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The ever-changing electrical synapse

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A wealth of research has revealed that electrical synapses in the central nervous system exhibit a high degree of plasticity. Several recent studies, particularly in the retina and inferior olive, highlight this plasticity. Three classes of mechanisms can alter electrical coupling over time courses ranging from milliseconds to days. Changes of membrane conductance through synaptic input or spiking activity shunt current and decouple neurons on the millisecond time scale. Such activity can also alter coupling symmetry, rectifying electrical synapses. More stable rectification can be accomplished through molecular asymmetry of the synapse itself. On the minutes time scale, changes in connexin phosphorylation can change coupling quasi-stably with an order of magnitude dynamic range. On the hours to days time scale, changes in expression level of connexins alter coupling through the course of circadian time, over developmental time, or in response to tissue injury. Combined, all of these mechanisms allow electrical coupling to be highly dynamic, changing in response to demands at the whole network level, in small portions of a network, or at the level of an individual synapse.

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Introduction

Synaptic communication is the most fundamental property of a nervous system. The two dominant forms of synaptic communication, chemical and electrical, serve complementary functions and frequently interact to provide a rich diversity of capabilities. Synaptic plasticity is essential to the ability of the nervous system to assimilate and respond to information from the environment. While plasticity has long been considered the domain of chemical synapses, electrical synapses have proven also to show remarkable plasticity on several time scales, making critical contributions to sensory adaptation and learning. This article will review recent advances in understanding the molecular mechanisms of electrical synaptic plasticity in the vertebrate central nervous system, and will provide some examples of how this plasticity contributes to the functional output of neural systems.

Electrical synaptic plasticity comes in three flavors

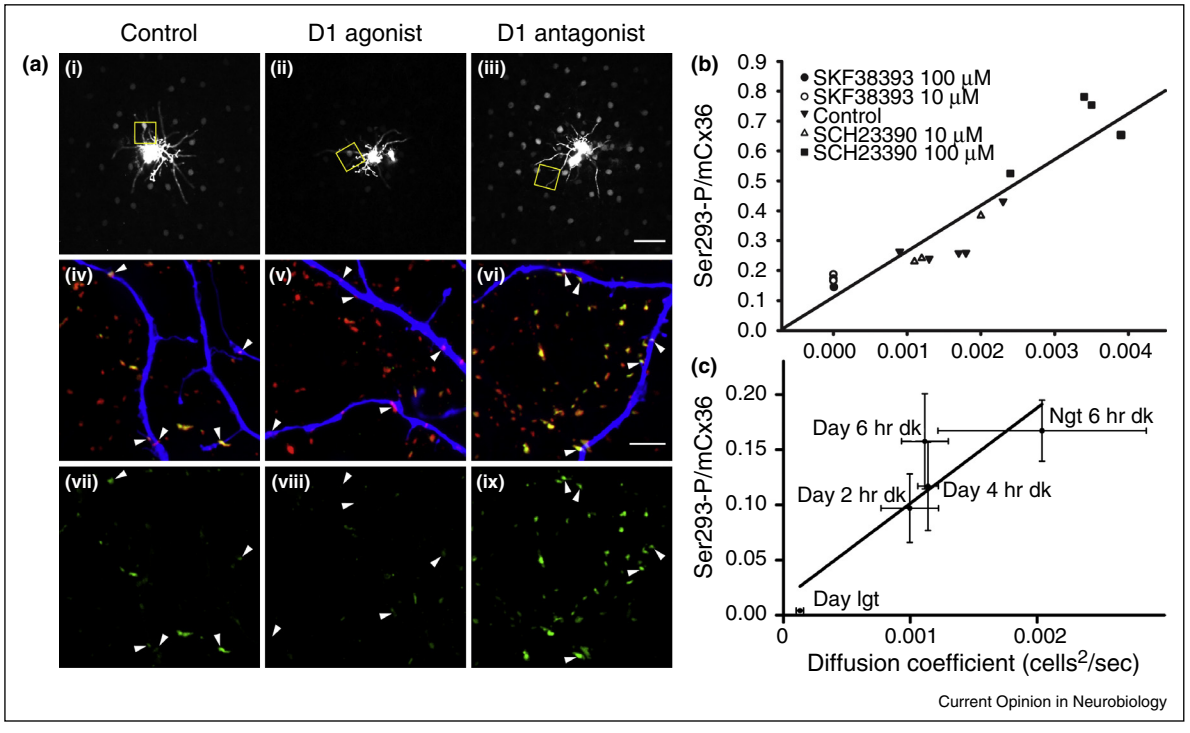
There are several mechanisms by which the strength of electrical coupling between two neurons can be changed. These can be distilled down to three groups of mechanisms: (1) those that alter membrane properties of the communicating cells, (2) those that change the conductance of the gap junction, and (3) those that change the expression level of connexins, the gap junction proteins. First, mechanisms that alter the membrane properties of the coupled cells can have a significant impact on electrical coupling. Opening of ion channels that reduce the membrane resistance of the coupled cells can impose transient decoupling. This was first demonstrated by Spira and Bennett [1] in neurons that control pharyngeal contraction in the sea slug *Navanax*. Such a transient decoupling has an onset time of a few milliseconds and can last for several seconds. An interesting corollary of this form of shunting inhibition is that it can lead to electrical rectification if the input resistances of the coupled cells differ. This is often the case with the coupled G and M cells of *Navanax* pharyngeal ganglia [1], and is also the case for heterologous coupling between AII amacrine cells and On cone bipolar cells in the mammalian retina [2].

Membrane conductances are not exclusively inhibitory to electrical coupling. In the club endings of goldfish auditory nerve afferents that form mixed chemical/electrical synapses on Mauthner cells, subthreshold Na^+ currents amplify spikelets propagated antidromically through the electrical synapses [3]. The magnitude of the elicited Na^+ current depends non-linearly on the membrane potential of the afferent, so changes of just a few millivolts can dramatically alter the efficacy of antidromic spike propagation. The presence of subthreshold Na^+ currents and differences in input resistance between the Mauthner cell and the club endings result in a strong asymmetry in coupling coefficients (the fraction of input voltage transmitted to the follower cell: V_2/V_1) for prodromic and antidromic spike propagation, favoring antidromic propagation. This electrical rectification is reinforced by molecular asymmetry in the gap junction, with Connexin 35 (Cx35), the closest fish homolog of mammalian Cx36, on

the presynaptic (club ending) side and the closely related Cx34.7 on the postsynaptic side [4••]. The molecular asymmetry accounts for about 4-fold rectification in favor of antidromic current flow from the Mauthner cell to the club endings; differences in membrane properties amplify that to an average of more than 20-fold. The rectification of current flow supports a form of lateral excitation among the numerous auditory afferents, which are not directly electrically coupled, favoring their synchronized firing [4••].

Changes in the connexin protein itself can potently alter coupling. In gap junctions made of Cx36, the connexin forming the majority of electrical synapses in the vertebrate central nervous system, the magnitude of tracer transfer and electrical coupling are directly regulated by phosphorylation of the connexin [5,6]. This can be seen in the strong correlation between the diffusion coefficients for tracer through networks of coupled neurons and the phosphorylation state of Cx36 (Fig. 1) [7••,8••]. The phosphorylation-driven changes in tracer coupling cover an order of magnitude change in diffusion coefficient, producing a large dynamic range for plasticity. Changes in tracer coupling in neurons have been correlated to indices of electrical coupling such as receptive field diameter in retinal AII amacrine cells [9] and intercellular electrical conductance in inferior olive neurons [10••], indicating that changes in tracer coupling correspond to real changes in electrical coupling. Tracer coupling, by its nature, reports a system-level average of the functional states of the participating gap junctions. Within a single cell, the phosphorylation states of individual gap junctions are highly variable [7••,11•], with gap junctions well under one micron apart being in vastly different phosphorylation states. This reveals that the functional state is controlled at the level of the individual synapse, and suggests that the dynamic range for plasticity of individual electrical synapses is likely larger than the order of magnitude average value.

Figure 1



Changes of tracer coupling in neurons correlate strongly with phosphorylation of Cx36. (A) Neurobiotin injection into single AII amacrine cells in the rabbit retina results in filling arrays of cells (i–iii) by tracer diffusion through gap junctions. Tracer diffusion is reduced by application of dopamine D1 receptor agonist SKF38393 (ii) and increased by D1 receptor antagonist SCH23390 (iii). Immunostaining of the regions outlined with boxes in i–iii for total Cx36 (red channel) and Cx36-phospho-Ser293 (green channel) is shown in iv–vi; the blue channel shows Neurobiotin-filled dendrites of the injected cell. The phospho-Ser293 channel is shown alone in vii–ix. The D1 agonist reduces and D1 antagonist increases Cx36 phosphorylation. Arrowheads show gap junctions on the injected cell. (B) Correlation between the average phosphorylation state of Cx36, defined as the ratio of phospho-S293 to total Cx36 on each Cx36 gap junction, and the diffusion coefficient for Neurobiotin derived by fitting tracer intensity data in somata of AII amacrine cells at various distances from the injected cell with a compartmental diffusion model. R^2 of the linear fit is 0.86. (C) Similar correlation of data for photoreceptor coupling in C57Bl/6 mouse photoreceptors with parallel measurements of Cx36 phosphorylation. Animals were collected at night in darkness or in the day in light, or adapted to darkness for various times during the day. R^2 of linear fit to the data is 0.81. For both rabbit AII amacrine cells and mouse photoreceptors, the dynamic range for Neurobiotin diffusion coefficient was 20-fold.Panels A and B adapted from Ref. [7••]; Panel C adapted from Ref. [8••].