From nephron to neuron: An exciting journey in search of a cure for epilepsy.

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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. 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]. More 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 fast inhibitory neurotransmission in the brain by acting on its putative ionotropic receptors type A (GABA\textsubscript{A}R). GABA\textsubscript{A}Rs are ligand-operated Cl\textsuperscript{-} ion channels. GABA binding to GABA\textsubscript{A}R leads to the opening of the channel allowing the entrance of Cl\textsuperscript{-} inside the neuron causing a hyperpolarization of the postsynaptic membrane. Thus, for GABA actions to be effective Cl\textsuperscript{-} levels have to be lower inside the neuron. The main molecules responsible for maintaining suitable Cl\textsuperscript{-} levels are cation/Cl\textsuperscript{-} cotransporters. Na\textsuperscript{+}/K\textsuperscript{+}/Cl\textsuperscript{-} cotransporter (NKCC1) introduces Cl\textsuperscript{-} inside the cell, whereas the K\textsuperscript{+}/Cl\textsuperscript{-} cotransporter (KCC2) transports Cl\textsuperscript{-} outside the cell keeping Cl\textsuperscript{-} levels below its electrochemical potential equilibrium, allowing an inward current when GABA binds the GABA\textsubscript{A}R. NKCC1 is expressed in both neurons and glial cell whereas KCC2 is only expressed in neurons. During development NKCC1 has been shown to be expressed in high levels while KCC2 levels are low at birth and they increase during postnatal development. This exchange in NKCC1/KCC2 expression leads to higher Cl\textsuperscript{-} levels inside the neuron and therefore GABA binding to GABA\textsubscript{A}Rs results in membrane depolarization during the neonatal stages [4-6]. Interestingly, alterations in NKCC1/KCC2 balance have also been described in epilepsy, both in patients and animal models [5,7-14]. This evidence has led to the hypothesis that an imbalance in the expression of these co-transporters may be at the origin of various types of epilepsies and could be considered as new therapeutical targets. In this regard, it is worth mentioning that other members of these families of co-transporters exist 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 co-transporters) and bumetanide (blocking the KCC co-transporters) [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 co-transporters and the interconnections between them [19,20]. The kinases involved in this complex regulation at the nephron level, may represent not only new therapeutic targets for kidney dysfunction but also a new field for research in epilepsy [21-23]. Future studies will be necessary to know whether new therapies for the epilepsies will come at the end of this intriguing research journey from nephron to neuron.

References


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