

Role of adult neurogenesis in the regulation of hippocampal-dependant behavior



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Adult Neurogenesis

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Scientific context

A growing body of evidence suggests that plasticity in the adult brain is involved in the pathophysiology of behavior. Recently, it has been proposed that adult neurogenesis, which occurs in the dentate gyrus of the hippocampus, is involved in hippocampal function and dysfunction. However, this fascinating hypothesis was mainly based on correlational studies, whilst direct evidences of a causal relationship between neurogenesis and behavior were scarce.

Objectives

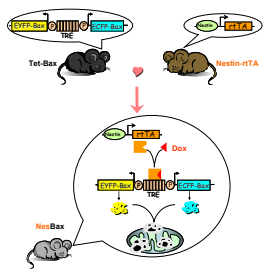
We developed a transgenic strategy to ablate hippocampal neuronal precursors in an inducible way. We used this mouse model to determine the impact of reducing adult neurogenesis on hippocampal functioning, i.e. hippocampal synaptic plasticity, learning and memory processes, mood-related disorders (anxiety and depression-like behavior), and drug-addiction

Principal Results

Validation of a transgenic model to block neurogenesis

A double transgenic model allowing specific ablation of hippocampal newborn neurons was designed :

Tet-Bax mouse in which the expression of two fusion Bax proteins is controlled by an inducible promoter encompassing tetracycline response elements (TRE).
Nestin-rTA mouse in which rTA that binds TRE in the presence of Dox, is controlled by the Nestin promoter.



Bigenic NesBax mouse in which Bax is over-expressed in nestin cells (progenitor cells) upon Dox treatment, leading to their death by apoptosis.

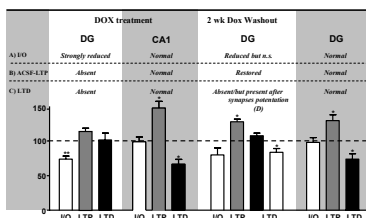
As expected we showed that in these mice, treatment with Dox leads to a decrease in the number of neuronal precursor cells (Nestin-IR), the number of 2-wk old newborn cells (BrdU-IR), the number of proliferating cells (HH3-IR), and the number of neuroblasts (DCX-IR), while it increases cell death (apoptotic cells).

Adult neurogenesis and hippocampal plasticity

Previous data suggested that newborn cells were involved in LTP maintenance. However, their role in LTD, and in the plastic properties of the DG network as they integrate their network were unknown.

We showed that reducing neurogenesis impairs synaptic transmission at medial perforant pathway synapses onto DG granule cells. Furthermore, LTP and LTD are largely compromised at these synapses.

Whereas the deficits in synaptic transmission and plasticity are completely rescued by restoring neurogenesis, these synapses regain their ability to express LTP much faster than their ability to express LTD.

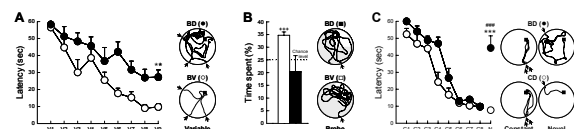


Adult neurogenesis and learning and memory

Neurogenesis is involved in spatial relational memory

We have investigated the role of newborn neurons in spatial relational memory, which requires encoding and flexible use of the positional relations between environmental cues.

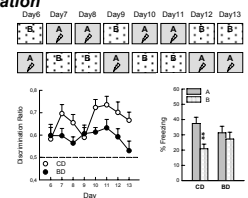
We showed that neurogenesis-depleted mice were impaired in learning a platform location in a navigation task. In contrast, they were able to find it when a hippocampal-independent procedure was used. However, when they were tested from a new starting point at the end of the learning phase, they were unable to find the platform despite previous learning of the platform location.



Neurogenesis is involved in contextual discrimination

We have investigated the role of newborn neurons in context discrimination, i.e. the capability to identify a familiar environment and detect any changes introduced in it.

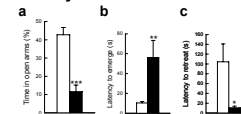
We showed that depleting neurogenesis impairs the animal's ability to disambiguate two contexts after extensive training. These data suggest that the continuous production of new dentate neurons plays a crucial role in extracting and separating efficiently contextual representation.



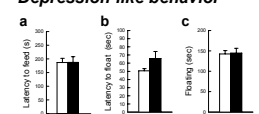
Adult neurogenesis and mood-related disorders

We showed that a deficit of neurogenesis increases anxiety-related behaviors, as measured by the avoidance of potentially threatening situations. In contrast, it does not modify behaviors that are related to the affective sphere underlying depression, such as the reinforcing properties of novelty, novelty suppressed feeding, or the forced swim test.

Anxiety



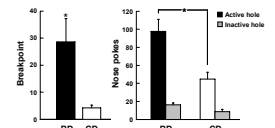
Depression-like behavior



Adult neurogenesis and drug addiction

Correlative evidence suggested that neurogenesis could influence vulnerability to drugs. Thus, neurogenesis is decreased in animals spontaneously vulnerable to drugs of abuse and after exposure to conditions that increase drug vulnerability (stress, glucocorticoids, repeated drugs administration).

We showed that motivation for cocaine (higher breaking point) and sensitivity to cocaine-associated environmental cues were higher in animals in which neurogenesis was decreased.



Conclusion

Thanks to the ANR financial support we have shown that adult neurogenesis impacts on hippocampal synaptic plasticity and is involved in many behavioral functions sustained by the hippocampus. The major results we have produced have been published in high ranking international journals.

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