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The Journal of Physiology

PERSPECTIVES

How do electrical synapses regulate their strength?

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Neuronal communication in the central nervous system is ensured by synapses through which neuronal events can be transmitted from one cell to the next. Classically, two major classes of synapses can be distinguished: (i) *chemical* synapses that use a chemical transmitter to activate or inhibit the postsynaptic neuron and (ii) *electrical* synapses that transmit information to the next cell by passive transmission of voltage in an analogue way (i.e. they do not require an action potential). While the basic function and plasticity of chemical synapses is relatively well established today, much less is known about the mechanism of activity-dependent plasticity at electrical synapses. Electrical synapses connect two adjacent neurons through intercellular channels that form gap junctions. They are widely expressed in the central nervous system of mammals and are particularly abundant in inhibitory interneurons (Pereda, 2014). Unlike chemical synapses, electrical synapses are bidirectional, reliable and conduct almost instantaneously. Functionally, electrical synapses are involved in many features of the network activity. Because of their ohmic nature, they can transmit excitation as well as inhibition, and it has been shown that they are involved in synchronous oscillatory activity.

The thalamic reticular nucleus (TRN) contains a homogeneous population of parvalbumin-positive γ-aminobutyric acid (GABA)-releasing neurons that surround the dorsal thalamus. TRN neurons inhibit thalamic relay cells and thus control the switch of their discharge from bursting to tonic mode occurring during the transition from sleep to wakefulness. These interneurons communicate essentially through gap junctions constituted of connexin36 (Cx36), the main connexin found in the mammalian brain.

Long-term depression of electrical coupling (eLTD) at electrical synapses in the TRN has been shown to occur when afferent cortical input to electrically coupled neurons is tetanized at 100 Hz (Landisman & Connors, 2005). This eLTD is mediated by activation of the metabotropic glutamate receptor (mGluR) and it can be induced by the sole stimulation of group I mGluR (Wang *et al.* 2015). Alternatively, eLTD can be induced at TRN electrical synapses with a physiological protocol based on the synchronous activation of both neurons (Haas *et al.* 2011). Functionally, modification of electrical coupling in TRN neurons is thought to modulate temporal and spatial transmission of information within the thalamo-cortical system. Today, the mechanisms underlying both forms of eLTD remain unclear.

In this issue of *The Journal of Physiology*, Sevetson and co-workers addressed this important issue by showing that, while mGluR-dependent eLTD and burst-induced eLTD occlude each other, Ca^{2+} entry through T-type calcium channels is required for the induction of burst-induced eLTD but not for mGluR-dependent eLTD (Sevetson *et al.* 2017). In fact, while the Ca^{2+} chelator BAPTA or the T-type calcium channel antagonist TTA-A2 blocked burst-induced eLTD, these compounds were found to have no effect on mGluR-dependent eLTD. Induction of burst-induced eLTD was blocked by caffeine or ryanodine, indicating that Ca^{2+} influx recruits intracellular pools of Ca^{2+}. Furthermore, blocking activation of the calcium-activated protein phosphatase calcineurin with FK-506 or cyclosporin A occluded induction of burst-induced eLTD.

This paper is important because it opens several interesting perspectives. First, the findings reported in Sevetson *et al.* (2017) indicate that there are at least two forms of eLTD at TRN electrical synapses that are independent in both their induction and expression mechanisms. While mGluR-dependent eLTD corresponds to a global phenomenon in which glutamatergic stimulation affects many neighbouring electrical synapses, the burst-induced eLTD is initiated by activity in pairs of coupled neurons and may thus correspond to a more local phenomenon. Second, the involvement of calcineurin in eLTD suggests that other forms of plasticity at electrical synapses might be induced. In fact, calcineurin controls activity of calcium/calmodulin-dependent protein kinase II (CaMKII), which is involved in NMDA receptor-dependent long-term synaptic plasticity (long-term potentiation; LTP) in cortical chemical synapses but also in some forms of LTP of electrical coupling (eLTP) (Pereda, 2014; Turecek *et al.* 2014). Moreover, Cx36, interacts with and is phosphorylated by CaMKII in a way similar to CaMKII interaction with glutamate receptors. eLTP has been shown to be induced in TRN neurons following stimulation of group II metabotropic glutamate receptors (Wang *et al.* 2015). However, no physiological induction of mGluR-dependent eLTP has been described so far nor the conditions to induce burst-dependent eLTP. At chemical synapses, the degree of synchrony between pre- and postsynaptic activity determines the polarity of synaptic modification (Debanne *et al.* 1994). Since eLTD is induced by synchronous bursting activity in electrically coupled neurons, it is tempting to suggest, by analogy with what we know about plasticity at chemical synapses, that eLTP might be induced by asynchronous bursting in weakly coupled TRN neurons.

To complete the library of plasticity rules at electrical synapses, one must also explore the existence of homeostatic plasticity (i.e. compensatory plastic changes to maintain the global network activity constant) at electrical synapses. There is no doubt that sooner or later both induction mechanisms of physiological eLTP and induction mechanisms of homeostatic plasticity will be elucidated at electrical synapses.

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Additional information

Competing interests

None declared.

Author contributions

Both authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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