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Computer Study of Presynaptic Inhibition Controlling the Spread of Action Potentials Into Axonal Terminals

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SUMMARY AND CONCLUSIONS

1. The effect of presynaptic, axoaxonal inhibition, that exerts its action by producing a local conductance increase, on the behavior of action potentials at postsynaptic axon terminals is analyzed computationally. The significance of the location and strength of the presynaptic inhibition, as well as the morphology and membrane properties of the axonal terminals, are considered.

2. Keeping the specific properties of terminal membrane and axoplasm constant, the critical "silent" *steady-state* conductance change (g_{crit}) that blocks propagation is linearly scaled with the terminal diameter raised to the 3/2 power. At the midpoint of a 5 λ long, 1 μm diameter axon that has the standard Hodgkin and Huxley (1952) kinetics at 18°C (and an input conductance of 8.7 nS), g_{crit} is 72 nS. At 0°C, g_{crit} = 200 nS, whereas at 30°C g_{crit} = 30 nS.

3. The critical conductance change that blocks propagation depends steeply on the density of excitable channels ($\bar{g}_{Na}$) at the terminal. For a geometrically uniform terminal at 18°C, the action potential can not be blocked by a local shunt when $\bar{g}_{Na} > 600$ mS/cm^2.

4. An axoaxonal synapse in the proximity of the *postsynaptic* release site has graded control over the spike amplitude (and, therefore, over the postsynaptic output) at that site. Presynaptic inhibition located remotely from the release site has an all-or-none effect at the release site.

5. Inhibition is more effective in attenuating the spike at the terminal when it impinges onto a passive terminal rather than on an excitable one.

6. The detectibility of the conductance increase as well as the change in action potential amplitude associated with the presynaptic inhibition is poor at only a short distance from the axoaxonal synapse. The presence of bottlenecks and varicosities at some axonal terminals enhances this decoupling effect even more. Thus presynaptic inhibition may reduce the potential near the output site of the affected axon significantly, without producing any noticeable conductance or voltage change at a distance of only several tens of micrometers (a few tenths of a space constant) away from it.

7. Varicosities and bottlenecks typically found along axonal terminals are the optimal loci for presynaptic inhibition to be most effective in attenuating the action potential at the terminal. Even with high density of excitable channels, propagation with such terminal geometry is insecure, and one, or few, quanta of inhibitory transmitter (a conductance change of several nanosiemens) can block propagation there. The increased sensitivity to small increases in conductance at such structural specializations makes the inhibition there operate more in an "on-off" fashion rather than in the graded manner found in a geometrically uniform terminal. The significance of these results for the strategic design of presynaptic inhibition is discussed.

INTRODUCTION

Presynaptic inhibition is a common strategy used by the nervous system to produce precisely timed and selective control over the output of a given pathway. The action of presynaptic inhibition, expressed by the reduction of transmitter release from the postsynaptic bouton, has been demonstrated in both invertebrates (Atwood et al. 1984; Dudel and Kuffler 1961; Glantz et al. 1985; Kretz et al. 1986; Pearson and Goodman 1981) and in the mammalian central nervous system (CNS) (Angel et al. 1965; Burke and Rudomin 1977; Clements et al. 1987; Eccles et al. 1962; Rudomin et al. 1981; Schmidt 1971; see reviews by Ryall 1978; Nicoll and Alger 1979). Axoaxonal synapses, which are the morphological basis for presynaptic inhibition, have been found by the use of ultrastructural studies in excitatory terminals (Atwood and Morin 1970; Fyffe and Light 1984; Wang-Bennett and Glantz 1985) as well as in inhibitory terminals (Kazushige et al. 1981; Nakajima et al. 1973). These inhibitory axoaxonal synapses are often found near the release site on the postsynaptic cell (e.g., Fyffe and Light 1984), but in the crustacean neuromuscular junction and brain, they are generally located a few micrometers and more away from it, on the terminal arbor between the axon and the active zones (e.g., Atwood et al. 1984; Wang-Bennett and Glantz 1985).

In principle there are two basic classes of mechanisms by which presynaptic inhibition may exert its action: *1*) reducing the amplitude of the action potentials at the release site, and *2*) directly influencing the release mechanism. Among the first class of mechanisms is production of a local conductance increase (which may or may not be accompanied by hyperpolarization or depolarization) at the postsynaptic membrane. As a result, the active current is shunted, and the depolarization produced by the attenuated spike at the postsynaptic release site is reduced. Another possible way to affect the action potential amplitude at the release site is to block the excitable channels that carry the inward current, either by producing subthreshold depolarization (e.g., by a buildup of extracellular K^+ near the release site, see Rudomin et al. 1981) that inactivates these channels, or by directly blocking them with an agent that is released at the axoaxonal synapse. Among the second class of mechanisms are direct transmitter-mediated inactivation of the calcium channels at the postsynaptic site (as suggested by Klein et al. 1980) or indirectly, through second messengers, by interfering with other stages of transmitter release (e.g., vesicle fusion, see also Peng and

Frank 1989). Clearly, these different mechanisms are not mutually exclusive and at some axoaxonal synapses they may function simultaneously.

Presynaptic inhibition has received very little theoretical attention. The only modeling study that is directly aimed at the question of presynaptic inhibition was performed by Atwood et al. (1984), where they explored the effect of a *conductance increase* on voltage attenuation at the terminal. One strength of their study is that the morphology of the modeled terminals is based on detailed electron-microscopic (EM) measurements; the action potential, however, was simulated as a step change in voltage, and the terminals were assumed to be passive. The more realistic case of a local conductance increase that interacts with a propagating transient action potential was not simulated, and, as Atwood and his colleagues noted, their results provide only a lower limit for the voltage attenuation produced by the shunting effect of axoaxonal synapses.

Surprisingly, although the effect of diverse parameters that reduce the safety factor for propagation along the axon were investigated thoroughly by the use of theoretical approaches (e.g., *local geometrical inhomogeneity*: Goldstein and Rall 1974; Khodorov et al. 1969; Moore et al. 1983; Parnas and Segev 1979; Rinzel 1977; *a local change in axial resistivity*: Stockbridge 1988; *a local change in the number and kinetics of the excitable channels*: Khodorov and Timin 1975; *local demyelinization*: Waxman and Wood 1984, and see review by Swadlow et al. 1980), there is no theoretical study that explores the interaction between propagating spikes and synapses (but see Segev and Rall 1988, for a computational study of the interaction between a local action potential and synaptic inhibition at a dendritic spine head membrane). The present study is aimed at filling this gap by specifically focusing on the effect of presynaptic inhibition that exerts its action by producing a *local conductance increase* on the action potentials at the postsynaptic axon. Questions such as: What is the magnitude of conductance change needed to block propagation? How does it depend on the location of the axoaxonal synapses as well as on the excitability of the terminal membrane? What is the detectibility of presynaptic inhibition when measured with an intracellular electrode at different sites along the terminal? How do geometrical specializations of the terminal arbor influence the efficacy of presynaptic inhibition? and What is the behavior of spike trains at the terminals when the axoaxonal inhibition is activated? are explored and the significance of the results for information processing by the nervous system is discussed.

METHODS

The propagation of action potentials into axonal terminals was simulated with a modified version of the compartmental model described by Parnas and Segev (1979) (see Segev et al. 1989 for a general introduction to compartmental modeling). The model allows construction of arbitrarily complex axonal trees and specification of the properties of each compartment independently. The simulated axon may be composed of excitable compartments, passive compartments, or synaptic compartments, each with its own length and diameter.

Unless otherwise stated, excitable compartments were described by the standard Hodgkin and Huxley (1952) channel kinetics and densities at 18°C. Passive compartments have a fixed membrane resistivity that equals that of squid membrane at rest (0 mV). Hence, $R_m = 1/[g_L + g_K(0) + g_{Na}(0)] = 1{,}407\ \Omega \cdot cm^2$. Synaptic inhibition was simulated as a very short passive ($R - C$) compartment with an additional parallel branch composed of a steady-state conductance (g_{syn}) in series with a zero e.m.f (i.e., a "silent" inhibition). The effect of a transient inhibitory conductance change in the form of an "alpha function" (Jack et al. 1975; Rall 1967; Segev and Rall 1988) and a synaptic battery (E_{syn}) that differs from the resting potential is deferred to the DISCUSSION. All computations were carried out assuming a specific capacitance, C_m, of 1 $\mu F/cm^2$ and an axoplasmic resistivity, R_i, of 90 $\Omega \cdot cm$.

To explore the interaction between a propagating action potential and a local conductance change per se, a morphologically simple axon was chosen as a reference case. The effect of more realistic terminal geometry, which includes varicosities and bottlenecks as well as branch points, was analyzed in the second part of the study. The reference axon has a uniform diameter of 1 μm (i.e., $\lambda = 200\ \mu m$) and a total of 100 (excitable and passive) compartments, each 10 μm (0.05 λ) long. The total cable length of that axon, L, is thus 5 λ, and the input conductance at its midpoint is 9 nS (the input resistance there is 111 MΩ). In each run the action potential(s) was initiated at one end of the axon ($L = 0$) and it traveled toward the terminal tip at the other end ($L = 5$), where a sealed end boundary condition ($dV/dx = 0$) was assumed. The temporal integration step was 10 μs with the use of a second-order predictor-corrector method. Computations were performed on a VAX-VMS 11/750 with a floating point accelerator. Simulating 6 ms of "axon time" (600 time steps) required ~3 min of central processing unit (CPU) time.

RESULTS

The effect of a steady-state silent inhibition on an action potential propagating in the reference axon is shown in Fig. 1. In each frame the action potential is recorded at intervals of 0.5 λ (100 μm) from each other; the right-most action potential is recorded at the terminal tip. The inhibition is located at a distance of 200 μm (1 λ) from the terminal tip which is where the middle trace (third trace from left, heavy line) in each frame is recorded. In *A* the inhibition is inactive (i.e., $g_{syn} = 0$). Along the uniform part of the axon the action potential travels with a constant velocity; when it approaches the sealed end boundary condition both the velocity and the amplitude of the action potential increase (Goldstein and Rall 1974). In the case shown here, the peak value increases from 91 mV in the uniform axon to 102 mV at the boundary.

B, *C*, and *D* of Fig. 1 show the effect of an increasingly more powerful inhibitory action (g_{syn} = 30, 60, and 75 nS, respectively). When the shunting effect of the synapse is introduced, the action-potential amplitude decreases near the synaptic region (heavy line in Fig. 1, *B–D*). If the inhibition is weak, as is the case in Fig. 1*B* (30 nS), the action potential succeeds in overcoming the region of low safety factor near the axoaxonal synapse and fully recovers beyond this region. This weak synaptic shunt delays the action potential at the terminal tip by 0.16 ms, as compared with the unperturbed case. With a further increase of g_{syn} to 60 nS (Fig. 1*C*), the action potential at the region of the axoaxonal synapse decreases even more, and, as expected near regions with a severe reduction in the safety

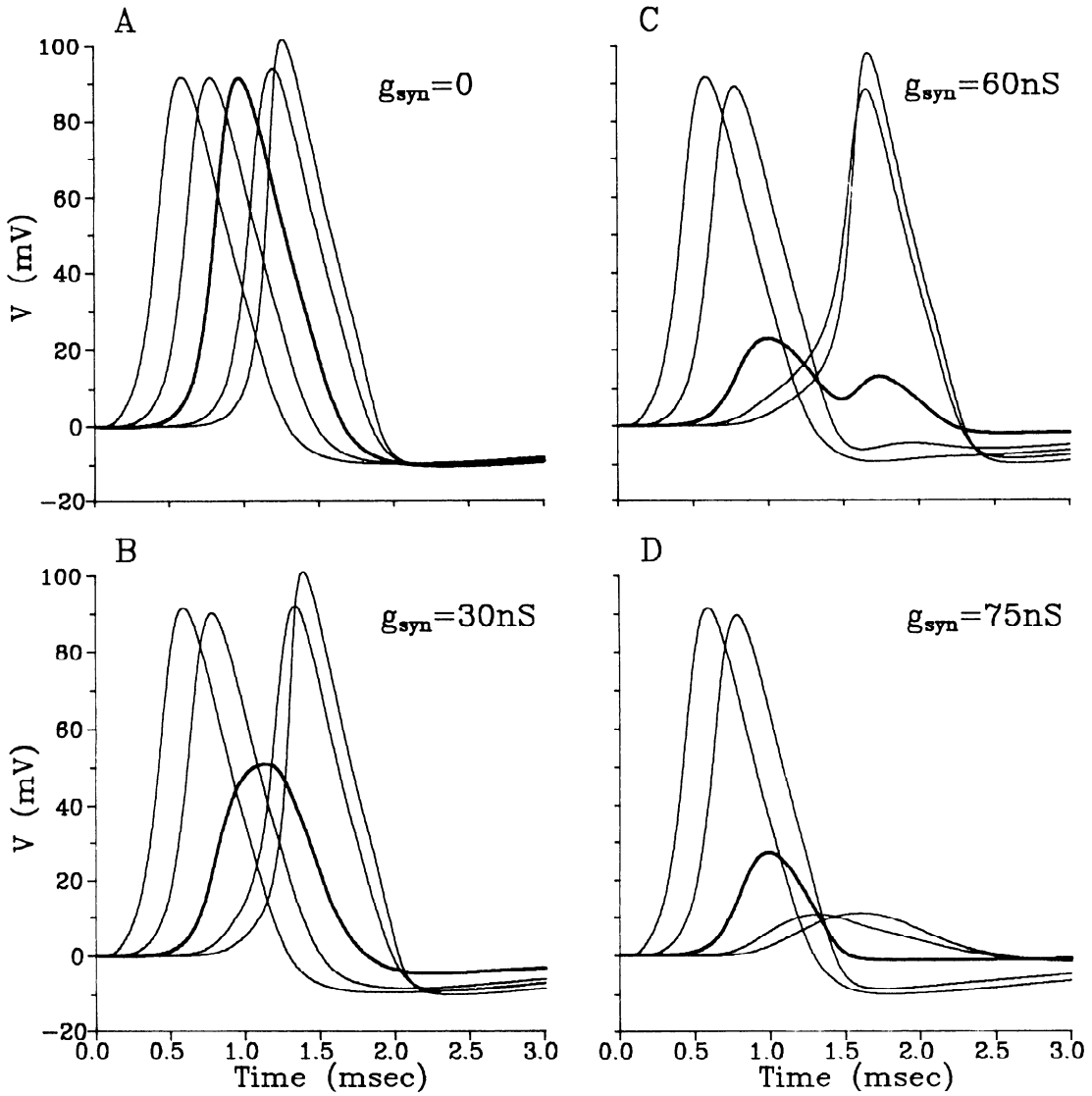

FIG. 1. A local steady-state silent inhibition delays and, when sufficiently powerful, can block propagation of an action potential along an excitable axonal terminal. The synapse is located at a distance of 1 λ from the terminal tip of the reference axon (see METHODS). In all 4 frames the action potential is recorded (from left to right) at a distance of 2, 1.5, 1, 0.5, and 0 λ from the terminal tip; the *middle trace* (heavy line) is recorded at the synaptic site. *A*: the inhibitory synapse is not active (g_{syn} = 0); both amplitude and velocity of the action potential increases near the sealed end (right-most spike). *B* and *C*: two examples of g_{syn} values that do not block the propagation. At the region of the synapse, the action potential is reduced, but, although delayed, it fully recovers beyond the synapse. *D*: a conductance change of 75 nS blocks the propagation beyond the synapse.

factor for propagation, it appears with a double peak (e.g., Khodorov et al. 1969; Parnas and Segev 1979). Although delayed by almost 0.5 ms, the action potential succeeds in propagating beyond the synapse and almost fully recovers at the terminal end. A further increase of g_{syn} beyond a critical value (g_{crit}) of 72 nS (~8 times the resting input conductance) results in a complete block of the action potential. An example of such a case is shown in Fig. 1*D* where g_{syn} = 75 nS; note the "local response" at the terminal segment as revealed by the slight increase in the voltage amplitude there (curve farthest to the right) compared with the more proximal point.

It is important to note that when all the specific parameters of the axon membrane and cytoplasm are held constant, the value of g_{syn} is scaled with $d^{3/2}$, where d is the axon diameter (i.e., like the input conductance). Hence, g_{crit} in a 2-μm terminal (with the same passive and excitable characteristics as above) is 204 nS, whereas a conductance change of only 27 nS is sufficient to block the action potential in an axon whose diameter is 0.5 μm.

Figure 2 shows that the effect of synaptic inhibition depends critically on the location of the axoaxonal synapse. When the synapse is located at a distance of 1 λ away from the axon termination (X_{syn} = 1), as was the case in Fig. 1, the voltage at the terminal tip undergoes a sharp transition from a peak of ~100 mV, for all g_{syn} < 72 nS, to a few millivolts depolarization for larger g_{syn} values. A different behavior is found when the inhibitory synapse is moved closer to the terminal tip. At a distance of 60 μm (X_{syn} = 0.3) from the terminal tip, there is no longer a clear "all-

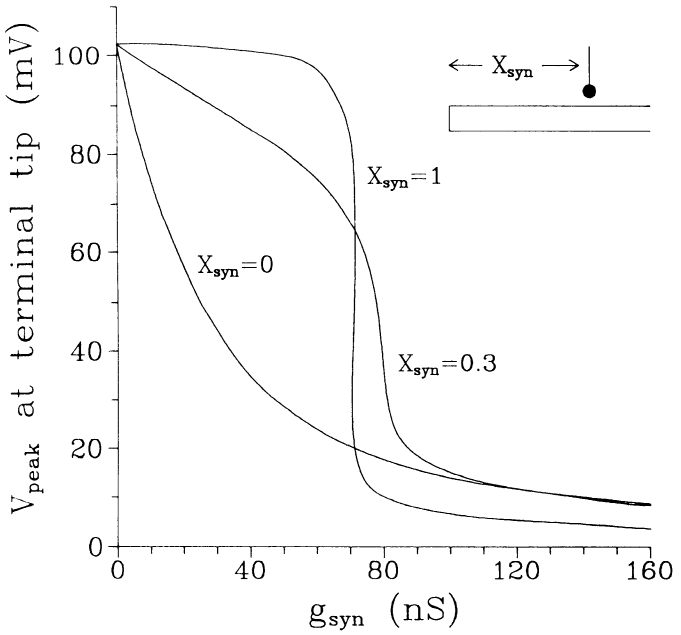

FIG. 2. Effect of presynaptic inhibition depends on the site of the synapse. An all-or-none effect is observed when the synapse is located electrically far from the terminal tip (X_{syn} = 1). In this case a sharp transition from a full-blown spike with a peak value (V_{peak}) of 102 mV at the terminal tip to a reduced V_{peak} is obtained when g_{syn} is increased beyond 72 nS. The threshold effect disappears, and graded control of the synapse over the voltage at the terminal tip can be obtained when the axoaxonal synapse is placed in the vicinity of the terminal tip (at X_{syn} = 0.3) and even more so when it impinges directly onto the tip (X_{syn} = 0). In the latter case, a relatively small conductance change is sufficient to reduce V_{peak} significantly.

or-none" effect of g_{syn}. Now the inhibitory synapse has graded control over the voltage at the terminal tip (at the output synapse). These features are also found when the inhibition impinges directly onto the terminal tip (X_{syn} = 0). The voltage there can be continuously controlled by adjusting g_{syn}, and even a small conductance change has a significant effect on the voltage at the tip. For example, when X_{syn} = 0 a 50% reduction in the action-potential amplitude (from 102 mV to 51 mV) is achieved with only a g_{syn} of 25 nS, whereas a conductance change of almost 80 nS is required when X_{syn} = 0.3.

The marked difference between the curve corresponding to X_{syn} = 0.3 and that corresponding to X_{syn} = 0 is a consequence of the presence of excitable membrane between these two sites. When X_{syn} = 0.3 and g_{syn} is not sufficient to reduce the voltage there below threshold, the (reduced) action potential propagates beyond the synapse and succeeds in only partially recovering along the short remaining distance (of 0.3 λ) that lies between the synapse and the terminal tip. In this case, the value of V_{peak} at the terminal tip depends on the voltage amplitude at the synaptic location; as g_{syn} gets larger (as the voltage amplitude at the axoaxonal synapse gets smaller), V_{peak} at the terminal end becomes correspondingly smaller. In contrast, when the axoaxonal synapse is located at the vicinity of the postsynaptic release site (as modeled here by the case of X_{syn} = 0), no additional active current can be produced beyond the synapse, and V_{peak} is controlled in a graded manner by the value of the local inhibitory shunt.

The conclusion from Fig. 2 is that in an excitable terminal, when an all-or-none reduction in the voltage at the output synapse is required, a distant presynaptic inhibition is more effective than a more adjacent inhibition. The block of the action potentials by such a distant inhibitory shunt, plus the voltage attenuation along this distance, ensures a negligible depolarization at the output synapse. On the other hand, graded control of the voltage at the postsynaptic release site can be achieved with relatively weak presynaptic inhibitions that are electrotonically adjacent to that site.

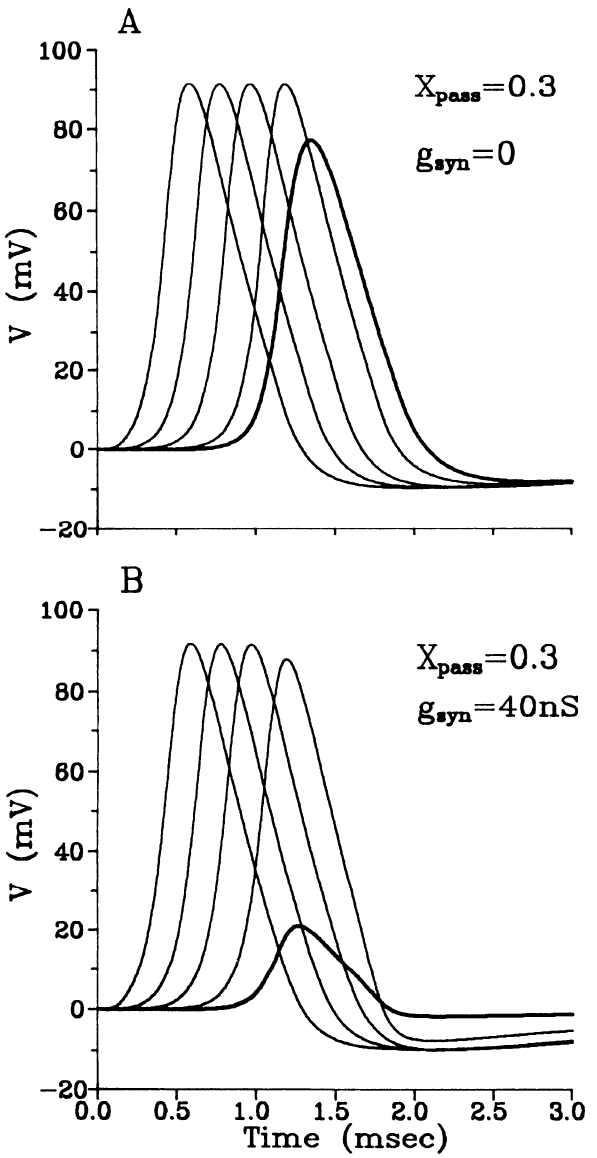

FIG. 3. Behavior of action potential along an axon with a passive terminal segment and with an axoaxonal synapse at the terminal tip. *A*: without presynaptic inhibition, the action potential attenuates along the passive terminal and produces a peak value of 77 mV at the tip (heavy line at right-most trace). *B*: when an inhibitory conductance, g_{syn} = 40 nS, is applied at the terminal tip (X_{syn} = 0), the voltage there is reduced to 21 mV (heavy line). Note that the action potential at proximal sites is insensitive to the presence of inhibition. The length of the passive region is 0.3 λ (60 μm in the modeled axon). The action potential is recorded (from left to right) at distances of 2, 1.5, 1, 0.5, and 0 λ from the terminal tip.

Dudel (1982, 1983) has raised the possibility that in crustacean motor axons some terminals may be inexcitable (passive). Figures 3 and 4 illustrate the effect of presynaptic inhibition on the spread of potential into a passive terminal. The simulated axon is identical in geometry to that of the reference axon, but now it has a 60 μm (0.3 λ) long *passive* terminal; the axoaxonal synapse is at the terminal tip. In Fig. 3 the propagation of an action potential in this axon is shown. As in Fig. 1, the right most action potential is recorded at the terminal tip ($X = 0$). In *A* the inhibition is not active; in *B* a 40-nS conductance change is introduced at the terminal tip. When the inhibition is not active (Fig. 3*A*) the action potential attenuates as it spreads into the terminal region and produces a peak of 77.3 mV at the tip as compared to a 102 mV in an excitable terminal, a 25% reduction (heavy line). (Note that the sealed end boundary condition results in a smaller attenuation than expected in an infinitely long axon.) When a g_{syn} of 40 nS is activated at the passive tip itself, the voltage amplitude there is reduced to 21 mV (Fig. 3*B*, heavy line). This should be compared with the corresponding excitable terminal of Fig. 2 (with $X_{syn} = 0$) where a conductance change of ~70 nS was needed to reduce V_{peak} at the terminal tip to that same value. Another interesting point is that the action potential recorded at the proximal (excitable) site just before the passive region (i.e., at 0.5 λ away from the tip) is almost unaltered by the inhibition (Fig. 3*B*). Thus presynaptic inhibition may reduce the potential near the output site of the affected axon significantly, but its effect on the action potential recorded more proximally may not be detected at all. This point is further analyzed below in Fig. 5 and in Fig. 7, which demonstrates that a more dramatic localization of the effect of inhibition is obtained in terminals consisting of varicosities.

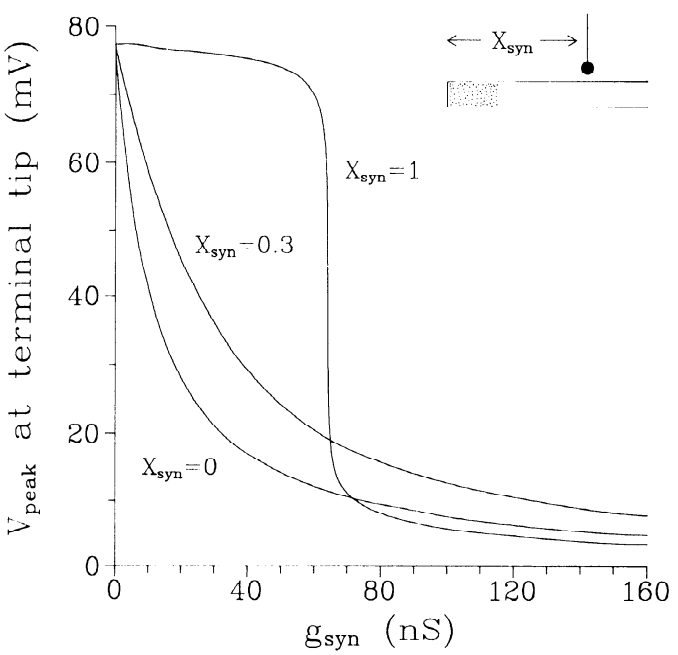

FIG. 4. The terminal tip is the optimal site of presynaptic inhibition located along a passive terminal for maximal reduction of the voltage at the tip. As in the excitable case of Fig. 2, an all-or-none effect is observed when the synapse is located electrically far from the terminal tip, along the excitable region of the axon ($X_{syn} = 1$). In this case, a sharp transition from the normally attenuated V_{peak} of 77 mV at the passive tip to <10 mV depolarization is obtained when g_{syn} is increased beyond 72 nS. This threshold behavior disappears when the synapse is moved into the passive region. In both $X_{syn} = 0.3$ and $X_{syn} = 0$, the voltage at the terminal tip can be gradually controlled by changing g_{syn}. The axoaxonal synapse is more effective when placed at the tip than when placed elsewhere in the passive region, including $X = 0.3$. The reference axon was used for the simulation with a 0.3 λ long passive terminal segment (schematic dots in *inset*).

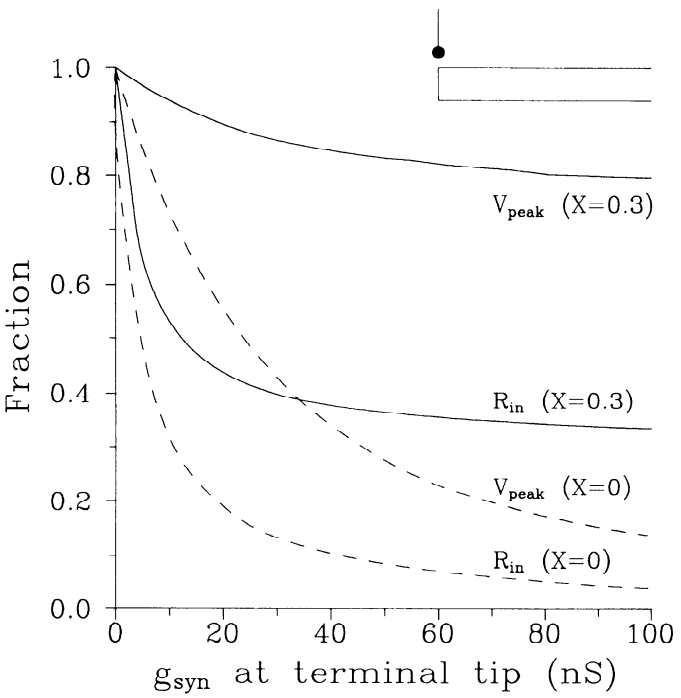

FIG. 5. Presynaptic inhibition is poorly detected even at only a short distance from the axoaxonal synapse. The fraction of decrease in both action potential amplitude (V_{peak}) as well as in the input resistance (R_{in}) at the site of axoaxonal synapse (dashed lines, see *inset*) and at a distance of 0.3 λ from it (continuous lines) is shown. Although both V_{peak} and R_{in} are reduced significantly at the site of the axoaxonal synapse, they are much less sensitive to the inhibitory action at the proximal site of recording. Terminal varicosities and bottlenecks make the detectibility of changes that are induced by the presynaptic action even less detectible than in a geometrically uniform terminal (see Fig. 8).

The significance of the location and magnitude of an inhibitory conductance change in a passive terminal is examined in Fig. 4. As in Fig. 2, the curves describe the effect of the location and magnitude of presynaptic inhibition on the potential amplitude at the terminal tip. The picture in Fig. 4 is generally the same as that in Fig. 2, with two main points to note: *1*) inhibition is more effective in passive terminals than in excitable terminals (note differences in ordinate values in Figs. 2 and 4); and *2*) along the passive region, the terminal tip is the optimal site for an axoaxonal synapse to reduce the terminal tip voltage maximally. Hence, as in the excitable case of Fig. 2, the curve corresponding to $X_{syn} = 0$ lies below the curve corresponding to $X_{syn} = 0.3$. A more thorough analysis regarding the optimal site of inhibition is given in Rall (1964), Jack et al. (1975), and Koch et al. (1983). Although they discuss the problem of the maximal effect of inhibition in reducing a dendritic located excitatory synapse, the analysis is also applicable to the case of a passive attenuation along axonal terminals, with their "soma" being replaced here by "terminal tip."

The detectibility of the conductance increase as well as

the change in action-potential amplitude associated with the presynaptic inhibition is examined in Fig. 5. The dashed curves show the normalized value of V_{peak} and of the input resistance (R_{in}) at the site of the axoaxonal synapse (at the terminal tip, $X = 0$; see *inset*). The continuous curves are the corresponding values as detected at a distance of 0.3 λ from the same steady synapse at $X = 0$. Both V_{peak} and R_{in} decrease steeply at $X = 0$ as the inhibitory conductance change increases. A much smaller decrease in both is observed at $X = 0.3$; there, the action-potential amplitude falls by only 20% even when the inhibitory conductance change is very large (100 nS; ~23 times the resting input conductance at that site). The relative decrease in the input resistance at $X = 0.3$ is more significant (a decrease of ~67% for $g_{syn} = 100$ nS, approaching the case of a "killed-end" boundary condition where the expected decrease in R_{in} at $X = 0.3$ is 70%), but it is still much smaller than the relative decrease in R_{in} measured at the site of the inhibitory conductance. Thus Fig. 5 clearly demonstrates that the detectibility of presynaptic inhibition is already poor at only a short distance from the synapse. It is even poorer when the axoaxonal synapse impinges at a terminal that is composed of varicosities and bottlenecks (see below).

A comparison between the efficacy of presynaptic inhibition in excitable and passive terminals as a function of the site of the axoaxonal synapse is demonstrated in Fig. 6. Assuming, arbitrarily, that the output synapse at the terminal tip has a threshold of 10 mV for neurotransmitter release, the figure shows the value of g_{syn} that reduces V_{peak} at the tip below that threshold as a function of x_{syn}. In an excitable terminal, a powerful (140-nS) inhibition must be activated at the terminal tip to achieve this drastic task of reducing the (increased) 102-mV peak at the terminal tip to a peak value of only 10 mV. A decreasingly powerful synapse is needed when the inhibition is moved away from the terminal tip. Very different behavior is observed in the passive terminal, where the synapse that impinges directly at the terminal tip itself is highly effective. Only about one-half of the conductance change (75 nS vs. 140 nS) is sufficient to reduce the (already attenuated) voltage there below threshold for neurotransmitter release. As the synapse is moved away from the terminal tip along the (60-μm) passive region (heavy line along abscissa), the g_{syn} needed is increased to reach a maximum of 130 nS at x_{syn} = 50 μm. Beyond that point, the g_{syn} needed is continuously reduced as the synapse is moved further out of the passive region and along the excitable region of the axon.

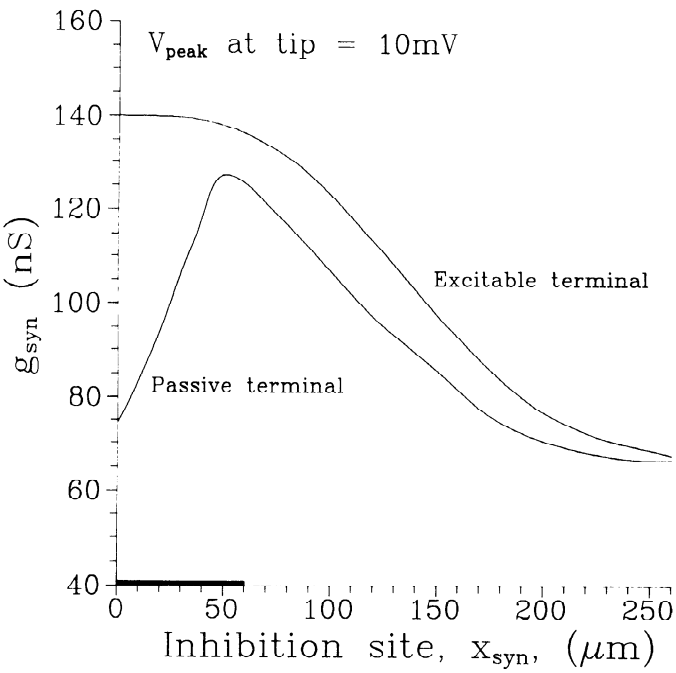

FIG. 6. Presynaptic inhibition is more effective at passive terminals than at corresponding excitable terminals. In this graph the inhibitory conductance that is needed to reduce V_{peak} at the terminal tip below 10 mV is plotted as a function of the site of the synapse (x_{syn}). When the terminal is excitable, a powerful g_{syn} of 140 nS is needed at the terminal tip to achieve this task, whereas a g_{syn} of only 75 nS is required when the terminal is passive. As the synapse is moved back from the tip, the required g_{syn} is continuously reduced when the terminal is excitable. In the passive terminal the required g_{syn} increases initially, then gradually decreases. The reference axon was used for the simulation with a 0.3 λ (60 μm) long passive terminal (heavy line on the abscissa).

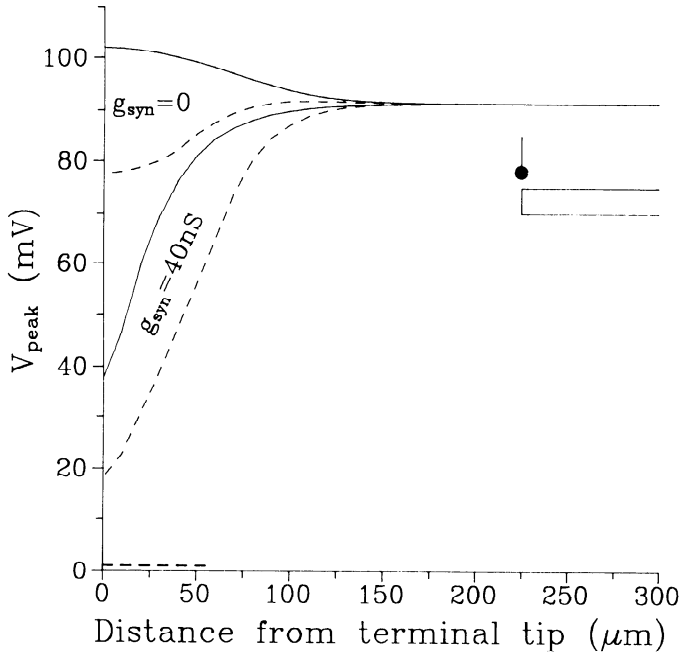

FIG. 7. The behavior of the action-potential peak as a function of distance along an excitable terminal (continuous lines) and a passive terminal (dashed lines) in the absence (*top traces*) and the presence (*bottom traces*) of presynaptic inhibition at the terminal tip. The action potential travels from right to left in inset. In the excitable case, when presynaptic inhibition is not active ($g_{syn} = 0$), the action-potential peak starts to grow at a distance of more than 100 μm (0.5 λ) from the terminal tip. In the corresponding passive case, the peak starts to attenuate along that distance. Introducing an inhibitory conductance change of 40 nS at the tip results in a 63% decrease in V_{peak} at the synaptic site when the terminal is excitable and a 75% decrease when the terminal is passive. The passive terminal is 60 μm (0.3 λ) long (dashed line on the abscissa).

The behavior of the voltage peak as a function of distance from a terminal tip that receives an axoaxonal synapse is shown in Fig. 7. Here, the action potential travels from right to left (*inset*) and the inhibitory synapse is located at the terminal tip itself ($x = 0$). The continuous lines are for the excitable case, whereas dashed lines are for the (0.3 λ = 60 μm) passive terminal (dashed line on the ab-

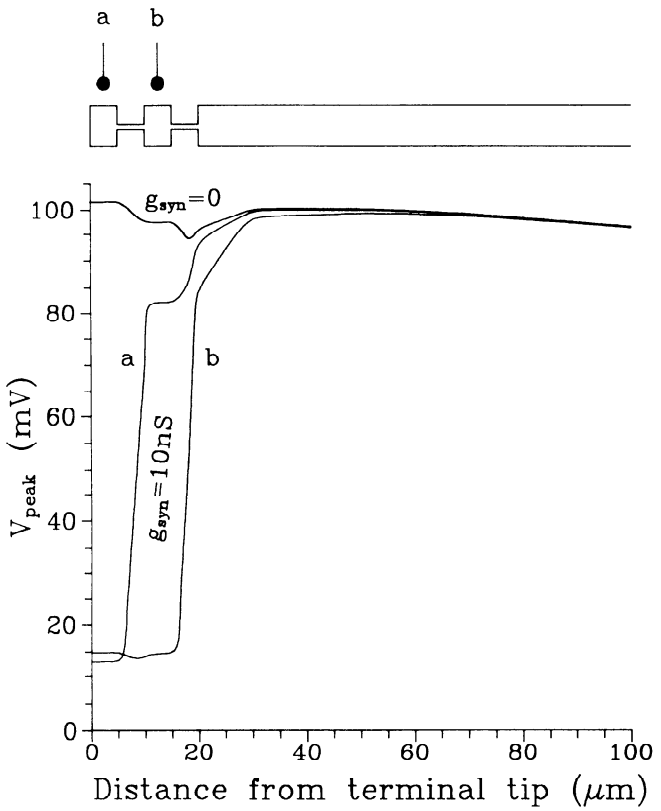

FIG. 8. Propagation along terminals with varicosities and bottlenecks is particularly sensitive to presynaptic inhibition. The schematic drawing at the top shows the modeled axon drawn to scale; it has the same abscissa as the figure. This 1-μm axon has an excitable terminal consisting of two varicosities, each 5 μm long and 1 μm thick, connected by two bottlenecks, each 5 μm long and 0.1 μm thick. The topmost curve shows the behavior of the action potential peak when the presynaptic inhibition is not activated. V_{peak} is slightly reduced at the inhomogeneous region but succeeds in recovering at the terminal tip. Introducing an inhibitory conductance change as small as 10 nS, either at the terminal varicosity (a) or at the next-to-last varicosity (b), blocks propagation at the terminal. The effect of this inhibition is almost undetectable 30 μm away from the terminal tip.

scissa). The top two curves show the unperturbed situation, where $g_{syn} = 0$. In the excitable case, a gradual increase in V_{peak} can be observed beginning at a distance of 120 μm (0.6 λ) from the terminal tip. In the passive case, there is a region where the peak initially grows slightly (indicating that at that region the boundary conditions are more effective in increasing the peak than are the passive properties that lie ahead in decreasing it). Thereafter, the voltage peak decreases and reaches a minimum of 77 mV at the terminal tip. The two bottom curves show the effect of an axoaxonal synapse at the terminal tip with g_{syn} = 40 nS. Both curves decline as they approach the synapse; the decline of the curve corresponding to the passive case (dashed line) is more rapid and it reaches a minimal value of 19 mV (a 75% decrease) compared with a 38 mV (a 63% decrease) in the excitable terminal. Again, this figure demonstrates clearly that at a distance of 0.5 λ (100 μm) from the synapse the action potential is almost unaltered by the inhibitory action.

Usually (but not always) axonal terminals consist of extensive chains of varicosities connected by thinner (sometimes by a factor of 10) segments or bottlenecks, as they are called. The release sites are principally confined to the varicosities, and, when axoaxonal synapses are present, they are located at the varicosities (Atwood et al. 1984; Atwood and Tse 1986; Fyffe and Light 1984; Jahromi and Atwood 1974; Smith 1978). What is the effect of such an arrangement on the action potentials at the terminal? This question is explored in Fig. 8, where an excitable axon with a diameter of 1 μm that terminates with two successive varicosities is simulated. The varicosities (each 5 μm long with a diameter of 1 μm) and bottlenecks (5 μm long and 0.1 μm in diameter) in the schematic representation of the axon terminal at the top part of the figure have the same scale as the x-axis in the figure. These dimensions lie within the range reported by Atwood et al. (1984). As in the previous figure, the action potential travels from right to left.

The topmost curve of Fig. 8 shows the unperturbed case (g_{syn} = 0). It demonstrates that the geometrical inhomogeneity of the terminal produces a region of low safety factor for propagation; the action potential is reduced as it approaches that region but then fully recovers to its original 102-mV peak value at the terminal tip (see Goldstein and Rall 1974; Khodorov and Timin 1975; Parnas and Segev 1979 for theoretical studies on the effect of geometry on the

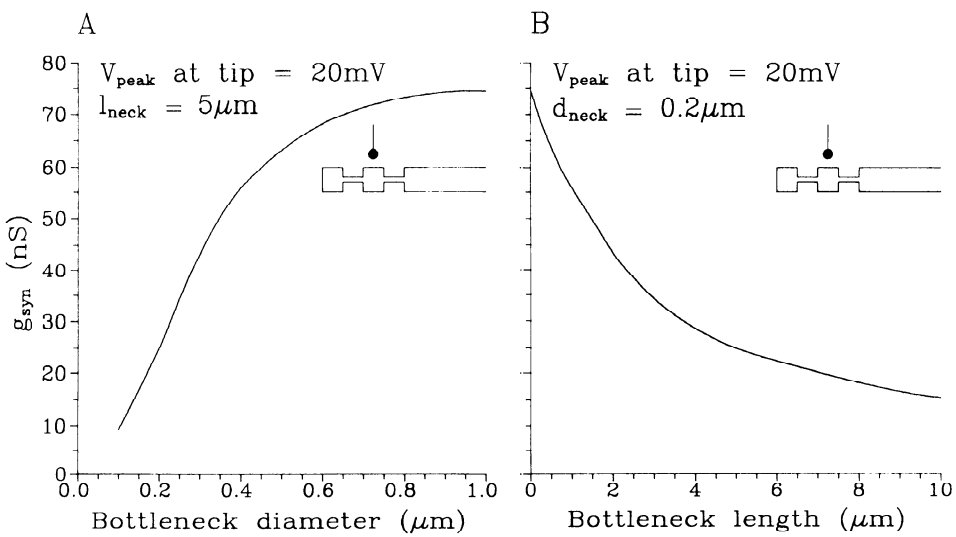

FIG. 9. Sensitivity to inhibitory action depends on the bottleneck diameter and length. In *A*, the value of g_{syn} that reduces V_{peak} at the terminal to 20 mV is plotted as a function of bottleneck diameter (keeping their length 5 μm). In *B*, that g_{syn} value is plotted as a function of the bottleneck length (keeping their diameter 0.2 μm). A steep reduction in g_{syn} value, from 75 nS to <10 nS, is obtained when d_{neck} is decreased from 1 μm to 0.1 μm (*A*). A reduction of five-fold (from 75 nS to 15 nS) is observed when ℓ_{neck} is increased from 0 to 10 μm (*B*).

spread of action potentials). An inhibitory conductance change as small as 10 nS, however, either at the distal varicosity (a) or at the more proximal one (b), is sufficient to completely block the propagation into the terminal and to reduce V_{peak} at the tip to ~15 mV. This is in marked contrast to the uniform case (Fig. 2), where a similar inhibitory action has only a minor effect. Hence the spike that travels along such a terminal geometry is very vulnerable, and a small shunt induced by the axoaxonal synapse results in subthreshold conditions for propagation. Note also that, as in the case with inhibition onto dendritic spines that have a small stem diameter, the consequence of thin bottlenecks is to restrict the effect of inhibition to the input region itself (Jack et al. 1975; Segev and Rall 1988). Figure 8 shows that at a distance of only 30 μm from the terminal tip the action potential remains essentially unaltered by the inhibitory conductance change (see DISCUSSION).

Bottleneck caliber and length were found to vary within a wide range of values (Atwood et al. 1984; see their Table I). In agreement with the steady-state calculation of Atwood et al. (1984), Fig. 9 demonstrates that the effectiveness of inhibition depends critically on the diameter of the bottleneck (d_{neck}). Setting the required peak value at the terminal tip to 20 mV, Fig. 9*A* shows that g_{syn} need only be ~10 nS when the diameter of both bottlenecks is 0.1 μm; when both diameters are tripled to 0.3 μm, the required g_{syn} becomes increased to ~45 nS. In contrast to Atwood et al. (1984), the effectiveness of inhibition also depends on the length of the bottleneck (ℓ_{neck}). A 10-fold increase in the length of the bottlenecks, from 1 μm to 10 μm (keeping d_{neck} = 0.2 μm), results in almost a 5-fold decrease in g_{syn} (Fig. 9*B*).

Hence, Figs. 8 and 9 support the conclusion that the typical varicose geometry of axonal terminals makes the action potential there particularly susceptible to inhibition. A small conductance increase that is induced by a few quanta of inhibitory transmitter can block propagation into the terminal and, thereby, markedly decrease the output of that terminal.

An interesting question worth exploring is how would different channel distributions and kinetics at the terminal affect the interaction between spikes and presynaptic inhibition. In Fig. 10, the consequence of varying the density of sodium channels ($\bar{g}_{Na}$) along the whole axon for both an axoaxonal synapse that is located proximally (*top curve* and corresponding *inset*) as well as for an inhibitory synapse at a next-to-last varicosity (*bottom curve*) is examined. When the synapse is located at the uniform region of the preterminal axon, the critical conductance change that blocks the action potential depends very steeply on the density of the sodium channels. Indeed, the action potential could not be blocked at all by a localized inhibitory synapse when $\bar{g}_{Na}$ was increased beyond a value of 600 mS/cm^2. Hence, under these conditions the inhibitory shunt is insufficient to reduce the depolarizing current below threshold for propagation. For the same density of sodium channels, however, a relatively small inhibitory conductance change at the next-to-last terminal varicosity does result in subthreshold conditions for spike firing (Fig. 10, *bottom curve* and corresponding *inset*). The flat relation between $\bar{g}_{Na}$ and g_{crit}, in this case, supports the conclusion that the geometry of the terminal is the dominant factor in making the spike there very susceptible and, therefore, sensitive to inhibition. Even a large increase in the density of the excitable channels at that region has a limited capability of improving the conditions for propagation into the terminal.

The critical conductance change that blocks propagation depends also on temperature because of its affect on the kinetics of the voltage-gated channels. When the temperature is reduced to 0°C (from 18°C), g_{crit} at a 1-μm uniform axon is increased to 200 nS (from 72 nS). At 30°C, however, where the Hodgkin and Huxley spike is insecure, a conductance change of 30 nS was sufficient to block propagation.

Finally, the behavior of a train of five action potentials (at 300 Hz) in a branching terminal is modeled in Fig. 11. Each of the daughter terminals consists of varicosities as in Fig. 8; the presynaptic inhibition on the lower branch is active (with g_{syn} = 7 nS), whereas the inhibition on the upper branch is not active (g_{syn} = 0). As can be seen, the whole train succeeds in propagating into the unperturbed terminal while the second and the forth spikes fail to invade the terminal that receives the presynaptic inhibition (all spikes are reduced in amplitude there). Clearly, different combinations of the location and magnitude of the axoaxonal inhibition on a given axonal tree would result in a variety of outputs from that tree.

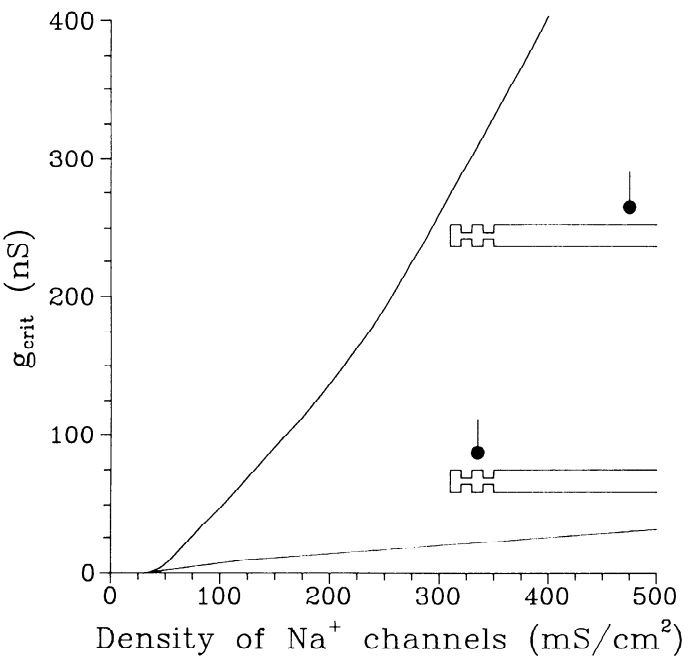

FIG. 10. The density of excitable channels is critical when the presynaptic inhibition is located at the preterminal axon but is of minor significance when the axoaxonal inhibition impinges on terminal varicosities. The *top curve* shows the case of a remote inhibition (see corresponding *inset*). When $\bar{g}_{Na}$ is reduced below 30 mS/cm^2, there is no propagation at all (i.e., g_{crit} = 0). Increasing $\bar{g}_{Na}$ results in a steep increase in g_{crit}. Hence, a single axoaxonal synapse along a uniform axon can not block propagation for $\bar{g}_{Na}$ > 600 mS/cm^2. The *bottom curve* shows the case of an axoaxonal synapse at the next-to-last terminal varicosity (*inset*). In this case, propagation block occurs with very weak inhibition; increasing $\bar{g}_{Na}$ results in only a minor increase of the critical value of the g_{syn} that blocks propagation. The simulated axon is identical in geometry to the axon in Fig. 8.

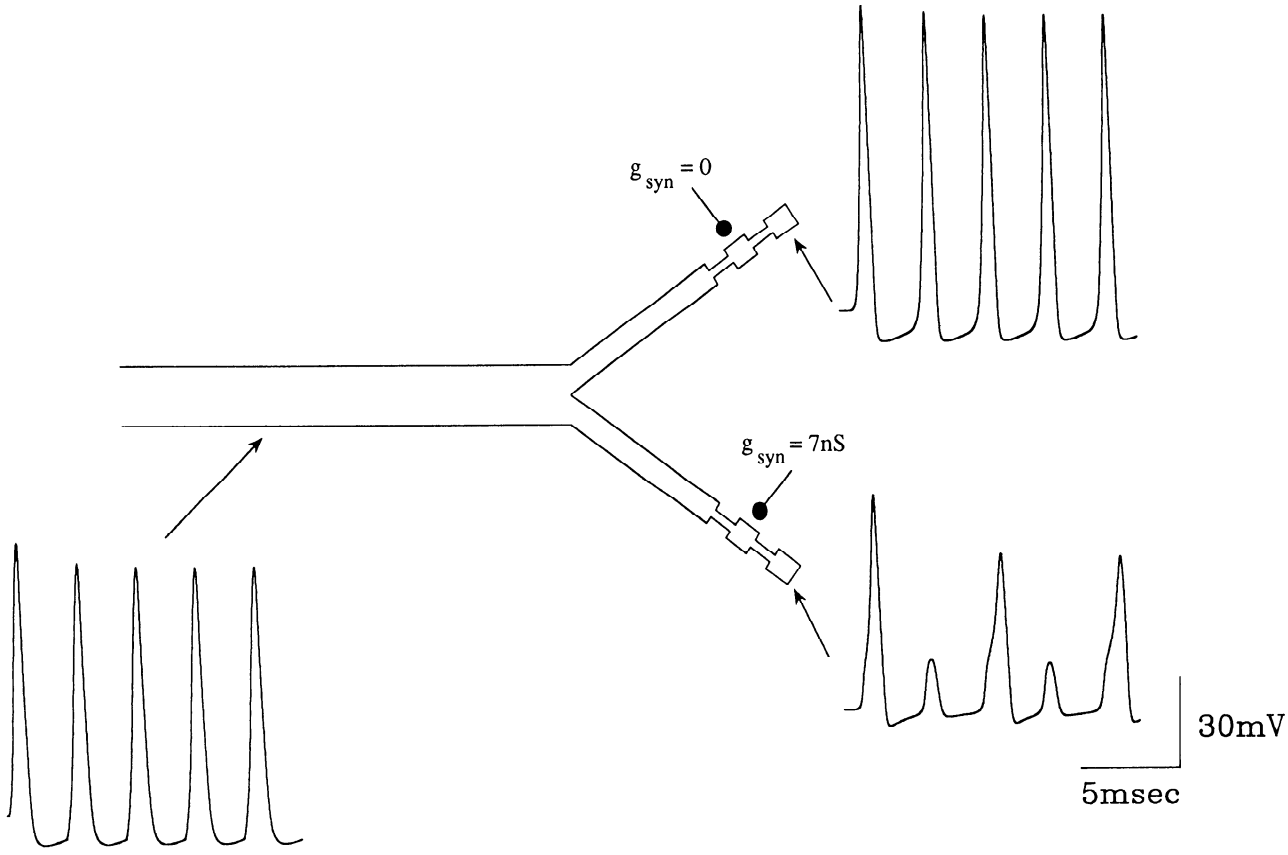

FIG. 11. Strategic placement of presynaptic inhibition can produce a differential block of propagation into the terminals of an axonal tree. A train of 5 action potentials at a frequency of 300 Hz is initiated at the preterminal (parent) axon. Propagation occurs without failure into the top terminal branch, where the axoaxonal synapse is not active ($g_{syn} = 0$). In contrast, the second and the fourth action potentials are blocked when a 7-nS inhibitory conductance change is introduced at the next-to-last varicosity of the lower terminal branch. Note that when inhibition is not present, the terminal varicosities do not filter the spikes even when they appear in high frequency. The parent branch has a diameter of 1.6 μm; the initial diameter of each of the (100 μm long) daughter branches is 1 μm. The dimensions of the varicosities and bottlenecks are as in Fig. 8. The train in the parent branch is recorded at a distance of 300 μm from the branch point, whereas trains in the daughter branches are recorded at their tips.

DISCUSSION

The conductance change produced by a single quantum of inhibitory transmitter was estimated to be in the range of 10 nS (Finger and Stettmeir 1981) and, recently, as large as 21.5 nS (Faber and Korn 1988). The present study shows that one, or few, of these quanta, when released from an axoaxonal synapse, can drastically reduce and even block the action potential at the release site of the postsynaptic axon. Depending on the input-output relation at the specific active zone that is being affected, this reduction in the voltage would lead to a decrease in transmitter output. The link between voltage and transmitter release was not dealt with in the present study; rather, the study focuses on the factors that determine the relation between the voltage at the terminal and the conductance change induced by the axoaxonal synapse. The main results are discussed below.

Terminal geometry

Fixing all other axon parameters, the effects of inhibitory conductance increase is linearly scaled with the axon diameter (d) raised to the 3/2 power. Namely, in each of the cases analyzed in the present study, the values of g_{syn} given are proportional to $d^{3/2}$ (i.e., to the input conductance), provided that the specific membrane and cytoplasm properties as well as the *electrical* structure (in cable units) of the examined axon with its axoaxonal synapse, are kept constant. Hence, if a steady-state silent inhibition is located along a 1-μm uniform axon sufficiently remote from the terminal tip, the critical conductance change that blocks an action potential with the Hodgkin and Huxley (1952) kinetics at 18°C is 72 nS (Figs. 1 and 2). This value is ~8 times the value of the resting input conductance. A conductance change of only 12 nS would be needed to produce the block when the same action potential propagates in a terminal whose diameter is 0.3 μm, as is often the case in unmyelinated axonal terminals in mammalian CNS (e.g., Fyffe and Light 1984; Humphrey et al. 1985; C. D. Gilbert, personal communication).

The present analysis demonstrates that axoaxonal inhibition near the postsynaptic output site is generally the most effective location for reducing the voltage at that site maximally (Figs. 2 and 4). The only exception is the case where a very small depolarization is required at the release site; then, a distant axoaxonal synapse may be more effective (compare the curves corresponding to $X_{syn} = 0$ and

$X_{syn} = 1$ in Figs. 2 and 4). In any case, such a distant synapse would produce an all-or-none effect at the output site. In contrast, the threshold effect of remote inhibition disappears when the axoaxonal synapse is in the vicinity of the release site. Then the voltage at that site (and, therefore, the transmitter output) can be controlled in a graded manner.

The typical structural specialization of axonal terminals was shown to have important consequences for presynaptic inhibition. The conductance load (or miss-match) that is encountered by the action potential at the transition between the thin bottlenecks and the thicker varicosities makes propagation at that region insecure (see also Goldstein and Rall 1974; Khodorov et al. 1969; Parnas and Segev 1979). Even in a very "hot" terminal, the safety factor for propagation in that region is severely reduced, and a relatively small inhibitory conductance change there can block active invasion into the terminal (Figs. 8–10). After the block, the voltage severely attenuates along the irregular structure of the terminal to produce a negligible depolarization at the terminal tip (see also Atwood et al. 1984). Thus the terminal varicosities provide a favorable location for an axoaxonal inhibitory synapse to attenuate the voltage at the terminal maximally. The increased sensitivity to small changes in conductance at such regions, however, makes the inhibition there operate more in an "on-off" fashion rather than in a graded manner as in a geometrically uniform terminal.

Another important finding from the experimental point of view is that the shunting effect of inhibition and the resultant decrease in the action potential under the axoaxonal synapse, as well as the conductance change associated with the activation of such a synapse, may not be detected by an intracellular electrode at a distance of only a few tenths of a space constant away from it (Figs. 1, 3, 5, and 7). First, the increase in the inward active current near regions where the spike tends to decrease (the driving force increases, see Khodorov et al. 1969; Parnas and Segev 1979) serves as a compensatory mechanism for the decrease in the action potential induced by the inhibitory conductance change. In addition, as was shown by Rall (1967), the detectibility of a local conductance change is already poor at a short distance from the site of the change (Fig. 5). The presence of bottlenecks at the terminal endings enhances this decoupling effect even more (Fig. 8). At any case, as found experimentally by Glantz et al. (1985), at any given point along the axon, the relative reduction in action-potential amplitude is expected to be smaller than the relative increase in the input conductance.

Membrane properties

There have been several suggestions concerning the nature of the membrane at the terminal. Dudel (1982) has suggested that in the crayfish some terminals may be passive; others have suggested that the terminal (in the mouse) may consist of different excitable channels than do the preterminal axon (Konishi and Sears 1984; Mallart and Brigant 1982; and see the theoretical study by Peres and Andrietti 1986). The present investigation demonstrates that, in a varicose terminal, the efficacy of presynaptic inhibition is relatively insensitive to the type and number of excitable channels at the terminal. The terminal geometry is the most dominant factor for the presynaptic inhibition, and, from the point of view of the inhibition, a passive terminal or a very hot terminal with different channel types are essentially the same. Obviously, questions regarding the type and properties of excitable channels at the terminal should not be ignored, because these channels determine both the amplitude and the width of the action potential there (see Segev and Rall 1988), and the amount of transmitter being released is sensitive to these parameters. Furthermore, the release mechanism itself is mediated by influx of Ca^{2+} ions and, possibly, also by other ions that may enter through these channels in the region of the active zone. Also, as Segev and Rall (1988) (Fig. 10) have shown, both the kinetics of the excitable channels as well as the kinetics of the channels that are involved in the inhibitory action play a role in determining the preferred timing (and the temporal resolution) between presynaptic inhibition and the postsynaptic action potential. These points were not elaborated further in the present study.

Unlike the case of terminals with varicosities, the density of excitable channels along uniform terminals has a pronounced effect on presynaptic inhibition. Figure 10 shows that a local inhibitory shunt may be incapable of blocking the propagation when the density of excitable channels is sufficiently high—as high as that estimated at the initial segment or at internodes of axons at the mammalian CNS (Hille 1984). In this case, a chain of several adjacent axoaxonal synapses may still succeed in blocking propagation along such a hot terminal.

Synaptic properties

In the present study, the inhibitory conductance change was modeled as a steady-state conductance change with an associated zero battery (relative to rest). The effect of the timing between action potentials and a transient inhibitory (alpha function) g_{syn} with different rise time and magnitude has been analyzed by Segev and Rall (1988) and, in the passive case, by Segev and Parnas (1983) and Koch et al. (1983). It should be pointed out that, usually, inhibitory channels have slow kinetics, therefore, their effect can be approximated by a steady-state conductance change. Also, the effect of a silent inhibition is more localized than the effect of an identical conductance change associated with a battery that differs from the resting potential. Indeed, an axoaxonal synapse that produces hyperpolarization is more effective in blocking the action potential than one with identical, silent conductance increase. Note also that a depolarizing presynaptic inhibition at a preterminal location can block propagation only if E_{syn} is more negative than the threshold for the spike. Unless this depolarization inactivates the excitable channels (and increases the spike threshold), g_{crit} should be markedly increased to compensate for the facilitatory effect of the depolarization induced by the synapse. When such a depolarizing axoaxonal synapse is placed near the terminal ending, and g_{syn} is sufficiently large relative to the input conductance at that region, the activation of this synapse tends to clamp the voltage at the terminal to E_{syn}.

Implications for integrative functions

The spatial arrangement of axoaxonal synapses along axonal terminals differs in different systems. Each arrangement dictates the type of operation being performed by these synapses and, to some extent, also the likely mechanism by which such synapses may exert their action. When the axoaxonal synapses are located away from the release site, as is frequently the case in crustaceans (Atwood et al. 1984; Glantz et al. 1985), presynaptic inhibition is expected to have a global vetoing effect over all release sites that are distal. In such cases, the most likely mechanism of presynaptic inhibition is the decrease of the postsynaptic spike (e.g., by a local shunt). Figures 1–4 show that with this mechanism in both passive and excitable terminals, an all-or-none inhibitory effect is achieved when the axoaxonal synapse is electrically distant from the release site, whereas a graded effect is obtained when the axoaxonal inhibition is electrically adjacent to that site. It was also demonstrated that presynaptic inhibition is more efficient in passive terminals. As with postsynaptic inhibition along the dendritic tree (Koch et al. 1983; Rall 1967; Segev and Rall 1988), strategic placement of axoaxonal synapses along the axonal tree can produce differential inhibition whereby propagation into certain branches is blocked while the transmission at other branches is unaltered (Fig. 11).

Axoaxonal synapses may impinge directly onto the postsynaptic boutons. This is commonly the case in Group Ia synapses in cat spinal cord (Fyffe and Light 1984). Such an arrangement may provide for very fine control over each postsynaptic site, much the same as does postsynaptic inhibition that impinges onto a dendritic spine that also receives an excitatory input (Segev and Rall 1988). However, in the case of dendritic spines the spine stem resistance decouples the effect of such inhibition from other spines. In contrast, an en passant inhibition that exerts its action by producing a local conductance increase may lead to a propagation failure into all the boutons that are more peripheral to it. One way to overcome such a nonspecific effect (with the use of a mechanism that acts on the spike amplitude) is to decrease the depolarization near the bouton to a value that reduces transmitter output but that is still suprathreshold for propagation (as might be the case in Fig. 1*C*, heavy line). A more likely mechanism that would preserve selective inhibitory control (without the global effect) is one that acts directly on the release mechanism.

In conclusion, the combination of terminal geometry and membrane properties together with strategic arrangement of presynaptic inhibition along the terminal arborization provides for a mechanism that can function on different levels of spatiotemporal resolution. A presynaptic inhibition that functions by reduction of the spike amplitude is, in general, a more global mechanism than one that acts directly on the release mechanism. The combination of these two classes of mechanisms can produce a system with a rich repertoire of operations.

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