Neurogenesis in the Adult Mammalian Brain

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Abstract

It is currently accepted that two regions of the adult mammalian brain continue to generate new neurons throughout life. The subventricular zone (SVZ) of the lateral ventricles gives rise to new neurons that migrate to the olfactory bulb to become new interneurons, and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) generates new granule cells. Newborn neurons have distinct morphological and functional properties that contribute to certain brain functions which distinguishes them from the surrounding older neurons. Persistent neurogenesis in the adult brain occurs in many mammalian species, presenting certain species-specific differentiations. Differences in the rate of adult hippocampal neurogenesis are also observed along the hippocampal septo-temporal axis.

The present review aims a. to present the features of the multistep adult neurogenesis process in the SVZ and SGZ, b. to identify the unique characteristics of these two neurogenic regions of the adult mammalian brain, and c. to comparatively evaluate existing knowledge on neurogenesis similarities and differences among evolutionary different mammalian species, trying to relate brain structure and function with perpetual plasticity.

Adult neurogenesis is a dynamic and complex process that promotes brain's plasticity under normal and pathological conditions. The comparative study of adult neurogenesis in mammalian species with phylogenetic proximity to humans, strengthens our knowledge in the field and creates unique opportunities for future novel therapeutics.

Keywords: Adult neurogenesis, marker expression, comparative neurogenesis.

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Erişkin Memeli Beyninde Neurogenesis

Öz

Günümüzde, erişkin memeli beyninin iki bölgesinde, yaşam boyunca yeni nöronların üretilmeye devam ettiği kabul edilmektedir. Ventriculus lateralis'in zona subventricularis'i (SVZ) tarafından üretilen yeni nöronlar, bulbus olfactorius'a göç ederek yeni internöronların oluşumuna neden olur. Bunun dışında hippocampus'un gyrus dentatus'unun (DG) zona subgranularis'i (SGZ), yeni granüler hücreler üretir.

Yeni oluşan nöronlar, belirli beyin fonksiyonlarına katkıda bulunan ve onları çevreleyen daha eski nöronlardan ayıran, belirgin morfolojik ve fonksiyonel özelliklere sahiptir. Birçok memeli türünün erişkin beyninde, bazı türlere özgü farklılıklar göstermekle birlikte, kalıcı neurogenesis şekillenir. Erişkin hippokampal neurogenesis hızındaki farklılıklar, hippocampus'un axis septo-temporalis'inde de gözlenmektedir.

Bu derlemede; a. SVZ ve SGZ'da çok basamaklı erişkin neurogenesis sürecinin özelliklerini sunmak, b. erişkin memeli beyninin bu iki neurogenic bölgesinin benzersiz özelliklerini tanımlamak ve c. evrimsel olarak farklı memeli türleri arasındaki neurogenesis benzerlikleri ve farklılıkları hakkındaki mevcut bilgileri karşılaştırarak değerlendirmek, beyin yapısı ve işleyişini kalıcı plastisite ile ilişkilendirmeye çalışmak amaçlanmıştır.

Erişkin neurogenesis, normal ve patolojik koşullar altında beyin plastisitesini yükselten dinamik ve kompleks bir süreçtir. Filogenetik olarak insanlara yakınlığı olan memeli türlerinde yapılan karşılaştırmalı yetişkin neurogenesis çalışmaları, bu alanla ilgili bilgilerimizi güçlendirmekte ve gelecekte oluşturulabilecek yeni terapötikler için eşsiz fırsatlar yaratmaktadır.

Anahtar Sözcükler: Erişkin neurogenesis, marker ekspresyonu, karşılaştırmalı neurogenesis.

Introduction

According to an old standing dogma in Neurosciences, new neurons can only be produced by the developing brain, not the adult brain. This idea was first challenged by J. Altman and G. Das in the 1960s[1], when with the use of tritiated

thymidine they showed for the first time the presence of newborn granule cells in the hippocampal DG of the adult rat. Their findings were confirmed many years later by studies that used the thymidine analogue 5-bromo-2'-deoxyuridine (BrdU) in order to mark newborn neurons of the adult brain; establishing this way the persistent neurogenesis in certain regions of the adult mammalian brain. In recent years, combined use of BrdU and other novel applications (e.g. retroviral labelling, transgenic animals) brought to light the mechanism of the new neurons production in the neurogenic regions of the adult brain, and the newborn neurons's contribution in the brain's plasticity and function. Moreover, it became clear that although adult neurogenesis is highly preserved across phylogenesis, interesting variations exist among the different mammalian species, including humans.

Text

Neurogenic regions of the adult mammalian brain

Neural stem cells (NSCs) can be found in many areas of the adult brain (hypothalamus, substantia nigra, corpus callosum, optic nerve). However, when these cells are isolated and cultured *in vitro* they reproduce only the initial stages of neuronal differentiation showing that extrinsic cues (i.e. local microenvironment) stimulate NSCs's intrinsic potential for stemness and provide the basis for adult neurogenesis[2]. It is nowadays widely accepted that the subventricular zone (SVZ) of the lateral ventricles (LV) and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) preserve a microenvironment which is permissive to the ongoing cell activity and neuronal differentiation of the residing NSCs, establishing them as the two neurogenic regions of the adult mammalian brain.

The SVZ and the SGZ share certain characteristics: 1. they contain multiple astrocytes, macrophages and microglia, 2. they present a rich vasculature and 3. they are in close proximity with certain neurogenesis-promoting layers (i.e. the ependymal cell layer for the SVZ and the bottom layer of the granule cell layer for the SGZ)[3,4]. Local astrocytes secrete trophic factors (FGF2, VEGF, CNTF-a,

IGFBPs) and exert paracrine action through Notch, Shh (Sonic hedgehog) and Wnts (Wingless) signaling, promoting the proliferating ability of the NSCs and regulating the dendritic morphology and the survival of the newborn neurons[5-7]. More recent data show that local astrocytes surround the newborn neurons and form functional perisynaptic processes on them, strengthening the neuronal-astrocytic interaction and promoting the functional integration of new neurons[8]. Other cell populations that reside in the neurogenic niche are the microglial and macrophage cells, but although they exist in small numbers even in the healthy brain, they seem to regulate the ongoing neurogenesis process only under pathological conditions[4].

The effect of the endothelial cells on the proliferative ability of the NSCs has been revealed in the healthy brain. An induction in the proliferation of endothelial cells leads to a parallel induction in the proliferation of NSCs both in the SVZ and SGZ[9,10], possibly through VEGF action, since VEGF receptors were found to be expressed by immature DCX-expressing newborn neurons[4]. Moreover, dividing NSCs and their progenies form dense clusters that were found to be in close proximity with the local vasculature, confirming the angiogenic regulation of the adult neurogenesis process[11]. Apart from local cell populations and vasculature in the neurogenic SVZ, the ependymal cell layer seems to regulate the ongoing cell genesis process. Ependymal cells through their noggin and pigment epithelium-derived factor expression promote the self-renewal and differentiation of the local NSCs, whereas NSCs proliferation is regulated by the local dopaminergic fibers[3].

Neurogenesis in the Adult SVZ

The NSCs of the adult SVZ follow a complex proliferation and differentiation process and generate new neurons that migrate to the olfactory bulb. During their maturation process, newborn neurons go through sequential developmental stages, each one of which is characterized by expression of certain cytoplasmic markers, distinct morphology and certain localization pattern, allowing for the complete investigation of the adult neurogenesis process. The NSCs of the adult SVZ display an astrocytic phenotype, thus being immunoreactive against the glial

fibrillary acidic protein (GFAP), vimentin, and exhibit radial glia properties, since they derive from the radial glia NSCs of the embryonic and early postnatal brain[12,13]. These cells are the type B cells of the adult SVZ which are further divided to type B1 and type B2 cells, which are incapable and capable for proliferation, respectively[14]. Type B cells are localized under the ependyma, are able for self-renewal and generate both neurons and glia (astrocytes and oligodendrocytes) *in vivo*[12]. They give rise to the transiently amplifying type C cells, which are the most actively dividing cells of the SVZ, immunoreactive against nestin[15].

Type C cells are found in clusters all along the LV wall and in close proximity with the chains formed by the type A newborn neurons. Newborn type A neuroblasts, that express doublecortin (DCX), polysialylated neural adhesion cell molecule (PSA-NCAM) and beta-tubulin (Tuj-1), are initially arranged in chains parallel to the LV wall and then migrate anteriorly towards the olfactory bulb, forming the rostral migratory stream[15]. Chains of type A cells are ensheathed by the astrocytic type B cells[14]. When they reach the olfactory bulb, they differentiate into new granule neurons or become periglomerular neurons[15].

When newborn neurons reach the olfactory bulb they turn radially towards the granule cell layer and the periglomerular cell layer and develop their GABA receptors, that define their later development[16]. Then, newborn neurons develop their functional glutamate receptors and form their dendritic spines, promoting their survival, maturation and functional integration into the existing neuronal circuit[16]. Even though the exact functional role of newborn olfactory neurons is still not elucidated, they were shown to play a critical role in olfactory learning, short-term odor memory and fine olfactory odor discrimination[3,17].

Gliogenesis was also found to occur in the adult SVZ, both in the healthy and in the injured brain. Type B cells of the adult SVZ were shown to generate small numbers of glial-restricted progenitor cells called the oligodendrocyte progenitor cells, positive to the chondroitin sulphate proteoglycan NG2, and mature myelinating oligodendrocytes in the normal brain[18]. Increased

oligodendrogenesis was noted in the SVZ of rodents that display demyelinating disorders and newborn oligodendrocytes, expressing Sox10, Sox9 and Olig2, were shown to be recruited into the myelin lesion sites in order to contribute to remyelination[19].

Neurogenesis in the Adult SGZ

As already discussed for the adult SVZ, NSCs residing in the adult SGZ proliferate and differentiate into new granule cells, expressing different cytoplasmic markers during their sequential developmental and maturation phases (figure 1). Newborn granule cells migrate only a short distance into the deeper layers of the granular cell layer[20]. The NSCs of the adult SGZ present many similarities with the NSCs of the adult SVZ, thus expressing astrocytic markers (GFAP) and displaying radial glia morphological properties[21]. Radial glia-like NSCs of the adult SGZ have a triangular cell body that is located in the SGZ and a long apical process that crosses the granular cell layer and ends to the outer layers of the hippocampal molecular layer[22]. Apart from GFAP, radial-glia like NSCs are immunoreactive against the brain lipid binding protein (BLBP) and the transcription factors paired box 6 (Pax6) and Sox2[23,24].

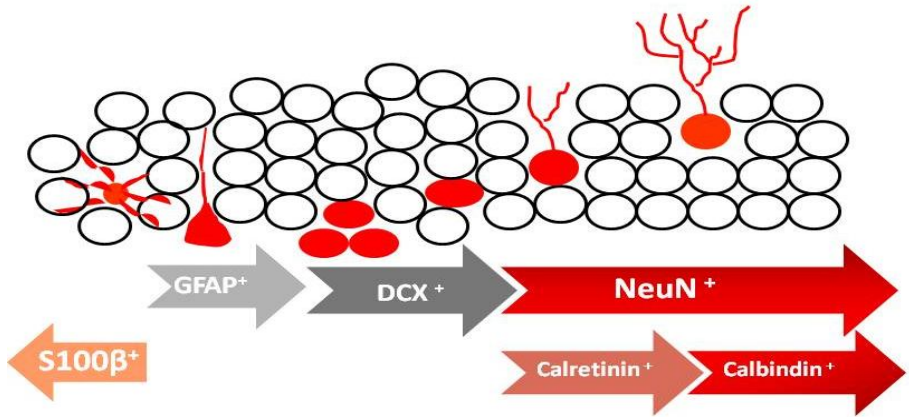
The NSCs of the adult SGZ go through symmetric and asymmetric cell divisions and give rise to neural precursor cells (NPCs) that are also located in the SGZ and are found in clusters[22]. The NPCs show an increased proliferating ability and thus their population is comprised of undifferentiated cells that continue to express markers of the radial glia lineage (Sox2, BLBP) to more differentiated cells that express markers and transcription factors of the neuronal lineage (DCX, PSA-NCAM, neuronal differentiation factor D/ NeuroD, Musashi-1, T-box brain gene 2)[25,26]. However, all cells of the heterogeneous NPCs population were found to be positive to nestin expression[23]. At their final developmental stages the newborn NPCs have fully functional GABA receptors and receive excitatory GABA signaling, which is essential for their synaptic integration and final maturation[27,28].

The NPCs give rise to the immature newborn granule cells that migrate into the granular cell layer, having a strong process that enters the granular cell layer and small processes that are distributed in the hilus[25]. Immature neurons are still immunoreactive against DCX, PSA-NCAM and NeuroD. As they head for their final maturation they progressively express neuronal nuclei (NeuN) and the calcium binding protein calretinin[23,29]. Although calretinin is pivotal for the further development of immature neurons and is massively expressed by newborn neurons of the mouse DG[30], new neurons of the rat DG are not immunoreactive against calretinin[31,32].

During the third meta-mitotic week, the calcium binding protein calbindin succeeds the expression of calretinin in the newborn mature granule cells, which are still immunoreactive against NeuN and Prox-1[23,33]. The new adult born mature granule cells are fully integrated in the hippocampal circuits forming inhibitory GABAergic and excitatory glutamatergic synapses with the local interneurons, granule cells and pyramidal neurons[28]. They promote the spatial memory formation and acquisition process in the hippocampus by contributing in the pattern separation process that takes place in the DG, separating the incoming from the entorhinal cortex new spatial information[34,35].

In the adult SGZ gliogenesis occurs in parallel with neurogenesis via asymmetric cell division or through transition astroglia[36]. Newborn astrocytes migrate radially through the granular cell layer and locate mainly in the border between the granular cell layer and the molecular layer, or remain in the SGZ[37]. They are immunoreactive against GFAP and when they are fully matured they also express the calcium binding protein S100β[37]. Newborn astrocytes secret trophic factors, like the fibroblast growth factor 2 (FGF2), VEGF and show paracrine action, further modulating the parallel neurogenesis process[25,38].

Figure 1: Graphical representation of the sequential developmental stages of newborn granule cells and astrocytes in the adult DG, presenting each stage's distinct morphology and marker expression.



Although DG was thought to be a homogeneous structure all along its septo-temporal axis, many studies prove the structural and functional dissociation of the septal and temporal DG part (39-41). Observed variations lead to inconsistencies in the ongoing neurogenesis process and although the septal and temporal DG part possess an equivalent neurogenic ability, recent studies revealed the comparatively higher division rates of the radial glia-like NSC's in the septal part and the enhanced maturation and functional integration rates of their progenies, whereas newborn granule neurons of the temporal part present higher survival rates[31,42,43].

Differences in SVZ and SGZ Neurogenesis among Mammalian Species

Adult neurogenesis is widely conserved throughout phylogeny and the ability of the SVZ and the SGZ to generate new neurons in the adult brain has been shown in many mammals, including humans (figure 2). However, even if SVZ neurogenesis persists through adulthood in almost all up to date studied mammalian species, SGZ neurogenesis seems to be absent in bats and shrews of the genus *Sorex*[44,45]. Although proliferation, migration, differentiation and maturation of adult-born neurons in the SVZ and SGZ is regulated similarly

across mammalian species, certain species-specific differentiations in the extent and rate of neurogenesis arise, related mainly to interspecies peculiarities in the extent of the life span, the anatomical features of the brain and the functional development of olfaction and memory.

Neurogenesis in the adult rodent brain was the first to be explored[1]. Even if neurogenesis in the adult mouse and rat brain presents quite many similarities, it has been shown that adult-born granule cells of the rat hippocampus obtain earlier their morphological and functional maturity, escape more efficiently the apoptotic cell death and are more involved in behavior[46]. The influence of genetic factors on adult hippocampal neurogenesis is so strong that leads to variations in the proliferation rate of NSCs, the migrating and differentiating ability of neuroblasts and the survival of newborn neurons even among different mouse strains[47,48].

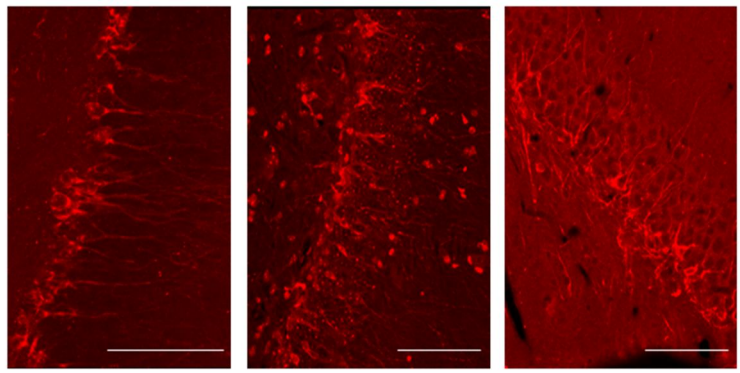
Up to date, many studies have revealed significant differences in the adult neurogenesis process between rodents and evolutionary higher mammals. These differentiations may be attributed to the shorter life span, rapid development and high reproductive rates of rodents. Variations in DG neurogenesis in particular, are considered to occur due to the different location, relative size and orientation of the hippocampus in the rodent brain as compared to the hippocampus of the gyrencephalic brain.

Gyrencephalic animals represent an excellent model for the study of adult neurogenesis promoting the translational research in humans. As expected, dynamics of proliferation, migration and maturation of adult-born neurons differ between gyrencephalic animals and rodents. The maturation time of newborn neurons in the sheep olfactory bulb and hippocampal DG was found to be much longer than that of rodents. In the sheep olfactory bulb and DG, no mature newborn neurons are observed before three months and four months after BrdU injection respectively, whereas in rodents neuronal maturation is achieved within one month after BrdU injection both in the olfactory bulb and the DG[49]. The rate and extent of the ongoing neurogenesis in the adult sheep brain seems to be

highly dependent on the animal's neuroendocrine activity during the rotating reproductive stages. The exposure of female sheep to novel male pheromones markedly doubled the number of newborn $BrdU^+$ cells in the hippocampus, showing the stimulating effect of the activated reproductive axis on hippocampal neurogenesis[50]. On the contrary, the number of $BrdU^+$ newborn cells in the SVZ and the SGZ was down-regulated by parturition, possibly enabling the maternal olfactory perceptual and memory over the first post-partum days[51].

Canines are considered valuable models for the study of many human neurodegenerative diseases, since the canine brain presents many similarities in anatomical organization and physiology with the human brain. The aging canine brain in particular, exhibits many pathophysiological changes of normal brain aging that are also developed in humans, like plaque formation, reduced cognitive function and decreased brain volume[52,53]. So, it is not surprising that adult neurogenesis is mainly studied in the aged canine brain, trying to unravel the effect of aging-dependent abnormalities on the ongoing neurogenesis. The number of newborn $BrdU^+$ cells in the canine SGZ presents a significant age-related decrease and this finding was directly correlated with a decline in the cognitive function observed in older canines[54]. The number of neuroblasts in the neurogenic niches was comparatively evaluated between young (2-3 years old) and old canines (15-18 years old), and DCX expression was found to be severely decreased with increasing age, resulting in a 96% drop in the aged canines[52,55]. A significant correlation between age and expression levels of the proliferation marker Ki67 in the SGZ was also revealed, reflecting the significant decrease in the proliferation activity of the neural precursor cells due to aging[52].

Figure 2: DCX+ newborn neurons in the infrapyramidal blade of the DG in the rat (A), sheep (B) and canine hippocampus (C). Note the characteristic morphology of the DCX+ cells which appears to be similar among mammalian species. Scale bar = 50 μm.



Double labeling for BrdU and cell-specific markers evidenced the ongoing generation of new neurons, astrocytes and oligodendrocytes in the hippocampus of the adult macaque brain[56,57]. The number of BrdU+ cells in the primate hippocampal DG showed a continuous increase over a six week period after BrdU injection[58], in contrast to the rodent dentate gyrus where the total number of newborn neurons increases only during the first week after BrdU injection and decreases significantly thereafter[59,60]. Co-labeling of newborn BrdU+ cells with mature neuronal markers in parallel with the study of their structural maturation revealed that newborn hippocampal neurons in non-human primates present a prolonged maturation time that may exceed six months, resembling that of sheep, in contrast to the rodent hippocampus where the whole newborn neuronal population reaches maturation at 30 days post BrdU injection[29,59]. Existing data also show the reduced rate of neurogenesis in the adult primate brain, estimating that in the macaque hippocampus, each day, a new neuron is generated for every 24,000 existing neurons, whereas in the mouse hippocampus the ratio is one new neuron per 2,000 existing neurons[47].

Features of adult neurogenesis in the primate brain (extended maturation time and reduced genesis rate) are also confirmed in the adult human brain. It was in

1998 when Eriksson and colleagues established the presence of adult hippocampal neurogenesis in humans, demonstrating for the first time the occurrence of $BrdU^+$ cells in the postmortem human hippocampus, and showing that these neurons (co-expressing NeuN, caldindin and neuron specific enolase (NSE)) are generated from dividing progenitor cells in the hippocampal DG[61]. Later studies isolated neural progenitor cells from the human DG and found that they were also capable for *in vitro* proliferation and maturation, as it has been already shown for precursor cells isolated from the adult human SVZ[62,63], and the ability of these cells for self-renewal and multipotency has been proven through neurosphere assays, both in the SVZ and the SGZ[64]. Birth dating of human brain neuronal cells through quantification of their levels of ^{14}C, proved that almost 700 new neurons are added in each hippocampus per day[65]. Interestingly, the same investigators revealed that in contrast to almost all mammals, adult neurogenesis is almost absent in the adult human olfactory bulb, mainly because olfaction in humans is not so essential as it is in other mammals[66]. Neuroblasts of the human SVZ were shown to migrate to the neighboring striatum to form new interneurons, contributing with the local astrocytes to the neuronal renewal of the striatum[67].

Conclusion and Suggestions

Up to date, the mechanism of new neurons genesis in the adult mammalian brain is well characterized, but future studies are needed in order to elucidate why neurogenesis is restricted to certain brain areas and the exact physiological function of new neurons that are added daily in the adult brain. Understanding of the intrinsic and extrinsic mechanisms that regulate adult neurogenesis may offer great new insight in the brain's plasticity under normal and pathological conditions and may promote novel therapeutic approaches in devastating neural disorders.

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