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Observations on impulse conduction along central axons

(neurophysiology/coding/corpus callosum)

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ABSTRACT **This note calls attention to the facts that (*i*) the conduction velocities of central axons may not be predicted on the basis of diameter alone, and (*ii*) that such structure–function relations as do exist may not be invariant. Data are presented which indicate that conduction velocities of rabbit callosal axons vary with the history of impulse conduction along the fiber. Increases and decreases of conduction velocity occur. Constant latency does not, therefore, constitute a necessary condition for identification of antidromically activated neurons, and variable latency does not constitute a sufficient condition for identification of synaptically activated neurons. The results are further discussed in terms of temporal coding of information in the central nervous system.**

Since neural information is coded in both space and time, one of the major challenges facing the neurobiologist is the delineation of the mechanisms which determine spatio-temporal patterning of electrical activity in the nervous system. In this regard, morphological and physiological studies have provided correlative data, some of which have been incorporated into structure–function relations for nervous tissue. One of the more simple structure–function relations has been the apparently linear relation between conduction velocity and fiber size for peripheral axons (1, 2). Such a relationship, if applicable to the central nervous system, could be of considerable heuristic value, for it would permit, based on measurements of fiber diameter, the prediction of conduction velocities along central axons which are relatively inaccessible to the micro-electrode. Such an approach has, in fact, been employed by many investigators, who have made inferences concerning, e.g., the number of synapses along a given pathway on the basis of latency measurements and data concerning fiber diameters. It is the purpose of the present note to comment on the facts that (*i*) the conduction velocities of central axons may not be predicted on the basis of fiber diameter alone, and (*ii*) that such structure–function relations as do exist may not be invariant, but on the contrary may vary with the history of impulse conduction along the axon. These points may be of considerable theoretical interest, since they are relevant to the mechanisms underlying temporal summation and coding of information in the central nervous system. They may also be of methodological value, with respect to interpreting conduction latencies, and defining criteria for antidromic and synaptic identification of neurons.

Axons in the peripheral nervous system exhibit a remarkable structural regularity, which is reflected by a strong correlation between conduction velocity and axon diameter. One aspect of the structural regularity of peripheral axons is a linear relationship between internode distance and fiber diameter (1–4), with the internode distances for 1 μm fibers usually being approximately 200 μm. In addition, the morphology of the nodes of Ranvier in the peripheral nervous system is relatively constant (5). It is expected on theoretical grounds (6) and has been demonstrated experimentally (1, 2) that for fibers which exhibit such a "dimensional similarity," there is a linear relationship between fiber diameter and conduction velocity. In the central nervous system, on the other hand, internode distances are often considerably shorter than for fibers of similar size in peripheral nerve (7–10), and it is not possible to predict internode distance from fiber diameter (7, 11). It has been argued theoretically (12, 13) that internode distances in peripheral nerve are such as to maximize conduction velocity at any given diameter, and that significant decreases in internode distance should produce slower conduction speeds. Central nodes of Ranvier are also significantly larger than peripheral nodes (8, 14), and this, too, should slow conduction. Ito and Takahashi (15) have, in fact, demonstrated slowing of conduction in dorsal root ganglia where internode distances are relatively short and where loading occurs due to branching. Thus, while fiber diameter will determine the *maximum possible* conduction velocity for a given fiber, the conduction rate which is actually realized will depend on parameters which remain relatively constant in the periphery, but which have been shown to vary significantly in the central nervous system. In contrast to peripheral nerve, therefore, conduction velocity cannot be accurately predicted in the central nervous system from fiber diameters alone.

But, assuming that static membrane properties and detailed morphology were well defined for a given fiber or set of fibers, could conduction speed be accurately predicted? The evidence suggests that this would not be possible, since conduction properties may vary systematically with the history of impulse activity of the fiber (16–19). Bullock (16) showed small increases in conduction velocity following single impulses in frog sciatic nerves. Bliss and Rosenberg (18) showed increased conduction velocities in recordings from unmyelinated olfactory nerve, while Gardner-Medwin (17) demonstrated an increase in conduction velocity with a concomitant threshold decrease lasting up to 100 msec following a single conditioning volley in cerebellar parallel fibers. Activity-dependent shifts in threshold have also been demonstrated by Newman and Raymond (20) in individual axons of frog sciatic nerve. A previous experiment (19) demonstrated variations in excitability and conduction velocity in rabbit callosal axons following a single preceding impulse. In the present paper we extend these observations, and comment on the significance of these variations with respect to the criteria for antidromic and synaptic identification of neurons and mechanisms of coding in the central nervous system.

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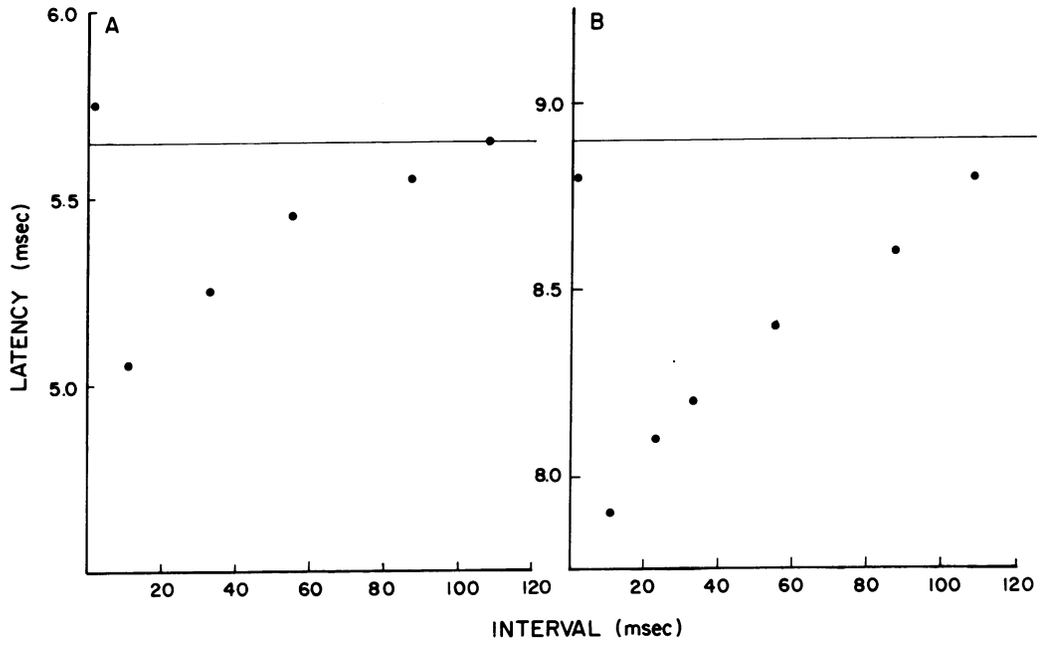

FIG. 1. Time course of latency variation to a test stimulus following a conditioning stimulus applied to either the corpus callosum near the midline (Fig. 1A), or the contralateral visual cortex (Fig. 1B). Stimuli were delivered at 3.3 sec intervals. Latency to antidromic activation is represented on ordinate; interval between conditioning and test stimulus is represented on abscissa.

MATERIALS AND METHODS

We have studied impulse conduction along callosal axons by measuring latency to antidromic activation of cell bodies following callosal and/or contralateral hemispheric stimulation. Recordings were obtained from single neurons in the left binocular visual cortex in the adult unanaesthetized, unparalyzed female Dutch rabbit. Under Nembutal anaesthesia, 12–20 stimulating electrodes were chronically implanted in and around the area of binocular representation of the right visual cortex. A bank of callosal stimulating electrodes slightly to the right of midline was subsequently implanted. Procedures for recording and restraining the animal have been described previously (21). Neurons which were antidromically activated following midline callosal stimulation were identified by collision techniques (21, 22) and by tests for post-collision recovery (21). These techniques are based on the fact that an antidromic impulse which is initiated at an appropriate interval following an orthodromic impulse which arises at or near the cell body will fail to invade the cell body due to a collision of the orthodromic and antidromic impulse. The period during which midline callosal stimulation will fail to result in antidromic invasion of the cell body equals the conduction time along the axon plus the refractory period of the axon at the site of stimulation. Additional confirmation of the antidromic activation of these neurons was provided by determination of refractory periods and, in many cases, by examination of spike waveform changes following the second of two closely spaced volleys. These criteria are fully discussed elsewhere (22–24). Once a unit was shown to be antidromically activated by stimulation of the midline corpus callosum, the latency to a test stimulus was determined at various intervals following a single suprathreshold conditioning stimulus which was delivered through the single callosal stimulating electrode. As in an earlier study of rabbit callosal axons (19), variations in both threshold and latency to a test volley followed a single conditioning volley. For this reason the stimulus threshold was determined at each conditioning stimulus-test stimulus interval, and the intensity of the test stimulus was always 1.2 × this threshold value. For some units, latency variations were also studied after trains of conditioning stimuli.

RESULTS

Fig. 1A shows the latency to antidromic activation to a test stimulus as a function of the interval after a single conditioning pulse applied to the midline corpus callosum for one callosal neuron. Latency to callosal stimulation decreased from a control value of 5.65 msec to a minimum of 5.05 msec at an interval of 11 msec following the conditioning pulse and remained smaller than control values until approximately 100 msec following the conditioning pulse. So as to demonstrate that the latency decrease was related to conduction path length, the cell was also activated antidromically by a stimulating electrode in the contralateral hemisphere. Contralateral cortical stimulation elicited a control antidromic response with a latency of 8.9 msec. The time course and proportional magnitude of the latency decrease (Fig 1B) were similar to those for callosal stimulation.

In order to demonstrate that latency decreases were not

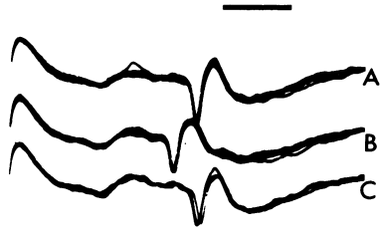

FIG. 2. Antidromic response of a callosal neuron following midline callosal stimulation. (A) Control; (B) response to stimulus 11 msec following spontaneous spike; (C) response to stimulus 169 msec following spontaneous spike. Stimulus was constant at 1.2 × control threshold. A and B show five superimposed traces. C shows three superimposed traces. Scale indicates 2 msec. Negativity upwards.

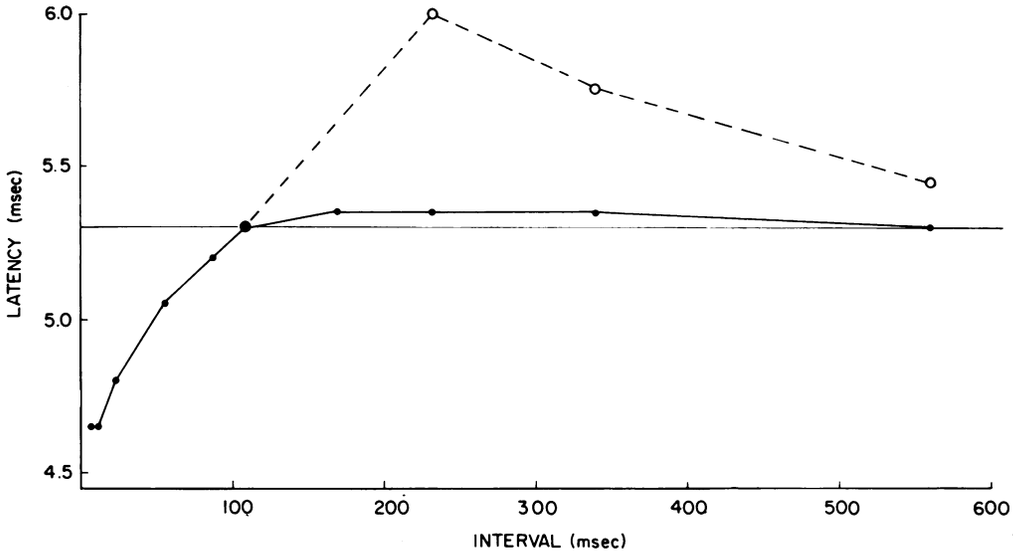

FIG. 3. Time course of latency variation to an antidromic test stimulus, at various intervals following a conditioning stimulus, consisting of a single pulse (1/3.3 sec, closed circles), or a train (20 pulses at a rate of 330/sec; 1 train/10.7 sec; open circles).

an artifact of electrical stimulation, antidromic conduction latencies were measured at various intervals following a spontaneous spike. Fig. 2 shows the antidromic response of one callosal neuron to midline callosal stimulation. Fig. 2A depicts a control response of 5.9 msec in the near absence of spontaneous activity. In Fig. 2B the callosal stimulus was triggered 11 msec following a spontaneous spike; latency under these conditions decreased to 5.25 msec.

Following the period of decreased latency some units showed a period of slightly increased latency and of increased threshold lasting several hundred msec or more. This is illustrated in Fig. 2C in which the antidromic latency at an interval of 169 msec after a spontaneous spike is increased to 5.95–6.05 msec. More pronounced latency increases were seen after antidromic trains. Fig. 3 illustrates the antidromic latency variation to midline callosal stimulation which was exhibited by a single callosal neuron with a baseline latency of 5.3 msec. The test stimulus was delivered at various intervals following a conditioning stimulus which consisted of either a single pulse (closed circles) or a train of 20 pulses delivered at 330 pulses per sec (open circles). Latency decreases following a conditioning stimulus consisting of a single pulse were similar to those shown in Fig. 1 and a slight latency increase resulted at intervals of 170–340 msec. Following a train of conditioning pulses, however, latency increased to over 113% of the control value at an interval of 232 msec, and to over 108% of control value at 340 msec.

As would be expected considering the data presented above, latency variations were often observed during periods of heightened spontaneous or orthodromically elicited activity. Fig. 4 shows the antidromic response of 1 unit to midline callosal stimulation during a period of quiescence (top trace) compared to that during a period of spontaneous activity (bottom trace). Although many of the axons studied in this and in the previous paper (19) were slowly conducting (<2 m/sec), variations in conduction velocity were also present for the faster conducting (2–6 m/sec) fibers. The detailed time course of the latency decreases and increases following single and multiple conditioning volleys in fast and slowly conducting axons will be described in a future publication.

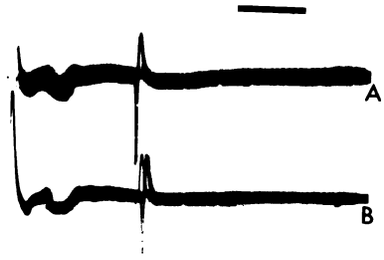

FIG. 4. Antidromic response of a callosal neuron to midline callosal stimulation recorded during a period of quiescence (Fig. 4A) and during a period of spontaneous activity (Fig. 4B). Scale indicates 10 msec.

DISCUSSION

A point of some practical interest concerns the criteria for identification of antidromic and synaptically activated units. While constant latency is usually considered a prerequisite for classification of an antidromically activated unit, the present data indicate that constant latency does not, in fact, constitute a necessary condition for identification of antidromically activated neurons. Conversely, a variable latency does not constitute a sufficient condition for classifying a unit as synaptically activated. We have observed latency variation (total range of latency decreases and increases) as large as several msec in the antidromic activation of callosal neurons. Had collision and other tests not been employed, these units might have been falsely classified as synaptically activated. In fact, the probability of inappropriately classifying a unit as synaptically activated would vary as a function of the spontaneous firing rate of the unit. We would stress that the generality of these comments remains to be demonstrated, since our observations have been limited to visual callosal axons in the rabbit. Nevertheless, careful use of impulse collision tests (21, 22), examination of refractory periods and waveform changes following the second of two closely spaced volleys (see, e.g., 22–24), together with systematic exploration of latency variability provide criteria for differentiating antidromic from synaptic activation.

The finding of significant variations in axonal conduction velocity and in threshold in the unanaesthetized, unparalyzed rabbit, in addition to the previous studies (16–19) on

variations in conduction properties, suggests that systematic variations in conduction velocity may represent a general feature of axonal physiology. The data outlined above may have important implications with respect to temporal summation and coding if one assumes a similarity in orthodromic and antidromic conduction properties. Chung *et al.* (25) have presented strong evidence that neural information may be coded by the *pattern* as well as the rate of impulses carried by an axon. The results of the present work indicate that the interval between two action potentials which are generated by a single callosal neuron will depend on where the impulse activity is measured. Under conditions of orthodromic impulse transmission, interspike intervals measured near the cell body will be relatively faithful to the intervals as seen at their site of origin, while interspike intervals measured near the axon terminal may be longer or shorter than those at the cell body. Changes in the conduction velocity of the second of two closely spaced impulses (i.e., those separated at initiation by less than approximately 3 through 50–100 msec) would be expected to decrease interspike intervals, while the changes for more widely spaced impulses would be expected to increase interspike intervals. The change in velocity of a second impulse in the wake of a first will necessarily depend on the fiber's membrane properties and history. We have observed variations in antidromic latency of as much as 3 msec as a function of prior activity. While some postsynaptic neurons may not discriminate a small change in the timing in the incoming signals, other neurons are exquisitely tuned to small differences in the presynaptic interspike interval. Yasargil and Diamond (26), for example, have shown that some postsynaptic neurons in the teleost Mauthner-spinal motor system are sensitive to differences as small as 150 μsec in the timing of incoming impulses. Changes of a magnitude which we have observed, occurring systematically as a result of prior activity of a given axon, may thus have functional significance with respect to the coding and decoding of neural messages.

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