

Amplification and Linear Summation of Synaptic Effects on Motoneuron Firing Rate

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Amplification and linear summation of synaptic effects on motoneuron firing rate. *J Neurophysiol* 85: 43–53, 2001. The aim of this study was to measure the effects of synaptic input on motoneuron firing rate in an anesthetized cat preparation, where activation of voltage-sensitive dendritic conductances may influence synaptic integration and repetitive firing. In anesthetized cats, the change in firing rate produced by a steady synaptic input is approximately equal to the product of the effective synaptic current measured at the resting potential (I_N) and the slope of the linear relation between somatically injected current and motoneuron discharge rate (f - I slope). However, previous studies in the unanesthetized decerebrate cat indicate that firing rate modulation may be strongly influenced by voltage-dependent dendritic conductances. To quantify the effects of these conductances on motoneuron firing behavior, we injected suprathreshold current steps into medial gastrocnemius motoneurons of decerebrate cats and measured the changes in firing rate produced by superimposed excitatory synaptic input. In the same cells, we measured I_N and the f - I slope to determine the predicted change in firing rate ($\Delta F = I_N * f$ - I slope). In contrast to previous results in anesthetized cats, synaptically induced changes in motoneuron firing rate were greater-than-predicted. This enhanced effect indicates that additional inward current was present during repetitive firing. This additional inward current amplified the effective synaptic currents produced by two different excitatory sources, group Ia muscle spindle afferents and caudal cutaneous sural nerve afferents. There was a trend toward more prevalent amplification of the Ia input (14/16 cells) than the sural input (11/16 cells). However, in those cells where both inputs were amplified (10/16 cells), amplification was similar in magnitude for each source. When these two synaptic inputs were simultaneously activated, their combined effect was generally very close to the linear sum of their amplified individual effects. Linear summation is also observed in medial gastrocnemius motoneurons of anesthetized cats, where amplification is not present. This similarity suggests that amplification does not disturb the processes of synaptic integration. Linear summation of amplified input was evident for the two segmental inputs studied here. If these phenomena also hold for other synaptic sources, then the presence of active dendritic conductances underlying amplification might enable motoneurons to integrate multiple synaptic inputs and drive motoneuron firing rates throughout the entire physiological range in a relatively simple fashion.

INTRODUCTION

Motoneurons transform synaptic inputs into frequency-coded spike train outputs. Increments of current cause firing

rate increases that can be predicted from the linear slope of the cell's intrinsic frequency-current (f - I) relation (Granit et al. 1966; Kernell 1970; Schwindt and Calvin 1973). In the decerebrate cat preparation studied here, excitatory synaptic currents have been shown to activate dendritic voltage-sensitive conductances that can contribute substantial amounts of additional depolarizing current (Bennett et al. 1998a; Lee and Heckman 1998b). The effects of those conductances are evident in motoneuron firing rate data obtained in humans (Gorassini et al. 1998; Kiehn and Eken 1997) and decerebrate animals (Bennett et al. 1998a; Lee and Heckman 1998a). However, the influence of those conductances on synaptic integration remains poorly understood. Therefore direct examination of motoneuron repetitive firing is necessary to more fully describe the relation between synaptic input and firing rate output in the presence of voltage-sensitive dendritic conductances.

In interpreting the impact of a synaptic input on firing rate, the most functionally relevant parameter is the current reaching the site of spike initiation, thought to be an axonal segment in close proximity to the soma (Colbert and Johnston 1996; Coombs et al. 1957; Stuart et al. 1997). Here we use intrasomatic microelectrodes to record the total synaptic current reaching the soma (Bernarder et al. 1994; Heckman and Binder 1988; Redman 1976), which we will refer to as the "effective synaptic current" [or I_N , following the terminology of Heckman and Binder (1988)]. If effective synaptic current and microelectrode current injected into the soma have equivalent effects, this can lead to a simple prediction of synaptically evoked changes in firing rate. The steady-state relation between injected current (I) and motoneuron firing rate (f) is linear over most of the physiological range of firing rates (Binder et al. 1996). As a result, the steady-state change in firing rate produced by a steady synaptic input (ΔF) can be predicted from the product of the effective synaptic current (I_N) and the slope of the f - I relation: $\Delta F = I_N * f$ - I slope (Powers and Binder 1995).

It is not known whether injected and effective synaptic currents always modulate motoneuron firing in an equivalent fashion. A given amount of effective synaptic current can indeed have the same effect on firing rate as the same amount of injected current (e.g., Granit et al. 1966; Kernell 1970; Schwindt and Calvin 1973). In those cases, amplification is

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absent, and the addition of excitatory synaptic current to a background of injected current causes a uniform firing rate increment across all levels of injected current. Alternatively stated, the f - I relation in the presence of such a synaptic input is parallel and shifted to the left along the current axis compared with the relation in the absence of synaptic input. However, much of the previous quantitative analysis of firing rate modulation in motoneurons is based on data obtained in anesthetized preparations (Granit et al. 1966; Powers and Binder 1995; Schwindt and Calvin 1973; reviewed in Binder et al. 1996; Crill 1983), in which there is likely to be little or no tonic activity in descending monoaminergic fibers (cf. Hounsgaard et al. 1988). In contrast, in the unanesthetized decerebrate preparation where descending monoaminergic fibers are thought to be tonically active (Hounsgaard et al. 1988), or in the presence of exogenously applied monoamines, the behavior of motoneuron dendrites can be dominated by the activation of a voltage-sensitive persistent inward current (Bennett et al. 1998b; Hounsgaard and Kiehn 1993; Lee and Heckman 1996). In addition, voltage-dependent mechanisms not associated with monoaminergic facilitation in this preparation, such as persistent sub-threshold sodium current (Hsiao et al. 1998; Nishimura et al. 1989), N -methyl- D -aspartate (NMDA) receptor currents (Brownstone et al. 1994), or calcium-dependent mixed cation (CAN) current (Perrier and Hounsgaard 1999; Reklung and Feldman 1997), may also be activated during repetitive firing. It has been proposed that induction of any or all of these persistent inward currents would amplify the synaptic current reaching the soma (Hounsgaard and Kiehn 1993; Kiehn 1991; Lee and Heckman 1996; Schwindt and Crill 1982).

Activation of voltage-dependent dendritic conductances makes it difficult to predict the effects of synaptic input on motoneuron firing rate. These effects are likely to depend on the relation between the voltage dependence of the persistent inward current and the range of membrane voltages present in the dendrites during repetitive discharge (cf. Schwindt and Crill 1982). For example, if the persistent inward current were fully activated within the depolarized voltage range traversed before the cell fires repetitively, then the I_N present during firing would be amplified compared with that measured at the resting membrane potential. If that amplification remained approximately constant across injected current settings, then the resulting synaptically induced shift in the f - I relation would be parallel to control conditions and greater-than-predicted (Schwindt and Crill 1995). Alternatively, the dendritic current could be maximal at relatively low levels of depolarization and become systematically smaller with increasing injected current due to decreased driving force (Burke 1967; Cope et al. 1987; Lev-Tov et al. 1983; Rall 1977; Rose and Cushing 1999; Segev et al. 1990). In that case, the f - I slope would be less in the presence of synaptic input than in its absence. In contrast, progressive increases in the activation of a dendritic current with increasing depolarization would cause I_N to be systematically greater across increasing injected current magnitudes. The f - I slope in the presence of such a synaptic input would therefore be greater than in the absence of synaptic input. In fact, both synaptically induced increases and decreases in f - I slope have been reported (Bennett et al. 1998a; Brownstone et al. 1992). Either type of change in f - I slope during synaptic activation (Kernell 1965; Shapovalov 1972) or a greater-than-expected shift in the f - I relation will lead to a difference

between predicted and observed synaptic effects on firing rate. Given this variety of mechanisms that contribute to uncertainty in predicting the effect of synaptic current on firing rate, direct examination is essential for a full understanding of this process.

The present study was designed to determine whether the simple model of synaptically evoked firing rate modulation based on data obtained in anesthetized cats (Powers and Binder 1995) also applies to motoneurons studied in unanesthetized, decerebrate cats. The effects of activating two different populations of primary afferents, one carrying muscle length information (group Ia muscle spindle afferents) and the other carrying cutaneous information (caudal cutaneous sural nerve afferents), were directly compared to examine possible input-specific differences. In addition, effects of concurrent activation of both inputs were investigated to compare summation of synaptic effects to that recently reported in anesthetized cats (Powers and Binder 2000). We measured the effective synaptic currents near the resting potential produced by the two different excitatory inputs, using the modified "voltage-clamp" technique of Heckman and Binder (1988). In the same motoneurons, we measured the steady-state relation between injected current and motoneuron firing rate. We found that the shifted f - I relations evoked by a steady synaptic input were nearly always parallel to the control f - I slopes over the range of injected current and synaptic input magnitudes studied here. In addition, the magnitude of the f - I shift was nearly always greater than the firing rate change predicted by the product of I_N and the f - I slope, indicating amplification of the effective synaptic current during repetitive firing. The amount of amplification did not appear to be related to those intrinsic properties recorded in the present study for each motoneuron and was similar for the two different excitatory inputs. When the two inputs were applied concurrently, the observed change in firing rate was approximately equal to the linear sum of their individual effects. Portions of these results have been previously presented in abstract form (Prather et al. 1998).

METHODS

Surgical and experimental procedures

Data were collected from 16 medial gastrocnemius (MG) motoneurons recorded in nine adult cats (2.5–3.5 kg) with the approval of the Emory University Institutional Animal Care and Use Committee. Anesthesia was induced in a closed chamber and maintained via a tracheal cannula throughout the initial dissection with a gaseous mixture of halothane (1.5–2.5%) in a 1:1 mixture of NO_2 : O_2 . Artificial respiration was adjusted to hold end-tidal CO_2 between 3 and 4%. The right carotid artery and jugular vein were cannulated for monitoring blood pressure and administering fluids, respectively. Atropine sulfate (0.54 mg/ml, 1 ml/20 lbs. body wt) was given intramuscularly to reduce bronchial secretion, and dexamethasone phosphate (1.0 mg/kg) was delivered intravenously to minimize edema. The lumbosacral enlargement was exposed by a laminectomy from L_4 to S_1 to provide access to MG motoneurons. The left hindlimb was dissected to expose the MG muscle nerve and caudal cutaneous sural nerve, and the triceps surae muscles were separated from their surrounding tissues. After separating the plantaris tendon, the remainder of the Achilles tendon was cut and attached to a servomotor that provided the muscle stretch stimulus. The animal was then mounted in a recording frame, and following ligation of the left carotid artery an intercollicular decerebration was performed. Anesthesia was discon-

tinued after the decerebration. At the end of the recording session, animals were killed using a lethal dose of intravenous pentobarbital sodium.

Intracellular recordings were made from MG motoneurons using glass micropipettes filled with 2 M K-acetate (resistances of 5–10 M Ω) connected to an Axoclamp-2A amplifier operated in bridge mode. When resting membrane potential was steady and action potential amplitude exceeded 70 mV, records were collected (DC to 10-kHz band-pass) and stored on computer (22-kHz digitization). Rheobase current (I_{rh}), input resistance (R_{in}), action-potential after-hyperpolarization half-decay (AHP), and axonal conduction velocity (CV) were measured using the protocols of Zengel et al. (1985).

A steady excitatory synaptic input was introduced from two different sources: repetitive electrical stimulation of afferents in the intact caudal cutaneous sural nerve (40- μ s pulses, 100 Hz, <5 T stimulus intensity) and activation of primary muscle spindle (group Ia) afferents by mechanical vibration of the triceps surae muscles (167-Hz sinusoid, 80- μ m amplitude). The intensity of sural nerve stimulation and the background level of muscle stretch were adjusted for each cell so that each source produced about the same mean level of depolarization. The effective synaptic current (I_N) produced by each source alone and in combination was then measured using an intrasomatically placed microelectrode and the modified “voltage-clamp” technique of Heckman and Binder (1988) (Fig. 1A). In this stimulus procedure, microelectrode injected current is combined with high-frequency repetitive activation of a synaptic input and consists of three consecutive 500-ms epochs: 1) injected current alone, 2) simultaneous injected current and synaptic input, and 3) synaptic current alone (see Fig. 1A). In practice, it is not necessary to precisely clamp the membrane potential at the resting value on a given trial, since I_N can be estimated from the responses to synaptic input in combination with several different levels of injected current (cf. Powers and Binder 1995, 2000). The value of I_N is determined by interpolating a line to the relation between injected current and membrane potential (relative to rest) during epoch 2 and determining the current value at which that relation crosses the zero voltage axis. In the example illustrated in Fig. 1A, when 10 nA of hyperpolarizing current was combined with repetitive activation of the sural nerve, the mean membrane potential was 3.1 mV below the resting potential (horizontal dashed line), whereas the membrane potential was 3.5 mV above rest when sural was activated in combination with 5 nA of hyperpolarizing current and 0.9 mV above rest with 7 nA of hyperpolarizing current (not shown). The effective synaptic current produced by the sural input was estimated by linear interpolation to be 7.7 nA in this cell.

Stimulus and recording procedures

Motoneurons were stimulated to fire repetitively using the following stimulus protocol. A range of suprathreshold 1-s current steps were injected to determine the slope of the f - I relation. Motoneurons were then stimulated to fire by various combinations of injected current and synaptic input. Midway through a 1-s period of injected depolarizing current, the synaptic input was initiated and maintained for 1 s. Each trial of injected current plus synaptic input was preceded and followed by a control trial of injected current alone (cf. Powers and Binder 1995). The interval between synaptic stimuli was ≥ 30 s to avoid changes in interneuronal excitability and possible wind-up of plateau mechanisms (Bennett et al. 1998a; Svirskis and Hounsgaard 1997).

Data analysis

In the decerebrate cat preparation, motoneuron excitability can fluctuate over time. To ensure that changes in excitability were not responsible for the observed rate changes, the firing rate induced by injected current alone during the initial 500 ms of the stimulus protocol was compared with the control trials of the same injected

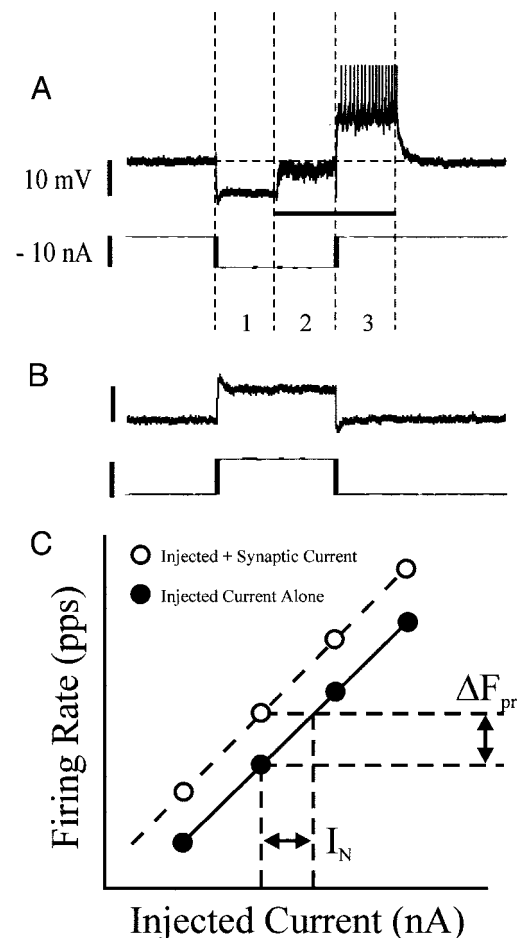


FIG. 1. Estimation of effective synaptic current and predicted firing rate changes. A: the top trace shows membrane voltage during 1) injected current alone, 2) injected current and repetitive activation of the sural nerve, and 3) sural activation alone. The membrane potential during combined injected current and synaptic activation (epoch 2) is used to estimate effective synaptic current. When a hyperpolarizing current step of 10 nA is combined with sural input, the membrane potential is held 3.1 mV below the resting potential (horizontal dashed line, -60 mV). When 5 nA of injected hyperpolarizing current was used, the membrane potential was depolarized 3.5 mV above the resting potential (not shown). With 7 nA of hyperpolarizing current in combination with sural input, the membrane potential was 0.9 mV above rest (not shown). The current required to precisely clamp the membrane at the resting potential was estimated by linear interpolation to be 7.7 nA. Amplification of synaptic current was clearly evident in these data. Synaptic current alone at the end of the trial produced repetitive discharge (mean 33 pps, spikes clipped for clarity) that accelerated from 26 to 49 pps during the sustained stimulus, whereas 10 nA of injected current did not elicit any firing (B). B, top trace: membrane potential, dashed line in A indicates resting potential; bottom trace: injected current. C: graphical illustration of the calculation of predicted change in firing rate (ΔF_{pr}) from the product of the effective synaptic current (I_N) and the slope of the frequency-current (f - I) relation obtained from the response to injected current alone. See text for further details.

current that preceded and followed each stimulus. Similarity in firing rates during these periods ensured that motoneuron excitability was similar between stimulus and control conditions. The effect of synaptic input on firing rate was then assessed by calculating the difference between the mean firing rate during the 500-ms epoch of injected current plus synaptic input and the mean firing rate of the bracketing control trials. This observed change in motoneuron firing rate (ΔF_{obs}) was compared with the predicted change (ΔF_{pr}) estimated from the product of the f - I slope and I_N measured at the resting potential. Figure 1C provides a graphic illustration of the calculation of ΔF_{pr} . If

effective synaptic current (I_N) has the same effect on firing rate as an equivalent amount of injected current (see INTRODUCTION), the predicted change in firing rate is calculated by moving along the control f - I relation (solid line) by the amount I_N . The effects of synaptic input on firing rate were examined using at least two different levels of injected current, and in many cases at several different levels (Fig. 3). The best fit linear regression was determined for the relation between injected current and firing rate for trials in which synaptic input was present (dotted line in Fig. 3) as well for the bracketing control trials (solid line). The f - I relation in the presence of synaptic input was then compared with that predicted based on shifting the control relation by an amount equal to I_N (dashed line). Changes in motoneuron firing rate that were significantly larger than the predicted values (see *Statistical analysis*) were taken as evidence of an amplified effect of synaptic current.

Statistical analysis

Synaptically induced changes in firing rate were measured at a number of different levels of injected current. Those data were used to generate f - I relations for electrode current alone and electrode current plus synaptic stimulus conditions. For each cell, the regression line of f - I data in the presence of synaptic input was calculated (dotted line in Fig. 3) and compared with a regression line for control (injected current alone) data that had been shifted along the x -axis (current) by an amount equivalent to the effective synaptic current measured at rest (dashed line in Fig. 3). If the activation of synaptic input did not change the slope of the f - I relation, then amplification could be inferred as a difference in the y -intercepts (firing rate axis) of the observed and expected regression lines. An analysis of covariance (ANCOVA) was used to test whether the f - I slope with combined injected current and synaptic activation was not significantly different from the expected regression. In those cells where the two slopes were not different, ANCOVA was further used to test the hypothesis that the y -intercepts of the observed and expected relations were significantly different, indicating the presence of amplification.

Potential sources of error

Both the estimates of I_N and f - I slope are subject to error, due to variability in the synaptic responses, slow drifts in resting potential, errors in electrode bridge balance and changes in cell excitability. Previous calculations of the errors associated with estimation of I_N suggest a 15% uncertainty in these estimates (Powers and Binder 1995). Measurements of synaptically evoked changes in firing rate will be affected by slow changes in the motoneuron's repetitive discharge properties. We attempted to minimize the effect of these changes by bracketing the responses to injected current in the presence of synaptic input with trials in which injected current was presented alone. Nonetheless, collection of firing rate data at several different levels of injected current with and without different synaptic inputs typically took 10–30 min, and changes in cell excitability over this time period were likely to contribute to the scatter in the f - I relations (see Fig. 3). Two different variations of the stimulus protocol were used in a subset of the cells to minimize this source of error (described in RESULTS). Although these various sources of error could contribute to differences between the predicted and observed changes in firing rate produced by a given synaptic input in individual cases, they should not have caused the systematic amplification observed across the entire sample.

There is another potential source of error that might cause systematic differences between predicted and observed changes in firing rate; however, this type of error should produce an underestimate of amplification magnitude. Predictions of the change in firing rate produced by a synaptic input were based on the effective synaptic current measured at the resting potential. For excitatory synaptic inputs, the membrane depolarization during repetitive discharge will reduce the

driving force for synaptic current (Burke 1967; Cope et al. 1987; Lev-Tov et al. 1983; Rall 1977; Rose and Cushing 1999; Segev et al. 1990). As a result, in the absence of amplification by active conductances, the effective synaptic current present during repetitive discharge will be less than that observed at rest (cf. Powers and Binder 1995, 2000). Consequently, our predicted firing rate change represents an overestimate of that expected to occur in a neuron that does not exhibit amplification. Comparison of this overestimated predicted firing rate against observed rates will cause an underestimation of synaptic effects on firing rates.

RESULTS

Amplified effect of synaptic current on motoneuron firing

A greater-than-expected increase in motoneuron firing rate caused by sural synaptic excitation is illustrated in Fig. 2. The *top traces* represent the instantaneous firing rate produced by 1-s steps of injected current (*bottom traces*) in the presence (*right*) or absence (*left*) of superimposed 100-Hz stimulation of the sural nerve (indicated by the solid bar). The firing rate elicited by 15 nA of injected current was 20 pps. That rate was increased to 41 pps when another 10 nA of injected current were added (superimposed firing rate traces on the *left*). It was expected that the cell would display the same firing rate increase if an equivalent amount of effective synaptic current were added instead of injected current. However, the addition of sural input (estimated to produce an effective synaptic current of 7.7 nA using the modified voltage-clamp technique in Fig. 1A) to the 15 nA of injected current increased firing rate to 67 pps. This enhanced effect of synaptic input can also be seen in Fig. 1A, since sural synaptic current alone caused the motoneuron to fire repetitively, whereas 10 nA of injected current did not (Fig. 1B). These data demonstrate that activation of the synaptic input under repetitive firing conditions caused a change in firing rate that was greater than predicted from measurements of I_N at resting potential. This result is consistent with the activation of a voltage-dependent persistent inward current (Lee and Heckman 1996; Schwindt and Crill 1995).

Amplification was present at several different background firing rates. Figure 3 illustrates the firing rates elicited in

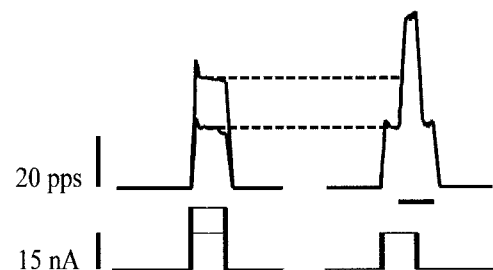


FIG. 2. The change in firing rate caused by sural input was greater-than-predicted, indicating the presence of amplification. The *top traces* represent the instantaneous firing rate produced in the cell of Fig. 1, A and B, by 1-s steps of injected current (*bottom traces*) in the presence (*right*) or absence (*left*) of superimposed 100-Hz stimulation of the sural nerve (indicated by the solid bar). The firing rate elicited by 15 nA of injected current was 20 pps. That rate was increased to 41 pps when another 10 nA of electrode current were added (superimposed firing rate traces on the *left*). When sural activation was combined with 15 nA of injected current, firing rate was increased to 67 pps. This represents a firing rate increase of 26 pps greater than that produced by an additional 10 nA of injected current, even though the effective synaptic current produced by sural activation was estimated to be <10 nA (7.7 nA).

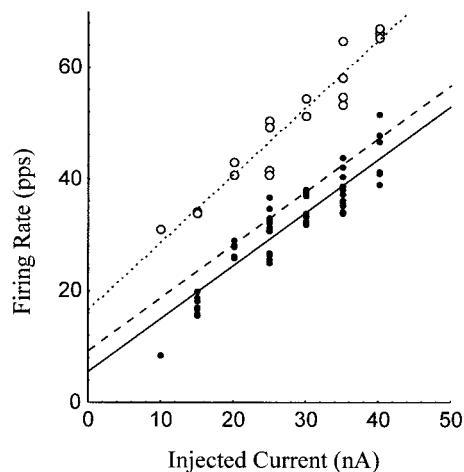


FIG. 3. Firing rate increases produced by Ia synaptic current were greater than predicted by the product of I_N and $f-I$ slope and occurred across a range of injected currents. Relation between discharge rate and injected current for injected current alone (●) and injected plus Ia synaptic current (○), along with the best-fit regression lines to the data (solid and dotted lines, respectively). The dashed line indicates the predicted $f-I$ relation in the presence of synaptic input, obtained by shifting the control $f-I$ relation along the current axis by the magnitude of the estimated effective synaptic current (4 nA). While the slopes of the dashed and dotted lines are not identical (1.00 and 1.21, respectively), their differences are not significant over the range of currents and firing rates tested here (ANCOVA test for parallelism, $P > 0.05$). Furthermore, the magnitude of observed amplification is greater than could be explained by such a difference. The possibility of changing $f-I$ slope during activation of synaptic input is further investigated in Fig. 4B.

another motoneuron by various amplitudes of injected current alone (●, solid regression line) and in combination with excitatory Ia input (○, dotted regression line). The dashed line illustrates the predicted $f-I$ relation in the presence of the Ia input, produced by shifting the control $f-I$ relation along the current axis by an amount equal to the effective synaptic current measured at rest (4 nA). Over the whole range of currents tested in this cell, the increments in firing rate generated by the addition of synaptic current exceeded expected values. While the slopes of the dashed and dotted lines are not identical (1.00 and 1.21, respectively), their differences are not significant (ANCOVA test for parallelism, $P > 0.05$). Furthermore, the magnitude of observed amplification is greater than could be explained by such a difference. The possibility of changing $f-I$ slope during activation of synaptic input is further investigated in subsequent sections.

The greater-than-expected increment in firing might reflect activation of a mechanism that relies on sustained somatic depolarization to develop, rather than one activated by synaptic input. This possibility was assessed by implementing the first of two modifications to our primary stimulus protocol. Firing rate increments were measured in response to the addition of either synaptic input or additional injected current introduced with a 1-s delay on a background of suprathreshold injected current. Figure 4A illustrates sequential stimulus trials in which either a synaptic input (current and firing rate records at left) or injected current (records at right) was added after a 1-s delay to a background of 23 nA of injected current. The added injected current (6.5 nA) was selected to match the effective synaptic current estimated at the resting potential in response to the combined stimulation of sural and Ia inputs. Despite the equivalence of conditions in these two trials, the synaptic input

produced substantially larger increases in motoneuron firing rate than the injected current, 26 pps versus 11 pps, respectively. These findings demonstrate that the enhanced effective-

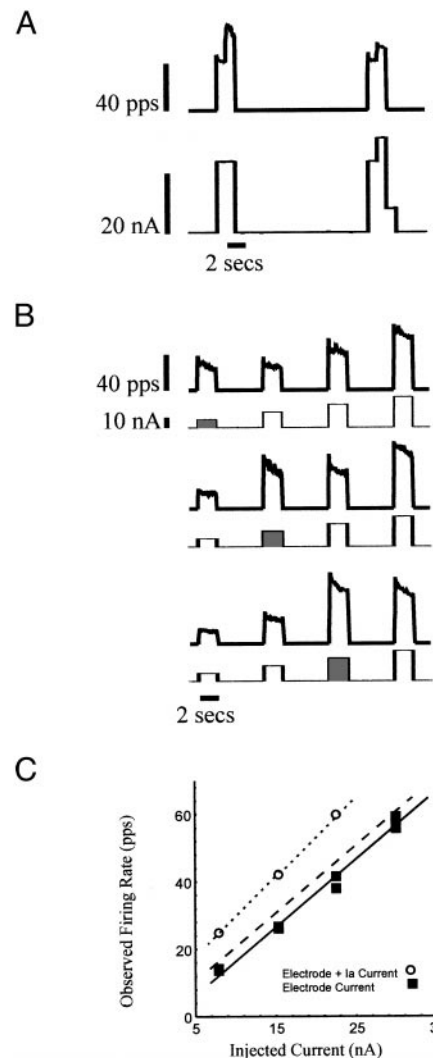


FIG. 4. The observed amplification was synaptically mediated, not due to a history-dependent mechanism or a long-lasting increase in $f-I$ slope. A: firing rates elicited by adding either combined Ia and sural synaptic input (current and firing rate records at left) or additional injected current (records at right) after a 1-s delay to a background of 23 nA of injected current. The added injected current was 6.5 nA, selected to match the effective synaptic current estimated at the resting potential in response to the combined stimulation of sural and Ia inputs. Synaptic activation incremented motoneuron firing rate by 26 pps, whereas injected current caused an increase of only 11 pps. These findings demonstrate that amplification of synaptic input could not be reproduced by injected current alone. Therefore amplification does not reflect activation of a mechanism that relies on sustained somatic depolarization to develop. B: firing rates elicited by addition of synaptic current to 1 of 4 injected current magnitudes. Injected current settings ranged from twice I_{th} for the cell (8 nA) to the largest positive current that did not polarize the electrode (30 nA). The 2 intermediate current settings were evenly spaced between those limits (15.3 and 22.6 nA). Synaptic current from Ia afferents was activated at each of the 1st 3 current settings in different stimulus trials (shaded regions). C: $f-I$ relation of firing rates displayed in B. The control $f-I$ relation is illustrated by the solid line. There is little scatter in the firing rates elicited in different trials by the same injected current (■). Firing rates evoked by injected current and activation of Ia afferents (○---○) were consistently and appreciably greater-than-predicted (---). Therefore the observed amplification is not due to a long-lasting increase in $f-I$ slope, but rather an increase in the magnitude of current reaching the soma during synaptic activation.

ness of synaptic inputs could not be reproduced by injected current alone, perhaps because the synaptic currents have access to amplification mechanisms in the dendrites that are not accessible to current injected in the soma. These data are consistent with the notion that voltage-sensitive plateau conductances, which are present along motoneuron dendrites (Bennett et al. 1998b; Carlin et al. 2000; Lee and Heckman 1996), participate in amplification of the synaptic current delivered to the soma.

The observed amplification could also have been caused by a long-lasting synaptically induced increase in the slope of the f - I relation (see INTRODUCTION). This was unlikely to have affected the results since the control f - I relation was calculated from responses to injected current alone, which were interspersed with responses to combined injected current and synaptic input. However, to demonstrate the stability of the control f - I relation more convincingly, a second modification was made to the stimulus protocol. Each cell was driven to fire using four levels of injected current, ranging from twice the rheobase current to the maximum positive current that did not polarize the electrode. The two intermediate current settings were evenly spaced between those limits. In Fig. 4B, the motoneuron was driven using current settings of 8, 15.3, 22.6, and 30 nA. The responses to a given amount of injected current alone were quite similar even though they occurred at different times following the application of the synaptic input (gray shaded regions in Fig. 4B). The control f - I relation is illustrated by the solid line in Fig. 4C, and it can be seen that there is relatively little scatter in the individual responses at a given level of injected current (■). Further, firing rates evoked by simultaneous application of injected current and activation of Ia afferents (○---○) were consistently and appreciably greater than predicted values (---).

Analyses of variance and covariance were used to compare f - I relations in the presence and absence of synaptic input, based on data obtained using either the modified technique described in Fig. 4B (4 of 16 cells) or the standard protocol (12 of 16). The distributions of f - I slopes were similar in the presence and absence of synaptic input (control: 1.72 ± 0.48 pps/nA, mean \pm SD, range = 0.84 – 2.63 pps/nA; Ia: 1.63 ± 0.52 pps/nA, 0.79 – 2.42 pps/nA; sural: 1.43 ± 0.56 pps/nA, 0.41 – 2.52 pps/nA; Ia + sural: 1.77 ± 0.55 pps/nA, 1.06 – 2.30 pps/nA; ANOVA: $F = 1.01$, $P = 0.40$). The f - I slope in the presence of synaptic activation was indistinguishable from the slope of the expected regression in 16 of 16 cells for the Ia input and 15 of 16 for the sural input (ANCOVA test of parallelism, $P > 0.05$). Synaptic current was amplified during repetitive firing, as indicated by a significant increase in y-intercept between observed and expected regression lines, in 14 of 16 cells (88%) for Ia input and 11 of 16 cells (69%) for sural input. Therefore in almost all cases, the difference between observed and expected synaptically induced rate changes was not due to a change in f - I slope, but rather a change in the amount of current reaching the soma during synaptic stimulation. The parallelism of f - I relations in the presence and absence of synaptic input indicates that for the injected current and synaptic input magnitudes studied here, the increment in effective synaptic current was not voltage dependent beyond its activation. These data are consistent with the notion that most of the amplification demonstrated by each cell occurs in the voltage range between resting potential and

the threshold for repetitive discharge (cf. Lee and Heckman 1996; Schwindt and Crill 1995).

Figure 5, A and B, illustrates the relation between observed and predicted firing rate changes for Ia (A) and sural (B) inputs. Those cases in which the observed firing rate changes were significantly different from predicted values are indicated by open symbols and the nonsignificant cases by filled symbols. In both panels, nearly all of the significant cases are above the line of identity (diagonal line). In the one case of a cell in which the

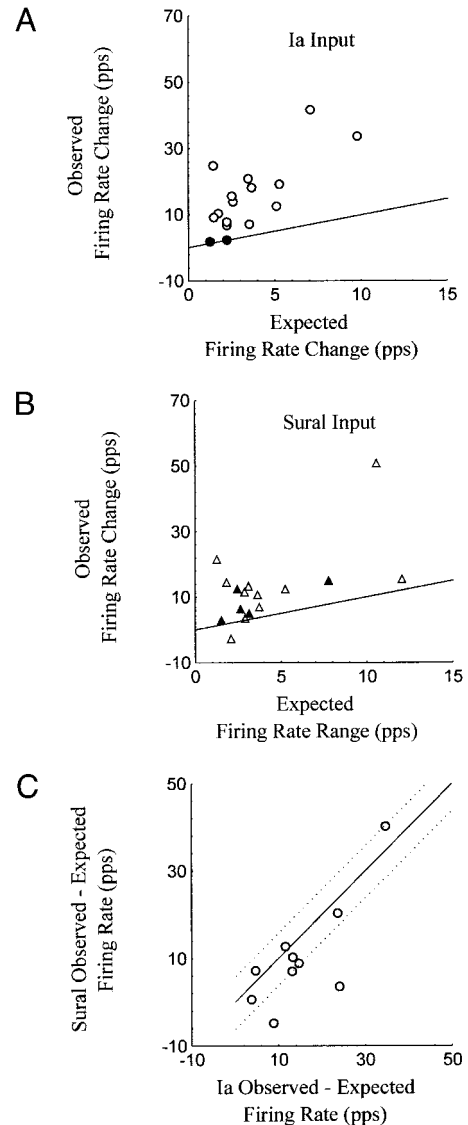


FIG. 5. Amplified effects of Ia and sural synaptic current on firing rate. Solid line indicates line of identity in all graphs. A: relation between the observed and predicted firing rate changes produced by Ia input. Open circles indicate cases in which the observed firing rate changes were significantly different from the predicted values. B: same as A, only for the sural input. In one case, a negligible difference between expected and observed firing rate is significant (Δ on the line of identity). Many data trials were used to compute that point, therefore significance was achieved, but amplification was not meaningful. In contrast, 2 insignificant cases (\blacktriangle) lay well off the line of identity. Those cases were computed from fewer data trials, therefore amplification did not achieve significance. C: comparison of the difference between observed and predicted rate changes for sural and Ia inputs. Only the cases in which the differences reached statistical significance for both inputs are included. Dotted lines above and below the line of identity indicate a ± 6 pps range.

sural input caused a firing rate decrease, the sural input was transiently inhibitory and produced a net decrease in firing rate. Only one cell failed to amplify either input. That cell was not different from other motoneurons in the synaptic current it received or its intrinsic properties, except that it had the largest observed I_{th} (22 nA). However, amplification of one or both inputs was evident in other cells that also had high rheobase (e.g., 16, 17, and 21 nA). There was no tendency for the magnitude of amplification to be less in cells with larger rheobase (Pearson's correlation, Ia: $R = -0.14$, $P = 0.60$; sural: $R = -0.06$, $P = 0.82$).

Direct comparison of Ia and sural amplification

Ia input was amplified in 14 of 16 motoneurons (88%). Cells that did or did not amplify Ia input were indistinguishable in their cellular properties (I_{th} , R_{in} , AHP, CV, $f-I$ slope; t -test for independent samples, $P > 0.31$ all cases). The two cells that failed to amplify Ia input had I_{th} of 6 and 22 nA, demonstrating that failure to amplify was not limited to only the least excitable motoneurons. Those two cells both received small synaptic currents (1.0 and 1.5 nA); however, amplification of Ia input was evident in six other cells where Ia I_N was between 0.5 and 1.5 nA. Therefore failure to amplify was not simply due to insufficient excitatory synaptic drive onto the amplification mechanisms. In addition, there was no correlation between the magnitude of Ia I_N and the amount of amplification observed in each cell (Pearson's correlation, $R = 0.33$, $P = 0.21$). Therefore with respect to both cellular properties and I_N magnitudes, the two cells that failed to amplify Ia input were indistinguishable from those cells that did display amplification.

Sural input was amplified in 11 of 16 motoneurons (69%). Cells that did or did not amplify sural input were indistinguishable in their cellular properties and I_N magnitudes (t -test for independent samples, $P > 0.19$ all cases). In 10 of those 11 cells that amplified sural input, Ia input was also amplified. The cell that amplified sural but not Ia input was not anomalous in its intrinsic properties or in the amount of effective synaptic current it received. As was the case for the Ia input, there was no correlation between sural I_N magnitude and the amount of amplification observed in each cell (Pearson's correlation, $R = 0.13$, $P = 0.63$). Therefore neither Ia nor sural synaptic input was uniformly amplified across the population of MG motoneurons. However, it was not apparent from these data which motoneuron characteristics regulated whether or not amplification was expressed in a given cell.

Ia and sural inputs were both amplified in 10 of 16 motoneurons (63%). Those 10 cells were indistinguishable from the remaining motoneurons that amplified only one or neither input (t -test for independent samples, $P > 0.24$ all cases). Over the observed range of injected currents and firing rates in those 10 cells, ANCOVA revealed that the shift in the $f-I$ relation was parallel and significant for both inputs in the same motoneuron. Observed firing rates exceeded expected values for both inputs in 9 of 10 cells. The lone exception was sural input in the cell for which sural was transiently inhibitory. On average, the observed change in firing rate was about three times larger than the predicted change in rate (3.3 ± 3.9). The average difference between observed and expected rate changes was slightly but not significantly larger for Ia input (14.2 ± 9.7 pps) than for sural input (9.6 ± 12.7 pps, paired t -test, $P = 0.13$).

However, this difference was primarily due to the influence of the motoneuron for which sural was transiently inhibitory and another cell in which the change in rate for Ia exceeded that of sural by 20 pps. Overall, Ia and sural inputs were indistinguishable in their amplified effects on firing rate (paired t -test, $P = 0.13$). The solid line in Fig. 5C is the line of unity, and the dotted lines indicate a range of ± 6 pps around this line. Data from 7 of 10 motoneurons fall within this range. The motoneuron in which the firing rate change due to Ia input exceeded that of sural by 20 pps lies well away from unity. That motoneuron was not exceptional in its intrinsic properties (I_{th} 11 nA, R_{in} 1.8 M Ω , AHP 14.3 ms), nor did it receive especially large sub-threshold synaptic currents (Ia: 2.6 nA; sural: 3.2 nA). It is not apparent why the response of this cell was so different from the general trend for Ia and sural to be amplified similarly.

Amplified synaptic effects exhibit linear summation

The potential for nonlinear interactions [e.g., reduction in driving force, shunting of current by adjacent conductances (Oakley et al. 1999)] leaves uncertainty about the influence of simultaneously active synaptic inputs on motoneuron firing. Direct examination revealed that the amplified Ia and sural inputs exhibited approximately linear summation (Fig. 6) over the amplitudes of I_N studied here. The observed increases in firing rate during combined Ia and sural activation correlated very well with the linear sum of rate increases due to Ia and sural separately ($R = 0.94$, slope = 0.77, y-int = 4.2 pps, $P < 0.001$). The slope of this relation is slightly less than unity, suggesting that summation may have been slightly less than linear. However, the nine data points are scattered about the line of identity, and the average increase in firing rate due to activation by combined input (26.0 ± 16.7) was statistically indistinguishable from the linear sum of the average effects of each input individually (Ia: 14.2; sural: 9.6 pps; paired t -test, $P = 0.42$).

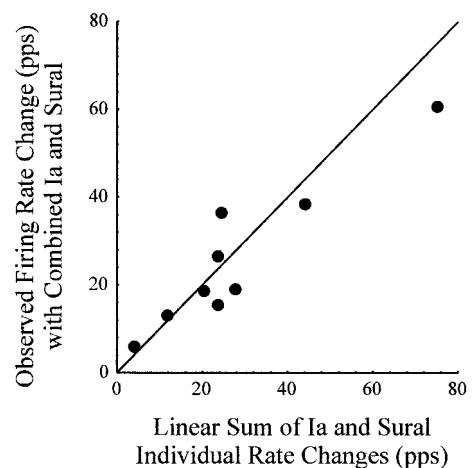


FIG. 6. Firing rate increases due to simultaneously applied Ia and sural input were generally close to the linear sum of increases due to each input individually. Solid diagonal line is the line of unity. The observed firing rate increases produced during combined Ia and sural activation were well correlated with the linear sum of rate increases due to Ia and sural separately ($R = 0.94$, slope = 0.77, y-int = 4.2 pps, $P < 0.001$), although the slope of this relation is slightly less than unity. See text for further details.

Amplification is dissociated from expression of plateau properties

Plateau properties were investigated in each motoneuron. A cell was classified as possessing plateau properties if it displayed one or more of the following traits: firing rate hysteresis during linearly increased and decreased injected current amplitude (Bennett et al. 1998a), firing rate acceleration during constant-amplitude injected current pulses, or sustained firing following termination of excitatory stimulus (Eken et al. 1989). Eight of the 16 cells exhibited clear evidence of these properties. Consistent with earlier reports (Lee and Heckman 1998a), the population expressing plateau properties had lower rheobase currents (t -test for independent samples, $P < 0.01$) and a nonsignificant trend toward higher input resistances ($P = 0.07$) than those cells that did not express plateaus. Motoneurons that did express plateaus were indistinguishable from cells that did not, with respect to AHP ($P = 0.28$) and axonal CV ($P = 0.38$). Interestingly, cells expressing plateau properties had steeper f - I slopes (2.3 ± 0.8) than cells without plateau properties (1.5 ± 0.5 , t -test for independent samples, $P = 0.02$). Both Ia and sural inputs were amplified in seven of the eight cells with plateau properties. In the remaining cell, Ia input was amplified, but sural input was not. Cells that did or did not express plateaus were indistinguishable in their amplification magnitude of Ia input (t -test for independent samples, $P = 0.26$) and sural input ($P = 0.47$). Therefore the amount of amplification expressed by each motoneuron, while varying across the population, did not vary systematically across any of the measured intrinsic properties or as a function of the expression of plateau properties.

DISCUSSION

The change in motoneuron firing rate produced by activation of synaptic inputs was significantly greater-than-expected in 14 of 16 cells in which the Ia muscle spindle afferent input was tested and in 11 of 16 where the sural nerve input was tested. Our results show that in the decerebrate cat, synaptic currents are amplified during repetitive firing, and this voltage-dependent amplification of synaptic current is an integral element of the motoneuron input/output relation. In contrast, in intact, pentobarbital-anesthetized cats, changes in firing rate produced by a variety of synaptic inputs are quite close to those predicted on the basis of the effective synaptic current measured at rest (Powers and Binder 1995). The differences between these two preparations probably reflect the relative predominance of a persistent inward current (Schwindt and Crill 1982) in the decerebrate preparation (Kiehn and Eken 1998; Lee and Heckman 1999), likely as a result of tonic activity in neurons providing monoaminergic inputs to motoneurons (cf. Hounsgaard et al. 1988).

Although the ionic basis of this persistent inward current in cat motoneurons is not known, in other motoneurons it has been shown to be mediated primarily by either an L-type calcium current (Hounsgaard and Mintz 1988), a persistent sodium current (Nishimura et al. 1989), or a mixture of these two currents (Hsiao et al. 1998). In some motoneurons, activation of a calcium-dependent mixed cation (CAN) conductance may lead to a persistent inward current, although multiple calcium spikes are generally required for significant

activation (Perrier and Hounsgaard 1999; Rekling and Feldman 1997). Alternatively, a voltage-dependent persistent inward current could result from a receptor-mediated effect, such as a voltage-dependent increase in synaptic current through NMDA-activated receptors, which has been suggested as a potential contributor to voltage-dependent amplification of synaptic potentials associated with fictive locomotion (Brownstone et al. 1994). However, NMDA receptors are unlikely to contribute significantly to the amplification process reported here, as sural and Ia inputs are similarly amplified but the contribution of NMDA receptors to the Ia excitatory postsynaptic potential (EPSP) is only minimal or entirely absent in adult cat spinal motoneurons (Engberg et al. 1993; Jahr and Yoshioka 1986; Kalb et al. 1992; Miller et al. 1997; Walmsley and Bolton 1994; cf. Flatman et al. 1987). Further study involving pharmacological manipulation of the conductances described above is needed to elucidate the mechanisms of amplification. Regardless of the exact mechanisms underlying persistent inward currents in cat motoneurons, the functionally relevant features of this class of current are its persistence, its relatively low threshold for activation, and the fact that a significant proportion of the responsible channels appear to have a dendritic location (cf. Bennett et al. 1998a; Carlin et al. 2000; Hounsgaard and Kiehn 1993; Lee and Heckman 1996).

Previous analysis of the effects of these persistent inward currents on motoneuron repetitive firing have focused on bistable discharge behavior, i.e., a specific type of plateau property characterized by self-sustained tonic discharge following brief presentation of an excitatory stimulus (e.g., Kiehn and Eken 1998; Lee and Heckman 1998a,b). The strength of this bistability varies systematically across the motoneuron pool and is strongest in motoneurons with the lowest thresholds for excitation (Lee and Heckman 1998a,b). If the mechanisms underlying bistability and amplification are similar, one might expect that cells that demonstrated bistability, or any other type of plateau property, might also amplify synaptic current more than cells that did not express plateaus. However, we found that almost all cells exhibited amplification, whereas only 8 of 16 cells exhibited plateau properties. This discrepancy might suggest that amplification and the induction of plateau potentials are executed by different mechanisms. Alternatively, the two behaviors may share a common mechanism, but dendritically located synaptic currents have better access to the underlying conductances than somatically injected currents. In addition, plateaus may already have been active at the time of recruitment in some cells, not permitting us to observe any of the criteria used to characterize the expression of plateaus (Bennett et al. 1998a; Lee and Heckman 1996). Several previous studies have suggested that amplification may be an important correlate of plateau expression (e.g., Dickenson and Nagy 1983; Hartline et al. 1988; Kiehn 1991; Kiehn et al. 1996; Rekling and Feldman 1997; Stafstrom et al. 1985); however, the requirements for amplification are less restrictive than those needed for activation of plateau potentials. For example, the sudden depolarization or acceleration in firing rate that is characteristic of plateau induction may require two stable equilibrium points on the steady-state current-voltage (I - V) relation of the cell (i.e., an N-shaped I - V relation that crosses the zero current axis) (Gutman 1991; Lee and Heckman 1998b; Schwindt and Crill 1980), whereas amplification will

occur whenever the persistent inward current leads to a decrease in the slope of the I - V relation.

Figure 7 provides a graphical illustration of this point, and shows that over a given range of membrane voltages, amplification could be similar in a cell that expresses plateau properties and another neuron that does not. Figure 7A shows hypothetical steady-state I - V relations for a portion of dendritic membrane in a neuron expressing a plateau (bold line) and another neuron without a plateau (thin line). For the neuron indicated by the bold line, the dendritic I - V curve exhibits a region of negative slope conductance, whereas in the neuron

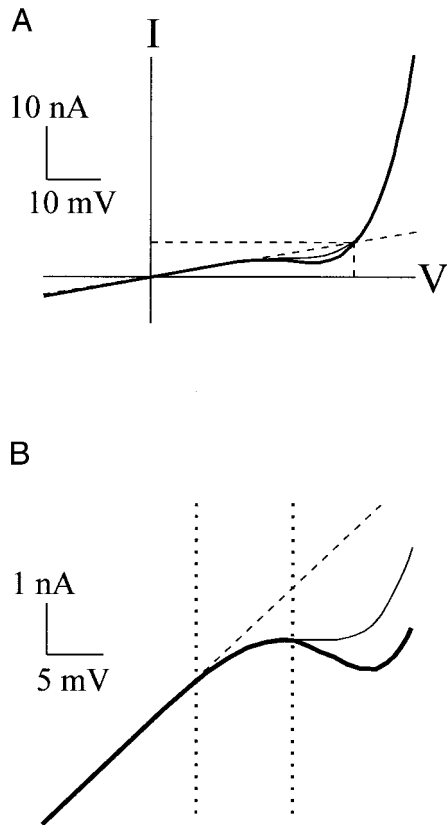


FIG. 7. A: hypothetical current-voltage (I - V) relations as seen from a proximal dendrite of a cat spinal motoneuron. The curves show the total steady-state voltage-clamp current that might be recorded from an electrode placed in a proximal dendritic branch. The thin line represents a cell in which amplification would occur in the absence of a plateau potential, whereas the thick line depicts a cell in which both amplification and a plateau potential would be present. B: expanded view of the portion of the curves enclosed by the dotted rectangle in A. The total current (I_{tot}) is composed of a linear leak current (i_L), a potassium current (i_K), and a sodium current (i_{Na}) such that $I_{\text{tot}} = i_L + i_K + i_{\text{Na}} = g_L \cdot (V - V_L) + g_K \cdot (V - V_K) + g_{\text{Na}} \cdot (V - V_{\text{Na}})$, where g_L , g_K , and g_{Na} represent the leak, potassium and sodium conductances, and V_L , V_K , and V_{Na} represent their equilibrium potentials (-70 , -80 , and $+50$ mV, respectively). The leak conductance is assumed to be voltage-independent and equal to $0.2 \mu\text{S}$, whereas the other 2 conductances show a sigmoidal dependence on membrane voltage: $g_{\text{max}}/[1 + \exp\{(V - V_h)/s\}]$, where g_{max} is the maximal conductance, V_h is the voltage for half-activation, and s indicates the steepness of the voltage dependence. The dashed diagonal line represents the leak component of the current. The curved lines represent 2 different I - V relations. In the I - V curve shown by the thin line, the slope of the relation is always positive, whereas the I - V curve shown by the bold line exhibits a region of negative slope. The voltage-dependent potassium conductance is the same in both curves and is defined by the following parameters: $g_{\text{max}} = 4 \mu\text{S}$, $V_h = -10$ mV, $s = -6$ mV. The voltage-dependent sodium conductance differs for the 2 curves (thin: $g_{\text{max}} = 0.06 \mu\text{S}$, $V_h = -42$ mV, $s = -4$ mV; bold: $g_{\text{max}} = 0.09 \mu\text{S}$, $V_h = -40$ mV, $s = -4$ mV). See text for further details.

indicated by the thin line, the slope of the I - V curve is always positive. The point is illustrated more clearly by Fig. 7B, which provides an expanded view of the portion of the I - V curves indicated by the dotted rectangle in A. Over the voltage region bounded by the vertical dotted lines, both curves show a continuous decrease in slope conductance compared with that due to the slope of the leak conductance (dashed diagonal line). As a result, in both neurons there will be voltage-dependent amplification of synaptic inputs, since a given increment in synaptic current will lead to an increasingly larger local dendritic depolarization. If sufficient steady depolarizing current is applied to bring the membrane to the voltage represented by the rightmost vertical line, the dendritic membrane represented by the bold I - V curve will jump to a depolarized voltage, i.e., it will exhibit the abrupt firing rate increase that characterizes the induction of a plateau. Nonetheless, for voltages below this point the membranes represented by the two I - V curves will exhibit identical amplification of synaptic inputs.

When Ia and sural inputs were presented simultaneously, the consequent firing rate changes were approximately equal to the linear sum of the amplified rate changes elicited by each input individually. Linear summation might be due to spatial segregation of different inputs onto different dendrites of motoneurons, but this seems unlikely because Ia monosynaptic inputs are widely distributed across the dendritic tree of MG motoneurons (Burke and Glenn 1996) and would therefore overlap with sural inputs. Linearity may be achieved instead by a balanced activation of different types of active dendritic conductances that boost or shunt the inputs (e.g., Bernardier et al. 1994; Cash and Yuste 1999; Lee and Heckman 1996; Margulis and Tang 1998; Nettleton and Spain 2000; Schwandt and Crill 1995; for review, see Yuste and Tank 1996). It is likely that the combined action of many types of active conductance are responsible for the observed linear summation; however, the current data do not allow their individual contributions to be discerned.

Even under the influence of current modulation by active conductances, the slope of the f - I relation during synaptically induced amplification was nearly always indistinguishable from that observed during activation by injected current alone. This similarity suggests that activation of amplification mechanisms does not disturb the processes of synaptic integration (cf. Binder et al. 1993). Our results thus illustrate a phenomenon by which excitatory inputs like those used here can smoothly grade motoneuron firing rate over the entire physiological range.

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