ADULT NEUROGENESIS IN THE DENTATE GYRUS

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INTRODUCTION

• During several years, adult neurogenesis was not accepted by the scientific community. It was not until the end of the twentieth century when it became a fact.
• At the beginning, neurogenesis was considered more of a vestigial process than an important one. However, its different functions and pathological implications made them an important mechanism of the brain.
• Lots of brain regions are suspected of being potential neurogenic sites, but only neurogenesis in the hippocampus and the olfactory bulb have been fully proved.

BASES OF NEUROGENESIS

• Neurogenesis in mammals has been only proven in two restricted areas of the brain: the subventricular zone of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG) (Figure 1).
• New-born cells originate from adult neural stem cells (NSCs), which are located together with endothelial cells, astrocytes and oligodendrocytes in a structure called neurogenic niche.
• After birth, they migrate into the correct location the granule cell layer (GCL) in the case of SGZ.

METHODS

• Search on the internet through “PubMed” database with “adult neurogenesis AND dentate gyrus” as key words.
• Due to the broad quantity of information with this simple inquiry, search criteria was adapted to articles only from 2005 and review format.
• Finally, there were chosen 20 relevant reviews from which we obtained other original articles for the understanding of the field.

FASES OF NEUROGENESIS IN THE DENTATE GYRUS

Adult neurogenesis is a gradual and multistep process with different stages which complies the expression of diverse molecular makers (Figure 4). In general neurogenesis goes through the maintenance and proliferation of NSCs, which subsequently lead to a fate specification step where types 2 and 3 are comprised. After the mitotic stage, type 4 neurons have to differentiate, survive, and mature in order to become granule neurons. Finally, type 5 neurons integrate gradually in the existing system.

MIGRATION

• Sagittal migration of neuroblasts and postmitotic cells. At the same time, they leave a trail that will become the axon.
• Radial migration to the GCL of neuroblasts and postmitotic cells, while their dendrites grow.

FUNCTIONAL IMPLICATIONS OF ADULT NEUROGENESIS

• DG is well-known for its implication in pattern separation of memories. Young neurons display a set of characteristics a little bit different than their older companions. Mainly because of that, they have a role in pattern integration (Figure 5).
• However, as they mature, they become indistinguishable from the previously integrated neurons. Consequently, they have a normal role in pattern separation (Figure 6).

PATHOPHYSIOLOGY: DEPRESSION

• There are lots of illnesses where neurogenesis is affected. The most studied one is depression.
• Different environmental conditions and antidepressants that confer antidepressant-like responses are associated with an increase in neurogenesis.
• The precise mechanisms are still a mystery. However, some possible actions of antidepressants include the increasing of diverse components well-known for enhancing neurogenesis (Figure 7).

CONCLUSION

• Despite the fact that DG is a key area of the brain, it is still not fully understood.
• Future studies in this field should be related in some way to neurogenesis, emphasizing even more the functional role of this process.
• We still lack information about the complete process of these new-born cells and so therapeutic efforts will be needed in order to understand completely this mechanism and use this knowledge for new therapeutic approaches.

REFERENCES


Figure 1. Schematic image of the adult neurogenic zone. DG, dentate gyrus; ML, molecular layer; GCL, granule cell layer; SGZ, subgranular zone; OB, olfactory bulb; RMS, rostral migratory stream; SVZ, subventricular zone; DG, dentate gyrus; ML, molecular layer; GCL, granule cell layer; SGZ, subgranular zone.

Figure 2. Section of the brain immunostained with Nestin staining. (a) general view of the hippocampal formation. (b) focus on the dentate gyrus. DG, dentate gyrus; ML, molecular layer; GCL, granule cell layer; SGZ, subgranular zone.

Figure 3. Interconnections within the hippocampal formation. The black arrow points from the entahorital cortex (EC), and then subsequent ascending axons come following the dentate gyrus, the CA3, the CA1 and then EC or the subiculum.

Figure 4. Different stages of neurogenesis. (Injection is not represented). ML, molecular layer; GCL, granule cell layer; SGZ, subgranular zone; DG, dentate gyrus; NSC, neural stem cell; TBM, transverse bipooral migration; GCL, granule cell layer; SGZ, subgranular zone; Dcx, doublecortin; PSA-NCAM, polysialylated form of neural cell adhesion molecule; CNPEn, cAMP response mediator protein 4; GFAP, glial fibrillary acidic protein.

Figure 5. How DG and new neurons might affect pattern separation. Each panel represents how a series of temporally discrete events.

Figure 6. Alternative theories of neurogenesis depletion on the DG long term. Each column represents how the DG would assure information about events presented over extended time scales.

Figure 7. Antidepressants can, on one hand, increase the amplitude of serotonergic and noradrenergic and, on the other hand, stimulate a variety of growth factors such as VEGF. Both mechanisms stimulate the signaling cascade of MAPK response elements (CREB) protein, which ultimately results in an increase of new-born cell survival and proliferation that leads to neuroplasticity.