Cholinergic circuit control of postnatal neurogenesis

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ABSTRACT
New neuron addition via continued neurogenesis in the postnatal/adult mammalian brain presents a distinct form of nervous system plasticity. During embryonic development, precise temporal and spatial patterns of neurogenesis are necessary to create the nervous system architecture. Similar between embryonic and postnatal stages, neurogenic proliferation is regulated by neural stem cell (NSC)-intrinsic mechanisms layered upon cues from their local microenvironmental niche. Following developmental assembly, it remains relatively unclear what may be the key driving forces that sustain continued production of neurons in the postnatal/adult brain. Recent experimental evidence suggests that patterned activity from specific neural circuits can also directly govern postnatal/adult neurogenesis. Here, we review experimental findings that revealed cholinergic modulation, and how patterns of neuronal activity and acetylcholine release may differentially or synergistically activate downstream signaling in NSCs. Higher-order excitatory and inhibitory inputs regulating cholinergic neuron firing, and their implications in neurogenesis control are also considered.

KEYWORDS
acetylcholine; ACh; adult neurogenesis; ChAT neuron; cholinergic circuit; neural stem cells; neurogenic niche; SVZ; SGZ; SEZ

Introduction
Resident neural stem cells (NSCs) in the brain present exciting possibilities for tissue regeneration and remodeling. During embryonic development, neurogenesis proceeds like clockwork, generating a full range of neurons in correct spatial and temporal sequences, enabling proper assembly of functional neural circuits. In the postnatal and adult mammalian brain, it is now well-accepted that NSCs are retained in discrete anatomical regions including the hippocampus and the walls of the lateral ventricles. Their continuous production of newborn neurons in the rodent lateral ventricular (LV) subventricular/subependymal zone (SVZ/SEZ) niche and in the hippocampal dentate gyrus subgranular zone (SGZ) (as well as potentially in the human striatum) offers endogenous sources for tissue regeneration and neural circuit plasticity. Maintaining a tissue stem cell population requires extra energy and resources, and when they acquire oncogenic mutations these proliferative cells can become a source for tumor formation, contributing harmful sequelae to the host tissue. While the need for neurogenesis during development to build the nervous system is rather clear, it remains relatively unclear what biological processes may be driving and sustaining new neuron production in specific regions in the postnatal/adult mammalian brain.

Postnatal neurogenesis in rodents provides a tractable experimental model to tackle molecular/cellular-level mechanisms regulating addition of new interneurons into established neural circuits. In the SGZ, astrocyte-like type 1 NSCs give rise to transient type 2 proliferative progenitors, which then produce DCX+ cells that mature into local dentate granule neurons. Ongoing SGZ neurogenesis in rodents contributes importantly to memory processing and neurological disease modeling, as well as having significant parallels in the human brain. LV neurogenesis is mediated by CSF-contacting GFAP+ glia functioning as NSCs, producing Mash1+...
transiently amplifying progenitors which in turn differentiate into DCX+ neuroblasts that migrate to and become interneurons in the olfactory bulbs.20,21 Generation of new neurons and glia from the LV niche contributes to experience-dependent plasticity in the postnatal brain,22,23 tissue remodeling after injury,24,25 and plays a critical role in olfactory-based rodent social behaviors.26-28 In the postnatal human brain, while some groups have reported potential olfactory bulb neurogenesis into adulthood,29,30 there is strong evidence that LV neurogenesis generates migrating interneurons for up to 2 y after birth.31 It has become increasingly clear that neuro-developmental defects can be significant contributors to various brain pathologies later in life. Thus the analogous process in rodents can help us understand experimentally how NSC production of new neurons may be influenced by sensory/neural-circuit inputs during early postnatal human brain development.

It has been well-demonstrated that self-renewal of postnatal NSCs and their differentiation into neurons are controlled by conserved, cell-intrinsic molecular pathways.32-34 Extracellular factors and cell-cell interactions within the neurogenic microenvironmental niche also play critical roles regulating neurogenesis.35-38 Likewise, neurotransmitters such as GABA, glutamate, dopamine, and serotonin also contribute important modulatory roles during postnatal neurogenesis39-44: it has been generally assumed that neurotransmitters function through bulk release/non-synaptic mechanisms in the postnatal/adult neurogenic niches. In this fashion they are cytokine or growth factor-like, controlling NSC properties as neurotransmitters are leaked from nearby neuronal synaptic contacts following activity-dependent release. GABA spill-over from local parvalbumin+ interneuron regulating SGZ NSC proliferation/differentiation is an excellent example.45-47

Postnatal/adult NSCs often proliferate and differentiate in close proximity to neurons firing action potentials: the LV niche is anatomically adjacent to the striatum; and the SGZ niche is an integral part of the hippocampus. Thus neuronal activity patterns are attractive modulators for NSC proliferation and differentiation. Conceptually, if NSC fate choices can be directly linked to specific instructions from neuronal activity patterns, this will have important impact on circuit-level plasticity through new neuron production, as well as in nervous system diseases. This review will focus on cholinergic circuit control of postnatal neurogenesis: due to the complexity of cholinergic receptor physiology/function, the exact roles for acetylcholine (ACh) in this context have been difficult to define. Classical approaches including lesioning of cholinergic fibers, as well as pharmacological modulation of nicotinic and muscarinic receptors, first revealed the importance of cholinergic signaling in postnatal neurogenesis control. Recent findings incorporating optogenetic manipulation of cholinergic circuit have uncovered a direct link between neuronal activity patterns and neurogenic proliferation. In this mini-review, we will summarize these anatomical, pharmacological, and functional experimental results, and speculate on local cholinergic circuit wiring diagram and its possibilities for higher-level brain inputs that connect to behavioral paradigms/disease states.

Anatomical lesions and their effects on postnatal neurogenesis

Cholinergic neurons in the mammalian brain can be generally categorized into local interneurons such as those in the central cortex, hippocampus, and striatum; or long-range projection neurons such as those in the magnocellular basal nucleus, pontomesencephalic tegmentum, cranial nerve motor nuclei, and motor neurons in the spinal cord.48-52 For the projection neuron subtype, motor neurons in the spinal cord and cranial nerves, parasympathetic cholinergic neurons in the spinal cord, and cholinergic neurons within the sympathetic nervous system have been well-described.53 Within the brain, projecting cholinergic neurons have been organized into subgroups depending on their anatomical locations and projections (Fig. 1A).54 The nucleus basalis group includes: the nucleus basalis of Meynert and magnocellularis (B), substantia innominata (SI), and horizontal diagonal band of Broca (HDB). The medial septal group includes the medial septal nucleus (MS) and vertical diagonal band (VDB). And the pontine cholinergic group in the upper brain stem includes cholinergic neurons in the pedunculopontine tegmental nuclei (PPT) and laterodorsal tegmental nuclei (LDT). Cholinergic neurons within the local interneuron subtype are rather diverse, and include ACh-synthesising neurons in the caudate-putamen; nucleus accumbens; striatum; main and accessory olfactory bulbs; anterior olfactory nucleus; olfactory tubercule; hippocampus; cerebral cortex; basolateral hypothalamus; and spinal cord.53 Despite this anatomical diversity among cholinergic neurons, there are relatively few genetic strategies to specifically target distinct subpopulations of
cholinergic neurons. In the context of postnatal neurogenic niches, cholinergic neurons from the medial septum and the diagonal band of Broca are believed to provide most of the cholinergic innervation to the SGZ niche (Fig. 1B).55,56 A newly identified cholinergic neuron population residing subependymally has recently been shown to modulate LV niche neurogenesis (Fig. 1C).57

A robust and efficient method to label all cholinergic neurons is to drive fluorescence reporter via Cre recombinase expression from choline acetyltransferase (ChAT, required for acetylcholine synthesis) gene regulatory elements,58 although this approach does not distinguish cholinergic neuron subtypes. Primary anatomic lesion studies, while less elegant due to nonspecific side effects, do allow for regional targeting of cholinergic neurons to access their potential functions during postnatal neurogenesis. Transection of the fimbria-fornix, which disrupts basal forebrain cholinergic projections to the hippocampus,59 has been reported to result in a concurrent decrease in dentate gyrus BrDU incorporation,60 suggesting decreased SGZ neurogenesis. Similarly, direct injection of N-methyl-d-aspartate (NMDA) to the cholinergic nuclei in the medial septal region to create excitotoxic lesions also reduced SGZ neurogenesis.61 Cholinergic neurons in the basal forebrain, medial septum, nucleus basalis of Meynert, and diagonal band of Broca all express high levels of p75 neurotrophin receptor (p75NTR). This exposes them to specific cellular elimination by precise
stereotoxic injection of 192-IgG-SAP (192-Saporin), a chemical conjugate of p75NTR mouse clonal antibody to the ribosome-inactivating protein sapoin. 192-Saporin-mediated removal of medial septal cholinergic neurons resulted in decreased SGZ neurogenesis, as well as decreased cellular proliferation in the LV niche. Together, these anatomical studies suggested that cholinergic neurons in the brain can play important roles to control postnatal neurogenesis.

**Muscarinic and nicotinic cholinergic receptor activation and signaling**

In addition to anatomical lesion studies, pharmacological approaches have also implicated cholinergic signaling as an important pathway controlling postnatal neurogenesis. ACh signals through both nicotinic and muscarinic acetylcholine receptors (nAChR and mAChR, respectively), which can be specifically targeted by pharmacological agents. Muscarinic agonists such as bethanechol, pilocarpine, and oxotremorine enhanced cellular proliferation when added to NSC cultures, hippocampal slices, or in vivo, while muscarinic antagonist had the opposite effect. Proliferation was also enhanced in cortical precursors following mAChR activation. While the effects are not as clear cut, nicotinic stimulation also appears to increase neurogenesis, as direct nicotine application in vivo increased LV Nestin\(^+\) cellular proliferation, resulting in subsequent BrdU-labeled NeuN\(^+\) granule neurons in the olfactory bulb. In the SGZ, pharmacological activation of the \(\alpha_7\)-subunit containing nAChRs have been shown to increase cellular proliferation. However, high doses of nicotine delivered chronically in vivo have an opposite effect in decreasing SGZ neurogenesis. Even though characterization of ACh receptor expression in neurogenic niches has not been extensive, LV NSCs have been reported to express \(\alpha_3\)- and \(\alpha_4\)- subunit containing nAChRs, similar to those residing in the rostral migratory stream which displayed \(\alpha_3\beta_4\) nAChR activity. In contrast to NSCs and DCX\(^+\) neuroblasts, Mash1\(^+\) transiently amplifying progenitors in the LV niche did not appear to express functional ACh receptors. In the SGZ, IHC and functional analyses have revealed the presence of M1 and M4 subunit mAChR expressions, as well as \(\alpha_7\) and \(\beta_2\) nAChR subunit expressions in immature hippocampal neurons. M1 and M4 mAChRs also co-label with proliferating SGZ cells shortly following BrdU administration.

These results suggest that adult neural stem/progenitor cell populations are sensitive to levels and timing of acetylcholine released, and that cholinergic receptor subtypes may mediate differential effects on cellular proliferation. mAChRs are metabotropic transmembrane proteins, coupled to G proteins, and activate various intracellular signaling pathways to provide sustained cellular responses. Meanwhile, nAChRs are pentameric, ionotropic channels consisting of several subunits: one alpha + 4 other subunits named beta, gamma, delta, and epsilon. nAChRs mediate fast cholinergic transmission in the peripheral and central nervous system. The subunit compositions of the various nAChRs determine their ionic permeability (e.g. Na\(^+\), K\(^+\), Ca\(^{2+}\)), affinity for ACh, channel current kinetics, and channel desensitization. In the brain, mAChR and nAChR types are present on neurons at both synaptic and extra-synaptic sites as well as on glial cells.

Low-level, sustained neuronal activity patterns that result in consistently low concentrations of neurotransmitter released are termed tonic firing patterns. On the other hand, more robust, synaptic, and temporally salient neuronal activities are referred to as phasic activity, occurring on much finer time-scales. Neuronal activity patterns of specific cholinergic populations can range from spontaneous low frequency spiking (tonic) to those that fire very irregularly or respond strongly to specific salient stimulation (phasic). The types of release will influence both the concentration and temporal profiles of ACh signaling, as well as the speed of ACh breakdown by acetylcholines- terases, which are particularly effective in synaptic clefts. One notable feature regarding nAChRs is their rapid desensitization following ACh-induced activation.

This results in short bursts of ACh release having a qualitatively different effect on the receiving cell than ACh continuously present or absent (Fig. 2). Anatomically speaking, activity-dependent ACh released from synaptic sites facilitate fast, high concentration neurotransmitter access to receptors (Fig. 2A), while bulk/volume ACh release that occurs at non-synaptic sites or from nearby synaptic spillover provide low level neurotransmitter via diffusion over larger areas (Fig. 2B, C). These principles of ACh differentially signaling through 2 receptors, with temporal dynamics on nAChR activation/desensitization, underlie key features of ACh's important functions during...
neural circuit modulation (Fig. 2D). In neurons, nicotinic and muscarinic signaling can often be antagonistic, inducing differential currents or polarizations, divergent calcium signaling profiles, or distinct regulations of LTP. However, there are also examples where mAChR and nAChR signaling can be cooperative, producing complimentary depolarizing currents and convergence onto common biological intracellular cascades. This context-dependent complexity in signaling capacity may provide a palette richness for NSCs to functionally read-out subtle changes in local ACh availability.

**Identification of resident cholinergic neurons in subependymal niche**

While cholinergic pharmacology has an effect on adult NSC proliferation in vivo, it remained unclear if these putative actions attributed to ACh are due to...
neuronal activity or are in fact indirect. To determine whether activity patterns from cholinergic neurons can directly control neurogenesis, one approach is to examine outcomes upon altering intrinsic excitability of these neurons. We conditionally deleted Ank3, a large adapter protein known to localize to neuronal axon initial segment, specifically in cholinergic neurons (ChAT^IRES-Cre/+; ank3^flox/flox). Similar to previous observations in cerebellar Purkinje neurons, Ank3-mutant ChAT^+ neurons showed an inability to precisely initiate and scale action potentials to electrical stimulation in ChAT^IRES-Cre/+; ank3^flox/flox mutant mice. There was a marked reduction in DCX^+ neuroblast chains along the LV niche, becoming progressively worse in adult mice. Ki67 and Mash1 IHC staining revealed a corresponding decrease in LV niche cellular proliferation, while caspase 3 staining showed no obvious increase in apoptosis. These results revealed that cholinergic circuit activity and precision are required to sustain the robustness of adult LV neurogenesis.

As cholinergic innervation is widespread in the brain, disrupting its activity will likely contribute to many effects, including modulation of non-cholinergic circuits. The observed neurogenesis defects in ChAT^IRES-Cre/+; ank3^flox/flox mutant mice can also be caused by decreased ACh release in the SEZ niche via direct cholinergic innervation. To examine this possibility closer, we looked for cholinergic processes along the LV wall, and detected large ChAT^+ neuronal cell bodies residing subependymally within the LV niche. DiI-filling of these subependymal ChAT^+ (subep-ChAT) neurons revealed complex neuronal processes that were largely aspiny, and projected their axonal processes locally in the subependymal space (Fig. 3). A morphological feature for these subep-ChAT neurons, which can be located in both young and adult mice (examined up to 6 months of age), is their planar appearance paralleling the ependymal surface above. More importantly, unlike neighboring striatal cholinergic neurons which are spontaneously active, the subep-ChAT neurons did not exhibit basal-level spontaneous activity in acute brain slice preparation. In vivo optogenetic stimulation of subep-ChAT neurons in P30 ChAT^IRES-Cre/+; Rosa26R-ChR2EYFP mice significantly increased the numbers of Ki67^+ proliferating cells and neurogenic progenitors in the LV niche. Conversely, in vivo optogenetic suppression of subep-ChAT neurons in P30 ChAT^IRES-Cre/+; Rosa26R-ArchaerhodopsinGFP mice decreased the numbers of Ki67^+, Mash1^+, and DCX^+ cells in the LV niche.

To determine whether LV NSCs can directly detect ACh release via cholinergic neuron activity, we performed whole-cell patch recording in NSCs, while simultaneously activating ChR2-expressing cholinergic inputs locally via 473 nm laser. This resulted in consistent frequency-dependent inward currents in NSCs, sensitive to both nicotinic and muscarinic blockade (Fig. 3). These neuronal activity-dependent responses from postnatal LV NSCs appeared distinct from synaptic “spill-over” mechanisms. Mechanistically, α3β4 nAChR as well as α7-subunit containing nAChRs have been reported to function during postnatal LV neurogenesis. Our IHC antibody staining and electrophysiological experiments revealed α3- and α4-subunit containing nAChR, as well as mAChR expression in nestin-CreER lineage-traced LV NSCs. Consistent with these results: α4β2 nAChR and M1/ M4 mAChR agonists have been shown to control SGZ neurogenic proliferation and differentiation; and β2-subunit nAChR mutant mice have reduced SGZ proliferation over the life of the animal.

These findings revealed subep-ChAT neurons as integral components of the cholinergic circuit controlling

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**Figure 3.** Subependymal cholinergic neuron bridging SEZ niche/neurogenesis to neural circuit-level control. Schematic representation of subep-ChAT neuron (green) providing ACh to modulate adult SEZ neural stem cells (NSC) production of new neuroblasts, which then migrate and assemble into neuroblast chains. Dashed lines represent putative excitatory (+, blue) or inhibitory (−, red) inputs onto subep-ChAT neuron dendrites. LV = lateral ventricle.
postnatal LV neurogenesis. Beyond these subep-ChAT neurons, it remains possible that there are other cholinergic neurons whose activity contributes to LV neurogenesis control. Anatomically, the nearest such population is located in the striatum: the well-studied tonically-active striatal cholinergic neurons. While genetic deletion of ChAT (removing ACh producing ability) in the striatal cholinergic population via Nkx2.1-Cre; ChAT\textsuperscript{fl/fl} mutant mice revealed no obvious LV neurogenesis defects,\textsuperscript{57} striatal cholinergic neurons may still play a role under physiological conditions that can be compensated for as needed by subep-ChAT neurons.

**Circuit level control of cholinergic neuron activity**

It is of great interest to understand, at the circuit level, how cholinergic neuron activity is regulated, resulting in postnatal neurogenesis control. Ank3 deletion from ChAT\textsuperscript{+} neurons showed that precise cholinergic circuit activity is required to sustain the robustness of adult LV neurogenesis. While IHC staining for p-rpS6, an activity-dependent marker for cholinergic neurons,\textsuperscript{104} revealed that subep-ChAT neurons are normally active in vivo, they lacked spontaneous activity in acute brain slice preparation, indicating their activity is contextually controlled by higher-level inputs. The sources for excitatory/inhibitory inputs onto subep-ChAT neurons are currently unclear, although CNS cholinergic neurons such as those found in the striatum, basal forebrain nuclei, hypothalamus, medial habenula, pontomesencephalic tegmentum, and medullary tegmentum, tend to have highly stereotyped patterns of afferent connectivity,\textsuperscript{105} serving as potential blueprints for subep-ChAT neuron connectivity. First, there is rich inter-connectivity between cholinergic cell groups, which form a contiguous plexus of overlapping dendritic arbors, collectively allowing each subsystem (e.g., striatum, basal forebrain, and pontomesencephalon) to receive and integrate information from various sensory modalities.\textsuperscript{106} Second, forebrain cholinergic neurons generally receive excitatory cortical inputs (Fig. 4).\textsuperscript{105} This pattern of innervation has been hypothesized to provide a means for global integration of ongoing neural activity, as cholinergic cell groups are frequently implicated in the modulation of attention and arousal associated with the reticular activating system.\textsuperscript{107} Furthermore, striatal cholinergic neurons adjacent to the LV niche, as well as those in the nucleus basalis, receive inputs from the intralaminar thalamus, as part of the reticular activating system (Fig. 4).\textsuperscript{105} All cholinergic neuron groups also receive noradrenergic input from the locus ceruleus and subceruleus.\textsuperscript{108} The basal forebrain, striatal, diencephalic, and pontomesencephalic cholinergic groups also receive sparse nigral or ventral tegmental dopaminergic inputs (Fig. 3).\textsuperscript{105}

Within the striatum as a specific example, cholinergic neuron activity patterns are dynamically controlled via distal excitation modulating intrinsic neuronal membrane properties.\textsuperscript{109,110} The large, aspyri cholinergic interneurons of the striatum, referred to as tonically active neurons (TANs), represent a particularly well-studied population of spontaneously firing cholinergic neuron. In TANs, spontaneous activity is
mediated by intrinsic membrane properties, specifically a sodium current and hyperpolarization-activated cation current which together drive tonic firing.\textsuperscript{89} Salient stimuli produce a characteristic pause in TAN firing, and TANs have long been viewed as important substrates for striatal associative and motor learning.\textsuperscript{111,112} In contextual recognition of salient stimuli driving action selection, the temporal, spatial, and motivational context of salient stimuli have all been shown to play a role in regulating spontaneous striatal cholinergic neuron activity.\textsuperscript{113} Similar pauses in cholinergic TAN activity are generated following stimulation of nigrostriatal afferents,\textsuperscript{110} and a burst-pause firing pattern is generated in response to stimulation of the intralaminar thalamus (Fig. 4).\textsuperscript{109}

Although subep-ChAT cells are silent under resting conditions, this is relatively rare among other cholinergic cell groups.\textsuperscript{90,114} It remains to be seen whether the distinct activity profiles of subep-ChAT neurons vs. neighboring striatal TANs in brain slice preparations are due to differences in intrinsic membrane properties or their inhibitory tone. Within the local microcircuitry, GABAergic inhibitory interneurons can also provide dynamic control to alter cholinergic neuron activity states.\textsuperscript{114} While it has been well demonstrated that GABA is an important protein for several cell types during postnatal LV neurogenesis,\textsuperscript{115,116} its sources in the niche remains largely unclear. Conceptually, since cholinergic neurons groups are broadly interconnected, it is an intriguing possibility that subep-ChAT neurons participate in and sample the cholinergic plexus to transform global cascades of activity within the cholinergic system into functional neurogenesis. Furthermore, if subep-ChAT neurons are involved in associative learning tasks, believed to be an important function for striatal cholinergic TANs, a similar configuration of circuit-level connectivity may allow subep-ChAT neurons to respond to environmentally salient stimuli to direct neurogenesis. The highly stereotyped connectivity patterns of other cholinergic groups provide a template and substrate for investigating the circuit wiring diagram of subep-ChAT neurons.

**Conclusion**

Like a computer needing hardware upgrades to run increasingly sophisticated software, it is tempting to speculate that postnatal neurogenesis endow particular neural circuits with this capacity. The fact that neuronal firing patterns can direct NSC proliferation takes this concept one step further, and proposes that perhaps certain critical neural circuits may functionally instruct NSCs for their own neuronal additions over time. There are parallels in the glial biology field: pioneering study by Barres and Raff in 1993 showed that oligodendrocyte precursor proliferation can be dependent on neurons generating action potentials.\textsuperscript{117} Neuronal activity-dependent increases in myelination is now a well-accepted observation, and recent studies extended this concept to show the lack of inhibitory post-synaptic currents on oligodendrocyte precursors contributing to white matter defects following hypoxic injury,\textsuperscript{118} as well as glioma cellular proliferation profiling from neuronal activity.\textsuperscript{119} It is likely that future studies will find additional examples, perhaps in the process revealing that the control of postnatal neurogenesis by neuronal activity may be the norm, rather than an exception for cells proliferating in the brain in health and disease.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

**Acknowledgments**

We thank members of the Kuo laboratory, Jerry Yakel (N.I.E. H.S), and Juan Song (U.N.C. Chapel Hill) for helpful discussions.

**Funding**

This work was supported by N.I.H. grant R01MH105416, R01NS078192, The March of Dimes, and George & Jean Brumley Endowment (C.T.K.).

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