pyramidal shock used throughout. Time bar: upper traces, 10 ms; lower traces, 100 ms. Spikes retouched.

threshold of the axon, being small for low-threshold axons and large for high-threshold axons.

A few axons showed a period of apparent inexcitability, starting about 25 to 45 ms after the cutaneous conditioning stimulus and lasting 70 to 100 ms. The start of one such curve can be seen in Fig. 4, increasing rapidly at about 45 ms. Figure 6 illustrates this phenomenon for a different PT,*m* neuron, tested by the single-shock procedure. At intervals less than 30 ms (Fig. 6, traces A and B) and greater than 140 ms (traces G and H), an antidromic spike appeared to stimulation of the medullary pyramid at a strength 13-times-threshold for that axon. However, at intermediate condition-test intervals (traces C and F), the antidromic spike failed to appear. During this period (Fig. 6, trace F), the orthodromic spikes evoked by spread of current to the nearby medial lemniscus recovered, having been suppressed by the prior cutaneous conditioning input. With respect to the response to medial lemniscus stimulation, the condition-test interaction was normal (17). During the period of apparent antidromic inexcitability, increasing stimulus strength to 40-times-threshold for the axon (25 mA for 0.05 ms) was without effect. This was not simply a failure of an antidromic spike to invade the soma, for on those spikes showing an A–B break, both components failed together. Using the gated-train shock procedure, the period of inexcitability was manifested as a complete failure to respond to the 312/s supramaximal shocks; it appeared as a silent period in the train of antidromic spikes. As observed with the period of increased excitability, the apparent duration of inexcitability was longer (as long at 300 ms) when tested with gated trains of shocks than when tested with single shocks.

Excitability Changes in Different Sets of Pyramidal Tract Neurons. Each PT neuron successfully isolated was classed as a member of some functional set, according to the criteria used recently in this laboratory (37, 39). Specifically they were classed as *s*a, *s*b, *m*, or 3U. An *s*a neuron in forepaw cortex responds ($P \geq 0.5$) only to stimulation of the contralateral forepaw, an *s*b neuron to stimulation of each forepaw, and an *m* neuron to stimulation of each of the four paws. The only neurons from the 3U category (unusual, unclassifiable, or untestable) to be used in this study were mute; that is, they did not respond to any cutaneous input. As previously reported (27), many of the *s*a and *s*b neurons received an inhibitory influence from the hindpaws.

Table 1 shows that not all PT neurons displayed a change in axonal excitability after cutaneous stimulation. In particular, none of the *s*a neurons showed a clearly detectable change in excitability to medullary pyramid stimulation; on a few *s*a neurons, intensive study of a questionable effect led to the judgment that no excitability change was actually present. By

TABLE 1

Number of Pyramidal Tract Neurons in Each Functional Set That Showed an Increase or No Change in Excitability after Contralateral Forepaw Stimulation

	sa	*sb*	*m*	Mute
Increase	0	9	97	6
No change	26	0	0	12

sharp contrast, all *s*b and *m* neurons tested showed a clear change in excitability after cutaneous stimulation within their excitatory receptive fields, but not outside those fields. This is illustrated for a PT,*m* neuron in Fig. 7. The responses to stimulation of each of the paws (column A of Fig. 7) show this to be a late-firing PT neuron, isolated in layer V. Stimulation of the medullary pyramid with a single subthreshold shock (85% of resting threshold for the axon) 46 ms after cutaneous stimulation evoked an antidromic spike for each of the four paws (column B). Using a gated train of shocks at the same strength (column C) resulted in a prolonged train of antidromic spikes for each of the four paws. Trace C2 of Fig. 7 is somewhat unusual, in that antidromic spikes appeared rather late in the gated train.

All *m* neurons tested for excitation by hand-clap and/or light-flash responded, and all showed increased axonal excitability after such inputs. Qualitatively, the duration of the effect seemed to vary directly with the strength of the hand-clap. The effect followed both the on and off light transients for all neurons so tested. An unconditioned response to hand-clap is illustrated in trace F of Fig. 7; trace G shows the effect of a hand-clap in the presence of a 200/s, subthreshold gated train of shocks to the medullary pyramid.

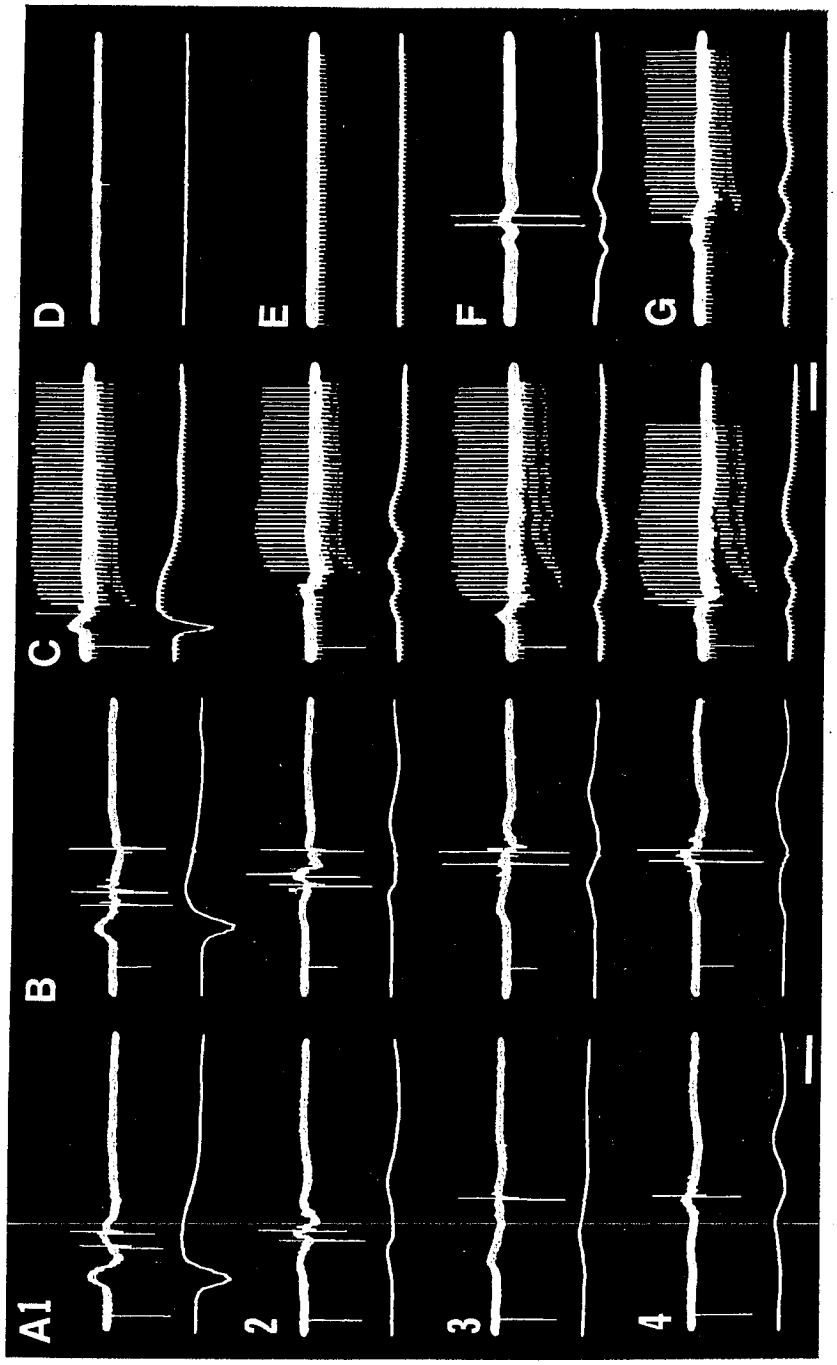
Some asymmetry of effect was found on the *s*b neurons, but not on the *m* neurons. Figure 8 shows the time course of the effect for a PT,*s*b neuron after contralateral and ipsilateral forepaw stimulation. The maximal excitability change after ipsilateral input was only three-fourths as great as that after contralateral input of the same strength, and the apparent rates of recovery differed. On the other hand, similar curves for the PT, *m* neuron shown in Fig. 2 are nearly alike. A full set of excitability curves for a different PT,*m* neuron is shown in Fig. 9. The great similarity in magnitude and time course of the effect evoked by the different conditioning input sites is evident.

The apparent period of inexcitability was seen on too few neurons to cast any light on the nature of the subset of PT neurons that show this effect. It was seen on one PT,*s*b neuron and on five PT,*m* neurons. It was

not systematically sought early in the study, though its conspicuous nature when using gated trains of medullary pyramidal shocks make it hard to overlook. The effect is infrequent to rare.

Anesthetic Effects. In one animal, anesthetized with α-chloralose (100 mg/kg), most neurons were unresponsive (mute) to peripheral stimulation. One *s*b neuron was identified, but failed to show any presynaptic inhibitory effects. A number of mute PT cells were also tested for excitability changes after stimulation of the paws. Only one of four of those cells showed such an effect, and that one only in response to stimulation of the contralateral forepaw. It appears that deep-chloralose anesthesia produces an animal that is much like the animal anesthetized with barbiturate in that its pericruciate cerebral neurons become unresponsive to peripheral stimulation. Barbiturates depress the peripheral responsiveness of *m* neurons preferentially, whereas they have little effect on *s*a neurons (21, 23, 40). In one animal, anesthetized with pentobarbital sodium, 30 mg/kg, 12 PT neurons were isolated; none was responsive to cutaneous stimulation. In the samples of Towe *et al.* (38), 87 to 88% of PT neurons were *m* cells, and only a small percentage were *s*a cells. Using this figure, it is estimated that at least 10 of the 12 PT neurons sampled in this cat under barbiturate should have been PT,*m* neurons. Then, applying the results of Table 1, all 10 should have shown a presynaptic inhibitory effect from all four paws. However, none of them showed any axonal excitability changes at all; not to cutaneous input, hand-claps, or light-flashes. In view of this finding, we conclude that both the pathways responsible for the orthodromic responsiveness of PT,*m* neurons to paw stimulation and the pathways responsible for the axonal excitability changes are blocked by barbiturate anesthesia. Thus, unlike more familiar examples of presynaptic depolarizations that are enhanced by barbiturates (28), this one is abolished.

Effects of Spreading Depression. In two animals, a crystal of KCl was placed on the cerebral cortex near the site of electrode penetration. In one, a PT,*m* neuron showing the increase in axonal excitability with a superimposed period of apparent inexcitability had first been isolated. In the other, a PT,*m* neuron showing the increase in axonal excitability had been isolated. In both instances, as responsiveness to cutaneous input disappeared, the pattern of axonal excitability changes continued, unaltered by the spreading depression. A PT,*s*b neuron showing the increase in axonal excitability with a superimposed period of apparent inexcitability was under study when a spreading depression developed. The pattern of axonal excitability changes continued, unaltered. During the spreading depressions, two additional PT neurons were isolated on the basis of their antidromic spikes; both were unresponsive (mute) to cutaneous stimulation. One showed a clear change and the other no change in axonal excitability af-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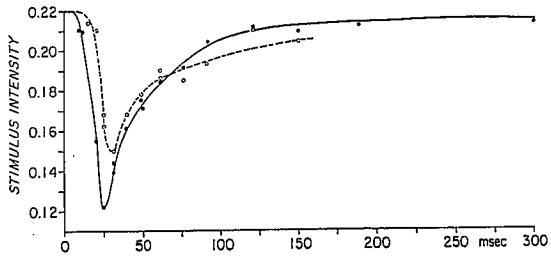

FIG. 8. Excitability curves for single PT,*sb* axon measured with single-shock procedure. Threshold strength for the antidromic response is plotted on the ordinate against time after paw shock; condition-test interval, on the abscissa. Decrease in threshold of the axon is shown after stimulation of contralateral (filled circles) and ipsilateral (open circles) forepaws at supramaximal shock strength.

ter stimulation of the contralateral forepaw. It is clear that neither effect, the increase in axonal excitability nor the period of apparent inexcitability, depends on orthodromic responsiveness of the neuron.

Antidromic Latency and Threshold. As in all previous studies, the majority of the PT neurons sampled had short antidromic latencies. Taking 2.3 ms as the division betwen fast and slow PT neurons (33), fully 70% of the sample consisted of fast PT neurons. Table 2 shows that the different functional sets did not distribute uniformly between the two categories. In particular, more *sb* and *m* neurons than expected were in the fast PT category, and more *sa* neurons than expected were in the slow PT category.

The distribution of antidromic latencies is shown in Fig. 10A, using an 0.2-ms bin-width. The resting thresholds to antidromic activation distributed in much the same manner (Fig. 10C), although they were not quite as "peaky" at low values. This might be interpreted as a simple reflection of the strong relationship between fiber size and threshold. However, the scatter plot of Fig. 10B shows this to be true only in a general sense.

FIG. 7. Increased excitability of a PT,*m* axon after stimulation of all four paws as tested with single-shock and gated-train-shock procedures. A—Responses of the neuron to stimulation of each of the four paws at supramaximal intensity. A1: Contralateral forepaw; A2; ipsilateral hindpaw; A3: contralateral hindpaw; A4: ipsilateral forepaw. In each pair, microelectrode, upper records; cortical surface, lower record. D—Lack of responsiveness of the neuron to stimulation of ipsilateral medullary pyramid with shock of intensity $I = 0.13$. When that same shock followed stimulation of the paws by 46 ms, an antidromic spike was initiated (B1 through B4). A train of shocks at 200/s to the pyramid at intensity 0.13 failed to excite the neuron antidromically (E), but when paws were stimulated during the train, a period of responding to the train resulted (C1 through C4). Hand-clap that evoked only two spikes (F) altered the excitability of the axon sufficiently to result in the train of spikes (G), during subthreshold gated train (E). Time bars: A, B, and D, 20 ms; C,E through G, 50 ms. Spikes retouched.

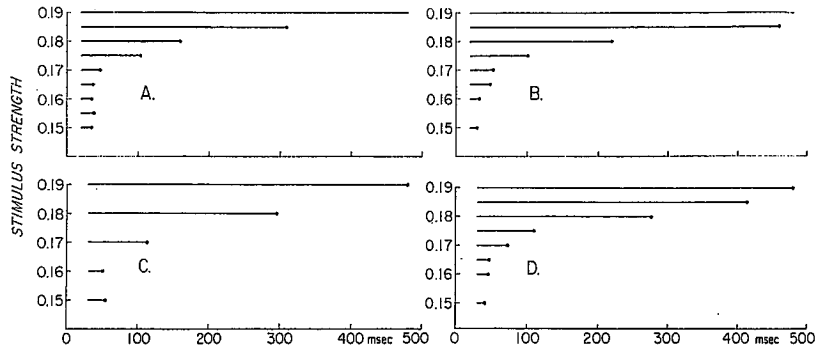

FIG. 9. Excitability curves for a PT,*m* axon as measured after stimulation of contralateral forepaw (A), ipsilateral forepaw (B), contralateral hindpaw (C), and ipsilateral hindpaw (D). For more detailed description of format, see caption of Fig. 2.

The data points are scattered such that the linear regression line: threshold = 0.195 + 0.094 × antidromic latency, is not very descriptive. Converting antidromic latencies to "equivalent fiber size," using three as the constant of proportionality (36) and calculating a regression line on the resultant data, yielded the equally nondescriptive line: threshold = 0.587 − 0.036 × antidromic latency. The scatter is large.

DISCUSSION

Increased Axonal Excitability. The rapid decrease in threshold for antidromic activation of PT,*s*b and PT,*m* neurons is perhaps best explained in terms of depolarization of PT axon terminals near the site of excitability testing. That the effect is not of cerebral origin is shown by its persistence during spreading depression. If the afferent input to the cerebral cortex improved antidromic invasion of the initial segment and soma, then this improvement should have disappeared, or at least have been markedly altered, during spreading depression, whereas the effect persisted without change. The effect is similar in character to apparent presynaptic depolarizing actions elsewhere in the nervous system (10), except for its sensitivity to barbiturate anesthesia.

TABLE 2

Number of Fast and Slow Pyramidal Tract Neurons in Each Functional Set

	*s*a	*s*b	*m*	3U
Fast PT	1	4	59	9
Slow PT	9	0	10	12

If this explanation is correct, then nearby terminals are affected in large numbers or the effect is large on each terminal, for the maximal change in axonal threshold measured at the medullary pyramid averaged about 30%, and on one axon reached 50%. This suggests an average membrane voltage change of perhaps 5 mV at the site of excitability testing. Because of its location, the most likely site for the proposed depolarizing action is on PT terminals within the ventromedial reticular formation—nucleus reticularis gigantocellularis (19, 25). Other nearby sites, such as the lateral reticular nucleus (19, 22) or the inferior olivary nucleus (17), could also be involved. When tested with two pairs of stimulating electrodes, one pair being 6 to 8 mm rostral to the other on the medullary pyramid, the change in axonal excitability was almost as often greater at the rostral site as it was at the caudal testing site. Thus, different axons may have different densities of terminals in the rostrocaudal direction, or the rostrocaudal distribution of presynaptic influences is different on different PT axons.

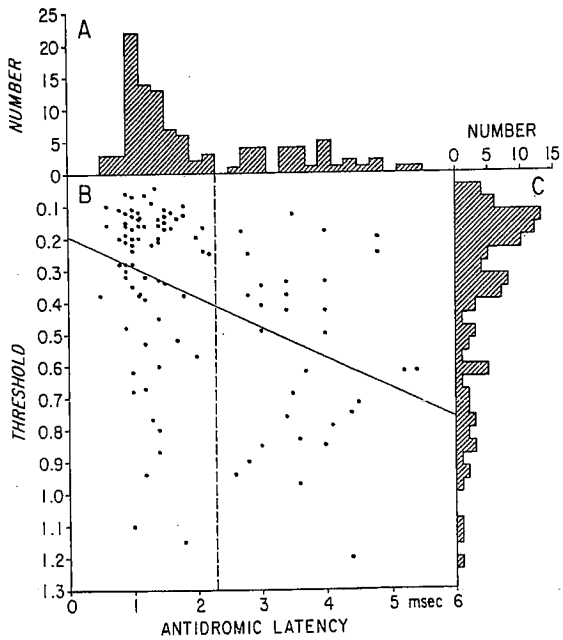

FIG. 10. Antidromic latencies and threshold strengths for 104 pyramidal tract (PT) neurons. Distributions of antidromic latencies (A) and thresholds (C) are plotted using 0.2-ms and 0.04-threshold unit bin-widths, respectively. C—Joint scatter plot of latency (abscissa) and threshold (ordinate). The 2.3-ms latency separation between fast and slow PT neurons is indicated by the dashed, vertical line. Regression line for all points, threshold $= 0.094 \times$ latency $+ 0.195$.

Period of Apparent Axonal Inexcitability. Presynaptic depolarization has been advocated by other investigators as an explanation for the increase in excitability on corticothalamic, corticotrigeminal, and corticospinal axons that follows sensory stimulation (8, 9, 13, 30). Those studies have shown that a decrease in axon excitability may also occur, the change being attributed to a presynaptic hyperpolarizing action (13, 29). It seems unlikely that the period of apparent inexcitability seen on some PT axons in the present study could be due to hyperpolarization on terminals near to or caudal to the testing site for no available amount of stimulus current (25 mA, 0.05 ms) would result in the appearance of an antidromic spike at the recording site in the cerebral cortex. The effect must occur at some point between the stimulating and recording sites and must be sufficiently great to block antidromic conduction.

During the period of apparent axonal inexcitability, the PT neuron continues to respond to afferent input produced by stimulus current spread into the medial lemniscus. The response to the afferent input appears normal (for the particular condition-test intervals) suggesting that the neuronal soma is not depressed. If the absence of antidromic responses during this period reflected failure of antidromic invasion of the intial segment, then that failure was due to the afferent input, for no such failure occurred with the antidromic stimulus alone, even at near-threshold stimulus strengths. Failure of antidromic invasion of the initial segment suggests that the neuron's hillock region would be strongly hyperpolarized, a condition that would be reflected in the responses of the neuron to afferent input. However, no change in responsiveness to afferent input was detected during this period. Furthermore, the failure of spreading cortical depression to alter the period of apparent axonal inexcitability indicates that the mechanism yielding this phenomenon does not involve cerebral cortex in the vicinity of the recording electrode.

Three possible mechanisms for this interesting phenomenon seem worth mentioning: (i) strong hyperpolarization on terminals of short collaterals; (ii) strong depolarization on terminals of short collaterals, driving the axonal membrane far up the sodium inactivation function; and (iii) active blocking action by hyperpolarization at some nodes of Ranvier. The first two of these mechanisms would involve PT collaterals into thalamic nucleus ventralis posterior, ventralis lateralis, or central médian, or into the basal ganglia, the red nucleus, the pontine nuclei, or the mesencephalic reticular formation (1, 4, 11, 14, 31, 41). Hyperpolarization on such terminals, as reported by Sessle and Dubner (29) for thalamic nucleus ventralis posterior medialis, could reduce the safety factor at some branch points sufficiently to block conduction. On the other hand, if the collaterals are short and their terminals suffer a strong depolarization, then the axon

membrane might be driven into "cathodal block" analogous to that demonstrated for the motoneuron soma (5).

The two foregoing mechanisms require the presence of synaptic endings on the terminals of PT collaterals in thalamus, midbrain, and/or pons. Axo-axonic synapses have been observed in the "ventrobasal" thalamus (15, 24, 34), though the corticofugal terminals have been diagnosed as presynaptic on the basis of their high vesicle content (16). However, the presence of synaptic vesicles within a terminal may not uniquely define that terminal as presynaptic (2, 12, 32).

The third possible mechanism involves an active hyperpolarization at some nodes of Ranvier, yielding an effect analogous to "Wedensky inhibition" (45). Nodal synaptic structures have been found in the central nervous system of vertebrates (3, 18, 44), though none have been described for the PT, basis pedunculi, or internal capsule. Further, because the vesicles occur in the nodal "sack," the axon has been interpreted as the presynaptic component, though the site of the vesicles may not be diagnostic. If this proposed mechanism exists, it offers a way of "closing a gate" to activity on the distal portion of an axonal tree, while leaving the proximal portion to function normally.

The Uniqueness of PT,sa Neurons. A striking finding in this study was that all PT,*sb* and all PT,*m* neurons showed an increase in axonal excitability after stimulation within their excitatory receptive fields, whereas no PT,*sa* neuron showed a measurable effect. PT,*sa* neurons have either no terminals in the medulla oblongata at all, or none close enough to influence axonal excitability, or they have such terminals but do not receive a presynaptic depolarizing influence. Whether PT,*sa* neurons receive such an influence elsewhere, or not at all, is unknown. Gugino *et al.* (13) did not differentiate their PT neurons into functional sets, and failed to mention whether some PT neurons showed no excitability changes after peripheral or cerebral conditioning stimulation. The differential distribution of this apparent presynaptic depolarizing action provides further evidence that the pyramidal system may include at least two functionally distinct systems (35). In addition, the complete segregation of this effect between sets of neurons distinguished by the size of their cutaneous excitatory receptive fields further reinforces belief in the fundamental nature of that distinction (39, 42).

Time Course. The markedly different time courses of increased axonal excitability obtained by the two methods of testing may have resulted from one or more of three possible mechanisms: (i) enhancement by repetitive presynaptic action: (ii) enhancement via postsynaptic spike activity or their associated after-potentials; and (iii) interaction between PT terminals. The gated train of shocks activates many PT axons which may synaptically

excite neurons that in turn (among other things) depolarize other PT terminals. On the other hand, the gated train of shocks may activate nearby ascending axons that (among other things) depolarize the PT terminals. In either case, the gated train would effectively prolong the presynaptic depolarizing action initiated by the afferent conditioning input. The degree of prolongation would vary directly with the test stimulus strength and with the resting axonal threshold. Both expectations were met in this study. It thus seems likely that the prolonged time course associated with the gated-train testing method resulted from enhancement by repetitive presynaptic action.

It remains possible that axon spikes, when initiated, might enhance the initial depolarizing action either through some effect of the spikes themselves or of their associated after-potentials. However, there seems to be no precedent for such an effect. On the other hand, terminals of some PT axons might synapse (among other places) onto terminals of other PT axons, depolarizing them. Those axons excited by the gated train of shocks would thus prolong the depolarizing action initiated by sensory stimulation. Such an interaction among axons that might otherwise appear to comprise a homogeneous set has been observed among group Ia afferent fibers (7). Such an interaction could also account for the cerebrally originating excitability changes observed on PT axons by Gugino *et al.* (13).

Threshold. Threshold determinations were difficult to make, for there was considerable trial-to-trial variation. That variation, however, was miniscule in comparison to the variation among axons. A clear relation between antidromic latency (or axon size) and resting threshold did not appear in the sample, due to two major factors. Because of the high current density near the electrode, a nearby, small axon might respond to a weaker stimulus than a more distant, large axon, thereby obscuring any well-ordered relation that might exist. Additionally, histological examination of the medullary pyramids reveals that the amount of myelin around any two axis cylinders of the same diameter is rarely the same; the ratio of axis cylinder diameter to axon diameter varies from 0.2 to 0.8, only rarely attaining the optimal value of 0.55, as calculated by Rushton (26). Thus, a well-ordered relation between antidromic latency (or axonal size, when calculated from latency data) and resting threshold could hardly exist.

Presynaptic Inhibition. If, indeed, the increase in PT axon excitability that follows sensory stimulation results from partial depolarization of nearby terminals of the axon, then the role of this depolarization in the operation of the system must be understood. Current thinking focuses on the amount of transmitter released from such terminals by an invading spike discharge (28), little attention being given to the consequences of increased transmitter release during presynaptic depolarization in the ab-

sence of invading spike discharges. The result is the concept of presynaptic inhibition, the idea that the efficacy of synaptic action can be decreased to the point of failure of transmission. A less conspicuous action would appear as a lengthening of synaptic delay, lengthened interspike intervals, and fewer spikes in relation to the excitatory event. The increase in transmitter release occasioned by the partial depolarization of the terminals (20) would partially offset this effect. With strong, synchronous input to motoneurons, the effect does not fully offset the decrease in efficacy of transmisison across the partially depolarized terminals (6). The excitability level of neurons supplied by partially depolarized terminals is increased. In particular, the effectiveness of nondepolarized terminals supplying the same neurons would be increased. Such a process might be significant to the animal, and might explain the existence of presynaptic depolarization on PT terminals. By partially depolarizing such terminals as an afferent barrage ascends the system, a transient increase in the "central excitatory state" might be effected. The apparently diverse distribution of PT terminals (35) provides an ideal medium for such an action.

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