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THE ELECTROMOTOR SYSTEM OF THE STARGAZER: A MODEL FOR INTEGRATIVE ACTIONS AT ELECTROTONIC SYNAPSES[1]

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Abstract

The electric organs of *Astroscopus* are modified from extraocular muscles and innervated by the enlarged oculomotor nuclei. The electromotor neuron somata are contacted by fine processes with which they form gap junctions. Presynaptic vesicles and active zones are also present, although physiological data give no indication of chemically mediated transmission. Antidromic stimulation produces long lasting graded depolarizations in the electromotor neurons. The latency is sufficiently short to indicate that the cells are electrotonically coupled, which was confirmed by direct measurement. Antidromic invasion may normally fail and is easily blocked by hyperpolarization revealing initial segment and axon spikes. Spinal stimulation evokes postsynaptic potentials (PSPs) and orthodromic impulses; the PSPs are not smoothly graded in amplitude. A medullary nucleus innervates the electromotor nucleus; the medullary cells also show short latency graded antidromic depolarizations and presumably are electrotonically coupled. Their coupling accounts for the variability in PSPs evoked by spinal stimulation. Apparent time constants differ greatly for direct stimulation of a single cell, decay of afterhyperpolarization, electrotonic spread from one cell to a neighbor, and decay of PSPs and graded antidromic depolarizations. The differences can be accounted for in terms of a highly interconnected network of electrotonically coupled cells, which was simulated computationally. Because of the long membrane time constant graded antidromic depolarizations summate. Because antidromic invasion is facilitated by depolarization, the antidromic depolarizations can show pronounced facilitation. The observed "plasticity" within this electrotonically coupled system provides a model for integrative actions at other sites of coupling.

Electrotonic synapses couple neurons in many nuclei in which activity is highly synchronized (cf. Bennett, 1977). Examples are pacemaker and relay nuclei controlling electric organ discharges and contractions of sonic muscles. This distribution follows from the speed and reciprocity of electrotonic as contrasted with chemical transmission. Electrotonic synapses themselves are not known to change their properties as a result of neural activity (with the exception of a few rectifying synapses where the junctional conductance is presumably a simple function of transjunctional potential) (Furshpan and Potter, 1959; Auerbach and Bennett, 1969; see also Spray et al., 1981a). However, cellular mechanisms modifying junctional conductance are becoming known (Bennett et al., 1981; Spray et al., 1981b, 1982), and gap junctions or coupling can be found transiently in developing nervous systems (LoPresti et al., 1974; Goodman and Spitzer, 1979; cf. Bennett et al., 1981).

Transmission at electrotonic synapses can be modified by interaction with chemical synapses (Spira and Bennett, 1972; Carew and Kandel, 1976; Spira et al., 1980), and facilitation and depression can occur as a result of changes in the presynaptic impulse or in postsynaptic excitability (Bennett, 1966, 1972; Tauc, 1969; Spira et al., 1980). Recently evidence has been obtained for electrotonic synapses in the hippocampus, where they may play a role in the susceptibility of this structure to epileptic activity (Schmalbruch and Jahnsen, 1981; Andrew et al., 1982). Epileptogenic agents might increase transmission at these synapses by broadening the presynaptic impulse (Rayport and Kandel, 1981), although such prolongation would have a pronounced effect at chemical synapses as well.

The present study explores a further electric organ control system, that of the stargazer, *Astroscopus*. As expected, electrotonic coupling occurs between neurons whose responses are generally synchronized. Graded antidromic stimulation produces long lasting graded depo-

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larizations that are electrotonic postsynaptic potentials (PSPs) spread from active to inactive cells. These PSPs show temporal summation and also pronounced facilitation. This augmentation in amplitude, which can closely resemble that at chemical synapses, is ascribable to increase in the presynaptic potential rather than to a change in junctional conductance. Because antidromic invasion of cell bodies fails in many neurons and axon and initial segment spikes leave a slowly decaying depolarization, antidromic invasion by subsequent impulses is facilitated, thus increasing the presynaptic potential. These effects for which simple electrical preconditions can be defined provide a model for facilitation of PSPs in other possibly electrotonically coupled networks where activity need not be highly synchronized (in mammals: Baker and Llinás, 1971; Llinás et al., 1971; Pinching and Powell, 1971; Sotelo and Llinás, 1972; Korn et al, 1973; Sotelo et al., 1974; Sloper and Powell, 1978; Gutnick and Prince, 1981).

Preliminary communications of some of these data were published, including Figures 11 and 14 (Bennett, 1968, 1971, 1972).

Materials and Methods

Fish 15 to 20 cm in length were obtained from the Gulf Coast of Texas and maintained in New York or Woods Hole in sea water tanks. For experimentation fish were curarized with 10 mg/kg of *d*-tubocurarine, placed in a fish holder, and perfused through the mouth with sea water. The brain and electric organs were exposed from the dorsal approach (Fig. 1). Usually the oculomotor nerves on both sides were dissected free, and each was held on a pair of hook electrodes for stimulation or recording. A monopolar electrode recorded antidromic and orthodromic volleys close to point of exit of one of the oculomotor nerves from the brain. The rostral spinal cord could be exposed for stimulation with wire electrodes.

The oculomotor nuclei were exposed by removal of the overlying tectum. Two microelectrodes in independent bridge circuits were used for intracellular recording and stimulation. A pair of wire stimulating electrodes was sometimes applied to the surface of either nucleus.

For electron microscopy Millonig's fixative containing 1% osmic acid was topically applied to the oculomotor nuclei. Tissue was removed and further fixed for 1 or 2 hr. The tissue was then dehydrated and embedded in Epon 812 according to the method of Luft (1961).

Results

Anatomy of the electric organ system. The electric organs are located immediately behind the eyes (Fig. 1, *A* and *B*) and extend from the dorsal surface to the roof of the oral cavity. The flattened electrocytes lie in the horizontal plane stacked one above the other. As the organs are modified from extrinsic ocular musculature they are innervated by the oculomotor nerves (Dahlgren, 1914). Figure 1*C* shows the brain and posterior part of the electric organs. On the right (down) the stout oculomotor nerve is exposed where it enters the organ. Part of the optic tectum has been removed to expose the right electromotor (or oculomotor) nucleus. In this methylene blue-stained preparation, individual electromotor neurons can be seen at its surface (Fig. 1*D*). Figure 2*A* shows a light micrograph of the nucleus. The round somata of the electromotor neurons do not contact each other directly but are separated by neuropil containing many small myelinated fibers, as well as larger fibers that include the efferent axons.

In electron microscope sections, gap junctions are frequently found between somata and small profiles. In Figure 2*B* two separate regions of gap junction appear in the section, and the small profile contains a large number of microtubules cut in cross-section. The small profiles often had apparent sites of chemical transmission as well as gap junctions. In the somewhat ornate arrangement in Figure 2*C*, the central profile formed a large area of gap junction with the soma on the left. The central profile appeared to transmit chemically to another small profile at the *upper right* (*XX*), where it formed a large "active zone." The central profile appeared to receive chemical transmission from the same profile on the *upper right* (*X*) and from another small profile on the *lower right*.

The identity of the nonsomatic elements at these synapses was not resolved. Profiles could contain mitochondria and microtubules as well as vesicles, but no separation into dendritic and axonal classes was possible. The presence of vesicles is suggestive of axonal origin, and presumably presynaptic axons would be included. The physiological data are consistent with electrical transmission from these axons (see below). Other electrotonically coupled nuclei are known in which coupling is exclusively dendrodendritic, exclusively by way of presynaptic fibers or by a combination of the two (cf. Bennett, 1977).

Electric organ discharge. After paralyzing doses of *d*-tubocurarine, electric organ discharges could still be recorded, although they were reduced in amplitude (Fig. 3; cf. Bennett and Grundfest, 1961). Consistent with dorsal innervation of the electrocytes, the polarity was dorsal negative. The discharges were quite variable in amplitude and frequency, but amplitude variation and timing were very similar on the two sides. Single pulses or long trains could be emitted, and frequency and amplitude could become quite regular in long lasting discharges in which a small second component could become apparent (Fig. 3, *E* and *G*).

Because curarization reduces the conductance change during the PSPs, the amplitude variations are probably exaggerated. In the normal animal discharging into an essentially open circuit, the responses would more closely approach the PSP reversal potential in each electrocyte, and a similar proportional change in conductance would produce less amplitude variation than in the curarized animal.

Antidromic and direct activation of the electromotor neurons. Stimulation of the oculomotor nerve produced potentials in the electromotor neurons of several kinds as illustrated in Figures 4 to 6. In most cases stimulation subthreshold for the axon of the penetrated cell produced graded depolarizations. These potentials were of short latency and followed the antidromic spike by less than 0.4 msec (Fig. 4*A*). This latency is very short for chemical transmission at room temperature (cf. Bennett et al., 1967b) and consistent with electrical transmission in view

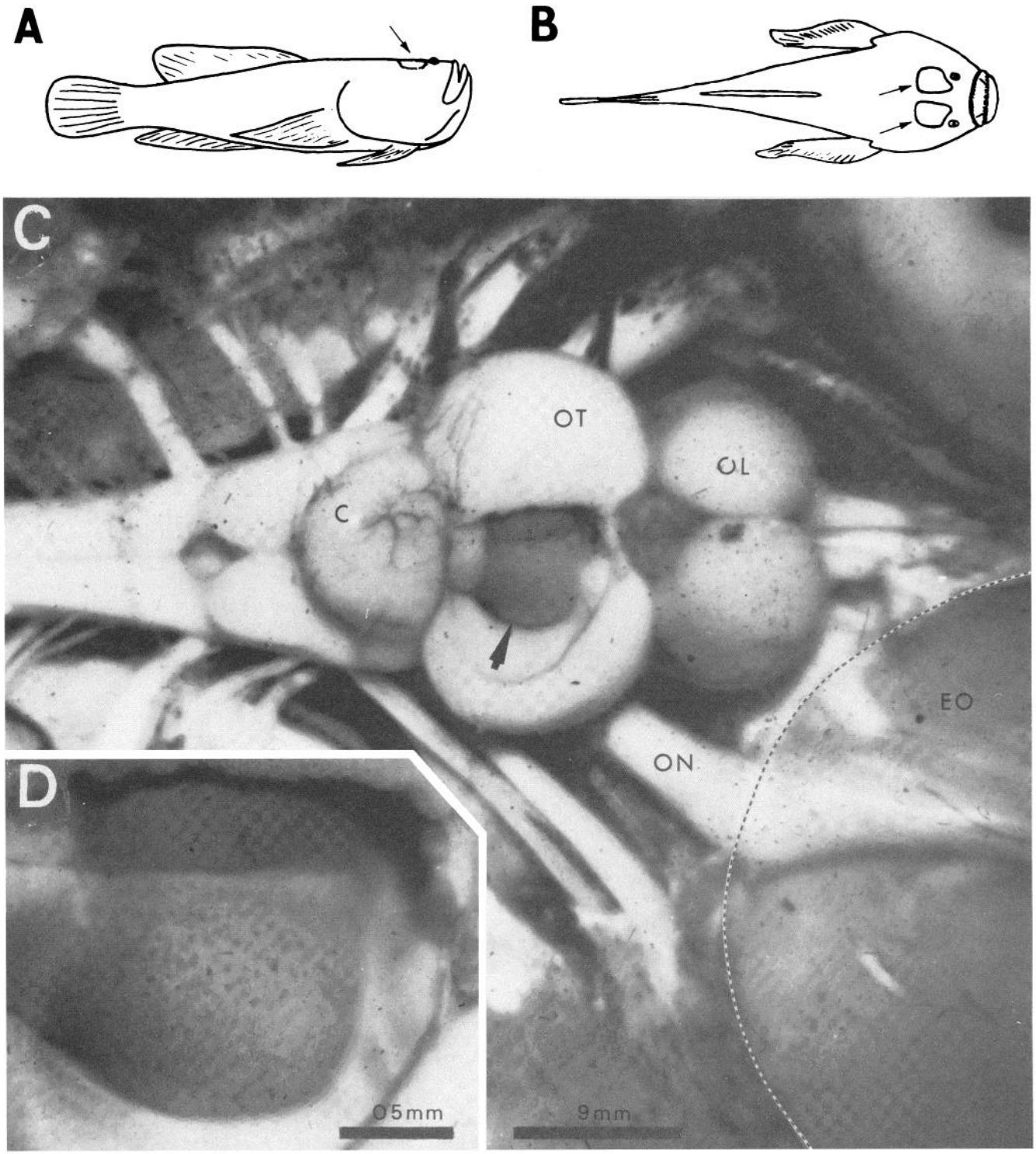

Figure 1. Location of the electric organ and electromotor nucleus. *A* and *B*, Diagrams of the fish from the side and top. The electric organs are indicated by *arrows*. *C*, The brain and electric organs were exposed by removal of overlying skin and cranium. The organs (*EO, dotted line*) are innervated by the large oculomotor nerves (*ON*). The hypertrophied electromotor nucleus (*arrow*) is readily seen after removal of the optic tectum (*OT*). *C*, cerebellum; *OL*, olfactory lobe. *D*, At higher magnification the electromotor neurons can be seen in the intact nucleus after methylene blue staining.

of the low pass characteristic of electrotonic junctions (Bennett, 1977) and the possibility of conduction delays in the coupling pathway. As shown below, the cells are electrically coupled. Because only a single major component was observed, it is to be ascribed to electrotonic spread from neighboring neurons. The graded depolarizations decayed with a time constant of about 50 msec (Fig. 4*C*). When stimulation reached threshold for the axon of the penetrated cell, an antidromic impulse was evoked which appeared superimposed on the potential spread from other activated cells.

Strong antidromic valleys were often followed by a late

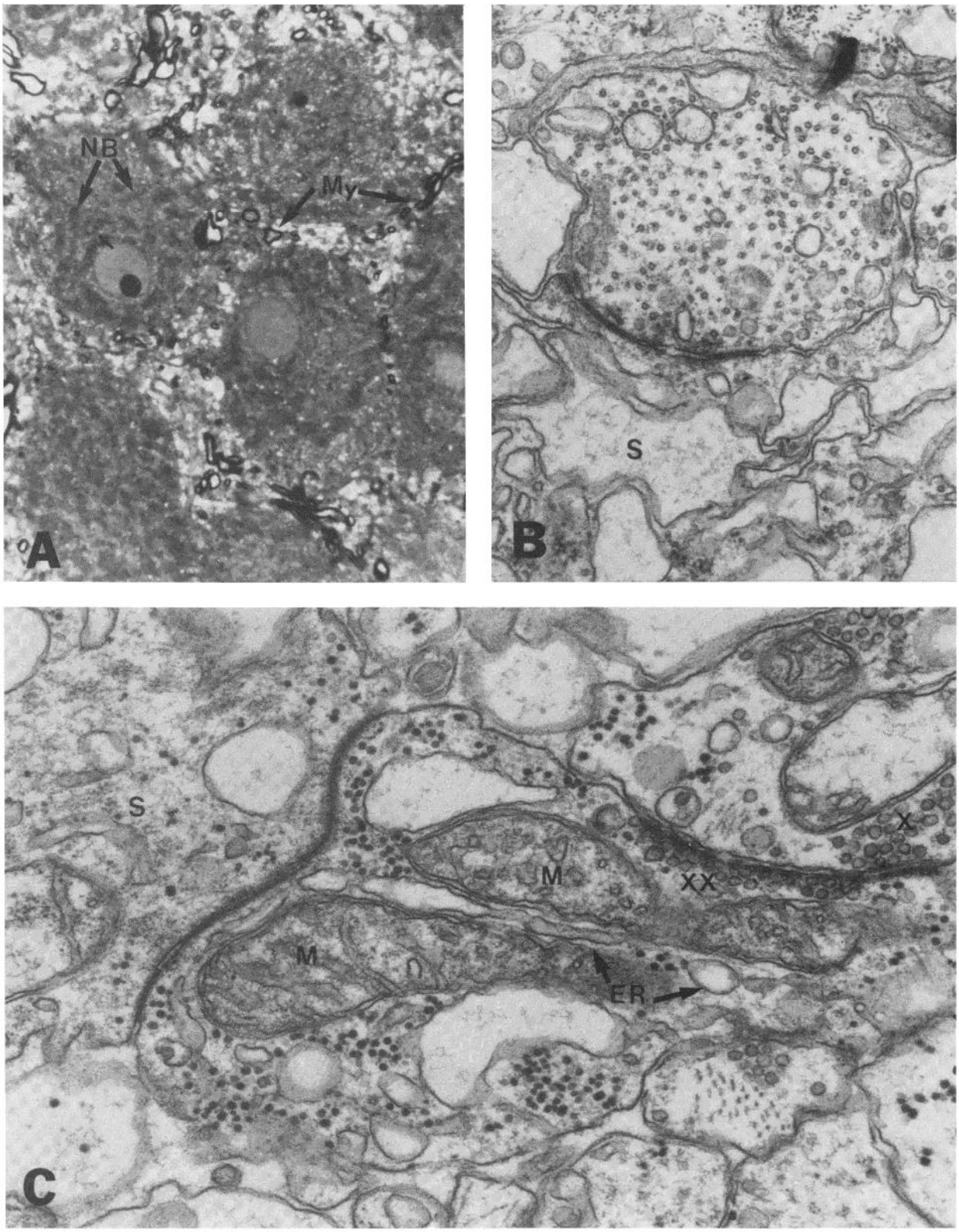

Figure 2. Structure of the electromotor nucleus. *A*, A light micrograph from a toluidine blue-stained Epon-embedded section. The oval cell bodies are separated by neuropil containing small myelinated axons (*My*). Magnification × 625. Nissl bodies (*NB*) are present in the cell cytoplasm. *B*, Electron micrograph of a profile forming gap junctions with a neuronal soma (*S*). The profile contains many microtubules seen in cross-section. Magnification × 25,000. *C*, Electron micrograph of a profile forming a large area of gap junction with a neuronal soma (*S*). This profile, containing large mitochondria (*M*), elements of smooth endoplasmic reticulum (*ER*), and many dense granules (presumably glycogen), also shows morphological characteristics of chemical transmission. It forms (morphologically defined) chemical synapses with the profile at the *upper right*, where it is both presynaptic (*XX*) and postsynaptic (*X*). It also appears to be postsynaptic to a profile on the *lower right*. Magnification × 40,000.

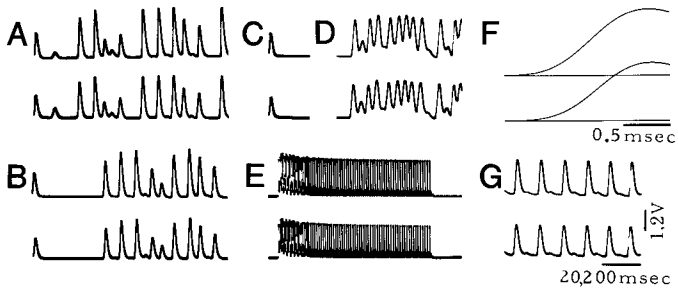

Figure 3. Electric organ discharge. Recordings were made between the interior of the mouth and the dorsal surface of the electric organs on either side. The fish had been curarized, which paralyzed it but only moderately reduced the electric organ discharge. Irregularity of amplitude and frequency is seen in *A*, *B*, and *D*. Single pulses could be emitted (*C*). Expanded sweep and higher gain in *F* show synchrony between the two sides. Electrical spread between sides in this situation is no more than 20% (Bennett and Grundfest, 1961). Slower sweep in *E* of a prolonged burst. Faster sweep in *G* of the late part of a discharge like that in *E* shows small components between the longer discharges. Sweep speed is the same in *A* to *D* and *G*.

component in the monopolar recording (Figs. 4 to 6). The origin of this response was not investigated, but its latency is consistent with its arising from impulses "reflected" from the soma of stimulated axons (cf., Goldstein and Rall, 1974).

The usual components of the antidromic spike were readily demonstrated by hyperpolarizing the cell soma. For the superimposed traces in Figure 5, *A* to *C*, the antidromic stimulus was held constant, and the threshold of the neuron varied spontaneously around this value to give sweeps with and without an antidromic response, which differed depending on the hyperpolarization applied. With no hyperpolarization a full antidromic spike was recorded, and there was an inflection high up on the rising phase, ascribable to invasion of the soma (Fig. 5*A*). Moderate hyperpolarization blocked the soma component revealing the initial segment spike which also had an inflection, presumably representing invasion of the initial segment region from the last node of the axon (Fig. 5*B*). Further hyperpolarization blocked the initial segment spike leaving the nodal spike (Fig. 5*C*). The

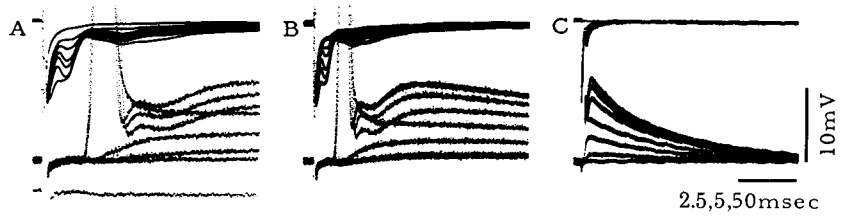

Figure 4. Graded responses to antidromic stimulation of the oculomotor nerve. Several superimposed sweeps at different stimulus strengths in each record. *Upper trace*, antidromic volley recorded at the exit point of the oculomotor nerve. *Second trace*, recording from an electromotor neuron. *Third trace in A*, external field outside the cell with near threshold antidromic stimulation. *A*, In two sweeps slow responses were evoked by stimulation subthreshold for the penetrated cell's axon. The latency of the larger response was 0.4 msec greater than the latency of the cell's antidromic spike. A stronger stimulus excited the cell's axon and evoked a larger, long lasting depolarization (see *B*). Near the axon's threshold only an initial segment spike was evoked (same cell in Fig. 5*A'*). Stronger stimulation evoked larger, long lasting depolarizations and caused invasion of the cell's soma. The soma spike was followed by a relative hyperpolarization that delayed the maximum of the long lasting depolarization. *B* and *C*, Recording at slower sweep speeds.

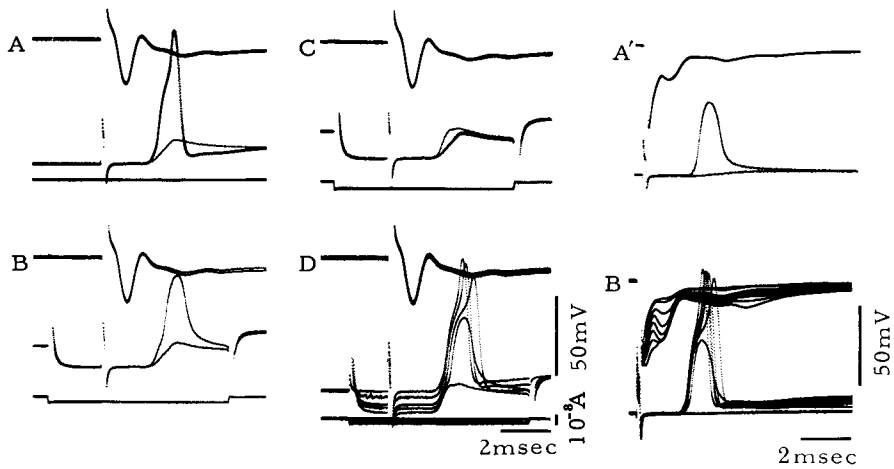

Figure 5. Components of antidromic spikes. *Upper trace*, antidromic volley. *Middle trace*, recording from an electromotor neuron. *Lower trace in D*, intracellularly applied current. Different cells in *A* to *D* and in *A'* and *B'*. In *A* to *C* the stimulus was kept constant at threshold so that the cell's axon was excited in only a fraction of the superimposed sweeps, and the antidromic response appears superimposed on a slow depolarization. *A*, The full-sized impulse. *B*, Hyperpolarization blocked invasion of the soma and exaggerated the inflection between the axon and initial segment spikes. *C*, Further hyperpolarization blocked the initial segment spike, revealing the axon spike. *D*, A constant well suprathreshold antidromic stimulus was given in each superimposed sweep. With increasing hyperpolarization the soma spike was delayed and blocked, and then the initial segment spike was blocked. *A'*, In this cell, whose axon was of lower threshold, a threshold antidromic stimulus evoked an initial segment spike that failed to invade the soma. *B'*, Stronger antidromic stimulation caused the impulse to invade the soma.

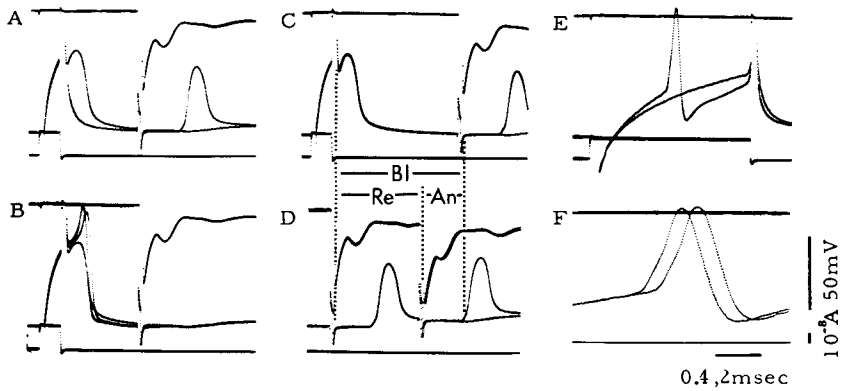

Figure 6. Interactions between directly evoked and antidromic impulses. Several superimposed sweeps in each record. Recordings and display as previously described. *A*, A brief direct stimulus at threshold was followed by a suprathreshold antidromic stimulus. The threshold response was an initial segment spike that occluded the antidromic impulse. *B*, A slightly stronger direct stimulus promoted invasion of the soma from the initial segment but had no further effect on the antidromic response. *C*, A directly evoked initial segment spike was followed by an antidromic stimulus at the critical interval for block (*Bl*), i.e., the antidromic response was not blocked in every sweep. *D*, Paired antidromic stimulation at the same strength as in *C* to show the refractory period (*Re*). The blocking interval (*Bl*) equals the refractory period (*Re*) plus the antidromic conduction time (*An*) *E*, A long lasting stimulus generates a full-sized spike at threshold. *F*, In an expanded sweep these directly evoked spikes are seen to have an inflection on their rising phases indicating propagation from initial segment to soma.

potential spread from other cells was unaffected by the hyperpolarization. The sequence of block with increasing hyperpolarization is also seen in Figure 5*D*.

In some neurons antidromic stimulation just above threshold for the axon of the penetrated cell caused an initial segment spike that failed to invade the soma (Fig. 5*A'*). In this case stronger stimulation could cause generation of a full sized spike (Fig. 5*B'*); evidently depolarization spread from other neurons facilitated invasion and, with progressively stronger stimulation, invasion occurred more rapidly.

A brief intracellular stimulus could initiate a small spike that was generated in the initial segment as indicated by its amplitude and by its block of the antidromic impulse (Fig. 6*A*). The maximum interval between stimuli at which a directly evoked impulse should block an antidromic response (*Bl* in Fig. 6*C*) is the sum of the time for the directly evoked (orthodromic) response to reach the peripheral site of stimulation plus the refractory period at that point. That this relation held is seen by comparison to Figure 6*D*, which shows the refractory period (*Re*) for paired antidromic stimulation and the antidromic conduction time (*An*), which for a uniform axon is an accurate measure of orthodromic conduction time. Block of antidromic responses in Figure 6, *A* and *C* was by refractoriness at the stimulation site; collision of propagating impulses would occur only for intervals between direct and antidromic stimuli less than the orthodromic conduction time.

Because direct stimulation could evoke an initial segment spike without a soma spike, the initial segment region must have been of lower threshold with this mode of activation. Stimulation with a long lasting pulse did evoke a full size spike at threshold, and this spike had an inflection on its rising phase indicating later activation of the soma facilitated by the maintained depolarizing current (Fig. 6, *E* and *F*). Stronger brief stimuli also caused invasion of the soma with, as expected, no difference in the effect on the antidromic response (Fig. 6*B*). Impulse initiation in initial segments is a common neuronal property, but failure to invade the soma on orthodromic activation is unusual and may have been contributed to by electrical coupling between the neurons (see below).

Orthodromic activation of the electromotor nucleus. Stimulation of the upper spinal cord could evoke activity of the electromotor nucleus and electric organ. Graded stimulation evoked responses that varied in amplitude but were not smoothly graded (Fig. 7, *A* and *E*). In the electromotor neurons large, long lasting PSPs were observed with a time course similar to that of the graded antidromic depolarizations. Strong stimuli evoked large efferent volleys which could be recorded at the point of exit of the oculomotor nerve. These responses were followed by negative going deflections generated by the electrocytes whose activity was not completely blocked by the level of curarization employed. Extracellularly in the nucleus a large efferent response was preceded by a large negative positive deflection. The PSPs in the electromotor neurons frequently had a small second peak about 2.5 msec after the onset of the PSP, and firing could occur from this point (Fig. 7, *E* and *F*). As described below, the double peak of the PSP can be accounted for by the tendency of the higher level neurons to fire in doublets. A small second phase is often seen in the electric organ discharges (Fig. 3*G*).

Strong spinal stimulation produced highly synchronous activity of most if not all of the electromotor neurons. Figure 8*A* shows a maximal response to spinal stimulation (*Or*) recorded bipolarly from right and left oculomotor nerves and monopolarly from the right nerve at its exit point. Antidromic stimulation (*An*) of the right nerve produced a monopolarly recorded volley (Fig. 8*B*) whose amplitude and dispersion were very similar to those of the orthodromic response. The antidromic volley was completely occluded by the orthodromic response, indicating the involvement of all of the efferent fibers (Fig. 8*C*). The antidromic volley occluded all but a small part of the monopolarly recorded efferent activity (Fig. 8*B*). The residual component may have resulted from spread from the left nerve or because some fibers had

branched off from the right nerve proximal to the antidromic stimulation site.

The 2-msec delay between high spinal stimulation and PSPs in the electromotor neurons is consistent with an intercalated nucleus. Neurons could be recorded from

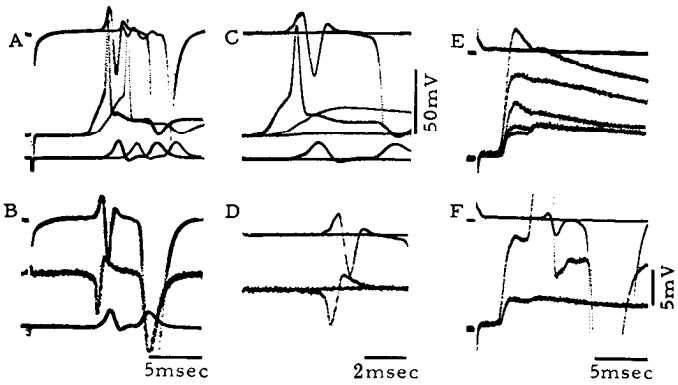

Figure 7. Responses of the electromotor neurons to high spinal stimulation. *Upper trace*, monopolar recording from one oculomotor nerve at its exit point. *Second trace*, microelectrode recording within the nucleus. *Third trace* (*A* to *C* only), bipolar recording from the other nerve. *A* to *D*, Stimulation 2 cm from the oculomotor nucleus. *A*, A constant stimulus evoked PSPs in the electromotor neurons with different rates of rise that led to different times of spike initiation. Correspondingly the bipolarly recorded efferent volley was of variable latency and dispersion. The longer latency, monopolarly recorded volley was greatly reduced because of out-of-phase addition of triphasic components. The organ discharge produced the second component in the bipolar recording and the late large negative component in the monopolar recording that went off screen. *B*, The extracellularly recorded field potential associated with synchronous activation of the electromotor neurons was large. *C* and *D*, Faster sweeps of records like those in *A* and *B*. *E* and *F*, Another experiment, stimulation 7 mm caudally. *A*, Graded PSPs were evoked by spinal stimulation, many of which had a second component about 3 msec after the onset. *B*, Impulses and efferent volleys could arise at the time of the later component.

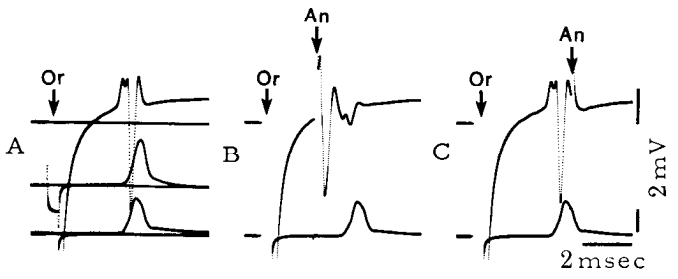

Figure 8. Involvement of all oculomotor axons in efferent volleys evoked by strong spinal stimulation. *Upper trace*, monopolar recording from the right oculomotor nerve near its exit point from the brain. *Middle trace* (*A* only), bipolar recording from the right oculomotor nerve after its entry into the electric organ. *Lower trace*, similar bipolar recording from the left oculomotor nerve. *A*, A strong spinal stimulus (*Or*) evoked a brief volley at all three recording sites (superimposed sweeps with and without a stimulus). *B*, A maximal antidromic stimulus (*An*) delivered to the right oculomotor nerve through the bipolar electrodes largely occluded the monopolarly recorded efferent response (spinal stimulus at *Or*). *C*, The efferent response completely occluded the antidromic volley, indicating that the efferent activity involved all the axons (stimulation at *Or* and *An*).

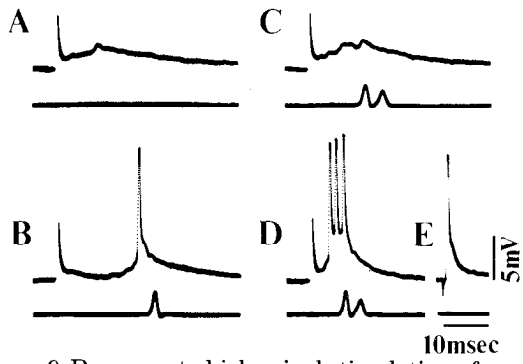

Figure 9. Response to high spinal stimulation of a medullary neuron projecting to the oculomotor nucleus. *Upper trace*, recording from the neuron. *Lower trace*, bipolar recording from one oculomotor nerve. *A* to *D*, High spinal stimulation evoked graded PSPs and spikes that correlated with efferent volleys. *E*, Antidromic spike in response to stimulation on the surface of the oculomotor nucleus.

near the midline of the medulla that had properties suggesting that they comprised this nucleus. They responded to stimulation on the surface of the oculomotor nucleus with abruptly rising spikes that were presumably antidromic (Fig. 9*E*). They also responded to spinal stimulation, but these responses were synaptically evoked and correlated, although imperfectly, with organ discharge (Fig. 9, *A* to *D*). In Figure 9*B* both the impulse in the medullary neuron and the efferent volley were of relatively long latency. In Figure 9*C* a double efferent volley occurred without impulses in the neuron; however, there were two prior depolarizations in the neuron that may have been activity electronically spread from other neurons of the nucleus. A stronger stimulus in Figure 9*D* evoked a short latency, three-spike response in the neuron and again a double efferent volley. The latency between impulse and efferent volley was not constant, which may have been contributed to by at least two factors: The activity of the medullary neurons may have been asynchronous, and the PSPs in the electromotor neurons could have had different rise times, resulting in different delays in transmission through the oculomotor nucleus (Fig. 7*A*).

Antidromic stimulation of the medullary neurons produced small depolarizations that were of short enough latency (as short as 0.3 msec) to indicate electrotonic coupling between these cells (Fig. 10, *B* and *C*). These depolarizations were capable of exciting the cells (Fig. 10, *D* and *E*). Some of the cells fired in doublets when giving an abruptly rising antidromic response (Fig. 10, *A* and *D*) or when activated synaptically (Fig. 10, *D* and *E*), presumably in this case by electrotonic spread from other excited neurons.

A few fibers afferent to the electromotor neurons were recorded from within the oculomotor nucleus. In response to surface stimulation on the contralateral nucleus, they gave abruptly rising spikes, indicating that they ended bilaterally in the nucleus (see also Fig. 16).

Electrotonic coupling. When the oculomotor nucleus was exposed by removing the overlying tectum, it was relatively easy to place electrodes in neighboring cells and to demonstrate electrotonic coupling directly. Antidromic spikes of two neighboring cells are shown in Figure 11*A*. Hyperpolarizing and depolarizing pulses were

passed in each cell and the resulting electrotonic potentials recorded in the other cell (Fig. 11, *C* to *F*). (Currents were too large to allow the potentials in the polarized cells to be measured with the bridge circuits employed.) The apparent time constants of the electrotonic potentials were 5 to 10 msec. Large depolarizing currents produced small components in the second cell, presumably resulting from spike activity in the stimulated cell (Fig. 11*B*).

Time constants and time courses. The different responses of the electromotor neurons exhibited markedly different time constants. The apparent input time constants demonstrated by applied pulses were less than 1 msec and probably too short to be reliably measured with a bridge circuit (Fig. 5, *B* and *D*). The relative hyperpolarizations following soma spikes decayed with time constants of a few milliseconds (Figs. 5*A* and 12*A*). When a single cell was stimulated, it produced only a brief depolarization in neighboring cells (Fig. 11*B*), and small brief components were often seen on the peaks of the graded antidromic depolarizations that probably represented impulse activity in adjacent neurons (Fig. 15*D*). The electrotonic potentials spread from polarization of neighboring cells had time constants of 5 to 10 msec (Fig. 11). The graded antidromic depolarizations (Fig. 4*C*) and PSPs from presynaptic fibers (Fig. 12) had much slower decays with time constants of about 50 msec. These disparate time courses can be explained in terms of electrotonic coupling of the cells as described below.

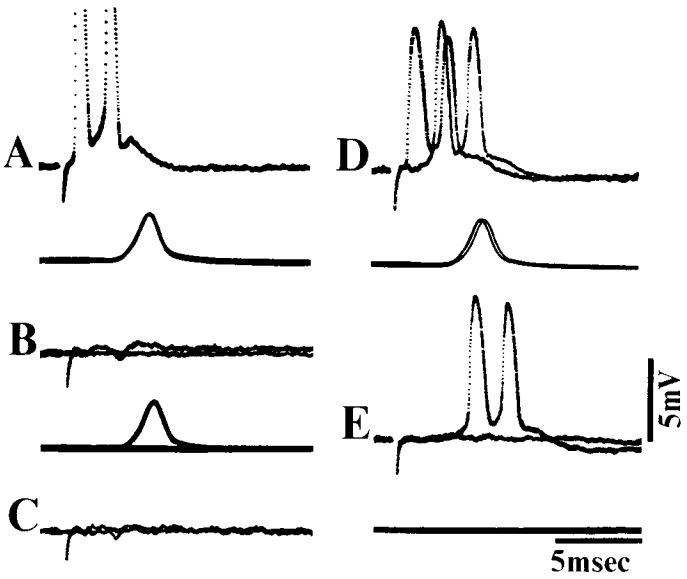

Figure 10. Antidromic stimulation of medullary neurons can produce doublet firing and excitation by graded depolarizations. Recording and stimulation were as in Figure 9 except for omission of nerve recording in *C*. *A*, A spike doublet was evoked by an antidromic stimulus. *B*, A stimulus just subthreshold for the cell's axon produced a positive-negative-positive sequence in the cell (two superimposed sweeps with and without stimulation). *C*, The potential subsequently recorded outside the cell at the same stimulus strength indicates that the positivities in *B* were depolarizations. *D*, Somewhat later, stimulation at threshold for the cell's axon. The short latency, antidromic response was a doublet as in *A*. The longer latency response seemed to be initiated by a slowly rising depolarization and also was a doublet. *E*, A similar doublet response occurred at longer latency with a stimulus too weak to initiate an efferent volley.

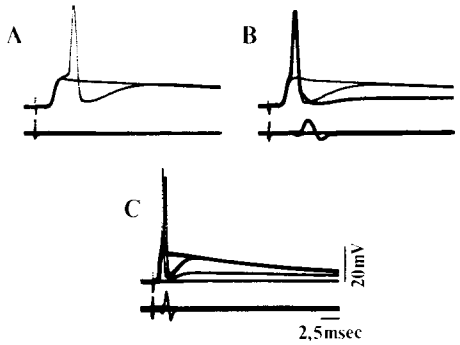

Figure 12. Evidence for passive decay of PSPs. Recording from an electromotor neuron (*upper trace*) and the ipsilateral efferent nerve (*lower trace*) while stimulating on the surface of the contralateral oculomotor nucleus. *A*, The stimulus produced a large PSP that was just threshold for the penetrated cell. The spike was followed by an undershoot that decayed in about 6 msec back to the level of the PSP without a spike. *B*, A stronger stimulus evoked an efferent volley as well. The afterpotential following this spike did not return to the level of the PSP but remained slightly above the base line (superimposed weak and strong stimulation). *C*, Slower sweep recording as in *B*. The afterpotentials following both weak and strong stimuli were long lasting depolarizations.

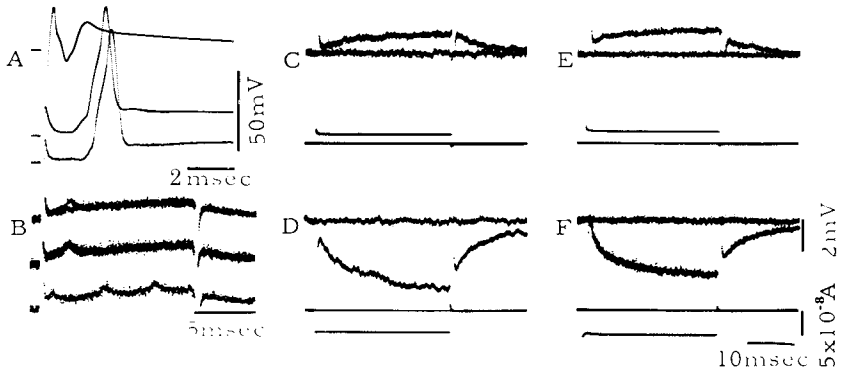

Figure 11. Electrotonic coupling of electromotor neurons. Two cells about 100 μm apart were penetrated by separate electrodes, each with its own bridge circuit. *A*, Antidromic volley in the oculomotor nerve (*upper trace*) and impulses in the two cells. *B*, Stimulating one of the cells produced in the other cell brief components superimposed on a slow electronic potential (three different stimulus strengths, threshold on the *upper trace*). *C* and *D*, De- and hyperpolarizing current in one cell produced electrotonic potentials in the other cell (current on *lower trace*). *E* and *F*, Current applied in the other cell had similar effects on the first cell. (From Bennett, 1971; used with permission from Academic Press, Inc., New York.)

It is likely that the slow decays represent the true membrane time constants of the cells, because the depolarizations causing them are widespread and presumably essentially uniform. Evidence that the decay of the orthodromic PSP is passive is shown in Figure 12 in which an electromotor neuron was recorded from, while an afferent volley was evoked by surface electrodes on the contralateral oculomotor nucleus. With a just threshold stimulus the cell's spike showed a transient undershoot, after which the PSP returned to its previous time course. This observation could suggest that the active phase of the PSP was long lasting. However when a stronger stimulus that evoked a large efferent volley was given, the PSP was greatly reduced in amplitude (Fig. 12, *B* and *C*). The difference can be accounted for in terms of the number of cells activated. If only a few cells were excited, then PSPs in them would be restored by electrotonic spread of PSPs from surrounding inactive cells. If all cells were active, all their membrane capacities would be charged to the level of the undershoot, and no PSP would spread from other cells. The PSP is not entirely abolished in Figure 12, and it is not certain what fraction of the electromotor neurons was activated. The residual depolarization could also be a long lasting afterpotential.

A diagram and equivalent circuit of the coupling between neurons are given in Figure 13*D*. If the charge on the capacity of a single cell is pulsed in a new valve, it will decay through the conductance of the junctions joining it to adjacent cells, as well as through the conductance of the cell's own membrane. Provided the potential in neighboring cells is low, the junctions act as a

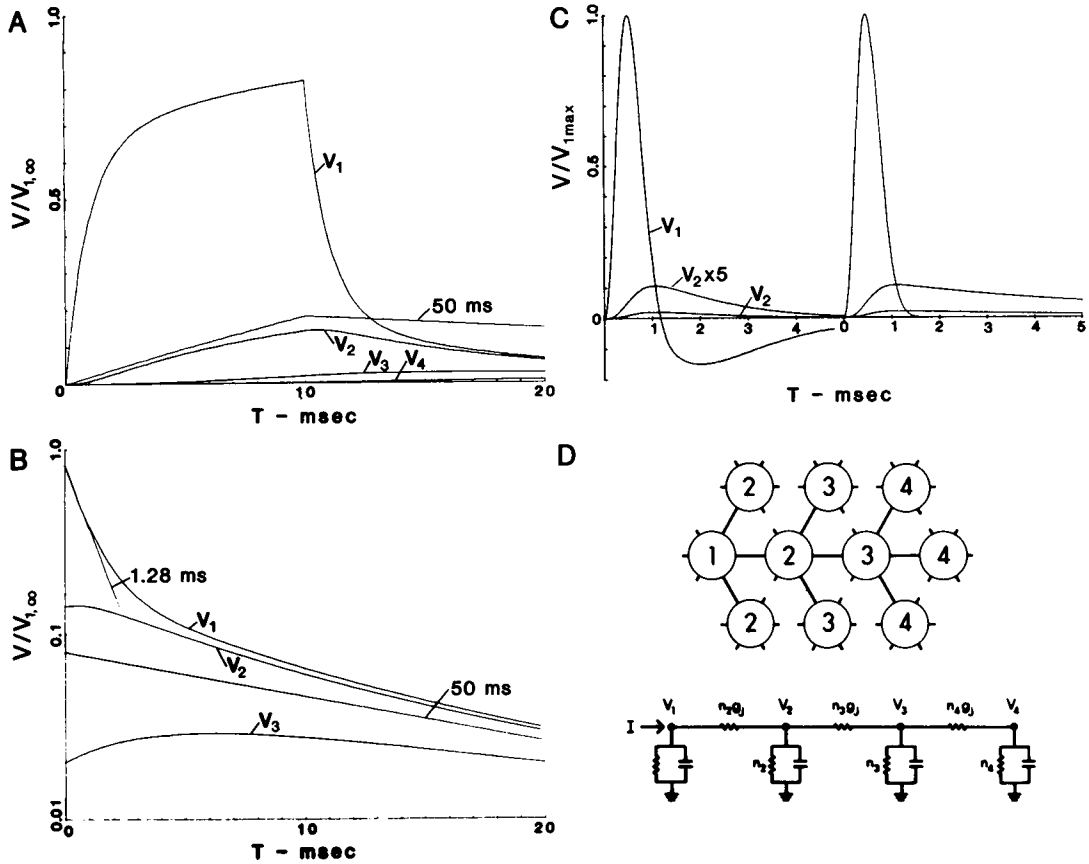

Figure 13. Simulation of electrotonic coupling and time constants. A central cell was assumed to be coupled to neighbors, which were coupled to their more distant neighbors, which were coupled to their still more distant neighbors to a total of four levels, as diagrammed in *D*. The equivalent circuit is also given in *D*. The conductance and time constant of a single cell were taken as 0.01 μS and 50 msec, respectively; junctional conductance was taken as 0.02 μS. It was assumed that there were 24 second order cells (n_2), 75 third order cells (n_3), and 150 fourth order cells (n_4). The input conductance of cell 1 was calculated to be 0.34 μS. Voltages in each order cell (V_{1-4}) were calculated iteratively from difference differential equations. *A*, The effect of a 10-msec current pulse in cell 1. The voltages are expressed in terms of the fraction of the steady state voltage in cell 1, $V_{1,\infty}$, for a long lasting pulse of the same amplitude. The voltages at each level rose during the pulse, the voltage fell abruptly in cell 1 at the end of the pulse, fell more slowly at level 2, and continued to rise at levels 3 and 4. The (steady state) coupling coefficients from cell 1 to levels 2 through 4 were 0.31, 0.14, and 0.12, respectively. At the end of the pulse, the ratio of potentials in levels 1 through 4 to the steady state potential in cell 1 were 0.82, 0.14, 0.02, and 0.002, respectively. The *line* labeled *50 ms* was the potential observed in each cell when each was equally depolarized by equal current pulses of 10-msec duration, again expressed as the fraction of the steady state voltage. *B*, Semilogarithmic plots of voltage decays after the pulse in *A*. There was an initial rapid decay in cell 1 with a time constant of 1.28 msec. The decay then slowed and nearly paralleled that at level 2, but was still somewhat faster than the membrane time constant (*line* labeled *50 ms*). *C*, Electrotonic spread of impulses in the same circuit. The potential in cell 1 was constrained to the indicated impulse-like form. The potential at level 2 is shown at 1 and 5 times its amplitude relative to the maximum of V_1. If the impulse was monophasic, the electrotonic potentials at level 2 decayed slowly (*right*). If the impulse had an undershoot, the electrotonic potential at level 2 was markedly shortened (*right*).

simple shunt. In order to produce the observed difference in effective input time constant (~1 msec) and membrane time constant estimated from uniform depolarization (~50 msec), the junctions must have conductance approximately 50-fold larger than the cells' own membrane conductance. If one cell were coupled to 24 neighboring cells, the junctional conductance would have to be twice as great as the cell membrane conductance. With hexagonal packing, one cell would be contacted by 12 neighbors, but this assumption requires a high enough junctional conductance that the coupling coefficient to the neighboring cells is too large. Inasmuch as cells may be coupled by way of presynaptic fibers ending on more than one cell as well as by dendrodendritic junctions, it seemed not unreasonable to double the number of second level cells over the case of hexagonal packing. Calculated responses to a current step are shown in Figure 13*A*. The time scale assumes a membrane time constant of 50 msec. The potential in the polarized cell (V_1) rises rapidly and then more slowly. At the end of the pulse, the potential drops rapidly and then more slowly. Rates of rise and fall in adjacent cells (V_2 to V_4) are much slower. The decays of V_1, V_2, and V_3 after the pulse in Figure 13*A* are plotted semilogarithmically in Figure 13*B*. The early decay of V_1 has a slope giving a time constant of about 1.3 msec. During this early decay, potentials in the first and second order cells reach almost the same value and then decay slowly together with an approximate time constant somewhat briefer than the 50-msec membrane time constant. The potential in the third order cells reaches a peak 7 msec after termination of the pulse and then slowly approaches decay with the membrane time constant. At long times the potentials in all cells would equalize and then decay with the membrane time constant.

The fast phase of decay in the polarized cell and the time course of the potential in the second order cells are in reasonable agreement with the data. The plateau phase in the calculations for the polarized cell may have too large a drift upward compared to the effects of current in Figure 5, *B* to *D*, but these records were taken at lower gain and were not intended to evaluate slow changes. The delay of changes in the second order cells at onset and termination of the pulse do not appear in the records of Figure 11, but probably they are obscured by the stimulus artifact. The value of the ratio of junctional to nonjunctional conductance may seem extraordinarily large. It is not unreasonable, however, because the long membrane time constant implies a very high membrance resistance, and the input conductances were a few tenths of a microsiemen (or input resistances of a few megohms), based on not very accurate bridge measurements. The very large ratio of junctional to nonjunctional conductance implies relatively great loading of the impulse-generating nonjunctional membrane. This loading probably contributes to the frequent occurrence of graded soma spikes and failure of antidromic invasion. Nevertheless, the input conductances are comparable to those of ordinary motoneurons and so do not require an unusual density of Na channels for impulse generation to occur. Although the junctional conductance between a pair of cells is twice one cell's nonjunctional conductance, the large number of third cells to which a single second order cell is coupled allows the coupling coefficient between first and second order cells to remain small. The steady state transfer resistances in Figure 11 are about 0.1 megohms, which from an input resistance of several megohms gives coupling coefficients of a few percent.

The connectivity of Figure 13*D* does not alone explain the brief time course of electrotonically spread impulses. In the model a monophasic impulse produced a PSP in a second level cell that was very slowly decaying (Fig. 13*C*, *right*) whereas the actual responses were quite brief. More satisfactory agreement could be obtained by employing an impulse with an afterhyperpolarization such as occurs when an impulse is superimposed on a large PSP (Fig. 13*C*, *left*). In essence, partial overlap of oppositely directed electrotonic potentials produces a decay that is more rapid than the membrane time constant.

Facilitation of graded antidromic potentials. The graded antidromic potentials were long lasting compared to the refractory period of the electromotor axons, and for this reason the antidromic potentials could summate (Fig. 14). Summation is impressively illustrated for tetanic stimulation in Figure 14*D*. The antidromic responses also showed dramatic facilitation, that is, increase in amplitude. The increase is ascribable to facilitation of antidromic invasion into the somata by depolarization remaining from the preceding response as illustrated for three cells in Figure 15, *A* and *B*. The soma spikes provide a larger "presynaptic" potential at the electrotonic synapses connecting the cells than do initial segment or nodal spikes, and thus the electrotonic "postsynaptic" potentials are greater. ("Pre-" and "postsynaptic" are in quotation marks because transmission is reciprocal and direction depends on which side is active.)

The facilitation of the graded antidromic potentials could involve marked changes in the time course. An early rapid phase could become pronounced, while the

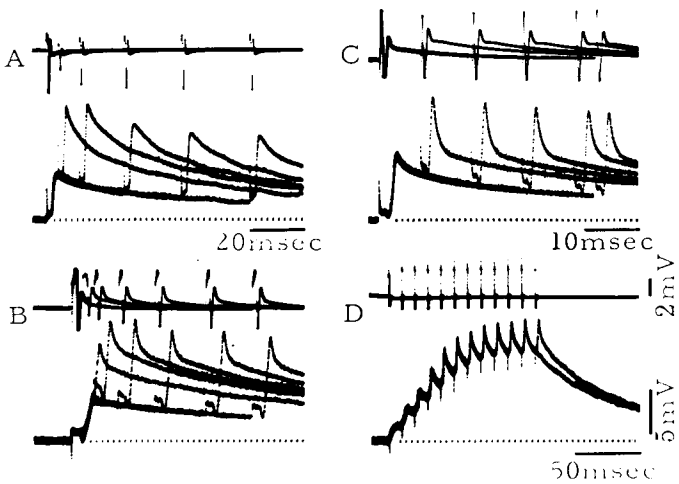

Figure 14. Summation and facilitation of graded antidromic depolarizations. *Upper trace*, monopolar recording from the oculomotor nerve antidromically stimulated. *Lower trace*, recording from four different electromotor neurons. *A* to *C*, Pairs of stimuli were given with different delays of the second stimulus (several superimposed sweeps in each record). Early and late phases showed summation and facilitation to different extents. *D*, A tetanus showed extensive summation and facilitation (two superimposed records with an additional stimulus in one). Faster sweeps in *B* and *C*. (From Bennett, 1968, p. 108. Reprinted by permission of Prentice-Hall, Inc. (© 1968), Englewood Cliffs, NJ.)

long lasting phase was less facilitated or even depressed (Fig. 14, *B* and *C*). Marked facilitation could also occur with little change in shape at longer interstimulus intervals (Fig. 14*A*). Facilitation could occur even at short intervals when the antidromic volley was markedly reduced in size. The reduction probably was due to both reduced amplitude of the axonal responses in their relative refractory period and reduction in the number of axons excited.

Facilitation also occurred "heterosynaptically" when stimulation of one oculomotor nerve increased the response to stimulation of the other nerve (Fig. 15, *C* and *D*). Actually much of the facilitation during repetitive stimulation of one nerve could be viewed as heterosynaptic, in that facilitated invasion of one cell and of the PSP it produced required that other cells also be depolarized. If they were not depolarized, current would flow into them from the first cell, reducing its level of depolarization and preventing antidromic invasion.

Orthodromic stimulation also facilitated the graded antidromic depolarizations. For Figure 16, the oculomotor nerves on both sides were stimulated independently and another pair of stimulating wires was placed on the surface of one oculomotor nucleus well away from the midline (S_1). A stimulus to the surface produced a long lasting PSP in cells on both sides of the midline. This stimulus must have involved presynaptic fibers because depolarizations were recorded in both motoneurons, whereas antidromic stimulation produced only ipsilateral depolarizations (except close to the midline; Fig. 15*D*). The response to antidromic stimulation on the side contralateral to the surface electrodes was facilitated by prior stimulation of the afferents (Fig. 16*B*); evidently the depolarizing PSP facilitated antidromic invasion. (The antidromic response on the ipsilateral side would also be facilitated, but the interpretation would be complicated by the fact that the surface stimulus would excite both electromotor neurons and afferents.)

Antidromic stimulation on the side ipsilateral to the surface electrodes facilitated the response to surface stimulation (Fig. 16*A*), whereas antidromic stimulation on the contralateral side had no effect (Fig. 16*C*). This observation suggests that antidromic depolarizations spread electrotonically into the presynaptic fibers, thereby reducing their thresholds to external stimulation.

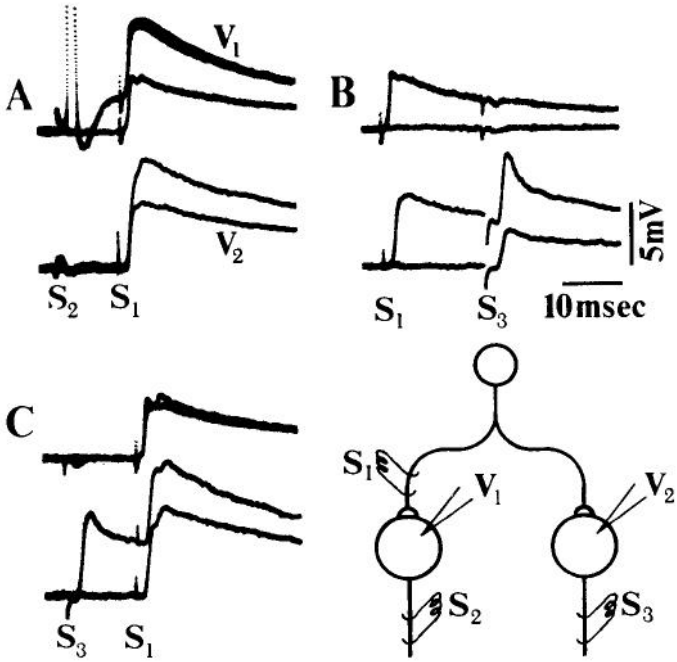

Figure 16. Facilitation of graded antidromic potentials by orthodromic PSPs. Recording from an oculomotor neuron on either side of the midline, stimulating each oculomotor nerve and stimulating on the surface of the oculomotor nucleus on one side as diagrammed. Two traces superimposed in each record with and without the conditioning stimulus. *A*, Antidromic stimulation on the side of the surface electrodes increases the response to surface stimulation recorded on both sides, which is consistent with electrotonic spread of antidromic depolarization into the presynaptic fibers. *B*, The PSP evoked by surface stimulation facilitates the graded antidromic depolarization evoked by stimulation of the contralateral nerve. *C*, Antidromic stimulation contralateral to the surface electrodes has no effect on the response to surface stimulation.

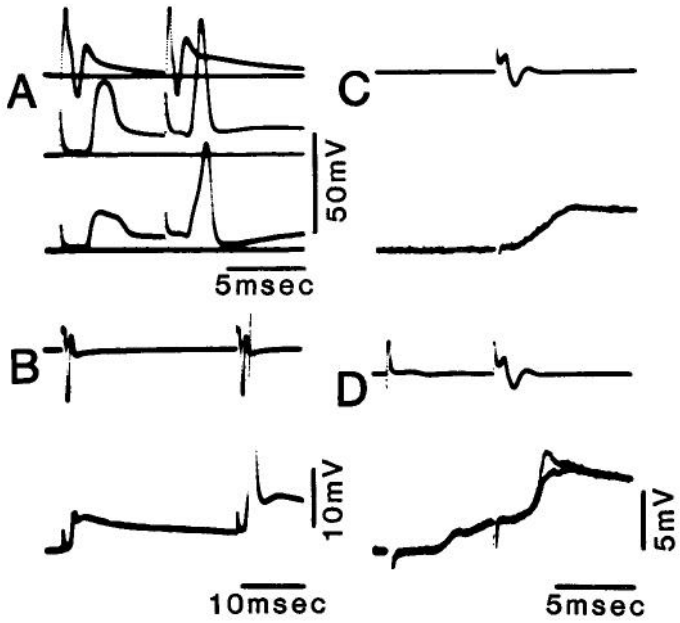

Figure 15. Facilitation of antidromic invasion by prior antidromic stimulation. *Upper trace*, monopolar recording of antidromic volley. *Lower trace(s)*, recording from oculomotor neurons. *A*, A pair of neurons gave initial segment spikes in response to the first antidromic stimulus; the second stimulus evoked initial segment spikes that superimposed on depolarization remaining from the first response were able to invade the soma. *B*, Facilitated invasion in a neuron in which the first stimulus produced only a nodal spike. *C*, Antidromic stimulation on the side of the monopolar recording produced a graded antidromic depolarization in a neuron near the midline. *D*, Stimulation of the contralateral nerve also produced a long lasting depolarization which summated with the depolarization produced by stimulation of the ipsilateral nerve. The ipsilaterally evoked depolarization was also facilitated in its rising phase and sometimes had a brief all-or-none component superimposed on it that may have resulted from a soma spike in a neighboring neuron.

Discussion

Cell characteristics. The electromotor neurons are somewhat different from ordinary motoneurons. Antidromic invasion has a low safety factor, and in many cells it fails unless there is depolarization spread from other cells. This property is in part ascribable to the high input conductance resulting from coupling of the cell bodies. In several other systems of coupled neurons, antidromic invasion fails invariably, independent of the size of the antidromic volley, although the cell bodies generate impulses in response to orthodromic stimulation (Bennett et al., 1967a, b, c). Increased input conductance associated with coupling does not account for the failure of invasion by near maximal antidromic volleys, because all cell bodies are simultaneously depolarized by the axonal impulses. Short initial segment regions requiring antidromic invasion directly from node to soma are likely to be responsible in some cases (Bennett et al., 1967b, c). In these closely coupled nuclei in which an impulse initiated in one cell propagates to all the others, it may be important that antidromic invasion fails so that the entire system is not excited by a single axon's firing through some malfunction.

The effective time constants of the electromotor neurons show a wide range. The differences can be accounted for by the electrotonic coupling of cells as diagrammed in Figure 15. A more realistic model would distinguish coupling by way of presynaptic fibers from that through dendrodendritic synapses and be based on studies of the actual connectivity. If coupling by way of presynaptic fibers is quantitatively important, the input time constants in the terminals are presumably long, which is not generally true of myelinated fibers. If the input impedance of the fibers were dominated by the cells on which they synapsed, no special properties would be required.

As at many axosomatic and axodendritic synapses with gap junctions, there are also active zones characteristic of chemical synapses; the synapses are "morphologically mixed." In electromotor nuclei in other electric fishes, and in some other synchronously firing nuclei (Pappas and Bennett, 1966; Bennett et al., 1967b, c, d), the PSPs give no evidence of a second, longer latency, chemically mediated component. Transmission seems to be exclusively electrotonic, and the morphologically observed active zones appear to have no transmissional function. However, horseradish peroxidase can be taken up by such axons and transported to the cell body (Tokunaga et al., 1980). The active zones may play a role in membrane recycling necessary for retrograde transport. The functional lesion responsible for their silence in transmission is unknown and could be in transmitter synthesis or packaging, coupling of depolarization to transmitter release, or absence of postsynaptic receptors.

Control of organ discharge. The organization of the electromotor system of the stargazer is unusual. In most other electric fishes the electromotor neurons fire in every organ discharge, and their activity is highly synchronized. The resulting organ discharges are generally all or none, varying only slightly as a result of refractoriness except in the electric eel where a wide modulation of amplitude occurs because of facilitation of PSPs in the main electric organ (cf; Bennett, 1971). Only the rajids have discharges that are quite variable in duration as well as amplitude, suggesting asynchronous activity of the electromotor neurons. The stargazer provides an intermediate case. The medullary neurons probably receive excitatory inputs from ascending fibers in the spinal cord as well as from higher centers. However, activity of the medullary neurons is poorly synchronized, although there is apparently some degree of coupling between them. Their activity excites the electromotor neurons, but the output volley need not be highly synchronous or include every electromotor axon. Nonetheless, the coupling between electromotor neurons must tend to increase the synchrony of their firing. The irregularity of the discharges in Figure 3 is not a result of electrical stimulation, because they were evoked by touch. The variations may, in part, be attributed to an effect of curarization, although less but still significantly variable discharges are observed in untreated intact animals (Bennett and Grundfest, 1961). Given this variability it becomes impossible to designate a command nucleus for organ discharge in the sense of highest level of the final command path. An asynchronous input to the medullary nucleus produces a less asynchronous output which generates in turn a less asynchronous output from the electromotor neurons. A simple all-or-none decision is not made at either nuclear level. Although strictly speaking there does not seem to be a command nucleus, the medullary nucleus almost fulfills the criteria, and it could be considered one that operated a little ineffectively.

Plasticity and electrotonic PSPs. The facilitation of the graded antidromic potentials is dramatic and, given the presence of synaptic vesicles at synapses within the nucleus, it would be well to review the evidence that the facilitation is based on electrical transmission. First, the cells are electrically coupled by direct measurement. Second, the graded antidromic depolarizations are generally quite smooth in time course; there do not seem to be two distinct components, one electrical and one chemical. Also, the latency is short enough to indicate electrotonic transmission. Granted that the graded depolarizations have only a single component, it must be electrotonically transmitted. The long duration arises from the long membrane time constant, which is seen in responses to both antidromic and orthodromic inputs. (Of course, passive decay would be equally slow for a chemical PSP produced by a brief conductance increase.) The orthodromic PSPs have the same form as the graded antidromic depolarization. Their synaptic delay was not measured because of unknown conduction time in the presynaptic fibers. Electrical transmission is suggested by increased excitability of presynaptic fibers in the nucleus following antidromic stimulation.

The graded antidromic depolarizations are facilitated by both antidromic and orthodromic stimulation, because antidromic invasion is marginal and, as was directly shown, invasion is facilitated by depolarization remaining from a previous volley. Thus larger potentials reach the coupling pathway between cells and produce greater electrotonic spread from active to inactive cells.

The EPSPs evoked in frog spinal motoneurons by ventral root stimulation probably have the same origin

as the graded antidromic depolarizations in *Astroscopus* and exhibit many of the same properties (Grinnell, 1966). The frog motoneurons are joined by gap junctions (Sonnhof et al., 1977; Taugner et al., 1979). Although the EPSPs are blocked by high Mg solutions as well as by high Ca solutions, this effect is due to block of antidromic invasion. Mn ions block presumably chemical PSPs but do not affect the ventral root EPSPs. In contrast to the short latency of the *Astroscopus* depolarizations the frog EPSPs have a latency of about 2 msec which is ascribed to conduction time in the dendrites. Facilitation of the EPSPs is produced by both orthodromic and antidromic stimulation and is also explicable as a result of facilitated antidromic invasion, perhaps from soma to dendrites as well as from axon to soma (Grinnell, 1966).

Earlier comparisons of chemical and electrical transmission led to the conclusion that electrical transmission is less well suited for modifiability to PSPs, although model systems, such as described here, were known (Bennett, 1966, 1972, 1977). Summation of electrotonic PSPs occurs simply as summation of charge on the postsynaptic membrane capacity, and can be pronounced, as in *Astroscopus*, if the membrane time constant is sufficiently long. At chemical synapses summation can also occur as a result of maintained transmitter release or postsynaptic action. Facilitation of electrotonic PSPs results from increase in the size of the presynaptic depolarization at the synapses. At chemical synapses increase in the presynaptic action potential produces facilitation, but increased transmitter release with little change in the action potential also is observed (Miledi and Slater, 1966). In *Astroscopus*, summation of electrotonic PSPs is likely to be important physiologically in increasing the fraction of electromotor neurons firing in response to near threshold volleys from the medullary nucleus. Because even with orthodromic stimulation the soma spike may fail (Fig. 6), facilitated invasion of the soma and increase in the PSPs that the neurons produce in each other could also be a factor in synchronizing responses.

Durations of changed excitability of 100 msec or more are not unreasonable for electrotonically coupled systems, either as a result of charge remaining on the membrane capacity as here or afterdepolarizations as in supramedullary neurons of the puffer (Bennett, 1966). Prolongation of action potentials associated with repetitive stimulation presumably could involve even longer inter-response intervals. Calculations as in Figure 13*C* show that peak PSP amplitude at an electrotonic synapse is very sensitive to prespike duration if the postsynaptic (or more accurately the coupling) time constant is long compared to the spike duration (unpublished calculations; see also Bennett, 1966).

Other kinds of modifiability of electrical transmission are known. Inhibitory synapses can short circuit a coupling pathway (Spira and Bennett, 1972; Spira et al., 1980). Synapses increasing cell input resistance can increase coupling (Carew and Kandel, 1976). With appropriate circuitry inhibitory neurons can even effectively reverse the sign of coupling between cells from excitatory to inhibitory (Spira et al. 1976).

Recently electrotonic coupling or its correlates, dye coupling and gap junctions, have been described at a number of additional sites in the mammalian CNS where activity may be quite asynchronous (*vide supra*). Whatever the functional role of these electrical synapses proves to be, the facilitatory and synchronizing action described between electrotonically coupled cells in *Astroscopus* may be relevant. Where synchronization is highly precise, summation and facilitation as in *Astroscopus* cannot occur, because every cell generates an impulse. In less synchronously responding systems, it is likely that electrical synapses play an integrative role. Their operation may well involve summation and facilitation which, as described here, result from changes in presynaptic impulses rather than from changes in the junctional conductances.

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