Molecular Aspects on Adult Neurogenesis

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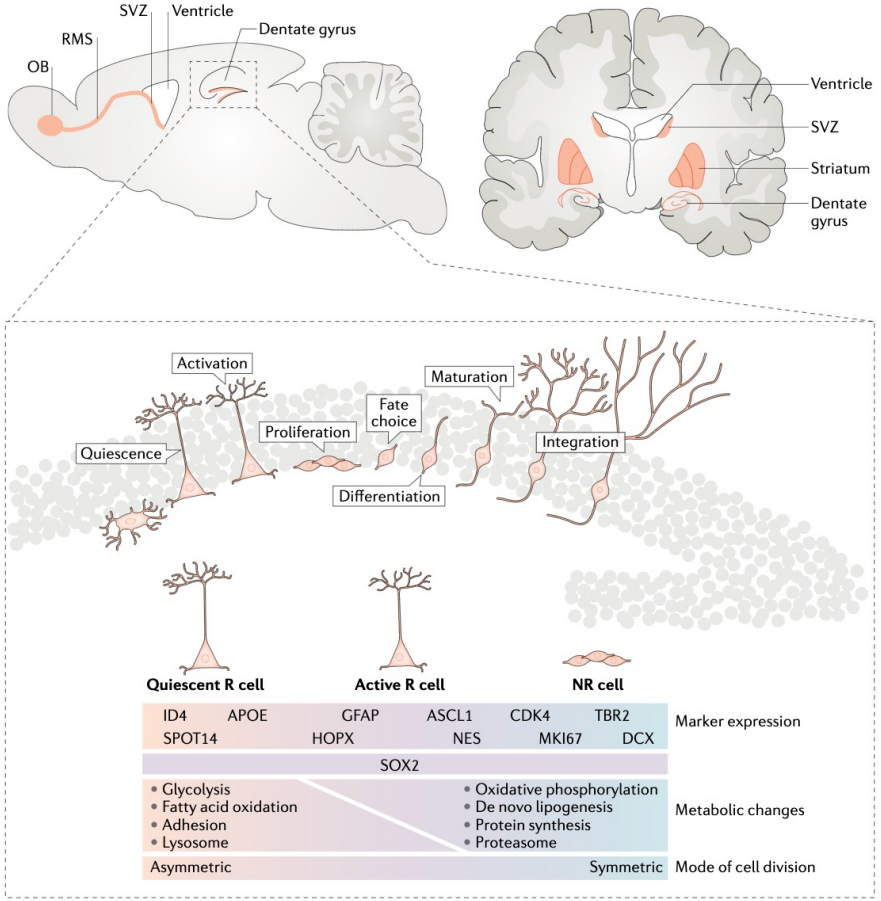
- Brief introduction to hippocampus adult **neurogenesis (gross anatomy, neurogenic niche)**
- Brief introduction to the endocannabinoid system
- Molecular mechanisms involved in modulating adult neurogenesis

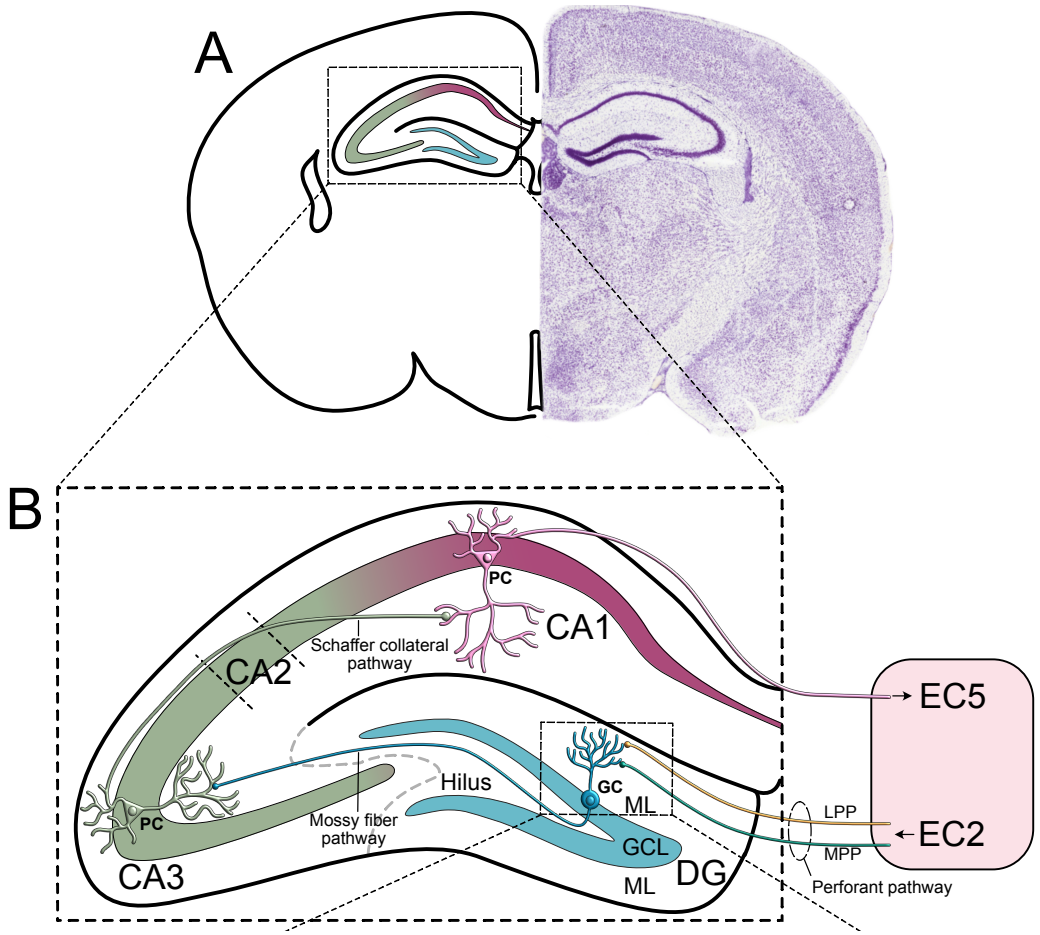
The adult hippocampal neurogenesis

Adult hippocampal neurogenesis is the process by which new functional neurons are continuously generated and integrated into the DG of the hippocampus, after embryonic development and throughout adulthood.

These new neurons impose a substantial remodeling of pre-existing circuits, involving the formation, competition and elimination of synaptic inputs and outputs in the DG, thus profoundly affecting different hippocampus-mediated functions, including **learning**, **memory** and **emotional behavior**.

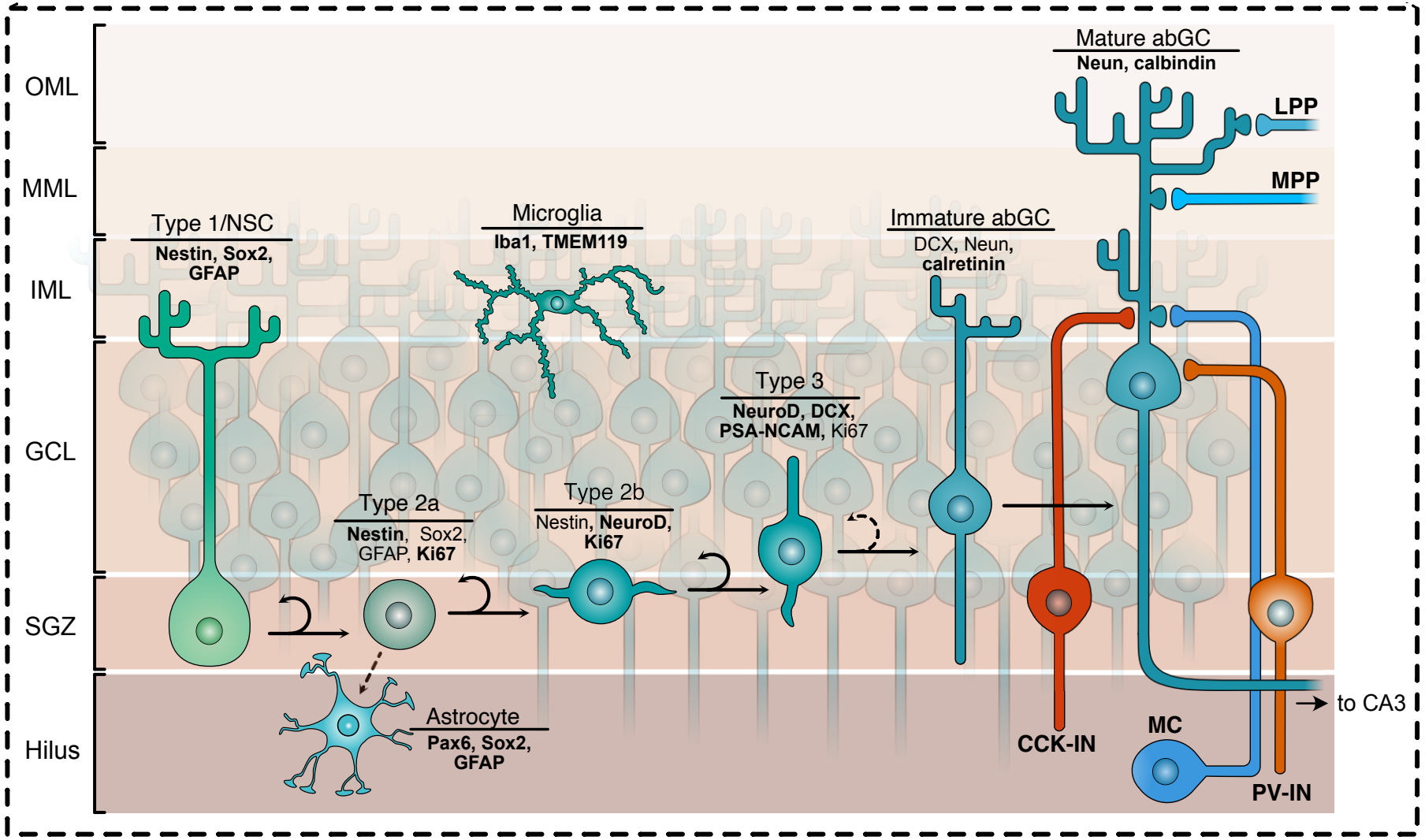


Neuroanatomy of the dentate gyrus



- The **hippocampus (archicortex)** is an essential part of the **brain's limbic system**
- DG forms a V-shaped structure embedded into the curved cornu ammonis (CA), which itself is composed of CA1, CA2 and CA3 areas. Histologically, the DG is divided into three layers: (i) the molecular layer (ML), (ii) the granule cell layer (GCL), and (iii) the hilus.

The hippocampal neurogenic niche



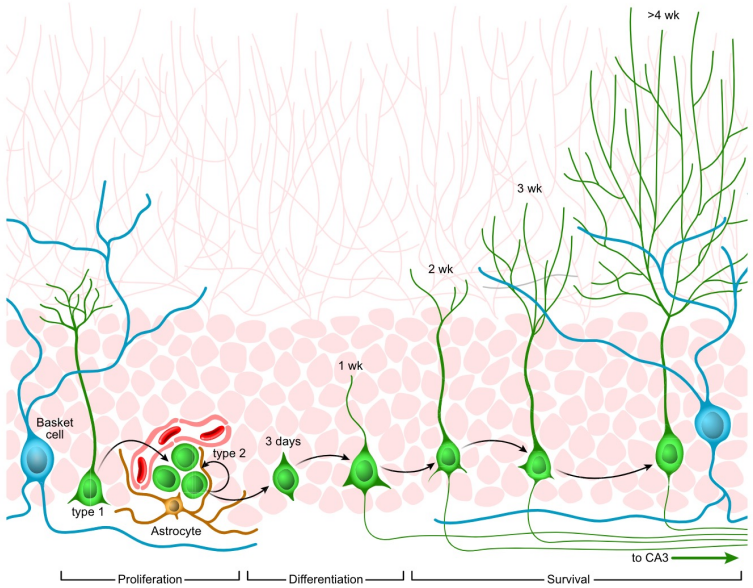
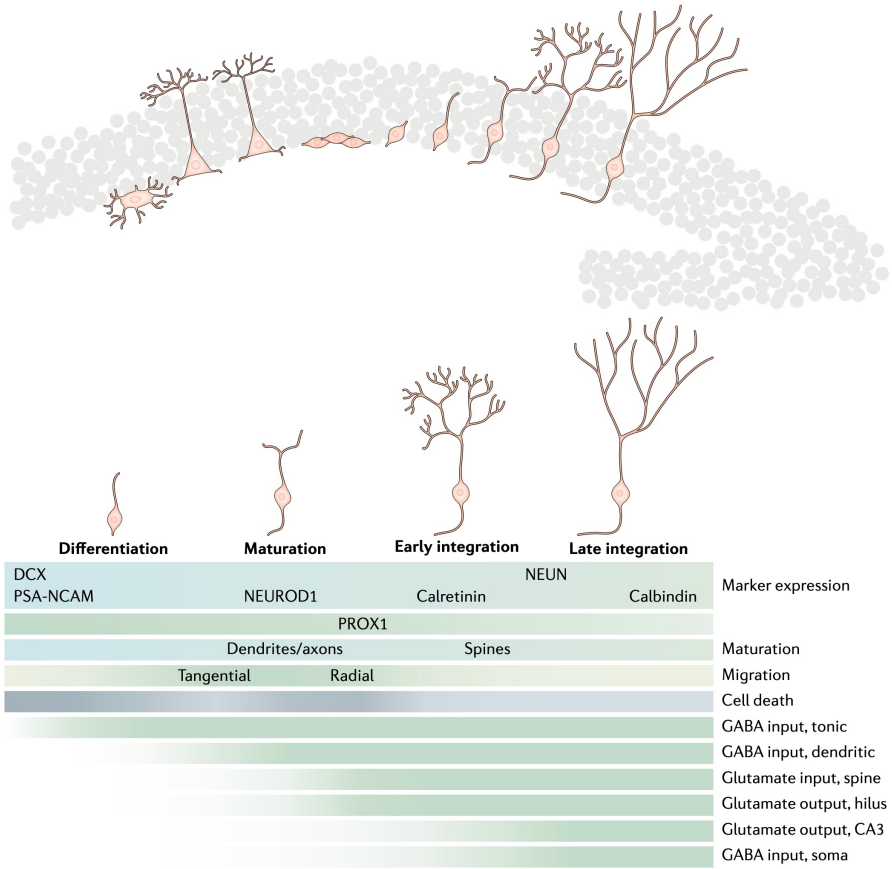
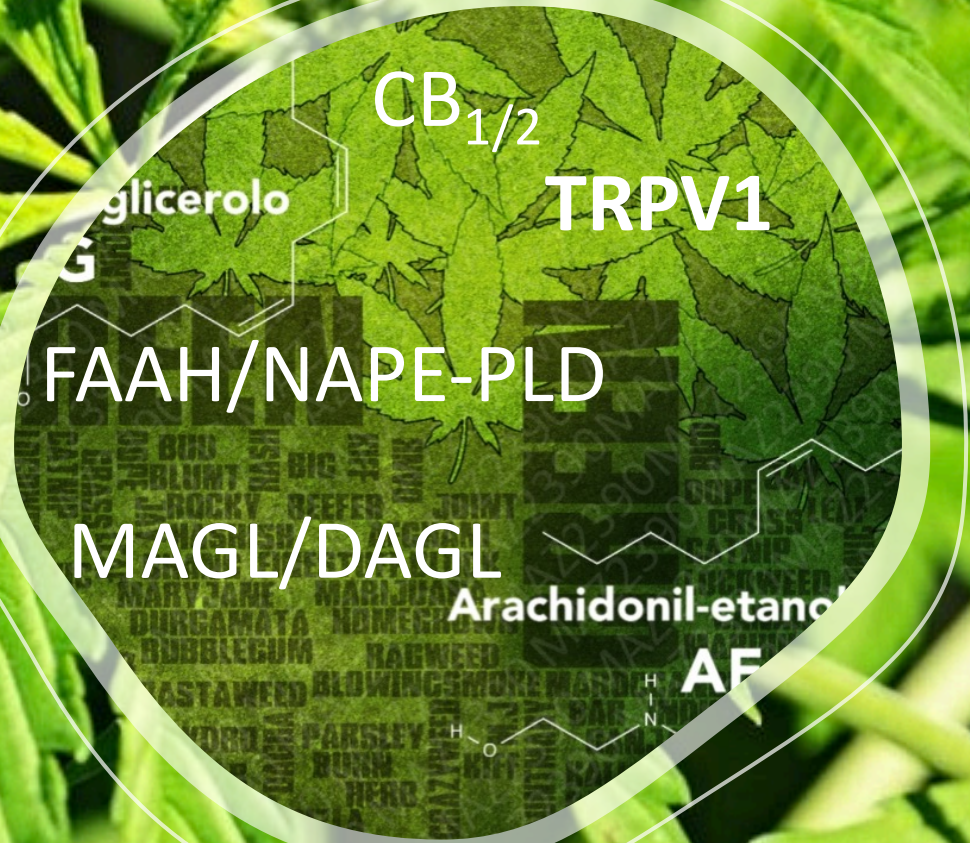


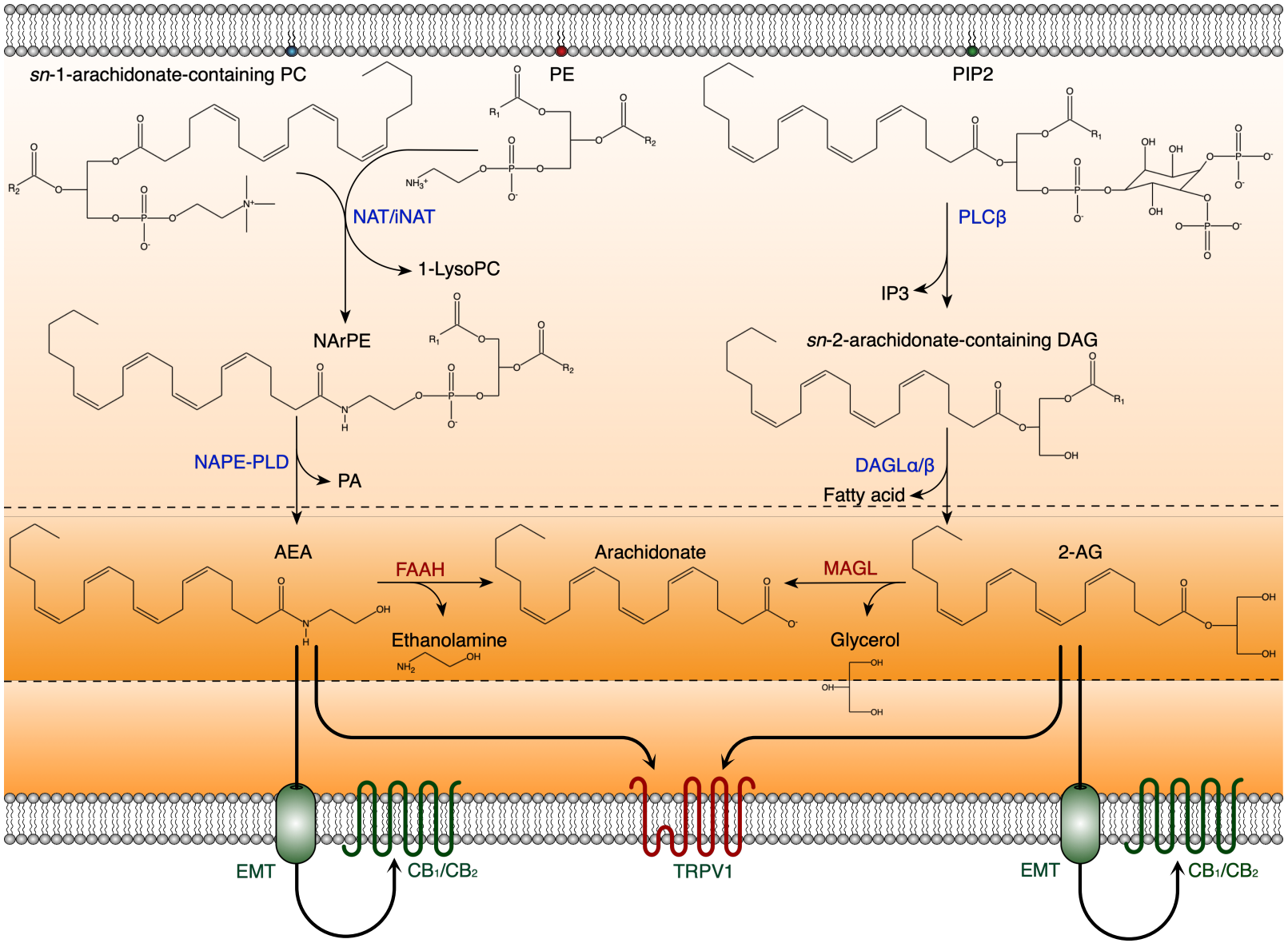
FIGURE 1. Illustration of the development of dentate gyrus granule cells from stem cells to fully mature neurons. New neurons arise from two populations of primitive cells, the slowly dividing type 1 cells, also known as radial glial cells, and the more rapidly amplifying type 2 neural progenitor cells. Over the next few weeks, cells differentiate into neurons, slowly developing dendritic arborizations and axonal projections. Between 2 and 3 wk of age, new neurons begin to receive excitatory input from cortical perforant path axons, and by 4–8 wk, their physiology and anatomy begin to approach those of fully mature neurons.



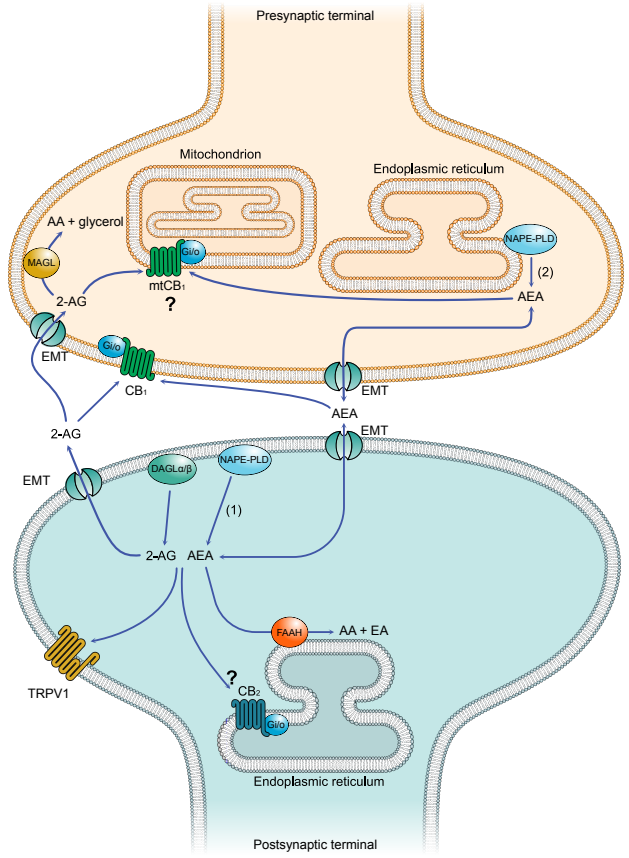
The endocannabinoid system

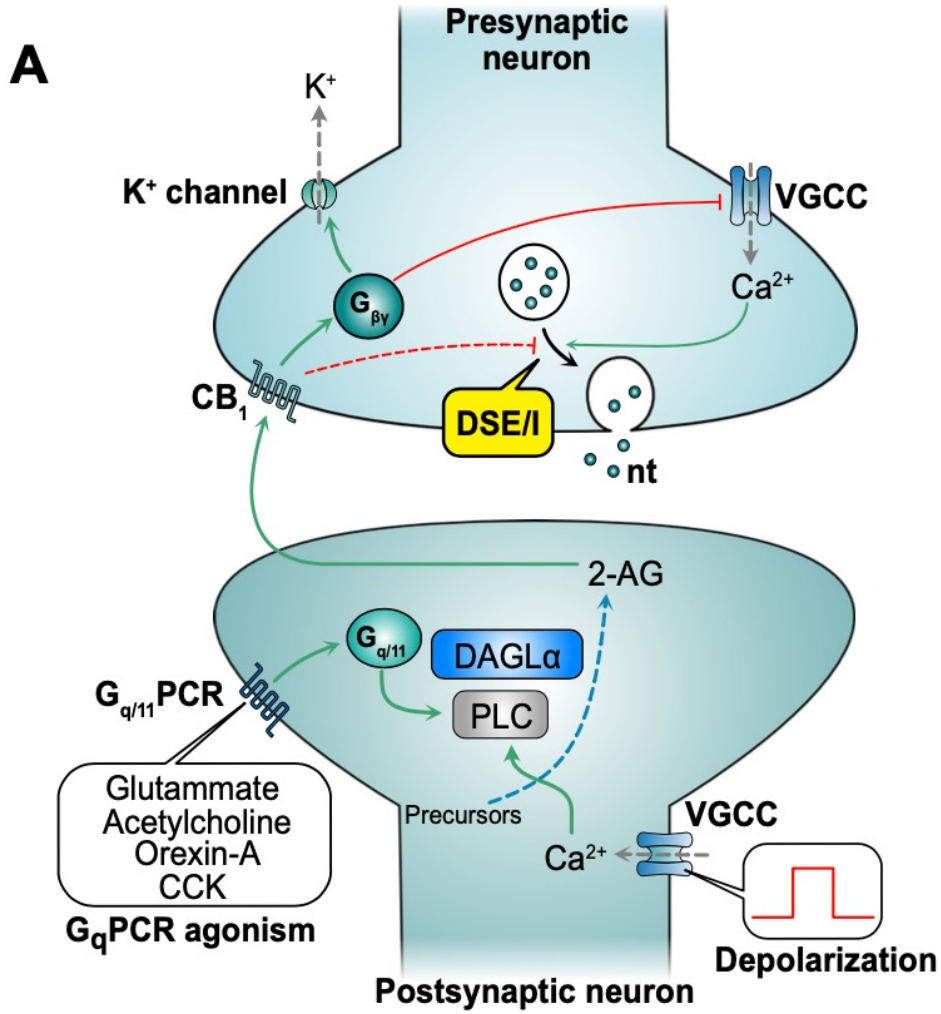


The endocannabinoid system

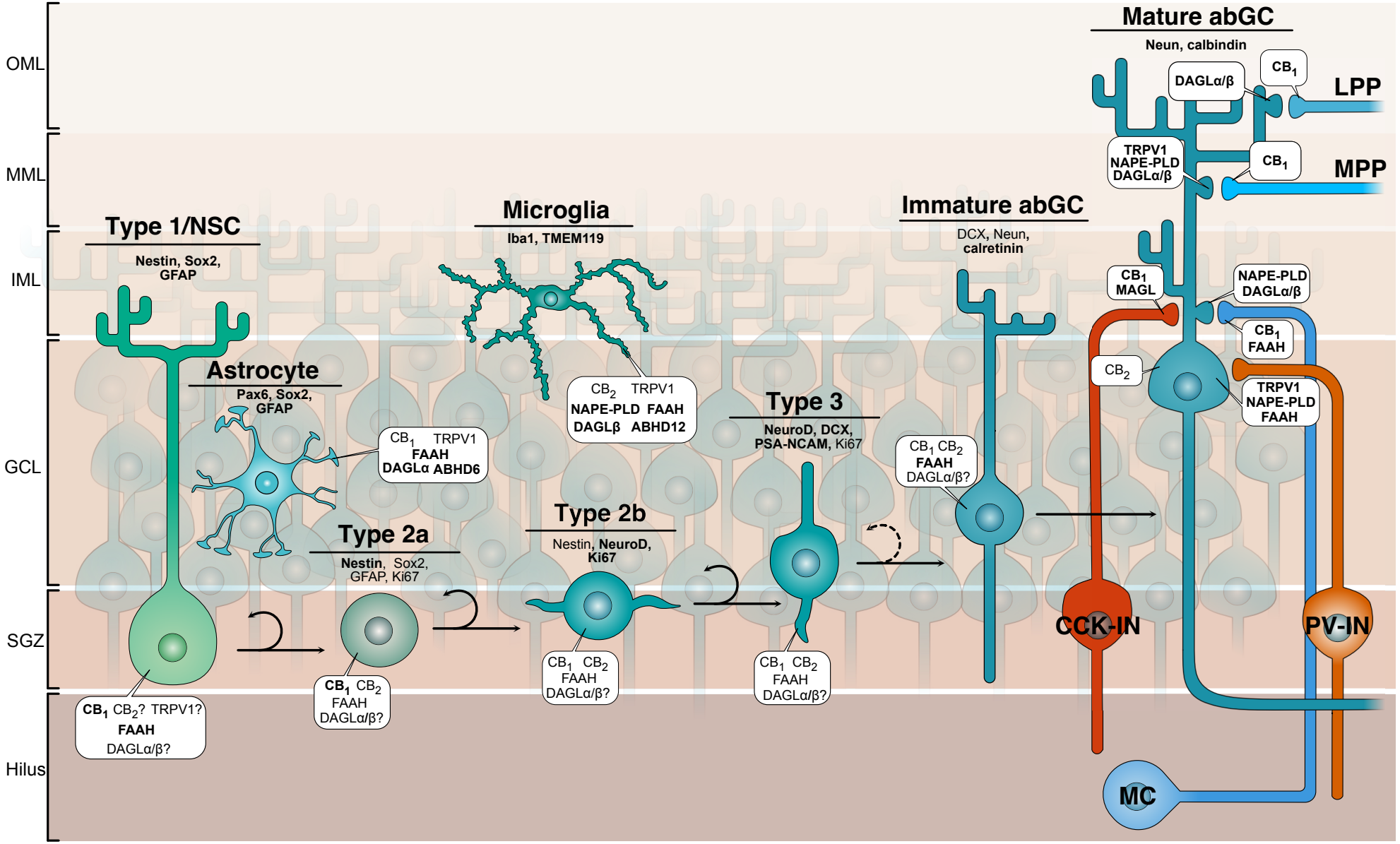


Endocannabinoid-mediated neuromodulation





The ECS in the hippocampal neurogenic niche

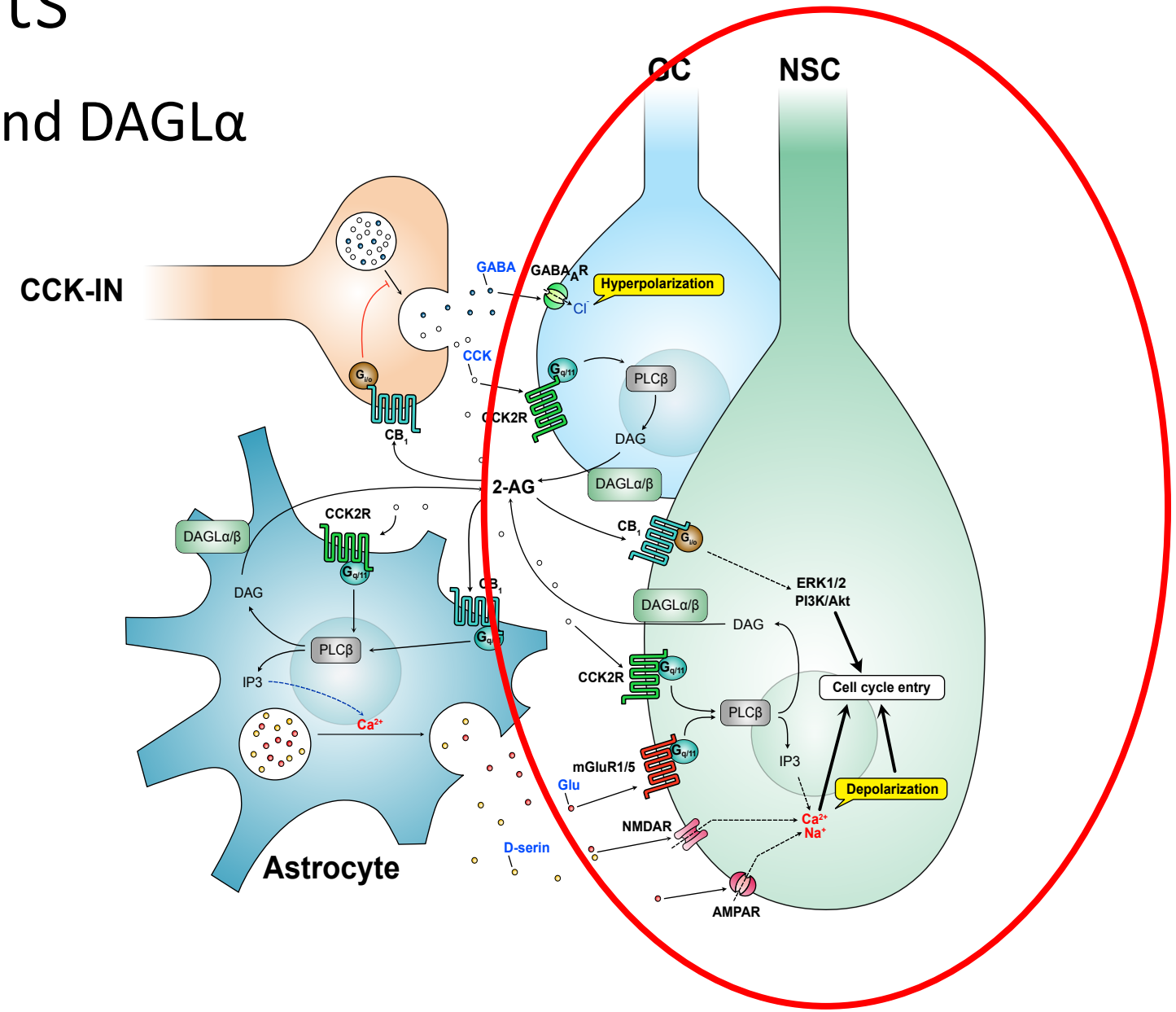


Key messages

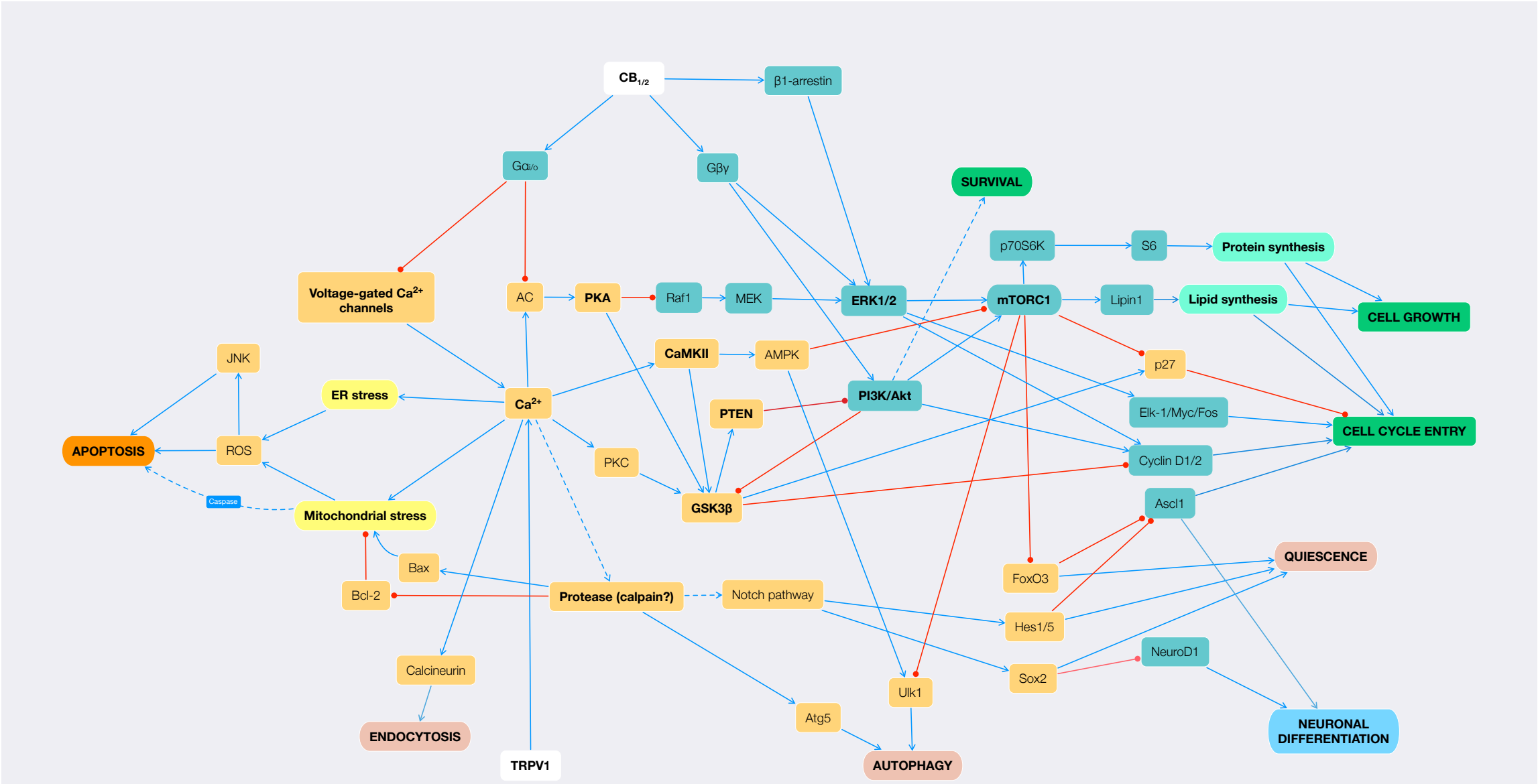
- The molecular components of the ECS are widely and dynamically expressed in every cell type of the neurogenic niche, as well as at every stage of its maturation and activity
- The eCB signaling is critically involved in regulating several biological processes, including neuronal and glial activation/proliferation, migration, and differentiation, which could directly or indirectly influence the fate and behavior of NSCs and their progeny

Direct effects

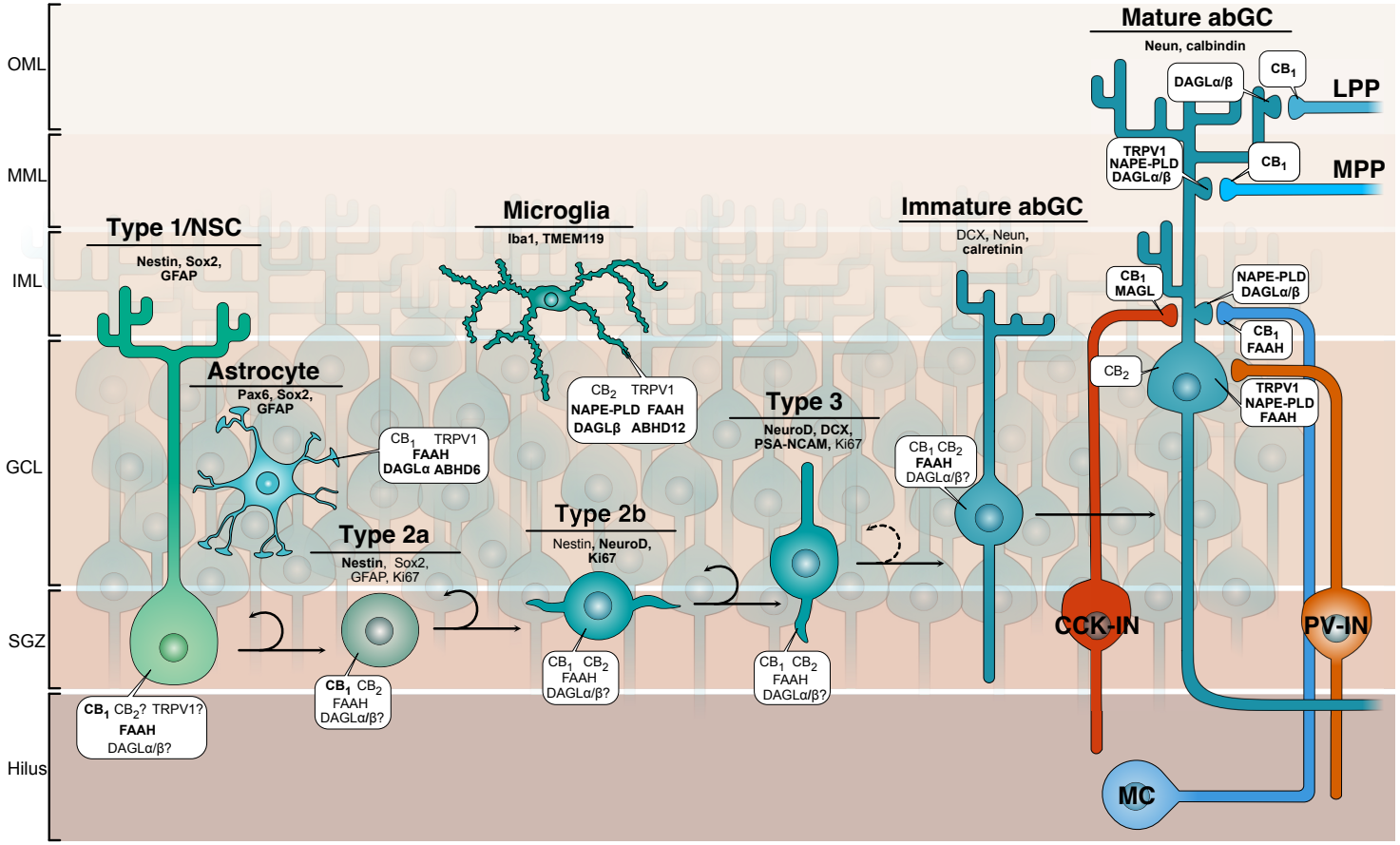
- NSCs express CB1 and DAGLα

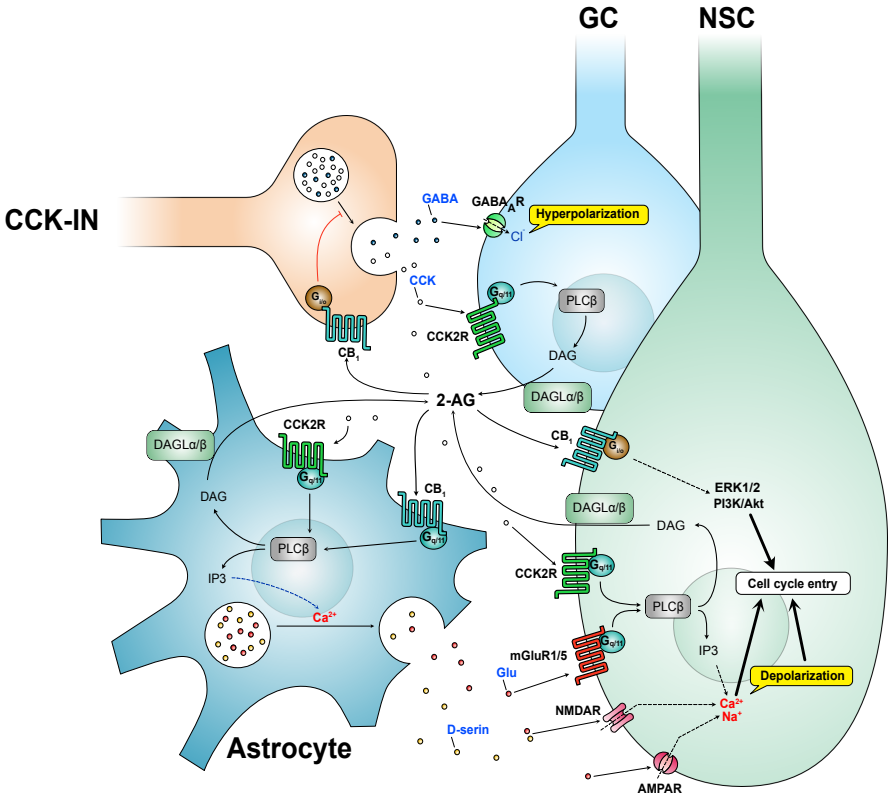


The endocannabinoid signaling

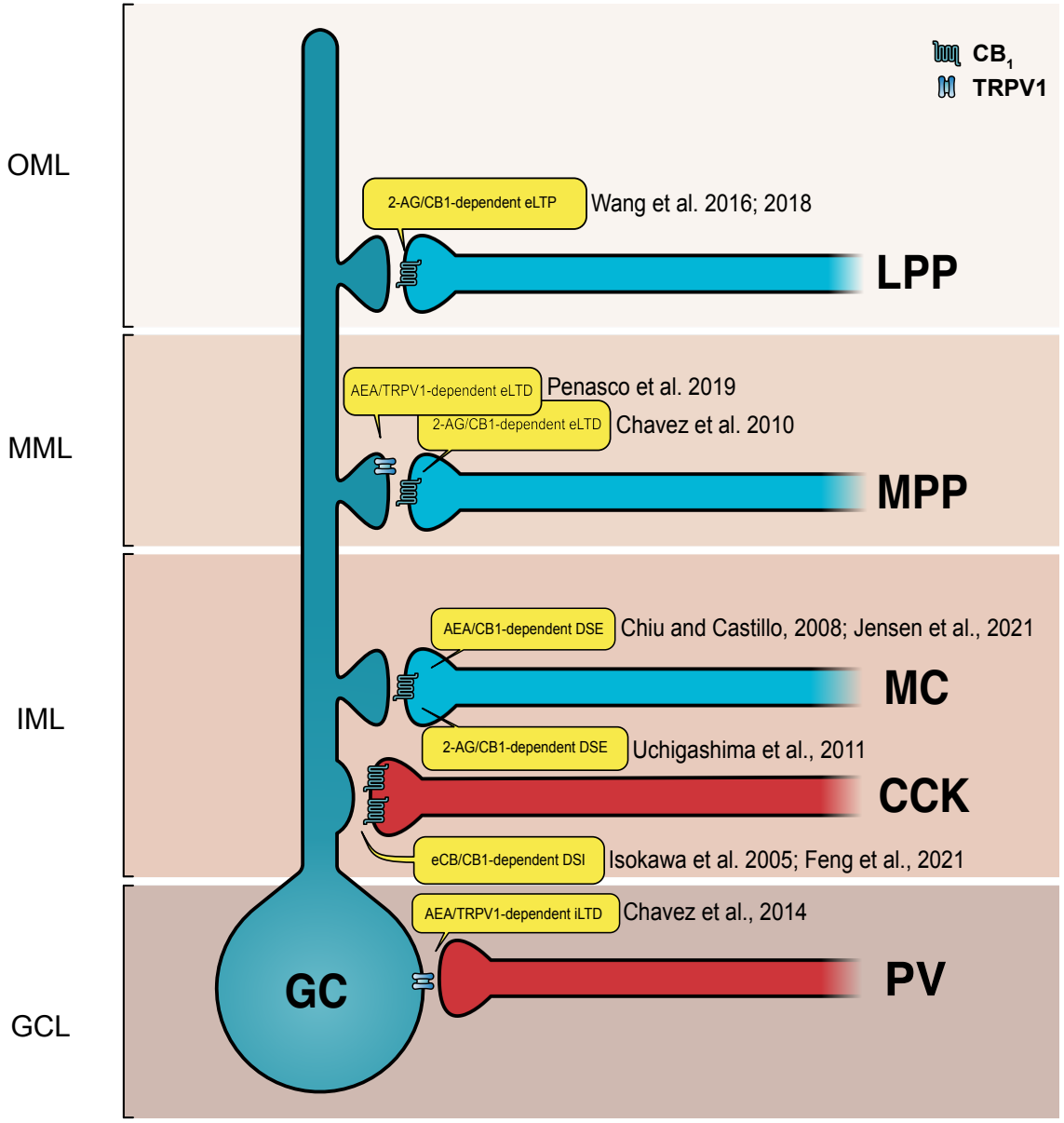


Indirect effects

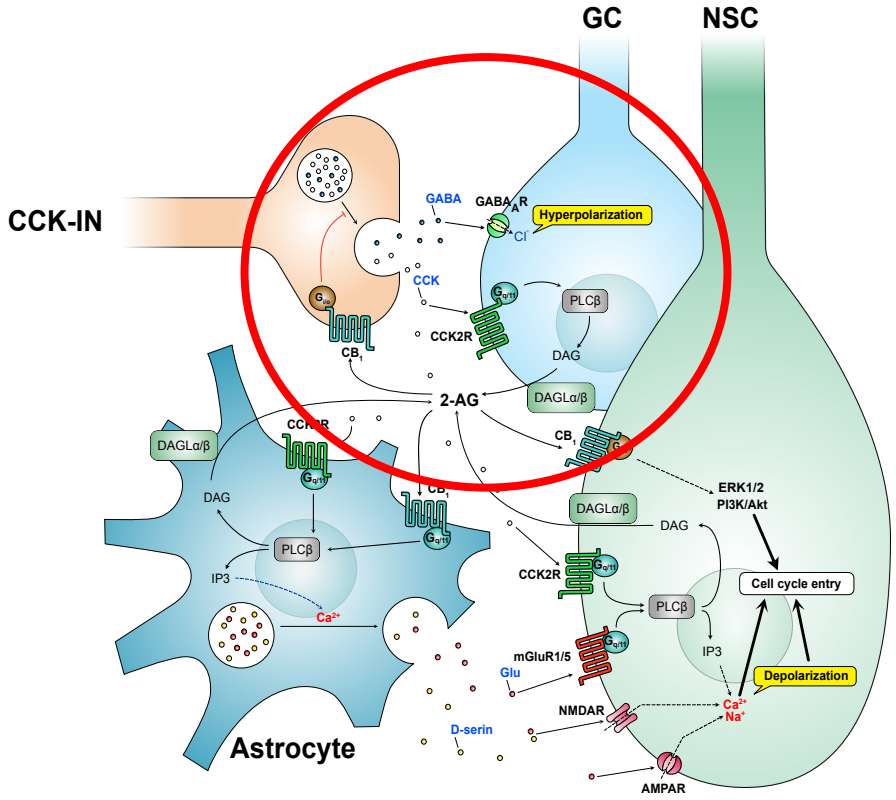




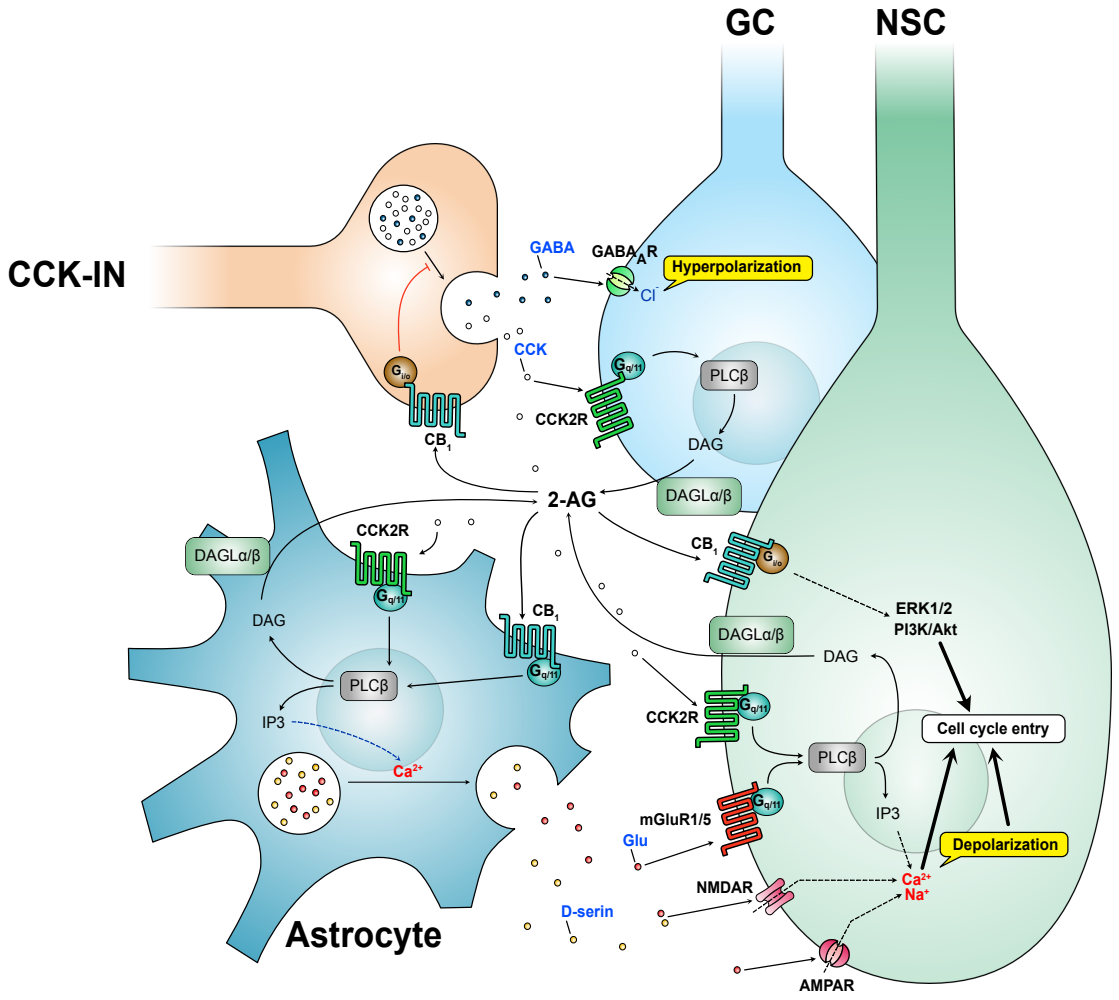
Impact of endocannabinoids in neuronal activity-dependent control of neurogenesis



Neuronal ECS may influence **neurogenesis** by regulating the balance between the tonic levels of GABA and glutamate derived from the synaptic spillover in the neurogenic niche



Impact of the endocannabinoid system in glial activity-dependent control of neurogenesis



Physiological relevance

- The hippocampal ECS may be influenced by exercise and learning and in turn it influences the effects of these physiological experiences on mood and cognition, at least in part, by regulating AHN
- There is a close relationship between ECS, stress, and AHN

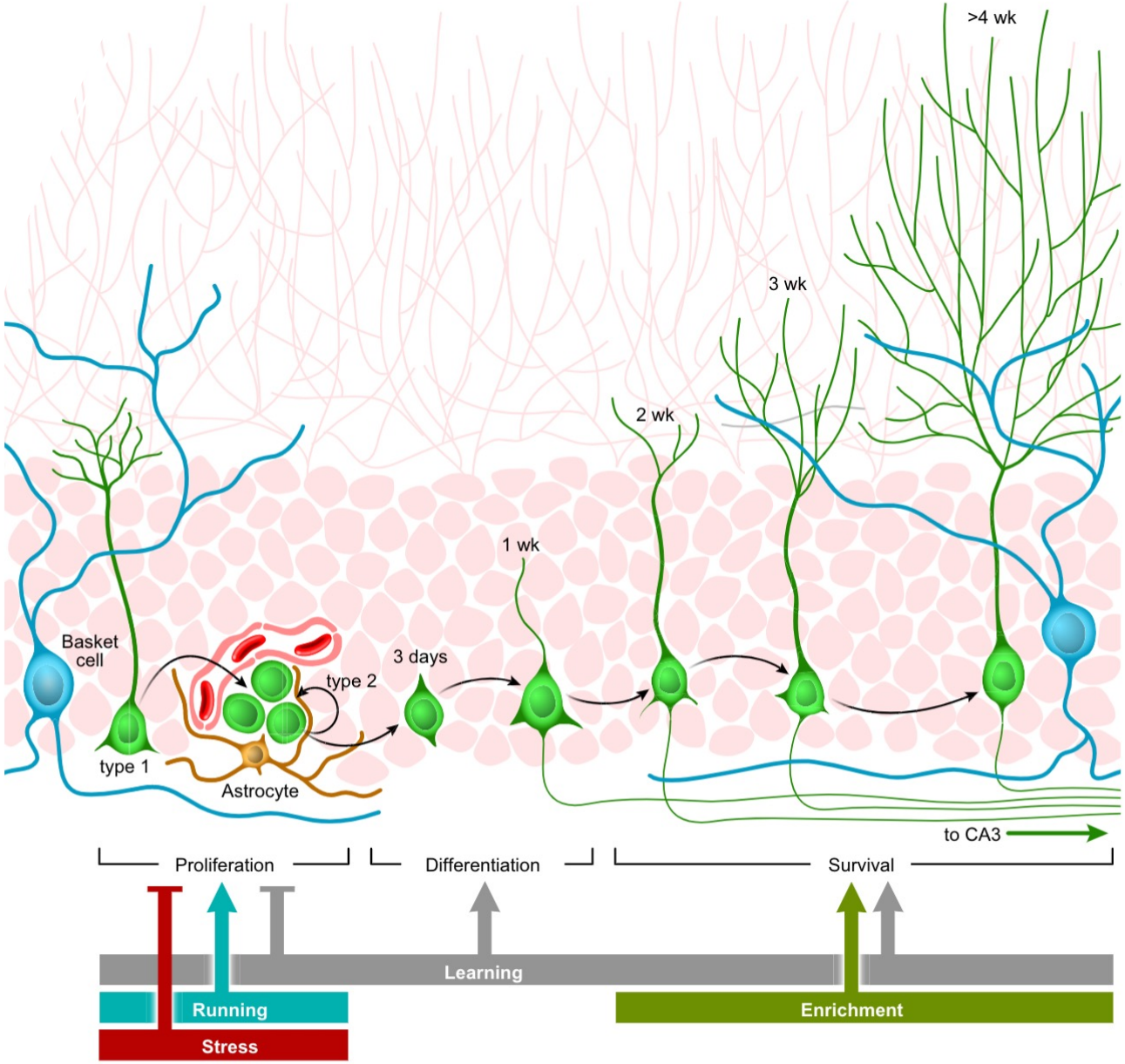


FIGURE 4. Regulation of neurogenesis by behaviors. Neurogenesis is regulated by many behavioral factors as well. Running is one of the most potent inducers of neurogenesis, targeting the proliferation of neural progenitor cells. Enrichment has a complementary effect, increasing the survival of neurons at a critical stage of their maturation. In contrast, stress is a severe negative regulator of new neuron birth, suppressing proliferation. The effects of learning are more complex, suppressing the neurogenesis process at some stages while increasing it at other stages.

Conclusions

- The endocannabinoids, the type-1 and type-2 cannabinoid receptors (CB1 and CB2), and the transient receptor potential vanilloid 1 (TRPV1) channel, along with the enzymes and proteins for eCB synthesis, degradation, and transport, constitute a widespread endogenous signaling system termed the “endocannabinoid system” (ECS)

- In determining temporally and spatially precise control of neuronal and glial activity, the ECS is part of a widely distributed and multimodal signaling network involved in modulating every step of adult hippocampal neurogenesis

- The anxiolytic and anti-depressant effects of endocannabinoid-based drugs could be partly attributable to the ECS’s ability to counteract alterations in adult hippocampal neurogenesis induced by chronic stressors

Thank you for the attention!