Editorial: Modulation of neurogenesis

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The human brain is comprised of billions of neurons whose interconnections are subject to plastic modifications to learn, to adapt to environmental changes, or to compensate for lost function due to brain trauma or disease. Human brain plasticity, however, does not encompass the spontaneous replacement of damaged or degenerated neurons, thus leading to permanent functional deficits and neurological and psychiatric disability. The enteric nervous system (ENS) of the gastrointestinal tract contains half a billion neurons that control diverse aspects of digestive physiology and similarly does not appear to efficiently self-repair when dysfunctional [1].

Rodent brain studies have shown that new neurons continue to be produced at adult stages in discrete niches of the subgranular layer of the hippocampus and of the subventricular zone. Within these two areas, neural stem cells undergo proliferation, asymmetric division, migration and differentiation [2]. There is intense debate regarding adult neurogenesis in these niches in the human brain, but it is largely agreed that in humans the rate of adult neurogenesis is much reduced comparing to rodents, and that it declines during the lifetime and in response to specific pathological conditions. Indeed, neurogenesis in brain niches appears affected by central nervous system (CNS) trauma, neurodevelopmental and neurodegenerative diseases and depression-like pathologies. In turn, preclinical and post-mortem studies also indicate that alterations of neuron production in the niches during development or during aging may contribute to CNS dysfunction or cognitive decline [3]. Based on this evidence there is general consensus that reinitiating neurogenesis may help to counteract specific brain diseases and CNS functional impairment.

Besides stimulating the neurogenic activity from niche components, an innovative approach towards achieving replacement of damaged neurons is the direct *in vivo* induction of fate conversion into neurons of non-neuronal cells residing within CNS or ENS circuits, a process referred to as *in vivo* reprogramming [4]. Considerable progress has been made in converting various source cell

types of mouse and human origin into clinically relevant neuronal types. This strategy holds a relevant therapeutic potential although many issues need to be tackled and solved before *in vivo* reprogramming can reach the stage of clinical application.

In this CNS Section of *Current Opinion in Pharmacology*, we present a series of review articles that summarize current knowledge on the modulation of neurogenesis in different ages of life by endogenous signaling pathways and by external stimuli, including nutrients, and drugs, substances of abuse and environmental pollutants. The emerging close relationship between brain and gut is also highlighted along with a consideration of, and future strategies to foster neurogenesis in CNS pathologies

Beckervordersandforth and Rolando [5] provide an up-to-date overview of the current knowledge on the organization and functions of the neurogenic niches of the brain, namely the subventricular zone (SVZ) and the hippocampal subgranular zone (SGZ), during development and on their alterations during aging and in pathological conditions. Several pharmacological approaches to various neurodegenerative pathologies are also discussed that target the neurogenic capacity of endogenous progenitors. Interestingly, the close relationships between niche cells and the surrounding microglia and astrocytic milieu are also discussed in the context of the role of activated glial cells in sustaining and promoting neuroinflammation which is at the basis of several brain disorders. The ability of SVZ and SGZ cells to generate new neurons, which is maximal during development up to adolescence, progressively declined with age, leading to memory and learning impairment and to a dramatic reduction in the potential to repair brain tissue damage. The possibility of rejuvenating the aging brain through the reactivation of the neurogenic potential of SVZ cells is discussed in the review by *Cutler and Kokovay* [6] which highlights the discovery of several rejuvenating growth factors and molecules circulating in the blood of young animals that could potentially restore neurogenesis in aged animals. *Cutler and Kokovay* also point out the importance of dietary intervention, a topic which is discussed in more detail in other reviews in this section and also discuss the detrimental role of prolonged inflammation during aging which could contribute to the progressive impairment of the neurogenic ability of the brain. Reducing neuroinflammation through glia-directed approaches (see also above) could prove useful to prevent or slow-down the progressive loss of brain neurogenic potential due to ageing.

Outside the “canonical” stem cell niches, NG2-expressing cells in the brain parenchyma represent an additional cell population endowed with proliferating and differentiating abilities. These cells

are the focus of the review by *Kirdajova and Anderova* [7] who provide a detailed overview of the role of NG2 cells during development and in the generation of mature and myelinating oligodendrocytes. They also address the yet-to-be fully understood capacity to generate new neurons, especially under pathological conditions. Despite unsatisfactory data on the spontaneous generation of neurons from these cells *in vivo*, their reprogramming towards a neurogenic fate by external pharmacological and/or genetic manipulation appears to bear interesting perspectives to both acute and chronic neurodegenerative disorders.

The control of neurogenesis at the genetic level is the topic of the two reviews by *D'Mello* [8] and by the *Bernardino* group [9]. The former is focused on the role of histone deacetylases (HDACs). Studies with KO mice have demonstrated a fundamental role for these epigenetic enzymes during neurodevelopment, that are expected to be extended to therapy for neurodegenerative disorders. The Bernardino review highlights the multiple steps in the neurogenesis where miRNAs are involved. Starting from precursor cell proliferation, differentiation, migration to integration and maturation, all stages leading to the birth of new neurons are controlled by different miRNAs and even more are remain to be identified. Although the understanding of the role of miRNAs in adult neurogenesis has significantly improved, there is still a long way to get a full understanding of this complex signaling pathway to treat and/or prevent neurological pathologies.

One of the emerging signaling system controlling neurogenesis is the cannabinoid system. *Maccarrone* and coworkers [10] summarize the current knowledge on the effects of the pharmacological manipulation of CB1 and CB2 receptors on adult neurogenesis, either via selective agonists/antagonists or by blocking the degradation of endogenous ligands. Increased cannabinoid activity promotes neurogenesis in animal models of psychiatric and neurological disorders. However, these encouraging data are counterbalanced by the high complexity and ubiquitous distribution of the cannabinoid system, which to date makes challenging to clearly identify the actual players responsible for the observed effects.

In view of the increasing worldwide incidence of anxiety and depression, the review by *Belzung* and co-workers [11] highlights a very interesting aspect of the activity of antidepressants - their ability to promote and restore adult neurogenesis in the hippocampus. This area of the brain is highly sensitive to stressful conditions, which are always accompanied by decreased learning and memory abilities. Additionally, it has been known for years that one major problem of antidepressant drugs inhibiting catecholamine reuptake (dopamine, serotonin and noradrenalin) is represented by the lag time of several weeks between starting therapy and the appearance of the first beneficial

effects, suggesting mechanisms other than modulation of neurotransmission. The discovery of adult neurogenesis in the hippocampus and of its sensitivity to stress and environmental cues has provided a new explanation for the effects of these drugs, which could be further implemented with future and targeted therapeutic strategies.

In their review, *Vetreno et al.* [12] focus on the effect of intermittent ethanol exposure in adolescents, another serious social problem with devastating health consequences. The phenomenon of weekend binge drinking has spread worldwide with a progressive reduction in the mean age of adolescents. Apart from immediate health consequences due to loss of social inhibition and involvement in car accidents, it is now evident that the effects of alcohol on adolescent brain are long-lasting since it is extremely plastic with a high rate of neurogenesis, and modulated by increasing hormonal concentrations. Repeated and massive ethanol intake dramatically alters this highly sensitive milieu, leading to reduced neurogenesis which is maintained during adulthood despite cessation of alcohol consumption. Cognitive deficits and impaired learning and memory skills are the most evident consequences of this deleterious behavior, the result of an imbalance between neurotrophic and neuroimmune signals in neurogenic niches.

Neurogenesis has been well documented in the spinal cord in response to injury, where it is driven and sustained by ependymal cells lining the central canal. These preclinical findings may be very important in the context of traumatic spinal injuries, which have a high prevalence among young adults and lead to negative consequences for their quality of life. *Moreno-Manzano* [13] focuses on the previously unforeseen high heterogeneity of ependymal glia, on their reactions to traumatic events thanks to their self-renewal and proliferating abilities, on the possibility to foster the reparative potential of endogenous ependymal cells, but also on the strategies to transplant exogenous cell populations in combination with pharmacological approaches after spinal cord injury. Although additional confirmation is needed in humans, the data suggest that new regenerative approaches to spinal cord injury could be soon available.

The complex connections between gut and brain neurogenesis have been analyzed from different points of view in the following reviews.

The group of *Campoy* [14] highlights the different pathways of communications along the so-called gut-brain-axis and how gut microbiota can influence brain development during the crucial first year of age. This relatively new field of research has opened up new possible views on the development

of neurological pathologies in infancy, such as autism spectrum disorders, multiple sclerosis and schizophrenia, along with future new strategies aimed at restoring the correct dialogue between gut microbiota and the brain to foster neurogenesis.

In adulthood, gut microbiota can significantly control brain function and neurogenesis, as discussed by the group of *Pani and Cavallucci* [15]. They specifically review the dual impact of nutrients on adult neurogenesis. Excessive calorie intake can limit adult neurogenesis, so that calorie restriction and fasting are currently viewed as "rejuvenating" options for the brain through the modulation of autophagy. On the other hand, nutrients impact on microbiota composition which in turn modulate the gut-brain-axis. Thus, science is now clearly demonstrating that the common saying "you are what you eat" is absolutely true.

Neurogenesis occurs in the enteric nervous system (ENS) as well as in the brain, and several intestinal pathologies are linked to developmental or acquired alterations in ENS cellular composition and functions. In their review, *Pachnis and Chng* [16] summarize how a detailed understanding of physiological neurogenesis in the ENS can pave the way for future therapeutic developments aimed at replacing missing cell populations or at reverting altered signaling pathways that lead to enteric pathologies.

Finally, another extremely hot topic is the impact of environmental pollution, especially particulate matter (PM), on neurogenesis during development and in adulthood. *Boda, Rigamonti* and *Bollani* [17] note that the current literature clearly demonstrates a higher incidence of neurodevelopmental and neurological disorders in highly polluted areas. PMs can easily distribute in the body, and depending on their physical size, can even reach brain circulation and cross the blood-brain barrier. Several mechanisms have been proposed including direct actions on neurogenic precursors and the recruitment and activation of microglia and astrocytes, that in turn promote the generation of a detrimental neuroinflammatory milieu.

In summary, the reviews presented in this issue of COPHAR provide an updated insight into pathological and physiological factors that can modulate neurogenesis in the mammalian brain and ENS. The contributions are largely based on rodent studies, from which conclusions are drawn with functional implications to humans. In noting that rodents are not small humans, they are nonetheless valuable experimental models to understand pathophysiology, identify potential drug targets and develop therapies.

We hope that this issue of COPHAR will stimulate discussion and new research directions to move forward on adult neurogenesis with relevant implications for the development of viable therapeutic approaches for neuron replacement and circuit functional restoration.

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SHORT BIO

Annalisa Buffo is an Associate Professor in Physiology at the University of Torino, Torino (Italy). She graduated in Biological Sciences at the University of Torino, Torino (Italy) in 1991 and was awarded her PhD in Neurological Sciences in 1998. In 2011, she was enrolled at the University of Torino (Italy) as Assistant Professor and worked for two years as visiting scientist with Magdalena Götz, Ludwig Maximilian Universität, Müenchen (Germany). Her research focuses on the role of glia and neural progenitor cells in brain plasticity and repair, and on the implementation of cell replacement approaches to promote functional recovery in CNS diseases.

Stefania Ceruti is Associate Professor in Pharmacology at the Università degli Studi di Milano, Milan (Italy). She graduated in Pharmaceutical Chemistry and Technology at the Università degli Studi di Milano in 1994 and got her PhD in Environmental and Food Toxicology in 1999. During her PhD, she worked as visiting researcher in the laboratories of Prof. Geoffrey Burnstock (University College London, UK) and of Prof. Peter Schubert (Max Planck Institute, Müenchen, Germany) and she focused on the role of the purinergic system in controlling glia functions. Her current research interests extend from the neurogenic potential of glial cells in acute and chronic neurodegenerative disorders to the role of glial cells in the modulation of chronic pain.