CHAPTER 15

Neoreticularism and neuronal polarization

Michael V.L. Bennett*

Department of Neuroscience, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10804, USA

Abstract: Santiago Ramón y Cajal made immense contributions to neuroscience, and the era in which his work is cited is likely to be longer than that for any other present or future neuroscientist. This commentary notes that there is qualification to the doctrine that neurons are distinct entities rather than reticular. Namely, gap junctions provide a private pathway between coupled cells, that, at an ultramicroscopic scale, can be considered cytoplasmic continuity. Cytoplasmic continuity permits, but does not require, conduction in either direction across an electrical synapse. Furthermore, sites of impulse initiation can differ in the same or different cells; there is no universal direction of impulse propagation and it may differ in the same cell under different conditions; thus, there are exceptions to the law of “dynamic polarization”. Cajal leaves ample evidence in his writings that he would have no difficulty in accepting these very minor modifications to the vast body of his contributions.

Introduction

Santiago Ramón y Cajal, or more commonly just Cajal, can arguably be considered the Watson and Crick of neuroscience. He was the real founder of the modern study of nervous systems. His descriptions were generally accurate, and he left an immense corpus of knowledge that is unchanging. His illustrations are esthetically pleasing, and they are still often used in introductions to symposia and seminars. I doubt that the work of any physiologist has had or will have as long a scientific “life” as the contributions of Cajal. In part, this longevity is due to the superb maps of the nervous system that he left us, and the geography that he discovered has changed but little. His physiological insights were phenomenal, and he clearly thought function when he looked at structure. However, several of his functional and structural concepts require updating. I will address two of them, the cellular basis of the nervous system as reviewed in his seminal work ¿Neuronismo o Reticularismo? and the doctrine of dynamic polarization.

Neuronismo

The doctrine that neurons were distinct cells had as its opponent principle, reticularism, which held that neurons were syncytial. Cajal obtained a vast amount of data in support of “neuronism”, and it is one of the nice ironies of science that one of his most important tools was the Golgi method invented by the foremost proponent of reticularism. Nevertheless, until the invention of the electron microscope, it would have been possible to argue that many of Cajal’s synapses and other contacts between neurons might in fact involve cytoplasmic continuity. Some invertebrate neurons, such as the squid giant axons and some annelid septate axons are syncytial and are formed by fusion of distinct cells (as opposed to being multinucleate and formed by nuclear division within a single cell). Some vertebrate neurons seem to show cytoplasmic continuity, for example, neurons controlling the electric organ in Mormyrid fishes (Fig. 1A). These neurons have contacts between thick dendrites that can appear to provide continuity, but electron microscopy demonstrates membranes between them, and of course gap junctions (Fig. 1B).

Neuronism requires transmission between cells, which Cajal asserted was by “contact or contiguity, not
Anastomoses between thick dendrites? Dendrodendritic connection between medullary electromotor relay neurons from a Mormyrid fish. The apparent cytoplasmic continuity seen in the (Cajal's) silver stained preparation (left panel) is shown by electron microscopy to be interrupted by a membrane containing gap junctions (right panel, arrows). A, axon terminals on the neurons. BV, blood vessel. From Bennett et al. (1967).

continuity. Electron microscopy establishes without doubt that chemically transmitting synapses involve a synaptic cleft and that there is no cytoplasmic continuity. Here of course we depend on our evidence that the cell membrane is a barrier that delimits the cytoplasm, a view not quite universally held. Moreover, there are proteins that extend into the synaptic gap and link the adjoining cells; thus, where one cell ends and the other begins can now be answered, no, requires an answer, at the molecular level.

The electrically transmitting synapses formed by gap junctions (Fig. 2A) provide a significant qualification to neuronism, since they provide cytoplasmic continuity for small molecules of the order of 1 kDa in molecular mass. (This is a rather soft number and depends on shape and charge as well as type of gap junction.) The continuity at the gap junction is not seen in thin sections with electron microscopy, but is inferred from electrical properties and intercellular movement of small molecules to which the non-junctional membranes are impermeable, as typified by dye coupling. The tracers that pass between cells do not enter when applied externally, and thus the passage between cells can be characterized as a private pathway, or, for small molecules, a region of cytoplasmic continuity (Fig. 2B). Some might bridle at calling a pathway with a diameter of 1.2 nm as cytoplasmic continuity. Still, frank cytoplasmic bridges may be impermeable to nuclei or mitochondria, and where does one draw the line? A common characterization of electrically coupled cells is that they form an electrical or functional syn-cytium, a reasonable characterization that preserves the basic tenet of neuronism that neurons are independent. The molecular subunits of gap junctions, the connexins, have been cloned and localized to gap junctions at light and electron microscopic levels (Fig. 2C, D).
Fig. 2. Microscopy of electrical synapses. (A) An axodendritic synapse, axon to the top. A large gap junction, enlarged in the inset, is on the right of the image (wide arrows). Small active zones with presynaptic vesicles are on the left (narrow arrows). (B) A diagram of a gap junction showing the aqueous channel between cells (by D.L.D. Caspar and D.A. Goodenough). (C) An anti-connexin 43 antibody (with fluoresceinated secondary antibody) labels the intercalated disc of heart. (D) The same antibody with an immunogold secondary antibody shows localization to a gap junction at much higher resolution. (From Bennett et al., 1967)

Although the intercellular channels of gap junctions are not resolved by current techniques of preparation of tissue for thin sectioning, structures crossing the eponymous gap are seen by negative staining with extracellular markers. These stains often also label the central part of the gap junction molecule where the channel is presumed to be. This labeling occurs in cells that have not been deliberately permeabilized, suggesting that the membrane integrity is not as perfect as one might suppose from the lack of cytoplasmic staining. Freeze fracture electron microscopy of gap junctions often reveals a central pit in the intramembrane particles, which are generally in the P face in vertebrate junctions. A corresponding projection may be seen in the E face pits, although this structure is very sensitive to warming before shadowing, perhaps because it is ice. The most convincing images of gap junction channels are provided in reconstructed images from isolated gap junctions in which the channels can assume a two dimensional crystalline array (Unger et al., 1999).

Gap junctions are generally electrically linear for small transjunctional voltages, consistent with an aqueous pathway. This property facilitated the view of gap junctions as providing cytoplasmic continuity. Recent studies demonstrate that most gap junctions in fact are not electrically linear for larger voltages, and show gating behavior comparable to that of the classical voltage dependent channels of excitable membrane. (Here classical is relatively recent compared to Cajal’s contributions. Hodgkin and Huxley propounded their
equations in 1952, work still occasionally referenced, and single channel gating was demonstrated by Neher and Sakmann and colleagues in the late 1970's). Gap junctions may also show gating in response to various drugs and ions, properties in common with the channels of (electrically) excitable membrane. In addition to gating in response to various stimuli, gap junctions can exhibit selective permeability on the basis of charge as well as size (Verselis and Veenstra, 2000; Niessen et al., 2000).

Although electron microscopy has greatly refined our view of synapses, there remain important aspects that are not yet resolvable. In the early days of describing electrical transmission and identifying the morphological substrate as gap junctions, it became apparent that axosomatic and axodendritic synapses with gap junctions were for the most part "mixed", i.e., there were both gap junctions and apparent chemical synapses that had presynaptic active zones with associated vesicles, widening of the synaptic gap, and increased density of the postsynaptic membrane (Fig. 2A, narrow arrows; cf. Bennett, 1997; George Pappas, Yasuko Nakajima, and later Konrad Akert and Clara Sandri were my anatomical collaborators in characterizing electrical synapses.) Yet these synapses transmitted entirely electrically; no chemical component could be identified in the postsynaptic potential, and they were more accurately described as "morphologically mixed". The missing chemical component in these synapses was not identified; it could have been in the synthesis of transmitter, in the release process or in the postsynaptic receptors. Since horseradish peroxidase was taken up by the presynaptic elements in several of these systems (Tokunaga et al., 1980; Bennett and Sandri, 1989), we suggested that the synapses were there to provide by membrane recycling uptake of molecules from the intercellular cleft for retrograde transport to the cell soma. Recently, it has been shown that at one site of morphologically mixed but purely electrical transmission, the postsynaptic cells lack glutamate receptors (Curti et al., 1999). Another and perhaps more damaging blow to prospects for morphological evaluation of synaptic efficacy is the presence of presynaptically silent synapses (Malgaroli et al., 1995; Malgaroli, 1999). These synapses look to be morphologically unexceptional chemical synapses, but apparently do not recycle membrane when their nerve fibers are activated. Constantino Sotelo also looked at many synapses with anatomical correlates of both chemical and electrical transmission. In one paper which we coauthored with Henri Korn (Korn et al., 1977), the electrophysiological evidence was consistent with dual electrical and chemical transmission, but I persuaded him to leave the "morphologically" modifying the description of the synapses as mixed.

From a personal, neotcreticulatist perspective, I could at this point in the development of our knowledge feel somewhat superior to the devotee of chemical transmission, who could not rely on microscopy to identify a functional chemical synapse. This complacency was recently shattered by observations that gap junctions formed of connexins labeled with green fluorescent protein have no functional channels if they contain fewer than several hundred channels, and this measurement is made with single channel resolution (Bukauskas et al., 2000). As the number of associated particles in a junctional plaque increases, the fraction of functional channels increases, but never becomes greater than about 10–15%. An earlier report suggested that only about 1% of gap junction channels were functional at the club endings on the Mauthner cell (Tuttle et al., 1986). Although these synapses can transmit both chemically and electrically, the postsynaptic potentials often have no chemical component until potentiated (Lin and Faber, 1988). However, the chemical component can be increased by potentiation or by increasing the size of the afferent volley, apparently as a result of "antidromic" electrotonic spread of the electrical postsynaptic potential into the presynaptic fibers (Faber et al., 1991).

How would Cajal react to the existence of gap junctions? He wrote (Purkiss' and Fox's translation) "...[I]n accepting the most exaggerated synaptical hypotheses ... everything that the physiologists, during 50 years of dogged and fruitful investigation, have taught us concerning localizations in the nervous centers is left without an explanation." But on the next page "I am neither exclusive nor dogmatic; I am proud of retaining a mental flexibility which is not afraid of corrections. Neuronal discontinuity... could sustain some exceptions."

Cajal was not aware of the synchrony that characterizes the activity of a number of groups of neurons. If so, he might have been more careful in asserting "localizations in the nervous centers". In a number of cases of synchronous firing, reticularism mediated by electrical continuity at gap junctions explains the synchronization (Bennett, 2000a,b). To be sure, mutual excitation can be mediated by chemical as well as by electrical transmission.

I have little doubt that Cajal, and also Sherrington, would have accepted axosomatic, axodendritic, and even
dendrodendritic sites of electrical transmission as true synapses, whether they also transmitted chemically (and whether they transmitted in one or both directions, see next section). It is because of more recent history that many neuroscientists have had difficulty accepting that transmission might be of this form; indeed to this day, some do not consider gap junction based communication between neurons as synaptic. One source of this attitude is Occam’s razor, which has nicked a number of prominent scientists when they assumed that the simplest answer must be the right one, ignoring that comparative physiology has demonstrated repeatedly that evolution finds multiple solutions to a given functional need (Bennett, 1985). Thus, when the controversy between electrical and chemical transmission was being resolved in most people’s minds on the side of chemical transmission, it reduced their cognitive dissonance to define the newly discovered electrically transmitting contacts between neurons as non-synaptic. An outstanding exception was Paul Fatt, who pointed out in Physiological Reviews (1954) that there were synapses where electrical transmission was likely to be present. His prognosis, from a pioneer in demonstrating that inhibition was chemically mediated and who worked at the fountainhead of modern views of quantal transmission, was put forth when chemical transmission was clearly moving ahead of electrical transmission in the race for acceptance. Fatt hypothesized that a large presynaptic structure was required to excite a large postsynaptic structure, and he pointed to the giant motor synapse of the crayfish as satisfying that criterion. His suggestion bore fruit when Furshpan and Potter (1959) demonstrated that transmission at this site is electrical (and as an added bonus, rectifying).

Fatt’s argument was not valid. Although he may have been inspired by the vertebrate neuromuscular synapse at which a small diameter presynaptic terminal excites a large postsynaptic cell, most chemical synapses do not simply relay an impulse from pre- to postsynaptic cell, and those that do have a large presynaptic terminal, e.g., the calyces of Held. The chick ciliary ganglion is another example where the presynaptic terminal is large, but in this case transmission is chemical in early development and becomes increasingly electrical in later life (Martin and Pilar, 1963). Whether the machinery of chemical transmission is lost is unclear; the terminal and cell become enveloped in myelin and inaccessible for microelectrode investigation; rapid transmission through the ganglion indicates that postsynaptic impulses are generated by electrical transmission, but do not exclude the continued presence of a chemical component. To labor the point: the actual interface at neuromuscular junctions is quite extensive, as the presynaptic fiber runs some distance along the fiber or branches profusely. Furthermore, the conductance of membranes is well correlated not with their areas but with the number of channels, and the conductance per unit area of activated postsynaptic membrane at chemical synapses is comparable to that of gap junctions and of nodal membrane of myelinated fibers, and the driving force of the presynaptic action potential is somewhat greater than that of the ligand gated channels; thus, a presynaptic terminal transmitting electrically can provide as much power as one transmitting electrically. To put a more modern face on it, the conductances of gap junction channels and of ligand gated channels can be comparable. Amplification from pre- to postsynaptic cell can be provided by ligand gated channels or by presynaptic action potentials.

Another reason for rejecting gap junctions as synapses arises from the view that synapses must exhibit unidirectional action, an attitude probably dating back to the time of Bell and Magendie and supported by Cajal’s evidence for dynamic polarization of neurons, as discussed below. Stimulate fibers leading into or out of a nucleus, and impulses go in only one direction. Gap junctions are basically reciprocal, although a few are rectifying. Thus, if a connection between cells conducts impulses in both directions, it can’t be a synapse. This argument to me is comparable to maintaining that if transmission is electrical, it can’t be synaptic. Furthermore, most synapses generate small postsynaptic potentials; impulses in general do not propagate through nuclei, and signals are transformed by both divergence and convergence (as Cajal well knew). We now know of many specialized contacts between neurons that transmit reciprocally, by both chemical and electrical means, and there is even retrograde transmission at certain chemical synapses (e.g., Hawkins et al., 1998; Wilson and Nicoll, 2001). No one is arguing that these are not synapses, although the modes of retrograde transmission remain controversial.

Let me finally state here what I view to be the only defensible definition of a synapse. A synapse is a morphologically or molecularly specialized site of functional interaction between neurons or between neurons and other cells. I specify molecularly specialized so as not to exclude possible cases where electron microscopy does not yet demonstrate differences in membrane
properties.) Generally, a synapse must have a close physical approximation between the interacting cells. For chemical transmission we allow the existence of paracrine chemical transmission, where the secreting cell is somewhat separated from the sensing cell, and differentiate that from synaptic transmission. In extreme separation the transmission becomes endocrine, although between frank endocrine glands and paracrine vari-cosities, there are portal circulations. With respect to electrical transmission, gap junctions between neurons are unquestionably synaptic, and I am confident than Cajal and Sherrington would agree with me as would Eccles and Katz. There are also field effects without apparent morphological specialization, and one could consider these the equivalent of paracrine actions. An in between case is provided by close apposition of somata or dendrites without intervening glia. The absence of glia is a specialization compared to most other regions of the nervous system, and evidently there is some electrical interaction (Vigmond et al., 1997). Is the absence of glia enough to make these contacts synapses? Do we know whether there are specializations in the apposed membranes that make electrical interactions stronger?

In a discussion of electrical synapses, a small divergence from questions of reticularism might be permitted. [I follow the Master, Cajal; there are numerous digressions in *Recuerdos de mi Vida* (1923).] There are electrically transmitting inhibitory synapses at the axon hillock of the Mauthner cell as described by Furukawa and Furshpan (1963), and subsequently Korn and Axelrad (1980) demonstrated a similar mechanism at basket cell synapses on the initial segment of Purkinje cells. The synapses have specializations of the associated glial cells resembling septate desmosomes and probably formed of homologous proteins. Transmission at the Mauthner cell inhibitory synapse is reciprocal (Korn and Faber, 1975), although the physiological meaning, if any, of the inhibition from Mauthner cell to inhibitory neuron has not been established. The highly specialized structures mediating the interaction unquestionably qualify them as synapses, by the above definition. The lack of close appositions between pre- and postsynaptic cells is required by their function and should not disqualify them as synapses; comparable widening of the intercellular cleft occurs at chemical synapses to reduce access resistance.

Although most gap junctions act as linear resistors under physiological conditions, electrical synapses need not conduct impulses in both directions because of low conductance, impedance mismatch or rectification (Bennett, 1966; Verselis and Veenstra, 2000). Thus, the older argument excluding electrical transmission on the basis of the doctrine of dynamic polarization is not valid. Pools of coupled neurons may also have sites of impulse initiation in different neurons and activity can then spread in all directions through the coupled network.

The recent discovery of neuron-specific connexins brings a currency to the topic of Cajal's views of "the neuron" (Condorelli et al., 1998; Teubner et al., 2001). He was a great general as well as comparative anatomist with uncommon physiological intuition. He would have been very interested in gap junctions and what they do.

In conclusion for this section, it has become clear that chemical transmission is the most common modality at synapses. However, the number of known electrical synapses is increasing, and they can be thought of as a respectable minority performing important roles in the operation of nervous systems, generally physiological but sometimes pathological. Although electrical synapses were thought to be primitive, molecular evolution suggests that they were later evolving than chemical synapses (cf. Bennett, 2000b). They are found not only in lower vertebrates, but in the neocortex of mammals (Fig. 3).

**Dynamic polarization**

In 1891 Cajal published:

> The transmission of the nervous impulse is always from the dendritic branches and the cell body to the axon or functional process. Every neuron, then, possesses a receptor apparatus, the body and the dendritic prolongations, an apparatus of emission, the axon, and an apparatus of distribution, the terminal arborization of the nerve fibers. I designated the foregoing principle: the theory of dynamic polarization. (*Recuerdos de mi Vida*, hereafter RdMV, p. 389)

Many of Cajal's drawings show little arrows indicating excitation flowing along dendrites toward the cell body. The primary evidence came from sensory inputs, where the activity indisputably came from the periphery (Fig. 4), but it was natural to extend the concept to neurons in other sites including the neocortex (Fig. 5). The general implication remains accurate, but in most neurons impulses arise in the cell body and propagate back out the dendrites. That impulses in mammalian neurons arise in the initial segment and from there invade the soma dendritic complex was first shown for spinal motoneurons of the cat (Coombs et al.; 1957; cf. Eccles, 1964).
The “back propagating” impulse was antidromic in that it went from axon towards the input part of the neuron, but orthodromic in that it was the normal direction for impulses to propagate. The finding was a little troublesome at the time because physiologists thought in terms of uniform membrane properties (Occam’s kind of supposition), and synaptic inputs would be larger in the dendrites. The data were rapidly rationalized in terms of lower threshold in the initial segment, higher threshold or inexcitability of the dendrite, averaging of dendritic inputs, and integration of excitation and inhibition at a single site. Impulse initiation in or near the soma in response to dendritic inputs has now been shown by direct measurement in a number of other central neurons with simultaneous dendritic and somatic recordings (e.g., Fig. 6, Stuart and Sakmann, 1994). We showed for teleost oculomotor neurons that ipsilateral vestibular inputs initiate impulses in the dendrites and contralateral vestibular inputs initiate impulses in the soma, from where they presumably propagate somatofugally out the dendrites as well as out the axon (Korn and Bennett, 1975). More recently, multisite patch clamp recordings from dendrites and somata demonstrates that impulses can arise in the axon initial segment or dendrites, depending on the strength of the synaptic input; small depolarizations in the distal dendrite excite the cell near the soma, but large depolarizations reach the higher threshold of the local, dendritic membrane before the potential in the soma reaches threshold (Fig. 7, Chen et al., 1997; Larkum et al. 2001). The mitral cell, diagramed by Cajal in Fig. 4, is now directly shown to have bidirectional propagation along the apical dendrite.

In describing the evolution of his ideas on dynamic polarization, Cajal wrote:

Only later, in 1897, did I hit upon the realization that, contrary to the general opinion, the soma or cell body does not always take part in the conduction of the nerve impulses which are received. The afferent wave is sometimes propagated directly
from the dendrites to the axon. I had then to substitute for the preceding incorrect formula this other, which I designated *Theory of axipetal polarization: The soma and the dendrites conduct in an axipetral direction, that is, they transmit the waves of nervous excitation towards the axon. Inversely, the axon or axis cylinder conducts in a somatofugal or dendrfugal direction, carrying the impulses received by the soma or by the dendrites towards the terminal arborization of the nerve fibre.* (RdmV, p. 390)

Nevertheless, and always the comparative anatomist, he thought that:

in various nerve centres of vertebrates ... [there were] concentric zones in which only dendritic processes came together. In such cases it was necessary to admit contact between dendrites of diverse origins and hence conduction indifferently cellulipetal or cellulifugal. (RdmV, p. 385)

Cajal's brother subsequently found "rich plexuses of axon terminations" in these regions (RdmV, p. 388), so that qualification could be excised. Nevertheless, dendrodendritic synapses, which we now know may be polarized or reciprocal, electrical and/or chemical, do not conform to those little arrows in a simple manner. Furthermore, Cajal, correctly, concluded that amacrine cells have multiple dendrites but no axon, thus suggesting conduction normally in either direction along the single processes.

We would now revise Cajal's view that, "The three parts of the neuron: body, dendrites and axon, conduct equally the nerve impulse." (*Textura del Sistema nervioso*, hereafter TSN, p. 88) We know that the excitability properties of the neuron vary over its surface. In some neurons dendrites appear to be inexcitable; in others there are varying degrees of excitability that modulate the input/output properties of the cell (e.g. Larkum et al., 2001).
Fig. 5. Dynamic polarization in the neocortex? Cajal's legend: "The probable direction of current flow and the pattern of axodendritic connections between cells in the cerebral cortex. A: small pyramidal cell; B: large pyramidal cell; C and D: polymorph cells; E: terminal fiber arising in another center; F: white matter collaterals; G: an axon that bifurcates in the white matter." Fig. 16 from Ramon y Cajal (1933).

It is my impression, not based on an exhaustive reading of his works, that Cajal did not know that impulses can propagate in either direction along axons at the time he formulated the doctrine of dynamic polarization. Thus, the physiologists’ concepts, and observations, of orthodromic and antidromic conduction would not have been in his mind. In writing the ultimate version of TSN (p. 114), however, he was fully cognizant that axons could conduct in both directions and his “opinion” was that dynamic polarization was a consequence of sensory receptors at the input part of the nervous system and muscles at the output. He recognized that conduction might go in the “wrong” direction in pathological states.

But when a change occurs in the neuronal connections, by experimental or pathologic lesions, so that the site of entry of the excitation in a nerve cell is now at the axonal apparatus, the direction of the propagation will change, and it will be possible for impulses to go from the axon to the cell body... (TSN, p. 115).

He was silent on whether impulses could cross contacts between cells in the wrong direction.

One of the difficulties for dynamic polarization was provided by the cells of the spinal sensory ganglia.

[T]he peripheral conducting branch, which is indisputably cellulosial, is exceptional in that in the adult it takes on all the structural and morphological characters of the axis cylinder. (RdmV, p. 385)

As a student, I was never very happy with the term telodendron for the sensory axon distal to the spinal ganglion. It seemed perfectly reasonable to me to call it a sensory axon, but by that time the controversy about dynamic polarization and the role of dendrites had shifted to another facet: were dendrites electrically excitable and how much influence did distal synapses have on neuronal signaling? Cajal had no problem with calling the peripheral process a dendrite, although it was myelinated:

the possession of an insulating myelin sheath in the dendrites is related not so much to the direction of the nerve current as to the considerable length of the conductor. (RdmV, p. 388).

Coda

In preparing my contribution for this volume, Changing Views of Cajal's Neuron, it was my intention to examine two small areas in which it had appeared to me that Cajal had erred. In seeking documentation for my views, I have become much more aware of the breadth and subtlety of his views and more impressed with him as a scientist, thinker, and human being. He wrote about his development of the reduced silver stain:

I was inspired by the hope of procuring a powerful weapon with which to fence against many technical innovators who were irresistibly inclined to the anarchistic vice of denying in the name of a new truth the truths already discovered by others. (RdmV, p. 521)

And later:

Here was another hard battle won for the neuron doctrine. Will it be the last?

I doubt it very much. The morbid desire to assert and to make prominent one's own personality, to be original above all
Fig. 6. In some neurons impulses arise in the soma or initial segment and propagate back out the dendrite. The fluorescence micrograph on the left shows the soma and apical dendrite of a neocortical pyramidal cell filled with Lucifer yellow through the patch pipette on the soma (arrow pointing up). The patch pipette on the dendrite is only faintly fluorescent (arrow pointing down). An impulse initiated by current applied in the soma propagates out the dendrite (upper record). An impulse initiated by current applied in the dendrite also appears first in the soma and then propagates out the dendrite, although the depolarization prior to the impulse is greater in the dendrite (middle record). An impulse evoked by synaptic activation due to electrical stimulation of afferent fibers also appears first in the soma and then the dendrite, although the excitatory postsynaptic potential is greater in the dendrites (lower record). From Stuart and Sakmann (1994).

things, wreaks ruin in our time. Following the course of least resistance, youth delights in reexamining values which it considers doubtful; and in the realm of science, instead of discovering new truths, it prefers to destroy its heritage of ideas from the past. (RdmV, p. 563)

There is no question that I was much younger at the time when gap junctions and electrical synapses were being described, and I admit to a somewhat iconoclastic predilection, now as then. Nonetheless, I maintain that I was taking pleasure in “discovering new truths” about synapses and neuronal connectivity. Gap junctions do not contradict an old truth, although it is (for me) entertaining to pretend that they do so.

Much of what I have proposed here deals with teleology. Cajal often used teleological or functional arguments in interpreting his findings:

We have seen that the position of the soma as well as the direction and mode of origin of the axon, vary in different nerve cells. Are these variations merely whims of Nature, arrangements without importance, or have they some physiologic significance? All appears to indicate that such arrangements are of actual use to the dynamics of the organ that presents them. [A knowledge of the ontogeny of their development] would not give us a clue of the goal or utilitarian design pursued by Nature to adopt them only in certain foci of gray matter. These laws of economy must be considered as the teleological causes… (TSN, p. 102).
Fig. 7. In mitral cells of the olfactory bulb impulses can arise near the soma or out near the glomerulus inputs, depending on strength of activation and inhibitory inputs. The apical dendrite can propagate impulses in either direction. (A) Drawing of a mitral cell filled with biocytin and recorded with patch electrodes on soma and distal apical (primary, p) dendrite. s: secondary dendrites. (B) Simultaneous recordings in proximal (continuous trace) and distal (dotted trace) apical dendrite. Olfactory nerve (ON) stimulation at the indicated strengths initiated impulses nearer the soma for weak stimulation (17 and 25 nA) and farther out the dendrite near the glomerulus (Glo) for stronger stimulation (33 nA). The synaptic depolarizations are larger near the glomerulus and for stimuli of 17 and 25 nA are superimposed on the synaptic depolarization near the soma evoked by the next stronger stimulus. (C, D) Inhibition alters the site of impulse initiation. Impulses evoked by ON stimulation alone arose first in soma and later in the dendrite; impulses evoked by ON stimulation during an IPSP evoked by stimulation of the external plexiform layer (EPL) arose first nearer the glomerulus (recordings from dendrite and from soma are superimposed with and without the IPSP in C); expanded sweeps of impulses in dendrite and soma are superimposed without the IPSP on the left of D and during the IPSP on the right of D. The larger impulse is that recorded from the soma. From Chen et al. (1997).

Lest the reader worries that Cajal was getting mystical, he states in a note:

Regarding final causes, we must declare that the terms goal, designs, improvements, etc. employed by us, are only expressions coined by usage. Indeed, according to us, there is no intentional direction, no preconceived plan in the evolution of Nature; only variations and adaptations which have prevailed because of their usefulness for survival. (TSN, p. 121).

Cajal is greatly deserving of homage. As autobiography, as well as scientific history, his Recuerdos de mi Vida is superb. I would like to include here a few quotes that I find wonderful.
[Neurons], those tiny cells, which keep hidden in the minuteness the mystery of life, are the whole man, in his two aspects, rational and physiological. Unified by the division of labour, they react to the stimuli of the environment, give us the illusion of free-will, and, in fine, perform our actions in their completeness. (RdmV, p. 446)

[3] Intellectual power, and its most noble expressions, talent and genius, do not depend on the size or number of the cerebral neurons, but on the richness of their connective processes. (RdmV, p. 459)

The perfection of function by exercise (physical education, speech, writing, piano-playing, mastery in fencing and other activities) are explained by either a progressive thickening of the nervous pathways or the formation of new cell processes (non-congenital growth of new dendrites and extension and branching of axon collaterals) capable of improving the suitability and the extension of the contacts and even of making entirely new connections between neurons primitively independent. (RdmV, p. 459)

With respect to the Nobel Prize:

What a cruel irony of fate to pair, like Siamese twins united by the shoulders, scientific adversaries of such contrasting character! (RdmV, p. 553)

Finally, the prize for Peace was awarded to the American Theodore Roosevelt. This decision produced great surprise, especially in Spain.

Is it not the acme of irony and humor to confer into a champion of pacifism the man of the most impeciously pugnacious temperament and the most determined imperialist that the United States have ever produced? (RdmV, p. 550)

And as he described his aging:

The industrious young men to whom I refer [his students] are already legion, especially if we include those of the past with those of the present. Among the former ones (some dead in the flower of their youth and others unfortunately lost to national science in the desert of the clinic) . . . (RdmV, p. 592)

I repeat, let us cultivate our garden—as Voltaire used to say—fulfilling so far as we can the double and austere duty of men and patriots. For the biologist, the supreme ideal consists in solving the enigma of his own ego, contributing at the same time to clarifying the formidable mystery which surround us. It matters not that our work be premature or incomplete; incidentally, until the long sought ideal dawns, the world will gradually be made pleasanter for man. Nature is hostile to us because we do not know it; its cruelties represent revenge for our indifference. To listen to its inmost heartbeats with the fervour of passionate curiosity is the same as to decipher its secrets; it is to turn the ireful stepmother into the most tender mother.

In what nobler and more humanitarian enterprise could the intelligence be employed? (RdmV, p. 596)

If I were religious, I would say “Amen”, but like Cajal, I am not.

References


