Adult Neurogenesis and Gliogenesis: Possible Mechanisms for Neurorestoration

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The subgranular zone (SGZ) and subventricular zone (SVZ) are developmental remnants of the germinal regions of the brain, hence they retain the ability to generate neuronal progenitor cells in adult life. Neurogenesis in adult brain has an adaptive function because newly produced neurons can integrate into and modify existing neuronal circuits. In contrast to the SGZ and SVZ, other brain regions have a lower capacity to produce new neurons, and this usually occurs via parenchymal and periventricular cell genesis. Compared to neurogenesis, gliogenesis occurs more prevalently in the adult mammalian brain. Under certain circumstances, interaction occurs between neurogenesis and gliogenesis, facilitating glial cells to transform into neuronal lineage. Therefore, modulating the balance between neurogenesis and gliogenesis may present a new perspective for neurorestoration, especially in diseases associated with altered neurogenesis and/or gliogenesis, cell loss, or disturbed homeostasis of cellular constitution. The present review discusses important neuroanatomical features of adult neurogenesis and gliogenesis, aiming to explore how these processes could be modulated toward functional repair of the adult brain.

Key words: Neurogenesis, gliogenesis, aging, neurodegeneration, neurorestoration

INTRODUCTION

The adult brain has some ability to adapt to changes in its environment. This ability is, in part, related to neurogenesis and gliogenesis. Neurogenesis modifies neuronal connectivity in specific brain areas, whereas gliogenesis ensures that myelination occurs and produces new supporting cells by generating oligodendrocytes and astrocytes [1]. Altered neurogenesis and gliogenesis have been revealed in a number of pathological conditions affecting the central nervous system (CNS); for instance, neuropsychiatric diseases [2], neurodegenerative diseases [3-6], and demyelinating diseases [7]. Understanding the extent to which adult neurogenesis and gliogenesis can be modulated to compensate for functional loss has been gaining attention [6, 8]. Most of the information in this field was obtained from rodent studies. Although these findings are instrumental in our understanding, they are not directly applicable to the human brain, mainly due to differences in the neurorestoration capacities of different species [9-12]. The purpose of this review is to bring together available evidence on adult neurogenesis and gliogenesis,
and to explore the potential application of new findings to human CNS diseases.

Recent studies detecting the concentration of $^{14}$C in the genomic DNA of the human brain demonstrated that the olfactory bulb, cerebellum, and cortex preserve only negligible levels of neurogenesis in adulthood, although substantial neurogenesis was reported in the hippocampus and striatum [13-17]. These results may dispute the hope that human adult neurogenesis can be modulated as a potential approach for neurorestoration. Here, we advise to carefully interrelate these data with the real importance of neurogenic processes for several reasons. Firstly, because the concentration of $^{14}$C reflects the average age of cells in a neuronal pool, existing methods may not be sensitive enough to detect subtle changes caused by the introduction of a small proportion of new neurons. Secondly, the selection of brain areas and sample sizes may not have been most appropriate due to the current lack of information about regional variations of the neurogenic capacity in human brains. Thirdly, the biological importance of low levels of neurogenic activity may have been underestimated because even a small number of new neurons in the adult human brain can evoke meaningful functional changes by integrating into existing neuronal circuits [18-20]. Finally, gliogenic activity and the presence of quiescent progenitor cells have been detected in numerous brain areas by other studies [1, 21-24]. In particular, glial cells can transform into neuronal lineage under certain circumstances. This review introduces main concepts and important questions in the field, aiming to direct attention to understand the interaction between neurogenesis and gliogenesis, from which factors may be found to improve neurorestoration in the human brain.

NEUROGENESIS AND GlioGENESIS IN THE ADULT BRAIN

Generation of new neurons in adult neurogenic regions is not necessarily de novo neurogenesis but may instead be the consequence of protracted development [21]. Neurogenesis and gliogenesis produce neurons and glia that can integrate within some regions of the mature brain. The newly generated cells can mediate certain types of plasticity, but the biological significance of neurogenesis and gliogenesis is regional/source dependent [10, 12]. Malfunction of such processes is found to be associated with some neurological and psychiatric diseases [1]. Such brain potential may provide alternative approaches to neurorestoration in CNS diseases, however it is important to point out that the number of neural stem cells (NSCs) decreases upon maturation, suggesting that the regenerative capacity of the CNS deteriorates with age. In line with this, altered neurogenesis has been found in neurodegenerative diseases that mostly affect the elderly population [3-6]. Nevertheless, studies in rodents pointed out that both neurogenic and gliogenic processes can stem from persisting NSCs, and quiescence has been proposed to be important for the long-term maintenance of adult NSCs [25]. Therefore, modulation between neurogenesis and gliogenesis may be an ideal way to take advantage of residual NSCs. It is encouraging that, using certain interventions, neurogenic rejuvenation can be induced in old mice [26, 27].

Primary neurogenic sites in the brain

The adult subgranular zone (SGZ) and subventricular zone (SVZ) are developmental remnants of the germinal regions originating in the hippocampal sulcus and lateral ganglionic eminence, respectively [28]. In fact, the unique ontogenesis of the SGZ and SVZ allows these two areas to preserve their capacity to generate proliferating cells in the brain during the entire mammalian lifespan. Adult SVZ and SGZ are capable of both neurogenesis and gliogenesis, especially after injury or certain stimulation. In adults, the primary neurogenic sites produce mainly neurons along with some astrocytes and oligodendroglia.

The subgranular zone

The main function of the SGZ is to provide new granule cells for the dentate gyrus [29]. In the human brain, approximately 700 new neurons are generated in the hippocampus per day [13]. These newly generated neurons may have functional significance as demonstrated in rodent studies in which hippocampus-dependent behaviors activated newly generated granule cells several times more often than older granule cells [19, 30, 31]. Spalding and co-workers (2013) identified three features of human hippocampal neurogenesis that are different from that of rodents — (1) in humans, a much larger proportion of hippocampal neurons are replaced in adulthood; (2) the age-dependent decline in the rate of hippocampal neurogenesis is less pronounced in humans; and (3) hippocampal neurogenesis results in a net increase in the neuronal number of the rodent dentate gyrus, whereas the continuous generation of new neurons in the human hippocampus provides a pool of neurons with specific functional properties [13]. These findings indicate that human hippocampal neurogenesis is important in maintaining hippocampal functions [29, 32].

Altered hippocampal neurogenesis may contribute to the severe pathology that occurs in this region in Alzheimer’s disease (AD) [3, 33, 34]. Based on evidence for a link between hippocampal adult neurogenesis and AD, animal studies have revealed that interventions beneficial for hippocampal neurogenesis (e.g.
anti-stress medications, physical activity, or administration of allopregnanolone) can improve cognition [35-39]. However, to be effective, these interventions must be introduced at an appropriate time and to an appropriate extent. This requires a better understanding of the variations in hippocampal neurogenesis that occur along with the progression of memory impairment in AD and other cognitive disorders.

The subventricular zone

In the adult rodent brain, neuronal progenitor cells generated in the SVZ travel through the rostral migration stream and settle down in the olfactory bulb, where they differentiate into local interneurons, granule cells, and periglomerular cells [40-44]. Adult neurogenesis in the rodent olfactory bulb is required for specific forms of olfactory behavior, and certain genetic manipulations result in conditional and selective enhancement of olfactory neurogenesis [45, 46]. In addition, gliogenesis has been found in the rodent olfactory bulb and the SVZ of multiple sclerosis patients [7, 47]. Olfactory neurogenesis is not the same in humans as in rodents. The difference may be partly due to the consequence of the varying importance of olfactory stimuli in ensuring the survival of the species or related to the different glomerular organization in the human and rodent olfactory systems [48].

Under specific circumstances, human olfactory neurogenesis can become noticeable, for example in depression and Parkinson’s disease (PD) [49, 50]. Regardless, compared to the substantial amount of new neurons produced in the rodent olfactory bulb, the level of neurogenesis in the healthy adult human olfactory bulb is low [14]. Nevertheless, the adult human SVZ preserves active neurogenesis [11, 51, 52]. If the SVZ-generated neural progenitor cells do not migrate to the olfactory bulb, the alternative destination of these cells may be the neighboring striatum as suggested by the pronounced striatal neurogenesis that has been detected in the human brain [15]. Interestingly, when olfactory bulb/striatum volume ratios were compared in non-primates, non-humans primates, and human, the greater the phylogenetic distance between animals and human the higher this ratio became [11]. This shift in the relative volumes is consistent with the markedly different reliance on these two brain structures. The pronounced neurogenesis in the human striatum may serve the structural refinement that is driven by cognition- and movement-related functional requirements [15].

The fate of NSCs is controlled by complex regulatory machinery, as witnessed by the findings that neurogenic activity of the SVZ can be influenced by GABAergic, dopaminergic, serotoninergic, cholinergic, and nitric oxide-releasing neurons [53-56]. For this reason, pharmacons affecting neurotransmitter levels (e.g. selective serotonin re-uptake inhibitors and reversible acetylcholinesterase inhibitors) may have therapeutic benefits in diseases where neurogenesis is impaired. On a similar note, there is hope that a better understanding of the anatomical features of striatal neurogenesis may identify factors that can facilitate rehabilitation in diseases that typically affect the striatum (e.g. stroke, Huntington’s disease (HD), and PD).

Parenchymal and periventricular cell genesis in adult brain

Most of the cell progenitors that are outside the primary neurogenic sites express a proteoglycan called nerve/glial antigen (NG2). NG2-positive cells have primary importance in adult gliogenesis with several key features [21]. Namely, they (1) are almost uniformly distributed in both grey and white matter, (2) have stellate morphology, (3) retain proliferative capacity in the adult brain, and (4) have an intimate association with neurons [57-60]. Like neurogenesis, altered gliogenesis is known to be involved in some neurological conditions, e.g. AD and demyelinating diseases [4, 7]. Despite recent advances in the field, the processes of gliogenesis in human brain still require elucidation; namely, how gliogenesis and neurogenesis are interrelated, whether gliogenesis can be exploited for the production of new neurons, what roles gliogenesis have in the progression of certain neurological diseases, and what regional differences in gliogenesis exist.

Parenchymal cell genesis

In addition to the primary neurogenic sites, the parenchyma is also capable of producing new cells [9, 59, 61-63]. In most CNS regions, parenchymal progenitors maintain a slow rate of constitutional gliogenesis, which is important for the renewal of oligodendrocytes and, to a smaller extent, astrocytes [61, 64, 65]. Substantial numbers of oligodendrocyte precursor cells are distributed widely in the adult CNS [66]. They are relatively quiescent but retain regenerative capacity to maintain white matter homeostasis [67]. In a mouse model with damaged white matter, residual oligodendrocyte precursor cells were found to respond to signals released by astrocytes, suggesting that they serve as a ‘back-up population’ for generating mature oligodendrocytes [68].

Adult astrogenesis has been reported in the mouse cortex and is mainly due to the local division of mature astrocytes [69]. Unlike neurons and oligodendrocytes, astrocytes remain capable of undergoing mitosis even in adulthood — at least in the mouse cortex and spinal cord [70, 71]. In fact, astrocytes have the hallmarks of stem cells because they are capable of perpetuating themselves throughout the entire lifespan of the brain and exhibit multipotency [72, 73]. Astrocytes do not proliferate in the healthy brain parenchyma, but some of them resume proliferation...
after brain injury [70, 74, 75]. Some astrocytes that re-enter the proliferative cycle acquire the potential to form self-renewing, multipotent neurospheres, which can subsequently produce functional neurons in the mouse cortex [70]. Factors that may trigger astrocyte destabilization/activation include sonic hedgehog (Shh), epidermal growth factor (EGF), and fibroblast growth factor (FGF) [77-80]. Notably, these growth factors are present in the parenchyma, and their production increases upon brain injury. Most reactive astrocytes, however, remain within their lineage and generate only astrocytes in vivo.

New neurons are also produced in the parenchyma, albeit not many [21]. In fact, in non-human mammals, parenchymal cell genesis has been identified as a potential mechanism for producing neuronal progenitors. The beneficial features of parenchymal progenitors are their abundance and widespread distribution [10, 81, 82]. Although newly produced cells demonstrate a propensity to differentiate, their functional integration may be restricted by the inherent features of the mature parenchyma [10, 81, 82]. The fate of the parenchymal progenitors depends on the environment of the specific brain regions in which they are generated [21] and consequently can be influenced by extrinsic factors. This creates an opportunity for intervention into the process of parenchymal neurogenesis and/or gliogenesis, e.g. by modifying the extrinsic environment in which the cells are located. Potentially, this could be used to counteract the specific pathological process in some CNS diseases.

Human fetal brain parenchymal cells initially express both glial and neuronal markers and are capable of differentiating into either neuronal or glial lineage [24]. However, more work is required to determine if new parenchymal cells can be generated in areas of the human CNS other than the primary neurogenic sites. Research so far suggests that new cortical neurons are not created, because cortical cells in stroke patients were found to be as old as the individual [17]. This suggests that parenchymal neurogenesis may not respond strongly to neuron loss in the human brain, but no further studies on cortical neurogenesis have been undertaken to confirm this.

**Periventricular cell genesis**

In the forebrain, uncommitted neural precursor cells initially reside in the luminal cell layer (ventricular zone) and later in the SVZ [83]. In addition to the uncommitted precursor cells, some ependymal cells are also able to act as NSCs in the adult brain [83, 84]. For instance, forebrain ventricular CD133-positive ependymal cells show NSCs characteristics in response to brain injury [85, 86]. Further, tanycytes in the adult hypothalamus and

![Fig. 1. Neurogenesis and gliogenesis in the adult brain. Potential neurogenic regions described in adult rodent (A1) and human (A2) brains. Solid pink lines indicate the rodent rostral migration stream and the known primary neurogenic regions in rodent and human brains. Pink dots in the rodent olfactory bulb and human striatum indicate the possible final destinations of SVZ-generated new neurons. Pink arrowheads mark some of the putative migration routes of the precursor cells before reaching their final destination (e.g. substantia nigra). Abbreviations: 3V, third ventricle; 4V, fourth ventricle; Aq, aqueduct; DG, dentate gyrus; Hip, hippocampus; LV, lateral ventricle; LVH, inferior horn of the lateral ventricle; OB, olfactory bulb; RMS, rostral migration stream; SN, substantia nigra. (B) Potential factors reported to modulate the balance between neurogenesis and gliogenesis in rodents and cell cultures. Negative signs mark inhibitory effects. Production of different cell types is region-dependent (as indicated in the lower part of panel B), and this preference may be altered in response to certain diseases or other conditions. For details see the main text.](image)
ependymal lining of the third ventricle function as multipotential progenitor cells [87, 88]. Finally, there is a consensus that the spinal cord central canal possesses ependymal cells with neural stem cell properties [89, 90].

Whether human adult ventricular ependymal cells have neurogenic potential or not is still unknown. More research is needed to assess the self-regenerative potential of brain regions that are not close to the SGZ and SVZ neurogenic regions but instead close to other parts of the ventricular system. One such region is the substantia nigra, which accommodates dopaminergic neurons and undergoes characteristic pathological changes in PD. Anatomically, the adult substantia nigra is situated in the proximity of the inferior horn of the lateral ventricle, the third ventricle, and the aqueduct; but it is distant from the SVZ (Fig. 1A). There is some evidence for neurogenesis in this region, such as a large number of polysialic acid-positive cells (indicative of immature neurons) are found in the substantia nigra pars reticulata of PD patients [91]. Further, neural progenitor cells could be isolated from the substantia nigra of PD patients [92]. However, the source of these NSCs is still unknown. Furthermore, allopregnanolone and platelet-derived growth factor (PDGF)-BB were reported to increase the number of dopaminergic neurons and convey a trophic effect on the surviving dopaminergic neurons [8, 93, 94]. It is unknown if the substantia nigra recruits newly produced neuronal and/or glial progenitor cells from the nearby periventricular zone rather than from the remote forebrain SVZ. If this could be determined, it would open up possibilities as to the methods that could be used to facilitate the survival of new neurons.

**INTERRELATION BETWEEN ADULT NEUROGENESIS AND GLIOGENESIS**

Studies using rodent models and cell cultures suggest that the interrelation between adult neurogenesis and gliogenesis can be exploited. Such observations, as described below, suggest that various modulatory processes may be utilized for disease prevention/treatment.

Proliferation and differentiation of NSCs are effectively stimulated by brain lesions [95]. Rodent experiments provide evidence that the stimulatory effect of hypoxia is mediated via the hypoxia-inducible factor (HIF)-1α pathway [96-99]. The balance between neurogenesis and gliogenesis is affected by numerous factors (Fig. 1B). Bone morphogenetic protein (BMP)-signaling, for example, has been found to oppose the function of oligodendrocyte transcription factor 2 (Olig2) by affecting its expression level [100]. In contrast, FGF and Shh are positive regulators of Olig2 [101]. Finally, infusion of EGF promotes oligodendrogenesis and reduces neurogenesis in the mouse SVZ [102].

In fact, astroglia from the mouse cerebral cortex may be directed toward neurogenesis by ‘direct reprogramming’; i.e., by forced expression of paired box 6 (Pax6) [103-106]. Astrocytes can also directly differentiate into neurons without reactivating progenitor hallmarks, such as cell division [103]. Further, single transcription factor SRY (sex determining region Y)-box 2 (Sox2) is able to convert astrocytes into proliferative neuroblasts in the adult mouse brain [60]. When supplied with brain-derived neurotrophic factor (BDNF) and noggin, or treated with valproic acid (VPA; a histone deacetylase inhibitor), these astrocyte-derived neuroblasts develop into neurons [60]. Finally, platelet-derived growth factor-α receptor (PDGFαR)-expressing and glial fibrillary acidic protein (GFAP)-positive neural stem cells isolated from the mouse SVZ can give rise to both neurons and oligodendrocytes [107] suggesting that PDGFαR signaling may regulate the balance between neurogenesis and oligodendrogenesis. Importantly, astrocytes have been generated from human pluripotent stem cells by exposing them to BMP, ciliary neurotrophic factor (CNTF), and neuregulin [76].

**SUMMARY**

Altered adult neurogenesis and gliogenesis appear to be associated with some of the neurological and neuropsychiatric diseases, indicating that modulation of the processes involved in adult neurogenesis and gliogenesis may provide a plausible strategy for treatment. However, still much of the specific information is missing, especially in the case of the human brain. It would be important to have more detailed information about (i) cell genesis in non-primary neurogenic sites, (ii) the migration routes of neural precursor cells, (iii) modulatory mechanisms that control the interplay between adult neurogenesis and gliogenesis, (iv) the pathogenic significance of altered neurogenesis and gliogenesis in brain diseases, and (v) effective ways to activate quiescent NSC without compromising the long-term potential of neurogenesis. Research into the relationship between neurogenesis and gliogenesis that is focused on these unknowns is likely to reveal valuable targets for interventions that may improve neurorestoration.

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