Neural Stem Cell

Subjects: Biochemistry & Molecular Biology | Clinical Neurology

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Stem cells have extensive proliferative potential and the ability to differentiate into one or more mature cell types. The mechanisms by which stem cells accomplish self-renewal provide fundamental insight into the origin and design of multicellular organisms. These pathways allow the repair of damage and extend organismal life beyond that of component cells, and they probably preceded the evolution of complex metazoans.

muscarinic acetylcholine receptor (mAChR) nicotinic acetylcholine receptor (nAChR) neural stem cell (NSC) hair follicle stem cell (HFSC) melanocyte stem cell (MeSC) intestinal stem cell (ISC) homeostasis nich

1. Introduction

The appearance of the nervous system is considered to be an evolutionally epochal event that fundamentally changed how control is achieved within a multicellular body. Recent progress in genomics, molecular phylogenetics, developmental biology, and the study of simple nervous systems in living animals such as Cnidaria has provided a wealth of new empirical information about the earliest stages in neuronal evolution. Ancestral Cnidarians diverged over 500 million years ago in animal evolution [1]. Cnidaria such as *Hydra*, which is a descendant of ancestral Cnidarians, are composed of multiple cell types that represent the fundamental architecture of multicellular organisms. *Hydra* also have multipotent interstitial stem cells, which differentiate into nerve cells [2], nematocytes [2], gland cells [3], and germ cells [4]. The nervous system of *Hydra* is simple and is composed of a nerve net that extends throughout the animal. The cnidarian nervous system is mainly peptidergic [5]. It has been suggested that classical molecules such as acetylcholine (ACh) also contribute to the *Hydra* nervous system from the results of pharmacological experiments [6]. The membrane-bound ACh receptor and acetylcholinesterase have been demonstrated and confirmed by genome analysis [7][8]. Although ACh and other ACh receptor agonists function in neuronal and/or neuromuscular communication to regulate muscle contractions in *Hydra*, ACh itself has not been detected.

ACh is the first substance proven to be a neurotransmitter [9]. ACh is the major parasympathetic mediator and is synthesized by the catalytic conversion of acetyl-CoA and choline to CoA and ACh by choline acetyltransferase (ChAT) (Figure 1) [10][11]. In cholinergic neurons, ACh is transported into synaptic vesicles via the vesicular ACh transporter (VAChT) and stored there until released by exocytosis (Figure 1). VAChT was first cloned and characterized in *Caenorhabditis elegans* [12]. After the release of ACh into the synaptic cleft, the neurotransmitter evokes membrane action potentials by binding to ACh receptors (Figure 1). Then, ACh is rapidly and specifically

degraded by acetylcholinesterase (AChE) and butyrylcholinesterase, which is a second, non-specific cholinesterase in mammals that also produces choline and acetic acid (Figure 1) [13][14]. By-products of choline are taken up into the presynaptic side of the synapse via the high-affinity choline transporter and reused for ACh synthesis (Figure 1) [15]. The organic cation, choline, is a substrate for carriers of organic cation transporters (OCTs). To date, three different OCTs (OCT1–3) that transport choline from the extracellular space into nerve cells have been identified [16]. ACh is stored at and released from VAChT in neurons [17]. Of interest, VAChT is expressed in a cell-type specific manner in non-neuronal cells [18]. The cells that do not express VAChT have no ability to store ACh but directly release ACh via OCTs [19][20]. Thus, OCTs are two-in-one choline and ACh transporters. These ACh synthetic pathways described above constitute the cholinergic system.

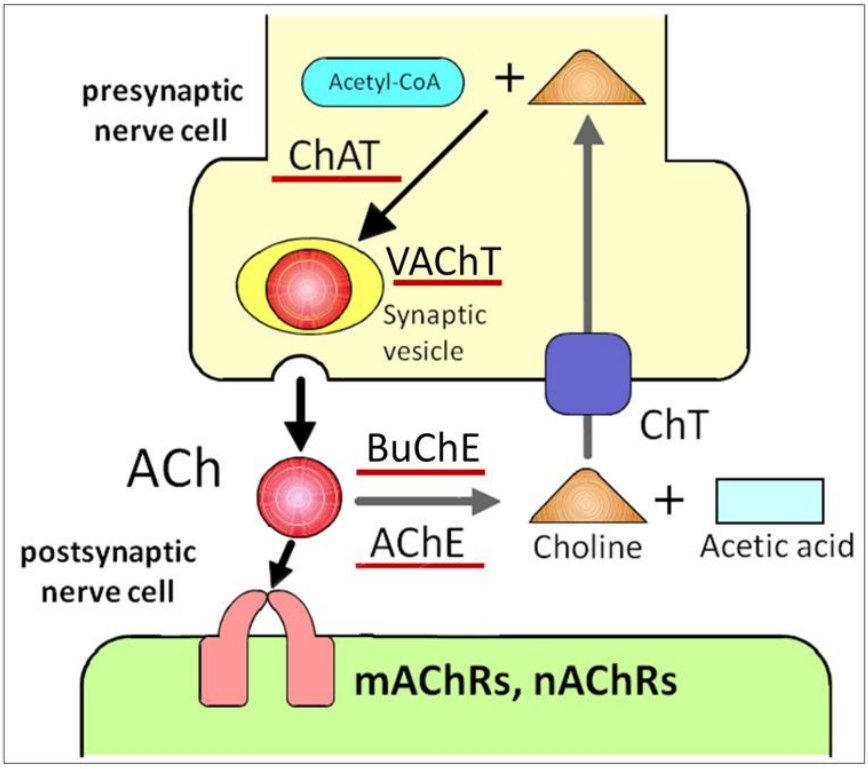

Figure 1. ACh release and receptor activation impacts neuronal activity. ACh is directly released into the synaptic cleft, followed by binding to nAChRs and mAChRs on the postsynaptic cell. Upon release, ACh is quickly degraded by extracellular AChE. ACh: acetylcholine, ChAT: choline acetyltransferase, VAChT: vesicular ACh transporter, mAChRs: muscarinic ACh receptors, nAChRs: nicotinic ACh receptors, AChE: acetylcholinesterase, BuChE: butyrylcholinesterase, ChT: choline transporter.

Schofield [21] originally hypothesized the existence of a microenvironment that is required for the maintenance of stem cells using hematopoietic stem cells and called such a region a “niche”. A niche is considered to be a subset of tissue cells and extracellular substrates that can indefinitely maintain stem cells and control their self-renewal and progenitor cell production in vivo (Figure 2). Specialized internal mechanisms and external signals confer the capacity of growth and differentiation to stem cells such as early embryonic cells in niches. Experimental evidence has revealed that ACh is widely distributed in biological systems beyond the nervous system. The widespread distribution suggests that ACh may be involved in regulation of stem cell functions such as proliferation,

differentiation, and the establishment of cell–cell interactions [22]. Thus, the study of cholinergic mechanisms focusing on the regulation of proliferation, differentiation, and maintenance of stem cells is of great interest. Our previous pharmacological studies revealed that ACh is synthesized in intestinal epithelial cells and plays a role in cell division and the differentiation of Leucine-rich repeat-containing G-protein-coupled receptor 5-positive ($Lgr5^+$) intestinal stem cells (ISCs) in the small intestine by binding to muscarinic ACh receptors (mAChRs) in crypt-villus organoids [23]. Furthermore, mAChRs and nicotinic ACh receptors (nAChRs) are involved in the proliferation of mouse embryonic and induced pluripotent stem cells [24][25][26]. This evidence leads us to propose the presence of a cholinergic niche that affects stem cell behavior.

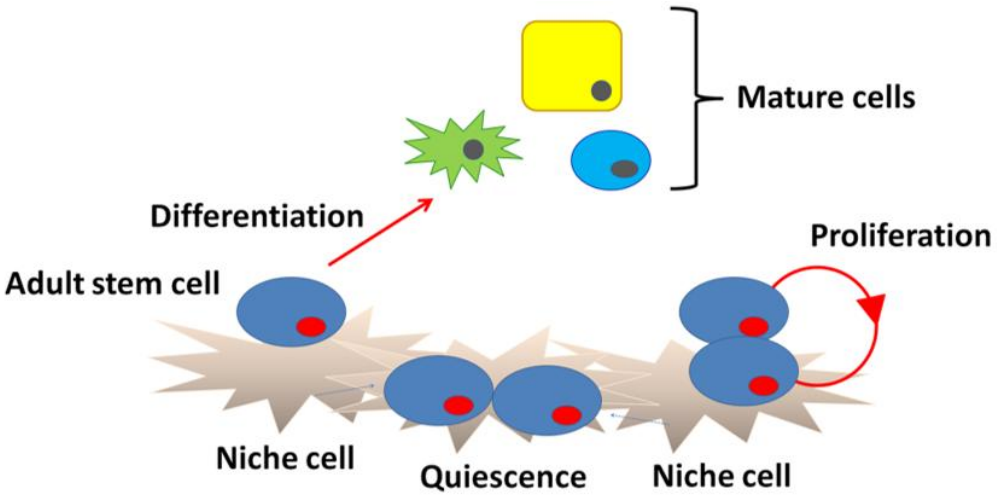

Figure 2. Niche structure. Niche cells under the basement membrane signal to stem cells to block differentiation and regulate division. Upon commitment, the stem cells differentiate into mature cells.

2. Neural Stem Cells (NSCs) in the Adult Mammalian Brain

Adult mammalian neural stem cells (NSCs) contribute to brain plasticity via the generation of new neurons throughout life [27]. Adult NSCs also have fundamental properties of self-renewal, relative quiescence, differentiation capacity, and residence within a specific environmental niche similar to other adult somatic stem cells (Figure 3) [28]. New neurons are derived from NSCs that reside in two major neurogenic niches, the subventricular zone (SVZ) in the lateral ventricles and subgranular zone (SGZ) in the dentate gyrus of the hippocampus [28][29]. In the adult SVZ niche, NSCs give rise to neurons and oligodendrocytes [28]. On the other hand, neurons and astrocytes, but not oligodendrocytes, are generated from NSCs in the adult SGZ [30]. In this section, I review cholinergic signaling involved in postnatal/adult neurogenesis and how patterns of neuronal activity differentially and/or synergistically modulate downstream signaling in NSCs.

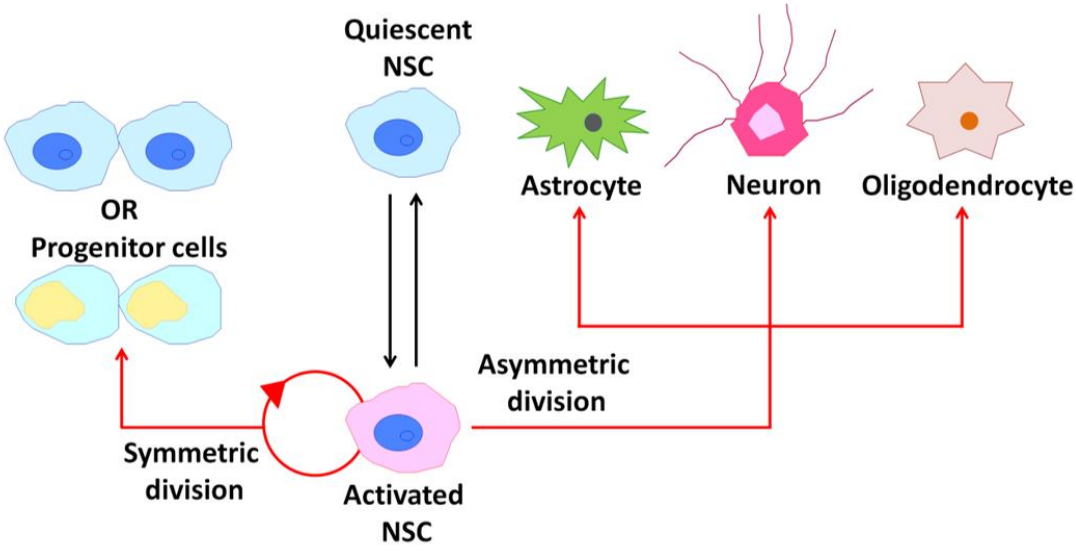

Figure 3. Behavior of neural stem cells (NSCs) within the adult mammalian brain. A schematic diagram illustrating the potential behavior of an NSC over its life cycle.

2.1. Cholinergic Activation of NSCs in the SVZ

Neurogenesis in the SVZ of the olfactory bulb (OB) continues throughout adulthood [31][32]. NSCs in the SVZ generate neuroblasts, which migrate tangentially through the rostral migratory stream toward the OB, and the neuroblasts finally differentiate into interneurons [33]. Within the dentate gyrus and OB, the interneurons abundantly express mAChRs and nAChRs [34], suggesting that the cholinergic system plays a role in regulating neurogenesis.

Accordingly, an in vivo nicotinic exposure experiment was carried out in the SVZ in adult rats, but no effect on proliferation was seen [35][36], suggesting that nAChRs may not be involved in adult OB neurogenesis. However, Mechawar and coworkers [37] used knockout mice to answer the question of whether nAChRs are involved in events downstream of NSC proliferation in the SVZ. They undertook a study of OB neurogenesis using $\beta2^{-/-}$ mice that were subjected or not subjected to chronic nicotine exposure and found that β2-containing nAChRs are specifically involved in the survival of newborn granule cells in the OB local circuits. Unexpectedly, the behavior of $\beta2^{-/-}$ mice indicated a less robust short-term olfactory memory than their wild-type (WT) littermates. Furthermore, a pharmacological study using donepezil, a potent AChE inhibitor, revealed that cholinergic stimulation promotes the survival of newborn neurons in the adult OB [38]. Two interesting studies suggested that adult NSCs in the SVZ are regionally specified at an early embryonic stage and then remain largely quiescent until reactivation in the postnatal period [39][40]. The key molecule for postnatal reactivation of SVZ NSCs may be ACh via activation of nAChRs.

2.2. Cholinergic Activation of NSCs in the SGZ

Adult hippocampal neurogenesis is tightly controlled by NSCs located in the SGZ of the mammalian dentate gyrus that proliferate, differentiate, are maintained, and integrate into the local circuitry throughout life [41][42][43][44][45]. The cholinergic system is involved in the regulation of adult hippocampal neurogenesis. The dentate gyrus receives input from the basal forebrain through GABAergic and cholinergic projection neurons [46][47]. Injection of fibroblasts

secreting ACh into the hippocampus reverses cognitive decline by increasing the proliferation of NSCs [48][49][50]. Furthermore, the administration of an AChE inhibitor increases NSC proliferation and promotes the survival of immature neurons through the α7 nAChR subtype [49][51][52][53].

In the SGZ, pharmacological activation of α7-subunit-containing nAChRs increases cellular proliferation [54]. Homomeric α7 nAChRs contribute to cognition, attention, learning, and memory through fast signal transduction [55][56]. α7 nAChRs have been implicated in diseases including epilepsy, autism, schizophrenia, and Alzheimer's disease [57][58]. As these disorders have altered adult neurogenesis in the SGZ of the dentate gyrus, α7 nAChRs may control the normal maturation and integration of immature neurons and promote their survival [59][60][61][62]. Furthermore, Otto and Yakel found that blocking or removing α7 nAChRs increases neurogenesis overall but decreases NSC pools and special discrimination in adult males only, demonstrating the sexually dimorphic regulation of adult neurogenesis [63]. It is difficult to discern the impact of α7 nAChR activation on adult neurogenesis. The different and contradictory actions of this receptor may be due to the timing and location of its activation as well as a sexually dimorphic fashion [63][64]. Other α7 subunit-containing nAChRs, including the α7β2 subtype, are expressed in a diverse array of cells in the hippocampus, and their loss contributes to multiple neuropsychiatric and neurodegenerative disorders [65][66][67][68][69]. Thus, the regulation of adult neurogenesis via α7 subunit-containing nAChRs may provide a potential therapeutic strategy for treating neurodegenerative and neurological diseases. In the SGZ, immunohistochemical staining and functional analyses have revealed that type 1 and 4 mAChRs (M1 and M4) are expressed in immature hippocampal neurons [38][70]. Additionally, bromodeoxyuridine (BrdU) labeling analysis has shown that proliferating SGZ cells expressing M1 and M4 are also labeled with BrdU, suggesting the modification of NSC/progenitor cell populations [49].

mAChRs, which are metabotropic, seven-transmembrane proteins coupled to G proteins, activate various intracellular signaling pathways to control cellular function, including that of adult stem cells [23][70][71]. On the other hand, nAChRs are pentameric, ionotropic channels that mediate fast cholinergic transmission in the peripheral and central nervous systems [72]. Furthermore, the nAChR subtype, α2β4, is also involved in adult ISC function [73][74]. mAChR and nAChR signaling probably cooperates to fine-tune effects on cells including adult stem cells.

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