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Review

Curious and contradictory roles of glial connexins and pannexins in epilepsy

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ABSTRACT

Glia play an under-recognized role in epilepsy. This review examines the involvement of glial connexins (Cxs) and pannexins (Panxs), proteins which form gap junctions and membrane hemichannels (connexins) and hemichannels (pannexins), in epilepsy. These proteins, particularly glial Cx43, have been shown to be upregulated in epileptic brain tissue. In a cobalt model of *in vitro* seizures, seizures increased Panxs1 and 2 and Cx43 expression, and remarkably reorganized the interrelationships between their mRNA levels (transcriptome) which then became statistically significant. Gap junctions are highly implicated in synchronous seizure activity. Blocking gap junctional communication (GJC) is often anticonvulsant, and assumed to be due to blocking gap junctionally-medicated electrotonic coupling between neurons. However, in organotypic hippocampal slice cultures, connexin43 specific peptides, which attenuate GJC possibly by blocking connexon docking, diminished spontaneous seizures. Glia have many functions including extracellular potassium redistribution, in part via gap junctions, which if blocked, can be seizuregenic. Glial gap junctions are critical for the delivery of nutrients to neurons, which if interrupted, can depress seizure activity. Other functions of glia possibly related to epileptogenesis are mentioned including anatomic reorganization in chronic seizure models greatly increasing the overlapping domains of glial processes, changes in neurotransmitter re-uptake, and possible glial generation of currents and fields during seizure activity. Finally there is recent evidence for Cx43 hemichannels and Panx1 channels in glial membranes which could play a role in brain damage and seizure activity. Although glial Cxs and Panxs are increasingly recognized as contributing to fundamental mechanisms of epilepsy, the data are often contradictory and controversial, requiring much more research.

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Contents

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1. Introduction

Relatively ignored for many years compared to neurons, glia are now increasingly implicated in diverse brain functions and neurological diseases. Glial cells are as numerous or more than neurons (Herculano-Houzel, 2009) with diverse phenotypes, particularly in the human CNS (Oberheim et al., 2006). Initially thought to be the 'servants' of neurons, providing structural/nutritional support, it is now increasingly evident that glia have many other functions and properties (Kettenmann and Verkhratsky, 2008). These include extracellular potassium and calcium regulation, control of the blood–brain barrier, extracellular space and cerebral blood flow, and release and re-uptake of neurotransmitters and other molecules (recently reviewed by Wang and Bordey, 2008; Kimelberg, 2010). Glia are now increasingly recognized as intrinsic to seizure generation (Heinemann et al., 2000; Tian et al., 2005; Wetherington et al., 2008; Oberheim et al., 2008; Jabs et al., 2008; Schwarcz., 2008; Friedman et al., 2009; Seifert et al., 2010; de Lanerolle et al., 2010). Glia are extensively connected via gap junctions (Cxs30 and 43, and to a lesser extent, Cx26, Nagy et al., 2004). In mouse hippocampus, the expression of Cxs43 and 30 mRNAs is several-fold that of neuronal connexins (Mylvaganam et al., 2010). This review focuses on the potential roles in epilepsy of glial connexins and pannexins, proteins which form gap junctions and membrane hemichannels (Cxs) and hemichannels (Panxs) (see schematic, Fig. 1), also reviewed recently by Steinhäuser et al. (2012).

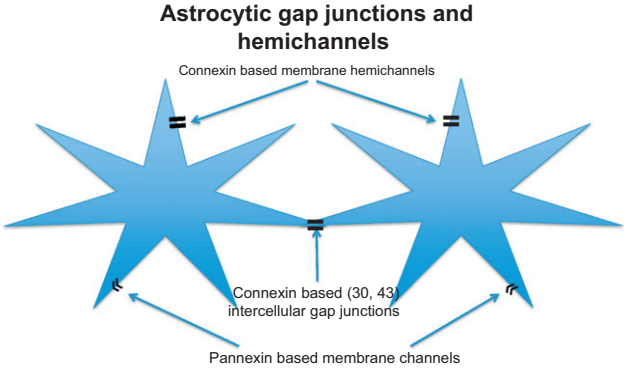

Fig. 1 – Schematic of connexins and pannexins. Note that connexins form both intercellular gap junctional channels and membrane 'hemichannels', whereas pannexins only membrane channels.

2. Gap junctions and seizures

Gap junctional communication (GJC) is now increasingly recognized as playing a potentially important role in epileptogenesis (i.e. setting the biological background for seizures to occur) and in seizure generation (Seifert et al., 2010). GJC is implicated in generating neuronal synchrony, rhythmicity, and epileptic seizures (Carlen et al., 2000; Traub et al., 2004; Perez-Velazquez and Carlen 2000). Gap junctional blockers reduce seizures in several *in vitro* (Jahromi et al., 2002; Samoilova et al., 2003; Gigout et al., 2006a,b) and *in vivo* seizure models (Bostanci and Bağirici 2006, 2007; Gadja et al., 2005, 2006; Gigout et al., 2006a,b). Also in human neocortical slices resected from patients with intractable epilepsy, gap junction blockers attenuated epileptiform discharges (Gigout et al., 2006a,b). In contrast, Voss et al. (2009) showed that seizure-like activity induced by perfusing with low-magnesium artificial cerebrospinal fluid in rat cortical slices was increased by four gap junction blockers; quinine, quinidine, carbenoxolone, and mefloquine. However, Medina-Ceja and Ventura-Mejía (2010) showed that quinine depressed epileptiform activity induced by 4-aminopyridine (4-AP) applied to the rat entorhinal cortex (EC) and the CA1 hippocampal region *in vivo*.

Alterations in gap junctional (GJ) expression may also be involved in epileptogenic processes, since seizure activity has been shown to alter or increase the mRNA expression and protein of GJs, particularly glial Cxs (Naus et al., 1991; Aronica et al., 2001; Li et al., 2002; Fonseca et al., 2002; Samoilova et al., 2003; Collignon et al., 2006; Gadja et al., 2006; Zappalà et al., 2006; Yao et al., 2009; Mylvaganam et al., 2010; Garbelli et al., 2011).

Certain diseases with epilepsy have been associated with altered glial GJC. Tuberous sclerosis, well known to be associated with epilepsy, is caused by mutations of the tumor suppressor genes TSC1 and TSC2. Deleting TSC1 in astrocytes caused the seizuregenic effects of impaired astrocytic GJC and potassium buffering in a mouse model of tuberous sclerosis Xu et al. (2009). These effects were reversed by rapamycin treatment, which inhibits the mTOR pathway, known to be activated in tuberous sclerosis (Tsai and Sahin, 2011). Another disease associated with severe seizures is the Rett syndrome, which is associated with mutations of the MECP2 gene causing a deficiency in the MeCP2 protein. Maezawa et al. (2009) have shown in a mouse model of Rett's syndrome that MeCP2 deficiency in mouse astrocytes can spread via gap junctions. Glial swelling, which in part is mediated by GJC and is a common concomitant of brain injury, will diminish the extracellular space in the brain, leading to increased ephaptic transmission and seizure activity (Shahar et al., 2009).