bilaterally placed if the pain were bilateral or midline in location; however, in all cases unilateral stimulation of the central gray matter afforded generalized pain relief.

Despite the fact that all six patients received partial to total relief from their intractable persistent pain by brain stimulation, only two patients reported alteration in acute pain threshold as tested by pin-prick stimulation or graded thermal energy. In contrast to these results in humans, stimulation-produced analgesia in animals is obviously accompanied by a marked elevation of the pain threshold, varying in magnitude according to the area tested (*2–4*).

At present we do not understand how the afferent mechanism involved in persistent pain differs from that operating in cases of acute pain. It is quite possible that the actual afferent input signal of persistent pain is far less intense than that of acute pain, but that its persistence in duration causes the suffering. For such low amplitude input, the success of stimulation-produced pain relief does not require an alteration in the threshold to acute pain. It is also true that the electrical energy applied to the human central gray matter in this study is far less than that previously applied to animals (*2–5, 8*). Our observation with patient 3 that the threshold to dolorimetry testing was elevated only at the higher voltage supports this view.

Two of our six patients who are still living have been using the stimulator as their sole means of pain control for more than 12 months.

Obviously, many more studies must be conducted before the knowledge already accumulated on the subject of stimulation-produced analgesia in animals can be applied to the benefit of human suffering. However, our results provide evidence for the potential usefulness of brain stimulation as a nondestructive method for controlling intractable persisting pain in humans.

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24 May 1976; revised 15 December 1976

## Electrically Coupled, Photosensitive Neurons Control Swimming in a Jellyfish

Abstract. *Central neurons in* Polyorchis *(Hydromedusae) were impaled with microelectrodes, and conventional resting potentials were obtained. The waveform of action potentials recorded concurrently with swimming events shows evidence of electrotonic coupling between these neurons, which are also directly photosensitive and receive excitatory synaptic input from other conduction systems.*

Considerable advances in our knowledge of coelenterate conduction systems and pacemaker interactions have been made in recent years (*1*), but, with few exceptions (*2–4*), all of our information has come from extracellular recordings. It is known that both nerves and epithelia can provide pathways for behavioral responses, but, since nerves frequently run among epithelial cells, it is often difficult to determine whether a conduction system is nervous or epithelial. Because of their small size, coelenterate cells are hard to record from with microelectrodes; in only one instance (*4*) has it been possible to show, by intracellular recording, that a particular axon is the pathway for a physiologically defined conduction system. As the lowest animals equipped with nerves, the coelenterates can provide important insights into the organization and evolution of nervous systems generally, but the lack of information on neuronal activity at the cellular level has reduced the significance of much of the coelenterate work for neurobiologists as a whole.

This report gives the first results from our work on a coelenterate preparation in which central neurons can be regularly impaled with microelectrodes (*5*). The species is the hydromedusan jellyfish *Polyorchis penicillatus* Eschscholtz. The neurons lie in the inner nerve ring, a bundle of neurons that runs around the margin of the bell near the base of the velum.

Studies on other hydromedusae [for example (*6, 7*)] indicate that the swimming pulse (SP) system, which generates and transmits the impulses for swimming, is located at the margin of the bell, probably in the inner nerve ring. A second conduction system, which uses pathways in one or both of the marginal nerve rings (*6, 7*), is the marginal pulse (MP) system, which coordinates tentacle

contraction (*8*). Light can affect the activity levels of these conduction systems, in what have been termed light-ON and light-OFF responses (*6, 7*).

If a portion of a *Polyorchis* margin is pinned down subumbrella side uppermost and illuminated from below, individual large neurons can be identified in the inner nerve ring. Electron microscopy (*9*) reveals that in any single cross section, the inner nerve ring is composed of some 200 nerve profiles of which, on average, five to ten have diameters in the range between 10 and 25 $\mu$m. When these large neurons are penetrated with microelectrodes, action potentials that correlate perfectly with swimming events are recorded, which indicates that the neurons are components of the SP system.

In the dark, these neurons have resting potentials of $-60 \pm 5$ mv. In their simplest form, the action potentials have a conventional waveform (*10*) consisting of an 80- to 100-mv positive phase lasting 10 msec and a 25-mv hyperpolarizing undershoot lasting as long as 350 msec. During spontaneous activity, this basic waveform is supplemented by a wide range of variant waveforms, which frequently fall into discrete classes (Fig. 1A). Different neurons show different variants. We could recognize no pattern in the order of appearance of the variant waveforms.

These recordings closely resemble those recorded from a variety of molluscan neurons. In the buccal ganglion cells of the pond snail *Planorbis* (*11*), the increased duration of variant action potentials can be shown, by simultaneous recordings from other cells in the ganglion, to represent the effect of synchronous firing of electrically coupled nerve cells. Although we have been unable to confirm coupling by recording simultaneously from two cells, we suggest that the variant waveforms seen in *Polyorchis* would, by analogy, represent the action of different combinations of synchronously firing, coupled neurons. Support for these interpretations comes from the finding (*9*) of gap junctions between the nerves of the inner nerve ring of *Polyorchis*. In other systems of electrically coupled neurons, coupling may reduce junctional delay, permit synchronous firing of numbers of neurons, or effectively increase the threshold of any one neuron to inputs that do not affect a large proportion of the coupled neurons (*11*). It is too early to say precisely what advantages such a system of coupling would have for *Polyorchis*, but all of these functions might apply.

Intracellular recordings from SP neurons show evidence of synaptic input in the form of excitatory postsynaptic potentials (EPSP's). These events can sometimes be directly correlated with MP's recorded extracellularly, but in many cases the EPSP's have no recordable extracellular correlate. The EPSP's representing MP input sum and facilitate and may elevate the membrane potential to spike threshold ($-40$ to $-50$mv) (Fig. 1B). No EPSP's could be recorded in the presence of 219 m*M* $Mg^{2+}$ (*12*). We have not yet recognized an identifiable inhibitory postsynaptic potential.

Action potentials that are evoked by EPSP's are observed during the light-OFF response of *Polyorchis*. Figure 1C is a typical record obtained when the light intensity was reduced, in this case, from 350 to 0.7 lux for 12 seconds. At light OFF, the neuron depolarized and spiked. Measurements from other records gave the latency for this depolarization as 150 to 200 msec. The depolarization was maintained for about 8 seconds and then declined. Immediately after light ON, the neuron hyperpolarized by some 18 mv and then slowly depolarized and spiked. The events are interpreted as representing two independent effects of the changes in light intensity. The spiking at light OFF appears to be mediated by EPSP's, while the hyperpolarization and subsequent depolarization at light ON would result from the direct effect of light on the neurons of the SP system. The evidence for this is as follows.

The action potentials evoked by light OFF (Fig. 1D) are preceded by a series of small, high-frequency EPSP's. After the ocelli are removed, this burst of EPSP's fails to occur, and there is no increase in spike frequency. The ocelli can therefore be assumed to be the receptors for the light-OFF response, and the EPSP burst the result of activity in some conduction system intermediate between the ocelli and the SP neurons. Although MP frequency increases at light OFF (Fig. 1C) and may contribute to the depolarization, the main EPSP burst frequently precedes the MP burst; therefore, another system must be chiefly responsible for mediating the OFF response.

Distinct from the EPSP-based depolarization at light OFF are the slow changes in membrane potential that accompany changes in light intensity. In experiments on preparations from which all ocelli had been removed, the only apparent effect of light OFF was a slow hyperpolarization of the neuron. With the ocelli intact, this hyperpolarization was obscured by the depolarizing EPSP ac-

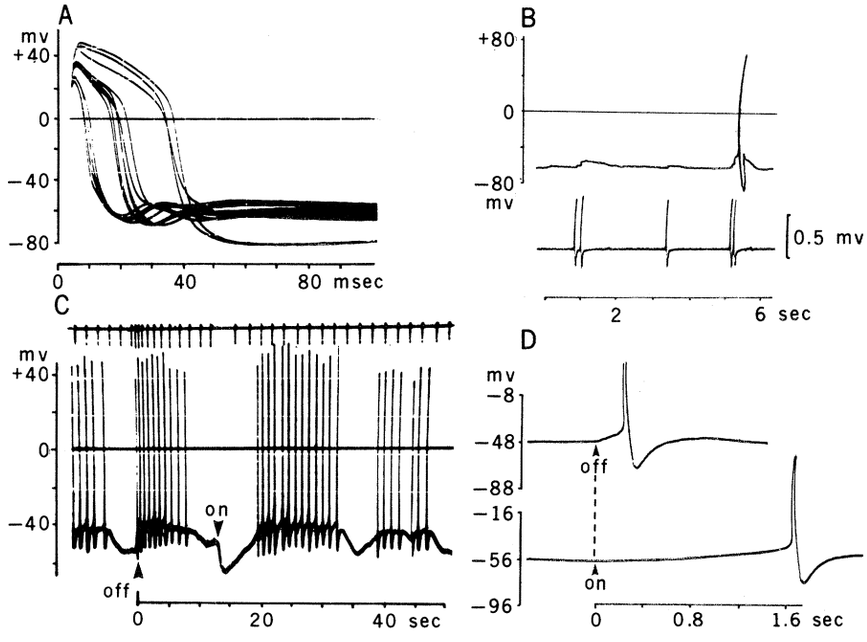


Fig. 1. (A) Thirteen superimposed spontaneous action potentials recorded from a single SP neuron over a period of 1 minute. The oscilloscope was triggered by the rising phase of each action potential, with the result that the initial portion of each was lost. (B) Upper trace, intracellular record of five EPSP's and a single action potential recorded from an SP neuron. The EPSP's are recorded concurrently with MP's monitored extracelluarly (lower trace) from a tentacle. (C) Lower trace, intracellular record of the events triggered by a decrease (OFF) and increase (ON) in light intensity. Upper trace, MP's recorded as in (B). (D) Single action potentials recorded intracelluarly from the same SP neuron at light OFF and light ON. Note the different latencies for the two action potentials and the presence of small EPSP's immediately before the action potential at light OFF. The upper portions of these action potentials are not included.

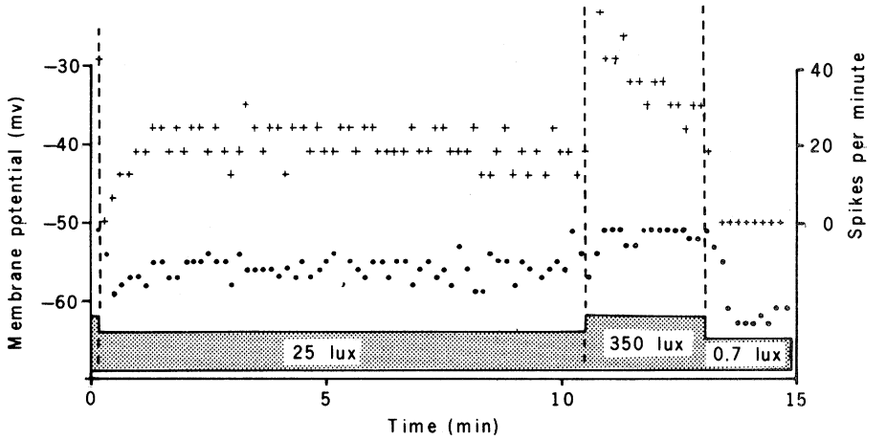


Fig. 2. Membrane potential (•) and spike frequency (+) in an SP neuron exposed to different light intensities (shaded area). Each dot gives the most negative membrane potential during each 10-second interval, and each cross, the spike frequency during that same period.

tivity of the OFF response, and only when the light was turned on again and the synaptic activity abolished was the magnitude of the underlying hyperpolarization revealed (Fig. 1C) (*13*). There appears to be little if any adaptation of the light-induced membrane-potential changes with time. In one experiment, the membrane potential was monitored continuously for 15 minutes, during which time the light intensity was changed three times. The results (Fig. 2) indicate that the membrane potential "follows" the ambient light intensity: the lower the light level, the more negative the membrane potential and the lower the spike frequency. The absence of any synaptic activity during these slow changes in membrane potential (Fig. 1D) and the ability of the neurons to maintain the light-induced changes in membrane potential for long periods suggest that the neurons are, in fact, very slowly adapting or nonadapting photoreceptors (*14*). These light-induced membrane-potential changes were recorded from all neurons penetrated, but, because coupling would be expected to spread potential changes between the cells, we cannot say conclusively that all the cells are directly photosensitive.

Photosensitive neurons have been described in several other invertebrates (*15, 16*), but we know of no examples of neurons whose resting potentials are, as appears to be the case for the SP neurons, dependent on ambient light levels. The SP neurons of *Polyorchis* also differ from many other photosensitive neurons (*16*) in that they are situated in a transparent tissue layer at the edge of the animal and are, thus, well located for light detection.

Observations on specimens maintained in aquariums indicate that *Polyorchis* responds to both increases and decreases in light intensity. As might be expected from the records of the OFF response presented above, reductions in light intensity evoke an immediate but brief burst of swimming. This ability of *Polyorchis* to respond rapidly to sudden shadowing may be an important means of avoiding predation. The effect of increases in light intensity was less obvious, but the number of medusae actively swimming in the aquariums varied with light intensity. In one experiment where 36 medusae were exposed for 10-minute periods to successive light intensities of 1400, 5500, and 22,000 lux, the proportion of swimming medusae in the latter half of each exposure period was 29, 34, and 48 percent, respectively. It is reasonable to assume that these variations in swimming activity are the direct result of the light-induced depolarizations and hyperpolarizations of the SP neurons described.

The finding of photosensitive neurons in *Polyorchis* and the elucidation of their role in the regulation of swimming have important implications for our understanding of the behavior of other coelenterates, many of which are photosensitive [for example (*7, 17*)] but have no known photoreceptor organs. Some eyeless medusae, such as *Stomotoca* (*18*), show diurnal changes in their vertical distribution in the sea, which might be controlled by the direct action of light on their SP systems.

For workers in other areas of neurobiology, we suggest that the *Polyorchis* results are of interest as evidence that the primitive nervous system is capable of conventional all-or-none action potentials, synaptic transmission, and the grouping of neurons into loose functional associations by coupling—features that are characteristic of nervous systems higher on the phylogenetic scale.

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13. With large changes in light intensity, the EPSP's of the OFF response initially predominated, but with smaller reductions the EPSP activity was short-lived, and the nerve hyperpolarized more rapidly.
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11 January 1977; revised 23 February 1977