Annu. Rev. Neurosci. 2004. 27:393–418
doi: 10.1146/annurev.neuro.26.041002.131128

First published online as a Review in Advance on February 26, 2004

ELECTRICAL SYNAPSES IN THE MAMMALIAN BRAIN

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Key Words gap junction, electrotonic synapse, electrical coupling, connexin, connexin36

■ **Abstract** Many neurons in the mammalian central nervous system communicate through electrical synapses, defined here as gap junction–mediated connections. Electrical synapses are reciprocal pathways for ionic current and small organic molecules. They are often strong enough to mediate close synchronization of subthreshold and spiking activity among clusters of neurons. The most thoroughly studied electrical synapses occur between excitatory projection neurons of the inferior olivary nucleus and between inhibitory interneurons of the neocortex, hippocampus, and thalamus. All these synapses require the gap junction protein connexin36 (Cx36) for robust electrical coupling. Cx36 appears to interconnect neurons exclusively, and it is expressed widely along the mammalian neuraxis, implying that there are undiscovered electrical synapses throughout the central nervous system. Some central neurons may be electrically coupled by other connexin types or by pannexins, a newly described family of gap junction proteins. Electrical synapses are a ubiquitous yet underappreciated feature of neural circuits in the mammalian brain.

INTRODUCTION

The mammalian brain excels at rapid information processing, thanks to its massively parallel architecture and the high operational speed (by biological standards) of its neuronal elements. Neurons generate rapid signals by controlling ionic current flow across their membranes. The most common mechanism for signaling between neurons is the neurotransmitter-releasing chemical synapse. Faster and simpler signaling can be achieved with electrical synapses, specialized junctions that allow ionic current to flow directly between neurons. The vast majority of electrical synapses are membrane-to-membrane appositions called gap junctions, which are clusters of transcellular channels composed of protein subunits termed connexins. This type of electrical synapse, also known as the electrotonic synapse, can mediate electrical coupling between cells, and it has functional properties strikingly different from those of chemical synapses (Bennett 1977). Most

notably, vertebrate electrical synapses are bidirectional. With their speed, simplicity, and reciprocity, electrical synapses are a unique feature of neuronal circuits in the mammalian brain. Nevertheless, the prevalence of electrical synapses has been recognized only in the past few years.

The notion that neurons communicate electrically is almost as old as the idea of bioelectricity itself (Eccles 1982, Cowan & Kandel 2001). Studies of crayfish and shrimp neurons offered the first compelling evidence for electrical synapses (Furshpan & Potter 1957, Watanabe 1958), and electrical synapses were revealed in the vertebrate central nervous system of teleost fish soon after (Bennett et al. 1959). Electrical synapses in mammalian brains proved much harder to find. Single-cell recordings provided the first strong evidence for mammalian electrical synapses in the mesencephalic nucleus of cranial nerve V (Hinrichsen 1970, Baker & Llinás 1971), the vestibular nucleus (Wylie 1973, Korn et al. 1973), and the inferior olivary nucleus (Llinás et al. 1974). The most convincing way to demonstrate electrotonic coupling is to record intracellularly from two neighboring cells simultaneously, a procedure that is exceptionally difficult to perform in the intact brain. Studies of electrical synapses in the mammalian brain languished for years, even as breakthroughs were made in the general physiology of gap junctions (Spray et al. 1979, 1981) and the molecular biology of connexins (Willecke et al. 2002).

Electrical synapses are now being intensively examined in mammals, thanks to recent technical developments in electrophysiology, isolated brain slice preparations, cell labeling and imaging, molecular cloning, and transgenics. In this review, we examine the burgeoning evidence that electrical synapses function throughout the mammalian brain and describe pertinent studies of nonmammalian and nonneuronal gap junctions. We do not review the roles of gap junctions in early neural development and the functions of glia, and we do not discuss gap junction–free forms of electrical communication (Jefferys 1995).

STRUCTURE AND MOLECULAR COMPOSITION OF ELECTRICAL SYNAPSES

Gap Junctions and Connexins

The most visible and common structural correlate of electrical synapses is the gap junction, which is seen most readily with electron microscopy using the freeze-fracture technique. Gap junctions are clusters of connexin-containing channels that are coextensive across regions of apposing membranes of coupled cells (Evans & Martin 2002). A gap of extracellular space separates the two membrane leaflets, usually by ~2–3 nm. Gap junctions between neurons have been observed in the majority of cases where electrophysiological evidence for electrical synapses is well established.

Neuronal gap junctions are often synonymous with electrical synapses, but there are apparent limitations to this assumption. Tissue preparation can both destroy

bona fide gap junctions and create spurious gap junction–like structures (Brightman & Reese 1969). Gap junctions are notoriously difficult to observe, and the absence of evidence for gap junctions cannot be construed as evidence for the absence of electrical coupling. Gap junction channels may be functional even when they are too widely dispersed to form conventional gap junctions (Williams & DeHaan 1981). Conversely, electrotonic coupling may be absent despite the presence of virtually normal-looking gap junctions (Raviola & Gilula 1973, De Zeeuw et al. 2003).

Connexins are a family of proteins with ~20 isoforms in humans and mice (Willecke et al. 2002). Across species there are ~40 connexin orthologues. In the most commonly used nomenclature, connexins are named for their predicted molecular weights (e.g., Cx36 has a mass of ~36 kDa). Each gap junction hemichannel, also known as a connexon, is a connexin hexamer. Most cells can express multiple connexins, and connexons can be homomeric or heteromeric. Only some combinations of homomeric connexons can form functional heterotypic channels; Cx36 may function only homotypically (Al-Ubaidi et al. 2000, Teubner et al. 2000).

Approximately half of the mammalian connexins are abundant in the central nervous system. Several are strongly expressed in astrocytes (Cx26, Cx30, Cx43) and oligodendrocytes (Cx29, Cx32, Cx47) (Nagy et al. 2001, Menichella et al. 2003, Odermatt et al. 2003), but most are not expressed in neurons (Rash et al. 2001a,b; Odermatt et al. 2003). Cx36, which is the mammalian orthologue of fish Cx35 (O'Brien et al., 1998), is expressed widely in the brain (Condorelli et al. 2000). Data from freeze-fracture replica immunolabeling indicate that Cx36 protein appears in neuron-neuron gap junctions but not in gap junctions between astrocytes and/or oligodendrocytes (Rash et al. 2001a,b). Single-cell reverse transcription (RT)-PCR shows that the Cx36 message is consistently present in neurons of the hippocampus and neocortex (Venance et al. 2000). When the gene for Cx36 is knocked out in mice, electrical coupling that normally occurs between certain neurons in the retina (Deans et al. 2002) and in the neocortex (Deans et al. 2001, Blatow et al. 2003), hippocampus (Hormuzdi et al. 2001), thalamic reticular nucleus (TRN) (Landisman et al. 2002), and inferior olivary nucleus (Long et al. 2002, DeZeeuw et al. 2003) is eliminated or profoundly reduced. If Cx36 is not the exclusive connexin involved in coupling these neurons, it is at least a necessary constituent.

As prevalent as Cx36 seems to be, it is probably not the only connexin involved in mammalian electrical synapses. Neurons known to be electrically coupled, but which may not express Cx36, include those of the locus coeruleus (Christie et al. 1989, Alvarez et al. 2002), the horizontal cells of the retina (Deans & Paul 2001), and perhaps the pyramidal cells in the hippocampus (MacVicar & Dudek 1981, 1982; Draguhn et al. 1998; Schmitz et al. 2001). Cx45 is expressed in neurons of olfactory epithelium and bulb (Zhang & Restrepo 2002), in horizontal cells (D.L. Paul, personal communication), and in other brain regions (Maxeiner et al. 2003), and it may be a neuronal gap junction protein. Despite an initial claim that Cx47 is expressed by central neurons (Teubner et al. 2001), it is now clear that Cx47 is a product of oligodendrocytes and not of neurons (Menichella et al. 2003, Odermatt et al. 2003).

Innexins and Pannexins

Connexins may not be the only channel-forming proteins in the electrical synapses of the mammalian brain. Clues for this possibility originated with studies of invertebrates, where electrical synapses are pervasive and indeed where they were discovered. The nervous system of the nematode *Caenorhabditis elegans*, for example, has 302 neurons with ~600 gap junctions interconnecting them (White et al. 1986). Invertebrate gap junctions are similar to vertebrate gap junctions, yet connexins have been found only in vertebrate species. The genomes of *Drosophila melangaster* and *C. elegans* have now been entirely sequenced, and they do not have connexin-like sequences.

A family of genes unrelated to connexins, called the innexins (invertebrate connexins), codes for the proteins in the gap junctions of *Drosophila*; *C. elegans*; and species of Mollusca, Annelida, and Platyhelminthes (Phelan & Starich 2001). Innexin proteins form functional gap junction channels (Landesman et al. 1999). More recently, innexin-like genes were discovered in mammals (Panchin et al. 2000). The mammalian genes are called pannexins (Px) (pan meaning everything). Apart from two conserved cysteine residues in their extracellular loops, connexins have little sequence similarity to the innexins and pannexins, yet the overall topologies of connexin and pannexin subunits are remarkably alike (Hua et al. 2003). The function of pannexins in mammals is currently unknown. There is, however, clear expression of Px1 and Px2 mRNA in certain neurons, including pyramidal cells and interneurons of the hippocampus, and expression of Px1 in pairs of *Xenopus* oocytes forms robust and nearly voltage-independent intercellular channels (Bruzzone et al. 2003). Whether pannexin-dependent electrical synapses exist among vertebrate neurons remains to be determined.

DISTRIBUTION OF ELECTRICAL SYNAPSES IN THE BRAIN

On the basis of the distribution of Cx36 expression alone, it seems likely that electrical synapses occur in every major region of the central nervous system (Condorelli et al. 2000), although compelling functional and morphological data have been collected for only a few areas. Here we highlight examples for which the evidence is strongest and the prospective functions are most interesting (Figure 1).

Inferior Olivary Nucleus

Neurons in the inferior olivary nucleus are the source of climbing fiber input to the cerebellar cortex. Thirty years ago, using both ultrastructural (Sotelo et al. 1974) and indirect electrophysiological (Llinás et al. 1974) evidence, researchers made a strong case for electrotonic interconnections between neurons of the cat inferior olive. Subsequent work used paired intracellular recordings to demonstrate

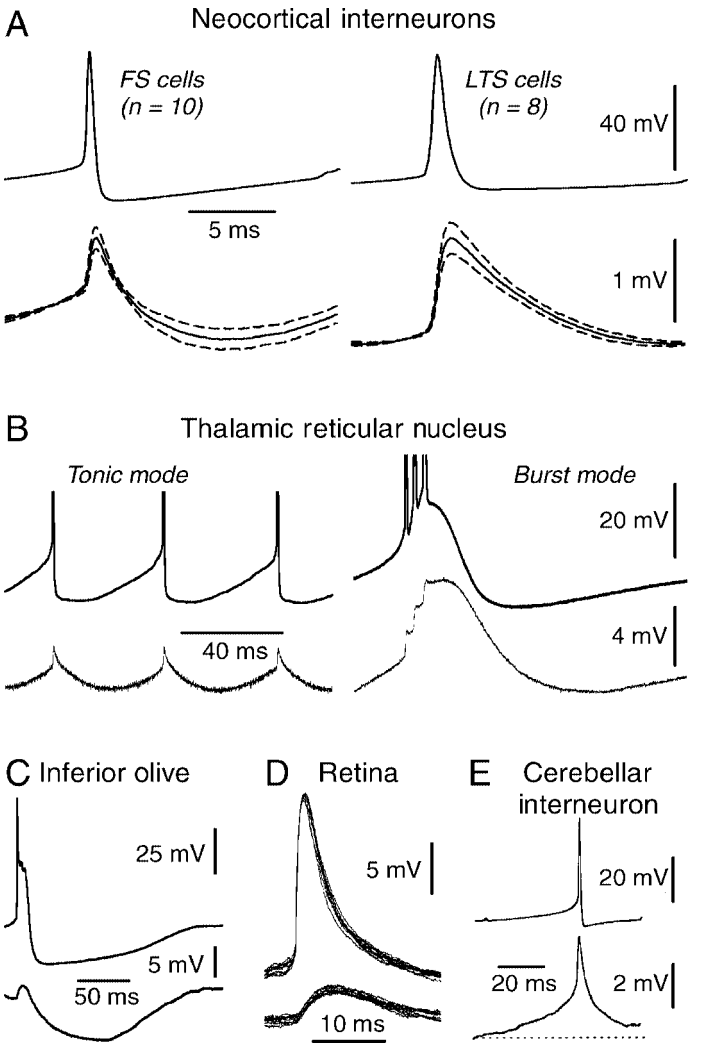

Figure 1 Electrical postsynaptic potentials in neurons from the mammalian brain. Each case illustrates simultaneous intracellular recordings from a pair of similar neurons, with presynaptic action potentials above and electrical postsynaptic potentials below. (*A*) Two types of inhibitory interneurons from the neocortex: fast-spiking (FS) cells and low threshold–spiking (LTS) cells. Traces are averaged from ten and eight neuron pairs, respectively, and the dashed lines are ±SD (J.R. Gibson, M. Beierlein, B.W. Connors, unpublished report). (*B*) Recordings from a pair of thalamic reticular neurons in tonically spiking mode (*left*) and bursting mode (*right*). Action potentials are truncated (from Long et al. 2004). (*C*) Inferior olivary neurons (MA Long, unpublished report). (*D*) AII amacrine neurons from the retina (Veruki & Hartveit 2002a). (*E*) Cerebellar interneurons (Mann-Metzer & Yarom 1999).

electrical synapses directly in the inferior olive of guinea pig (Llinás & Yarom 1981), rat (Devor & Yarom 2002), and mouse (Long et al. 2002) in vitro. Injections of Lucifer yellow (Benardo & Foster 1986) or neurobiotin (Devor & Yarom 2002) yielded dye coupling. The gap junctions between olivary neurons appear to contain Cx36, as demonstrated by both freeze-fracture immunolabeling (Rash et al. 2000) and thin-section electron microscopic immunocytochemistry (Teubner et al. 2000).

Many inferior olivary neurons have an unusual propensity to generate large, spontaneous, synchronous, subthreshold fluctuations of membrane voltage at 2–8 Hz (Figure 2*A*) (Benardo & Foster 1986, Devor & Yarom 2002). Indirect evidence implies that these rhythms emerged from an electrically coupled network of neurons that are, when uncoupled, inherently quiescent (Manor et al. 2000). This was recently tested in mice with a null mutation for Cx36. Both the prevalence and the strength of electrical synapses were dramatically reduced in Cx36 knockout mice, as expected, but spontaneous subthreshold rhythms were similar in size, shape, and frequency to those of wild-type animals (see Figure 2*A*,*B*,*C*) (Long et al. 2002, De Zeeuw et al. 2003). Subthreshold rhythms and the spikes they evoked were strongly synchronized among neighboring cells in the wild-type olive; however, synchrony was abolished in the Cx36 knockout mouse (Figure 2*D*). These results imply that electrical synapses are necessary for the synchronization, but not the generation, of olivary rhythms. An alternate interpretation is that the uncoupled olivary neurons of the developing Cx36 knockout mouse express an abnormal complement of ion channels that yields intrinsic rhythmicity in individual neurons (De Zeeuw et al. 2003).

Thalamic Reticular Nucleus

The TRN is a thin layer of GABAergic neurons that surround and inhibit the relay nuclei of the dorsal thalamus. The TRN receives excitatory synapses from both thalamocortical and corticothalamic collaterals. It can influence the activity of the entire thalamocortical system, and it participates in rhythmic forebrain activity (McCormick & Bal 1997). TRN neurons have mutually inhibitory connections, but evidence suggests that this is not the whole story. TRN neurons have dendritic bundles and specialized dendrodendritic contacts (Ohara 1988). In situ hybridization showed heavy labeling for Cx36 mRNA in the TRN but not in relay nuclei (Condorelli et al. 2000). Cx36-like immunoreactivity was seen in all neurons of the TRN, but gap junctions remain elusive (Liu & Jones 2003). The most definitive evidence for electrical synapses was obtained from simultaneous recordings of neighboring pairs of rat and mice TRN neurons (Figure 1*B*) (Landisman et al. 2002). The prevalence, strength, biophysical properties, and Cx36-dependence of electrical connections between TRN neurons (Landisman et al. 2002, Long et al. 2004) are almost indistinguishable from those between inhibitory interneurons of the neocortex (Gibson et al. 1999, Deans et al. 2001).

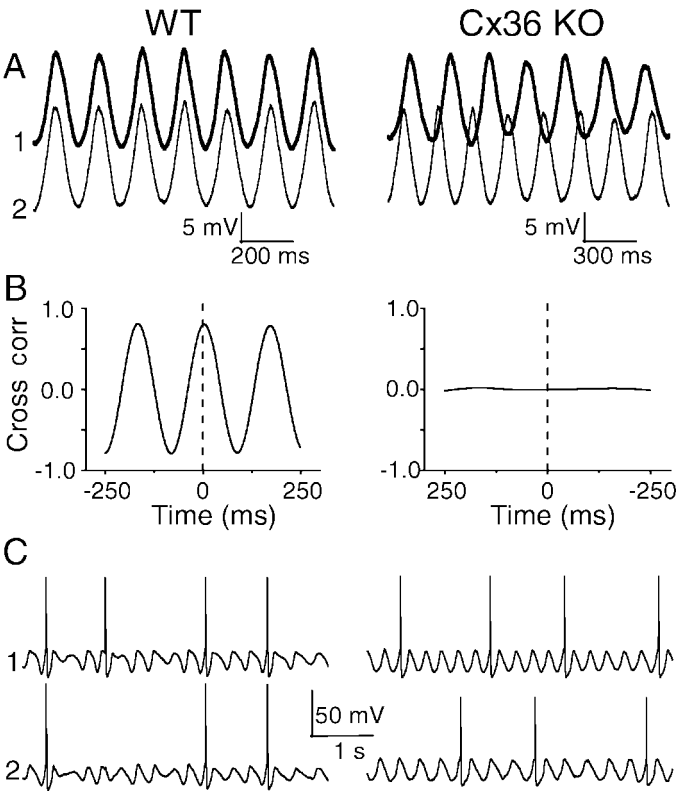

Figure 2 Subthreshold and suprathreshold synchrony in electrically coupled inferior olivary neurons. Left panels are from wild-type (WT) mice. Right panels are from Cx36 knockout (KO) mice. (*A*) Paired whole-cell recordings showing spontaneous subthreshold rhythmic activity in WT and KO cells. (*B*) Cross-correlograms demonstrate very high synchrony among the WT cells and no synchrony among the KO cells. (*C*) Subthreshold rhythms evoke occasional, but highly correlated, spikes in the WT and entirely uncorrelated spikes in the KO cells (from Long et al. 2002).

Electrical coupling in the TRN seems to be restricted to cells no more than 40 μm apart (Long et al. 2003). In this sense, coupling in the TRN resembles the spatially localized coupling in the inferior olivary nucleus (Devor & Yarom 2002). Furthermore, when subthreshold rhythms of $\sim$10 Hz were induced in TRN neurons with an agonist of metabotropic glutamate receptors, rhythms were synchronized only among small, closely adjacent clusters of coupled neurons (Long et al. 2003). Electrical synapses may coordinate local groups of TRN neurons, whereas more distant interactions within the TRN may occur via inhibitory connections.

Hippocampus

The excitatory cells of the hippocampus have been implicated in a variety of electronic interactions, some of which may involve electrical synapses (Jefferys 1995). Spencer & Kandel (1961) observed "fast prepotentials"—small, spike-like events of a few millivolts in the soma—and attributed them to action potentials from distal dendritic sites within the same neurons. MacVicar & Dudek (1981, 1982) suggested a different interpretation. With evidence from dye coupling, indirect electrophysiological tests, dual-intracellular recordings, and freeze-fracture gap junction observations, they argued that there are dendrodendritic and dendrosomatic electrical synapses between pyramidal cells in the CA3 region as well as between granule cells of the dentate gyrus. More recently, computer simulations of high-frequency oscillations led to suggestions that pyramidal cells may be electrotonically coupled through axoaxonal gap junctions (Draguhn et al. 1998, Traub et al. 2002). Physiological support for this idea now includes dye coupling and the successive propagation of antidromic spikelets from axon to soma to dendrite (Schmitz et al. 2001).

Despite its long history, the hypothesis that mature pyramidal and granule cells interact via electrical synapses is not quite compelling. Recent studies using paired whole-cell recordings have repeatedly revealed electrical synapses among inhibitory interneurons (see below) but not among excitatory cells. Although Cx36 mRNA has been observed in CA3 pyramidal cells (Condorelli et al. 1998, Venance et al. 2000), Cx36 protein has not been found. Fast hippocampal oscillations thought to require axoaxonal coupling were unaffected by the absence of Cx36 in two different studies of one knockout mouse (Hormuzdi et al. 2001, Buhl et al. 2003) and were only slightly reduced in a different Cx36 knockout mouse (Maier et al. 2002). It is conceivable that some other connexin, or a pannexin, accounts for coupling between pyramidal cells. Axoaxonal gap junctions have not been observed in the hippocampus (or any other cerebral cortical region). Although ultrastructural evidence for gap junctions between interneurons is abundant, reports of gap junctions between excitatory cells of the hippocampus are scant and suffer from uncertainties about the cell types involved. In short, the evidence that hippocampal pyramidal cells are electrically coupled is intriguing but limited.

Evidence that inhibitory interneurons of the hippocampus are interconnected by electrical synapses is more persuasive. Dendrodendritic gap junctions between interneurons are frequently seen in areas CA1 and CA3 (Kosaka & Hama 1985) and in the dentate gyrus (Kosaka 1983). Several types of gap junction–coupled interneurons have been identified (Katsumaru et al. 1988, Fukuda & Kosaka 2000), and dye coupling has been observed between inhibitory cells of the hilus and the CA1 (Michelson & Wong 1994). Paired-interneuron recordings have shown electrical coupling directly, and single-cell RT-PCR revealed Cx36 mRNA (Venance et al. 2000). Furthermore, although electrical coupling between pairs of interneurons was abundant in the CA3 and dentate regions of wild-type mice, it was absent in cells of Cx36 knockout mice (Hormuzdi et al. 2001).

The functions of electrical synapses between hippocampal interneurons are unknown. Most studies have focused on the possibility that they play a role in generating or modulating synchronous oscillations or seizure-like activity. Some researchers used gap junction–blocking drugs as a diagnostic test for gap junctions (e.g., Draguhn et al. 1998, Skinner et al. 1999, Jahromi et al. 2002), but the interpretation of these experiments must be tempered because of the notoriously nonspecific effects of the drugs (see below). Measurements in Cx36 knockout mice have implicated electrical synapses in the generation of gamma-frequency (30–70 Hz) rhythms, but not of fast ripples (140–200 Hz) or slower theta (5–10 Hz) rhythms (Hormuzdi et al. 2001, Traub et al. 2003, Buhl et al. 2003).

Neocortex

In the mature neocortex, as in the hippocampus, the case for electrical synapses between interneurons is currently much stronger than the case for electrical synapses between excitatory principal neurons (Galarreta & Hestrin 2001a). The first evidence for neocortical coupling came from studies of the mature primate sensorimotor cortex. Beautiful electron micrographs by Sloper (1972) and Sloper & Powell (1978) show numerous dendrodendritic and dendrosomatic gap junctions with features that strongly suggest inhibitory interneurons. In an elegant corroboration of this work, Fukuda & Kosaka (2003) recently described dendrodendritic gap junctions between the parvalbumin-immunolabeled interneurons of primary somatosensory, auditory, and visual areas in mature rats. Despite decades of ultrastructural investigations of the neocortex (Peters 2002), convincing gap junctions involving excitatory neurons in the neocortex have been described very rarely (see Peters 1980).

Recent electrophysiological studies strongly reinforce the ultrastructural evidence: Inhibitory cells are often coupled, whereas mature excitatory cells are rarely (if ever) coupled. Paired whole-cell recordings in rat neocortex showed that parvalbumin-expressing, fast-spiking (FS) interneurons are coupled to one another frequently ($>60\%$ of tested pairs) and strongly (mean coupling coefficients $\sim$0.07, ranging as high as 0.4; mean cell-cell coupling conductances $\sim$1.6 nS, ranging up to 5.5 nS) (Figure 1*A*) (Galarreta & Hestrin 1999, Gibson et al. 1999). Electrical coupling between FS cells is not limited to the adolescent ages commonly studied in vitro; it persists in fully mature mice (Galarretta & Hestrin 2002). Using intracellular recording and staining followed by electron microscopy, Tamás and colleagues (Tamás et al. 2000) confirmed that electrically coupled FS interneurons, as well as electrically coupled non-FS interneurons (called regular-spiking nonpyramidal cells by Szabadics et al. 2001), formed dendrodendritic gap junctions.

A striking feature of neocortical circuitry is the variety of distinct types of GABAergic interneurons in the neocortex. In both rats (Gibson et al. 1999) and mice (Deans et al. 2001), somatostatin-expressing interneurons of a type called low threshold–spiking (LTS) cells were often electrically coupled to each other (Figure 1*A*), but they were coupled only occasionally and weakly to the FS

interneurons. Another type of interneuron, termed the multipolar bursting (MB) cell, was also coupled to cells of the same type but not to FS cells (Blatow et al. 2003). In layer I of the neocortex, the late-spiking (LS) inhibitory interneuron made electrical synapses to other LS cells 83% of the time, but it coupled to non-LS interneurons only 2% of the time (Chu et al. 2003). Thus, the surprising evidence to date suggests that the large majority of neuronal gap junctions in the neocortex interconnect inhibitory interneurons of the same type. In effect, each type of interneuron forms an extended, gap junction–coupled network that is nearly independent, electrotonically, of each other type of coupled interneuron network.

Electrically coupled networks of interneurons are large. The probability and strength of coupling falls with intersomatic distance, and beyond 200 μm no coupling has been detected between pairs of either FS or LTS cells (Amitai et al. 2002). Considering this spatial profile of coupling along with measures of the density of interneurons, one infers that each interneuron is coupled to between 20 and 40 neighboring interneurons. It is not known whether such interneuron syncytia extend indefinitely across the cortical mantle, or whether they have distinct boundaries.

Direct tests of electrical coupling between pairs of excitatory cells (i.e., pyramidal cells or spiny stellate cells) or between pairs of excitatory and inhibitory cells in the neocortex have yielded generally negative results (Galarretta & Hestrin 1999, Gibson et al. 1999), and other studies using closely spaced paired-cell recordings from excitatory neurons have not reported coupling (e.g., Thomson & Deuchars 1997). This is consistent with the meager ultrastructural evidence for pyramid-pyramid gap junctions. The presence of Cx36 mRNA in some spiny neocortical neurons (Venance et al. 2000) suggests that Cx36 may serve as the substrate for the rare electrical coupling seen between interneuron-pyramidal cell pairs in the immature cortex (Venance et al. 2000, Meyer et al. 2002; cf. Galarretta & Hestrin 1999, Gibson et al. 1999). An early report showed dye coupling between mature pyramidal neurons (Gutnick & Prince 1981), but studies during development emphasized its postnatal transience (Connors et al. 1983, Peinado et al. 1993, Rorig et al. 1995, Bittman et al. 1997). Furthermore, dye coupling may not be a reliable measure of gap junction coupling among postnatal cortical neurons (Knowles et al. 1982, Connors et al. 1984, Gutnick et al. 1985, Rorig et al. 1996).

Cx36 appears to be necessary for the large majority of electrical coupling among the three types of neocortical interneurons tested to date. Single-cell RT-PCR showed consistent expression of Cx36 in several types of interneurons (Venance et al. 2000), and a histochemical reporter enzyme driven by the Cx36 promoter identified a variety of interneurons that included both parvalbumin- and somatostatin-expressing cells (Deans et al. 2001). When electrical coupling was tested in Cx36 knockout mice, it was nearly absent among FS interneurons (Deans et al. 2001, Hormuzdi et al. 2001), LTS interneurons (Deans et al. 2001), and MB interneurons (Blatow et al. 2003). Occasional weak coupling detected in some interneuron pairs of Cx36 knockout mice implies that another connexin

or a pannexin may account for a small fraction of the electrical synapses in the neocortex.

FS interneurons in vivo often display remarkably tight synchrony of spiking under physiological conditions (Swadlow 2003), and electrical coupling may account for some of this synchrony. When coupled pairs of FS neurons are stimulated in vitro, in the absence of functional chemical synapses, their electrical synapses alone can mediate robust, temporally close spike synchrony (Galarreta & Hestrin 1999, Gibson et al. 1999, Mancilla et al. 2003). Many FS pairs are connected by both electrical and GABAergic synapses, and this combination may actually facilitate synchronous states under some conditions (Támas et al. 2000, Galarreta & Hestrin 2001b, Lewis & Rinzel 2003). Synchronous activity can also occur among much larger cohorts of spatially extended interneurons. For example, agonists of mGluRs or muscarinic cholinergic receptors excite LTS cells and induce close spike synchrony and more widely correlated subthreshold rhythmic fluctuations (Beierlein et al. 2000). This type of synchronous activity is greatly reduced among the LTS cells of Cx36 knockout mice, implying that it depends on electrical synapses (Deans et al. 2001). Similarly, muscarinic receptor–induced rhythms in MB interneurons also require electrical coupling and Cx36, although synchronous activity in this system also depends on intact GABAergic synapses (Blatow et al. 2003).

Other Regions of the Central Nervous System

The retina is a famously coupled place, where nearly all types of neurons participate in electrical networks (Vaney 2002). Both homologous and heterologous electrical synapses occur in the retina. Paired-cell recordings of AII amacrine cells showed that their electrical synapses are functionally similar to those between neocortical interneurons (Figure 1*D*) (Veruki & Hartveit 2002a). Heterologously coupled pairs of AII amacrine cells and ON bipolar cells have a functional asymmetry in electrical coupling strength that is most likely due to the different input impedances of the two cell types (Veruki & Hartveit 2002b). When Cx36 is knocked out in mice, scotopic vision is strongly impaired (Guldenagel et al. 2001) because obligatory Cx36-dependent electrical synapses are lost between rods and cones and between AII amacrine cells and bipolar cells (Deans et al. 2002).

The olfactory bulb is, like the retina, a wonderland of extraordinary synaptic relationships that include electrical synapses. Neurons in both the bulb and the olfactory epithelium express Cx36 (Zhang & Restrepo 2003), and gap junctions appear between granule cells (Reyher et al. 1991). Mitral cells with dendrites in the same glomerulus of the bulb are probably coupled, whereas mitral cells projecting to different glomeruli are never coupled (Schoppa & Westbrook 2002). Electrical coupling in the olfactory bulb may play a role in coordinating oscillations (Friedman & Strowbridge 2003).

The locus coeruleus is a small cluster of widely projecting noradrenergic brainstem neurons implicated in the modulation of arousal and attention (Usher et al.

1999). There is strong evidence that electrical synapses synchronize subthreshold rhythms generated in the locus coeruleus of rodents (Christie et al. 1989, Alverez et al. 2002).

Electrical synapses occur at all levels of the mammalian motor system. Cx36 immunoreactivity is present within the neuronal gap junctions of the immature rat spinal cord (Rash et al. 2001b). Young motor neurons are electrically coupled (Fulton et al. 1980) in functionally relevant clusters (Walton & Navarrete 1991). Although motor neuron coupling declines steeply during the first postnatal week, Cx36 is still expressed in the adult (Chang et al. 1999). The progressive loss of gap junctions between developing motor neurons may reduce their correlated activity, which in turn may trigger synaptic competition between neuromuscular inputs (Personius & Balice-Gordon 2001). Electrical synapses may also help to synchronize spinal locomotor rhythms (Tresch & Kiehn 2000) and respiratory rhythm-generating neurons in the brainstem (Rekling et al. 2000). Higher in the motor system, within the neostriatum, electrical synapses occur between GABAergic local interneurons (Koos & Tepper 1999) and between the output cells (the medium spiny neurons) (Venance et al. 2003). The inhibitory interneurons of the cerebellar cortex are also coupled (Sotelo & Llinás 1972, Mann-Metzer & Yarom 1999). In each of these circuits, electrical synapses may enhance synchronous neuronal activity.

The literature abounds with additional claims for electrical synapses in the brain. Most of the evidence for these synapses is less than airtight. On the basis of the trends described above, however, persuasive evidence for electrical synapses may soon accrue for all brain regions.

FUNCTIONAL PROPERTIES OF GAP JUNCTIONS

Connexin Channels

The gating and permeation characteristics of gap junction channels have been extensively studied and reviewed (e.g., Harris 2001, Sáez et al. 2003). The salient properties of these channels are that the pores are wide (12–14 Å), single-channel conductances are variable and often large (10–300 pS), ion selectivity is relatively poor, and moderately large organic molecules (including tracers such as Lucifer yellow, neurobiotin, and fluorescien derivatives, and endogenous substances such as cAMP, cGMP, IP_3, glucose, and Ca^{2+}) can often permeate. Each of these traits varies broadly across connexin subtypes.

The central neuron-specific connexin, Cx36, has the smallest single-channel conductance of any connexin described, ~10–15 pS (Srinivas et al. 1999). Cx36 channels may be particularly impermeable to positively charged dyes such as neurobiotin (287 Da) (Teubner et al. 2000). Most attempts to produce dye coupling with Lucifer yellow or neurobiotin in demonstrably electrically coupled central neurons have failed (e.g., Gibson et al. 1999, Landisman et al. 2002), although some dye coupling between neocortical interneurons has been reported (Connors

et al. 1983, Benardo 1997). Dye coupling across Cx36-dependent gap junctions may be limited to systems that are strongly coupled, such as the AII amacrine cells of the retina (Deans et al. 2002).

Estimates based on biophysical data and ultrastructure imply that the number of connexin channels open at any given time is low (Lin & Faber 1988, Pereda et al. 2003). For example, on the basis of their size, the gap junctions interconnecting mature interneurons of the neocortex have ~150–380 connexin channels (Fukuda & Kosaka 2003). If we assume these are Cx36 channels (Deans et al. 2001) with a unitary channel conductance of 14 pS (Teubner et al. 2000) and a mean junctional conductance of ~0.2 nS in the mature cortex (Galarretta & Hestrin 2002), only ~4–9% of junctional channels are generally open. Immature (2–3 weeks of age) rat neocortical interneurons are more strongly coupled, with a mean estimated junctional conductances of 0.7–1.6 nS (Galarreta & Hestrin 1999, Gibson et al. 1999), but the size of their gap junctions is unknown.

Gap junction channels are gated by transjunctional voltage (V_j), the difference between the internal voltages of the interconnected cells (Furshpan & Potter 1957, Spray et al. 1979, Harris 2001). For most connexin channels, conductance is maximal when $V_j = 0$ and it declines symmetrically with deviations in either direction. The gating process is quite slow. Among connexins, Cx36 channels are the least voltage-dependent. Even with very large deviations of V_j ($\pm$100 mV), junctional conductance declines by less than half (Srinivas et al. 1999, Al-Ubaidi et al. 2000). This is consistent with measurements from pairs of neocortical interneurons, where no voltage-dependence was apparent when V_j was varied by $\pm$40 mV (Gibson et al. 1999). It seems unlikely that the slow and very weak voltage-dependence of Cx36 channel gating has biological significance.

Some connexins may function outside gap junctions. Hexameric hemichannels, or connexons, serve as nonjunctional, plasma membrane–spanning pores (Goodenough & Paul 2003, Sáez et al. 2003). The first reliable evidence for this came from neurons, the horizontal cells of catfish retina (DeVries & Schwartz 1992). In catfish horizontal cells, Cx26 connexons may mediate an unusual mechanism of feedback regulation of cone synapses (Kamermans et al. 2001). Cx36, however, appears unable to form functional hemichannels (Al Ubaidi et al. 2000), and the horizontal cells of mammalian retina may contain neither Cx36 nor Cx26 (Deans & Paul 2001). Although Cx43 hemichannels have interesting functions in astrocyte membranes (Ye et al. 2003), to date there is no evidence for operational hemichannels in native neurons of the mammalian brain.

Modulation and Regulation

One of the most important properties of chemical synapses is their ability to change strength as a function of prior activity and chemical regulation. Gap junctions can also be modified in diverse ways, although little is known about the specific mechanisms that regulate the electrical synapses of the brain.

ACTIVITY-DEPENDENT PLASTICITY Evidence of activity-dependent plasticity of mammalian electrical synapses is essentially nonexistent. Notable experiments in fish, however, show that the electrical synapses formed between auditory nerve endings (club endings) and Mauthner cells (large reticulospinal neurons) can either increase or decrease their junctional conductance as a function of prior neural activity (Yang et al. 1990, Pereda & Faber 1996, Pereda et al. 1998). The electrical synapses at club endings operate in parallel with excitatory, glutamatergic chemical synapses located within the same terminals. High-frequency stimulation of the auditory axons tends to enhance the strength of both the electrical and chemical components of these mixed synapses. Enhancement may last for hours, and it seems to depend on a close interaction between Cx35 channels and neighboring glutamatergic receptor–channels within the same synaptic endings (Pereda et al. 2003, Smith & Pereda 2003). Potentiation of the gap junctions depends on postsynaptic NMDA (N-methyl-D-aspartate) receptors and an increase of postsynaptic $[Ca^{2+}]_i$ (Yang et al. 1990, Pereda & Faber 1996), which leads to the activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaM-KII) (Pereda et al. 1998). Thus, there are remarkable mechanistic parallels between the long-term potentiation of mammalian glutamatergic synapses (Nicoll 2003) and that of fish electrical synapses.

The prospects for finding plasticity in mammalian electrical synapses are very good. Although the molecular basis for gap junction plasticity is unknown, the sequences of fish Cx35 and mammalian Cx36 are similar (O'Brien et al. 1998) and include several shared consensus phophorylation sites (Mitropoulou & Bruzzone 2003). Mixed electrical-chemical synapses have been observed in the mammalian spinal cord (Rash et al. 1996), neocortex (Sloper & Powell 1978, Fukuda & Kosaka 2003), brainstem (Sotelo et al. 1974, Rash et al. 2000), and elsewhere.

PH AND [Ca] SENSITIVITY The conductance of gap junction channels is reduced when intracellular $[H^+]$ or $[Ca^{2+}]$ increases. Whether either or both of these constitutes a physiological mechanism of channel regulation has long been debated (Rose & Rick 1978, Rozental et al. 2001). In most coupled systems of cells, Ca^{2+} is a much less potent regulator of gap junction conductance than $[H^+]$ is, and in general, $[Ca^{2+}]_i$ must rise to pathologically high concentrations for gap junctions to close.

Neural activity can either acidify or alkalinize the intracellular pH of central mammalian neurons by several tenths of a pH unit (Chesler 2003). The conductance of many gap junctions is exquisitely sensitive to the pH of the cytoplasm and nearly insensitive to extracellular pH (Spray et al. 1981). Cytoplasmic acidification tends to close channels, whereas alkalinization tends to open them. The effect of pH_i on junctional conductance varies widely across connexin types. In some cases the relationship is very steep and centered on the normal resting pH_i, suggesting physiological relevance. The regulation of central neuronal gap junctions by pH has not been studied in detail. Electrical coupling between HeLa cells transfected with Cx36 is readily abolished by acidification with 100% CO_2 (Teubner et al. 2000), but this was not further quantified. Acidification of central neurons reduces

the incidence of dye coupling in some cases (Church & Baimbridge 1991, Rorig et al. 1996) but not in others (Connors et al. 1984), whereas alkalinization may increase dye coupling (Church & Baimbridge 1991). Dye coupling is an imperfect assay of gap junction function, however, and direct tests of the pH sensitivity of central electrical synapses are needed.

NEUROTRANSMITTER MODULATION AND CONNEXIN PHOSPHORYLATION A variety of endogenous substances can modulate gap junctions. A few of these are well known as neurotransmitters. Impermeable extracellular agents almost always influence gap junctions via intracellular second messengers rather than by affecting channel properties directly. In the best-studied cases, gap junction channels are modified by kinases that phosphorylate one or more sites on the cytoplasmic domains of the connexins. All connexin subtypes have multiple phosphorylation sites for several types of kinases, and these may influence channel gating directly or regulate the assembly, trafficking, and turnover of gap junction channels (Lampe & Lau 2000).

Studies of retinal neurons have provided the most comprehensive evidence that the modulation of electrical synapses plays a physiologically important role (Piccolino et al. 1984, DeVries & Schwartz 1989). The action of dopamine in the retina is particularly well understood, although details differ depending on the species studied (Weiler et al. 2000). In general, an increase in ambient light triggers release of dopamine from amacrine or interplexiform cells. Dopamine then binds to D_1 receptors on horizontal cells and AII amacrine cells and activates their adenylyl cyclase. cAMP concentration then increases and activates cyclic AMP-dependent protein kinase (PKA), and PKA-mediated phosphorylation of connexins reduces the probability of channel opening, thus lowering gap junction conductance (McMahon et al. 1989). Because of extensive coupling with adjacent horizontal cells, receptive fields of horizontal cells in the absence of dopamine are larger than the spread of their dendrites. When their electrical synapses are suppressed by dopamine, receptive fields narrow considerably. Although most of this work was performed on fish and reptilian retinas, similar effects of dopamine have also been observed in mammalian retinas (e.g., Hampson et al. 1994). Dopamine is certainly not the only endogenous modulator of electrical synapses in retinal neurons. Nitric oxide, arachidonic acid, retinoic acid, and low intracellular pH all reduce gap junction coupling between horizontal cells (DeVries & Schwartz 1989, Miyachi et al. 1994, Weiler et al. 2000).

In an interesting twist, the electrical synapses between club endings and Mauthner cells in goldfish are actually enhanced by activation of dopamine receptors and PKA (Pereda et al. 1992). Fish Cx35 and mammalian Cx36 share a similar PKA consensus site (Mitropoulou & Bruzzone 2003), so there is a good chance that Cx36—and the mammalian electrical synapses constructed of it—are also modulated by PKA activation.

Dopamine and other neurotransmitters may also regulate neuronal coupling in the mammalian brain (Roerig & Feller 2000), although most evidence is indirect.

In the nucleus accumbens and striatum, activation of D_1 receptors tends to decrease dye coupling, whereas D_2 receptors often enhance coupling (O'Donnell & Grace 1993). In the supraoptic nucleus of the hypothalamus, a variety of manipulations including hormones, physiological state (i.e., lactation or dehydration), local synaptic activation, elevation of nitric oxide or cGMP, and histamine receptors increase dye coupling, whereas cAMP reduces it (Cobbett & Hatton 1984, Yang & Hatton 1987, Hatton 1998).

Pharmacology

Drugs are indispensable tools in experimental neurobiology. The substances that influence the function of gap junctions and hemichannels are chemically diverse (reviewed by Harris 2001, Rozental et al. 2001). Lipophilic compounds such as long-chain alcohols (heptanol and octanol) and the gaseous anesthetic halothane have long been known to reduce gap junction function (Johnston et al. 1980, Rozental et al. 2001). More recently, fatty acid amides such as oleamide, anandamide, and arachidonic acid were found to have a similar effect (Venance et al. 1995, Boger et al. 1998). All these drugs tend to have only partial efficacy, poor selectivity for different connexins, and significant effects on other cellular processes. Some of the derivatives of glycyrrhetinic acid, including carbenoxolone (originally isolated from licorice root), reversibly reduce connexin channel conductances (Davidson & Baumgarten 1988), albeit with partial efficacy and variable selectivity. Carbenoxolone has a reputation for being reasonably specific, but this is undeserved. The generally toxic effects of the drug are illustrated by the symptoms of licorice overindulgence, which include hypertension and hypokalemia due to interference with cortisol degradation (Walker & Edwards 1994). Several studies have reported that carbenoxolone does not influence neuronal membrane or chemical synaptic functions (e.g., Yang & Michelson 2001, Kohling et al. 2001, Schmitz et al. 2001). However, others have described significant effects of carbenoxolone on processes other than gap junctions, including increased action potential threshold and reduced repetitive firing rates (Rekling et al. 2000, Rouach et al. 2003).

A few other gap junction blockers have recently shown promise. All-*trans* retinoic acid potently reduced electrical coupling between horizontal cells of fish retina (Zhang & McMahon 2000) and other gap junction–coupled systems. Quinine, the antimalarial drug, selectively blocks Cx36 and Cx50 and moderately reduces Cx45. It has little effect on other connexins (Srinivas et al. 2001), but it does have a variety of nonjunctional effects. Mefloquine, a quinine derivative, is 100 times more potent than quinine in blocking Cx36 and seems much more specific (Srinivas & Spray 2003).

To summarize, most of the currently available blockers of connexins tend to be low in potency, only partially effective, and poorly selective. Caution is required when using them as experimental tools. Octanol, halothane, and carbenoxolone in particular have been widely used in neurophysiology, and their positive effects were often the primary evidence for implicating electrical synapses in the phenomena

under study. On the basis of the well-documented effects of these drugs on a wide range of nonconnexin ion channels, receptors, and enzymes, however, this is a dubious practice.

FUNCTIONS OF ELECTRICAL SYNAPSES

The generic capabilities of electrical synapses have been extensively reviewed (e.g., Bennett 1977, 1997; Jaslove & Brink 1987; Galarreta & Hestrin 2001a). Electrical synapses are faster than chemical synapses, but this advantage is minimized at mammalian body temperatures, where chemical synaptic delays are only 150 μsec (Sabatini & Regehr 1996). Perhaps the most singular attribute of electrical synapses is bidirectionality. Electrical synapses in the brain often interconnect neurons of similar type, size, and input resistance, using Cx36-dependent gap junctions (e.g., Galarreta & Hestrin 1999, Gibson et al. 1999, Deans et al. 2001, Hormuzdi et al. 2001, Landisman et al. 2002, Long et al. 2002); these features lead to coupling strengths that are closely symmetrical. Thus, defining which cell is pre- or postsynaptic often depends on circumstances or can even be ambiguous. This is fundamentally different from the unidirectional (or in rare cases highly asymmetrical) operations of nearly all chemical synapses. The dynamics of electrical synapses are also unique. They tend to be more reliable than the generally stochastic chemical synapses, but because of membrane capacitance and dendritic cable properties, they also closely resemble first-order low-pass electrical filters (Galarreta & Hestrin 1999, Landisman et al. 2002). Relatively small signals that are also slow, such as afterhyperpolarizations (Figure 1*C*), burst envelopes (Figure 1*B*), or subthreshold oscillations (Figure 2*A*), are communicated more effectively than are action potentials, which are much larger but briefer (Figure 1). Chemical synapses have interesting short-term dynamics as well, but they are widely variable and distinctly different from the dynamics of electrical synapses (Zucker & Regehr 2002).

When two or more electrically coupled neurons are active under laboratory conditions, the most consistent and robust outcome is synchronization. The speed and reciprocity of gap junctions allow each coupled cell to influence, by the rapid transfer of small currents, voltage deflections in its coupled neighbors. In the mammalian brain, both action potentials (Galarreta & Hestrin 1999, Gibson et al. 1999, Mann-Metzer & Yarom 1999, Landisman et al. 2002) and subthreshold fluctuations (Benardo & Foster 1986; Christie et al. 1989; Beierlein et al. 2000; Long et al. 2002, 2004) readily synchronize in many neuronal types, even with moderate electrical coupling strengths. Synchronization is decidedly not the whole story (Marder 1998). Computational models of coupled neurons predict that weak coupling can sometimes lead to antiphasic or asynchronous spike firing, and the stability of the synchronous and antisynchronous states may depend strongly on firing frequency and the detailed properties of the neurons (e.g., Sherman & Rinzel 1992, Chow & Kopell 2000, Lewis & Rinzel 2003, Pfeuty et al. 2003). The fact that many neural networks have chemical synapses (inhibitory, excitatory, or both)

operating in parallel with electrical synapses immensely complicates analysis of their dynamics.

The function of electrical synapses may not be entirely electrical. Neuronal gap junctions could well be more important for the specific neuron-to-neuron passage of small organic signaling molecules than for conducting ionic current. Dye coupling supports the feasibility of this idea (Hatton 1998, Roerig & Feller 2000), but there is almost no direct evidence for physiologically relevant chemical coupling in a mammalian system (cf. Dunlap et al. 1987).

One way to test the function of a neural element is to eliminate it, and Cx36 knockout mice have provided the best opportunity to date for understanding the functions of electrical synapses (Deans et al. 2001, Guldenagel et al. 2001, Hormuzdi et al. 2001). The cellular phenotype of the mutant animal is exquisite: Electrical synapses were all but eliminated in the normally well-coupled neurons of the neocortex, hippocampus, TRN, inferior olive, and retina (described above). Neuronal and chemical synaptic properties, to the extent they have been measured, are minimally altered in knockout mice. In the intact knockout mouse, forebrain rhythms are subtly affected (Buhl et al. 2003), but there is no obvious seizure disorder. If the mouse has a behavioral phenotype (apart from that due to retinal deficits), it is not an immediately obvious one (Kistler et al. 2002). No studies of cognitive or affective effects have yet been published. As with most mutant models, the lack of palpable deficits in the Cx36 knockout may be due to compensatory changes during development. If that is the case, the compensations are quite interesting because they do not involve the simple replacement of Cx36 with another connexin type. Compensation instead must involve rewiring the brain with chemical synapses or altering its excitability by changing intrinsic membrane properties (De Zeeuw et al. 2003). Definitive behavioral tests of electrical synaptic functions await the application of more discriminating genetic manipulations or more selective gap junction blockers.

ACKNOWLEDGMENTS

We thank our colleagues for their many contributions, and Jessica Kostarides for editorial assistance. Our research was supported by the National Institutes of Health, the American Epilepsy Foundation, the Defense Advanced Research Projects Agency, and a Fox Postdoctoral Fellowship.

The *Annual Review of Neuroscience* is online at http://neuro.annualreviews.org

LITERATURE CITED

Al-Ubaidi MR, White TW, Ripps H, Poras I, Avner P, et al. 2000. Functional properties, developmental regulation, and chromosomal localization of murine connexin36, a gap-junctional protein expressed preferentially in retina and brain. *J. Neurosci. Res.* 59:813–26

Alvarez VA, Chow CC, Van Bockstaele EJ, Williams JT. 2002. Frequency-dependent

synchrony in locus ceruleus: role of electrotonic coupling. *Proc. Natl. Acad. Sci. USA* 99:4032–36

Amitai Y, Gibson JR, Beierlein M, Patrick SL, Ho AM, et al. 2002. The spatial dimensions of electrically coupled networks of interneurons in the neocortex. *J. Neurosci.* 22:4142–52

Baker R, Llinás R. 1971. Electrotonic coupling between neurons in the rat mesencephalic nucleus. *J. Physiol.* 212:45–63

Beierlein M, Gibson JR, Connors BW. 2000. A network of electrically coupled interneurons drives synchronized inhibition in neocortex. *Nat. Neurosci.* 3:904–10

Benardo LS. 1997. Recruitment of GABAergic inhibition and synchronization of inhibitory interneurons in rat neocortex. *J. Neurophysiol.* 77:3134–44

Benardo LS, Foster RE. 1986. Oscillatory behavior in inferior olive neurons: mechanism, modulation, cell aggregates. *Brain Res. Bull.* 17:773–84

Bennett MVL. 1977. Electrical transmission: a functional analysis and comparison with chemical transmission. In *Cellular Biology of Neurons, Handbook of Physiology, The Nervous System*, ed. ER Kandel 1(1):357–416. Baltimore: Williams & Wilkins. 717 pp.

Bennett MV. 1997. Gap junctions as electrical synapses. *J. Neurocytol.* 26:349–66

Bennett MVL, Crain SM, Grundfest H. 1959. Electrophysiology of supramedullary neurons in *Spheroides maculates*: I. Orthodromic and antidromic responses. *J. Gen. Physiol.* 43:159–88

Bittman K, Owens DF, Kriegstein AR, LoTurco JJ. 1997. Cell coupling and uncoupling in the ventricular zone of developing neocortex. *J. Neurosci.* 17:7037–44

Blatow M, Rozov A, Katona I, Hormuzdi SG, Meyer AH, et al. 2003. A novel network of multipolar bursting interneurons generates theta frequency oscillations in neocortex. *Neuron* 38:805–17

Boger DL, Patterson JE, Guan X, Cravatt BF, Lerner RA, Gilula NB. 1998. Chemical requirements for inhibition of gap junction communication by the biologically active lipid oleamide. *Proc. Natl. Acad. Sci. USA* 95:4810–15

Brightman MW, Reese TS. 1969. Junctions between intimately apposed cell membranes in the vertebrate brain. *J. Cell Biol.* 40:648–77

Bruzzone R, Hormuzdi SG, Barbe M, Herb A, Monyer H. 2003. Pannexins, a novel family of gap junction proteins expressed in the brain. *Proc. Natl. Acad. Sci. USA* 100:13644–49

Buhl DL, Harris KD, Hormuzdi SG, Monyer H, Buzsaki G. 2003. Selective impairment of hippocampal gamma oscillations in connexin-36 knock-out mouse in vivo. *J. Neurosci.* 23:1013–18

Chang Q, Gonzalez M, Pinter MJ, Balice-Gordon RJ. 1999. Gap junctional coupling and patterns of connexin expression among neonatal rat lumbar spinal motor neurons. *J. Neurosci.* 19:10813–28

Chesler M. 2003. Regulation and modulation of pH in the brain. *Physiol. Rev.* 83:1183–221

Chow CC, Kopell N. 2000. Dynamics of spiking neurons with electrical coupling. *Neural Comput.* 12:1643–78

Christie MJ, Williams JT, North RA. 1989. Electrical coupling synchronizes subthreshold activity in locus coeruleus neurons in vitro from neonatal rats. *J. Neurosci.* 9:3584–89

Chu Z, Galarreta M, Hestrin S. 2003. Synaptic interactions of late-spiking neocortical neurons in layer 1. *J. Neurosci.* 23:96–102

Church J, Baimbridge KG. 1991. Exposure to high-pH medium increases the incidence and extent of dye coupling between rat hippocampal CA1 pyramidal neurons in vitro. *J. Neurosci.* 11:3289–95

Cobbett P, Hatton GI. 1984. Dye coupling in hypothalamic slices: dependence on in vivo hydration state and osmolality of incubation medium. *J. Neurosci.* 4:3034–38

Condorelli DF, Belluardo N, Trovato-Salinaro A, Mudo G. 2000. Expression of Cx36 in mammalian neurons. *Brain Res. Brain Res. Rev.* 32:72–85

Condorelli DF, Parenti R, Spinella F, Trovato

Salinaro A, Belluardo N, et al. 1998. Cloning of a new gap junction gene (Cx36) highly expressed in mammalian brain neurons. *Eur. J. Neurosci.* 10:1202–8

Connors BW, Benardo LS, Prince DA. 1983. Coupling between neurons of the developing rat neocortex. *J. Neurosci.* 3:773–82

Connors BW, Benardo LS, Prince DA. 1984. Carbon dioxide sensitivity of dye-coupling among glia and neurons of the neocortex. *J. Neurosci.* 4:1324–30

Cowan WM, Kandel ER. 2001. A brief history of synapses and synaptic transmission. In *Synapses*, ed. WM Cowan, TC Südhof, CF Stevens, pp. 1–88. Baltimore: Johns Hopkins Univ. Press. 767 pp.

Davidson JS, Baumgarten IM. 1988. Glycyrrhetinic acid derivatives: a novel class of inhibitors of gap-junctional intercellular communication. Structure-activity relationships. *J. Pharmacol. Exp. Ther.* 246:1104–07

Deans MR, Gibson JR, Sellitto C, Connors BW, Paul DL. 2001. Synchronous activity of inhibitory networks in neocortex requires electrical synapses containing connexin 36. *Neuron* 31:477–85

Deans MR, Paul DL. 2001. Mouse horizontal cells do not express connexin26 or connexin36. *Cell. Commun. Adhes.* 8:361–66

Deans MR, Volgyi B, Goodenough DA, Bloomfield SA, Paul DL. 2002. Connexin36 is essential for transmission of rod-mediated visual signals in the mammalian retina. *Neuron* 36:703–12

De Zeeuw CI, Chorev E, Devor A, Manor Y, Van Der Giessen RS, et al. 2003. Deformation of network connectivity in the inferior olive of connexin 36-deficient mice is compensated by morphological and electrophysiological changes at the single neuron level. *J. Neurosci.* 23:4700–11

Devor A, Yarom Y. 2002. Electrotonic coupling in the inferior olivary nucleus revealed by simultaneous double patch recordings. *J. Neurophysiol.* 87:3048–58

DeVries SH, Schwartz EA. 1989. Modulation of an electrical synapse between solitary pairs of catfish horizontal cells by dopamine and second messengers. *J. Physiol.* 414:351–75

DeVries SH, Schwartz EA. 1992. Hemi-gap-junction channels in solitary horizontal cells of the catfish retina. *J. Physiol.* 445:201–30

Draguhn A, Traub RD, Schmitz D, Jefferys JG. 1998. Electrical coupling underlies high-frequency oscillations in the hippocampus in vitro. *Nature* 394:189–92

Dunlap K, Takeda K, Brehm P. 1987. Activation of a calcium-dependent photoprotein by chemical signalling through gap junctions. *Nature* 325:60–62

Eccles JC. 1982. The synapse: from electrical to chemical transmission. *Annu. Rev. Neurosci.* 5:325–39

Evans WH, Martin PE. 2002. Gap junctions: structure and function (review). *Mol. Membr. Biol.* 19:121–36

Friedman D, Strowbridge BW. 2003. Both electrical and chemical synapses mediate fast network oscillations in the olfactory bulb. *J. Neurophysiol.* 89:2601–10

Fukuda T, Kosaka T. 2000. Gap junctions linking the dendritic network of GABAergic interneurons in the hippocampus. *J. Neurosci.* 20:1519–28

Fukuda T, Kosaka T. 2003. Ultrastructural study of gap junctions between dendrites of parvalbumin-containing GABAergic neurons in various neocortical areas of the adult rat. *Neuroscience* 120:5–20

Fulton BP, Miledi R, Takahashi T. 1980. Electrical synapses between motoneurons in the spinal cord of the newborn rat. *Proc. R. Soc. London Ser. B* 208:115–10

Furshpan EJ, Potter DD. 1957. Mechanism of nerve-impulse transmission at a crayfish synapse. *Nature* 180:342–43

Galarreta M, Hestrin S. 1999. A network of fast-spiking cells in the neocortex connected by electrical synapses. *Nature* 402:72–75

Galarreta M, Hestrin S. 2001a. Electrical synapses between GABA-releasing interneurons. *Nat. Rev. Neurosci.* 2:425–33

Galarreta M, Hestrin S. 2001b. Spike transmission and synchrony detection in networks

of GABAergic interneurons. *Science* 292: 2295–99

Galarreta M, Hestrin S. 2002. Electrical and chemical synapses among parvalbumin fast-spiking GABAergic interneurons in adult mouse neocortex. *Proc. Natl. Acad. Sci. USA* 99:12438–43

Gibson JR, Beierlein M, Connors BW. 1999. Two networks of electrically coupled inhibitory neurons in neocortex. *Nature* 402:75–79

Goodenough DA, Paul DL. 2003. Beyond the gap: functions of unpaired connexon channels. *Nat. Rev. Mol. Cell Biol.* 4:285–94

Guldenagel M, Ammermuller J, Feigenspan A, Teubner B, Degen J, et al. 2001. Visual transmission deficits in mice with targeted disruption of the gap junction gene connexin36. *J. Neurosci.* 21:6036–44

Gutnick MJ, Lobel-Yaakov R, Rimon G. 1985. Incidence of neuronal dye-coupling in neocortical slices depends on the plane of section. *Neuroscience* 15:659–66

Gutnick MJ, Prince DA. 1981. Dye coupling and possible electrotonic coupling in the guinea pig neocortical slice. *Science* 211:67–70

Hampson EC, Weiler R, Vaney DI. 1994. pH-gated dopaminergic modulation of horizontal cell gap junctions in mammalian retina. *Proc. R. Soc. London Ser. B* 255:67–72

Harris AL. 2001. Emerging issues of connexin channels: biophysics fills the gap. *Q. Rev. Biophys.* 34:325–472

Hatton GI. 1998. Synaptic modulation of neuronal coupling. *Cell Biol. Int.* 22:765–80

Hinrichsen CF. 1970. Coupling between cells of the trigeminal mesencephalic nucleus. *J. Dent. Res.* 49(Suppl.):1369–73

Hormuzdi SG, Pais I, LeBeau FE, Towers SK, Rozov A, et al. 2001. Impaired electrical signaling disrupts gamma frequency oscillations in connexin 36-deficient mice. *Neuron* 31:487–95

Hua VB, Chang AB, Tchieu JH, Kumar NM, Nielsen PA, Saier MH Jr. 2003. Sequence and phylogenetic analyses of four TMS junctional proteins of animals: connexins, innexins, claudins and occludins. *J. Membr. Biol.* 194:59–76

Jahromi SS, Wentlandt K, Piran S, Carlen PL. 2002. Anticonvulsant actions of gap junctional blockers in an in vitro seizure model. *J. Neurophysiol.* 88:1893–902

Jaslove SW, Brink PR. 1987. Electrotonic coupling in the nervous system. In *Cell-to-Cell Communication*, ed. WC De Mello, pp. 103–47. New York: Plenum

Jefferys JG. 1995. Nonsynaptic modulation of neuronal activity in the brain: electric currents and extracellular ions. *Physiol. Rev.* 75:689–723

Johnston MF, Simon SA, Ramon F. 1980. Interaction of anaesthetics with electrical synapses. *Nature* 286:498–500

Kamermans M, Fahrenfort I, Schultz K, Janssen-Bienhold U, Sjoerdsma T, Weiler R. 2001. Hemichannel-mediated inhibition in the outer retina. *Science* 292:1178–80

Katsumaru H, Kosaka T, Heizmann CW, Hama K. 1988. Gap junctions on GABAergic neurons containing the calcium-binding protein parvalbumin in the rat hippocampus (CA1 region). *Exp. Brain Res.* 72:363–70

Kistler WM, De Jeu MT, Elgersma, Y, Van Der Giessen RS, Hensbroek R, et al. 2002. Analysis of Cx36 knockout does not support tenet that olivary gap junctions are required for complex spike synchronization and normal motor performance. *Ann. NY Acad. Sci.* 978:391–404

Knowles WD, Funch PG, Schwartzkroin PA. 1982. Electrotonic and dye coupling in hippocampal CA1 pyramidal cells in vitro. *Neuroscience* 7:1713–22

Kohling R, Gladwell SJ, Bracci E, Vreugdenhil M, Jefferys JG. 2001. Prolonged epileptiform bursting induced by 0-Mg^{2+} in rat hippocampal slices depends on gap junctional coupling. *Neuroscience* 105:579–87

Koos T, Tepper JM. 1999. Inhibitory control of neostriatal projection neurons by GABAergic interneurons. *Nat. Neurosci.* 2:467–72

Korn H, Sotelo C, Crepel F. 1973. Electronic coupling between neurons in the rat lateral

vestibular nucleus. *Exp. Brain Res.* 16:255–75

Kosaka T. 1983. Neuronal gap junctions in the polymorph layer of the rat dentate gyrus. *Brain Res.* 277:347–51

Kosaka T, Hama K. 1985. Gap junctions between non-pyramidal cell dendrites in the rat hippocampus (CA1 and CA3 regions): a combined Golgi-electron microscopy study. *J. Comput. Neurol.* 231:150–61

Lampe PD, Lau AF. 2000. Regulation of gap junctions by phosphorylation of connexins. *Arch. Biochem. Biophys.* 384:205–15

Landesman Y, White TW, Starich TA, Shaw JE, Goodenough DA, Paul DL. 1999. Innexin-3 forms connexin-like intercellular channels. *J. Cell Sci.* 112:2391–96

Landisman CE, Long MA, Beierlein M, Deans MR, Paul DL, Connors BW. 2002. Electrical synapses in the thalamic reticular nucleus. *J. Neurosci.* 22:1002–9

Lewis TJ, Rinzel J. 2003. Dynamics of spiking neurons connected by both inhibitory and electrical coupling. *J. Comput. Neurosci.* 14:283–309

Lin JW, Faber DS. 1988. Synaptic transmission mediated by single club endings on the goldfish Mauthner cell. I. Characteristics of electrotonic and chemical postsynaptic potentials. *J. Neurosci.* 8:1302–12

Liu XB, Jones EG. 2003. Fine structural localization of connexin-36 immunoreactivity in mouse cerebral cortex and thalamus. *J. Comp. Neurol.* 466:457–67

Llinás RR, Baker Sotelo C. 1974. Electrotonic coupling between neurons in cat inferior olive. *J. Neurophysiol.* 37:560–71

Llinás R, Yarom Y. 1981. Electrophysiology of mammalian inferior olivary neurones in vitro. Different types of voltage-dependent ionic conductances. *J. Physiol.* 315:549–67

Long MA, Deans MR, Paul DL, Connors BW. 2002. Rhythmicity without synchrony in the electrically uncoupled inferior olive. *J. Neurosci.* 22:10898–905

Long MA, Landisman CE, Connors BW. 2004. Small clusters of electrically coupled neurons generate synchronous rhythms in the thalamic reticular nucleus. *J. Neurosci.* 24:341–49

MacVicar BA, Dudek FE. 1981. Electrotonic coupling between pyramidal cells: a direct demonstration in rat hippocampal slices. *Science* 213:782–85

MacVicar BA, Dudek FE. 1982. Electrotonic coupling between granule cells of rat dentate gyrus: physiological and anatomical evidence. *J. Neurophysiol.* 47:579–92

Maier N, Guldenagel M, Sohl G, Siegmund H, Willecke K, Draguhn A. 2002. Reduction of high-frequency network oscillations (ripples) and pathological network discharges in hippocampal slices from connexin 36-deficient mice. *J. Physiol.* 541:521–28

Mancilla JG, Lewis TJ, Pinto DJ, Rinzel J, Connors BW. 2003. Synchrony of firing in coupled pairs of inhibitory interneurons in neocortex. *Soc. Neurosci. Abstr.* 173.4

Mann-Metzer P, Yarom Y. 1999. Electrotonic coupling interacts with intrinsic properties to generate synchronized activity in cerebellar networks of inhibitory interneurons. *J. Neurosci.* 19:3298–306

Manor Y, Yarom Y, Chorev E, Devor A. 2000. To beat or not to beat: a decision taken at the network level. *J. Physiol.* 94:375–90

Marder E. 1998. Electrical synapses: beyond speed and synchrony to computation. *Curr. Biol.* 8:R795–97

Maxeiner S, Kruger O, Schilling K, Traub O, Urschel S, Willecke K. 2003. Spatiotemporal transcription of connexin45 during brain development results in neuronal expression in adult mice. *Neuroscience* 119:689–700

McCormick DA, Bal T. 1997. Sleep and arousal: thalamocortical mechanisms. *Annu. Rev. Neurosci.* 20:185–215

McMahon DG, Knapp AG, Dowling JE. 1989. Horizontal cell gap junctions: single-channel conductance and modulation by dopamine. *Proc. Natl. Acad. Sci. USA* 86:7639–43

Menichella DM, Goodenough DA, Sirkowski E, Scherer SS, Paul DL. 2003. Connexins are critical for normal myelination in the CNS. *J. Neurosci.* 23:5963–73

Meyer AH, Katona I, Blatow M, Rozov

A, Monyer H. 2002. In vivo labeling of parvalbumin-positive interneurons and analysis of electrical coupling in identified neurons. *J. Neurosci.* 22:7055–64

Michelson HB, Wong RK. 1994. Synchronization of inhibitory neurones in the guinea-pig hippocampus in vitro. *J. Physiol.* 477(Pt. 1): 35–45

Miyachi E, Kato C, Nakaki T. 1994. Arachidonic acid blocks gap junctions between retinal horizontal cells. *NeuroReport* 5:485–88

Mitropoulou G, Bruzzone R. 2003. Modulation of perch connexin35 hemi-channels by cyclic AMP requires a protein kinase A phosphorylation site. *J. Neurosci. Res.* 72:147–57

Nagy JI, Li X, Rempel J, Stelmack G, Patel D, et al. 2001. Connexin26 in adult rodent central nervous system: demonstration at astrocytic gap junctions and colocalization with connexin30 and connexin43. *J. Comp. Neurol.* 441:302–23

Nicoll RA. 2003. Expression mechanisms underlying long-term potentiation: a postsynaptic view. *Philos. Trans. R. Soc. London Ser. B* 358:721–26

Odermatt B, Wellershaus K, Wallraff A, Seifert G, Degen J, et al. 2003. Connexin 47 (Cx47)-deficient mice with enhanced green fluorescent protein reporter gene reveal predominant oligodendrocytic expression of Cx47 and display vacuolized myelin in the CNS *J. Neurosci.* 23:4549–59

O'Brien J, Bruzzone R, White TW, Al-Ubaidi MR, Ripps H. 1998. Cloning and expression of two related connexins from the perch retina define a new subgroup of the connexin family. *J. Neurosci.* 18:7625–37

O'Donnell P, Grace AA. 1993. Dopaminergic modulation of dye coupling between neurons in the core and shell regions of the nucleus accumbens. *J. Neurosci.* 13:3456–71

Ohara PT. 1988. Synaptic organization of the thalamic reticular nucleus. *J. Electron Microsc. Tech.* 10:283–92

Panchin Y, Kelmanson I, Matz M, Lukyanov K, Usman N, Lukyanov S. 2000. A ubiquitous family of putative gap junction molecules. *Curr. Biol.* 10:R473–74

Peinado A, Yuste R, Katz LC. 1993. Extensive dye coupling between rat neocortical neurons during the period of circuit formation. *Neuron* 10:103–14

Pereda AE, Bell TD, Chang BH, Czernik AJ, Nairn AC, et al. 1998. Ca^{2+}/calmodulin-dependent kinase II mediates simultaneous enhancement of gap-junctional conductance and glutamatergic transmission. *Proc. Natl. Acad. Sci. USA* 95:13272–77

Pereda AE, Faber DS. 1996. Activity-dependent short-term enhancement of intercellular coupling. *J. Neurosci.* 16:983–92

Pereda A, O'Brien J, Nagy JI, Bukauskas F, Davidson KG, et al. 2003. Connexin35 mediates electrical transmission at mixed synapses on Mauthner cells. *J. Neurosci.* 23:7489–503

Pereda A, Triller A, Korn H, Faber DS. 1992. Dopamine enhances both electrotonic coupling and chemical excitatory postsynaptic potentials at mixed synapses. *Proc. Natl. Acad. Sci. USA* 89:12088–92

Personius KE, Balice-Gordon RJ. 2001. Loss of correlated motor neuron activity during synaptic competition at developing neuromuscular synapses. *Neuron* 31:395–408

Peters A. 1980. Morphological correlates of epilepsy: cells in the cerebral cortex. In *Antiepileptic Drug—Mechanism of Action, Advances in Neurology*, ed. OH Glaser, JK Penry, DM Woodbury, 27:21–48. New York: Raven

Peters A. 2002. Examining neocortical circuits: some background and facts. *J. Neurocytol.* 31:183–93

Pfeuty B, Mato G, Golomb D, Hansel D. 2003. Electrical synapses and synchrony: the role of intrinsic currents. *J. Neurosci.* 23:6280–94

Phelan P, Starich TA. 2001. Innexins get into the gap. *BioEssays* 23:388–96

Piccolino M, Neyton J, Gerschenfeld HM. 1984. Decrease of gap junction permeability induced by dopamine and cyclic adenosine 3′:5′-monophosphate in horizontal cells of turtle retina. *J. Neurosci.* 4:2477–88

Rash JE, Dillman RK, Bilhartz BL, Duffy

HS, Whalen LR, Yasumura T. 1996. Mixed synapses discovered and mapped throughout mammalian spinal cord. *Proc. Natl. Acad. Sci. USA* 93:4235–39

Rash JE, Staines WA, Yasumura T, Patel D, Furman CS, et al. 2000. Immunogold evidence that neuronal gap junctions in adult rat brain and spinal cord contain connexin-36 but not connexin-32 or connexin-43. *Proc. Natl. Acad. Sci. USA* 97:7573–78

Rash JE, Yasumura T, Davidson KG, Furman CS, Dudek FE, Nagy JI. 2001a. Identification of cells expressing Cx43, Cx30, Cx26, Cx32 and Cx36 in gap junctions of rat brain and spinal cord. *Cell Commun. Adhes.* 8:315–20

Rash JE, Yasumura T, Dudek FE, Nagy JI. 2001b. Cell-specific expression of connexins and evidence of restricted gap junctional coupling between glial cells and between neurons. *J. Neurosci.* 21:1983–2000

Raviola E, Gilula NB. 1973. Gap junctions between photoreceptor cells in the vertebrate retina. *Proc. Natl. Acad. Sci. USA* 70:1677–81

Rekling JC, Shao XM, Feldman JL. 2000. Electrical coupling and excitatory synaptic transmission between rhythmogenic respiratory neurons in the preBotzinger complex. *J. Neurosci.* 20:RC113

Reyher CK, Lubke J, Larsen WJ, Hendrix GM, Shipley MT, Baumgarten HG. 1991. Olfactory bulb granule cell aggregates: morphological evidence for interperikaryal electrotonic coupling via gap junctions. *J. Neurosci.* 11:1485–95

Roerig B, Feller MB. 2000. Neurotransmitters and gap junctions in developing neural circuits. *Brain Res. Rev.* 32:86–114

Rorig B, Klausa G, Sutor B. 1995. Beta-adrenoreceptor activation reduces dye-coupling between immature rat neocortical neurones. *NeuroReport* 6:1811–15

Rorig B, Klausa G, Sutor B. 1996. Intracellular acidification reduced gap junction coupling between immature rat neocortical pyramidal neurones. *J. Physiol.* 490:31–49

Rose B, Rick R. 1978. Intracellular pH, intracellular free Ca, and junctional cell-cell coupling. *J. Membr. Biol.* 44:377–415

Rouach N, Segal M, Koulakoff A, Giaume C, Avignone E. 2003. Carbenoxolone blockade of neuronal network activity in culture is not mediated by an action on gap junctions. *J. Physiol.* 553:729–45

Rozental R, Srinivas M, Spray DC. 2001. How to close a gap junction channel: efficacies and potencies of uncoupling agents. In *Methods in Molecular Biology, Connexin Methods and Protocols*, ed. R Bruzzone, C Giaume, 154:447–76. Totowa, New Jersey: Humana

Sabatini BL, Regehr WG. 1996. Timing of neurotransmission at fast synapses in the mammalian brain. *Nature* 384:170–72

Sáez JC, Berthoud VM, Brañes MC, Martínez AD, Beyer EC. 2003. Plasma membrane channels formed by connexins: their regulation and functions. *Physiol. Rev.* 83:1359–400

Schmitz D, Schuchmann S, Fisahn A, Draguhn A, Buhl EH, et al. 2001. Axo-axonal coupling: a novel mechanism for ultrafast neuronal communication. *Neuron* 31:831–40

Schoppa NE, Westbrook GL. 2002. AMPA autoreceptors drive correlated spiking in olfactory bulb glomeruli. *Nat. Neurosci.* 5:1194–202

Sherman A, Rinzel J. 1992. Rhythmogenic effects of weak electrotonic coupling in neuronal models. *Proc. Natl. Acad. Sci. USA* 89:2471–74

Skinner FK, Zhang L, Velazquez JL, Carlen PL. 1999. Bursting in inhibitory interneuronal networks: a role for gap-junctional coupling. *J. Neurophysiol.* 81:1274–83

Sloper JJ. 1972. Gap junctions between dendrites in the primate neocortex. *Brain Res.* 44:641–46

Sloper JJ, Powell TP. 1978. Gap junctions between dendrites and somata of neurons in the primate sensori-motor cortex. *Proc. R. Soc. London Ser. B* 203:39–47

Smith M, Pereda AE. 2003. Chemical synaptic activity modulates nearby electrical synapses. *Proc. Natl. Acad. Sci. USA* 100: 4849–54

Sotelo C, Llinás R. 1972. Specialized membrane junctions between neurons in the vertebrate cerebellar cortex. *J. Cell Biol.* 53:271–89

Sotelo C, Llinás R, Baker R. 1974. Structural study of inferior olivary nucleus of the cat: morphological correlates of electrotonic coupling. *J. Neurophysiol.* 37:541–59

Spencer WA, Kandel ER. 1961. Electrophysiology of hippocampal neurons. IV. Fast prepotentials. *J. Neurophysiol.* 24:272–85

Spray DC, Harris AL, Bennett MV. 1979. Voltage dependence of junctional conductance in early amphibian embryos. *Science* 204:432–34

Spray DC, Harris AL, Bennett MV. 1981. Gap junctional conductance is a simple and sensitive function of intracellular pH. *Science* 211:712–15

Srinivas M, Hopperstad MG, Spray DC. 2001. Quinine blocks specific gap junction channel subtypes. *Proc. Natl. Acad. Sci. USA* 98:10942–47

Srinivas M, Rozental R, Kojima T, Dermietzel R, Mehler M, et al. 1999. Functional properties of channels formed by the neuronal gap junction protein connexin36. *J. Neurosci.* 19:9848–55

Srinivas M, Spray DC. 2003. Specific block of connexin36 gap junction channels. *Soc. Neurosci. Abstr.* 370.10

Swadlow HA. 2003. Fast-spike interneurons and feedforward inhibition in awake sensory neocortex. *Cereb. Cortex* 13:25–32

Szabadics J, Lorincz A, Tamás G. 2001. Beta and gamma frequency synchronization by dendritic gabaergic synapses and gap junctions in a network of cortical interneurons. *J. Neurosci.* 21:5824–31

Tamás G, Buhl EH, Lorincz A, Somogyi P. 2000. Proximally targeted GABAergic synapses and gap junctions synchronize cortical interneurons. *Nat. Neurosci.* 3:366–71

Teubner B, Degen J, Sohl G, Guldenagel M, Bukauskas FF, et al. 2000. Functional expression of the murine connexin 36 gene coding for a neuron-specific gap junctional protein. *J. Membr. Biol.* 176:249–62

Teubner B, Odermatt B, Guldenagel M, Sohl G, Degen J, et al. 2001. Functional expression of the new gap junction gene connexin47 transcribed in mouse brain and spinal cord neurons. *J. Neurosci.* 21:1117–26

Thomson AM, Deuchars J. 1997. Synaptic interactions in neocortical local circuits: dual intracellular recordings in vitro. *Cereb. Cortex* 7:510–22

Traub RD, Draguhn A, Whittington MA, Baldeweg T, Bibbig A, et al. 2002. Axonal gap junctions between principal neurons: a novel source of network oscillations, and perhaps epileptogenesis. *Rev. Neurosci.* 13:1–30

Tresch MC, Kiehn O. 2000. Motor coordination without action potentials in the mammalian spinal cord. *Nat. Neurosci.* 3:593–99

Usher M, Cohen JD, Servan-Schreiber D, Rajkowski J, Aston-Jones G. 1999. The role of locus coeruleus in the regulation of cognitive performance. *Science* 283:549–54

Vaney DI. 2002. Retinal neurons: cell types and coupled networks. *Prog. Brain Res.* 136: 239–54

Venance L, Piomelli D, Glowinski J, Giaume C. 1995. Inhibition by anandamide of gap junctions and intercellular calcium signaling in striatal astrocytes. *Nature* 376:590–94

Venance L, Rozov A, Blatow M, Burnashev N, Feldmeyer D, Monyer H. 2000. Connexin expression in electrically coupled postnatal rat brain neurons. *Proc. Natl. Acad. Sci. USA* 97:10260–65

Venance L, Vandecasteele M, Glowinski J, Giaume C. 2003. Striatal output neurons are connected through electrical and unidirectional chemical synapses in rat brain slices. *Soc. Neurosci. Abstr.* 370.9

Veruki ML, Hartveit E. 2002a. AII (rod) amacrine cells form a network of electrically coupled interneurons in the mammalian retina. *Neuron* 33:935–46

Veruki ML, Hartveit E. 2002b. Electrical synapses mediate signal transmission in the rod pathway of the mammalian retina. *J. Neurosci.* 22:10558–66

Walker BR, Edwards CR. 1994. Licorice-induced hypertension and syndromes of

apparent mineralocorticoid excess. *Endocrinol. Metab. Clin. N. Am.* 23:359–77

Walton KD, Navarrete R. 1991. Postnatal changes in motorneuron electrotonic coupling studied in the in vitro rat lumbar spinal cord. *J. Physiol.* 433:283–305

Watanabe A. 1958. The interaction of electrical activity among neurons of lobster cardiac ganglion. *Jpn. J. Physiol.* 8:305–18

Weiler R, Pottek M, He S, Vaney DI. 2000. Modulation of coupling between retinal horizontal cells by retinoic acid and endogenous dopamine. *Brain Res. Rev.* 32:121–29

White JG, Southgate E, Thomson JN, Brenner S. 1986. The structure of the nervous system of the nematode *Caenorhabditis elegans*. *Philos. Trans. R. Soc. London Ser. B* 314:1–340

Willecke K, Eiberger J, Degen J, Eckardt D, Romualdi A, et al. 2002. Structural and functional diversity of connexin genes in the mouse and human genome. *Biol. Chem.* 383:725–37

Williams EH, DeHaan RL. 1981. Electrical coupling among heart cells in the absence of ultrastructurally defined gap junctions. *J. Membr. Biol.* 60:237–48

Wylie RM. 1973. Evidence of electrotonic transmission in the vestibular nuclei of the rat. *Brain Res.* 50:179–83

Yang QZ, Hatton GI. 1987. Dye coupling among supraoptic nucleus neurons without dendritic damage: differential incidence in nursing mother and virgin rats. *Brain Res. Bull.* 19:559–65

Yang XD, Korn H, Faber DS. 1990. Long-term potentiation of electrotonic coupling at mixed synapses. *Nature* 48:542–45

Yang QZ, Michelson HB. 2001. Gap junctions synchronize the firing of inhibitory interneurons in guinea pig hippocampus. *Brain Res.* 907:139–43

Ye ZC, Wyeth MS, Baltan-Tekkok S, Ransom BR. 2003. Functional hemichannels in astrocytes: a novel mechanism of glutamate release. *J. Neurosci.* 23:3588–96

Zhang DQ, McMahon DG. 2000. Direct gating by retinoic acid of retinal electrical synapses. *Proc. Natl. Acad. Sci. USA* 97:14754–59

Zhang C, Restrepo D. 2002. Expression of connexin 45 in the olfactory system. *Brain Res.* 929:37–47

Zhang C, Restrepo D. 2003. Heterogeneous expression of connexin 36 in the olfactory epithelium and glomerular layer of the olfactory bulb. *J. Comput. Neurol.* 459:426–439

Zucker RS, Regehr WG. 2002. Short-term synaptic plasticity. *Annu. Rev. Physiol.* 64: 355–405

Annual Review of Neuroscience
Volume 27, 2004

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