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Review

Emerging pharmacological approaches to promote neurogenesis from endogenous glial cells

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ABSTRACT

Neurodegenerative disorders are emerging as leading contributors to the global disease burden. While some drug-based approaches have been designed to limit or prevent neuronal loss following acute damage or chronic neurodegeneration, regeneration of functional neurons in the adult Central Nervous System (CNS) still remains an unmet need. In this context, the exploitation of endogenous cell sources has recently gained an unprecedented attention, thanks to the demonstration that, in some CNS regions or under specific circumstances, glial cells can activate spontaneous neurogenesis or can be instructed to produce neurons in the adult mammalian CNS parenchyma. This field of research has greatly advanced in the last years and identified interesting molecular and cellular mechanisms guiding the neurogenic activation/conversion of glia. In this review, we summarize the evolution of the research devoted to understand how resident glia can be directed to produce neurons. We paid particular attention to pharmacologically-relevant approaches exploiting the modulation of niche-associated factors and the application of selected small molecules.

Contents

Abbreviations: +, positive; AMPK, AMP-activated protein kinase; Ascl1, Achaete-scute homolog 1; Atoh7, Atonal basic-helix-loop-helix transcription factor 7; β-cat, beta-catenin; BDNF, brain-derived neurotrophic factor; BLBP, brain lipid-binding protein; BMP, bone morphogenetic protein; Brn2, murine brain-2 transcription factor; cAMP, cyclic adenosine monophosphate; CNS, Central Nervous System; Creb1, cAMP responsive element binding protein 1; Crx, cone-rod homeobox gene; DAPT, N-[N-(3,5-difluorophenacetyl)-l-alanyl]-S-phenylglycine t-butyl ester; DCX, doublecortin; Dll, delta-like; Dlx, related to the Drosophila distal-less homeobox transcription factor; DNA, deoxyribonucleic acid; Dnmt3b, DNA methyltransferase 3b; EGF, epidermal growth factor; FGF, fibroblast growth factor; GABA, gamma-aminobutyric acid; GF, growth factor; GLAST, Glutamate Aspartate Transporter; GSK3β, glycogen synthase kinase 3 beta; HB-EGF, heparin-binding EGF-like growth factor; HDAC, histone deacetylase; Hes, hairy and enhancer of split; HK2, hexokinase; Hmga2, high mobility group AT-hook 2; IFN-γ, interferon gamma; IGF1, insulin growth factor 1; IL-1β, interleukin 1 beta; iPSC, induced pluripotent stem cell; Jag1, Jagged 1; Jak/Stat, Janus kinase/signal transducer and activator of transcription; JNK, c-Jun N-terminal kinase; Klf4, Kruppel-like factor 4; LDHA, lactate dehydrogenase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; Math3, mouse Ath3 (Atonal basic-helix-loop-helix transcription factor 3); Mbd1, methyl-CpG binding domain protein 1; MEF2, myocyte enhancer factor-2; MG, Müller glia; miRNA, microRNA; MNU, N-methyl-N-nitrosourea; Myc, myelocytomatosis oncogene; Myt1L, Myelin Transcription Factor 1 Like; NeuN, neuronal nuclear antigen; NeuroD1, Neurogenic differentiation 1; NG2, neural/glial antigen 2; Ngn2, Neurogenin2; NICD, Notch intracellular domain; NMDA, N-Methyl-D-aspartate; nNOS, neuronal nitric oxide synthase; NSC, neural stem cell; NT3, neurotrophin-3; Oct4, octamer-binding transcription factor 4; Olig2, oligodendrocyte lineage transcription factor 2; P, postnatal day; p16, cyclin-dependent kinase inhibitor 2A; p21, cyclin-dependent kinase inhibitor 1; p53, Tumor protein p53; Pax6, Paired Box 6; PDGFRα, Platelet-derived growth factor receptor alpha; PGE2, Prostaglandin E2; PKA, protein kinase A; Plp, proteolipid protein; QA, quinolinic acid; RA, retinoic acid; Rbpj, recombining binding protein suppressor of hairless; RC2, radial glial cell marker-2; REST, Repressor element 1 (RE1)-silencing transcription factor; RNA, ribonucleic acid; ROCK, Rho-associated protein kinase; ROS, reactive oxygen species; Shh, Sonic hedgehog; SGZ, subgranular zone; SIRT1, Sirtuin 1; Smo, Smoothened; Sox2, SRY (sex determining region Y)-box 2; Sox4, SRY (sex determining region Y)-box 4; Sox9, SRY (sex determining region Y)-box 9; SVZ, subventricular zone; TF, transcription factor; TGFβ, transforming growth factor; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor; VPA, valproic acid; Wnt, wingless-type MMTV integration site family.

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1. New neurons in the mature Central Nervous System: the dream of a new brain

Neurodegeneration after injury or disease is a chronic and incurable condition whose disabling effects may continue for years or even decades. While the contribution of neurodegenerative pathologies including stroke, Alzheimer's and Parkinson's diseases to the global disease burden is growing fast, regeneration of functional neurons still remains an unmet need.

Strategies to replace lost neurons can rely on either transplantation of exogenous cells or the exploitation of endogenous sources. The field of cell transplantation has developed over a long time now, and progressed enormously, to the extent that it appears to be very close to proposing for clinical trials authentic human neurons derived from human embryonic stem cells [1]. However, the use of human stem cells faces both ethical issues and the challenge to overcome immunorejection. Induced pluripotent stem cells (iPSCs) can represent an excellent alternative for autologous applications. Still, the field needs further advancement in differentiation protocols and solutions to manage risks of introduction of genetically manipulated material. In this evolutionary landscape, further complicated by the costs of stem cell therapies based on good manufacturing practices and delicate surgical procedures, exploitation of endogenous neural cells has recently gained an unprecedented attention. Today this field of research has become very active despite initial disappointments due to the failure to obtain replacement of neurons after damage by endogenous neural stem cells (NSCs) of the adult germinative niches [2,3]. Crucial to attract researchers' interest were the clear demonstrations that the Central Nervous system (CNS) can activate spontaneous neurogenesis, and that endogenous glia can be instructed to produce neurons by reprogramming (see below).

Targeting local glia comprising astrocytes and neural/glial antigen 2 (NG2)-expressing glia (NG2 cells) appears particularly desirable in view of neuronal replacement because of their abundance and ubiquitous distribution in the CNS. Moreover, these glial cells set up a complex reaction to injury that partly increases their similarity to NSCs and can include a cytogenic response leading to some degree of amplification, thereby allowing to direct some elements toward neurogenesis while avoiding glial cell depletion [4].

In this review we will revise the current status of research devoted to understand if and how resident glia can be directed to produce neurons, with specific attention to in vivo data. We will discuss mechanisms and factors, either intrinsic or environmental, which may be of relevance for potential pharmacological approaches aimed at boosting the production of new neurons from endogenous sources. Our focus will be mostly on studies on the mammalian brain, spinal cord and retina, which, due to its peculiar inherent regenerative properties, has been intensely investigated with outcomes possibly exploitable also for other systems.

2. Parenchymal neurogenesis: who, when, where

2.1. Spontaneous parenchymal neurogenesis

Adult neurogenesis in the constitutive germinal niches of the subventricular zone (SVZ) and hippocampal subgranular layer (SGZ) is highly conserved in different mammalian species. Whether other CNS regions can be neurogenic has been the subject of a long debate that is still partly unresolved. Initial studies referred to the rest of the CNS parenchyma as non-neurogenic. This concept was mainly derived from the observation that when heterotopically transplanted outside the constitutively active neurogenic niches, NSCs differentiated almost exclusively into glial cells and not in neurons [5–7]. These observations were consistent with the absence of neurogenesis in the mature healthy CNS parenchyma in rodents, as reported after initial controversial evidence for the spinal cord, cortex and striatum by numerous studies [8–13].

By contrast, comparative analyses indicated that in some mammalian species low-level neurogenesis can occur also outside the two canonical niches. Neuroblasts were observed in the striatum and neocortex of rats, rabbits, guinea pigs and primates and in the amygdala, piriform cortex and adjoining perirhinal cortex of primates (see [14,15]). Furthermore, striatal neurogenesis has now been suggested also in humans [16]. The observation of parenchymal neurogenic processes in intact animals may suggest their participation in homeostatic functions and normal brain activity. However, no data are currently available that support this idea. Further, the timing and the transient nature of neurogenic events observed in some of these cases (e.g. transient activation of neurogenesis in the guinea pig at weaning age [15]) rather favors their interpretation as events related to temporary forms of plasticity.

Of note, injury can induce neurogenic events also in regions that are normally non-neurogenic. Newly generated neurons were observed after acute degeneration both in the striatum (experimental stroke, [17]; quinolinic acid (QA)-induced excitotoxic lesion, [18]) and the neocortex (transient ischemia, [19]; focal apoptosis, [10,13]) as well as in a genetic model of progressive striatal neurodegeneration [20].

Although the SVZ can contribute neuroblasts to the injured parenchyma [2,21], several studies provided initial evidence that neurogenic events in non-neurogenic regions were a local SVZ-independent phenomenon. In both rabbits under physiologic conditions and in mice during striatal progressive neurodegeneration,