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Chloride homeostasis and GABA signaling in temporal lobe epilepsy

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Changes in neuronal chloride homeostasis affect $GABA_A$ receptor-mediated transmission and may contribute to epileptic activities. Work on human epileptic tissue suggests that Cl^- homeostasis is impaired in some temporal lobe pyramidal cells. GABAergic depolarization of these neurons contributes to rhythmic, interictal events. Intra-neuronal Cl^- is controlled in part by two electroneutral cation-chloride cotransporters. NKCC1 mediates Cl^- influx, while KCC2 extrudes Cl^- thus assuring that GABAergic signals hyperpolarize neurons. After stress, such as trauma or denervation, the expression and/or function of the cotransporters are altered. KCC2 is down-regulated in some pyramidal cells from both patients with temporal lobe epilepsy and animals with acquired focal epilepsies. The resulting depolarising GABAergic signals contribute to the generation of interictal-like activity. Is a defective Cl^- homeostasis also crucial for the genesis of ictal events? Ictal discharges are associated with intense interneuron firing and activation of GABA receptors. Depolarizing responses to GABA are evident during ictal events generated by convulsants in both animal epilepsy models and human tissue. K-Cl cotransport by KCC2 is increased by the Cl^- load in neurons. Paradoxically, the resulting increase in extracellular K^+ generates a prolonged depolarization that may sustain seizure discharges.

Defects in GABAergic signaling have often been linked to the epilepsies. Suppressing fast inhibition mediated by $GABA_A$ receptors initiates interictal-like activities in healthy brain tissue[1,2] and specific subgroups of interneurones seem to be especially sensitive to the neuronal death associated with temporal lobe epileptic syndromes[3–5]. However, defects in the neuronal homeostasis of chloride have only recently been linked to epileptiform activities. Intra-neuronal levels of chloride control GABAergic signaling post-synaptically[6]. So changes in chloride homeostasis can affect the strength and even the sign of GABAergic signals. We will describe work on tissue from patients with pharmaco-resistant epilepsies of the temporal lobe which provided the first insight that chloride homeostasis might be altered in the epilepsies[7,8]. We will examine molecules that control chloride homeostasis, evidence that they are modulated by pathological stressors including denervation, anoxia and the sclerotic cell death associated with some focal epilepsies. We ask whether changes in chloride

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homeostasis contribute to ictal events, arguing that potassium efflux mediated by K-Cl cotransporters may contribute to a prolonged ictal excitation. Finally, we examine how differences in chloride regulation may contribute to neonatal epilepsies and ask whether molecules targeting chloride homeostasis might be effective anti-epileptic drugs.

HUMAN INTERICTAL ACTIVITY AND Cl-HOMEOSTASIS

The first hint of a link between defects in Cl-homeostasis and temporal lobe epilepsy (TLE) emerged in work on slices of tissue from adult patients[7]. The subiculum, downstream from the sclerotic CA1 region, generated a spontaneous interictal-like activity. This population synchrony was suppressed by either GABAergic or glutamatergic antagonists, suggesting that both transmitter systems were involved in its expression. Depolarized reversal potentials for isolated GABA-mediated synaptic events in some subicular pyramidal cells suggested that Cl-homeostasis was altered.

More specific evidence of changes in Cl-homeostasis in brain tissue from patients with TLE, from in situ hybridisation and immunostaining, suggests expression of two cotransporter molecules, NKCC1 and KCC2 may be altered. Expression of the Na-K-2Cl cotransporter, NKCC1[9], which usually functions to import Cl^-, appears to be increased in epileptic tissue, while expression of the Cl-extruding K-Cl cotransporter, KCC2[10], seems to be reduced[8,11,12]. NKCC1 appears to be functional in tissue from adult TLE patients and contributes to the genesis of interictal activity[8]. Earlier work on human epileptic tissue, showed some evidence suggestive of changes in Cl-homeostasis[13,14]. Later results, from slice and animal models of focal epilepsies have confirmed that changes in Cl-homeostasis can contribute to epileptiform activities by reducing the strength of hyperpolarizing GABAergic signaling, sometimes resulting in depolarizing responses[15–17].

However, cellular studies in human tissue reveal a situation more complex than a uniform down-regulation of KCC2 and up-regulation of NKCC1. Firstly, GABA reversal potential (E_{GABA}) differs between cells suggesting that basal Cl-homeostasis is not affected similarly in all neurones. Instead there is quite a wide variation in driving force for GABAergic inhibition: in most principal cells it remains hyperpolarizing while GABAergic events depolarize only a minority of ~20 % of subicular pyramidal cells (Figure 1). The proportion of cells depolarized during interictal events was similar to that of cells where E_{GABA} was depolarized with respect to resting potential[8]. Secondly, immunostaining reveals no KCC2 signal in only a proportion of this minority of cells[8]. Perhaps low levels of KCC2 in some neurones of this interictal network cannot effectively assure hyperpolarizing responses to GABA, possibly KCC2 is expressed but inactivated by post-transcriptional mechanisms, perhaps other Cl-regulating molecules are involved. Thirdly, while changes in Cl-homeostasis seem to account for the generation of interictal-like activity in the subiculum, distinct mechanisms, possibly involving rearrangements in excitatory synaptic connectivity, may be responsible for a distinct interictal-like activity generated in the CA2 region[18]. Finally mechanisms of the interictal population synchrony remain to be explored. A population activity dependent on both GABAergic and glutamatergic signaling seems at first similar to the giant depolarizing potentials (GDPs) of immature hippocampus[19] where interneurones may play a permissive role in rhythmogenesis[20,21]. However interictal events of human epileptic tissue seem to be initiated by inhibitory cell firing[22], suggesting some interneurones should induce principal cell firing in the human epileptic subiculum.

GABA AND Cl^- REGULATION SYSTEMS

These data point to a defect in GABAergic signaling due to altered Cl-homeostasis in some epilepsies. Neuronal Cl-homeostasis depends in part on Cation Chloride Cotransporters (CCCs). They are glycoproteins with 12 membrane-spanning segments and two cytosolic termini[23,24]. Adult pyramidal neurons are known to express the Na-K-2Cl cotransporter (NKCC1) and the K-Cl cotransporter isoforms, KCC2 and KCC3[25]. The KCC2 isoform is exclusively expressed in central neurons. Alternatively spliced variants may support distinct

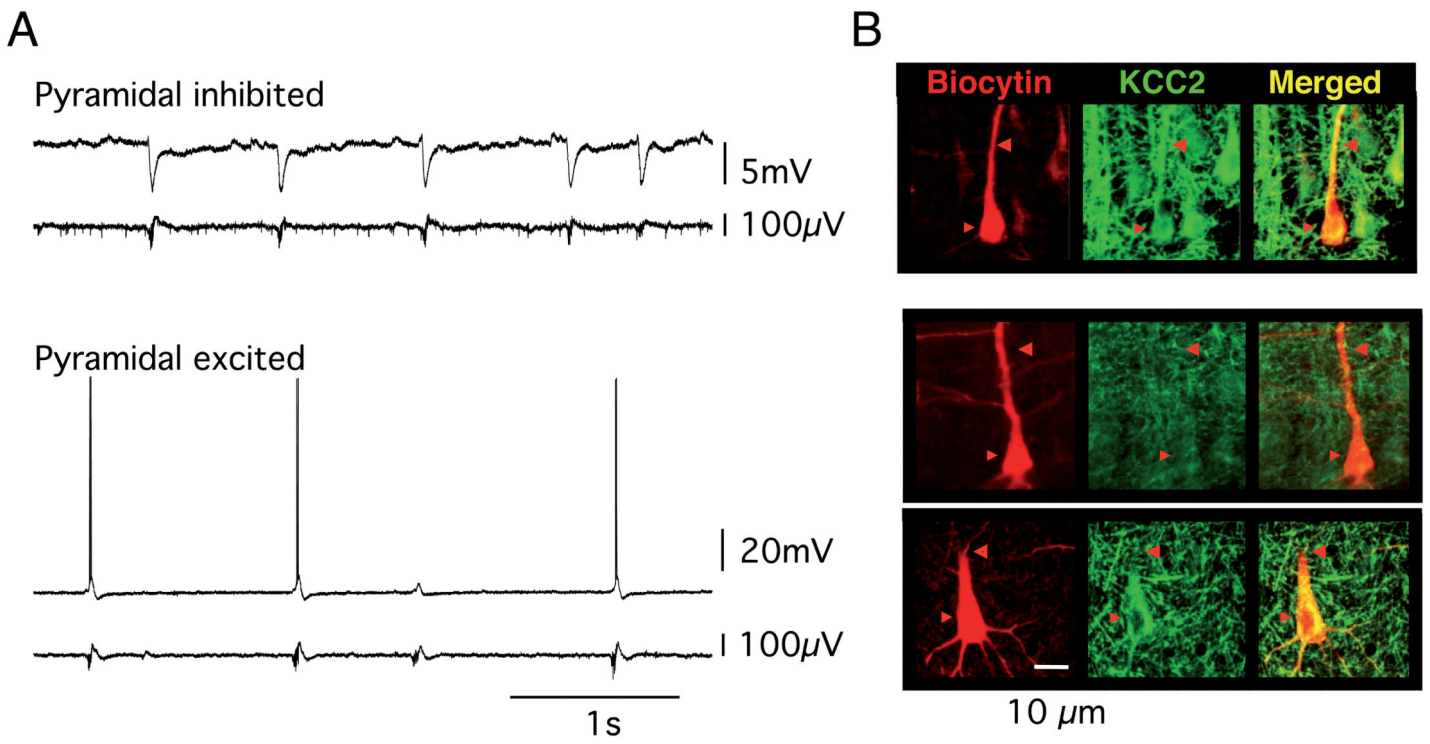

Figure 1. Correlation of pyramidal cell behavior during interical discharges with KCC2 expression in the human postoperative subiculum. (***A***) Combined intracellular (top trace) and extracellular recordings (bottom trace) of a pyramidal cell inhibited by GABA(≈80%, upper recording) and a pyramidal cell depolarized and excited by GABA (≈20%, lower recording) during interictal events.

(***B***) Immunostaining for KCC2 (green) in cells identified by biocytin filling (red). All cells hyperpolarized during epileptiform events expressed KCC2 (yellow on merging, top cell). Most cells depolarized during interictal discharges did not express KCC2 (middle cell) but some of them have a clear staining for KCC2 (bottom cell).

Modified from[7,8].

regulatory mechanisms, via phosphorylation for instance, but their physiological role is unclear. The available evidence suggests that CCCs exist as homodimers *in vivo* and dimerization probably plays a role in the regulation of their function[26–28].

Neuronal CCCs are secondary transporters that do not consume ATP but rather derive energy for ion transport from gradients established by the Na-K ATPase. Thus, Cl^- extrusion via KCCs is driven by the K^+ gradient, while NKCC1-mediated Cl^- uptake depends on the Na^+ gradient[29–31]. Since KCC2 operates close to its thermodynamic equilibrium, even a small increase in extracellular K^+ will reverse transport, from Cl^- efflux to influx. Even so, activity-dependent increases in internal Cl^- shift the equilibrium so that KCC2 may induce large transient increases in external K^+. CCCs are electroneutral with a stoichiometry for KCCs of 1:1; K:Cl and for NKCC1 of 1:1:2; Na:K:Cl. Thus electrophysiological methods cannot directly measure CCC transport. Most work has relied instead on Cl-permeable channels, such as $GABA_A$ and glycine receptors, to estimate intracellular Cl^- which has also been measured with specific optical probes[32–34].

Synaptic events mediated by GABA or glycine have often been used to assess cotransporter function, but two reservations should be noted. First, while the basal IPSP reversal potential is related to cotransporter action, function is better measured by imposing a defined Cl^- load on a neuron and measuring the consequent shift of E_{GABA}[6,35,36]. A second distinct point is that the direction – hyperpolarizing or depolarizing – of post-synaptic potential changes provoked by a GABA or glycine mediated synaptic event does not completely describe its

effects on post-synaptic excitability. The conductance increase due to receptor activation reduces local excitability at the synaptic site, whether the membrane is depolarized or hyperpolarized[37,38].

An adequate pharmacology would facilitate work on the function of these cotransporters. The loop diuretic furosemide blocks both NKCC1 and KCCs with similar potency at millimolar (mM) concentrations, but also affects N-methyl D-aspartate (NMDA) and $GABA_A$ receptors[39]. The diuretic, bumetanide, has a much higher affinity for NKCC1 than for KCC2 and 1–10 uM provides a selective inhibition[24]. Intracellular Cs^+, sometimes used in pipette solutions to enhance space clamp, is an antagonist of KCC2[24,40].

NKCC1 and KCC2 seem to be expressed at distinct subcellular neuronal sites. Immuno-histochemistry shows significant expression of KCC2 on somatic and dendritic membrane including spines but not at axonal sites[41,42]. This localization agrees with point measurements of E_{GABA}[43–45]. KCC2 expression by dendritic spines may contribute to morphogenic functions. KCC2 interacts with the cytoskeleton and may be involved in neuronal maturation[46] and specifically in spine formation[47]. Defining patterns of neuronal NKCC1 expression is difficult due to a questionable specificity of available antibodies[25].

A heterogenous membrane expression of KCC2 and NKCC1, should impose gradients in subcellular Cl^- and so generate differences in basal E_{GABA} at different neuronal sites. Indeed physiological data suggests an NKCC1-mediated Cl^- import may occur at the axon initial segment of mature neurons. Depolarized reversal potentials have been measured for GABAergic synaptic events induced by axo-axonic cells[43,45] and responses to GABA[44,48] at the axon initial segment. However E_{GABA} is typically measured from somatic responses to the activation of GABAergic synapses and axo-axonic inputs may have a relative small influence on this value. Other transporters, including the Cl^-/HCO_3^- exchanger, AE3, may also contribute to control of somatic levels of Cl^-[44].

The $GABA_A$ receptor is permeable to HCO_3^- as well as Cl^- [49,50]. HCO_3^- carries significant current, which may exceed Cl^- currents in neurons with especially hyperpolarized resting potentials in vitro[51]. Resting membrane potential (V_m) is more positive in hippocampal neurons in vitro, so their E_{GABA} values are less strongly influenced by the HCO_3^- current[6]. Slice preparation may affect internal Cl^- values[52] and of course values of E_{GABA} determined for neurons in slices do not provide accurate data on E_{GABA} values in the intact animal, where Cl-loads may be much higher.

CHANGES IN Cl^- REGULATING SYSTEMS IN PATHOLOGICAL STATES

Neuronal Cl-regulation is affected in multiple pathophysiological conditions[53,54]. KCC2 expression is down-regulated, leading to a decreased efficacy of inhibition, or even to excitatory actions of GABA, in response to kindling[55], in models of concussion[56], and by ischemia[57–59], after axotomy[60, 61], after mechanical isolation of the neocortex[16], and in nerve section models of chronic spinal pain[62–64]. Such trauma-induced down-regulation of KCC2 is often accompanied by an up-regulation of NKCC1[8,65].

Thus the acquired epilepsies[17] may be a particular example of a more general response to brain trauma. Possibly, changes in KCC2 and NKCC1 expression and function participate in epileptogenesis, alternatively they may be protective or adaptive mechanisms triggered by the trauma. Thus the down-regulation of KCC2 could usefully decrease energy expenditure in pathological states associated with an energy deficit[25]. In a similar way, the Na-K ATPase is down-regulated by neuronal damage[66,67]. Alternatively, changes in Cl-homeostasis could contribute to more general processes of neuronal de-differentiation induced by trauma. They may, for instance, tend to promote rewiring of damaged circuitry for recovery[7,24].

In these diverse traumatic situations, KCC2 down-regulation may be related to activation of the TrkB receptor by BDNF (Brain Derived Nerve growth Factor)[62]. Exogenously applied BDNF was first shown to down-regulate KCC2 via TrkB receptors in culture[55]. Similarly, following epileptiform activity induced by zero-magnesium, the efficacy of Cl^- extrusion is reduced in parallel with KCC2down-regulation[36], a mechanism aggravated by

NKCC1 dependent Cl^- import[52]. Work with animals expressing specific point mutations of the TrkB receptor has shown that both the Shc/FRS-2 (src homology 2 domain containing transforming protein/FGF receptor substrate 2) and PLCγCREB (phospholipase Cγ-cAMP response element-binding)pathways must be activated to reduce KCC2 transcription. In contrast, the activation of Shc/FRS-2 alone via the TrkB receptor enhances KCC2 synthesis[36]. This observation points to divergent actions of BDNF on neuronal Cl^- regulation. It could explain how BDNF exerts opposing actions on KCC2 synthesis in mature and immature, or in intact and damaged neurons[65]. The source of the BDNF involved in the different forms of trauma is not always clear. BDNF is secreted by various types of neurons[68]. It seems more likely however, that the BDNF involved in responses to de-afferentation is liberated by activated microglia. In a nerve section model of spinal neuropathic pain, microglia migrate to sites of damage and liberate BDNF thus altering Cl-homeostasis via TrkB receptors[62,63].

In these studies, traumatic stimuli reduce KCC2 transcription and thus the total cellular pool of the transporter, typically measured by immunoblots of the protein. However, KCC2 function depends on the fraction of cellular protein present in the cell membrane, rather than the total protein pool. Thus, as for other transporters, changes in membrane trafficking contribute crucially to KCC2 function[69,70]. Cotransporter function might also be modulated by changes in the intrinsic ion-transport rate, but details of whether and how this parameter is modulated are not yet clear.

NKCC1 and KCC2 function is also regulated by phosphorylation. For instance, the kinases WNK (With No lysine (K) kinase) and SPAK(Ste20p-related Proline Alanine-rich Kinase)/OSR1(oxidative-stress-responsive kinase1) both activate NKCC1, and inhibit KCC2[71–73]. The phosphorylation state of KCC2 is changed by trauma, oxidative stress, or epilepsy[69,74]. It affects trafficking including degradation[69,70,74], and may alter the rate of co-transport by KCC2[74]. Early work stressed a reciprocal regulation in which phosphorylation activates NKCC1 and inhibits KCCs while de-phosphorylation inhibits NKCC1 and activates KCCs[75]. However more recent work has shown that phosphorylation at different sites of the KCC2 molecule may exert opposing functional effects[69,70].

Both short- and relatively long-term changes in transporter function can be explained by changes in membrane expression or co-transport rate due to phosphorylation state or by changes in expression due to altered transcription. But transporter function may be persistently altered over months and years after traumatic injuries and in the epilepsies[7,8]. One possible explanation is that of a maintained stimulus due perhaps to chronic inflammation. Maintained neuropathic pain is associated with the persistent release of pro-inflammatory cytokines and chemokines from glial cells[76]. Pro-inflammatory molecules are also involved in the pathogenesis of epilepsy and are present in the chronically epileptic brain[77]. Cells of the blood-brain barrier, whose permeability increases after a seizure, are targets for cytokine signaling[78]. Thus inflammatory mechanisms may contribute to the evolution of chronic epilepsy[79]. It would be especially interesting if pro-inflammatory molecules control, directly or indirectly, neuronal cotransporter function.

Cl-HOMEOSTASIS AND ICTAL ACTIVITIES

Mechanisms of initiation of ictal events in focal epilepsies are not well understood. The human condition is quite well modeled by chronic animal models such as pilocarpine or kainate-treatment[80]. They exhibit a similar pattern of sclerotic hippocampal cell death and show a delay between an initial convulsion and the emergence of recurring seizures. However, chronic epilepsy models have so far provided few insights into mechanisms of ictogenesis. Instead most concepts derive from work on slices from healthy animals exposed to convulsants[81–83].

Recent work on the genesis of epileptiform activities has emphasized a glial contribution[84–86] and glial control of external levels of both potassium and glutamate may be compromised in an epileptic brain[78,87]. However synaptic mechanisms involving both glutamatergic and GABAergic signaling certainly contribute to ictal

discharges. Indeed convulsants activate interneurones particularly strongly[88,89] and ictal events are suppressed by agents, such as opiate receptor agonists, that selectively reduce interneurone activity[81].

The chloride flux due to high-frequency activation of inhibitory synapses engages Cl-homeostatic mechanisms. The cotransporters KCC2 and NKCC1 may then contribute to, and even favour, seizures. If Cl-extrusion mechanisms cannot maintain low levels of intracellular chloride[48,90,91], synaptic signals mediated by inhibitory cell firing may change from hyperpolarizing to depolarizing. Such a dynamic switch should enhance and prolong an ictal event. Furthermore, even if the polarity of GABAergic events is reversed, the KCC2 transporter continues to export not only Cl^- but also K^+ ions[92]. The strong activation of $GABA_A$ receptors during an ictal event leads to a large electrogenic uptake of Cl driven by the depolarizing HCO_3^- current (Figure 2). The resulting surge in external K^+[93] adds to that due to massive neuronal firing. It increases neuronal excitability at both somato-dendritic and also axonal sites with a consequent increase in antidromic firing[94,95]. The water influx into cells tends to reduce extracellular volume, enhances ephaptic neuronal interactions and increases local concentrations of glutamate and K^+[96].

A seizure-promoting action of KCC2 due to an increase in external K^+ is also consistent with the anticonvulsant actions of carbonic anhydrase (CA) inhibitors. Intracellular CA activity is needed to replenish the HCO_3^- and drive further Cl^- uptake[50,93]. A KCC2-mediated extracellular K^+ transient may also partly explain the anti-convulsant actions of furosemide[97,98]. However elevated extracellular K^+[99] reverses KCC2 co-transport of K and Cl[75] so the surge in external K^+ should be self-limiting.

Cl-REGULATION AND EPILEPTIFORM ACTIVITIES IN THE YOUNG

In contrast to the adult brain, seizure activity in neonatal rat hippocampus up-regulates KCC2 activity via activation of TrkB receptors[100]. Interestingly, TrkB may also trigger events that enhance KCC2 expression in the normal neonate, so initiating the hyperpolarizing shift of E_{GABA} during development[101]. BDNF-TrkB signaling also affects $GABA_A$ receptor trafficking: in the neonate it induces an increase in membrane $GABA_A$ receptors, but a decrease is initiated in more mature neurons[102]. TrkB activation then synergistically enhances both the voltage and conductance effects of GABAergic inhibition in immature neurons, but has opposite effects in the mature brain possibly due to the activation of different signaling pathways.

In the adult, an activity-dependent acidosis may be a key factor in seizure termination[103]. In contrast, neonatal seizures may be terminated in part by a seizure-induced increase in the efficacy of GABAergic inhibition[100]. We note that carbonic anhydrase is not expressed by neonatal pyramidal neurons[104]. In its absence, transport mediated by KCC2 after strong GABAergic activity during a seizure should not produce a pro-convulsant increase in extracellular K^+. NKCC1 may play a key role in loading neonatal pyramidal cells with Cl^-, since the antagonist bumetanide seems to suppress neonatal seizures [105], and also reduces the resistance to pro-GABAergic drugs that occurs due to Cl accumulation during recurring ictal-like events in slices[52].

MOLECULES REGULATING Cl-HOMEOSTASIS AS TARGETS FOR ANTI-EPILEPTIC DRUGS

There is a major need for new drug targets in temporal lobe epilepsies[106,107]. Might pathways controlling Cl-homeostasis be a useful target?

A compromised control of intracellular Cl may contribute to interictal rhythmogenesis. However, as we have discussed, residual cotransporter activity should tend to elevate extracellular K^+ in response to repetitive activation of inhibitory synapses and so contribute to the prolonged depolarization underlying an ictal event. Anti-epileptic drugs need to counter ictal rather than interictal events. Nevertheless there has been interest in the diuretic molecule, bumetanide[108], which can be used to block the Cl-importing cotransporter, NKCC1, without affecting the exporting transporter, KCC2.

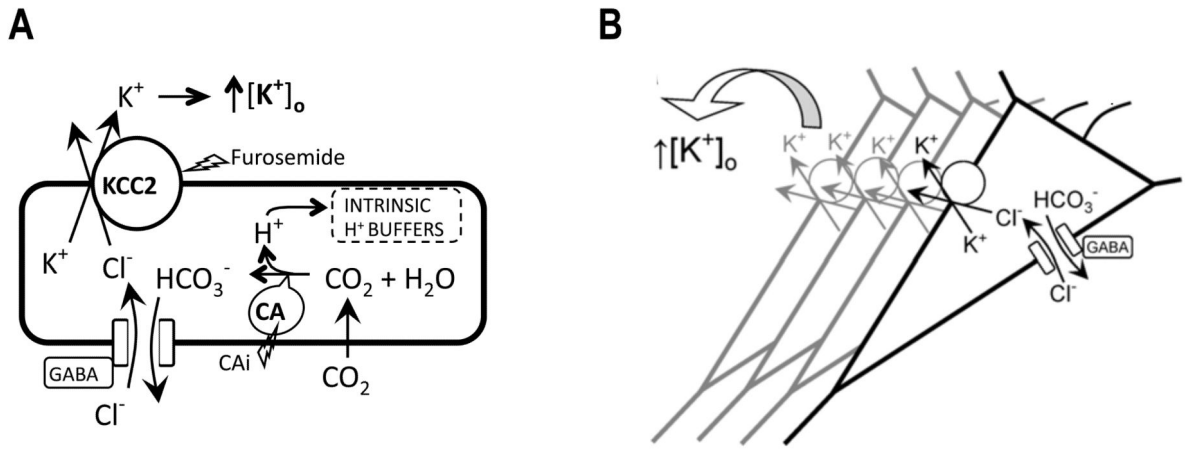

Figure 2. KCC2 in the generation of seizure-promoting $[K^+]_o$ transients. (***A***) HCO_3^- efflux via $GABA_A$ receptor's channel causes a depolarization of the membrane potential that drives a conductive uptake of Cl^-, and net hydration of CO_2 catalyzed by cytosolic carbonic anhydrase (CA) replenishes HCO_3^- during its efflux[50]. H^+ ions are produced at the same rate as HCO_3^- ions and bound by intrinsic cytosolic buffers, which is essential in the maintenance of the HCO_3^- electrochemical gradient during prolonged $GABA_A$ receptors activation. The HCO_3^--dependent intra-neuronal accumulation of Cl^- drives K-Cl cotransport by KCC2, thereby giving rise to a net efflux of K^+. (***B***) During intense activation of $GABA_A$ receptors in a population of neurons, the KCC2-mediated net efflux of K^+ can be large enough to lead to a large increase $[K^+]_o$, which is a characteristic feature of seizure activity. Note that the chain of events depicted in ***A*** can be blocked by furosemide or by membrane-permeable carbonic anhydrase inhibitors (CAi), both of which are known to exert anticonvulsant actions.

Modified from[93].

Bumetanide should tend to shift the driving force for GABAergic actions in a hyperpolarizing direction. This action suffices to suppress interictal-like activity in slices of adult human epileptic tissue[8]. Similar results have been reported in different models of neonatal epilepsies[52,109,110]. However bumetanide is reported not to have anti-ictal effects in chronically epileptic animals[111] and in some neonatal slice models[111,112].

It has been suggested that compounds that selectively enhance KCC2 actions should increase the efficacy of postsynaptic inhibition and thereby act as anticonvulsant drugs[108]. Paradoxically, however, the role of KCC2 in promoting ictal discharges (Figure 1), suggests that the opposite may be true. Indeed, furosemide, which inhibits both KCC2 and NKCC1, has anti-epileptic actions in focal cortical epilepsies[97,98], although the high doses needed to block KCC2[93] probably preclude the use of this molecule as an anticonvulsant.

Proteins that regulate the expression, trafficking and activity of the cation-chloride cotransporters may offer alternative targets for anticonvulsant drugs. In practice however, the importance of cotransporter function in regulating electrolyte balance and cell volume throughout the body implies that some means of targeting such molecules to neurons, or perhaps subsets of neurons, will also be needed

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