Neurogenesis and neuronal regeneration in status epilepticus

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Summary

Neurogenesis in the adult central nervous system has been well documented in several mammals including humans. By now, a plethora of data has been generated with the aim to understand the molecular and cellular events directing neurogenesis providing the basis for modulation of neurogenesis for therapeutic purposes, in particular in neurodegenerative diseases. Here, we review the current knowledge on neurogenesis, in particular in the frame of epilepsy, since seizures have massive effects on neurogenesis. Vice versa, some studies suggested that aberrant neurogenesis might contribute to the development or manifestation of epilepsy and, moreover, chronic inhibition of neurogenesis in epilepsy might contribute to comorbidities of epilepsy such as cognitive deficits. Thus, a better understanding of neurogenesis in the context of epilepsy is still required for future therapeutic purposes.

Adult neurogenesis

While neurogenesis, i.e. the generation of new neurons in the adult central nervous system has been documented in several mammalian species already in the mid 1960s (Altman and Das 1965), the real awareness for neurogenesis in the adult brain arose upon the observation of neurogenesis in the adult, even elderly, human brain (Eriksson, et al. 1998). Neurogenesis occurs predominantly in two brain regions, the subgranular zone (SGZ) of the dentate gyrus (DG) and the subventricular zone (SVZ) of the lateral ventricles. While SGZ-derived newly born neurons stay within the DG of the hippocampal formation und functionally integrate into the preexisting neuronal network, SVZ-derived immature neurons migrate along the rostral migratory stream into the olfactory bulb, where they functionally integrate and acquire electrophysiological characteristics of mature DG granule cells (Carleton, et al. 2003, van Praag, et al. 2002). Progress regarding adult human neurogenesis and its role in brain function is still quite sparse, mainly due to the lack of appropriate biomarkers and imaging tools to detect neurogenesis (for example (Ramm, et al. 2009)). Nevertheless, in vivo optical imaging in animal models has been developed and successfully applied to follow quantitative changes in neurogenesis (Couillard-Despres, et al. 2008, Villeda, et al. 2011).

Adult hippocampal neurogenesis has implications for learning and memory and vice versa (Kempermann 2002), although, the existence of animal models expressing normal learning and memory performance despite the lack of adult neurogenesis has introduced some controversy in the field (Jaholkowski, et al. 2009). Moreover, the fact that neurogenesis is massively declined in aging

without necessarily creating cognitive deficits underscores a putative role of adult neurogenesis in fine-tuning the brain's capacity in specific aspects of learning and memory (Couillard-Despres 2012). For example, the addition of new neurons into a preexisting neuronal network might allow the system to adapt appropriately to new challenges. As a consequence, defects in neurogenesis might cause problems for the individual to adapt to changes in the environment and contribute to psychiatric disorders such as depression, anxiety and schizophrenia (Sah, et al. 2012).

While a lot of knowledge on neurogenesis has been created in animal models, the functional relevance of neurogenesis in the adult human brain and the contribution to neurological and psychiatric diseases is still of hypothetic nature. Nevertheless, a comprehensive study correlating the learning performance in epilepsy patients before undergoing hippocampal resections with the level of neurogenesis in the resected hippocampi measured by immunehistological means and with the potential of neural stem cells isolated from these hippocampi to proliferate and to differentiate into neurons strongly suggested a role of hippocampal neurogenesis in cognition (Coras, et al. 2010).

Adult neurogenesis and epilepsy

It is well established that in animal models of temporal lobe epilepsy acute seizures dramatically elevate the levels of SVZ- as well as hippocampal neurogenesis, at least transiently over a period of one to two weeks (Parent, et al. 1997) (for review see (Andres-Mach, et al. 2011)). Here, neurogenesis is

quantitatively enhanced at the level of progenitor proliferation as well as accelerated at the level of maturation and integration of the newly generated neurons. The initial rise in neurogenesis is followed by a long-lasting low level of neurogenesis in animal models of epilepsy (Hattiangady, et al. 2004). Importantly, reduced cell proliferation has been also observed in the hippocampus of children with frequent seizures (Mathern, et al. 2002).

Besides the quantitative changes in neurogenesis after epilepsy, major qualitative alterations, in particular at the level of spatial integration of new neurons have been noticed. Typically, newly generated neurons in the adult hippocampus migrate only a short distance into the granule cell layer, where they integrate. Surprisingly, after seizure, new neurons seem to migrate either the opposite direction into the hilus or all the way through the granular layer into the molecular layer (Parent, et al. 2006). The molecular reasons for the displacement of newly generated neurons are unknown at present. Moreover, displaced neurons in the epileptic hippocampus might actually not exclusively derive from new neurons but result from a displacement of preexisting mature neurons (Fahrner, et al. 2007). In addition, seizures induce mossy fiber reorganization also in the absence of neurogenesis (Parent, et al. 1999). Nevertheless, the high excitability, the synaptic input from mossy fibers and their little inhibitory input might suggest a critical role of new neurons in the manifestation of epilepsy.

Another well-described qualitative feature of neurogenesis in epilepsy is the persistence of hilar basal dendrites. These basal dendrites are typical for immature hippocampal neurons, which in comparison to mature neurons are

known to be hyperexcitable. Therefore, an attractive hypothesis might be that in epilepsy some of the newly generated neurons remain highly excitable for a protracted period of time and thus contribute to the manifestation of epilepsy (Ribak, et al. 2000). Nevertheless, in summary, it is still under debate to what extent seizure-induced neurogenesis might contribute to the formation of an epileptic hippocampus.

Newly generated DG neurons, as well as their mature counterparts, extend their axon along the mossy fiber pathway into the CA3 region of the hippocampus. While mossy fiber sprouting after epilepsy is a well-known feature since decades, it became only recently clear that apparently only the new neurons respond to epilepsy with axonal sprouting. Moreover, such axons synapse on the displaced hilar neurons (Pierce, et al. 2007). These data suggest that other mechanisms in addition to mossy fiber sprouting might contribute to enhanced hippocampal excitability during epileptogenesis.

Does neurogenesis contribute to comorbidities of epilepsy?

Although intriguing, it is difficult at present to assign a causal role of seizure-induced neurogenesis to the manifestation of epilepsy. However, the reduced levels of neurogenesis in chronic epilepsy might have a strong contribution to cognitive deficits. Indeed, chronic epilepsies are strongly associated with cognitive deficits (for review (Hermann and Seidenberg 2007)). Based on the association of neurogenesis with cognitive functions, the possibility to enhance cognition with stimulators of neurogenesis is heavily investigated at

the moment (Couillard-Despres, et al. 2011). Indeed, a recent study provided proof of principle for such a therapeutic strategy. Treatment of mice with the antidepressant fluoxetine promoted neurogenesis and learning performance in mice with chronic epilepsy (Barkas, et al. 2012).

In summary, neurogenesis-associated cognitive deficits in epilepsy might arise at different levels. First, the low rate of neurogenesis in chronic epilepsy might reduce the hippocampal network's ability for learning and memory formation. Second, ectopically (hilar) displaced neurons may disturb normal network function. Thus, a biphasic modulation of neurogenesis, i.e. inhibition of seizure-induced neurogenesis during the early phase and a stimulation of neurogenesis in the chronic phase might be an interesting therapeutic concept for the future treatment of cognitive disabilities in epilepsy (Fig 1).

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Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figure

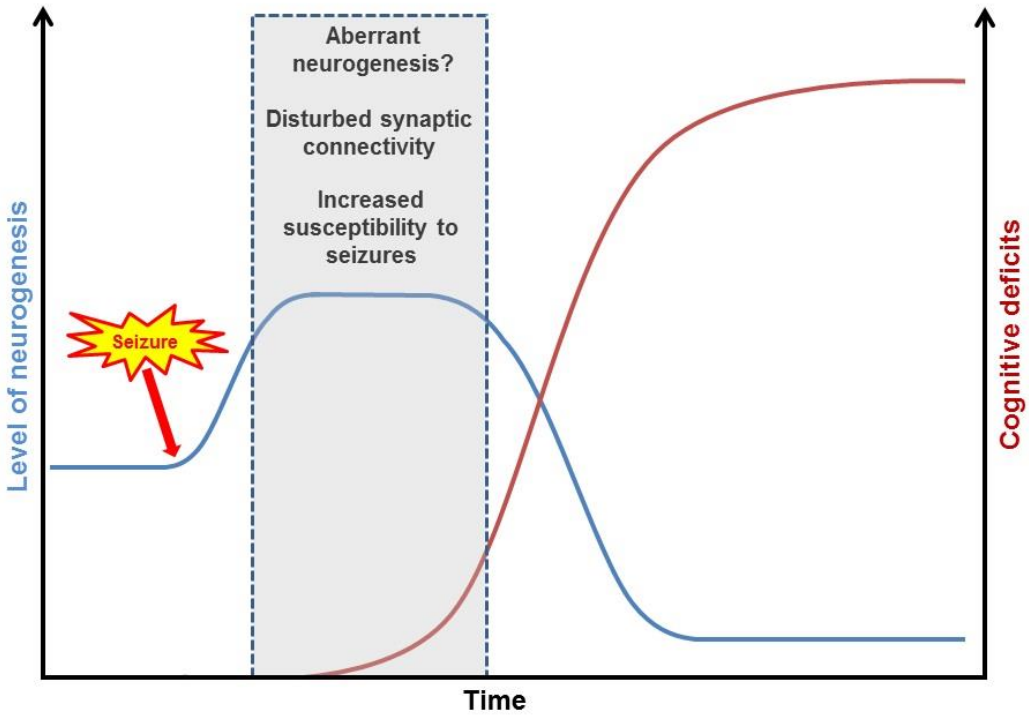

Figure 1: Correlations between epilepsy, neurogenesis and cognition

Acute seizures elevate neurogenesis. At present it is still under discussion if aberrant neurogenesis contributes to the manifestations of epilepsy, but it might increase the susceptibility to seizures. Chronic seizures impair neurogenesis, which might contribute to cognitive declines associated with status epilepticus.