



Presynaptic mechanisms of neuronal plasticity and their role in epilepsy

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Synaptic communication requires constant adjustments of pre- and postsynaptic efficacies. In addition to synaptic long term plasticity, the presynaptic machinery underlies homeostatic regulations which prevent out of range transmitter release. In this minireview we will discuss the relevance of selected presynaptic mechanisms to epilepsy including voltage- and ligand-gated ion channels as well as cannabinoid and adenosine receptor signaling.

Keywords: epilepsy, axon, RNA editing, potassium channels, glycine receptor, homeostatic regulation, neuropsychiatric disorders, hippocampus

INTRODUCTION

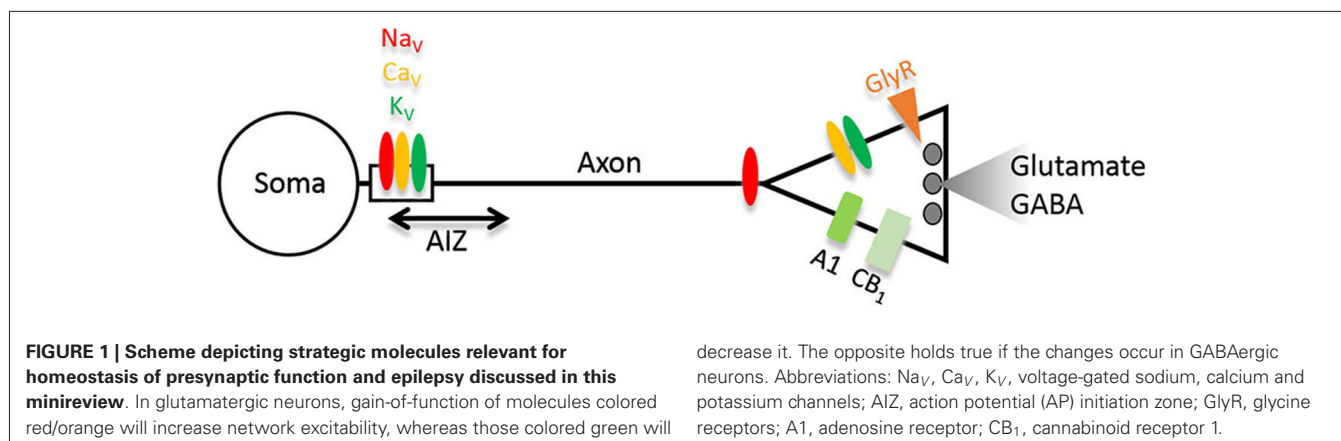
Many studies highlighted the importance of homeostasis in neuronal signaling either within neurons, then called “intrinsic plasticity” or between neurons, referred to as “synaptic scaling” (Davis and Bezprozvanny, 2001; Eichler and Meier, 2008; Turrigiano, 2011). Classic synaptic plasticity in its non-homeostatic “Hebbian” form and pathological disturbances need counterbalancing homeostatic scaling mechanisms (Abbott and Nelson, 2000). The latter was mainly regarded from the postsynaptic perspective (Thiagarajan et al., 2005; Groth et al., 2011). However, in addition to presynaptic expression of synaptic long term plasticity (Nicoll and Schmitz, 2005), slow homeostatic regulations occur in the presynapse, e.g., in form of chronic receptor or ion channel modulations.

PRESYNAPTIC ION CHANNEL AND GLYCINE RECEPTOR PLASTICITY

Because transmitter release is controlled by action potential-(AP)-triggered calcium influx in the synaptic terminal, regulation of ion channels which shape the axonal AP and terminal depolarization is an effective mechanism of presynaptic plasticity. With this definition, the AP initiation zone (AIZ) could be viewed as part of the presynaptic equipment. A striking form of homeostatic plasticity has been documented for the AIZ: this entire subcellular structure including voltage-gated Na⁺ (Na_v) and K⁺ (K_v) channels can be shifted along the axon (Figure 1), thereby counteracting hyperexcitation by increasing thresholds for AP generation (Grubb and Burrone, 2010). Such axonal remodeling may be facilitated via ion channel trafficking

regulated by alternative splicing, as shown for “shaw-related” Kv3 channels (Gu et al., 2012). Other important constituents of presynaptic control are “shaker-related” Kv1 channels (Wang et al., 1994). Their role is well demonstrated for the large glutamatergic mossy fiber boutons of dentate granule cells, which impinge on hippocampal CA3 pyramidal cells (Geiger and Jonas, 2000; Bischofberger et al., 2006). Here, K_v channels could gain further importance during temporal lobe epilepsy (TLE), when seizures invade the hippocampus and feedforward inhibition of CA3 pyramidal cells via interneurons is compromised (Lawrence and McBain, 2003). Indeed, seizures trigger a transcriptional upregulation of Kv1.1 channels in granule cells, thereby delaying their AP responses considerably, as recently shown in a TLE mouse model (Kirchheim et al., 2013). Consistent with the view that Kv1.1 is a promising antiepileptic target, Kv1.1 knockout mice develop epilepsy (Wenzel et al., 2007) and lentiviral overexpression of Kv1.1 ameliorates seizures in an animal model of neocortical epilepsy (Wykes et al., 2012). The interaction of activity-dependent downscaling and potentiation of presynaptic excitability may involve the adenylyl cyclase pathway (Nicoll and Schmitz, 2005) but it is still unclear how exactly these seemingly opposed mechanisms interact in the same presynaptic compartment.

Epilepsy often comes with cognitive dysfunction and neuropsychiatric comorbidities (García-Morales et al., 2008). We discovered a molecule which in this regard may have an important impact: an RNA variant of the neurotransmitter receptor for glycine (GlyR). The GlyRs are subject to increased RNA editing in resected hippocampi of TLE patients (Eichler et al., 2008)



which profoundly influences biophysical receptor properties. The reason is an amino acid substitution in the ligand binding domain leading to gain-of-function receptors with increased neurotransmitter affinity (Meier et al., 2005; Eichler et al., 2008; Legendre et al., 2009) and spontaneous channel activity (Kletke et al., 2013; Winkelmann et al., 2014). In addition, RNA splicing governs presynaptic GlyR expression (Winkelmann et al., 2014), and in hippocampal neurons, the lack of the GlyR β subunit (Weltzien et al., 2012) which governs postsynaptic receptor clustering (Meyer et al., 1995; Meier et al., 2000, 2001; Eichler et al., 2009; Förster et al., 2010; Kowalczyk et al., 2013), certainly facilitates GlyR expression and function at presynapses (Figure 1). Presynaptic GlyRs are tightly packed (~ 200 receptor channels in a cluster with ~ 100 nm radius; Notelaers et al., 2012, 2014a,b), which implies that a single presynaptic cluster from the spontaneously active GlyR RNA variant will have a considerable functional impact on synaptic neurotransmitter release, even if the contribution of the glycinergic system to this brain region appears limited (Zeilhofer et al., 2005). Consistent with the excitatory nature of presynaptic chloride channels and the well documented presynaptic GlyR expression in the hippocampus (Kubota et al., 2010; Ruiz et al., 2010; Waseem and Fedorovich, 2010; Winkelmann et al., 2014), we found that the spontaneously active GlyR RNA variant actually increased presynaptic excitability and the functional impact of glutamatergic neurons or parvalbumin-positive interneurons *in vivo* and, depending on the type of neuron, triggered cognitive dysfunction or anxiety in our mouse model of epilepsy (Winkelmann et al., 2014). In agreement with the proposed critical role of presynaptic GlyRs in the regulation of neural network excitability, application of a low, non-receptor-saturating, glycine concentration ($10 \mu\text{M}$) to corticohippocampal slice preparations was sufficient to enhance epileptiform activity induced by block of K_v1 channels (Chen et al., 2014).

RETROGRADE AUTOCRINE AND PARACRINE SIGNALING

Although the idea of cannabis as a potential antiepileptic drug is ancient, it remained elusive how it could work reliably (Adams and Martin, 1996; Miller, 2013). Recent discoveries on endogenous cannabinoid receptors (CB), of which particularly CB₁ is widely expressed in presynaptic terminals of excitatory and inhibitory neurons (Figure 1), could lead to a better

understanding of CB mechanisms in epilepsy (Alger, 2004; Katona and Freund, 2008; Hill et al., 2012). In GABAergic neurons, activation of CB₁, e.g., via neuronal activity-dependent retrograde post-to-presynapse release of CBs anandamide or 2-AG has been shown to decrease synaptic GABA release, a mechanism termed depolarization-induced suppression of inhibition (DSI; Ohno-Shosaku et al., 2001; Wilson et al., 2001). Consistently, elevated CB₁ presence observed in epilepsy models and TLE patients (Goffin et al., 2011; Karlócai et al., 2011; Bojnik et al., 2012) has been interpreted as proconvulsive (Chen et al., 2003, 2007). On the other hand, CB₁ is also expressed on glutamatergic terminals, where its activation reduces glutamate release (Domenici et al., 2006; Kawamura et al., 2006). Furthermore, CB₁ activation increases inward rectifier K⁺ (Kir) currents (Mackie et al., 1995; Chemin et al., 2001) mediated via postsynaptic channels which are also upregulated in TLE (Young et al., 2009; Stegen et al., 2012). In summary, while elevation of CB₁ at GABAergic synapses and reduction at glutamatergic synapses likely constitute endogenous adaptations to epilepsy, exogenous CB₁ overexpression and activation in principal neurons, possibly via receptors physiologically rarely activated, could effectively protect against seizures (Blair et al., 2006; Guggenhuber et al., 2010; Hofmann and Frazier, 2013).

Adenosine triphosphate (ATP) is released from astrocytes and can enhance neuronal excitability through its direct action onto purinergic receptors. However, ATP can also exert indirect effects upon its enzymatic conversion to adenosine and signaling through adenosine A1 receptors, which reduces synaptic glutamate release (Nicoll and Schmitz, 2005; Boison, 2013; Dias et al., 2013). Therefore, adenosine signaling is another mechanism of presynaptic homeostasis with recognized relevance to epilepsy; while too much adenosine clearance via gliosis-enhanced adenosine kinase activity is a proconvulsive factor, adenosine augmentation in the epileptic focus represents a powerful anticonvulsive principle (Boison, 2012).

PERSPECTIVE

In agreement with the proposed critical role of presynaptic compartments in the regulation of neural network homeostasis, diverse pharmacological agents with a presynaptic mode of action were reported to be effective in the treatment of epilepsy. In

particular drugs which provide rapid adaptation against excessive excitation, e.g., via use-dependent inhibition of Na_v or Ca_v channels (phenytoin, carbamazepine, lamotrigine, topiramate, and levetiracetam), likely act primarily in axons (Stefani et al., 1996; Wu et al., 1998; Catterall, 1999; Vogl et al., 2012). Interestingly, these drugs also have effects on psychiatric symptoms (Barbosa et al., 2003; Lexi-Comp, 2009; Andrus and Gilbert, 2010) indicating common underlying mechanisms of cognitive dysfunction and psychiatric symptoms of epilepsy. With more research on neuron type-specific roles in behavior (Lovett-Barron et al., 2014; Winkelmann et al., 2014), new antiepileptic strategies could ground on these insights and specifically target presynaptic molecules in the affected cell types.

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