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REVIEW

Postnatal neurogenesis as a therapeutic target in temporal lobe epilepsy

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Summary After it was first identified that seizures increase neurogenesis in the adult brain of laboratory animals, the idea that postnatal neurogenesis may be involved in epilepsy became a topic of widespread interest. Since that time, two perspectives have developed. They primarily address temporal lobe epilepsy (TLE), because the data have either been based on animal models of TLE or patients with intractable TLE. The first perspective is that postnatal neurogenesis contributes to the predisposition for seizures in TLE. This premise is founded in the observations showing that there is a dramatic rise in neurogenesis after many types of insults or injuries which ultimately lead to TLE. As a result of the increase in neurogenesis, several changes in the dentate gyrus occur, and the net effect appears to be an increase in excitability. One of the changes is the formation of a population of granule cells (GCs) that mismigrate, leading to ectopic granule cells in the hilus (hilar EGCs) that exhibit periodic bursts of action potentials, and contribute to recurrent excitatory circuitry. Atypical dendrites also form on a subset of GCs, and project into the hilus (hilar basal dendrites). Hilar basal dendrites appear to preferentially increase the glutamatergic input relative to GABAergic synapses, increasing excitability of the subset of GCs that form hilar basal dendrites. The alternate view is that postnatal neurogenesis is a homeostatic mechanism in epilepsy that maintains normal excitability. This idea is supported by studies showing that some of the new GCs that are born after seizures, and migrate into the correct location, have normal or reduced excitability.

Here we suggest that both perspectives may be important when considering a therapeutic strategy. It would seem advantageous to limit the numbers of mismigrating GCs and hilar basal

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dendrites, but maintain normal neurogenesis because it is potentially homeostatic. Maintaining normal neurogenesis is also important because it has been suggested that a decrease in dentate gyrus neurogenesis contributes to depression. It is challenging to design a strategy that would achieve these goals, and it is also difficult to propose how one could administer such a therapy prophylactically, that is, as an ''antiepileptogenic'' approach. Another issue to address is how a therapeutic intervention with these goals could be successful if it were administered after chronic seizures develop, when most patients seek therapy. Although difficult, a number of approaches are possible, and technical advances suggest that there are more on the horizon.

Contents

Background

Postnatal neurogenesis

It is now widely accepted that neurogenesis occurs throughout the lifetime of mammals (Gage et al., 2008). The two places where this is best established include the dentate gyrus subgranular zone (SGZ; Fig. 1) and the subventricular zone (SVZ), adjacent to the ventricular walls (Gage et al., 2008). Here we focus on the dentate gyrus primarily, because a substantial body of research about neurogenesis in epilepsy has focused on dentate gyrus neurogenesis. Temporal lobe epilepsy (TLE) is emphasized, because pathophysiology in the dentate gyrus is most relevant to this type of epilepsy. However, other types of epilepsy may also be important to consider, because it is possible that pathology in the dentate gyrus, or its effects on downstream targets (the hippocampus and elsewhere) contribute to other types of seizure syndromes. It is also important to bear in mind that the SVZ appears to generate cells that migrate into diverse parts of the brain, beyond the site of termination that is considered to be the main target, the olfactory bulb (Shapiro et al., 2009). Because of the potential for the SVZ to generate cells that migrate to diverse locations, it is possible that many types of epilepsy are influenced by the postnatal neurogenesis in the SVZ. Another consideration is that some types of neurons may be generated by cells outside the SGZ and SVZ. A recent report suggested that oligodendrocyte precursors that express NG2 (NG2 cells) in the piriform cortex may become cortical neurons (Rivers, 2008), which is potentially important in epilepsy, because the piriform cortex is an area which is epileptogenic, and sustains injury in animal models of epilepsy (Gale, 1992; Loscher and Ebert, 1996; McIntyre and Gilby, 2008).

In the postnatal dentate gyrus, the majority of progenitors reside in the SGZ, which is situated just below the granule cell layer (GCL), at the border with the hilus (Fig. 2). Early progenitors are radial glia-like type 1 cells, which can be identified by expression of the astrocytic marker glial-fibrillary acid protein (GFAP), nestin or other markers (Fig. 2). Although classification into type 1a cells, type 2a cells, type 2b cells, and type 3 cells, implies a sequential maturation in this order, it has not been proven definitively. However, it is clear that the progenitors typically commit to a neuronal fate and become GCs. Thus, under normal conditions, migrating GCs move into the GCL, where it is thought that they initially reside within the ''inner'' third of the layer, close to the hilus, before moving to the center and outer parts of the layer (Gage et al., 2008; Ge et al., 2008;