Epilepsy is a serious neurological condition that affects about 1% of the world population and therefore represents a health issue of public concern. Despite the intensive research and clinical work carried out for years in this field, there are types of epilepsy that remain untreatable and some treatments are accompanied by undesirable side-effects. This is due, at least in part, to the fact that the causes of epileptic seizures have not been fully elucidated. Seizures take place when a group of excitatory neurons start firing synchronically in an uncontrolled fashion in the brain. Neuronal communication is regulated via a complex balance of excitatory and inhibitory inputs. If this equilibrium is altered due to hyperexcitation or reduced inhibition, uncontrolled excitatory discharges may occur leading to an epileptic seizure. Seizures may manifest as positive signs corresponding to the function of the area where those neurons belong (focal or partial seizures), or they may even recruit other neuronal groups, reaching the ascending and descending reticular system and leading to generalized seizures. Our knowledge about the cellular and molecular mechanisms underlying epileptic seizures is still limited and often we are not certain as to what conditions or alterations lead to an epileptic brain. In recent years, the idea is gaining strength that impairment of the inhibitory systems could be at the root of epileptic seizures [1].

Specifically, a crucial role has been proposed for interneurons secreting γ-Aminobutyric acid (GABA) as their primary neurotransmitter [2-4]. GABA amino acid neurotransmitter is responsible for most of the inhibitory systems, and GABA binding to GABA receptors (GABAAR) leads to the opening of ionotropic receptors type A (GABAAR). GABAARs are ligand-operated Cl- ion channels. GABA binding to GABAAR introduces Cl- inside the cell, whereas the K+ /Cl- cotransporter (KCC2) transports Cl- outside the cell keeping Cl- levels below its electrochemical potential equilibrium, allowing an inward current when GABA binds to the GABAAR. The balance between these families of cotransporters exists in the nephron (KCC1, KCC3, KCC4, NKCC2) where they are also in charge of ion exchange at this level [15]. These molecules have already been targeted for kidney related disorders with the use of “loop diuretics” such as furosemide (blocking the KCC cotransporters) and bumetanide (blocking NKCC cotransporters) [1]. In this way, Nephrology studies provided us with new tools to act in the brain. This approach has already been employed for epilepsy research both in experimental studies and clinical trials [16-18]. Further, more recent studies in the nephron have provided new information about the molecular activity-dependent mechanisms regulating the activation /deactivation of both KCC and NKCC – type cotransporters and the interconnections between them. SPAK (Ste20-related proline alanine-rich kinase) and OSR1 (oxidative stress response 1) kinases phosphorylate and activate NKCC, while they have the opposite effect on KCC. SPAK/OSR1 act in combination with the WNK (With No lysine = K) type kinases (WNK1-4). SPAK/OSR1 and WNK act as intracellular Cl- sensors reducing their activity when Cl- concentration decreases, thus closing the regulatory loop [19-20]. The kinases involved in this complex regulation of Cl- intracellular concentration at the nephron level, may represent not only new therapeutic targets for kidney dysfunction, but also a new field for research in epilepsy. Indeed, SPAK/OSR1 and WNKs kinases have been described in neurons regulating NKCC and KCC2 cotransporter activity in a similar way as they do in the nephron [21-27]. Previous studies have shown that peripherally administered loop diuretics targeting K+/Cl- cotransporters can effectively reach the brain [16, 26], although current research is focusing on finding compounds with better bioavailability to the brain and, hopefully, fewer side effects [17, 28]. Another promising line of research is looking at inhibiting SPAK/OSR1 and WNKs kinases. Some success has already been achieved using in vitro techniques and genetic (knock out, RNAi) mouse models [22-26], but so far, no compounds targeting these kinases have been tested in vivo. Future studies will be necessary to determine whether new therapies for the epilepsies will come at the end of this intriguing research journey from nephron to neuron.
Funding

CdC received support from FIS-FEDER [grant numbers 01/3018, PS09/01154] and JCCM, Consejería de Sanidad [grant numbers 04048-00, GC.05011]. The funding bodies played no role in design, collection, analysis, or interpretation of data; nor in the writing of the manuscript; nor in the decision to submit the manuscript for publication.

References


12. Puskárkov M, Seja P, Heron SE, Williams TC, et al. (2014) A variant of KCNC2 from patients with febrile seizures impairs neuronal Cl- extrusion and dendritic spine formation. EMBO Rep 15: 723-729. [Crossref]


17. Erker T, Brandt C, Tolllner K, et al. (2016) The bumetanide prodrug BUM5, but not bumetanide, potentiates the antiseizure effect of phenobarbital in adult epileptic mice. Epilepsia 57: 698-705. [Crossref]


20. Markadieu N, Rios K, Spiller BW, McDonald WH, Welling PA, et al. (2014) Short forms of Ste20-related proline/alanine-rich kinase (SPAK) in the kidney are created by aspartyl aminopeptidase (Dnpep)-mediated proteolytic cleavage. J Biol Chem 289: 29273-29284. [Crossref]


