The Generalized Vertebrate Neuron

Conventional terminology of neuron structure lags behind current functional-anatomical concepts.

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A recent investigation of the structure of an invertebrate receptor neuron (*1*) has emphasized the impression that morphologic concepts of neuron structure, as expressed in current treatises of biology, physiology, and anatomy, have failed to keep pace with recent advances in physiology and cytology. A few neurologists, and notably Bishop (*2*) and Bullock (*3*), have attempted to reexamine the arbitrary postulates and confused terminology which characterize certain descriptions of the "typical" or generalized neuron.

It is probable that the key to the confusion of current terminology is a continuing emphasis on the external morphology of neurons, as revealed especially by the elective staining method of Golgi. This method in the hands of Ramón y Cajal and others provided the first breakthrough in the understanding of the diverse configurations of nerve cells and of their interrelations, and it is noteworthy that the contradictions and perplexities at the turn of the century among eminent neurohistologists received a more objective analysis by Ramón y Cajal in his famous textbook (*4*) than is to be found today in many treatises dealing with the subject of the nerve cell.

Perhaps the most damaging dogma, refuted by well-known facts for over half a century, is the persistent definition of dendrites as receptor portions of a neuron which *arise from the nucleated cell body or perikaryon.* This point of view is undoubtedly more prevalent today among morphologists than it was 50 years ago, because of the continued use of the motoneuron as the example par excellence of a "typical" neuron. This misleading example has led to the second serious dogma—namely, that the axon is a nerve-cell process which arises from the cell body, or (and the exception is important) from a dendrite close to the cell body.

It is of some interest that, in the face of the glaring exceptions to the "typical neuron" offered by the primary sensory neurons of every sensory system, the solution for many morphologists has been adaptation of the nomenclature of the sensory neuron to that of the "typical" synaptically excited neuron, rather than a questioning of the basic premises upon which the descriptive definitions of parts of the "typical" neuron are based.

Several passages from some of the best available textbooks in English illustrate the contradictions which arise when the peripheral portion of the myelinated process of a spinal ganglion cell (which has no synaptically activated dendrites associated with the cell body) is dealt with in terms of the "typical" motoneuron image.

1) A major American neuroanatomy textbook gives an inaccurate as well as a functionally inadequate definition of dendrites, as follows: "Dendrites are direct expansions of the cell body and contain Nissl bodies and mitochondria."

2) An excellent British histological textbook, in two statements, first assumes that only dendrites can convey nerve impulses toward the cell body (as in motoneurons) and then attempts to explain away the glaring exception (I plead guilty to the same misdemeanor on previous occasions). The statements are as follows: "The neuron shows a dynamic polarity with respect to its processes-nerve impulses being directed towards the cell body by the dendrites and away from the cell body by the axon." Then, "It should be noted that, although the peripheral process of a sensory ganglion cell is *functionally* a dendrite, in its anatomical features it is apparently identical with the axonal process of a motor nerve cell."

3) An outstanding American histology textbook also resigns itself to acceptance of a basic contradiction between functional and morphological concepts, in relation to sensory ganglion cells: "From the globular or pear-shaped body a single process arises which divides like the letter T into a peripheral or dendritic branch (structurally an axon) of a peripheral nerve, and into a central or axonic branch. . . . "

4) Finally, a distinguished neuroanatomy textbook, speaking of sensory ganglion cells, refuses to accept the contradiction of terms as they are applied by the sources just quoted and unceremoniously disposes of the problem by defining the dendrites of sensory neurons out of existence: "These cells . . . are devoid of dendrites." An excellent histology textbook concurs in this view and drives home the rule in a clarifying sentence: "the dendron may or may not be present in a neuron. Dendrons or dendrites of a neuron are processes which invariably stay within the environs of the cell body."

This approach automatically excludes the peripheral arborizations, or transducing portions, of sensory neurons from the definition of dendrites, presumably because these structures are excited by environmental stimuli (mechanical, thermal, chemical, photic) rather than by synpatic activity.

Nature of Dendrites

The stretch receptor neuron of lobsters and crayfish, described by Alexandrowicz (*5*), helps to clarify the problem by illustrating that a neuron analogous in function to a spinal sensory ganglion cell of vertebrates can refute all of the foregoing statements, which are based on the vertebrate sensory ganglion cell. It therefore throws further doubt upon the generalizing definitions that are limited to vertebrate neurons. The stretch receptor

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neuron of crayfish possesses a multipolar cell body close to the receptor organ, with afferent processes not only having the attribute of transducer arborizations (sensitive to stretch) but also bearing synapses (*1, 6*). It is evident, therefore, that these peripheral arborizations of a sensory neuron resemble both the terminal (transducing) arborizations of vertebrate sensory neurons and the "dendrites" of vertebrate motoneurons, which they resemble in configuration. This fact seems to me to support conclusively Bishop's suggestion that the term *dendrite* be applied to the receptive pole of neurons, whether the neuron is excited by virtue of synaptic or transducer activity. The dendrites of stretch receptor neurons of invertebrates, by possessing both transducer and synaptic structures, illustrate that the key function is more general than transduction or synaptic excitation, and that it can be categorized as "response (spike potential) generation."

Law of Dynamic Polarization

It is of considerable interest that the basis for a rational nomenclature of nerve-cell structure, applicable to all neurons, exists in Ramón y Cajal's final version of his "law of dynamic polarization" (*4*), which he says was enunciated by him as early as 1897. In this version he avoided the pitfall of assuming the somatipetal conduction of dendrites by stating the "law" in a form that may be freely translated as follows: "Dendrites and cell body conduct axipetally, that is, toward the axis cylinder. Inversely, the axon conducts somatofugally and dendrifugally, that is, from its origin to its terminal arborizations."

Although this version is superior to the usually quoted earlier form of the "law," it falls short of Ramón y Cajal's goal of a complete generalization by including the cell body as a focal point. Again, it is the sensory neuron which refutes the generality of this "law" and supplies the clue to a more general statement. First, it is doubtful that the cell body of a spinal ganglion cell of vertebrates conducts axipetally; rather, it is invaded from the axon by the spike potential (*7*). Second, the distal process of this neuron is in function (spike conduction) and structure an axon, yet it conducts toward the soma rather than somatofugally.

Irrelevance of Position of Cell Body

It seems probable that Ramón y Cajal would have arrived at a complete generalization except for a failure to recognize that the perikaryon is primarily the trophic center of the nerve cell and that *its position is therefore irrelevant as far as the major "neural" or electrochemical functions of the neuron are concerned.* The statement that the position of the perikaryon is irrelevant seems contradictory, because of the presence of synaptic structures on the cell bodies of many neurons, until it is recognized that the membrane of the cell body is the part which is involved in synaptic transmission, and that the chromidial neuroplasm or perikaryon is a cytoplasmic zone related primarily to the "trophic aspect of nerve cell function" (*8*). The stretch receptor neurons of crayfish illustrate strikingly that the chromidial neuroplasm is segregated in such a way as to permit continuity of the "filamentous neuroplasm" from dendrites to axon. In spinal ganglion cells of vertebrates this type of segregation reaches an extreme with the separation of "chromidial neuroplasm" from the mechanisms of production and conduction of the nerve impulse.

Redefinition of Structure in Terms of Function

In Ramón y Cajal's definition of neuron structure in general functional terms (*4*) we find a point of view more modern than some expressed in current treatises, especially in his recognition of the common role of receptor processes in sensory neurons and "dendrites" in synaptically excited neurons. He states that all nerve cells have a receptive apparatus—the cell body and dendrites; a transmission apparatus—the axon; and distribution or emissive apparatus—the telodendria.

This statement, as indicated above, can only become generally applicable if dendrites are assumed to be equivalent to receptor terminals, as required by the considerations presented by Bishop (*2*), and if one then defines the receptive apparatus as consisting of dendrites, including receptor terminals, and surface membranes of the cell body and axon hillock of synaptically excited neurons.

In these terms, the internal portion of the cell body (chromidial neuroplasm), which is probably associated with synthesizing functions of the cell rather than with membrane functions, can logically be defined as a separate functional component of the cell, located in a variety of positions in various nerve cells. For example, in sensory epithelia of vertebrates and invertebrates, the chromidial neuroplasm or perikaryon may be located in close relation to receptor terminals. In stretch receptor neurons of crayfish the perikaryon is found within the dendritic membrane, as in many vertebrate "multipolar" neurons. In bipolar sensory ganglion cells of vertebrates the perikaryon is found within the axon and may be covered by a myelin-like sheath.

Finally, an especially interesting situation is found in the so-called "unipolar" ganglion cells, in which the perikaryon is merely attached to the rest of the neuron along the course of the axon and clearly may be regarded as an appendage of the "neural apparatus."

If one examines Ramón y Cajal's generalized neuron further, one finds, in addition to the confusing effect of including the perikaryon in the "neural aspect" of neuron structure, that the crucial function of impulse or "spike" origin is not included, and it could not have been included at that time. Since recent neurophysiological investigations (*9*) have placed the "spike" origin at or near the axon origin (the initial unmyelinated segment or initial node of Ranvier), it becomes possible to relate basic functional aspects of neuron function to general aspects of neuron structure, as follows: response (spike) generation, to the "dendritic zone" (transducer and synaptic surfaces); impulse origin, at or near the axon origin (the initial axon segment or axon "neck"); impulse conduction, to the axon; and synaptic transmission or neurosecretory emission, to the axon telodendria.

The departures from traditional interpretations required for this point of view are as follows.

1) Recognition of the primarily trophic role of the perikaryon in the neuron, and therefore of the irrelevance of its position with respect to the "dynamic polarization" of the neuron. Its position is related to the outgrowth and metabolic maintenance of processes rather than to the conducting polarization of the neuron.

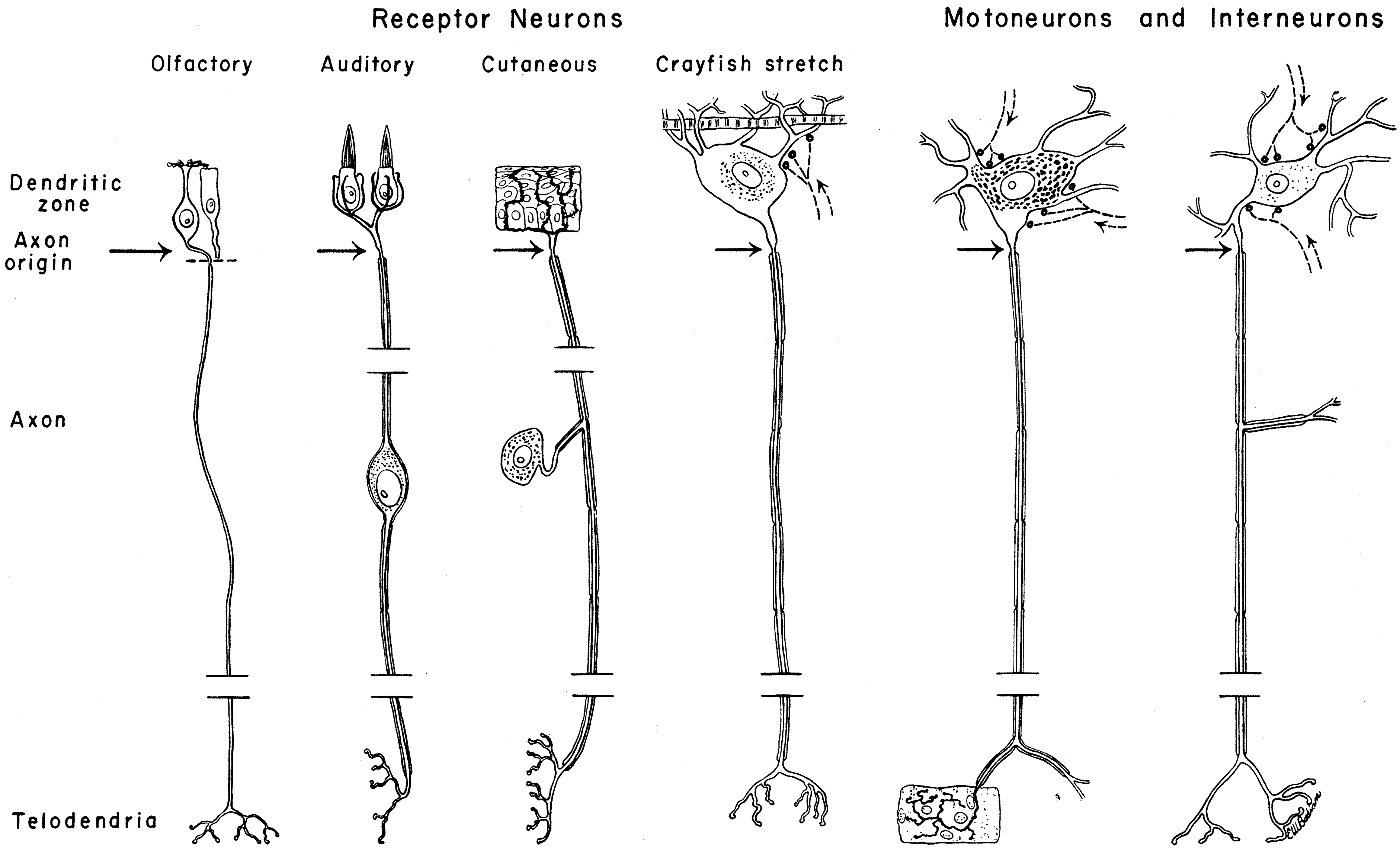

Fig. 1. Diagram of a variety of receptor and effector neurons, arranged to illustrate the idea that impulse origin, rather than cell-body position, is the most reasonable focal point for the analysis of neuron structure in functional terms. Thus, the impulse conductor or axon may arise from any response generator structure, whether transducing receptor terminals or synapse-bearing surfaces (dendrites, cell body surface, or axon hillock). The interior of the cell body (chromidial neuroplasm, or perikaryon) is conceived of as related primarily to the outgrowth of axon and dendrites and to metabolic functions other than membrane activity. Thus, the position of the perikaryon in the neuron is not critical with respect to the "neural aspects" of neuron function—namely, response generation, conduction, and synaptic transmission. Except for the stretch receptor neuron of the crayfish, the neurons shown are those of vertebrates.

2) Recognition of the fundamental similarity of transducer and synaptic activity. Dendrites are then readily defined as neuron processes with response generator function.

3) Recognition that the site of impulse origin is the pivotal position in the neuron, irrespective of cell-body location. This site may not necessarily be a fixed point in a particular neuron but conceivably could shift from initial segment to first node of Ranvier in a cell from time to time, for example.

4) Recognition that all synapse-bearing surfaces (dendrites, cell body surface, and axon) are related to response generation rather than to the synthesizing functions of the chromidial neuroplasm (perikaryon). Thus, in functional terms, the axon may be said to arise from any response generator structure, such as receptor terminal, dendrite, cell body, or axon hillock, since its role is to conduct signals away from the response generating region. *According to this view, axons do not arise from "cell bodies" which are separated from the response generating region*, as in bipolar neurons of the VIIIth cranial nerve, or in unipolar neurons of the general sensory ganglia. These cell bodies may be considered imbedded in, or attached to, the axon somewhere along its course. Indeed, in the unipolar neurons of general sensory ganglia, and in neurons of the mesencephalic nucleus of the trigeminal nerve within the brainstem, the "cell body" may be considered to be attached to the axon much closer to the telodendria than to the "dendritic zone"—that is, distally in the receptor organ. These cells, incidentally, resemble the predominant type of invertebrate neuron—namely, the unipolar ganglionic neuron.

Finally, it should be emphasized that the great variety of neuron differentiation in invertebrate phyla, as well as in vertebrates, has inevitably produced neurons which do not fall readily into any simple nomenclatural system, such as that proposed (*3*). Neurosecretory neurons of the vertebrate hypothalamus, for example, do not possess synaptic telodendria, as the term is ordinarily understood (*8*). Certain vertebrate axons possess axo-axonic synapses along the course of the myelinated axon (*7*), and so on. Nevertheless, it seems worth while to reexamine our conventional anatomical terminology periodically to discover whether it continues to serve a useful purpose or stands in the way of essential integration with the concepts of related disciplines. Previous reviews (*3, 8*), especially Bullock's (*3*), have emphasized that the basic role of the neuron is that of its relation to other cells, and that perhaps no single functional or anatomical feature will prove to be completely general among all neurons. Thus, rigid definitions of neuron parts must inevitably be contradicted by exceptional cases.

Figure 1 summarizes schematically a generalized conception of vertebrate neuron structure, in which impulse origin rather than cell-body location is taken as the focal point. It illustrates the following definitions of major neuronal parts.

Dendritic zone: the receptor membrane of a neuron, either consisting of a set of tapering cytoplasmic extensions (dendrites) which receive synaptic endings of other neurons or differentiated to convert environmental stimuli into local-response-generating activity. Mitochondrial concentrations may be present.

Axon: a single, often branched and usually elongated, cytoplasmic extension morphologically and perhaps uniquely differentiated to conduct nervous impulses away from the dendritic zone. It is characteristically uniform in caliber and ensheathed by neuroglial or neurilemma cells. Sheath differentiation and axon caliber are related to speed of conduction.

Perikaryon: the "cell body" or nucleated cytoplasmic mass, which is usually characterized by the presence of chromidial substance. This portion of the neuron is the focal point of embryonic outgrowth of dendrites and axon, of axon regeneration, and perhaps of enzymatic synthesis in the differentiated neuron. It may be located in the dendritic zone or within the axon, or it may be attached to the axon.

Axon telodendria: the usually branched and variously differentiated terminals of axons which show membrane and cytoplasmic differentiation related to synaptic transmission or neurosecretory activity. Mitochondrial concentrations, "synaptic vesicles," or secretory granules are commonly present in bulblike terminals. Like the dendritic zone, the telodendria do not transmit all-or-none conducted potentials. They transmit electrical or chemical signals capable of producing generator potentials in the dendritic zone of other neurons and in muscle, and stimulatory effects in innervated glandular cells or in distant cells via the humoral route (neurohormones).

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