The Intrinsic Electrophysiological Properties of Mammalian Neurons: Insights into Central Nervous System Function

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This article reviews the electroresponsive properties of single neurons in the mammalian central nervous system (CNS). In some of these cells the ionic conductances responsible for their excitability also endow them with autorhythmic electrical oscillatory properties. Chemical or electrical synaptic contacts between these neurons often result in network oscillations. In such networks, autorhythmic neurons may act as true oscillators (as pacemakers) or as resonators (responding preferentially to certain firing frequencies). Oscillations and resonance in the CNS are proposed to have diverse functional roles, such as (i) determining global functional states (for example, sleep-wakefulness or attention), (ii) timing in motor coordination, and (iii) specifying connectivity during development. Also, oscillation, especially in the thalamo-cortical circuits, may be related to certain neurological and psychiatric disorders. This review proposes that the autorhythmic electrical properties of central neurons and their connectivity form the basis for an intrinsic functional coordinate system that provides internal context to sensory input.

OUR PRESENT UNDERSTANDING OF BIOELECTRICITY BEgan with the pioneering work of Bernstein (*1*), who indicated that K^+ concentration gradients determine the potential across the surface membrane in muscle and nerve cells. However, it was not until the 1950s, when Hodgkin, Huxley, and Katz demonstrated the central role of specific voltage-dependent membrane conductances in the generation of the nerve impulse, that the study of the ionic base for single-cell electroresponsiveness began in earnest (*2*). The development of our concepts relating to neuronal excitability has rested fundamentally on these important early studies.

Our views of the electrophysiology of mammalian neurons were strongly influenced by the results of a set of experiments by Coombs, Eccles, and Fatt (*3*) on mammalian spinal motoneurons. These authors concluded that the ionic basis for the electrical activity in motoneurons was probably similar to that in peripheral nerve fibers; that is, action potentials were produced by a transient inward Na^+ current followed by outward K^+ current generated by conductances similar to those demonstrated by Hodgkin and Huxley in the squid giant axon. At that time the dendritic tree of these neurons was considered to be electrically passive and to add, more or less linearly, the incoming synaptic potentials.

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The "Platonic" Mammalian Neuron

After these early studies, it was assumed that all cells in the central nervous system (CNS) were electrophysiologically similar to motoneurons. The consequence was that complexity in the mammalian brain was believed to be attained by the connectivity of close to ideal or "Platonic" nerve cells serving as threshold elements, rather than by the elaboration of their electrophysiological properties. The ultimate result of this view was that the role of intrinsic electrophysiological properties and the "spontaneous" activity these properties generate were ignored (*4*). A parallel effort in invertebrates, notably, in molluskan central neurons (*5*), provided a different view. Because of their large size, quite sophisticated electrophysiological techniques could be used to study these neurons. This research revealed a host of different voltage-dependent conductances in addition to those generating the peripheral nerve spike. However, such findings were interpreted by many neurobiologists as pertaining only to invertebrate forms and as being present only to compensate for the small number of neurons in invertebrates compared to the mammalian brain. Researchers of vertebrates and those of invertebrates disagreed as to the significance of the electrophysiological properties of individual neurons in CNS functions.

Today, due largely to in vitro studies with brain slices, during which the extracellular ionic environment can be controlled, and more recently to the use of cultured nerve cells and single-channel recording techniques (*6*), there has been a fundamental change in our thinking regarding the electrical properties of mammalian neurons. These cells are now recognized as dynamic elements demonstrating a wide range of electroresponsive properties and endowed with many different voltage- and ligand-dependent ionic conductances (Table 1). In addition, neurochemical and molecular biological studies have revealed a number of intracellular messenger systems (*7*) and numerous transmitter and neuromodulatory substances (*8*). Furthermore, mammalian CNS neurons express a larger fraction of the genome than any cell in the organism (*9*). Indeed, questions relating to molecular and developmental issues and to repair, plasticity, and intercellular communication enormously enrich neuroscience and serve to unify the concepts relating to vertebrate and invertebrate neuroscience.

Table 1. Voltage-dependent ionic conductances in mammalian central neurons as studied in vitro. Abbreviations: ACh, acetylcholine; CNS, central nervous system; DA, dopamine; depol., depolarization; DRG, dorsal root ganglion; emb., embryonic; FTX, funnel web spider toxin; GP, guinea pig; hyper., hyperpolarization; I_{AR}, anomolous rectifier current; inact., inactivating; I_M, current activated by muscarinic agonists; INST, instantaneous; NE, norepinephrine; OL, olivary; PNS, peripheral nervous system; S, serotonin; TEA^+, tetraethylammonium; TTX, tetrodotoxin; 5HT, 5-hydroxytryptamine; and 4AP, 4-aminopyridine. The activation threshold is reported with respect to that for the Na^+-dependent action potential.

Cell type and species	Activation threshold	Inactivation	Inhibitor	Activator	Ineffective	Reference	Location
			Persistent sodium conductances in CNS				
Sensorimotor cortex							
GP	Low	Slow	TTX, QX-314			(*65, 66*)	
Cat	Low, fast	Slow	TTX, QX-314		Ba^{2+}, Co^{2+}	(*67, 68*)	
Hippocampus							
CA1 pyramidal, rat	Low	Slow	TTX, 0 Na^+		Mn^+, Cd^{2+}	(*69*)	Soma
CA3 pyramidal, GP (isolated and intact soma)	Low	Slow	QX-314			(*70*)	
Thalamus							
GP	Low	Slow	TTX, 0 Na^+	TEA^+	Ba^{2+}, Co^{2+}, Cd^{2+}	(*40*)	
Cerebellum							
Purkinje cell, GP	Low	Slow	TTX, 0 Na^+	TEA^+, lidocaine	Ba^{2+}, Co^{2+}, Cd^{2+}	(*13, 71*)	Soma
Nuclear cell, GP	Low	Slow	TTX		Co^{2+}, Cd^{2+}	(*72*)	
			High-threshold calcium conductances in CNS				
Sensorimotor cortex							
GP	<-50 to -40 mV	Slowly or none	Mn^{2+}, Co^{2+}	Ba^{2+}, TEA^+	0 Na^+, TTX	(*66*)	Soma and dendrites
Cat	-30 to -40 mV		Mn^{2+}, Co^{2+}, Cd^{2+}	Ba^{2+}	TTX	(*68*)	Soma and dendrites (largest in dendrites)
Olfactory cortex							
GP	Fast	Slow	Cd^{2+}	TEA^+, Ba^{2+}, Cs^+	Low Na^+, TTX	(*73*)	
Hippocampus							
CA1 pyramidal, rat	High		Mn^+, Cd^{2+}			(*69*)	
CA3 pyramidal, GP	Slow	None up to 800 ms	Mn^{2+}, low Ca^{2+}		TTX	(*74*)	
CA3 pyramidal, GP	-45 to -20 mV, peak, 50–100 ms		Co^{2+}	Ba^{2+}	TTX	(*75*)	Probably soma
CA1, CA3 pyramidal, GP	-40 to -30 mV, peak, 100–300 ms, slow	None up to 700 ms	0 Ca^{2+}, Cd^{2+}, verapamil	Ba^{2+}	TTX	(*76*)	Dendrites
CA1 pyramidal, GP, isolated neurons	-40 mV, peak, 2–5 ms		Co^{2+}, Cd^{2+}	Ca^{2+}, Ba^{2+}		(*77*)	
CA3 pyramidal, rat, cultured slice	>-30 mV		Muscarine		TTX	(*78*)	
CA1 pyramidal, GP, isolated dendrites	Slow				QX-314	(*70*)	Dendrites
Neostriatum							
Rat	High		Mg^{2+}, Co^{2+}	TEA^+	TTX	(*79*)	
Rat	High		Cd^{2+}, ACh	TEA^+	0, Na^+, TTX	(*80*)	
Caudate							
Rat	>-40 mV, peak, 50–80 ms	Two phases	Cd^{2+}, Co^{2+}, Mn^{2+}	Ba^{2+}, TEA^+, BAY K 8644	TTX	(*81*)	
Thalamus							
GP	High		Cd^{2+}, low Ca^{2+}	Ba^{2+}		(*40*)	Dendrites
Mammillary body							
GP	High	Slow	Co^{2+}, Cd^{2+}	TEA^+	TTX	(*82*)	
Superior colliculus							
GP	<-60 mV	Voltage-dependent	Cd^{2+}	Ba^{2+}		(*83*)	
Locus ceruleus							
Rat	Fast	Fast, near NA spike threshold	Mg^{2+}, Co^{2+}	Cs^+, Ba^{2+}	TTX	(*84*)	Probably dendrites
Substantia nigra pars compacta							
GP	30–40 mV from rest		Cd^{2+}, Co^{2+}, Mn^{2+}		TTX	(*85*)	Dendrites
Inferior olive							
GP		Fast	Co^{2+}, Mn^{2+}, Cd^{2+}, D600	Ba^{2+}, TEA^+		(*15*)	Dendrites

(Continued on page 1656)

Table 1 *(continued)*

Cell type and species	Activation threshold	Inactivation	Inhibitor	Activator	Ineffective	Reference	Location
Cerebellum							
Purkinje cell, GP	−45 mV (from soma) −55 mV (from dendrites)		Mn^+, Co^{2+}, Cd^{2+}, FTX	TEA^+	TTX, 0 Na^+, nitrendipine, Ω conotoxin	(*11, 13, 23, 26*)	Dendrites
Dorsal horn							
Neonate rat	High	No	0 Ca^{2+}, Co^{2+}, Mn^{2+}	Ca^{2+}, TEA^+	TTX	(*86*)	
Motoneuron							
Spinal, neonatal rat	High	No	Mn^{2+}, Cd^{2+}	Ba^{2+}, TEA^+	TTX	(*87*)	
Spinal, cat	High			Ba^{2+}		(*88*)	
Vagal, GP	High		Cd^{2+}, Co^{2+}, Mn^{2+}			(*89*)	
Embr. mouse, in culture	High		Co^{2+}, Cd^{2+}			(*90*)	
High-threshold calcium conductances in PNS							
Superior cervical ganglion							
Rat	−30 mV, max at 0 mV, 4th order	Complete	Cd^{2+}		0 Na^+, TTX	(*91*)	
Rat	≈−30 mV		Epinephrine, Cd^{2+}, low Ca^{2+}	TEA^+	TTX	(*92*)	
DRG							
Rat	>−20 mV		Ni^{2+}, Cd^{2+}	Ba^{2+}, Sr^{2+}		(*58*)	
Low-threshold calcium conductances in CNS							
Hippocampus							
CA1 pyramidal, GP, isolated dendrites	Slow				QX-314	(*70*)	
CA1 pyramidal, GP	Low, fast	Yes at <−50 mV	Cd^{2+}			(*93*)	
Neostriatum							
Rat	Low	Slow	Mg^{2+}		TTX	(*79*)	
Caudate							
Rat	>40 mV, slow		Co^{2+}			(*81*)	
Thalamus							
GP	<−65 mV	−45 mV	Co^{2+}, Cd^{2+}, Mn^{2+}	Ba^{2+}		(*40*)	
Cat	Slow, low					(*94*)	
Mammillary body							
GP	−60 mV	Fast		Cs^+		(*82*)	
Dorsal raphe							
Rat	−60 mV		Ni^{2+}		5HT, phenylephrine	(*95*)	
Substantia nigra pars compacta							
GP	−60 or −70 mV		Cd^{2+}, Co^{2+}, 0 Ca^{2+}		TEA^+	(*85*)	
Pontine reticular formation							
Rat	Low	Yes	Mg^{2+}		TTX	(*96*)	
GP		Yes	Cd^{2+}, octanol		TTX	(*97*)	
Inferior olive							
GP		<−45 mV	Co^{2+}, Cd^{2+}, 0 Ca^{2+}, octanol			(*15, 98*)	Soma
Dorsal horn							
Neonatal rat	<−65 mV		0 Ca^{2+}, Co^{2+}, Mn^{2+}	Ba^{2+}, TEA+	TTX	(*86*)	
Motoneuron							
Cat	Depol. ≈10 mV	No				(*99*)	Soma
Cat	Low, rapid	None or slow		Ba^{2+}	QX-314	(*88*)	Soma
Neonatal rat		Not up to 200 ms	Cd^{2+}, Co^{2+}		TTX	(*100*)	
Low-threshold calcium conductances in PNS							
DRG							
Rat	Start at −50 mV	Fast, max at −30 to −20 mV	Ni^+, Cd^{2+}, reduced 1/5 by Ba^{2+}	Sr^{2+}		(*58*)	

Table 1 *(continued)*

Cell type and species	Activation threshold	Inactivation	Inhibitor	Activator	Ineffective	Reference	Location
			A and A-like transient potassium conductances in CNS				
Hippocampus							
CA3 pyramidal, GP	>−60 mV	Two phases	4AP		TTX, Mn^{2+}, muscarine	(*101*)	
Multipolar, emb. rat and mouse, in culture	Peak, 3–5 ms	>−50 mV	4AP, TEA^+ (weak)		TTX	(*102*)	
Thalamus							
GP	Fast	Slow	4AP			(*40*)	
Superior colliculus							
Cell type I, GP			Cs^+			(*82*)	
Locus ceruleus							
Rat	From hyperpol.	Slow	4AP, TEA^+, Ba^{2+}, Co^{2+}			(*84*)	
Dorsal raphe							
Rat	Depol. from hyperpol. levels		4AP, NA, phenylephrine			(*103*)	
Rat		Yes	4AP		Cd^{2+}, TEA^+	(*104*)	
Pontine reticular formation							
Rat		4AP				(*96*)	
Motoneuron							
Vagal, GP	≈−75 mV, max ≈−95 mV in 300 ms	Time- and voltage-dependent	4AP		TEA^+, Cs^+	(*89*)	
Spinal cord							
Emb. rat and mouse, in culture	Peak, 3–10 ms	>−50 mV	4AP		TTX, TEA^+	(*102*)	
			A and A-like transient potassium conductances in PNS				
Superior cervical ganglion							
Rat	−60 mV	Fast, complete	4AP	Ca^{2+}		(*105*)	
Rat	−60 to 0 mV, 1st order	Exponential, not voltage-dependent	TEA^+ (weak), 4AP (weak)		0 Ca, Cd^{2+}	(*106*)	
DRG							
GP, in culture	Hyperpol., ≈−60 mV, relatively rapid	Complete, <−40 mV, two states		Intracellular 4AP	$[Ca^{2+}]_o$	(*107*)	
			Anomalous rectifying conductances in CNS				
Olfactory cortex							
GP	Fast, 100 to −110 mV	Slow	Cs^+, Ba^{2+}		TTX, TEA^+, Cd^{2+}	(*108*)	
GP	−55 to −35 mV	Slow			TTX	(*73*)	
Hippocampus							
CA1 pyramidal, GP (I_Q)	<−80 mV, faster than I_M		Cs^+		Ba^{2+}, muscarinic agonists	(*109*)	
CA1 pyramidal, GP (I_M)	−40 to −70 mV		Ba^{2+}, carbacol, muscarine, bethanechol		Cs^+	(*109*)	
CA1 pyramidal, GP	Subthreshold depol.		Mn^{2+}, Ca^{2+}, TTX	Ba^{2+}		(*110*)	
Rat, in culture (I_{AR})	>−70 mV	None	0 Na^+, Cs^+	High $[K^+]_o$	TEA^+, 4AP, Ba^{2+}	(*111*)	
Superior colliculus							
Cell type II, GP			Cs^+		Ba^{2+}	(*83*)	
Inferior olive							
GP, $g_{K(INST)}$	Hyperpol.	Time-dependent	4AP			(*112*)	
GP, $g_{K(OL)}$	Hyperpol.		Co^{2+}, Mn^{2+}, Cd^{2+}, Cs^+, 0 Ca^{2+}, 4AP		Ba^{2+}, TEA^+	(*112*)	
Similar to I_Q, GP	Requires Ca^{2+} or Ba^{2+}		Harmaline			(*112*)	

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Table 1 *(continued)*

Cell type and species	Activation threshold	Inactivation	Inhibitor	Activator	Ineffective	Reference	Location
			Anomalous rectifying conductances in PNS				
Superior cervical ganglion							
Rat (I_M)	≈−70 mV	Not time-dependent	Muscarine, angiotensin II			(*113*)	
			Calcium-activated potassium conductances in CNS				
Sensorimotor cortex							
GP	Possibly Ca^{2+}	Slow	Co^{2+}, Mn^{2+}		TTX	(*66*)	
Hippocampus							
CA1 pyramidal, rat	Ca^{2+}		Co^{2+}, Mn^{2+}, Ba^{2+}		Cl^-	(*114*)	
CA1 pyramidal, GP	<−45 mV		Mn^{2+}, Cd^{2+}, 0 Ca^{2+}, TEA^+		Cs^+, $[Na]_o$, muscarinic agonists	(*115*)	
CA1 pyramidal, rat			NE (β-1), Cd^{2+}			(*116*)	
Thalamus							
GP			Cd^{2+}, Co^{2+}, Mn^{2+}			(*40*)	
Superior colliculus							
Cell type I and II, GP			0 Ca^{2+}, Cd^{2+}, 4AP			(*83*)	
Dorsal raphe							
Rat						(*103*)	
Substantia nigra pars compacta							
GP			Ba^{2+}		TEA^+	(*85*)	
Pontine reticular formation							
Neonatal rat			Cd^{2+}, TEA^+			(*96*)	
Inferior olive							
GP	Ca^{2+}		Co^{2+}, Mn^{2+}, Cd^{2+}			(*15*)	
Cerebellum							
Purkinje cell, GP	Ca^{2+}		Co^{2+}, Mn^{2+}, Cd^{2+}, FTX			(*13, 23*)	
Motoneuron							
Vagal, GP	At resting potential		Cd^{2+}, Co^{2+}, Mn^{2+}			(*89*)	
Spinal, cat	Depol. of ≈10 mV, 1st order	No				(*117*)	
Spinal, cat	Depol. of ≈10 mV	No			TEA^+	(*118*)	
Spinal, neonatal rat			Cd^{2+}		TEA^+, Cs^+	(*87*)	
			Calcium-activated potassium conductances in PNS				
Superior cervical ganglia							
Rat	Faster than g_K, potential-dependent	No	Cd^{2+}			(*91*)	
Rat	>−20 mV	No	TEA^+, Mn^{2+}			(*105*)	
Rat					Apamin	(*119*)	
			Other potassium conductances in CNS				
Inferior olive							
$g_{K(INACT)}$	Deinactivated by hyperpol.	Slow, time-dependent	4AP	Co^{2+}, Cd^{2+}, 0 Ca^{2+}	Ba^{2+}	(*112*)	
$g_{K(S)}$	5HT					(*112*)	
			Chloride conductances in CNS				
Spinal neurons							
Embr. mouse, in culture	Voltage-dependent	Current lasts seconds	Cd^{2+}, Co^{2+}, Mg^{2+}, D600		Cs^+, TEA^+	(*90*)	
In culture, rat	Cs^+					(*120*)	

Voltage-Activated Ionic Conductances

Research into "unusual" ionic conductances in neurons of higher vertebrates began with the study of dendritic excitability, in particular the demonstration of Ca^{2+}-dependent spikes in avian Purkinje cell dendrites (*10*) and in mammalian neurons (*11–13*). This finding implied not only the existence of true dendritic excitability and of Ca^{2+} as a charge carrier in mammalian neurons, but it also took on added significance because Ca^{2+} was known to be an important second messenger in the regulation of cellular function (*7*). Other voltage-dependent Ca^{2+} conductances have been described recently (*14*).

Perhaps the most unexpected of these neuronal conductances was the so-called low-threshold Ca^{2+} conductance initially identified in inferior olivary (IO) cells (*15*) and most commonly but not uniquely observed in neurons that have oscillatory properties. This conductance, which is similar but not identical to the one encountered in the starfish egg (*16*), is essentially inactivated at the membrane resting potential and is deinactivated by membrane hyperpolarization. Such behavior initially appeared paradoxical, as one of the central doctrines of neurophysiology had been that membrane depolarization from the resting potential increases excitability, whereas membrane hyperpolarization decreases it. This view was obviously an oversimplification; for, in IO neurons, an otherwise subthreshold depolarization can produce action potentials if superimposed on either a depolarizing or a hyperpolarizing membrane potential change. This feature allows central neurons to behave as single-cell oscillators or as resonators (*17*).

Other seemingly odd conductances involving Na^+ or K^+ ions have also been found in mammalian neurons. Of these, the so-called noninactivating or persistent Na^+ conductance, initially described in Purkinje cells (*13*), can generate long plateau potentials, which can regulate excitability in a delicate manner. It does so by generating prolonged, low amplitude, membrane potential changes (known as plateau potentials). Because of their slow kinetics and small unitary conductance, activation of these channels does not generate action potentials, but rather, serves as a trigger for spike initiation by the fast Na^+ channel. This conductance, seen most clearly in the soma, has since been encountered in cells in the hippocampus, neostriatum, caudate, thalamus, mammillary body, dorsal raphe, substantia nigra, pontine reticular formation, dorsal horn, and spinal motoneuron (Table 1).

In addition to the inward currents carried by Na^+ and Ca^{2+} ions, outward currents generated by K^+ conductances are also plentiful in mammalian CNS neurons. In fact, up to 12 varieties have been identified (*18*). Two of these are the most prevalent: (i) the A conductances initially described in invertebrates (*19*), and (ii) the Ca^{2+}-dependent K^+ conductances [$g_{K^+(Ca^{2+})}$] also initially described in invertebrates (*20*). Finally, ligand-activated voltage-dependent and voltage-independent conductances play an important role in neuronal integration and in oscillations. However, they are not treated here because other reviews are available (*21*).

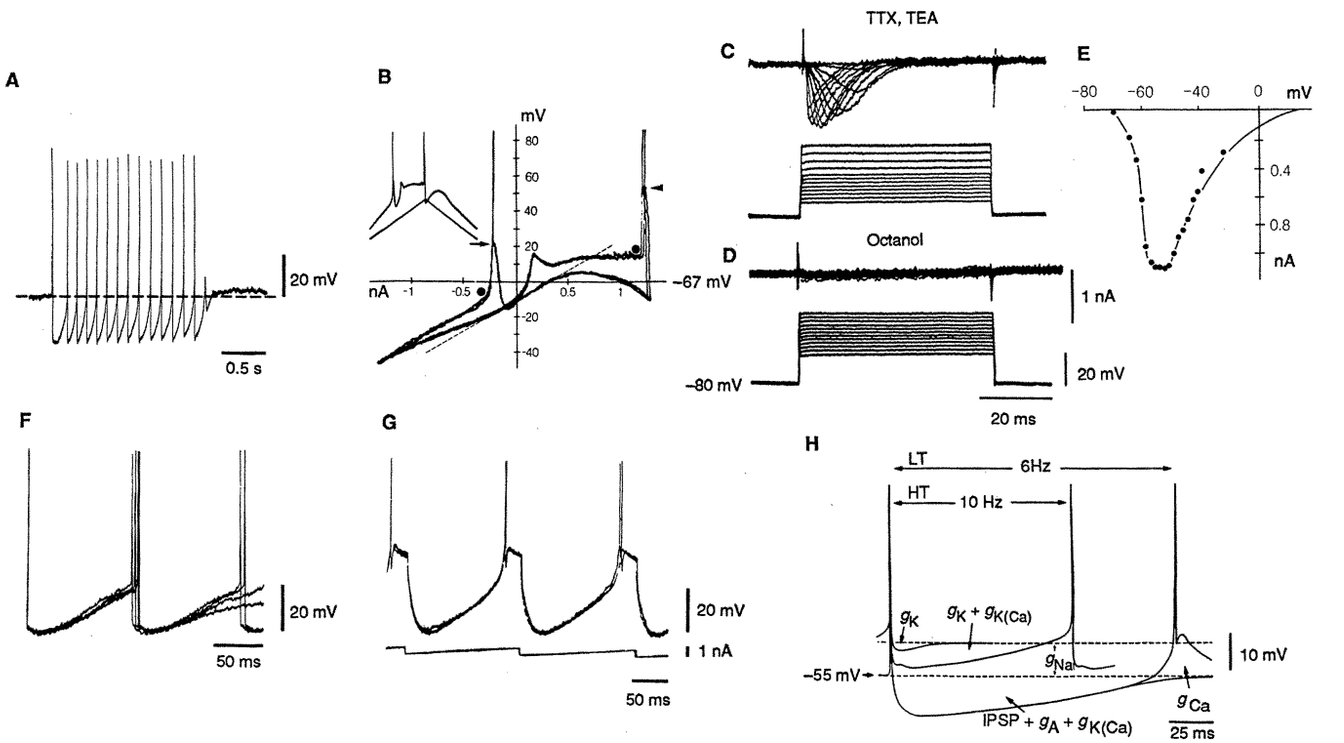

Fig. 1. Intrinsic oscillatory activity in mammalian neurons in vitro. (**A**) Spontaneous firing of an IO neuron recorded intracellularly in vitro. The action potentials rise from a membrane potential more negative than the initial resting potential (broken line). [Reprinted from (*32*) with permission, copyright 1986, The Physiological Society, Oxford] (**B**) Demonstration of two firing levels (dots) when the cell is activated by a double ramp (400 ms, 6.3 nA/s) current pulse [inset shows the current injection (lower trace) and the voltage response of the cell (upper trace)]. Resting potential, −67 mV. [Reprinted from (*112*) with permission, copyright 1987, Society for Neuroscience] (**C** to **E**) Voltage-clamp results from IO cells in vitro (*121*). In (C), transient Ca^{2+} current (I_{Ca}) (superimposed upper traces) generated by step depolarizations (lower traces). TEA, tetraethylammonium. In (D), a similar set of voltage steps reveal the total block of the I_{Ca} after bath application of octanol (20 μ*M*). In (E) the voltage-current relation for a set of records similar to those in (C). (**F** and **G**) Two frequencies of thalamic cell oscillations. In (F) the cell is above the resting potential and fires at 10 Hz. In (G) the rebound oscillation after small hyperpolarizing steps has a frequency of 6 Hz. In (**H**) the different conductances thought to be involved in these two oscillatory states are illustrated, where g_K is the delayed rectifier, $g_{K(Ca)}$ is the Ca^{2+}-dependent K^+ conductance, g_A is the transient K^+ conductance, g_{Na} is the persistent Na^+ conductance, HT is the high-threshold oscillation, and LT is the low-threshold oscillation generated by the low-threshold Ca^{2+} conductance. This latter conductance is generally observed as a rebound from an inhibitory postsynaptic potential (IPSP). [(F) through (H) reprinted from (*40*) with permission, copyright 1984, The Physiological Society, Oxford]

Spatial Distribution of Ionic Conductances over the Plasmalemma

Ionic conductances are distributed nonuniformly in the neuronal membrane. For instance, high-threshold Ca^{2+} conductances are found mostly, but not uniquely, on dendrites. To determine whether this nonuniformity can be verified directly, ion-sensitive probes and labeling techniques are being used. For instance, the use of Ca^{2+}-sensitive dyes has demonstrated that Ca^{2+}-selective channels are located, as expected from electrophysiological findings (*13*), in the smooth portion of the dendritic tree of Purkinje cells (*22*). More recent brain slice studies with fura-2 injected intracellularly into Purkinje cells (*23*) have allowed the sites of Ca^{2+} entry to be clearly imaged; these studies also confirm the original electrophysiological findings, suggesting the presence of "hot spots," that is, areas of increased channel density. Moreover, by using immunocytochemical procedures, Na^+-selective channels were found to be restricted to the soma and axon hillocks of retinal ganglion cells (*24*), and the use of fluorescent labeled tetrodotoxin (TTX) demonstrated a similar Na^+-channel distribution in Purkinje cells (*25*). The latter finding is also in agreement with the intracellular results in vitro (*13*).

Electrophysiological studies from other central neurons suggest that a differential distribution of ionic channels on the cell membrane may be ubiquitous. Thus, extracellular field potential recordings from the IO (*15*) indicate that the low-threshold Ca^{2+} conductance predominates in the cell body, whereas the high-threshold conductance resides in the dendrites (*26*). The distribution of these two types of Ca^{2+} conductance in other neurons (Table 1) may be similar to that in IO neurons. However, variations on this theme must be expected, and it is likely that, as for K^+ channels (*18*), many types of Ca^{2+} channels may be expressed.

The mechanism by which the distribution of these conductances is established and maintained is also of interest. Because membrane channels are constantly replaced without major change in their distribution (*27*), a strict control must be operating locally in the cytoplasm and may involve the cell nucleus. Differentiated gene expression and replacement of channels carried to the membrane via the cytoskeletal system must operate to maintain given types and quantities of channels at specified sites. If modulation of gene expression is required, a two-way communication must exist between the plasmalemma and the nucleus. The possibility that a microtubular system may be capable of guiding specific receptors to specific portions of the cell has been indicated for epithelial cells (*28*), but whether a similar system exists in central neurons, and whether different dendrites may be independently controlled, are so far undetermined.

Neuronal Oscillation and Resonance

The findings summarized here demonstrate that some central neurons have ionic conductances organized to endow them with electrical autorhythmicity. In addition, in many neurons the kinetics of these ionic voltage-dependent conductances are such that the cells may respond preferentially to inputs at a certain frequency or frequencies, that is, they behave as resonators.

As an example of how the intrinsic electrical properties of single cells contribute to single and multiple cell oscillation, one can consider the neurons in the IO as studied in vitro (Fig. 1, A and B). In these cells, in addition to the Na^+ and K^+ conductances that generate the fast action potential, there are at least three other conductances: at the soma, the low-threshold Ca^{2+} conductance and a $g_{K^+(Ca^{2+})}$; and in the dendrites, a high-threshold Ca^{2+} conductance similar to that found in the dendrites of Purkinje cells and a $g_{K^+(Ca^{2+})}$. In the firing of these neurons the Na^+ action potential is followed by a dendritic Ca^{2+} spike, which activates, via the $g_{K^+(Ca^{2+})}$, a powerful afterhyperpolarization. The afterhyperpolarization, which lasts 80 to 100 ms, is followed by an abrupt rebound response arising from a potential negative to the resting level. This rebound potential is generated by the low-threshold Ca^{2+} conductance and is often large enough to trigger a fast Na^+-dependent spike (Fig. 1B). An example of the time course and voltage-dependence of the Ca^{2+} current generating this low-threshold spike is illustrated in Fig. 1, C to E.

Thus, the ionic conductances in these cells are organized such that the membrane potential rebound that follows the afterhyperpolarization is often large enough to generate a second action potential. This second action potential triggers the whole sequence of events again, and the process may continue until the rebound becomes subthreshold and the oscillations cease (Fig. 1A). IO cells tend to fire at frequencies that are directly modulated by their intrinsic electrical properties. To determine if this organization of the IO has an effect on their postsynaptic target cells, the Purkinje cells in the cerebellum, the complex action potential was recorded (*29*) from individual Purkinje cells in different folia of the cerebellar cortex (*30,*

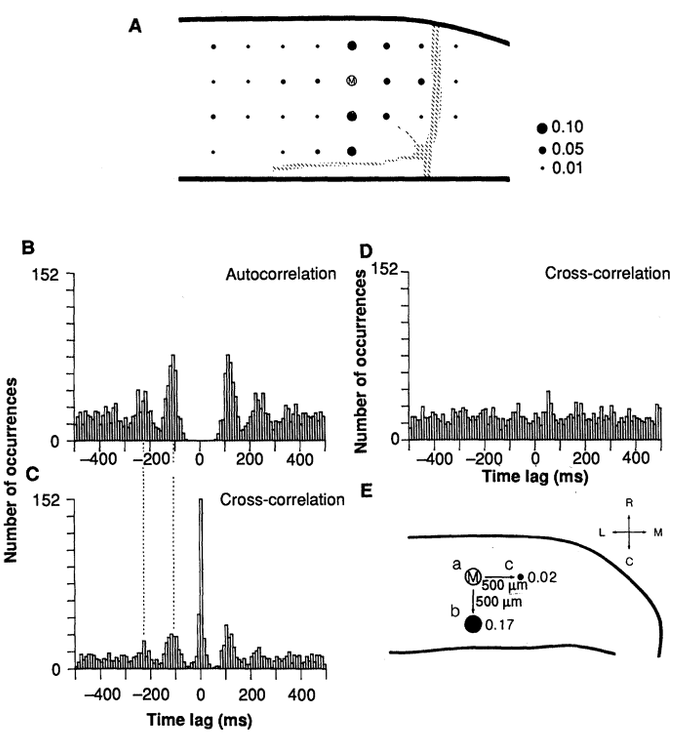

Fig. 2. Parallel organization of the olivo-cerebellar system. (**A**) Diagram of a cerebellar folium. The dots illustrate the sites of simultaneous Purkinje cell recordings with 28 extracellular microelectrodes. The electrode spacing was 200 μm. The degree of cross-correlation beween the firing of a given neuron [master cell (M)] and the rest of the population is given by the diameter of the dot over the recording site. Note the rostro-caudal organization of the cells, demonstrating a high degree of firing cross-correlation. (Dashed lines indicate blood vessels.) (**B**) Histogram demonstrating that the autocorrelation of the master cell has a dominant frequency of 10 Hz. (**C**) Cross-correlation between the master cell and that in position b in (E). (**D**) Cross-correlation between the master cell and that in position c in (E). The degree of cross-correlation relates sharply to the location of the Purkinje cells in the cortex. (**E**) Diagram of cerebellar folium: a, b, and c correspond to the location of three simultaneous microelectrode recordings of Purkinje cells. M is master unit. The distance between (a) and (b) and (a) and (c) is 500 μm. In inset, L, R, M, and C correspond to lateral, rostral, medial, and caudal directions, respectively. The diameters of the dots at (c) and (b) correspond to the degree of cross-correlation with respect to the firing of the master cell in (a). Recordings were obtained in the Crus IIa (*122*).

31). As expected from the in vitro results, the rhythmic activity of IO cells resulted in a synchronous activation of a large percentage of the Purkinje cells in a given folium (Fig. 2). This synchrony was shown by determining the cross-correlation function of complex spike activity from 28 simultaneously recorded Purkinje cells (*31*). A high degree of synchrony (less than 1-ms interval between the onset of complex spikes in different neurons) was found; this synchrony was in agreement with the fact that in addition to autorhythmicity (*32*), IO cells are electrically coupled with each other (*15, 33*). Indeed, the experiment demonstrated that neighboring Purkinje cells in a given folium will be synchronously activated by the climbing fiber afferents over a rectangular area of cerebellar cortex 200 μm in the mediolateral direction and at least 600 μm in the rostro-caudal direction. These results indicate then that the Purkinje cells are activated at the frequency of the IO firing, in the sense that the climbing fiber activation generates Ca^{2+} action potentials in dendrites of Purkinje cells, and the activation is followed by a large K^+ conductance change.

Because cerebellar Purkinje cells are inhibitory (*34*), the rhythmic and synchronous activation of these cells generates powerful, synchronous synaptic inhibitory potentials in their target cells, the cerebellar nuclear neurons (*35*). Further, because cerebellar nuclear neurons have electrical properties similar to those of thalamic cells, the large inhibitory potentials generate rebound responses in these cells. The rebound responses in turn activate motoneurons via the descending brainstem pathways to the spinal cord (*36*). This cascade of synchronous activity ultimately produces the "physiological tremor," which has a frequency of 10 Hz (*37*). These results indicate that the nervous system may use oscillation and resonance as a component of motor coordination or execution (*38*). Furthermore, because the IO innervates the entire Purkinje cell population, this nucleus can address the cerebellar cortex in a parallel and distributed manner and can alter the set of Purkinje cells activated in each cycle of its 10-Hz rhythmic firing.

The organization of the IO nucleus demonstrates that the oscillatory properties of single neurons, arising from a congruous set of electrical events, can activate a large number of neurons over a wide area. The ability to project oscillatory rhythms and to generate synchronous firing in large populations of cells may be one of the important properties of intrinsic electroresponsiveness.

Two Main Forms of Brain Activity

How do the oscillatory properties of central neurons relate to the information-carrying properties of the brain as a whole? In principle, one may propose that intrinsic electroresponsiveness generates internal computational states that serve as the reference frame, or context, for incoming information. That is, brain function is proposed to have two distinct components, one which is private or "closed" and is responsible for qualities such as subjectivity and semantics, and an "open" component that is responsible for sensory-motor transformations that deal with the relations between the private component and the external world. More precisely, the intrinsic activity is proposed to be part of the vectorial coordinate space that allows sensory-motor transformation to occur in the context of the particular functional state of the CNS at a given instant (*39*). For instance, attention or expectation (both intrinsic functional states) can modify the relevance of given sensory stimuli.

Another example of the importance of neuronal oscillation in brain function is provided by the thalamus. In addition to the repetitive firing that these cells can generate upon active depolarization, thalamic neurons oscillate at two distinct rhythms (*40*). If the cell is slightly depolarized it may oscillate at 10 Hz (Fig. 1F). If the cell is hyperpolarized it tends to oscillate at 6 Hz (Fig. 1G). In Fig. 1H the possible conductances involved in the two forms of oscillations are shown. At membrane potentials slightly depolarized from the resting potential (−65 mV), the cells will fire rhythmically and serve as relay elements carrying information to and from the cortex (Fig. 3A, last panel). If the membrane potential is more negative than −65 mV, the cells tend toward burst firing (*40, 41*) (Fig. 3A, first panel). This latter firing pattern results in the entrainment of cortical neurons and the generation of oscillatory events such as the alpha rhythm or as spindling, which accompanies drowsiness. Both

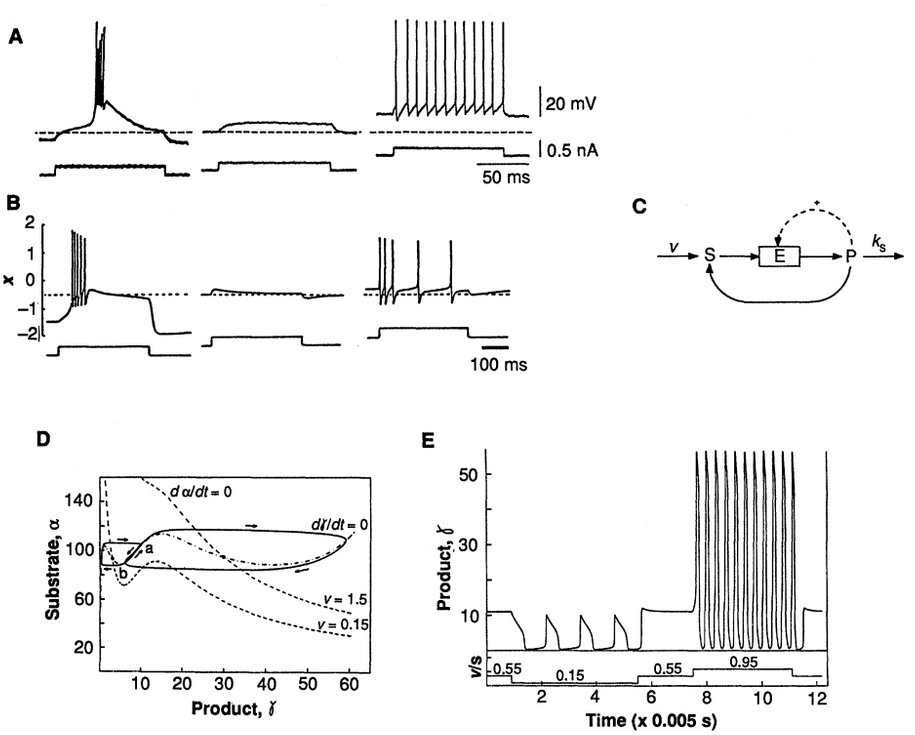

Fig. 3. Mathematical modeling of oscillatory events. (**A**) Intracellular recording from a thalamic neuron demonstrating the firing properties in response to a depolarizing current pulse delivered from a hyperpolarized level, the resting potential (dashed line), and a depolarized level (recorded in vitro). [Reprinted from (*123*) with permission, copyright 1982, Macmillan Magazine Ltd.] (**B**) A similar set of traces generated by the numerical solution of a set of differential equations. (Left trace) Burst firing when membrane is hyperpolarized, (middle trace) lack of firing at resting level, and (right trace) tonic firing at depolarized level produced by square current injections of similar amplitudes. [Reprinted from (*46*) with permission, copyright 1985, The Royal Society, London] (**C**) Diagram of the chemical model developed by Goldbeter and Moran (*47*). Abbreviations: E, allosteric enzyme; k_s, rate constant; P, product; S, substrate; and v, rate of substrate input. (**D**) Phase plane diagram predicted by model of biochemical system shown in (C) demonstrating two limit cycles for two values of v. Arrows and the a and b indicate directions of the two cycles. (**E**) Two modes of oscillatory behavior predicted by model of biochemical system. [(C) through (E) reprinted from (*47*) with permission, copyright 1988, Springer-Verlag]

of these oscillatory events can be recorded by scalp electrodes (*42*).

Thus the oscillatory capability of thalamic neurons, born out of their intrinsic conductances, can directly effect overall brain function. In fact, through the influence of brainstem oscillators (*43*), thalamic neurons are the key elements that gate the sleep-wakefulness cycle. These oscillators are not only essential in the regulation of the state of consciousness (wakefulness and sleep) and of the different states of sleep (synchronized and slow wave), but they are also intricately related during development to such periodic functions as respiratory movements (*44*). Also of interest is the possibility that this particular mechanism may be important in regulating attention. Crick has used the term "searchlight" to indicate the mechanism by which the brain attends to specific aspects in the external world while momentarily ignoring unrelated information. Crick has proposed that thalamo-cortico-thalamic interactions, not unlike resonance, may be associated with such a function (*45*).

One of the problems in considering the role of neuronal oscillations in brain function has been the difficulty in relating the properties of single cells to those of neuronal assemblies. To a certain extent this problem has been due to the lack of formal tools relating oscillatory events to neurobiological function. Neuronal oscillation is now being studied not only from an electrophysiological but also from a mathematical point of view. The work of Rose and Hindmarsh (*46*), and of Goldbeter and Moran (*47*), is relevant to intrinsic neuronal oscillation of the type found in thalamic neurons. They have extended the work of Fitzhugh (*48*), who demonstrated that differential equations can simulate oscillatory states similar to those observed in neurons. These studies are relevant in that they provide a general mathematical formulation of intrinsic rhythmicity that can be used as a heuristic tool to simulate the properties of neuronal ensembles based on electrophysiological results from individual elements. Both models (*46, 47*) use phase plane analysis, which is specially suited to describing the behavior of two-variable systems exhibiting periodicity (*49*). In general in such analysis, oscillatory properties of single cells may be demonstrated by plotting two of the variables that describe a phase plane. In this plot the characteristics of the nullclines (lines along which one or the other variable is not changing with time, that is $dx/dt = 0$) determine the dynamic behavior of the cell such that regions of negative slope are associated with oscillatory behavior.

The general form of the equations used by Rose and Hindmarsh (*46*) is given by three variables, x, y, and z. These describe the resting potential (x), a recovery variable (y), and a slow adaptation variable (z). The properties of the equations were represented by using either xy or xz phase plane analyses. Although the xz phase plane analysis is useful in allowing a direct comparison between the equations and the properties of the thalamic neurons, the xy phase plane gave a more accurate portrait of the solutions. To generate the two types of oscillations found in thalamic neurons, the parameters in the equations were varied to yield a xz phase plane with five equilibrium points. The equation then generated two unstable domains separated and flanked by the three stable regions, which induced an upper or lower limit cycle in response to an applied current pulse, depending on the location of the x nullcline. The location of the nullcline in response to the current pulse depended on the value of the steady state current. When a current pulse was applied the model moved from a stable resting potential to stable oscillations. This finding indicated that the numerical solution to the complete set of equations (solving for x, y, and z) should give results similar to the behavior of thalamic neurons, which switch from a passive response to either tonic or burst firing. This was indeed the case (Fig. 3A). The current pulse, subthreshold at the resting membrane potential, will activate the cell if the membrane is either depolarized or hyperpolarized from that value. Similar properties were displayed by the mathematical model of Rose and Hindmarsh (*46*) (Fig. 3B).

The model by Goldbeter and Moran (*47*) is based on that of an autocatalytic reaction in which an allosteric enzyme (E) transforms a substrate (S) into a product (P). The substrate is supplied at a constant rate, while the product, which potentiates the enzyme, is removed at a rate proportional to its concentration (with a rate constant k_s) (Fig. 3C). In the absence of product recycling, this system is capable of only two types of dynamic behavior depending on the value of v, that is, the rate of substrate input; it either evolves toward a stable steady state or toward a regime of sustained oscillations. Oscillations occur in a range bounded by two critical values of v. These oscillations correspond to a limit cycle in the phase plane formed by the concentration of substrate and product. Such periodic behavior accounts for the metabolic oscillations of glycolysis in yeast and muscle (*47*).

However, in the presence of product recycling, two rather than one oscillatory domains are found. These two domains are very similar to those observed electrophysiologically in the in vitro studies (*40*). Indeed, for certain values of v, the product nullcline has two regions of negative slope, and the system is capable of switching back and forth between two stable limit cycles when v is changed (Fig. 3D). Thus two modes of periodicity exist under similar, but not identical, conditions. Figure 3D illustrates the predicted trajectories for two values of v. The form of the product nullcline produces a small amplitude and a large amplitude limit cycle. The two well-separated domains of oscillations share a portion of the phase plane trajectory, moving from a to b on the small cycle and in the opposite direction during the large cycle. The model shows two distinct modes of oscillatory behavior of product γ when the value of v/s changes with time (Fig. 3E).

In these two models the occurrence of multiple modes of oscillation is linked in the phase plane to the existence of a nullcline with two regions of negative slope. Although the two are in many ways equivalent, it is reassuring that, as indicated by Goldbeter and Moran (*47*), well-defined molecular events can reproduce such oscillatory behavior. Chemically mediated oscillation, especially as it relates to the $g_{K^+(Ca^{2+})}$ (Table 1), is an important component of the intrinsic electrical properties of neurons.

The findings indicate that the limit-cycle properties of electrophysiological elements may be treated mathematically in a rigorous manner. These models represent the initial step in implementing oscillatory parameters to the successful connectivity networks that are being so actively developed (*50*). Because of the state-dependent nature of the electroresponsiveness responsible for neuronal ensemble oscillation, such oscillations may be considered to be dissipative structures (*51*). In particular, such states may be generated "as needed" (*52*) (for example, sleep) in a less deterministic manner than the close to invariant reflex-like sequences that are often considered when studying other types of neuronal functions.

Dynamic Linkage

Another aspect of oscillation and resonance in the overall function of the CNS relates to the organization of circuits during ontogeny. Tremor is a universal characteristic of motor behavior in the vertebrate embryo (*53*). These circuits are produced initially by synchronous intrinsic spontaneous activity of spinal motoneurons. Because such activity is the product of the oscillation and resonance of particular sets of neurons, one can propose that it may be an important factor in the organization of those properties of connectivity that must be tuned by function (*54*). That is to say, once the connectivity has reached some degree of specificity by, for instance,

the presence of adhesive surface molecules (*55*), the electrical activity could be the next step in the precise specification of neuronal circuits (*54*). For this property of oscillation and resonance to be useful, such electroresponsiveness should be present in the neurons that participate in this tremor pathway at early stages.

This is in fact the case. Groups of motoneurons in young animals demonstrate oscillatory activity similar to that recorded from the IO nucleus (*56, 57*). These motoneurons have low-threshold Ca^{2+} action potentials (*56*). Similar currents have been observed in embryonic dorsal root ganglion cells (*58*). The low-threshold conductance becomes less prominent in these two types of cells during development. This finding has been interpreted as indicating that constant reverberation is important in specifying neuronal connectivity via physiological tremor, or via the processes known as afference or efference copy (*59*). During maturation, as specificity is attained, this immature electrical activity becomes less prominent.

To specify the connectivities as stated above, important cell biological and biochemical events must occur to stabilize synaptic inputs and localize the excitable sites to particular areas on the cell surface. Such stabilization would probably be best served by inward Ca^{2+} movement. Calcium entry would then not only generate electrophysiological activity in the cell, but also act as a second messenger to trigger the biochemical cascades necessary to modify the local distribution and activation of ionic channels and the regulation of gene expression. Increased intracellular Ca^{2+} influences gene expression (*60*). This type of mechanism must ultimately be responsible for the stabilization of the connectivity as specified by the sensory-motor oscillatory reentry that occurs during embryonic tremor.

Conclusions

Especially during development, oscillation and resonance allow single elements in the CNS to be woven into functional states capable of representing and embedding (*61*) external reference frames into neuronal connectivity (*39*). In addition to these embedding properties, oscillation and resonance generate global states such as sleep-wakefulness rhythms (*42*) and probably emotional and attentive states (*62*). Although sensory nerve pathways deliver messages to the CNS that are quite invariant with respect to given sensory stimuli, the manner in which the CNS treats these messages depends on the functional state of each relay station (*63*). Thus, rather than a simple mirror of the external world, the CNS embodies a dialogue between the internal states generated by the intrinsic electrical activity of the nerve cells and their connectivity, which represents the internal context, and the information that reaches the brain from the senses. This latter point may also be significant to CNS pathology if one considers that alterations of this intrinsic reference frame may underlie much that is important to certain neurological and psychiatric conditions (*64*).

Still more fundamental, however, is the possibility that the functional organization of the CNS, based in part on the intrinsic activity of neurons, may be the key to understanding the nature of subjectivity. In principle one can see how the intrinsic activity of neurons, which reflect a closed reference system, may be the stage on which our image of the external world is ultimately generated.

REFERENCES AND NOTES

1. J. Bernstein, *Arch. Ges. Physiol.* **1**, 173 (1868).
2. A. L. Hodgkin and A. F. Huxley, *J. Physiol. (London)* **117**, 500 (1952); ———, B. Katz, *ibid.* **116**, 424 (1952).
3. J. S. Coombs, J. C. Eccles, P. Fatt, *ibid.* **130**, 326 (1955).
4. By spontaneous is meant activity that is not related directly to any sensory stimuli or the result thereof. Reflexology in its present sense assumes that nervous activity arises from sensory input.
5. E. Kandel, *Cellular Basis of Behavior* (Freeman, San Francisco, 1976).
6. B. Sackman and E. Nehr, Eds. *Single Channel Recordings* (Plenum, New York, 1983).
7. P. Greengard, *Science* **199**, 146 (1978); E. J. Nestler and P. Greengard, *Protein Phosphorylation in the Nervous System* (Wiley, New York, 1984).
8. F. E. Bloom, *FASEB J.* **2**, 32 (1988).
9. W. E. Hahn, N. Chaudhari, L. Beck, K. Kilber, D. Peffley, *Cold Spring Harbor Symp. Quant. Biol.* **47**, 465 (1983); R. J. Milner and J. G. Sutcliff, *Nucleic Acids Res.* **11**, 5497 (1983).
10. R. Llinás and R. Hess, *Proc. Natl. Acad. Sci. U.S.A.* **73**, 2520 (1976).
11. R. Llinás, M. Sugimori, K. Walton, *Soc. Neurosci. Abstr.* **3**, 58 (1977).
12. P. A. Schwartzkroin and M. Slawsky, *Brain Res.* **135**, 157 (1977); R. K. S. Wong, D. A. Prince, A. I. Basbaum, *Proc. Natl. Acad. Sci. U.S.A.* **76**, 989 (1979).
13. R. Llinás and M. Sugimori, *J. Physiol. (London)* **305**, 171 (1980).
14. R. W. Tsien, D. Lipscombe, D. V. Madison, K. R. Bley, A. P. Fox, *Trends Neurosci.* **11**, 431 (1988).
15. R. Llinás and Y. Yarom, *J. Physiol. (London)* **315**, 549 (1981); *ibid.*, p. 569.
16. S. Hagiwara, S. Ozawa, O. Sand, *J. Gen. Physiol.* **65**, 617 (1975).
17. By single-cell oscillator I mean a neuron capable of self-sustained rhythmic firing independent of synaptic input. By single-cell resonation, I mean rhythmic firing occurring in response to electrical or ligand-dependent oscillatory input. Resonance implies that the intrinsic electroreponsive properties of the target neurons are organized to respond preferentially to input at specific frequencies.
18. B. Rudy, *Neuroscience* **25**, 729 (1988).
19. J. A. Connor and C. F. Stevens, *J. Physiol. (London)* **213**, 1 (1971).
20. R. W. Meech and N. B. Standen, *ibid.* **249**, 211 (1975).
21. S. Grillner, *Science* **228**, 143 (1985); L. K. Kaczmarek and I. B. Levitan, *Neuromodulation* (Oxford Univ. Press, Oxford, 1987).
22. W. Ross and R. Werman, *J. Physiol. (London)* **389**, 319 (1987).
23. D. W. Tank, M. Sugimori, J. A. Connor, R. R. Llinás, *Science* **242**, 773 (1988).
24. D. A. Wollner and W. A. Catterall, *Proc. Natl. Acad. Sci. U.S.A.* **83**, 8424 (1986).
25. M. Sugimori, R. Llinás, K. Angelides, *Soc. Neurosci. Abstr.* **12**, 463 (1986).
26. The low-threshold Ca^{2+} conductance is synonymous with the T channels, and the high-threshold Ca^{2+} conductance refers to the N and L channels [M. C. Nowycky, A. P. Fox, R. W. Tsien, *Nature* **316**, **440** (1985)], but also to the newly described P channels in Purkinje cells (R. R. Llinás, M. Sugimori, J. W. Lin, B. Cherksey, *Proc. Natl. Acad. Sci. U.S.A.*, in press), which are not blocked by dihydropyridine or Ω conotoxin.
27. M. M. Salpeter and R. H. Loring, *Prog. Neurobiol.* **25**, 297 (1985).
28. W. J. Nelson and P. J. Veshnok, *J. Cell Biol.* **103**, 1751 (1986); Y. Sambuy and E. Rodriguez-Boulan, *Proc. Natl. Acad. Sci. U.S.A.* **85**, 1529 (1988).
29. The axons of IO cells synapse on cerebellar Purkinje cells as climbing fibers; there is one climbing fiber per Purkinje cell. Climbing fiber activation results in a stereotypic action potential burst (the complex spike) in Purkinje cells.
30. J. Bower and R. Llinás, *Soc. Neurosci. Abstr.* **9**, 607 (1983).
31. K. Sasaki and R. Llinás, *Biophys. J.* **47**, 53a (1985).
32. R. Llinás and Y. Yarom, *J. Physiol. (London)* **376**, 163 (1986).
33. C. Sotelo, R. Llinás, R. Baker, *J. Neurophysiol.* **37**, 541 (1974).
34. M. Ito, M. Yoshida, K. Obata, N. Kawai, M. Udo, *Exp. Brain Res.* **10**, 64 (1970).
35. R. Llinás and M. Muhlethaler, *J. Physiol. (London)* **404**, 215 (1988).
36. R. R. Llinás and R. A. Volkin, *Exp. Brain Res.* **18**, 68 (1973).
37. C. D. Marsden, J. C. Meadows, G. W. Lange, R. S. Watson, *Electroencephalogr. Clin. Neurophysiol.* **27**, 169 (1969).
38. R. Llinás, in *Movement Disorders: Tremor*, L. J. Findley and R. Capildeo, Eds. (Macmillan, London, 1984), pp. 475–477; A. Cohen, *J. Neurosci. Methods* **21**, 113 (1987).
39. A. Pellionisz and R. Llinás, *Neuroscience* **16**, 245 (1985).
40. H. Jahnsen and R. Llinás, *J. Physiol. (London)* **349**, 227 (1984).
41. M. Deschenes, M. Paradis, J. P. Roy, M. Steriade, *J. Neurophysiol.* **51**, 1196 (1984).
42. M. Steriade and M. Deschenes, *Brain Res. Rev.* **8**, 1 (1984).
43. M. Steriade and R. Llinás, *Physiol. Rev.* **68**, 649 (1988).
44. Thus, in utero respiratory movements occur only during rapid eye movement (REM) sleep [H. Rigatto, M. Moore, D. Cates, *J. Appl. Physiol.* **61**, 160 (1986)].
45. F. Crick, *Proc. Natl. Acad. Sci. U.S.A.* **81**, 4586 (1984).
46. R. M. Rose and J. L. Hindmarsh, *Proc. R. Soc. London* **225**, 161 (1985).
47. A. Goldbeter and F. Moran, *Eur. Biophys. J.* **15**, 277 (1988).
48. R. Fitzhugh, *Biophys. J.* **1**, 445 (1961).
49. N. Minorsky, *Nonlinear Oscillations* (Van Nostrand, Princeton, NJ, 1967).
50. D. W. Tank and J. J. Hopfield, *Sci. Am.* **257**, 104 (December 1987).
51. G. Nicolis and I. Prigogine, *Self-Organization in Nonequilibrium Systems* (Wiley, New York, 1977). This type of dissipative structure would ensure sufficient computational variance through oscillation reentry and the generation of the so-called attractor states [A. T. Winfree, *The Geometry of Biological Time* (Springer, New York, 1980)]. Indeed, in neuronal networks with recurrent connectivity, chaotic firing may gravitate toward a stable pattern (an attractor) despite the initial conditions of the circuit.
52. By "as needed" I mean that a given firing pattern in a central nucleus or cortical area is not simply the product of synaptic input and connectivity, but that intrinsic electrical properties have an additional formative role that becomes evident under some modulatory conditions, for example, membrane hyperpolarization. These intrinsic properties shape the anatomically specified, but functionally permissive, brain circuits into complex functional states.

53. V. Hamburger and M. Balaban, *Dev. Biol.* **7**, 533 (1963).
54. R. Llinás, in *Mind Waves*, C. Blakemore and S. Greenfield, Eds. (Basil Blackwell, Oxford, 1987), pp. 339–358.
55. G. M. Edelman, *Proc. Natl. Acad. Sci. U.S.A.* **81**, 1460 (1984).
56. K. Walton and R. Llinás, *Soc. Neurosci. Abstr.* **12**, 386 (1986).
57. ———, *Proc. Int. Physiol. Sci.* **16**, 118 (1986).
58. E. Carbone and H. D. Lux, *J. Physiol. (London)* **386**, 547 (1987).
59. Y. I. Arshazsky, M. B. Berkinblit, O. I. Fukson, I. M. Gelfan, G. N. Orlovsky, *Brain Res.* **43**, 272 (1972); *ibid.*, p. 472.
60. M. E. Greenberg, E. B. Ziff, L. A. Greene, *Science* **234**, 80 (1986); J. I. Morgan and T. Curran, *Nature* **322**, 552 (1986).
61. This might occur by a process of synaptic stabilization [J. P. Changeux and A. Danchin, *Nature* **264**, 705 (1976)].
62. W. J. Freeman, *Mass Action in the Nervous System* (Academic Press, New York, 1975). Cortical oscillatory events at 40 Hz have been encountered in relation to attention [J. J. Bouyer, F. Montaron, J. M. Vahnee, M. P. Albert, A. Rougeul, *Neuroscience* **22**, 863 (1987)]; these findings confirm reports of fast somatoparietal rhythms under similar behavioral conditions in different mammals [S. Rougeul, J. J. Bouyer, L. Dedet, O. Debray, *Electroenceph. Clin. Neurophysiol.* **46**, 310 (1979)].
63. During sleep the thalamic neurons do not respond to visual stimuli, although the visual pathway to that nucleus is not significantly altered by the sleeping state [L. Maffei, G. Moruzzi, G. Rizzolatti, *Science* **149**, 563 (1965)].
64. This notion becomes particularly relevant when considering, for instance, tremor in Parkinson's disease or enhanced physiological tremor. These abnormalities are related to the low-threshold Ca^{2+} action potentials. In the latter case, harmaline has been shown to generate tremor (*36*) and to increase rebound excitation (*112*). Similar increase in excitability probably related to other conductances may underlie epileptic activity. From a psychiatric point of view, the question of authorhythmic behavior becomes relevant when considering that dreaming is of necessity the product of intrinsic activity, as are the hallucinatory states in certain psychoses. This implies that intrinsic thalamo-cortical activity is paramount in the genesis of such forms of psychopathology. That intrinsic electroresponsiveness is relevant to such states is suggested by pharmacological studies of thalamic neurons in vitro. Haloperidol (an antipsychotic agent) decreases the low-threshold Ca^{2+} conductance, whereas dopamine, which is involved in psychotic conditions, has a potentiating effect on this conductance [E. Geijo-Barrientos and R. Llinás, *Soc. Neurosci. Abstr.* **13**, 1012 (1987)].
65. B. W. Connors, M. G. Gutnick, D. A. Prince, *Soc. Neurosci. Abstr.* **7**, 593 (1981).
66. ———, *J. Neurophysiol.* **48**, 1302 (1982).
67. C. E. Strafstrom, P. C. Schwindt, W. E. Crill, *Brain Res.* **236**, 221 (1982).
68. C. E. Stafstrom, P. C. Schwindt, M. C. Chubb, W. E. Crill, *J. Neurophysiol.* **53**, 153 (1985).
69. B. A. MacVicar, *Brain Res.* **333**, 378 (1985).
70. L. S. Benardo, L. M. Masukawa, D. A. Prince, *J. Neurosci.* **2**, 1614 (1982).
71. M. Sugimori and R. Llinás, *Soc. Neurosci. Abstr.* **6**, 468 (1980).
72. H. Jahnsen, *J. Physiol. (London)* **372**, 129 (1986).
73. A. Constanti, M. Galvan, P. Franz, J. A. Sim, *Pfluegers Arch.* **404**, 259 (1985).
74. R. K. S. Wong and D. A. Prince, *Brain Res.* **159**, 385 (1978).
75. D. Johnston, J. J. Hablitz, W. A. Wilson, *Nature* **286**, 391 (1980).
76. D. A. Brown and W. H. Griffith, *J. Physiol. (London)* **337**, 303 (1983).
77. A. R. Kay and R. K. S. Wong, *ibid.* **392**, 603 (1987).
78. B. H. Gahwiler and D. A. Brown, *Neurosci. Lett.* **76**, 301 (1987).
79. H. Kita, T. Kita, S. T. Kitai, *Exp. Brain Res.* **60**, 63 (1985).
80. V. Misgeld, P. Calabresi, H. U. Dolt, *Pfleugers Arch.* **407**, 482 (1986).
81. E. Cherubini and L. Lanfumey, *Neuroscience* **21**, 997 (1987).
82. A. Alonso and R. Llinás, *Soc. Neurosci. Abstr.* **13**, 536 (1987).
83. J. Lopez-Barneo and R. Llinás, *J. Neurophysiol.* **60**, 853 (1988); *ibid.*, p. 869.
84. J. T. Williams, R. A. North, S. A. Shedner, S. Nishi, T. M. Egan, *Neuroscience* **13**, 137 (1984).
85. R. Llinás, S. A. Greenfield, H. Jahnsen, *Brain Res.* **294**, 127 (1984).
86. K. Murase and M. Randic, *J. Physiol. (London)* **334**, 141 (1983).
87. B. P. Fulton and K. Walton, *ibid.* **317**, 25P (1981); V. Harada and T. Takahashi, *Proc. Jpn. Acad.* **57(B)**, 394 (1981); K. Walton and B. P. Fulton, *Neuroscience* **19**, 669 (1986).
88. P. C. Schwindt and W. E. Crill, *J. Neurophysiol.* **44**, 827 (1980).
89. Y. Yarom, M. Sugimori, R. Llinás, *Neuroscience* **16**, 719 (1985).
90. D. G. Owen, M. Segal, J. L. Barker, *Nature* **311**, 567 (1984).
91. O. Belluzzi, O. Sacchi, E. Wanke, *J. Physiol. (London)* **358**, 109 (1985).
92. M. Galvan and P. R. Adams, *Brain Res.* **244**, 135 (1982).
93. J. V. Halliwell, *J. Physiol. (London)* **341**, 10P (1983).
94. M. Deschenes, J. P. Roy, M. Steriad, *Brain Res.* **239**, 289 (1982).
95. T. M. Burlhis and G. K. Aghajanian, *Synapse* **1**, 582 (1988).
96. R. W. Greene, H. L. Haas, R. W. McCarley, *Science* **234**, 738 (1986).
97. C. S. Leonard and R. Llinás, *Soc. Neurosci. Abstr.* **13**, 1012 (1987).
98. R. Llinás and Y. Yarom, *ibid.* **12**, 174 (1986).
99. P. C. Schwindt and W. E. Crill, *J. Neurophysiol.* **43**, 1700 (1980).
100. K. Walton and R. Llinás, *Soc. Neurosci. Abstr.* **12**, 382 (1986).
101. B. Gustafsson, M. Galvan, P. Grafe, H. Wigstrom, *Nature* **299**, 252 (1982).
102. M. Segal, M. A. Rogawski, J. L. Barker, *J. Neurosci.* **4**, 604 (1984).
103. G. K. Aghajanian, *Nature* **315**, 501 (1985).
104. M. Segal, *Brain Res.* **359**, 347 (1985).
105. M. Galvan and C. Sedlmeir, *J. Physiol. (London)* **356**, 115 (1984).
106. O. Belluzzi, O. Sacchi, E. Wanke, *ibid.* **358**, 91 (1985).
107. H. Kasai, M. Kameyama, K. Yamaguchi, J. Fuduka, *Biophys. J.* **49**, 1243 (1986).
108. A. Constanti and M. Galvan, *J. Physiol. (London)* **335**, 153 (1983).
109. J. V. Halliwell and P. B. Adams, *Brain Res.* **250**, 71 (1982).
110. J. R. Hotson, D. A. Prince, P. A. Schwartzkroin, *J. Neurophysiol.* **42**, 889 (1979).
111. M. Segal and J. L. Barker, *ibid.* **51**, 1409 (1984).
112. Y. Yarom and R. Llinás, *J. Neurosci.* **7**, 1166 (1987).
113. A. Constanti and D. A. Brown, *Neurosci. Lett.* **24**, 289 (1981).
114. B. E. Alger and R. A. Nicoll, *Science* **210**, 1122 (1980).
115. D. A. Brown and W. H. Griffith, *J. Physiol. (London)* **337**, 287 (1983).
116. D. V. Madison and R. A. Nicoll, *ibid.* **372**, 221 (1986).
117. E. F. Barrett, J. N. Barrett, W. E. Crill, *ibid.* **304**, 251 (1980).
118. P. C. Schwindt and W. E. Crill, *J. Neurophysiol.* **46**, 1 (1981).
119. T. Kawai and M. Watanabe, *Br. J. Pharmacol.* **87**, 225 (1986).
120. D. Hughes, R. N. McBurney, S. M. Smith, R. Zorec, *J. Physiol. (London)* **392**, 231 (1987).
121. R. Llinás and Y. Yarom, unpublished data.
122. R. Llinás and M. Sasaki, unpublished data.
123. R. Llinás and H. Jahnsen, *Nature* **297**, 406 (1982).