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Review article

Potassium dynamics and seizures: Why is potassium ictogenic?

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ABSTRACT

Potassium channels dysfunction and altered genes encoding for molecules involved in potassium homeostasis have been associated with human epilepsy. These observations are in agreement with a control role of extracellular potassium on neuronal excitability and seizure generation. Epileptiform activity, in turn, regulates potassium homeostasis through mechanisms that are still not well established. We review here how potassium-associated processes are regulated in the brain and examine the mechanisms that support the role of potassium in triggering epileptiform activities.

1. Introduction

Cellular and network mechanisms underlying epileptic seizures are still uncertain. Many hypotheses have been postulated, and the role of extracellular potassium fluctuations as major determinant in brain hyperexcitability is definitely one. Experimental studies from our team (Gnatkovsky et al., 2008; Fröhlich et al., 2010; Trombin et al., 2011; Uva et al., 2017; Librizzi et al., 2017) and from other groups (Viitanen et al., 2010; Levesque and Avoli, 2013; Yekhlef et al., 2015) and computational model studies (Bazhenov et al., 2004; Fröhlich et al., 2008, 2010; Gentiletti et al., 2017; Durand et al., 2010) have recently revived the concept that extracellular potassium changes promote neural network excitability alterations associated to seizures. In order to clarify the role of potassium ions (K^+) in seizure generation and propagation, we review the pioneering studies that first associated extracellular potassium concentration $[K^+]_o$ and neuronal hyperexcitability and analyze the experimental evidences that link $[K^+]_o$ changes to seizure precipitation. We also examine the most validated mechanisms underlying potassium dynamics during an epileptic seizure *and*and compare data obtained from animal epilepsy models with the findings derived from studies on human post-surgical brain tissue.

Evidence of $[K^+]_o$ increase involvement in seizure generation dated back to 1942 (Cicardo and Torino, 1942). These authors demonstrated in dogs that the content of potassium in brain cerebrospinal fluid CSF was enhanced during abnormal and excessive electrical stimulation. Years later, other studies confirmed that potassium-enriched CSF could induce epileptic seizures (Pedley et al., 1969; Zuckermann et al., 1968) and a mechanism underlying the role of K^+ in network hyperactivation was hypothesized for the first time. It was postulated that a transient $[K^+]_o$ increase is able to trigger a massive neuronal depolarization (Benini and Avoli, 2006) that leads to network hyperactivity and further $[K^+]_o$ accumulation (Green and Taylor, 1964; Fertziger and Ranck, 1970). This effect is due to the net movement of K^+ out of neurons into the interstitial space associated with each action potential. Indeed, the $[K^+]_o$ increases in the vicinity of active neurons that discharge at high frequency during epileptiform seizure (Fertziger and Ranck, 1970). This study suggested a possible correlation between network activation and $[K^+]_o$ changes during the generation of a seizure, and introduced for the first time the so–called “potassium accumulation hypothesis”. This hypothesis postulated that high $[K^+]_o$ is sufficient to trigger neuronal depolarization coupled to both enhancement in excitability and higher firing rate, which in turn further increases the extracellular potassium levels.

In the mid ’70 a new method to measure ions in the brain with ion-selective resins was introduced. Glass microelectrodes filled with a potassium-sensitive resin were utilized to measure voltage changes proportional to $[K^+]_o$ (Prince et al., 1973). Recordings from hippocampal slices with potassium-sensitive microelectrodes revealed that $[K^+]_o$ increases and is maintained at high concentration during an *in vitro* seizure-like event (SLE; Fig. 1), confirming the potential role of potassium on seizure maintenance and progression (Prince et al., 1973; Moody et al., 1974; Heinemann et al., 1977). Unfortunately, in *vivo* $[K^+]_o$ measurements during seizure activity failed to provide significant experimental support to the potassium accumulation hypothesis (Somjen, 1979) and the idea that K^+ is a key element in seizure initiation was transitorily rejected. More recently, the correlation between ictal activity and potassium dynamics was re-assessed and the role of potassium rise in seizure precipitation was reconsidered (Pumain

Abbreviations: 4-AP, 4-aminopyridine; $[K^+]_o$, extracellular potassium concentration; NKCC1, sodium-potassium-chloride co-transporter 1; KCC2, potassium-chloride co-transporter 2; K^+, potassium ions; SLEs, seizure-like events

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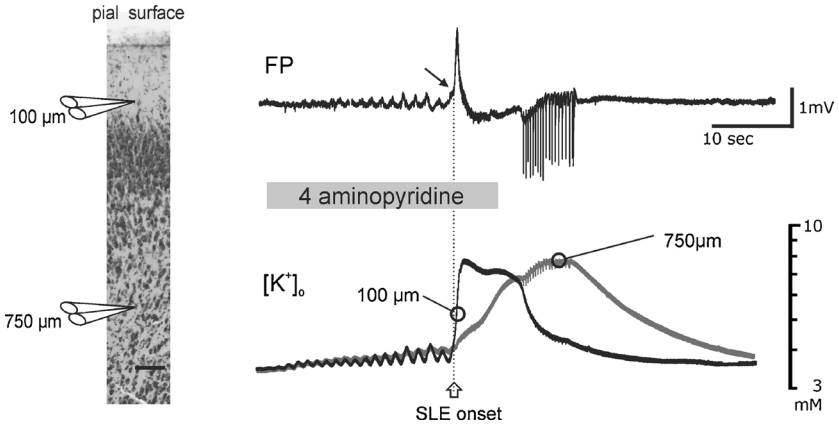

Fig. 1. Seizure like events correlate to changes in extracellular potassium. Simultaneous recording of field potential (FP, upper trace) and extracellular potassium changes ($[K^+]_o$ lower traces) with ion-selective electrodes positioned at different depths 100 and 750 µm in the piriform cortex left panel of the *in vitro* isolated guinea pig brain preparation. Large and fast $[K^+]_o$ changes are associated to SLE onset in the cortical area. A seizure-like event (SLE) is induced by brain perfusion with 50 µM 4-aminopyridine (grey bar). Modified from Uva et al. (2017).

and Heinemann, 1985; Heinemann et al., 1986; Pumain et al., 1987; Avoli, 1996; Avoli et al., 2002; Fröhlich et al., 2008, 2010; Raimondo et al., 2015; Librizzi et al., 2017).

2. Normal and pathological potassium homeostasis

Alterations in potassium homeostasis due to pathological changes in the expression and in the function of membrane channels and transporters permeable to potassium ions are associated to seizures in experimental studies on animal models, and have been reported in human epilepsies (Fröhlich et al., 2008; Raimondo et al., 2015; D'Adamo et al., 2013; Köhling and Wolfart, 2016; Maljevic and Lerche, 2013). In the next chapters we briefly review the main channels and transporters involved in extracellular potassium homeostasis and examine their dysfunctions underlying human epilepsies.

2.1. Potassium channels

Potassium channels are the most widely distributed neuronal and glial ion channels in peripheral and central nervous system. The most common types of potassium channels involved in neural network hyperexcitability control are here discussed. The voltage-gated K^+ channels (K_v) involved in action potential repolarization and in the control of cell membrane polarization form the largest family of potassium channels (12 sub-families; Gutman et al., 2005). The Ca-dependent K^+ channels (K_{Ca}) show sensitivity to intracellular Ca^{2+} changes associated to the generation of an action potential (Marrion and Tavalin, 1998). K_{Ca} are divided in three subfamilies: small-, intermediate- and big-potassium conductance channels (Sah and Faber, 2002). They contribute, together with K_v channels, to the repolarization of the neuronal membrane after action potential generation. K_{Ca} are also important to set the resting membrane potential of neurons (Brown and Adams, 1980) and to regulate firing frequency and firing frequency adaptation (Sah, 1996). Finally, Na-dependent K^+ channels (K_{Na}) mediate the delayed outward current K_{Na} and regulate neuronal excitability during repetitive firing of action potentials (Bhattacharjee and Kaczmarek, 2005).

In humans, channelopathies due to genetic mutation of different types of potassium channels are linked to excitability disorders (for review see Villa and Combi, 2016; Brenner and Wilcox, 2012; Köhling and Wolfart, 2016; Shah and Aizenman, 2014; D'Adamo et al., 2013), and the name "channelepsy" has been proposed for K^+ channels defects leading to epilepsy (D'Adamo et al., 2013).

Mutations of K_v channel subunits of this family of channels have been found in epileptic encephalopathies (*K_v1.2*; Syrbe et al., 2015), in progressive myoclonus epilepsy (*K_v3.1*; Muona et al., 2015), in genetically-determined forms of temporal lobe epilepsy (*K_v4.2*; Singh et al., 2006) and in cases of benign infantile epilepsies, such as the benign familial neonatal convulsions (*K_v7.2* and *K_v7.3*; Singh et al., 1998; Soldovieri et al., 2014). Evidence for an association of human epilepsy with K_{Ca} channels has been found in idiopathic generalized epilepsies with and without associated paroxysmal dyskinesia (Du et al., 2005; Lorenz et al., 2007). Mutations of the slack K_{Na} subunit are associated to different forms of focal epilepsies (Lim et al., 2016), like the autosomal dominant nocturnal frontal lobe epilepsy (Heron et al., 2012; Kim et al., 2014; Møller et al., 2015) and the epilepsy of infancy with migrating focal seizure (Barcia et al., 2012; Ishii et al., 2013; Ohba et al., 2015; Rizzo et al., 2016; Vanderver et al., 2014).

2.2. K^+-Cl^- cotransporter KCC2

The neuronal K^+-Cl^- co-transporter (KCC2) represents the main Cl^- extruding mechanism in hippocampal and neocortical principal neurons. KCC2primarily maintain the Cl^- ions driving force underlying the hyperpolarization mediated by $GABA_A$ receptors (Blaesse et al., 2009; Rivera et al., 2004). Recently, its contribution in regulating extracellular potassium changes has been considered. Interneuronal GABAergic networks have been demonstrated to be active players in seizure generation by inducing augmentations in $[K^+]_o$ (Avoli et al., 1996a; Gnatkovsky et al., 2008; Avoli and de Curtis, 2011; Librizzi et al., 2017; Fig. 2). Intracellular Cl^- loading occurring during intense GABAergic transmission leads to K^+ ions efflux that results in $[K^+]_o$ increase (Viitanen et al., 2010; Kaila et al., 2014; Löscher et al., 2013; Hamidi and Avoli, 2015). The key role of the $GABA_A$ receptor-mediated signaling in the generation of $[K^+]_o$ transients mediated by KCC2 activity and its participation in ictogenesis has been recently considered (Kaila et al., 1997; Jauch et al., 2002; Viitanen et al., 2010; Hamidi and Avoli, 2015). Unfortunately, the lack of selective KCC2 blockers leaded to controversial results. The non-selective KCC2 inhibitor, furosemide, strongly suppressed epileptic afterdischarges both in rat hippocampal slices and *in vivo* (Jauch et al., 2002; Viitanen et al., 2010), possibly by inhibition of GABA-mediated $[K^+]_o$ transients. More recently, Avoli et al. confirmed the role of KCC2 cotransport on *in vitro* ictogenesis. The selective, but competitive, inhibitor of KCC2 cotransport, VU0240551, shortened the duration of 4-aminopyridine (4-AP) evoked epileptiform events recorded in rat brain slices and reduced their amplitude, whereas the enhancement of KCC2 activity led to an increase in their duration (Hamidi and Avoli, 2015). On the contrary, the utilization of a more potent and selective KCC2 cotransport blocker, VU0463271, failed to counteract seizure generation in both *in vitro* and *in vivo* experiments. Other authors demonstrated that VU0463271 increased spiking activity of cultured hippocampal neurons and promoted recurrent epileptiform discharges in brain slices and during *in vivo* recordings (Sivakumaran et al., 2015). The same research team provided evidence for KCC2 inactivation during neuronal hyperexcitability and postulated that KCC2 contributes to the pathophysiology of status epilepticus (Silayeva et al., 2015). These findings show that the role of KCC2 on seizure susceptibility and its role as a possible