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Bridging the Gap – The Ubiquity and Plasticity of Electrical Synapses

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Abstract

- There is a substantial emerging literature on the complexity and plasticity of the apparently simple electrical synapses [ES]. Here we draw attention to some of the most recent findings in this rapidly evolving field.
- ES are ubiquitous, found in all multicellular animals and structurally underlain by gap junctions. Gap junctions are topographically similar in vertebrates and invertebrates, but based on different mutually exclusive connexins and innexins respectively.
- It is now clear that ES may be modulated and exhibit plasticity in addition to promoting synergy between coupled neurons according to the strength of coupling. Strong electrical coupling promotes synchronous activity while weak coupling may desynchronise coupled neurons.
- Chemical synapses may modulate ES conductances and may regulate the degree of coupling between neurons. Because ES act as low pass filters, prolonged spike after-hyperpolarisations can allow them to act as inhibitory connections, but modifications of conductances can allow them to act as high pass filters and there is gathering evidence that their gain can be modulated and is activity dependent.
- ES may be modulated by anaesthetics at clinically relevant concentrations and volatile anaesthetics can reduce coupling between strongly electrically coupled neurons in a dose dependent manner. This may prove to be important during anaesthesia, given the ubiquity of ES in the mammalian brain.
- ES appear to be seasonally modulated in the brain of the mollusc *Lymnaea stagnalis*, but the underlying mechanisms remain to be elucidated.
- Although neurons have distinct structures they do not necessarily act as single functional units and groups of electrically coupled cells may act as functional syncitia which suggests that Cajal's neuron doctrine and Golgi's reticular theory are not mutually exclusive.

Keywords: *Ubiquity; Plasticity; Electrical Synapses*

Ubiquity of gap junctions and electrical synapses

Gap junctions connect the cytoplasm of neighbouring cells and are found in most tissues of most animals with the exceptions of skeletal muscle, blood cells and other mobile cells. There were prolonged arguments in the early part of the 20th century about the nature of synapses, were they chemical (based on Cajal's neuron doctrine; [1,2]) or electrical (based on Golgi's reticular theory, [3])? The argument seemed to have come out in favour of chemical synapses by the 1950s, but at this point Furshpan and Potter demonstrated the existence of electrical transmission at the giant motor synapses of the crayfish [4,5]. Later it was revealed that gap junctions, which are now known to be the morphological structures underlying electrical synaptic transmission [6,7], are ubiquitous in the brains of mammals, fish and

birds [8,9]: "they are "distributed throughout the entire brain" [10]. Furthermore, they are found throughout the animal kingdom, e.g. in *Caenorhabditis elegans* [11], and there are functional descriptions in many invertebrates including the mollusc *Lymnaea stagnalis* [12]. However, there are clear structural differences between mutually exclusive vertebrate connexins and the invertebrate innexins which make up the connexons and innexons respectively [13,14], but both have four transmembrane domains [15] and intracellular N- and C-termini. However, the topographies of both types of molecule are similar [13,15] and in both cases the proteins may form hemichannels that mutually align to form gap junctions, through which molecules may pass from the cytoplasm of one cell to another. The related pannexins are not relevant to the present discussion, but more detail on them can be found elsewhere [13-15].

Recently Oshima., *et al.* [11] have demonstrated that in *Caenorhabditis* the innexin-6 gap junction channels are made up of 16 subunits, probably a general feature of all innexin channels, whereas chordate connexin channels are made up of 12 subunits. The implication is that innexin channels have potentially greater conductances than those of connexins. Interestingly, "the physiological properties of gap junction channels appear to be determined by the connexin expressed, independent of tissue type" [16] and this is probably also true of innexins. Within the vertebrate brain gap junctions are found between glial cells [17], particularly astrocytes, and between neurons and glial cells both in culture [18] and *in vitro* [17], although there is controversy as to whether these connections are fully retained in the adult brain. However, gap junction expression appears to be a requirement prior to normal chemical synapse formation [20,21] and both chemical synapses and ES may remain in close proximity to one another in the adult brain [22].

Modulation and Plasticity of electrical synapses

One of the main features of non-rectifying electrical synapses (ES) is the lack of delay normally associated with chemical synapses for which reason they may promote synergy between coupled neurons [23,24]. However, plasticity of ES is demonstrable and they can be dynamically modulated by a wide range of neuromodulators such as dopamine, noradrenaline, glutamate [25], nitric oxide [26] and various other neuroactive compounds. For example, activation of metabotropic glutamate receptors caused reduced electrical coupling between neurons of the rat thalamic reticular nucleus [27]. In addition, chemical synapses may modulate the conductance of ES and thus regulate the degree of electrical coupling between neurons [28] and this voltage dependency [7] is likely to be a facet of specific connexins or innexins.

Although ES are apparently simple structures the emergent properties of coupled neurons may be highly plastic dominated by modulation of the biophysical properties of the cells involved [29], particularly the input resistance and the coupling resistance of the connected cells. Furthermore, the connexin (20 types) and innexin (25 types) proteins vary from one cell to another and influence the exact biophysical and biochemical properties of the junctions [13]. Phosphorylation of individual connexins, and by implication innexins, may modify cell to cell communication and movement of small molecules between the cells [30].

Do electrical synapses synchronise neural activity? It was previously assumed that the main role of ES was to synchronise neurons or groups of neurons [24,31,32], but due to the fact that they tend to act as low pass filters a deep and prolonged after-hyperpolarisation can allow them to act as inhibitory connections [33] and to allow them to synchronise or desynchronise the spiking activity of mouse Golgi cells depending on the input properties of the presynaptic signal [34]. Similar results have been modelled by Hull., *et al*. [32] for unmyelinated tadpole brainstem neurons where synchronization of rhythmic firing can be maintained or shunting through gap junctions may cause propagation failure. In other neural simulations, modification of the coupling coefficient may cause neurones to oscillate out of phase when weakly coupled and in phase when strongly coupled [35]. Strong electrical coupling between pairs or small numbers of neurons has been observed in the somata of mouse primary afferents located in the mesencephalic trigeminal (Mes V) nucleus and originating in jaw-closing muscles [23]. Here signals are enhanced by sodium and potassium conductances which allow the gap junctions to act as high pass filters, allowing the higher frequencies associated with the rising phase of the action potential to cross the gap junctions between the cells. This promotes strongly synchronised spiking to occur between Mes V neurons due to voltage dependent amplification of conductances which improve the efficacy of coupling. This finding supports the gathering evidence that the gain of ES may be varied

[25] and there is also evidence that the gain is activity dependent in the mammalian brain [36]. We conjecture that similar mechanisms may exist in other strongly coupled neurons, such as those in *Lymnaea* [31,37,38].

Further roles for ES Other types of interactions may also occur at ES. For example, rectifying electrical synapses were first demonstrated in the crayfish in 1959 [4]. More recently it has been suggested that ES may act as coincidence detectors in simulated systems [35]. In addition, interactions between chemical synapses and nearby ES can regulate electrical coupling at goldfish Mauthner cells [28] where the ES have an inhibitory effect due to their anatomical arrangement close to the Mauthner cell initial segment, altering the relative charge across the membrane [6,39].

Modulation of ES coupling by anaesthetics Given the plasticity inherent in ES, it should come as no surprise that they are also modulated by general anaesthetics in both astrocytes [40] and neurons [41]. Volatile anaesthetics applied at clinically relevant concentrations can reduce coupling between strongly electrically coupled neurons in a dose dependent manner by modifying their input resistance and other passive properties of their membranes [38]. An earlier study suggested that ES are less sensitive to most anaesthetics than chemical synapses [42], but Juszczak and Swiergiel [43] are of the opinion that anaesthetic compounds may confound behavioural studies because they block gap junctions, often in the clinical concentration range, although there are issues over which types of anaesthetic are most effective. Nevertheless, it is apparent that "suppression of gap junction function could compound the mechanisms of anaesthetic action" [41]. This would also be true in myocardial cells where the volatile anaesthetic enflurane is known to decouple gap junctions, perhaps altering conduction velocity and contractility [44].

Seasonal modulation of coupling ES appear to be seasonally modulated in the brain of *Lymnaea* [38,45] in which biogenic amines show dramatic seasonal variability [46] and in which chemical synaptic connectivity is also variable on a seasonal basis [47,12]. Temperature changes also have an effect on ES in *Lymnaea* as rising temperatures can reduce coupling coefficient between strongly coupled neurons [26], but this would appear to be opposition to the increased coupling found between these same neurons in the summer months [38], raising questions as to the mechanisms by which coupling is increased during warm weather.

Conclusion

Over the last two decades there has been a huge outpouring of research into electrical synapses which has demonstrated that ES are plastic, modifiable and of course ubiquitous. The very ubiquity of gap junctions indicates their importance in cell to cell communication in almost all tissues throughout the animal kingdom. If a phase model of computation is correct [48] then ES will have the direct role in computation of changing the phase of the action potential as it passes points of interference which will change the pathway in the neural network. Although neurons have distinct structures they do not necessarily act as single functional units and groups of cells may act as functional syncitia, sometimes firing in synchrony [49]. For these reasons, the neuron doctrine and the reticular theory are being revised into a new more holistic theorem of the functions of the nervous system.

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