Neurotransmitter Regulation of Adult Neurogenesis: Putative Therapeutic Targets

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Abstract: The evidence that new neuron addition takes place in the mammalian brain throughout adult life has dramatically altered our perspective of the potential for plasticity in the adult CNS. Although several recent reports suggest a latent neurogenic capacity in multiple brain regions, the two major neurogenic niches that retain the ability to generate substantial numbers of new neurons in adult life are the subventricular zone (SVZ) lining the lateral ventricles and the subgranular zone (SGZ) in the hippocampal formation. The discovery of adult neurogenesis has also unveiled a novel therapeutic target for the repair of damaged neuronal circuits. In this regard, understanding the endogenous mechanisms that regulate adult neurogenesis holds promise both for a deeper understanding of this form of structural plasticity, as well as the identification of pathways that can serve as therapeutic targets to manipulate adult neurogenesis. The purpose of the present review is to discuss the regulation of adult neurogenesis by neurotransmitters and to highlight the relevance of these endogenous regulators as targets to modulate adult neurogenesis in a clinical context.

Keywords: Neuronal progenitors, stem cells, hippocampus, olfactory bulb, neuropeptide, neurodegeneration, depression, subgranular zone, dentate gyrus.

INTRODUCTION

The dogma that new neuron generation in mammals is strictly a developmental phenomenon, with no new neurons being added to the adult brain, received almost instinctive support because of the prevalent view that such stability may be required for the maintenance of learned behavior in mature neuronal circuits [1]. A direct consequence of this dogma was the conceptual restriction of adult structural plasticity to architectural remodeling of dendrites, their spines, axons and their terminals [1]. This left little room for the possibility of modification of existing neuronal networks by new neuron addition in adulthood. Despite intriguing observations in the 1960s of newborn neurons in the adult rodent brain, it took almost four decades to finally lay this dogma to rest [1, 2]. It is now clear that several mammalian species including rodents, tree shrews, marmosets, macaques as well as humans retain the ability to generate new neurons throughout adult life [3]. The discovery of adult neurogenesis besides changing notions of limited reorganization in established neuronal circuits, has also served to galvanize interest in the possibility of recruiting endogenous precursors or transplanting stem cells to promote the repair of vulnerable neuronal circuits in neurological and psychiatric disorders [4].

The process of adult neurogenesis encompasses the proliferation of progenitors, survival and maturation through specific stages, migration to site of integration and functional recruitment into existing neuronal circuitry [5]. While there exists debate on whether progenitors in the neurogenic niches constitute adult CNS stem cells which require, in their strictest definition, fulfillment of criteria such as unlimited self renewal and the ability to generate all CNS lineages, these progenitors clearly do retain multipotency and a limited self renewal capacity [4, 6]. For the purposes of this review we will utilize the broader terminology of “precursor" cell, which encompasses both the CNS stem cell and limited lineage progenitors. In addition to the existence of two major neurogenic niches [4], namely the subventricular zone (SVZ) bordering the lateral ventricles and the subgranular zone (SGZ) in the dentate gyrus subfield of the hippocampal formation, several studies [7] suggest the possibility that adult neurogenesis may be a more widespread phenomenon with precursor cells also giving rise to new neurons in the cortex [8,9], amygdala [10], substantia nigra [11] and hypothalamus [12] (Fig. 1). Further evidence supporting the view that precursor cells may reside in multiple adult brain regions comes from ex vivo studies, where precursor cells have been isolated and maintained either as neurospheres or adhered precursors from both the neurogenic niches, the SVZ [13,14] and SGZ [15,16] as well as non-neurogenic regions in the adult CNS such as the striatum, hypothalamus, retina, corpus callosum, cortex, septum and the spinal cord [17-21] (Fig. 2). Recent reviews have discussed extensively the possibilities of more widespread neurogenesis [4,7], and our review will focus on regulation of adult neurogenesis within the major neurogenic sites of the SVZ and SGZ.

NEUROGENESIS IN THE SUBVENTRICULAR ZONE – OLFACTORY BULB

The subventricular zone (SVZ), lining the lumen of the lateral ventricles, harbors the highest numbers of precursor cells [22]. The SVZ is composed of the ependymal layer (E) facing the lumen, adjacent to which lie the proliferative cells (Fig. 3). Precursor cells in the proliferative zone have been divided into three types: ‘type B’ cells are considered to be the multipotent precursor cells which give rise to a transient...
amplifying pool of cells labeled as ‘type C’; which in turn give rise to the neuroblasts or the ‘type A’ cells (Fig. 3) [23]. Although the characteristics of the multipotent precursor cells in the SVZ are not completely understood and remain controversial, thus far the strongest evidence supports the view that glial fibrillary acidic protein (GFAP)-positive astrocyte-like “type B” cells that reside in the subependymal layer are likely to be the multipotent neural precursors in the SVZ [23, 24]. This class of cells has been likened to radial glia that serve as neuronal precursors during embryonic development, and though distinct from mature astrocytes share the similarity of expressing GFAP. These GFAP-positive precursor cells have been described to be predominantly unipolar or bipolar, and morphologically distinct from canonical multipolar astrocytes that do not appear to act as precursors [25]. A challenge to the view that Type B cells serve as multipotent precursors has come from reports that the ciliated ependymal cell [26] may be the actual precursor cell, although this has proved controversial with contradictory findings that do not support this view [23, 25].

Approximately 30,000 new cells are born per day in the rodent SVZ, and daughter cells have been shown to migrate along the rostral migratory stream (RMS) to the olfactory bulb (OB) where they integrate into existing circuitry differentiating into OB interneurons, with a higher proportion forming granule cells and small numbers (<3%) generating peri-glomerular cells (Fig. 3) [5, 22, 27]. Neurogenesis in the OB is associated with substantial attrition of cells, and a relatively small proportion of the cells that divide in the SVZ actually integrate into the OB as functional mature neurons [28]. However, the process of new neuron generation in the OB is highly sensitive to environmental cues both intrinsic and extrinsic, and survival as well as plasticity of new neurons is dynamically modulated by both activity and experience [22, 29, 30]. While there is a significant reduction in the number of surviving neurons in the OB of anosmic mice [28], enriched odor experience enhances the survival of newborn neurons with concomitant improvements in olfactory memory [30]. Reproductive and maternal behavior that are linked to heightened olfactory discrimination and function, have been reported to enhance olfactory bulb neurogenesis [31, 32]. Reduced OB neurogenesis during aging has also been correlated with deficits in fine olfactory discrimination [33]. Reports suggest that newly generated neurons

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**Fig. (1).** Schematic of a sagittal section from an adult rat brain showing regions (indicated with a bullet point) in which adult neurogenesis has been reported. A. Sagittal section with the major neurogenic niches of the subventricular zone (SVZ-blue) lining the lateral ventricles (LV) and the subgranular zone (SGZ-green) in the dentate gyrus (DG) region of the hippocampal formation. SVZ precursors travel along the rostral migratory stream shown in blue to eventually integrate into olfactory bulb (OB) circuitry. B. Coronal section showing the lateral ventricle with the adjacent SVZ. C. Coronal section showing the hippocampal formation with the SGZ region in the DG subfield. Full forms of abbreviations used to indicate regions with reported adult neurogenesis: Amyg- amygdala, Hyp- hypothalamus, Str- striatum, SNr- substantia nigra.
that have most recently been added into OB circuitry are highly tuned and sensitive to novel odorant cues [34], supporting the hypothesis that ongoing neurogenesis in the OB may provide a substrate for structural or physiological plasticity required for adaptations in olfactory perception in the adult brain.

NEUROGENESIS IN THE SUBGRANULAR ZONE OF THE HIPPOCAMPAL FORMATION

The hippocampal formation is the other major neurogenic niche in the adult brain, where precursor cells reside within the SGZ along the border between the granule cell layer and the hilus in the dentate gyrus (DG) subfield [5] (Fig. 4). Precursor cells that divide in the SGZ undergo a stage specific maturation that is characterized by both morphological and immunological features [35]. Within the SGZ after cell division, only about half of the daughter cells persist and migrate into the granule cell layer, start sending out dendritic arbors into the molecular layer and project efferents to the CA3, eventually functionally integrating into the granule cell circuitry of the DG [36-39]. Precursor cells have been classified into three types within the SGZ [34] (Fig. 4): (1) the multipotent precursor cell in the SGZ, much like within the SVZ, also termed Type B cell or alternatively Type I cell is GFAP-positive, radial glia-like and relatively quiescent; (2) the nestin-positive, GFAP-negative Type 2 cells constitute the majority of the transient amplifying pool of precursors, and are further divided into the Type 2A-doublecortin (DCX) negative cells and the Type 2B which are DCX-positive; (3) the neuroblast category within the SGZ is also called the Type 3 cell which is antigenically DCX-positive and nestin-negative. The stages in precursor maturation to a newborn neuron involve a sequential stepwise progression from Type1 to Type3.

While the emerging consensus in the field is that radial glia-like Type B/Type I cells constitute the multipotent precursors in the SGZ, there is substantial controversy on the “stem cell” like properties of this precursor [6, 40-42]. Given the limited ability of DG derived precursor cells to generate secondary and tertiary neurospheres in culture [41, 42], it has been suggested that the SGZ harbors a restricted potential progenitor that is largely committed to a neuronal lineage. An intriguing possibility that has been hypothesized is that multipotent precursors may reside in the lateral ventricle lining adjacent to the hippocampal formation and could migrate into the SGZ, where they may then serve as more restricted lineage progenitors which undergo a defined number of cell divisions [41].

According to one estimate [43], up to 9,000 cells divide daily in the rodent SGZ. A large proportion (~50%) of these newly born cells undergoes cell death and those that persist
predominantly (~85%) go on to form mature granule cell neurons [39]. This process of maturation and functional integration into granule cell layer circuitry occurs over a time period of about 3-4 weeks [35]. During this process of maturation, adult born new neurons recapitulate aspects of hippocampal development [44], in particular the early presence of depolarizing gamma amino butyric acid (GABA) receptors and giant depolarizing potentials [45, 46]. Newborn neurons are easily excitable and exhibit long term potentiation (LTP) more readily than mature neurons [47]. Further, their survival and recruitment into mature circuits is also dynamically modulated by neuronal activity [46, 48]. Together these features, serve to generate a “plastic” pool of newborn neurons that have been suggested to add a key additional repertoire of plasticity to the adaptive responses of the hippocampal formation to varying environmental stimuli.

The correlative association of neurogenesis with hippocampal function is further suggested by studies that demonstrate increased hippocampal neurogenesis in response to hippocampal-dependent learning tasks [49], environmental enrichment [50] and therapeutic agents like antidepressants [51, 52], all of which are associated with beneficial effects on hippocampal function. In contrast, sustained exposure to stress or animal models of depression both of which are linked to hippocampal damage and dysfunction impairs hippocampal neurogenesis [53, 54]. More causal links between hippocampal neurogenesis and function have been demonstrated by studies in which new neuron production has been blocked using irradiation, pharmacological agents or genetic approaches and have demonstrated deficits in specific hippocampal-dependent tasks such as contextual fear conditioning, trace eye-blink conditioning and working memory tasks like the delayed non-match to sample tests with long delays [55-57]. In contrast, there is still debate about the effects of ablatting neurogenesis on spatial learning tasks, with no effects reported on the Morris water maze [55, 58, 59], but with effects seen in variants of the Morris water maze test where ablated animals exhibit deficits to recall the site of a hidden platform when tested after 1 month [60]. Further, irradiated...
Fig. (4). Schematic of hippocampal neurogenesis. I. Sagittal section of the adult rat brain with a coronal slice at the level of the hippocampal formation. II. A hippocampal coronal section showing the dentate gyrus (DG), CA3 and CA1 subfields. Within the DG (blue) is shown the neurogenic niche of the SGZ (green). Precursors undergo proliferation (A - cluster of dividing cells in schematic) and then exhibit stage-specific markers as they mature eventually integrating into granule cell layer circuitry both receiving afferents and sending out efferents (B and C in schematic). A. Proliferating precursors in the SGZ are immunopositive for the proliferating cell nuclear antigen (PCNA - arrow) whereas mature granule cell neurons are shown labeled with the marker Neuronal nuclei protein (NeuN). B. Precursors exhibit the stage-specific marker doublecortin (DCX - arrowhead). C. Precursors that have incorporated the mitotic marker 5-bromo-2-deoxyuridine (BrdU) during cell division eventually acquire a mature neuronal fate and newborn neurons (BrdU+/NeuN+ - arrowmark) are shown dispersed in the granule cell layer. III. SGZ precursors cells have been classified into the quiescent multipotent precursor Type I cell, transit amplifying Type 2 cells which are further divided into Type 2A and 2B and the Type 3 neuroblasts. These categories exhibit distinct expression patterns of specific antigen with the Type I cell being immunopositive for the astrocytic marker glial fibrillary acidic protein (GFAP) and the intermediate filament marker nestin. Type 2 cells are nestin positive and GFAP negative but are classified as 2A if they are negative for doublecortin (DCX) expression and as 2B if they are positive for DCX. Type 3 neuroblasts are immunopositive for DCX but negative for nestin expression. Neuroblasts then go on to form immature granule cell (GC) neurons that transiently expressing the calcium binding protein, Calretinin and the NeuN before acquiring a mature GC cell phenotype and expressing NeuN and the calcium binding protein, Calbindin.
animals also under perform on other spatial tests like the Barnes maze [61]. Interestingly, recent reports [62] suggest that ablation of neurogenesis improves performance on variants of working memory tests like the radial arm maze in which animals are required to forget irrelevant information suggesting that neurogenesis may also have adverse effects such as memory interference. Further, antidepressant-mediated behavioral effects on tasks like the novelty suppressed feeding test and the forced swim test are lost in animals that lack neurogenesis due to irradiation or the ability to enhance neurogenesis in response to antidepressants due to genetic perturbations [63, 64]. It has been suggested that neurogenesis may be required for antidepressants to induce changes in relative DG-CA1 activity, a feature that appears to underlie specific behavioral changes in response to antidepressant treatment [64]. Taken together this raises the strong possibility that new neuron addition may play an important role in both physiological functions of the hippocampal formation such as learning and memory, and also be recruited by therapeutic agents such as antidepressants to mediate some of the beneficial effects of these agents on hippocampal function. Several reviews have discussed the functional relevance of adult hippocampal neurogenesis [5, 22, 65, 66]. While substantial work is required to unravel the precise role that newborn neurons play in specific hippocampal functions, studies thus far support the idea that neurogenesis has an important role in distinct hippocampal dependent functions and behaviors.

**ADULT NEUROGENESIS IN A CLINICAL CONTEXT**

Adult neurogenesis does occur in the human SVZ and SGZ [67, 68]. Adult neurogenesis is perturbed by a decline in healthy physiological states, as well as in pathophysiological conditions. Aging is associated with robust decreases in both olfactory bulb [69] and hippocampal neurogenesis [70, 71], and senescence is linked to deficits in fine olfactory discrimination [33] and hippocampal dependent cognitive tasks [72]. Other environmental cues that perturb normal physiology such as sleep deprivation [73], chronic stress exposure [54] and alcohol consumption [74] also result in reduced hippocampal neurogenesis. Pathological conditions like anosmia decrease OB neurogenesis and olfactory function [29]. Animal models of neurological disease like ischemia [75-77], traumatic brain injury [78] and epilepsy [79] are associated with robust increases in precursor proliferation in both the SVZ and SGZ, and in some instances this proliferative increase is translated into an actual increase in neurogenesis, potentially as an attempt to repair damage. Whether these putative compensatory responses contribute to the establishment of aberrant neocircuitry is an area of active scientific interest [80]. In the case of neurodegenerative disorders, Alzheimer’s disease has been linked to increased neurogenesis [81, 82] and in contradictory reports to a specific decline in the long-term survival of newborn neurons in the hippocampal formation [83]. Additionally, a reduction of proliferating precursors in the SVZ and SGZ has been reported with dopamine depletion and in Parkinson’s disease patients [84]. Huntington’s mouse models report opposing effects on SVZ (increase) [85] and SGZ (decrease) precursor proliferation [86, 87], in contrast with the increased hippocampal neurogenesis observed in Huntington’s disease patients [88]. In the case of psychiatric disorders, while several animal models of depression do exhibit a decline in hippocampal neurogenesis [54, 89, 90], thus far a clinical correlate for this has not been observed, although hippocampal atrophy has been reported in patients suffering from major depression [91, 92]. Postmortem human studies have reported a decline in proliferative precursors in the SGZ of schizophrenic patients [93], with no change being reported in depressed individuals [93]. Further validation is clearly required to understand the regulation of adult neurogenesis in both animal models and human cases of CNS disorders. Thus far studies addressing the regulation of adult neurogenesis in either disease models or patients, and the consequence of altered neurogenesis on the pathophysiology of the disease are still at nascent stages but have uncovered tantalizing clues that highlight the need for further active research in this vein.

The concept that endogenous neurogenesis may serve as an important therapeutic target has also been the focus of intense scientific interest. The fact that enriched environment exposure can ameliorate the effects of physiological states like aging [94] and pathophysiological conditions such as animal models of Huntington’s disease on hippocampal neurogenesis and cognitive function [86] suggests that extrinsic cues can substantially modulate new neuron addition even in the context of compromised conditions. This raises the possibility that modulation of endogenous neurogenesis may be of therapeutic relevance. In this line of scientific investigation, recent evidence indicates that diverse classes of antidepressant treatments serve to enhance hippocampal neurogenesis through effects on proliferation and survival of precursors [52, 95-97].

Further, this neurogenic increase has been strongly implicated in the behavioral effects of antidepressants on tests like the novelty suppressed feeding and the forced swim tests [63, 64]. Building evidence has resulted in a provocative “neurogenic” theory of depression that posits a decline in neurogenesis in depression and an increase in neurogenesis as an important target for the beneficial effects of antidepressants [98-100]. Preclinical evidence thus far supports a role for adult hippocampal neurogenesis as a target for antidepressants and in the modulation of hippocampal dependent cognitive functions suggesting that this process may be therapeutically relevant for the treatment of depression and some of the cognitive dysfunction seen in patients with senile dementia or Alzheimer’s disease. In contrast, it remains unclear if modulating endogenous neurogenesis in the SVZ or SGZ would have a substantial palliative effect on the symptomatology of diseases like Parkinson’s with a primary deficit in basal ganglia circuitry [101]. For Parkinson’s disease the hope stems largely from the prospect of using lessons from the major neurogenic niches to induce neurogenic changes that promote repair in basal ganglia or through the usage of stem cell transplantation. The possibility of transplanting precursors has also been a hotbed of scientific activity and several reviews have discussed stem cell transplantation in detail [102-104]. In the context of therapy, adult neurogenesis has emerged as a preclinical target of interest and promise for neurological, neurodegenerative and neuropsychiatric disorders.

**ENDOGENOUS REGULATORS OF ADULT NEUROGENESIS**

Understanding the pathways that modulate adult neurogenesis has both basic and clinical relevance, as this mechanistic understanding may provide deeper insights into the fundamental biology underlying new neuron addition in the mature brain and reveal ways to tap this potential for thera-
Neurotransmitter Regulation of Adult Neurogenesis

Neurotransmitters besides their classical role in neuronal communication have been suggested to moonlight as trophic factors during brain development [110]. In keeping with this theme, several neurotransmitter pathways have also been shown to play an important role in the regulation of adult neurogenesis. The amino acid and monoamine neurotransmitters as well as neuropeptides have distinct and diverse effects on aspects of neurogenesis such as turnover, survival and phenotypic integration (Table 1).

GLUTAMATE

Glutamate plays a central role during development, shaping activity dependent processes such as the birth and death of new neurons and their eventual cytoarchitecture, influencing both synapse establishment and elimination. During embryonic neurogenesis, glutamate has effects on the proliferation, survival, migration and differentiation of precursors [111]. Glutamate retains an important role in modulating adult neurogenesis [111]. While glutamatergic effects on developmental and adult neurogenesis bear both common and distinct features these are yet only partially elucidated.

Glutamate exerts its effects through the ionotropic AMPA/KA and NMDA families and the metabotropic glutamate (mGlu) receptor family [112]. Glutamatergic neurotransmission regulates several components of the process of adult hippocampal neurogenesis, but far fewer studies imply glutamate in SVZ neurogenesis. Studies in nestin-GFP mice have identified AMPA/KA and NMDA responsivity in nestin-positive precursors in the SGZ, and also the presence of functional glutamate transporters on these cells [113]. Based on in vitro studies SGZ precursor cells express the NMDA receptor subunits NR1, NR2A and NR2B [114] and in support of this, recent in vivo evidence has shown the presence of NR1 and NR2B on some Type I and Type 2A precursors in the SGZ [115]. Further, hippocampal precursor cells through NMDA receptors appear to directly sense excitatory changes and exhibit elevations of intracellular calcium. This excitation is linked to the modulation of NeuroD, a basic helix-loop-helix transcription factor that results in a switch from proliferation to differentiation, thus setting up an ‘excitation-neurogenesis’ coupling [116]. A recent elegant study using a retrovirus based single cell gene knockout approach has demonstrated a role for NMDA receptors in regulating SGZ precursor survival [48]. Collectively, these studies suggest a role for NMDA mediated signaling in SGZ precursor survival, proliferation, and differentiation. However, it is important to note that there is still debate about whether the effects of NMDA are directly on SGZ precursors or are mediated through effects on the neurogenic milieu [117]. Reports suggest that the NMDA receptor subunits may exhibit stage-specific variations in their expression patterns [115] and comparing across studies will require rigorous attention to the stage of precursor cell that is being addressed. The picture is far less clear vis a vis glutamate receptor expression in SVZ precursors. While in vitro precursors from the neonatal SVZ do appear to express functional AMPA/KA, NMDA and mGlu3 receptors [118], SVZ astrocytes that are likely adult precursors lack AMPA and NMDA responses, but are strongly immunopositive for glutamate expression. Interestingly, DCX-positive neuroblasts in the SVZ have recently been reported to express functional NMDA and AMPA/KA receptors [119]. Taken together it appears that SVZ and SGZ differ with respect to glutamatergic receptor expression, and it remains to be seen if this may also reflect in differences in response to glutamate.

In vivo pharmacological studies indicate that NMDA inhibits precursor cell proliferation, while blockade of the NMDA receptor with MK-801 significantly increases precursor proliferation in the adult SGZ [120, 121]. This proliferative increase in response to NMDA antagonist treatment is accompanied by a concomitant increase in the number of cells expressing nestin and polysialylated neural cell adhesion molecule (PSA-NCAM) [122]. Also in hippocampal slice cultures, NMDA (MK801, APV) and AMPA (CNQX) receptor antagonists increased precursor number [123], while the Group I mGluR antagonist (LY367385) decreased the number of proliferating precursors [124]. Further, lesion of the entorhinal cortex, the source of largely glutamatergic afferents to the DG causes an increase in SGZ precursor proliferation [120]. It is difficult to compare studies of selective receptor manipulation with lesion experiments that are associated with broad loss of neurotransmitters and compensatory receptor alterations. Clearly, glutamate, depending on the receptor it works through, may have opposing effects on precursor proliferation. Understanding which glutamatergic receptor drives glutamate responsiveness at distinct precursor stages may help to elucidate the sometimes opposing effects of glutamate on precursor turnover. As the effects of glutamate occur on proliferating precursors that do not appear to receive synaptic contacts [117], it is possible that the glutamatergic effects are extrasynaptic and possibly involve consequences on the neurogenic milieu, including astrocytes that are both a source and a buffer for glutamate.

Far fewer studies have addressed the role of glutamate in SVZ neurogenesis. A single in vivo study reported a decline in SVZ precursor proliferation with mGlu5 receptor antagonists or in mGlu5 knockout mice [125]. In vitro studies on SVZ neurospheres indicate that glutamate may enhance transit amplifying precursor proliferation via group II mGlu receptors [117]. It has been hypothesized that glutamate may be tonically released by SVZ astrocytes and a possible role in evoking AMPA-mediated GABA release from neuroblasts in the niche has been suggested based on the evidence of similar effects during embryonic development [118]. This is of course highly speculative at present and remains to be ascertained.
Table 1. Neurotransmitter Regulation of Adult Neurogenesis

<table>
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<tr>
<th>Subventricular Zone</th>
<th>▲ Increase ▲</th>
<th>▼ Decrease ▼</th>
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<tbody>
<tr>
<td>Proliferation</td>
<td>Glutamate mGlut5 [125]</td>
<td>GABA</td>
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<tr>
<td></td>
<td>mGlut2 [117]</td>
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<td></td>
<td>Acetylcholine [154]</td>
<td>Dopamine</td>
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<td></td>
<td>Dopamine [165, 166, 167]</td>
<td>D₂-like [167]</td>
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<td></td>
<td>5-HT₂A/C [206]</td>
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<td></td>
<td>PACAP [219]</td>
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<td></td>
<td>VIP [219]</td>
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<tr>
<td>Survival</td>
<td>Acetylcholine [152]</td>
<td>Dopamine modulates dopaminergic glomerular interneuron differentiation [166]</td>
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<td>Differentiation</td>
<td>Norepinephrine α₂ AR [183]</td>
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<tr>
<th>Subgranular Zone</th>
<th>▲ Increase ▲</th>
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<tbody>
<tr>
<td>Proliferation</td>
<td>Glutamate mGlut2 [230]</td>
<td>Glutamate NMDA [114, 115, 120, 121]</td>
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<td></td>
<td>Acetylcholine [152, 153]</td>
<td>AMPA [123]</td>
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<tr>
<td></td>
<td>Dopamine [167]</td>
<td>GABA</td>
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<td>Norepinephrine [181]</td>
<td>GABAα [117]</td>
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<td>Serotonin [63, 197, 198]</td>
<td>Substance P</td>
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<td>5-HT₁A [206]</td>
<td>NK-1 [66, 220]</td>
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<td>NPY [214, 215]</td>
<td>Acetylcholine nAchR [158]</td>
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<td>CBI [227, 228]</td>
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<tr>
<td>Survival</td>
<td>Glutamate NMDA [48, 122, 231]</td>
<td>Acetylcholine nAchR [157-159]</td>
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<td></td>
<td>mGlut1 [124]</td>
<td>Norepinephrine α₂ AR [184]</td>
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<td>GABA [144]</td>
<td>Opioids μOR [226]</td>
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<td>Acetylcholine [152, 153, 154]</td>
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<td>Differentiation</td>
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**Possible mechanisms**

- **Proliferation:** CREB, BDNF, vEGF, Ca²⁺
- **Survival:** PLC, pERK, Bcl-2, CREB, BDNF
- **Differentiation:** NeuroD, Hes1, Id2

The table summarizes the known effects (increase and decrease) of the different neurotransmitters and neuropeptides on precursor proliferation, survival and differentiation in the two major neurogenic niches of the subventricular zone (SVZ) and the subgranular zone (SGZ). Specific receptors via which the neurotransmitters are known to regulate adult neurogenesis in both these sites have been cited. Possible common mechanisms underlying the diverse effects of multiple neurotransmitters on adult neurogenesis have also been mentioned. Numbers in square brackets indicate appropriate references.
In a clinical context, glutamate may be key in mediating the precursor proliferation and neurogenesis changes in the SGZ that arise in ischemia, traumatic brain injury and seizure models [75, 76, 78, 79]. While MK801 administration prevents stroke induced increases in SGZ precursor proliferation [126], it has no effect on enhanced neurogenesis following cortical infarct induced by photothrombosis [127]. Unraveling whether neurogenesis is an adaptive process that acts to alleviate specific symptoms or a maladaptive change that triggers dysfunctional circuitry formation will determine whether glutamate in this regard can be treated as a friend or a foe. Further, the physiological decline in neurogenesis seen with aging can be ameliorated on treatment with the NMDA receptor antagonist CGP-43487 [128], raising the possibility of pharmacological interventions that capitalize on such approaches. Preclinical evidence has identified mGlu receptors as possible drug targets to treat depression [129, 130], group II mGlu receptor antagonist, MGS0039 [131] and the AMPA receptor potentiator, LY451646 enhance both neurogenesis and induce antidepressant like behaviors in animal models [132, 133]. Glutamatergic effects on neurogenesis may also contribute to the antidepressant effects of treatments like electroconvulsive seizure [134] and to the cognitive benefits of interventions like running and enriched environment [135]. Glutamate has also been implicated in the damaging effects of stress on hippocampal cytoarchitecture [111]. Future studies are required to resolve where in the continuum glutamate may move from being neuroprotective to excitotoxic in reference to new neuron addition in the adult mammalian brain.

**GAMMA-AMINOBUTYRIC ACID (GABA)**

GABA, like glutamate, has robust effects on embryonic neurogenesis influencing distinct aspects of the process, including precursor cell division, migration and neurogenesis [136]. GABA exerts its effects through the ionotropic GABA\(_A\) receptors and the metabotropic GABA\(_B\) receptor [137]. Due to the nature of the Cl\(^-\) gradient, the extrusion of Cl\(^-\) through the GABA-A channel exerts excitatory depolarizing effects during development, in contrast to the inhibitory hyperpolarizing effects of GABA in the mature brain [46, 136]. It is these depolarizing effects of GABA that are thought to underlie its developmental role [46, 136]. Much like their embryonic counterparts, adult precursor cells also respond to GABA by exhibiting depolarization and acquire the more classical inhibitory adult GABA responsivity as they mature [138]. Adult precursors appear to progress through stages in which they first respond to paracrine GABA signals followed by the appearance of GABA responses driven through synaptic inputs and then the onset of glutamatergic responsivity [46, 138-140]. GABA is ideally poised to exert activity-dependent dynamic effects on adult precursors through both paracrine and synaptic mechanisms.

Adult precursor cells in the SVZ and SGZ exhibit functional GABA\(_A\) receptors, but the expression of GABA\(_B\) and GABA\(_C\) receptors as well as subunit composition of GABA receptors across precursor stages is not known [141, 142]. Within the SVZ, GABA has been reported to be released from precursors in an as yet poorly understood manner and to exert autocrine/paracrine effects through tonic activation of GABA\(_A\) receptors [120, 141]. Precursors within the SVZ also express GABA Transporters (GAT-1, GAT-4), which could further act to modulate the local ambient levels of GABA [120, 143]. Slice culture studies suggest that GABA\(_A\) receptors act to decrease precursor proliferation in the SVZ [141]. It has been hypothesized that precursors in the SVZ may modulate local GABA levels through GABA uptake and set up a “negative feedback loop” to influence precursor proliferation, thus establishing a “tempo” for adult neurogenesis [46, 139]. SVZ precursors entering the RMS still do not have GABA synaptic inputs but exhibit excitatory responses to GABA through GABA\(_A\) receptors [143]. GABA level increases also appear to cause a decline in precursor migration rates [143]. Thus far effects of GABA on neuronal differentiation and functional integration of SVZ precursors into the OB have not been addressed.

SGZ precursors respond to both ambient GABA, the likely source for which are local hilar interneurons, and synaptic GABA release through GABAergic inputs [139]. These effects of GABA are observed on type 2 precursors in the SGZ [117, 139]. Both tonic and phasic activation has been observed in SGZ precursors in response to GABA [117, 139]. However, any influence on precursor proliferation is yet not clear. In vivo studies suggest that GABA\(_A\) agonists (phenobarbital and pentobarbital) cause a decline in proliferation while antagonists (picrotoxin and pentylenetetrazol) increase precursor turnover [117]. As a caveat of these studies, the broad ranging effects after systemic administration of these drugs makes it difficult to ascertain precisely how GABA may be modulating SGZ precursor turnover. Effects of GABA on survival of precursors are suggested by partial lesion experiments of the medial septal pathway, which specifically reduced GABAergic input to the hippocampal formation without affecting cholinergic fibres and showed a decrease in the survival of BrdU-positive cells [144]. Slice culture experiments indicate that GABA enhances expression of the proneural gene NeuroD in nestin-GFP positive SGZ precursors, suggesting that fate commitment to a neuronal lineage may be regulated by GABA-mediated depolarization [116, 117]. Further support for this comes from in vivo evidence that administration of a GABA\(_A\) agonist promotes new neuron formation in the DG [139]. In fact, GABA-induced excitatory responses seem necessary for the maturation and synaptic integration of newborn neurons in the DG [139]. Conversion of GABA-induced depolarization into hyperpolarization in newborn neurons through genetic manipulation of chloride transporters impaired GABA and glutamatergic synapse formation and dendritic arborization [139].

Thus far the evidence points to GABA as being one of the principal modulators of new neuron generation in the adult neurogenic niches [46]. The idea of GABAergic neurotransmission as a target to modulate adult neurogenesis may bear relevance to wide-ranging CNS disease conditions. Neurosteroids like pregnenolone-sulphate increase hippocampal neurogenesis in aged animals through effects on GABA\(_A\) receptors and are known to work as cognitive enhancers [145]. Seizures, ischemia and traumatic brain injury are associated with robust increases in SGZ precursor proliferation and in some cases neurogenesis [75, 76, 78, 79]. Whether changes in GABA levels and GABA-mediated depolarization of precursors contribute to these consequences needs to be determined. Intriguing reports suggest that new-
born neuron development in the adult brain is more pro-
tracted than that in the neonate [146], and it has been sug-
gested that this may be due to lower GABA-mediated excita-
tory network activity. In this context, the fact that seizures
can hasten the integration of newborn neurons in the DG
[147] and at the same time also increase GABA levels in the
milieu [148] raises the possibility that GABA acts to influence
neurogenesis changes caused by seizures. GABA may also
play a role in the effects of stress and animal models of
depression on neurogenesis as these paradigms modulate
GABAergic receptor expression [129]. This is supported by
recent evidence that conditional mutant mice with a het-
erozygous inactivation of the gamma2 subunit of GABA
receptors display both decreased hippocampal neurogenesis,
through reduced survival of precursors, and also behavioral
inhibition to stressful stimuli [149]. GABAergic neurotrans-
munication through modulation of GABA receptors or trans-
porters could also be an interesting target to regulate migra-
tion of SVZ precursors, and in the context of redirecting pre-
cursors to sites of damage this has bearing on devising
strategies to promote repair. It is possible to envisage that
GABA could serve to integrate diverse cues that regulate
network activity and translate this into effects on the turn-
over, survival, migration, dendritic development and synap-
tic integration of new neurons into mature networks.

ACETYLCHOLINE

Acetylcholine (Ach) is known to modulate both olfactory
processing and hippocampal learning and memory, functions
in which adult neurogenesis has been strongly implicated
[150, 151]. Given this information and the presence of cho-
linergic innervation near the neurogenic niches, it is possible
to hypothesize a role for Ach in the regulation of adult SVZ
and SGZ neurogenesis. Initial studies using immunotoxin
192iG-Saporin lesions of basal forebrain cholinergic neu-
rions caused a significant decrease in SGZ precursor prolif-
eration and survival, with an associated deficit in Morris-
Water Maze performance [152, 153]. In contrast, cholinergic
lesions did not appear to alter SVZ precursor turnover [152,
153, 154]. Corroborative evidence indicates that cholinergic
fibres make contacts with PSA-NCAM positive precursors in
the SGZ [155]. Within the SVZ-OB system, cholinergic fi-
bres are not observed to make contacts with precursors in
either the SVZ or RMS although they are seen in close prox-
imity within the neighboring striatum, but they do appear to
make contacts with PSA-NCAM positive OB immature neu-
rions [155]. Further supporting the idea that Ach may regu-
late hippocampal neurogenesis, the cholinesterase inhibitor,
physostigmine, caused a significant increase in the number
of proliferating SGZ precursors [153]. In contrast, a study
with another cholinesterase inhibitor donepezil did not alter
proliferation but significantly enhanced the survival of SGZ
precursors [156].

Acetylcholine exerts its effects through the nicotinic
(nAChR) and muscarinic (mAChR) acetylcholine receptors.
PSA-NCAM positive precursors within the SGZ and in the
OB are found to express the α7 and β2 nAChR subunits and
M1 and M4 mAChRs [153, 155]. The mAChR antagonist
scopolamine decreased SGZ precursor survival whereas ad-
ministration of the nAChR agonist nicotine was found to re-
duce precursor proliferation and promote apoptosis in the
SGZ [157-159]. Interestingly, mutant mice lacking the β2
nAChR subunit appear to exhibit decreased SGZ precursor
proliferation restricted to a specific age (7-10 months) but
not seen in young (3 months) or aged (22-24 months) mu-
tants [160]. Clearly, further studies including in vitro ex-
periments are required to address the role of specific AchRs
in regulating adult neurogenesis and to determine if these
effects are mediated directly at the level of the precursor.

From the point of view of therapeutic interventions, the
effects of Ach on neurogenesis may be pertinent to the cog-
nitive impairment seen in aging dementia and Alzheimer’s
disease, both of which are associated with cholinergic dys-
function [161]. In this regard, studies indicate that the cho-
linesterase inhibitor (Aricept) used therapeutically in Alz-
heimer’s disease does enhance SGZ precursor survival [155,
156]. It has been suggested that the prosurvival effects of
Ach may be mediated via the transcription factor cAMP
response element binding protein (CREB) that regulates
precursor survival in the SGZ [156]. Further, cholinergic lesions
resulted in adverse effects on neurogenesis and watermaze
performance, which were ameliorated by treatment with a
cocktail of neurogenesis promoting molecules like basal fi-
broblast growth factor (FGF), retinoic acid and nerve growth
factor (NGF) indicating the possibility of interventional
therapies in animal models with cholinergic dysfunction
[154]. At present how or whether Ach neurotransmission
contributes to the regulation of neurogenesis seen in animal
models of depression, stroke, seizure, Huntington’s disease
and Alzheimer’s disease is unknown. In summary, to iden-
tify how the neurogenic effects of Ach could be tapped for
therapy there is an urgent need to better understand the regu-
lation of adult neurogenesis by Ach in both normal and
disease conditions.

DOPAMINE

Dopamine (DA) exerts trophic effects during embryonic
neurogenesis modulating diverse aspects of development
such as proliferation, differentiation as well as maturation of
precursors [162, 163]. Recent evidence indicates that DA has
a stimulatory effect on neurogenesis in the mature mammal-
ian brain [164]. Lesions of dopaminergic projections to the
forebrain using 6-hydroxydopamine (6-OHDA) and 1-
methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) result in
a significant decline in precursor proliferation in the SVZ
and SGZ [165-167], an effect thought to be mediated in the
SVZ at the level of turnover of the transit-amplifying Type C
cells. These lesion effects appear to be due to a decline in
dopamine levels as they can be rescued by levodopa treat-
ment of lesioned animals [167]. Interestingly, while prolif-
eration in the SVZ declines with 6-OHDA lesions there is an
increase in the number of SVZ precursors expressing the
proneural gene Pax6 [166]. Further, in DA lesioned animals
there is a robust shift in precursor differentiation in the OB
towards a dopaminergic glomerular interneuron fate suggest-
ing effects of DA on fate choice of SVZ precursors [166].
DA modulation of precursor proliferation appears to be con-
served across species reduced SVZ precursor proliferation is
also seen in non-human primates with MPTP lesions and in
humans suffering from Parkinson’s disease [167, 168]. Fur-
ther, a decline in SGZ precursors was also seen in Parkin-
sonian patients [167]. More studies have focused on the ef-
effects of DA on SVZ, as compared to SGZ neurogenesis.
Within the SVZ, transit amplifying Type C cells appear to
have synapse-like structures associated with dopaminergic afferents that are suggested to originate from the substantia nigra based on tracing studies [168]. In the SGZ while dopaminergic afferents are indeed present in close proximity to the precursors it is not known if they make synapse-like contacts [167].

Dopaminergic neurotransmission is mediated via the D1-like (D1 and D5) and D2-like (D2, D3 and D4) receptors. Within the SVZ, there is strong D3 expression and based on immunohistochemical analyses Type C precursors are thought to express D2-like receptors, while Type A cells are immunonegative for both D1 and D2-like receptors [167]. In vitro evidence indicates the expression of D1 and D2-like receptors on SVZ neurosphere cultures [167, 169, 170]. The DA lesion induced decline in SVZ precursor proliferation is rescued by treatment with D2-like agonists, through an increase in proliferation of the Type C cells [167]. In vitro studies indicate that dopamine as well as D2-like agonists, bromocriptine and apomorphine increase precursor proliferation, while the D1-like agonist, SKF38393 did not appear to have an effect [167, 169]. Contradictory reports suggest an increase in primary neurospheres derived from the SVZ of animals given chronic administration of the D2-like agonist, haloperidol and further a decline in neurospheres cultured with DA or the D2-like agonist quinpirole [170]. These studies were interpreted as evidence of reduced proliferation of Type B cells in response to DA, but given the lack of evidence of DA receptors on B cells in vivo this is still contentious. Further, D3 agonists increase SVZ precursor proliferation in rats but not mice suggesting that the effects of dopamine via this receptor in the SVZ may also exhibit species differences [171]. In the SGZ, studies suggest that chronic haloperidol treatment does not appear to modulate hippocampal neurogenesis [172]. Thus far the majority of the evidence points to a stimulatory effect of DA on precursor proliferation in the SVZ and SGZ, as well as effects on fate choice in the OB.

Dopaminergic neurotransmission has been the major target for development of antiparkinsonian and antipsychotic drugs [173]. Interestingly, Parkinsonian and schizophrenic patients show comorbidity for mood [174, 175] and cognitive deficits [176, 177] that have been preclinically linked to changes in adult neurogenesis, and a decline in precursor proliferation has been observed in Parkinson’s [167] and schizophrenic patients [93]. Given the role of DA in both the pathophysiology and treatment of these diseases, this neurotransmitter has the possibility of alleviating some of the clinical sequelae of these diseases through regulation of adult neurogenesis. Although in this review we have discussed DA effects on the major neurogenic niches, it is important at this juncture to mention that there has been considerable scientific debate on the possibility of neurogenesis in the substantia nigra and striatum, and its modulation by DA [164]. These studies, though at present controversial have attracted attention due to the clinical interest in the possibility of repairing nigrostriatal circuit dysfunction in neurodegenerative disorders like Parkinson’s and Huntington’s disease. Dopaminergic neurotransmission may also have a role to play in the decline in hippocampal neurogenesis seen with chronic cocaine administration [178] and in animal models of stress/depression [54].

**NOREPINEPHRINE**

Several studies have evoked a non-neurotransmitter role for norepinephrine (NE) during brain development with effects on proliferation and differentiation of embryonic precursors [110,179]. In adulthood, a dense noradrenergic innervation is observed in the SGZ neurogenic niche, but in comparison within the SVZ the innervation is very sparse [180-182]. Suggesting a role for norepinephrine in adult hippocampal neurogenesis, we observed a robust decline in SGZ precursor proliferation with no effects on precursor survival or differentiation in lesion studies using the noradrenergic neurotoxin, DSP-4 [181]. Further, chronic treatment with a selective norepinephrine reuptake inhibitor reboxetine enhanced SGZ precursor proliferation [51]. Both the lesion and reuptake inhibitor studies showed effects selectively on SGZ precursors with no changes observed in the SVZ [51,181].

Noradrenergic receptors are classified into α1, α2, β1, β2 and β3 classes, however it is unknown which of these receptors are expressed by adult precursors. Recent reports have implicated the α2 adrenergic receptor in the regulation of adult neurogenesis both in the SVZ and SGZ [183, 184]. The α2 adrenergic receptor acts both as a presynaptic autoinhibitory feedback receptor and is also present postsynaptically. Treatment with the α2 adrenergic receptor antagonist dexefaroxan while not altering SVZ precursor proliferation, appears to enhance precursor survival in the OB [183]. Further, dexefaroxan treatment selectively increased survival and differentiation of SGZ precursors with no effects on their proliferation [184]. Given the effects of α2 adrenoceptors on memory function, it will be particularly interesting to address whether neurogenic changes contribute to the cognitive effects of these receptors [185, 186].

Amongst the agents that directly modulate NE and also regulate adult hippocampal neurogenesis are major classes of antidepressants [187]. While the effects of NE in mediating the neurogenic actions of antidepressants are unknown this line of investigation holds promise for the identification of possible novel ways to modulate adult neurogenesis and potentially regulate mood related behavior. Further, NE exerts potent anticonvulsant effects and given the robust effects of seizures on adult neurogenesis [188], it will be interesting to address how NE fits into the picture in this regard. Studies on the role of noradrenergic neurotransmission in regulating adult neurogenesis are still at early stages. However, the fact that NE has an important role in modulating neurogenesis linked functions like olfaction [189], memory and mood [190], and that dysfunction is associated with neurodegenerative [191] and psychiatric disorders [192] highlights the importance of future studies to address how NE may regulate adult neurogenesis.

**SEROTONIN**

Amongst the monoamines, a trophic role in development, and a regulation of adult neurogenesis was first evoked for serotonin (5-HT) [193-195]. The serotonergic system, one of the earliest to develop in the immature brain has been shown to influence precursor proliferation, survival, and neuronal morphology [193,195,196]. In the adult brain the first report to suggest a role for 5-HT in neurogenesis came from studies of decreases in SVZ and SGZ precursor proliferation
following 5-HT depletion using both neurotoxic lesions and serotonin synthesis inhibitors [198]. Supporting the idea that this proliferative decline was due to a lack of 5-HT, reinnervation by 5-HT neurons or transplantation with fetal serotoninergic neurons was capable of promoting a rescue [198, 199]. However, there are still discrepancies in the reported results of the effects of 5-HT depletion on adult hipocampal neurogenesis with either a decrease or no effect on proliferation observed [197, 200-202]. Further support for the idea that 5-HT may regulate adult neurogenesis comes from several studies that indicate an increase in hippocampal neurogenesis, through effects on SGZ precursor proliferation and survival, following chronic treatments with serotonin selective reuptake inhibitors (SSRI) like fluoxetine [51, 63, 203]. These effects appear to involve proliferative increases in transit amplifying Type 2A cells in the SGZ [204]. In contrast to studies with SSRIs, 5-HT transporter knockout mice that have elevated 5-HT levels did not show any changes in SGZ precursor proliferation or survival at a young age (7 weeks and 3 months) and actually exhibited a decreased proliferation as they aged (14.5 months) [204]. Further, there are reports that the neurogenic effects of SSRIs like fluoxetine may be dependent on the genetic background, based on studies with inbred mouse strains [205]. Taken together, these studies suggest a stimulatory effect of 5-HT on adult hippocampal neurogenesis, however some of the conflicting results obtained indicate that the effects of 5-HT on SGZ neurogenesis may involve a yet to be elucidated, complex interplay of several factors.

The complexity of the neurogenic effects of 5-HT is underscored by the fact that 5-HT acts through a large family (7 receptor families, 5-HT1-7 and 14 receptor subtypes) of serotoninergic receptors, some of which have been reported to exert opposing effects on adult precursor proliferation [208]. Although it is not known if adult precursors in the SVZ and SGZ express functional 5-HT receptors, in vivo studies with 5-HT receptor selective agonists and antagonists have been reported to change SVZ and SGZ precursor proliferation. In the SVZ, the 5-HT1A agonist, 8-OH-DPAT stimulates the proliferation of precursors, whereas the 5-HT1B agonist, sumatriptan causes a decrease in SVZ precursor proliferation, with the 5-HT1B antagonist, GR127935 resulting in an increase in SVZ precursor turnover [206]. SVZ precursor cell division is also increased by the 5-HT2A agonist (DOI) as well as a 5-HT3 (RO600175) selective receptor agonist [206]. Within the SGZ, 5-HT1A receptor stimulation increases basal precursor proliferation, and can rescue the decreased turnover of SGZ precursors seen in 5-HT depleted animals created by injections of the 5-HT synthesis inhibitor (PCPA) [206, 207]. While 5-HT1B receptors do not appear to alter basal SGZ precursor proliferation, the 5-HT1B agonist sumatriptan can rescue the decline seen in 5-HT depleted animals [206]. In the SGZ, although the 5-HT2A agonist DOI had no effect, acute 5-HT2A blockade caused a decrease in precursor proliferation [206], whereas our unpublished results indicate that chronic treatment with 5-HT3A antagonists increases SGZ precursor turnover. A recent study indicates that treatment with the 5-HT3 agonist RS 67333 increases SGZ precursor proliferation [208]. Taken together, these studies suggest that 5-HT may have differential effects via distinct 5-HT receptors on SVZ and SGZ precursors. However, we do not know which of the 5-HT receptors are expressed by precursors in these neurogenic niches and whether this expression is modulated during precursor progression through different developmental milestones. Also, it is unclear if 5-HT effects on precursors are synaptic or through non-synaptic changes in ambient 5-HT. Experiments are required to address the precise role of 5-HT and its distinct receptors in regulating adult neurogenesis.

Elevated levels of serotonin have been hypothesized to contribute to the antidepressant-mediated increases in hippocampal neurogenesis, whilst a reduction in this monoamine may underlie the decline in neurogenesis observed in animal models of depression and stress [209, 210]. Support for this hypothesis comes from studies in which both the neurogenic and behavioral changes in response to chronic treatment with the antidepressant fluoxetine are lost in 5-HT1A receptor knockout mice [63]. However, these mutant mice continue to display increased neurogenesis in response to a different class of antidepressants the norepinephrine selective reuptake inhibitor desipramine, adding weight to the idea that antidepressants belonging to different classes may recruit diverse pathways to modulate hippocampal neurogenesis. A recent report suggests that genetic background may be critical in determining whether neurogenic responses to antidepressants, and the 5-HT1A contribution to the same, are required for the behavioral effects of these therapeutic agents in mouse models [211]. A recent elegant study demonstrates that 5-HT4 receptor agonists can exert a rapid effect on both neurogenesis as well as depression related behaviors suggesting that this receptor may be an important target in the development of faster acting antidepressants [210]. While treatment with SSRIs have been reported to reverse the decline in hippocampal neurogenesis seen in depression models [53], an atypical antidepressant tianeptine that enhances serotonin reuptake also prevents stress-induced decreases in SGZ precursor proliferation [212], adding complexity to our understanding of the actions of 5-HT in the neurogenic decline in depression models. The emerging picture indicates that there is indeed a role for 5-HT in both basal neurogenesis and in the changes seen in depression models and with antidepressants. This also provides strong impetus for studies to dissect out the intricacies of how 5-HT regulates neurogenic effects in both normal physiology and in pathological contexts. While the majority of preclinical studies have focused on 5-HT and its neurogenesis effects with relevance to depression, given the broad modulatory influences of this neurotransmitter system future studies need to address whether the neurogenic effects of 5-HT can be exploited for treatment of neurological, neurodegenerative and psychiatric disorders.

**NEUROPEPTIDES**

Besides the canonical neurotransmitters, neuropeptides also have an important role in nervous system physiology [213]. Several recent studies indicate that neuropeptides may also act to dynamically modulate adult neurogenesis. Neuropeptide Y (NPY) has been reported to stimulate SGZ precursor proliferation via the Y1 receptor and Y1 knockout mice show decreased basal hippocampal neurogenesis [214, 215]. NPY has also been evoked to play a role in seizure-induced neurogenesis and Y1 receptor knockout mice show a significant decline in seizure-mediated SGZ precursor proliferation [216]. Besides a possible role in epileptogenesis,
NPY is also a relevant target that has been preclinically linked to depression with reduced NPY seen in depression models [217] and an antidepressant-like effect of NPY administration being observed in models of depression [218]. The neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP) also has a stimulatory effect on proliferation of adult precursors derived from the DG, and intracerebroventricular infusion of PACAP in the adult mouse increased both SGZ and SVZ precursor proliferation [219]. These effects of PACAP could be direct as adult precursors express the PACAP receptor PAC1 [219]. Although substance P has not been shown to directly modulate hippocampal neurogenesis, disruption of its preferred receptor, neuropeptide, galanin-1 (NK-1), in mutant mice results in both increased SGZ precursor proliferation as well as antidepressant-like behavior [66, 220]. NK-1 antagonists have been recently demonstrated to exhibit antidepressant-like activity and the neurogenesis modulatory effects of NK-1 are particularly interesting in this regard [221]. While the role of vasoactive intestinal peptide (VIP) in regulating adult neurogenesis is yet to be examined, at high concentrations it is reported to increase SVZ precursor proliferation in vitro [219]. The neuropeptide, galanin is thought to exert an anticonvulsant effect in seizure models, and genetic perturbation of the GalR2, but not GalR1, receptor results in an inhibition of seizure-stimulated neurogenesis in the DG [222, 223].

Endogenous opioids have been suggested to reduce adult hippocampal neurogenesis based on studies with the opiates morphine and heroin. Chronic treatment with morphine or self-administration of heroin in animal models results in a decline in SGZ precursor proliferation [224], raising the possibility that a neurogenic decline may contribute to some of the behavioral effects of these drugs. Adult SGZ precursors exhibit release and binding of β-endorphin and express μ and δ opioid receptors indicating that opioids could have a direct effect on these cells [225]. Reduced signaling through μ and δ opioid receptors in vitro resulted in a reduction in cell proliferation and drove progenitors towards neuronal lineage and reduced glial fate choice [225]. Further, recent studies with μ opioid receptor knockout mice, reveal no effect on precursor proliferation in the SGZ but a significant increase in the survival of precursors correlating with more granule cell neurons in both homozygote and heterozygote mice [226]. Taken together, these studies suggest a role for endogenous opioids in modulating multiple aspects of hippocampal neurogenesis, namely birth, survival and fate determination.

Besides the endogenous opioids, a role for endocannabinoids in adult neurogenesis has also been evoked. Endocannabinoids via the cannabinoid 1 (CB1) receptor increase SGZ precursor cell division and CB1 stimulation also promotes antidepressant-like behavior in animal models, an effect that requires the CB1-mediated neurogenic changes [227, 228]. A role for endocannabinoids in stress-induced decreases in hippocampal neurogenesis, has also been suggested based on a study wherein treatment with an endocannabinoid reuptake inhibitor attenuated both predator odor-induced decreases in SGZ proliferation and associated defensive-burying behaviors [229]. Collectively, these studies point to a role for neuropeptide neurotransmission as an important facet in the regulation of ongoing neurogenesis in the adult mammalian brain, and point to possible new targets to recruit and modulate endogenous precursors.

CONCLUSIONS AND FUTURE PERSPECTIVES

A deeper understanding of how new neuron generation in the mature mammalian brain is regulated, holds immense hope for the future possibility of tapping this potential to restore, repair, replace and regenerate damaged neuronal circuits. Given the restricted ability to provide only symptomatic relief for a large number of CNS diseases, this glimmer of hope has opened up a completely new avenue for the development of possible curative as well as palliative treatment strategies. For this possibility to be achieved, both studies that address the very fundamental biology of new neuron addition as well as more translational approaches that focus on neurogenesis in disease models will have to go hand in hand. Current therapies for several brain disorders are largely based on modulating specific neurotransmitter signaling, and given the building evidence that neurotransmitters can regulate diverse aspects of adult neurogenesis (Table 1), existing drugs may now have a novel cellular target. While this field is indeed promising, it is important as a word of caution to realize that only a deeper understanding of the basic biology of new neuron generation will allow us to evaluate which neurological and psychiatric disorders may benefit, and how, from targeting this process for therapy. Nonetheless, new neuron generation as a drug target with its implications for neurological, neurodegenerative and psychiatric disorders is amongst the major exciting neuroscience discoveries of our times.

ACKNOWLEDGEMENTS

We express our regrets to authors whose work was not cited due to space constraints. We acknowledge Avinash R. Vaidya, Himanish Ghosh and Dr. Uma Ladiwala for technical assistance with the figures. V.V is supported by a Wellcome Trust International Senior Research Fellowship (04082003114133) in Biomedical Science in India.

ABBREVIATIONS

6-OHDA = 6-Hydroxydopamine
5-HT = 5-Hydroxytryptamine, Serotonin
8-OH-DPAT = 8-Hydroxy-2-(di-n-propylamino)-tetralin
Ach = Acetylcholine
AMPA = Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APV = DL-2-Amino-5-phosphonovaleric acid
Bcl-2 = B-cell lymphoma 2
BrdU = 5-Bromo-2-deoxyuridine
Ca²⁺ = Calcium ion
CB1 = Cannabinoid receptor 1
CGP-43487 = D-(E)-2-amino-4-methyl-5-phosphono-3-pentenoic acid
Cl⁻ = Chloride ion
CNQX = 6-Cyano-7-nitroquinoxaline-2,3-dione
CNS = Central nervous system
CREB = cAMP response element binding protein
DA = Dopamine
DCX = Doublecortin
gDNA = Dentate gyrus
DOI = 2,5-Dimethoxy-4-iodoamphetamine
DSP-4 = N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine
FGF = Fibroblast growth factor
GABA = Gamma amino butyric acid
GAT = Gamma amino butyric acid transporter
GFAP = Gliarial fibrillary acidic protein
GFP = Green fluorescent protein
Hes-1 = Hairy and enhancer of split 1
Id2 = Inhibitor of DNA binding 2
LTP = Long term potentiation
LY367385 = (MCPG) (+) -
MAChR = Muscarinic acetylcholine receptor
mGlu = Metabotropic glutamate receptor
mGluR = Metabotropic glutamate receptor
MGS0039 = (1R,2R,3R,5R,6R)-2-Amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid
MK-801 = (5R,10S)-(+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate
MPTP = 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
nAChR = Nicotinic acetylcholine receptor
NE = Norepinephrine
NGF = Nerve growth factor
NK-1 = Neurokinin 1
NMDA = N-methyl-D-aspartic acid
NPY = Neuropeptide Y
OB = Olfactory bulb
PCPA = p-Chlorophenylalanine
pERK = Phosphorylated extracellular-signal-regulated kinase
PLC = Phospholipase C
PSA-NCAM = Polysialylated neural cell adhesion molecule
RMS = Rostral migratory stream
RO600175 = S-2-(6-chloro-5-fluoro-indol-1-yl)-1-methyl-ethylamine
SGZ = Subgranular zone
SKF38393 = 1-Phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol Hydrochloride
SSRI = Selective serotonin reuptake inhibitor
SVZ = Subventricular zone
vEGF = Vascular endothelial growth factor
VIP = Vasoactive intestinal peptide

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