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Control of Somatosensory Input by Cerebral Cortex

Abstract. *Direct stimulation of the pyramidal tract increases the size of the excitatory receptive fields of neurons in the somatosensory cortex of the cat. This effect reflects greater transmission of cutaneous information through the dorsal column nuclei as a result of the facilitation of cells in these nuclei by pyramidal tract fibers.*

In the cat, each cell of the dorsal column nuclei—the primary somatosensory relay nuclei located at the caudal end of the brain stem—is either inhibited or facilitated, but not both, by stimulating the anterior cerebral hemisphere (*1*). The facilitation comes exclusively by way of pyramidal tract fibers, while the inhibition depends upon activation of bulbar reticular neurons through various cortical efferent routes (*2*). Anderson and his co-workers (*3*) have proposed a model of the synaptic organization within these nuclei in which essentially all cells facilitated by cortical stimulation are interneurons. By this model, primary afferent fibers ending on cuneothalamic relay neurons undergo a presynaptic inhibition which is mediated by the cortically (pyramidally) excited interneurons that are found deep in the nuclei. Thus, cortical or pyramidal stimulation should depress the transmission of cutaneous information through these nuclei—an effect not easily reconciled with the observations presented here.

The primary datum in this report is whether or not stimulation of a particular patch of skin causes an individual neuron in the somatosensory cortex to discharge. The aggregate of all the patches of skin which, when stimulated, cause the neuron to discharge constitutes the neuron's excitatory receptive field. The field may include only a few square millimeters of skin or it may occupy a large fraction of the body surface, usually as a continuous area. Because the pattern of evoked discharge of a neuron varies with the site (as well as with the intensity) of stimulation, a region of maximal effectiveness may be identified; this region is designated as the "center" of the receptive field, whether or not it is the centroid of the area. Cells that form a vertical column through the cerebral cortex have receptive fields of widely different sizes, but the fields overlap extensively and tend to have the same "center" region.

In cats anesthetized with α-chloralose and paralyzed with decamethonium bromide, one anterior cerebral hemisphere and the medullary pyramids were surgically exposed; occasionally the dorsal column nuclei were also exposed. The evoked activity of single neurons in the primary somatosensory cortex that is associated with the contralateral forepaw was recorded extracellularly. This region was located just medial to the caudal edge of the coronal sulcus, at the site of maximum amplitude of the *b*-wave (*4*) and about 8 mm caudolateral to the main origin of the pyramidal tract (*5*). Studies in our laboratory show that this coronal recording site contains few pyramidal tract neurons (3 percent of a sample of 570 neurons), the number increasing sharply 4 mm rostromedially, so it is highly unlikely that recurrent collaterals from such neurons penetrate in any number, if at all, into the coronal recording site. A large recording electrode was placed at the lateral tip of the cruciate sulcus to monitor the pyramidal antidromic response produced by stimulating the medullary pyramids. For such stimulation, advantage was taken of the fact that the corticospinal and corticobulbar fibers that comprise the pyramidal tract assemble into a compact and exclusive bundle on the ventral surface of the medulla (caudal brain stem). When bipolar stimulating electrodes are placed over the exposed surface of this bundle, they can either activate the pyramidal tract fibers exclusively or, by increasing the stimulus intensity, activate adjacent fibers of the medial lemniscus as well. Since the latter comprise one leg of the main route to the somatosensory neurons in the cerebral cortex, care was taken to activate only pyramidal tract fibers (stimulus intensity was so low that only an *a*-wave was evoked in the cortex).

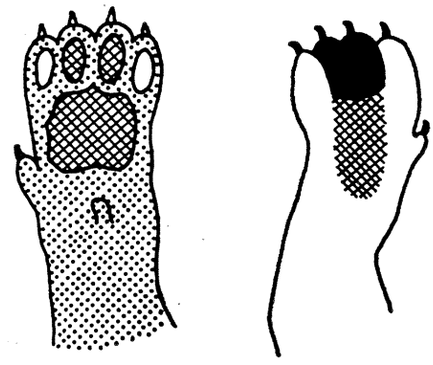

Fig. 1. Cutaneous receptive field of touch neuron isolated 424 μ deep in coronal cortex. Black area shows extent of "normal" field; black, hatched, and dotted areas show size of field immediately after a 15-second train of shocks at 312 per second applied to bulbar pyramids. Black and hatched areas are touch-sensitive; dotted area is hair-sensitive. Neuron's field included black area, touch only, 4 minutes later.

The experimental procedure was to isolate a single neuron in the somatosensory cortex, find its natural stimulus (for example, hair deflection, skin tap, and so forth), carefully define the nature and extent of its excitatory receptive field, and then determine how this field is altered by activating pyramidal tract fibers. Since pyramidal fibers have a brief and weak effect on neurons of the dorsal column nuclei (pyramidal neurons usually discharge with a burst of spikes about 3 msec apart), long stimulus trains (312 per second) were applied to the pyramidal tract to exaggerate their effect. Monitoring electrodes on the cuneate nucleus did not reveal "convulsive" activity. Receptive field measurements were attempted during the pyramidal conditioning stimulation. Additional measurements were then made immediately after and were continued until the receptive field had returned to its original state. The long train of high-frequency stimulation probably hyperpolarized the synaptic terminals of the pyramidal tract fibers, yielding the phenomenon of posttetanic potentiation (evidenced by potentiation of a small, surface-negative wave dependent upon pyramidal stimulation and confined to the dorsal column nuclei). If this were true, when the pyramidal tract was intact each testing stimulus from the skin would reflexly

reactivate the pyramidal neurons and thus greatly prolong and exaggerate their effect. The spinocervical system does not seem to be involved in this effect.

Of 73 cortical neurons adequately tested, 63 were clearly affected by the pyramidal conditioning stimulus. Receptive fields of 38 neurons were increased in size while those for 6 were decreased; response thresholds were decreased for an additional 16 neurons and elevated for 3 neurons. Thus, excitability was enhanced six times more frequently than it was depressed. Although touch-sensitive neurons predominated in the sample, neurons with other modality sensitivities were similarly affected. Interestingly, the receptive fields of neurons isolated in the upper three layers of the cortex more than doubled in size, on the average, while the fields of deeper lying neurons increased by only half. Not only did receptive fields increase in area, but they also occasionally included a new modality. That is, some neurons, exclusively touch-sensitive before pyramidal stimulation, also became responsive to hair deflection after conditioning stimulation. Figure 1 shows the receptive field changes observed for such a neuron immediately after a 15-second pyramidal tetanization at 312 per second. The black area on the dorsum of digits 3 and 4 (Fig. 1, left) defines the initial area that was responsive to tap stimulation. Upon cessation of the conditioning stimulus, the neuron responded to tapping throughout the black and hatched areas and also responded to light puffs of air delivered anywhere within the stippled area. The neuron gradually returned to its previous condition over a 4-minute period. The increase in sensitivity to touch was confined to skin supplied by the median nerve, whereas the region sensitive to hair deflection spanned the innervation fields of all three forelimb nerves. Even when response was limited to one modality, changes in field size often extended into areas of skin that were supplied by different forearm nerves, attesting to the extensive convergence of afferent input in the somatosensory system.

The pattern of evoked response varies according to the locus of stimulation. When the site of stimulation is near the "center" of the receptive field, the neuron discharges after a brief latency with several closely spaced spikes. The latency of response increases as the site is moved away from this region, slightly at first and then extensively near the borders of the receptive field, the discharge train decreasing to one spike. But the changes in pattern with site of stimulation are not often uniform—they are more often abrupt as one moves from the "center" or some other "hot spot" toward the periphery. Upon pyramidal stimulation, the borders of these "hot spots" move rapidly outward to exceed the confines of the former receptive field and engage previously unresponsive areas in an exquisite sensitivity. Although most fields were tested with a manually manipulated blunt probe, some quantification could be obtained with an electrically driven mechanical tapper. By tapping at the rate of once per second on the edge of the receptive field of one carefully studied cell, its erratic and low probability response gradually became regular during pyramidal stimulation; its response latency progressively shortened and the cell soon produced several spikes in a burst. Upon cessation of stimulation, the response at first improved even more and then gradually weakened until it had attained its previous condition. The decay time varied from 1 to 6 minutes, according to the neuron, and averaged 3 minutes. Repeating the conditioning stimulation after complete recovery of the neuron reproduced the entire sequence. Some summation could be seen by reconditioning before recovery was complete (Fig. 2). The normal field, shown in black, expanded after 15 seconds of pyramidal tetanization to include the hatched area of Fig. 2*A*. Three minutes later, the field had subsided to the condition shown in Fig. 2*B*, at which time another 15-second pyramidal tetanization was delivered. The receptive field reexpanded to a slightly larger area (Fig. 2*C*) and 6 minutes later still showed some enhancement (Fig. 2*D*).

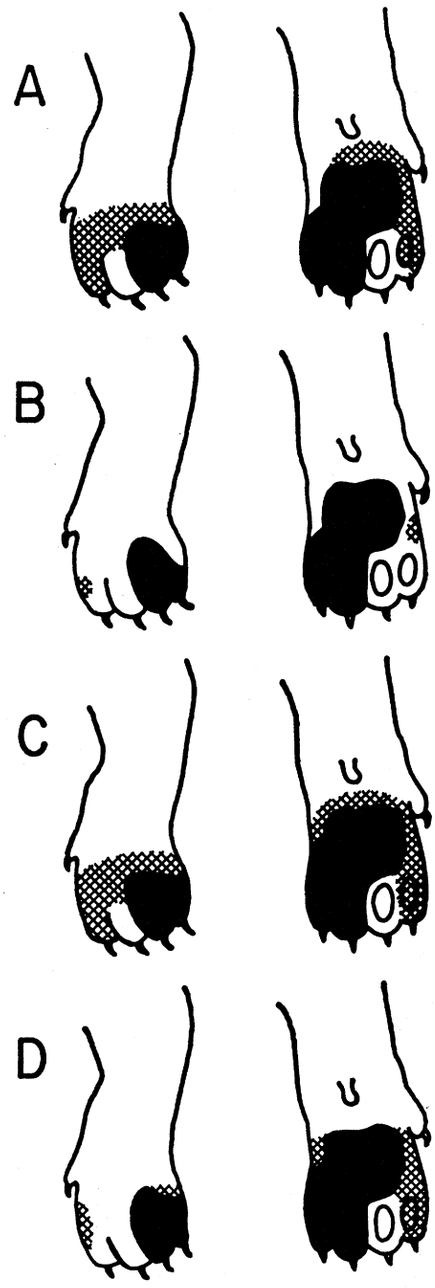

Fig. 2. Cutaneous receptive field of touch neuron isolated 780 μ deep in coronal cortex. Black, "normal" field; black and hatched, "conditioned" field. (*A*) Touch receptive field immediately following a 15-second train of 312 shocks per second to bulbar pyramid. (*B*) State of field 3 minutes later. (*C*) Field after second 15-second train of pyramidal shocks, as in *A*. (*D*) State of receptive field 6 minutes after end of second train of conditioning shocks.

Complete unilateral transection of the pyramidal tract at a midolivary level (histologically verified) abruptly shortened the facilitatory or inhibitory effect to 0.25 to 4 minutes, with an average of 1.75 minutes. This shortening can be accounted for by the failure of the testing stimuli from the skin to successfully reactivate pyramidal fiber terminals in the cuneate nucleus, these fibers being disconnected from their parent axons. Thus, the pyramidal influence could not be artificially prolonged, as it had been when the pyramids were intact.

That both the excitatory and the inhibitory effects survived the pyramidal tract transection proves that the effects do not depend upon antidromic invasion of recurrent collaterals from pyramidal tract neurons. Identical trains of stimuli applied to the central

end of the transected pyramidal tract, effectively activating all recurrent collaterals of these neurons, had no measurable effect on the cortical neurons tested. However, intentional involvement of the adjacent medial lemniscus fibers profoundly altered the responsiveness of all neurons tested. During such conditioning input, no responses could be obtained from the cortical neurons by adequate stimulation of their excitatory receptive fields during stimulation, but complete responsiveness returned within 1 second upon cessation of stimulation. Such involvement was obtained either by sufficiently increasing the strength of stimulation at the ventral surface of the brain stem (pyramidal bundle) to produce orthodromic events in the cerebral cortex (*6*) or by penetrating the pyramidal bundle and inserting the electrodes into the medial lemniscus. However, during weak stimulation confined to the pyramidal tract the receptive fields of coronal neurons were enhanced. It is thus evident that the excitatory effects, and perhaps the inhibitory effects, result from pyramidal tract facilitation of a particular set of neurons in the cuneate nucleus.

Evidently the pyramidal tract—a uniquely mammalian possession that connects the cerebral cortex directly with so many brain stem and spinal neurons, both sensory and motor—constitutes one route by which the cerebral cortex can modify its own afferent input. Suggestive as the findings are, the role that this system of fibers plays in perception and attention remains to be demonstrated.

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Hormones as Allosteric Effectors

In his article, "Plant hormones and regulators" (*1*), van Overbeek makes the cautionary point that certain responses to both plant and animal hormones occur much too rapidly to be mediated through an action at the gene level. He suggests that there may be "several sites of primary hormone action, just as there are several doors that can be opened by one key." However, it is important to emphasize that different sites of action (such as at the DNA template and at the cell membrane) need not imply fundamentally different methods of action. To carry van Overbeek's analogy further, doors that can be opened by one key presumably have identical or similar locks. The concept of hormones as allosteric effectors, propounded by Monod, Changeaux, and Jacob (*2*), provides a plausible common denominator among apparently divergent locking mechanisms. As these authors have stated, "it seems difficult to imagine any biochemical mechanism other than allosteric which could allow a single chemical signal to be understood and interpreted simultaneously in different ways by entirely different systems." Thus rapid manifestations of hormone action could result from direct allosteric modification of extranuclear enzymic or structural proteins. Such an action would not differ in essence from hormonal control of enzyme biosynthesis through allosteric interaction with repressor proteins on operator genes. A similar view, as specifically applied to auxins, has recently been expressed by Südi (*3*) in the suggestion that "similar allosteric sites of a great number of functionally different proteins make up auxin receptor sites."

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1 June 1966

Signal versus Noise in the Evoked Potential

Various methods have been developed over the last two decades which allow the detection of cortical evoked potentials with scalp electrodes. The most widely used method summates electrical activity occurring over the same time interval following a repetitive stimulus, and a number of specialized computers which do this are commercially available. One assumption in this method is that potential changes evoked by each stimulus presentation (the signal) will be time-locked and will summate with repetition. A second and corollary assumption is that remaining potential changes (the noise) will be random and cancel out with enough repetitions.

The second assumption is met with practical sample sizes only within a certain variance (or standard deviation) of error, and therefore the signal must to some extent be composed of noise. Where it is assumed that the signal and noise are independent, and that the noise remains the same under conditions of stimulus or no stimulus, the amount of noise in the signal is related to the obtained ratio of signal to noise; thus, 2 : 1 ratio would mean that approximately half the signal was noise. Larger ratios would produce corresponding decreases in the amount of noise in the signal. Therefore, it seems incumbent upon investigators to present data regarding the degree to which the signal exceeds the noise or, at least, to acknowledge that this has been examined. In fact, failure to use noise, or control, data (summation over the same temporal interval but with the light or other stimulus occluded) makes it difficult to determine whether a cortical event related to the stimulus did indeed occur. The ease with which the simple presence or absence of a signal may be determined, even with low ratios of signal to noise, probably accounts in part for the omission of noise data in some reports [*Science* **150**, 1162 (1966); **148**, 980 (1965); **145**, 180, 182 (1964); **141**, 1285 (1963)]. Failure to present noise data is even more serious when attempts are made to interpret variations in small components of the signal. For example, conclusions regarding differences between earlier and later components of potentials in aged subjects [*Science* **151**, 1013 (1966)] must be considered tentative until it is demonstrated that such differences cannot be attributed to variations in the noise. Thus disregard of noise in summation techniques weakens an otherwise impressive research tool.

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