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Electrotonic Processing of Information by Brain Cells

Recent research augurs an important role for neuronal local circuits in higher brain function.

Francis O. Schmitt, Parvati Dev, Barry H. Smith

Great advances have been made in major areas of neuroscience over the years, but strikingly lacking are unifying conceptual principles capable of relating brain cell activities to psychological processes such as learning, memory, perception, consciousness, and other "higher brain functions." Essential to the development of such principles will be a more profound understanding of the bioelectrical and other processes of neuronal interaction that are implicated in higher brain functions.

The last two decades have seen a revolution in concepts of information processing and transfer in and between brain cells, concepts that have dominated neurological thinking for many years (*1–5*). One significant change is in the concept of the dynamic functional polarization of the neuron, according to which the neuron is a one-way, information-transmitting, cellular system with a sometimes vast but passive receptive dendritic surface, with integrative capabilities focused at the axon hillock, and with an axonal self-regenerative mechanism for rapid transmission of the message to axonal terminals. The new view of the neuron, based primarily on recent electron microscope evidence (*6*) and supported by intracellular electrical recording, holds that the dendrite, far from being only a passive receptor surface, may also be presynaptic, transmitting information to other neurons through dendrodendritic synapses. Such neurons may simultaneously be the site of many electrotonic current pathways, involving components as small as dendritic membrane patches or individual dendrites. Electrotonic currents, originating in various loci, flow through a vast network; the information-processing product of these currents is transmitted to other brain regions by projection neurons—that is, neurons with long axons.

The second significant recent change has been modification of the concept that transmission of information between neurons requires the propagation of "spike" action potentials. Evidence is accumulating that small graded changes in potential in one neuron can synaptically influence electrical activity in other neurons (*1, 3, 7, 8*). In dendritic networks, distances between interactive sites are measured in micrometers, as contrasted with the millimeter or centimeter distances characteristic of spike propagation. Attenuation of a passively conducted electrical signal is correspondingly less significant in such localized dendritic networks, and thus obviates the need for spikes. That some neurons characteristically interact without the benefit of spikes has been repeatedly demonstrated. In such neurons, changes in membrane potential of less than a millivolt may suffice to alter synaptic transmission (*7, 9*).

Paralleling the evolution of a new view of electrical information processing in neurons has been the emergence of knowledge of fast bidirectional transport and biochemical signaling between brain cells. Such molecular exchange may function not only to provide metabolic

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support for electrical activity but also to transmit information between neurons.

From a consideration of the many modes of interaction between brain cells, there emerges a concept of a vast network (coexistent and closely interacting with that portion of the nervous system devoted to rapid, spike-mediated, long-distance transmission) in which information is processed electrotonically through graded changes in membrane potential. The resulting electrotonic currents are transmitted through dendrodendritic synapses along short axons, as well as by ephaptic means.

In this article we describe recently developed ideas that may eventually forge a link between the data and concepts of neural activity and those of higher brain function.

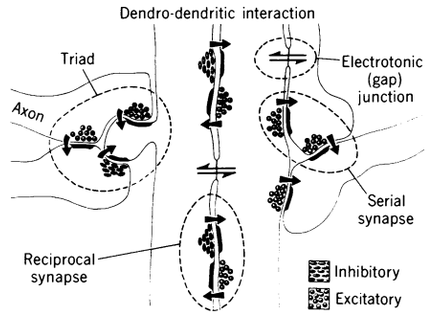

Fig. 1. Diagram illustrating that dendrites may be both pre- and postsynaptic to each other, forming reciprocal synapses, two of which are shown between the same dendrite pair. In triads, an axon synapses on two dendrites, and one of these dendrites synapses on the second. In serial synapses, a dendrite may be postsynaptic to one dendrite and presynaptic to another, thus connecting a series of dendrites. Dendrites also interact through low-resistance electrotonic ("gap") junctions (two of which are shown). Except for one axon, all structures shown are dendrites.

The Quiet Revolution Concerning Neuronal Circuitry

Application of electron microscopy to neurobiology has required alteration of traditional concepts of neuronal and synaptic organization, as well as of those of the nature of the neuropil (*4*). These developments have been well described by Rakic (*5*) in his discussion of local circuit neurons. Convergence of presynaptic axons onto the dendrites of the postsynaptic neuron may be regarded as a special aspect of a much more complex general picture which includes dendrodendritic, somatodendritic, dendrosomatic, somatosomatic, somatoaxonic, and axoaxonic chemical synapses (*6*). It has thus become apparent that the dendrite and the soma may act presynaptically, transmitting information to postsynaptic neurons and to other structures by ephaptic as well as by synaptic means. The concept of dynamic polarization in the neuron doctrine has been further eroded by the discovery of direct electrotonic coupling through gap junctions between neurons of the central nervous system (*10*) and by the implications of dendrodendritic electrical coupling in particular (*11*).

This quiet revolution in our concepts of synaptic organization (*3*, *4*) significantly alters our understanding of neuronal interaction because it suggests the concept of neuronal "local circuits" whose components may include many neurons joined through dendrodendritic junctions or may involve regions along individual dendrites or even patches in the neuronal membrane. Some neuronal local circuits primarily between dendrites resulting from "unconventional" modes of synaptic connectivity are illustrated in Fig. 1.

It is apparent that complex information processing may proceed in dendritic networks without primary involvement of neuronal somata and axons, as characteristically occurs in through-projection neuronal circuits. The term "local circuit" may describe synaptically activated systems such as reciprocal synapses, multiple dendrodendritic and axonal interactions in glomeruli of the lateral geniculate nucleus, or nonsynaptic ephaptic interactions in dendritic bundles in cerebral cortex, as well as interneuronal circuitry such as that of the Renshaw cell and the motor neuron in the spinal cord.

Local circuitry and the major role of dendritic interaction are well illustrated in the retina and the olfactory bulb, in contrast to circuits of conventional relay or projection neurons (Fig. 2A), in which transmission occurs from the dendrite through the soma and axon to the synapse. Information processing occurs in the retina (Fig. 2, B and C) without self-regenerative action potentials except in the amacrine cells (whose spikes are not essential for retinal function) and in ganglion cells whose axons form the optic nerve (*12*). "Reciprocal" synapses have been observed between pairs of horizontal cells and between bipolar and amacrine cells; the amacrine cells are axonless, and their dendritic processes interact through "serial" synapses (*7*). Similarly, in the olfactory bulb (Fig. 2, D and E), granule cells are axonless and function primarily through dendrodendritic interaction via graded potentials (*3*, *13*). The mitral cell, which is the projection neuron of the olfactory bulb,

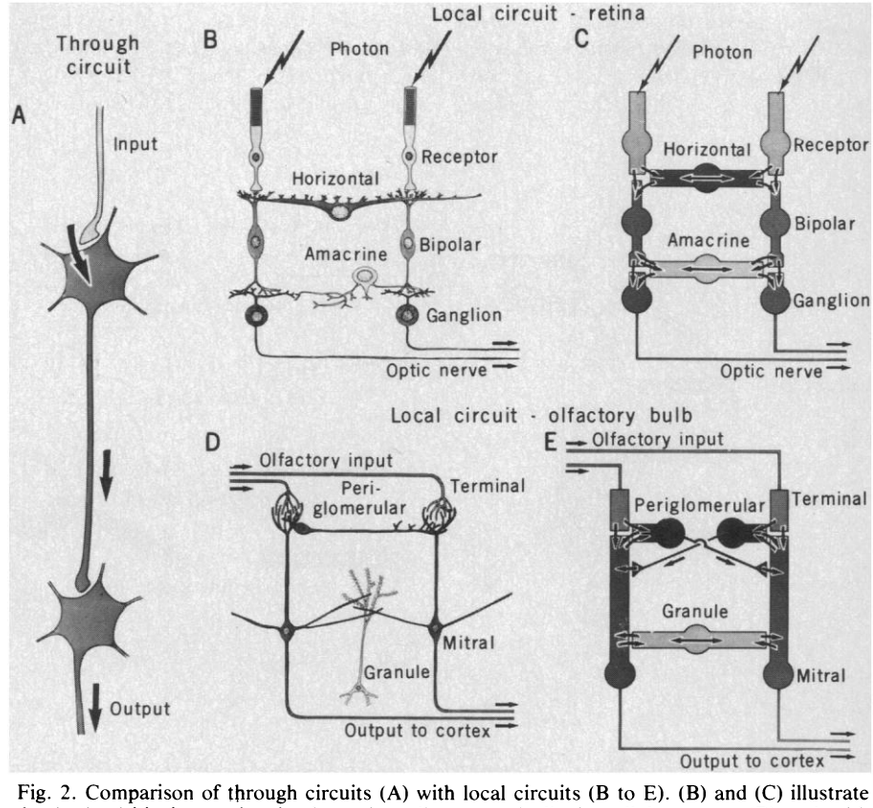

Fig. 2. Comparison of through circuits (A) with local circuits (B to E). (B) and (C) illustrate dendrodendritic interaction in the retina: diagrammatically in cellular arrays (B) and with respect to interneuronal information transfer (C). (D) and (E) illustrate dendrodendritic interaction in the olfactory bulb: diagrammatically in cellular arrays (D) and with respect to interneuronal information transfer (E). [After Shepherd (*3*)]

also participates in dendrodendritic interactions.

It is functionally significant that the number and proportion of neurons that have exclusively local synaptic connections increase systematically in phylogeny, reaching their peak (in absolute and relative numbers) in the human brain (*5*). These neurons develop late in ontogeny, and it has been hypothesized that they are not as well specified genetically as the long-axon neurons, providing a pool of modifiable neurons essential for the learning process (*14*). With the phylogenetic and ontogenetic increase in the numbers of these neurons, there is a concomitant and dramatic increase in the number and complexity of neuronal, and particularly dendritic, processes. For example, dendritic ramifications of short-axon stellate cells whose cell bodies are situated in the more superficial layers of the human neocortex are considerably more complex than those of similar short-axon cells in deeper layers (*15*), an observation in accord with the generally accepted notion that small-celled supraganglionic layers of the neocortex represent phylogenetically newer structures that reach their peak of development in man. Furthermore, it is the elaboration of such processes (and not increases in cell numbers) that is probably responsible for the development of neocortex and its neuropil. The rhesus monkey fetus, for example, has its maximal number of neurons at the 100th gestational day, although the sulci and gyri are then only minimally developed; the enormous increase in cortical surface that occurs during the next 60 gestational days and after birth is due primarily to elaboration of the neuropil (*16*).

This revolution in our understanding of the synaptic, structural, and functional relations of neurons suggests a new, dynamic view of neuronal interaction in which bioelectric information is received and processed at many highly localized regions of the dendritic membrane and then integrated and transmitted through a dendritic network. The electrophysiological data support this view and indicate that graded electrotonic potentials, rather than regenerative spikes, may be the language of much of the central nervous system.

Bioelectric Mechanisms in Local Circuits

The concept that graded changes in potential in one neuron can influence the electrical activity in other neurons, articulated in 1959 by Bullock (*1*), has received strong experimental support. In most dendrites and in many short axons, voltage signals can spread effectively by electrotonic means alone (*17*). In cell processes with unusually high membrane resistance, the signal can be conducted over distances as large as a centimeter with very little attenuation (*18*). The effectiveness of electrotonic conduction as a mechanism of signal transmission raises a number of interesting electrophysiological questions: How do synapses, particularly dendrodendritic synapses, respond to graded changes of membrane potential? Do such synapses differ in mechanism or in sensitivity from synapses in which transmitter release is triggered by action potentials? What are the mechanisms for nonsynaptic interactions?

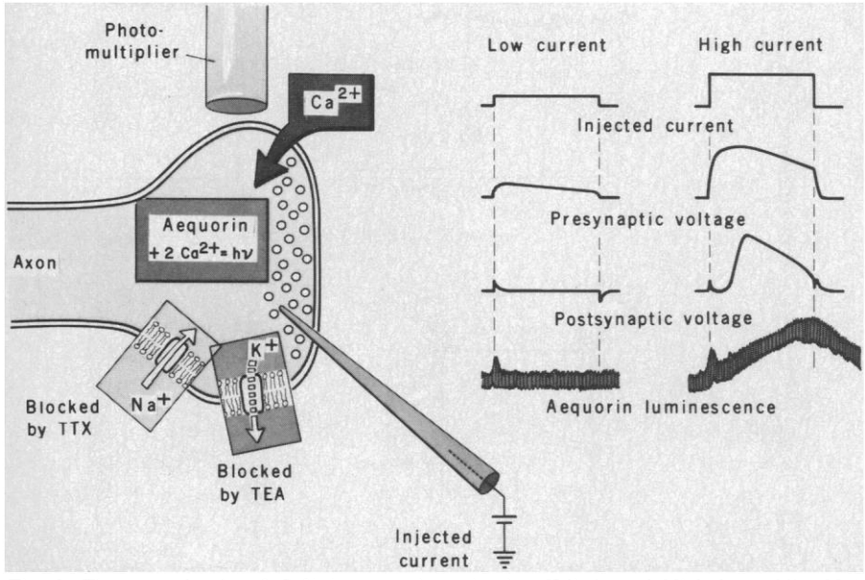

Fig. 3. The central role of Ca^{2+} in synaptic activation [Llinás and Nicholson (*23*)]. Na^+ conductance was blocked by treatment with tetrodotoxin (*TTX*) and K^+ conductance by intracellular injection of tetraethylammonium (*TEA*). Depolarization in such preparations can then be only via Ca^{2+}. The amplitude of current injected into the presynaptic terminal is correlated with the level of Ca^{2+} entry (indicated by intensity of aequorin fluorescence) and with the postsynaptic depolarization.

Dendrodendritic Synapses and Synaptic Sensitivity

The response of a dendrodendritic synapse to a change in the presynaptic membrane potential has not been directly measured because the small size of the structure makes impalement with an electrode difficult. Indirect approaches, with single-unit recording of mitral and periglomerular cells in the olfactory bulb, suggest that these cells interact with recurrent inhibition through dendrodendritic synapses (*19*), a hypothesis that is consistent with the electron micrograph data. Field potential analysis of deeper layers of the olfactory bulb indicates that mitral and granule cells interact through similar mechanisms (*20*).

In the olfactory bulb, the dendrites of the axonless, spikeless granule cells exhibit presynaptic specializations, and transmitter release results from graded changes of local potentials (*21*). Investigations of the retina have shown that the photoreceptor cell is constantly depolarized in the dark and that light input reduces this depolarization, causing a graded decrease of transmitter release at its base and a change in potential of the postsynaptic cell (*7*). Graded control of transmitter release can result from extremely small changes in the presynaptic membrane potential (*9*). It is now known that a large membrane potential change, such as is represented by an action potential, is not the necessary or even the primary cause of transmitter release viewed at the molecular level; release of transmitter from vesicles is not produced by the transmembrane electrical gradient as such, that is, a breakdown of membrane structure due to a high electrical field. Rather, it is the presynaptic membrane's permeability to calcium that determines transmitter release (*22, 23*), the amount of which is directly proportional to the calcium influx (*24*). The ability of a synapse to respond to small changes in the presynaptic membrane potential depends chiefly on the resultant change in

calcium influx (Fig. 3), although other factors, such as the amount of transmitter released per quantum and the density of receptors in the postsynaptic membrane, must also be considered.

Modulation of the permeability of the presynaptic membrane to calcium ions may control synaptic sensitivity, that is, the ratio of the change in the postsynaptic potential in response to a change in the presynaptic potential (*25*). The presynaptic membrane's permeability to calcium ions is a sigmoidal function of the membrane potential (*24*). Hence, a change in membrane potential produces maximal change in calcium influx if, at the initiation of the change, about half the calcium channels are open (*26*). The influx of calcium also depends on its extracellular concentration, an increase in which reduces the membrane potential necessary for optimal synaptic sensitivity (*24*). Thus, the presynaptic potential, the extracellular calcium concentration, and even the membrane composition can influence the sensitivity of a synapse and hence the functioning of an entire dendritic net.

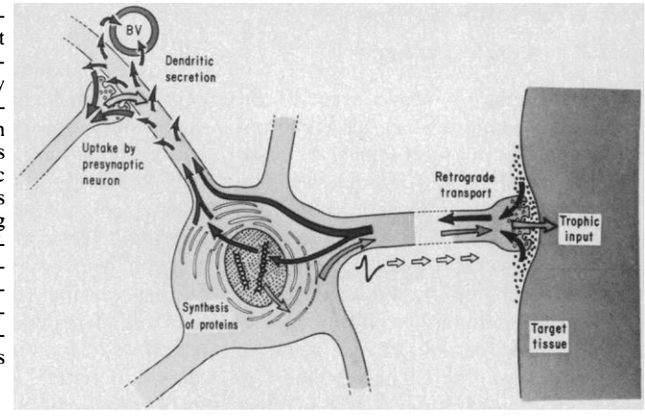

Fig. 4. Diagram illustrating neuron–target cell interaction. This interaction is mediated by anterograde and retrograde transport within axons and dendrites and by transsynaptic transfer of substances including those having trophic action. The effect of transported substances on gene expression and on the neuronal environment, including blood vessels (*BV*), is also indicated.

Electrotonic Coupling Through Gap Junctions

Electrotonic coupling, another mechanism of neuronal interaction, has been demonstrated to occur in the central nervous system. The frequency with which gap junctions are observed in electron microscope data correlates well with the electrophysiological evidence, indicating that they are a morphological substrate of this coupling (*27*). For example, gap junctions have been observed in about one-tenth of the neurons in the mesencephalic nucleus of the fifth nerve in the rat, between two-thirds of the neurons with high-threshold axons in the lateral vestibular nucleus of the rat, and between the dendrites of the inferior olive in the cat (*11, 27, 28*).

The full physiological significance of electrotonic coupling between neurons is still unknown (*29*). An obvious function is the synchronization of the firing of coupled neurons, as in the excitation of the pacemaker cells that control the electric organs of electric fish (*30*). The dynamic properties of cellular ensembles can be altered through such electrical coupling. For example, in the mollusk a population of cells manifests oscillatory behavior when electrically coupled (*31*). Further, electrotonic junctions are frequently observed to occur immediately adjacent to chemical synapses. How their mutual interaction may modify excitability of the neuronal circuits involved is not yet understood.

The biophysics of the molecular channels constituting electrotonic junctions, still little investigated, presents a challenging problem. There are frequently hundreds of channels in a single electrotonic junction or plaque as seen in freeze-fracture electron micrographs. The diameter of each channel has been deduced to be about 20 Å (*32*), which is but several times greater than that of the diameter of the hydrated, charge-carrying, inorganic ions. If the channel walls, which are considered to be proteinaceous, are negatively charged like most neuronal proteins, the interaction of the charged wall with the flow of charge carriers (chiefly inorganic ions) through the channel may strongly influence its electrical properties, that is, conductivity and capacitance. The possibility also exists of a transductive coupling, such as a chemomechanical or mechanochemical transduction between the ionic current and the protein subunits constituting the channel wall. Such a transductive process may gate or regulate the coupling between cells and hence may constitute a mechanism for information processing.

Cell Membrane and Field Effects

Electrical activity in a neuronal local circuit, although driven primarily by depolarizing or hyperpolarizing inputs from chemical synapses and electrotonic junctions, will be influenced significantly by the electrical characteristics of the cell membrane and by variations in the extracellular electric field and ionic environment. Dendritic membrane not bearing synaptic specialization is generally assumed to be passive in nature, responding only with graded electrotonic activity (*33*). That such membrane may actually be quite varied and specialized is suggested by numerous experiments, in particular those demonstrating dendritic spikes.

Dendritic membranes of some neuronal types such as hippocampal pyramidal cells (*34*), Purkinje cells of the cerebellum (*35*), neocortical pyramidal cells in the infant (*36*), and chromatolyzed motor neurons (*37*) are electroresponsive and capable of supporting spike action potentials. In the cerebellum and the hippocampus, the electroresponsive excitable membrane appears to be localized at the bifurcations in the dendritic tree, where voltages originating in more peripheral portions of the dendritic tree can be selectively amplified.

The possibility of electrotonic interaction between dendrites on the basis of their proximity or overlap has been proposed by Adey and co-workers (*2, 38*) as another mechanism for dendrodendritic processing of electrical signals. Such interaction could modulate the apparent electrical impedance of the dendrites and may underlie some of the rhythmic electrical events characteristic of areas such as the cerebral cortex, where there is large overlap between the dendritic trees of different neurons (*38*). Certain anatomic structures such as dendritic bundles (*39*) appear to be ideally suited for the interaction of dendrites through extracellular fields (*40*).

The property of independent and parallel processing is a crucial feature of local circuits. Although local circuit neuronal modules operate on an individual basis, they interact with adjacent modules and perhaps with more distant modules and neuronal circuits to form a "lateral" computation system. The output of these systems may not be the simple sum of the outputs of the components: there may be nonlinear interactions between local fields, such that the resultant potential may obey other than simple algebraic summation rules.

Interneuronal Molecular Transfer and Information Processing

The challenge to the concept of the polarized, spiking neuron has come not only from electrophysiological but also from chemical data. Although we may tend to think of the transactions between neurons and particularly within dendrodendritic networks largely in electrical terms, it is also important to consider the active bidirectional transneuronal molecular exchange of substances, some of which are not immediately related to bioelectric mechanisms. It is now clear that in neurons with both short and long axons there is a busy and fast intraneuronal molecular traffic between dendrites, somata, and axonal terminals such that information received at any one point may influence the entire neuron and its relations with other neurons in the same structural and functional domain (*41*) (Fig. 4). On this basis, it is not unreasonable to think of chemical as well as of electrical circuits, fields, and information processing. Connectivity in chemical "circuits" need not be defined by synaptic specializations in the same way as are electrical circuits; hence chemical circuits contribute considerable functional capability to the nervous system.

Chemical Signals in Neuronal Communication

Transneuronal molecular transport has now been demonstrated for a variety of substances, ranging from viruses to amino acids and sugars (*42, 43*). Using intracellular microiontophoretic injection of tritiated compounds, Kreutzberg and his collaborators (*44*) have shown rapid bidirectional dendritic (as well as axonal) transport and release of amino acids, nucleosides, glycoproteins, and acetylcholinesterase in cat spinal motor neurons and in neurons of the rabbit visual system. Such markers have shown a differential pattern of release and uptake; for example, glycine, or a metabolite of it, is apparently transferred rather specifically between dendrites, whereas released acetylcholinesterase is taken up preferentially in capillary basement membranes, and the released glycoproteins become part of the dendritic greater membrane. Adenosine, once released, is taken up by both neurons and glia. Highly directed transfer of compounds of low molecular weight has been shown between electrically coupled segments of crayfish lateral giant axons (*45*) and between Retzius cells of the leech (*46*). These transfers are thought to occur via gap junctions.

Most of the data reported to date concern the transfer of substances such as nucleosides and amino acids. Peptides and proteins may also be involved (*43, 47*). Relatively small peptides may, of course, contain structurally encoded information that could conceivably reflect a given neuron's history. There is, in fact, increasing evidence of the important role of peptides in the nervous system (*48*). In minute amounts, such peptides can initiate profound cellular effects because of built-in "amplification" mechanisms operating through adenylate cyclase. It is possible that yet unknown peptides released by dendrites in one local circuit may regulate other dendrodendritic nets and even projection circuits.

Functional Significance of Molecular Transfer

The neuronal molecular transfer system might be thought of as providing primarily for conservation of valuable metabolites that cannot be readily transported across the blood-brain barrier. We suggest, however, that chemical and metabolic coupling within dendrodendritic nets may be critical to information processing as well as to "trophic," homeostatic processes. The messages so exchanged may or may not consist of structural encoding in molecules, and rather simple structures such as transmitters or adenosine may also play an important role. For example, Black and his collaborators (*49*) have shown reciprocal regulatory relationships of transmitter enzymes between presynaptic cholinergic and postsynaptic adrenergic neurons in the superior cervical ganglion. The developmental increase in tyrosine hydroxylase activity in this system is dependent on intact preganglionic innervation. Presynaptic choline acetyltransferase levels are, in turn, dependent on intact postsynaptic adrenergic neurons. Acetylcholine is necessary but not sufficient for the anterograde tyrosine hydroxylase effect. Whatever the messengers, it is important to emphasize that transmitter molecules may have nonelectrogenic and nonreceptor-related postsynaptic functions (*50*); for example, they may even act at the level of gene expression. Obviously, a system that regulates the level of transmitter-synthesizing enzymes will alter the behavior of the neuron insofar as electrical information processing is concerned.

A rather different suggestion as to how a low-molecular-weight transneuronal signal may operate to alter information processing has been offered by Lux and Schubert (*51*). Their hypothesis is based on the fact that free extracellular adenosine, which has been shown to be released during neuronal activity, leads to an increased formation of cyclic adenosine monophosphate (AMP) in the target neuron (*52*). The effects of cyclic AMP are, in turn, believed to be mediated by regulation of the phosphorylation of key cellular proteins by protein kinases (*53*). This may alter membrane permeability, and thus neural excitation or inhibition (*54*).

Because of dendritic cable properties, electrotonic currents elicited by depolarizing or hyperpolarizing inputs to the dendritic periphery are attenuated as they travel to the soma. The degree of attenuation is determined by the dendritic length constant: the greater the length constant, the less the attenuation. The length constant itself is directly dependent on the apparent membrane resistance (*17*). If, as Lux and Schubert (*51*) have suggested, changes in membrane permeability induced by the adenosine-activated cyclic AMP system increase membrane resistance, then the length constant of the dendrite will similarly increase, and signal transmission will be facilitated. Thus, the released adenosine may not only reflect activity but also modulate the character and efficiency of dendritic input. One system may effectively bias a second system, potentiating either excitatory or inhibitory responses.

Transneuronal molecular exchange occurs, of course, both in long-axon and in short-axon neurons. There is, however, an important consideration of potentially great functional significance. Whereas in a typical long-axon motor neuron the same message is conveyed by axoplasmic transport to many terminals of the same axon, in dendrodendritic networks one dendrite may send and receive different signals at different microregions so that the functional response (for example, phosphorylation of membrane protein) may also be highly localized.

The molecular transfer system that we have been describing does not provide only metabolic support for the electrical information processing system; rather, the evidence indicates that active bidirectional molecular transfer has a role parallel to that of the conduction and transmission of electrical impulses in the operation of the nervous system. There may be cases, as Bloom (*55*) has suggested, in

which it is not the production of a postsynaptic potential but, rather, the metabolic changes that are produced that are the more important result of the synaptic event. Furthermore, chemical gradients produced by synaptically released material may modulate the activity of whole populations of neurons. We suggest that it is from the interweaving of the electrical and chemical systems that the neuronal information-processing system arises. Future neuroscience research will have to strive to deal with the multiple, simultaneous, and interactive processes of these systems, which seem likely to be involved in higher integrative brain function.

Neural Substrate of Higher Brain Function

Earlier in this article, we have provided evidence concerning the properties of those portions of the central nervous system that function primarily by electrotonic interaction rather than by spike-wave excitation and in which dendrodendritic and reciprocal synapses, as well as gap junctions, characterize the neuronal circuitry which we call local circuits, following the notation of Rakic (*5*). Here, we turn from reasoning on the basis of hard evidence to inferential reasoning and speculation, suggesting that the immensely complex aggregates of local circuits may indeed prove to be neural substrates of higher brain function.

The leap from neuronal local circuitry to higher brain function, although a substantial one, is not without precedent: Cajal (*56*), for example, held similar views throughout his lifetime. Local circuits do not at present offer a direct explanation of learning, memory, or other cognitive processes, but they have many of the requisite properties such as speed of processing, sensitivity, a high density of computational structures, and potential for complex interactions that would seem to be required by systems subserving higher brain function.

By the very nature of the tight interweaving of local circuits and the fact that the intraneuronal and interneuronal distances over which they operate are very short (of the order of micrometers or less), their processing of input data can be extremely rapid. Their use of graded potentials provides them with a discriminatory capability that cannot be matched by an all-or-nothing process. Ability to operate effectively with low-level graded potentials requires high sensitivity of the systems; the available evidence indicates that local circuits have this attribute as well. Synapses of through-projection neurons are activated by spike potentials having a magnitude of 50 to 100 mv. Llinás (*24*) points out that the sensitivity of a synapse depends mainly on the mechanisms that open channels for calcium ions, which in turn play a critical role in the fusion of transmitter-containing vesicles with the presynaptic membrane. Under appropriate conditions, the Ca^{2+}-stimulated chain of membrane-related events may be triggered by a field of but a few tenths of a millivolt.

Comparable sensitivities are found in sensory transduction processes. Thus, one quantum of light and one or but a few molecules of olfactant or tastant suffice, after processing by the relevant local circuits, to produce action potentials in the through-projection neuronal systems that convey sensory information to the appropriate stations in the central nervous system. Linkage between the receptor neurons and the spike-mediated sensory input to the brain is through a complex local circuit network, which, as a virtually spikeless microcosm, operates by electrotonic coupling rather than by relatively low sensitivity synapses characteristic of projection neurons. If a substantial fraction of the synapses of local circuit neurons have high sensitivity, the system would be capable of functioning at signal levels one or two orders of magnitude lower than those of spike potentials, thus providing a neuronal net with very different properties from those dealt with in conventional neurophysiology.

Ultrastructural data concerning reciprocal, serial, or other synaptic complexes suggest the existence of many small computational units or modules providing for highly localized, as well as rapid, parallel processing of input. In contrast, the tight, elaborate weave of fine neuronal processes of the central neuropil at various sites constitutes a logical mechanism for the integration of bioelectrical and biochemical activity of individual modules by synaptic or ephaptic connectivity within vast networks. The enormous complexity of the electrical and chemical interactions possible in such systems suggests that operational and output characteristics may not be predictable on the basis of unit properties alone; certain emergent properties related to field interaction may also be important. Even if all such local circuit systems, including those of the neocortex, are considered to be individual analytical data processing devices without integrative capability, their aggregate properties resulting from their interactions may provide integration. In some instances, as in the retina and olfactory bulb, where the nature of the interaction between local circuits is, to some degree, understood, substantial integration is evident. The cerebral cortex is virtually terra incognito. What we know about the richness and subtlety of human cognitive processes suggests the importance of the interaction and integration of many levels of nervous system function.

Of course, complexity as such need not necessarily result in "plasticity" or modifiability, which is yet another attribute of higher brain function. The retina, for example, rich in local circuits, functions as a highly sensitive and reliable signal detection and transduction device. That it "learns" in a behavioral sense is, at best, doubtful. Similarly, the capacity for learning in the spinal cord, medial geniculate, and ventrobasal thalamus is questionable, although all these brain regions contain local circuits with potential for chemical and electrical modifiability. It should be noted that, from a developmental point of view, the small cells which give rise to a large fraction of the dendritic processes involved in local circuits are laid down after the more rigidly genetically determined, long-axon projection neurons; it has been argued (*14*) that a greater degree of modifiability thereby accrues to local circuit neurons. Neuronal local circuits are regionally differentiated with respect to such plastic properties. The retina and the olfactory bulb are specialized for the reliable processing of sensory input; the cerebral cortex may be specialized for the modifiability required for learning and other higher brain functions.

Techniques and theories different from those commonly used in neuroscience today may be required to analyze effectively the function both of components of local circuits, that is, individual functional modules, and the ensemble or systems aspects. Some of these new approaches, such as the in-depth mathematical modeling of local circuits for calculation of the extraneuronal as well as the intraneuronal aspects of electrotonic cable theory and analysis of current source density and ionic flux, can be specified at the present time (*57*). Other aspects will suggest themselves as investigators develop new techniques and new insights as to how this important part of the nervous system may operate to subserve higher brain function. The challenge is worthy of the active and creative participation of investigators from many disciplines within the neuroscience community.

Summary

In contrast to well-studied through-projection neurons that propagate information from one region to another in the central nervous system, short-axon or axonless neurons form local circuits, transmitting signals through synapses and electrical junctions between their dendrites. Interaction in this dendritic network proceeds without spike action potentials. Interaction is mediated by graded electrotonic changes of potential and is transmitted through high sensitivity (submillivolt threshold) synapses rather than by the lower sensitivity (20- to 100-mv threshold) synapses typical of projection neurons. A crucial feature of local circuits is their high degree of interaction both through specialized junctional structures and through the extracellular fields generated by local and more distant brain regions.

The anatomical evidence for the nature and distribution of neuronal local circuits in the nervous system is surveyed. Bioelectric mechanisms are discussed in relation to the special properties of local circuits, including dendrodendritic synapses, synaptic sensitivity, electrotonic coupling, and field effects. Intraneuronal and interneuronal transport of various types of substances suggests that the biochemical and the bioelectrical parameters are functionally interwoven. Through such interactions neuronal local circuits, with their distinctive properties, may play an essential role in higher brain function.

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