Electrical Synapses

High-speed Communication in the Maintenance of Neuropathic Pain

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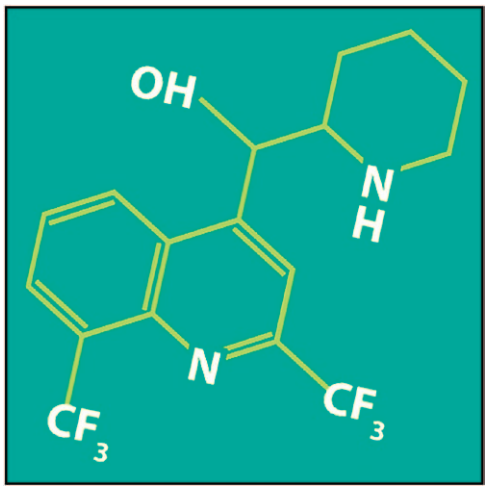
IN this issue of Anesthesiology, Chen *et al.*[1] evaluated the role of a neuronally expressed electrical synapse (also called a gap junction) in neuropathic pain in rats. Electrical synapses are not well known to anesthesiologists or pain physicians although they were first described in the early 1900s by Golgi.[2] An electrical synapse is formed by gap junctions between two neurons that directly abut each other with a distance of approximately 3 nm. The 1906 Nobel Prize for Physiology and Medicine was jointly awarded to Golgi, a proponent of the electrical synapse, and Santiago Ramon y Cajal, who described the more familiar chemical synapse. This prize was controversial as the two ideas were then thought to be mutually exclusive. In retrospect, the choice of the Nobel Committee was prescient as now it appears that not only do both methods of signaling exist, but they also interact importantly.



"Mefloquine is a well-tolerated drug used for the treatment of malaria and now an attractive candidate as an analgesic with a distinct mechanism."

Electrical synapses provide a fast and simple signaling mechanism through specialized junctions that allow for bidirectional ionic current flow (fig. 1). Electrical synapses are formed by two hemichannels on opposing cells, each of which is made up of six connexin protein subunits. There are multiple connexin isoforms in humans and mice, which are named for their predicted molecular weights, for example, Cx36 studied by Chen *et al.*[1] has a mass of approximately 36 kDa. Interestingly, specific central nervous system cell types differentially express connexin protein isoforms. For example, astrocytes highly express Cx43, whereas neurons highly express Cx36.

Chen *et al.*[1] evaluated the role of electrical channels composed of Cx36 in the anterior cingulate cortex (ACC) of mice using the chronic constriction injury model of neuropathic pain. Functional magnetic resonance imaging studies show an enhanced neuronal activity in the ACC in anticipation of painful stimuli and in chronic pain conditions, and surgical lesioning of the ACC alters the affective response to noxious stimuli but not the ability to localize it. This suggests that the anterior cingulate is an area of association cortex that is important to the interaction between the affective and primary nociceptive response to injury. Interestingly, Chen *et al.*[1] only saw an up-regulation of Cx36 in the ACC consistent with hyperalgesia after chronic constriction injury, not in other brain areas evaluated. They then went on to use short-hairpin RNA against Cx36 delivered directly to the ACC by implanted cannula to block its expression and found that they could reverse mechanical allodynia and thermal hyperalgesia after nerve injury. Given the known role of the ACC in the affective component of pain, it would have been interesting to evaluate the behaviors (such as conditioned place avoidance) after the above manipulations to more determine whether the change in nociception was actually secondary to a change in the perceived unpleasantness of the stimuli. An important translational step was the use of systemically administered gap junction blockers, which were also shown to reverse the pain behaviors without affecting motor function. One of these gap junction blockers, mefloquine, a quinine derivative, is selective for Cx36 and is already routinely given to patients for the prevention and treatment of malaria.

In contrast to electrical synapses, the classic chemical synapse consists of a presynaptic neuron that releases neurotransmitters from synaptic vesicles that cross a wider

Image: A. Johnson.

Corresponding article on page 169. Figures 1 and 2 were enhanced by Annemarie B. Johnson, C.M.I., Medical Illustrator, Vivo Visuals, Winston-Salem, North Carolina.

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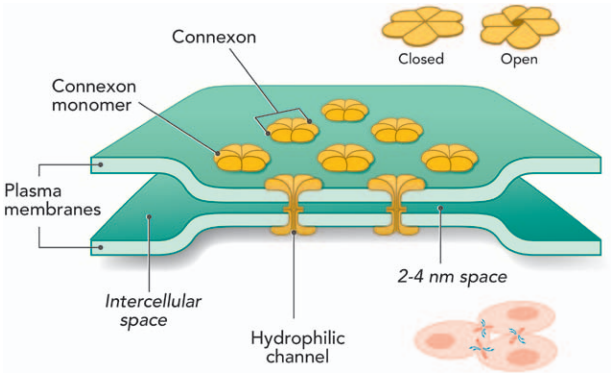

Fig. 1. Electrical synapses. Specific types of gap junctions on one cell in close apposition to identical gap junctions on another cell form an electrical synapse. These connections are very fast and not modulated.

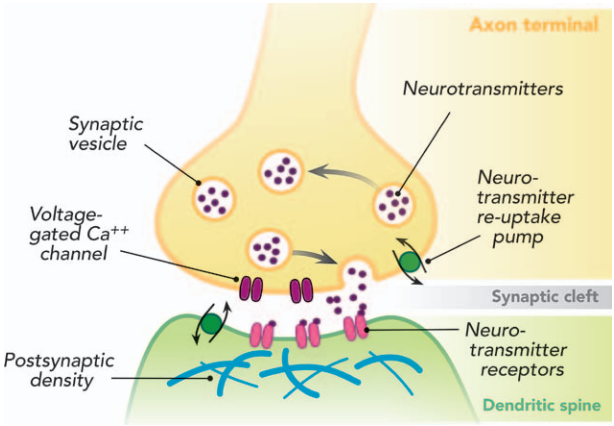

Fig. 2. Chemical synapses. The more commonly known chemical synapse has a complex presynaptic apparatus that causes the release of chemical neurotransmitter that acts to influence the likelihood of activation of the postsynaptic receptor on a neighboring cell. This process is slower and highly modulated.

synaptic cleft to activate one of the various types of ionotropic or metabotropic receptors on the postsynaptic cell (fig. 2). Electrical synapses differ from chemical synapses in that they are able to transmit information faster and lack gain control from presynaptic and/or postsynaptic modulation. Chemical and electrical synapses interact such that electrical synapses can provide the blueprint for the formation of chemical synapses during development and chemical synapses can in turn alter the electrical coupling of neuronal populations.[3] This close relation suggests that in disease states the excess release of neurotransmitters from chemical synapses can not only affect postsynaptic receptors but also can fundamentally change the regional activity of the nervous system through effects on electrical synapse formation.

Because electrical synapses couple cells of similar size and type, they can synchronize regional activity at a speed that allows for a range of processes such as sensory perception and memory formation. One form of the synchronized, rhythmic network activity occurs in the gamma frequency range (30 to 80 Hz). Gamma oscillations are associated with conscious somatosensory processing, can be elicited by painful stimuli, and are thought to be important mediators in the maintenance of neuropathic pain and other facets of the conscious experience.[4,5] Knockout of Cx36 in mice disrupts gamma oscillations suggesting a unique function in neuronal information processing.[6] Perhaps, most exciting in the work of Chen *et al.* is the proposed mechanism of Cx36 in the generation of pain. Providing additional support for a mechanistic role for electrical channels composed of Cx36 in gamma oscillations and neuropathic pain, the power of gamma oscillatory activity was increased in rats that underwent chronic constriction injury compared with control. Systemic administration of mefloquine almost completely reversed the increase in oscillatory activity in the ACC induced by nerve injury. Furthermore, brain slices were used to investigate the interaction between Cx36-mediated electrical transmission and synaptic plasticity traditionally thought to mediate neuropathic pain. The frequency of mini excitatory post-synaptic currents (mEPSCs) represents a presynaptic effect of enhanced probability of glutamate release, whereas the amplitude represents a postsynaptic effect of enhanced activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors. The frequency and amplitude of mEPSCs in the anterior cingulate were enhanced in rats that had undergone chronic constriction injury, suggesting that increased activity of the electrical synapse mediated by Cx36 impacts on both presynaptic and postsynaptic modulation. Treatment with systemic mefloquine resulted in a decrease in both the amplitude and frequency of mEPSCs. A reduction in paired pulse facilitation further supported a role in presynaptic modulation, while enhanced inward rectification supported the claim for enhanced postsynaptic activity. Both alterations were reversed with systemic mefloquine. These studies suggest a fast modulatory role of electrical channels composed of Cx36 on presynaptic and postsynaptic chemical channels and present a novel target for interruption of neuropathic pain in the maintenance phase.

In summary, Chen *et al.* have provided the evidence for a modulatory role of gamma oscillations induced by electrical synapses composed of Cx36 in neuropathic pain in the ACC. The up-regulation of Cx36, enhancement in gamma oscillations, and presynaptic and postsynaptic modulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor–mediated synaptic transmission could be reversed by systemic treatment with mefloquine. Mefloquine is a well-tolerated drug used for the treatment of malaria[7] and now an attractive candidate as an analgesic with a distinct mechanism.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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