

The Pharmacology of Neurogenesis: conceptual advances and remaining challenges.

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“Once the development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the nerve paths are something fixed, ended, and immutable. Everything may die, nothing may be regenerated”. This “no new adult brain cells” dogma expressed by the great Spanish neuroscientist Santiago Ramón y Cajal a century ago (1). Despite challenges to the dogma in the 1960s, most of which were greeted with skepticism, **it** remained the prevailing view up to the 1980s when more convincing results reported the genesis of new brain cells over the entire lifespan of mammals (2).

Eliminato: this dogma

A Medline search of the term “neurogenesis” in 2017 retrieved more than 22,800 papers with an exponential increase starting from early 90s. Among them, the entry “adult neurogenesis” occurs in over 8,000 papers from the beginning of the 21st century. These numbers underpin the growing interest in this topic and the possible therapeutic exploitation of adult neurogenesis for currently incurable brain pathologies. Some confusion may arise in the use of the term neurogenesis, since it sometimes broadly refers to the generation of both new neurons and glial cells from multipotent precursors. To avoid any misunderstandings, in the present Special Issue of *Biochemical Pharmacology* we refer to a second more restricted meaning, specifically the generation of new neurons from resident neural stem cells (NSCs) or multipotent progenitors (2).

Two main regions in the brain show continuing neurogenesis during adult life: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampus (3, 4). Within these two areas, NSCs undergo proliferation, asymmetric division, migration and differentiation. As

described in several contributions in this Special Issue (2, 5, 6), these processes are affected by central nervous system (CNS) injuries, neurodegenerative diseases and depression-like pathologies.

New technologies and technical approaches have allowed the identification of additional parenchymal pools of progenitors endowed with the intrinsic ability to generate new neurons. The logical subsequent step of this discovery is to understand how their capacity to generate specific neuronal subtypes can be controlled and driven to replace lost cells due to pathological events. In particular, the possibility of re-direct resident NG2 cells, astrocytes, and retinal Müller glia to produce functional neurons has been extensively investigated over the past few decades. The exhaustive review by Boda and coworkers (7), describes several intrinsic and extrinsic factors that can be manipulated to foster the neurogenic conversion of glia. In this respect, the most innovative and promising strategy to avoid the potential risks of introducing exogenous genetic material is represented by cocktails of small molecules which have proven able to successfully reprogram reactive astrocytes directly to functional neurons (8-10). This direct reprogramming towards the neuronal lineage without passing through a dedifferentiated progenitor stage reduces the risks for uncontrolled proliferation and tumor generation.

Although the neurogenic potential of NG2 cells has been extensively studied (9, 11), they are primarily considered as the major source of new oligodendrocytes that potentially can lead to remyelination in demyelinating disorders, like multiple sclerosis (12). Accordingly, considerable effort has been focused on the development of new strategies to potentiate their proliferation and neuronal differentiation via the manipulation of a variety of signaling molecules, growth factors, hormones and even neurotransmitters (11).

The major challenge is that NSCs react to both acute **events** and chronic brain disorders with increased proliferation and generation of neuroblasts, which encounter difficulties to fully integrate in existing networks. Thus, besides promoting the neurogenic conversion of NSCs, a full understanding of the permissive and inhibitory factors in the extracellular milieu is mandatory. As for many other processes in the human body, various physiological conditions, such as sex and age (13, 14), and daily life activities, such as nutrition (15) can profoundly influence adult neurogenesis.

In this respect, the sex dimorphism of the brain and its effect on NSC functions are addressed in this Special Issue by Heberden and colleagues (13). Indeed, male and female sex steroid hormones produced by the gonads can reach the brain through the circulation or they can be directly synthesized

Eliminato: challenges

in the CNS. Here they exert both peculiar and common functions: estrogens stimulate cell proliferation, while androgens and progestogens protect cells from apoptosis, increase cell survival and favor neuronal renewal. In parallel, all the three classes exert positive effects on NSC differentiation. More importantly, they can also help in counteracting the deleterious effects of stroke or ischemia. Regarding possible clinical applications, promising results have been obtained in preclinical animal trials after administration of some phytochemicals (i.e., soy phytoestrogens, naringenin, and resveratrol); however, in humans, observational and interventional studies led to contrasting results. In addition, the effects of several synthetic steroid agonists (i.e., diarylpropionitrile, propylpyrazole triol and tamoxifen), have also been investigated (13).

As noted, another interesting aspect of everyday life that needs to be taken into account when studying adult neurogenesis is the nutritional intake. Indeed, as described by Fidaleo and coworkers (15), excess nutrients can lead to an impairment of neurogenesis by premature exhaustion of the NSC pool, while calorie restriction has the opposite effect. Interestingly, these effects are mediated by several nutrient-sensing cascades (i.e., insulin, mTOR, CREB, Sirtuin) that can be potentially modulated by already approved or experimental drugs and may have important clinical applications in metabolic diseases, aging and acute brain damage (15).

Due to the recent significant increase in the average life expectancy, understanding the molecular mechanisms of aging has become of primary importance, as also demonstrated by the huge amount of funds allocated to this research field. The current knowledge regarding the correlation between adult neurogenesis and aging is covered in the review by Apple and colleagues (14). During aging, NSCs (either in the SVZ or in SGZ) and their progenitors exhibit reduced proliferation and neuron production, which is thought to contribute to age-associated cognitive impairment and reduced brain plasticity (13, 15). Interestingly, both hormone therapy and calorie restriction can be envisaged as strategies to stimulate neurogenesis and resolve cognitive decline in the elderly.

In addition to the defects in adult neurogenesis that have been detected in several brain pathologies (2, 5, 6), marketed drugs and drugs of abuse can have a significant impact on the ability of the brain to generate new neurons. As comprehensively discussed by Eliwa and coworkers (16), various classes of monoaminergic antidepressants (including tricyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors and norepinephrine reuptake inhibitors) increase adult hippocampal neurogenesis by acting predominantly on cell proliferation, maturation, and survival (16). More

specifically, chronic antidepressant treatment can stimulate NSC proliferation and promote the survival of adult-born neurons in rodents and primates. These findings are of immediate clinical relevance, since antidepressant drugs increase the number of progenitor cells in the SGZ of depressed patients as well, leading to the suggestion that this effect could contribute to their efficacy. Less clear results have been obtained with new innovative therapies, e.g., ketamine, that act via non-monoaminergic mechanisms (16).

As reviewed by Castilla-Ortega and colleagues (17), the impact of cocaine on adult hippocampal neurogenesis is a complex phenomenon which involves, besides endocannabinoids, a number of other neurobiological factors. In particular, these authors have identified two cognitive events that link cocaine assumption and hippocampal functions: i) the formation of robust memories for cocaine-stimuli associations that may be established during the initial experiences with the drug, and that contribute to drug craving, and ii) the global cognitive decline that emerges after chronic cocaine exposure and impedes the acquisition of new and beneficial information. Thus, the negative outcomes of drugs of abuse can be manifest through the persistent impairment of adult hippocampal neurogenesis, with a dramatic impact on cocaine addiction (17).

As is evident from the papers mentioned, the biomedical research community is only now beginning to fully comprehend the importance and contribution of adult neurogenesis to brain physiology and pathology, and how to foster its beneficial outcomes by reducing in parallel its negative aspects. In this respect, in this Special Issue we have also deemed interesting to explore some innovative and unconventional approaches. The first is represented by miRNAs, whose discovery has profoundly modified the comprehension of the modulation of biological processes at the molecular level. In their article, Saraiva and colleagues depict a scenario where miRNAs play a major role in adult neurogenesis, and also in neurodegenerative processes suggesting that therapeutic approaches based on miRNAs represents a promising avenue for future drug discovery (5).

From an historical perspective, the traditional medicine systems which have represented the only therapeutic option in Far Eastern countries such as China, India and Pakistan for centuries (18) also appear to involve aspects of neurogenesis. In Traditional Chinese Medicine (TCM) system acupuncture, phytotherapy and other techniques are widely used to guarantee the overall well-being of the organism, in this instance humans. The principles of TCM lie in the philosophical approach to the universe, which includes the concepts of Yin and Yang equilibrium and the optimal flow of the energy

flux termed Qi. These concepts represent the basis for TCM practitioners to select the best therapeutic approach for the individual patient, personalized medicine from a precomputer age. Following the global interest in better understanding TCM considerable efforts have been applied to analyse the effects of acupuncture and Chinese phytotherapy in “Western” scientific, e.g., molecular, terms. This has led to interesting results in the field of neurogenesis, as described for acupuncture by Shin and colleagues (5). Insertion and manipulation of needles in specific acupoints leads to the local release of a plethora of neurotransmitters and neuromodulators, including growth factors, which in turn sustain neurogenesis. Interestingly, based on available data in neurological diseases, it would be better to choose the best acupoint to be stimulated by evaluating its ability to promote growth factor release, instead of considering its “traditional” characteristics (5). Additionally, various plants traditionally employed to restore brain capacities in the elderly behave as potent modulators of endogenous neurogenesis, as reviewed by Zheng and coworkers (19). Traditional medicine approaches should therefore be taken into consideration as possible complementary supports to inform other pro-neurogenic pharmacological approaches

This Special Issue depicts an overview of currently available knowledge on the modulation of neurogenesis in the adult brain, by endogenous signaling pathways, by drugs and/or by physiological and pathological conditions, with the ultimate aim of assessing whether a possible translation of experimental data on adult neurogenesis to patients remains an unattainable hope or whether encouraging results are emerging.

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