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Review

Adult hippocampal neurogenesis: regulation by HIV and drugs of abuse

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Abstract. New dentate granule cells are continuously generated from neural progenitor cells and integrated into the existing hippocampal circuitry in the adult mammalian brain through an orchestrated process termed adult neurogenesis. While the exact function remains elusive, adult neurogenesis has been suggested to play important roles in specific cognitive functions. Adult hippocampal neurogenesis is regulated by a variety of physiological and pathological stimulations. Here we review emerging evidence showing that HIV infection and several drugs of abuse result in molecular changes that may affect different aspects of adult hippocampal neurogenesis. These new findings raise the possibility that cognitive dysfunction in the setting of HIV infection or drug abuse may, in part, be related to alterations in hippocampal neurogenesis. A better understanding of how HIV and drugs of abuse affect both molecular and cellular aspects of adult neurogenesis may lead to development of more effective therapeutic interventions for these interlinked epidemics.

Keywords. Neurogenesis, hippocampus, HIV, drug abuse.

Introduction

Neurogenesis, a process of generating functionally integrated neurons from progenitor cells, was previously thought to occur only in the developing central nervous system (CNS). However, it has recently been established that multipotent neural progenitor cells (NPCs) are present in discrete regions of the adult mammalian brain and are capable of giving rise to functional neurons and glia [1 – 4]. In most mammals, active neurogenesis continues throughout adulthood in the subventricular zone of the lateral ventricle to generate interneurons in the olfactory bulb and in the subgranular zone of the dentate gyrus to generate granule cells in the hippocampus. In other areas of the intact brain, active adult neurogenesis appears to be very limited or nonexistent under normal conditions, but may be activated after pathological insults [5]. Rapid advances in the field of adult neurogenesis have led to the demonstration of dynamic regulation of different aspects of adult neurogenesis by both physiological and pathological stimulations [3, 6]. Accumulating evidence also suggests that adult neu-

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rogenesis is involved in specific cognitive functions, such as learning and memory [7–9].

HIV infection and drug abuse are interlinked epidemics throughout the world [10–13]. On their own, either HIV or substance abuse lead to neurocognitive deficits [14–17]. HIV-infected individuals demonstrate impairment in attention, executive function, psychomotor speed, and motor and learning skills [18–20]. Although the use of highly active antiretroviral therapy (HAART) over the past several years has significantly reduced the incidence of severe HIV dementia, this reduction appears to be counterbalanced by an increase in prevalence due to improved survival rates [21–24]. In addition, mounting evidence suggests that HIV-infected patients with a history of drug abuse have accelerated and more severe neurocognitive dysfunction and psychomotor slowing compared with non-drug-abusing patients [25, 26]. However, the molecular and cellular basis of neurocognitive deficits in the setting of HIV infection and drug abuse is still poorly understood. It is critically important to identify cellular and molecular targets of CNS injury for the development of therapeutic strategies for this population of individuals. Here we discuss emerging evidence of the impact of HIV infection and substance abuse on adult hippocampal neurogenesis, with an emphasis on potential molecular and cellular mechanisms. Interested readers can consult several recent comprehensive reviews on adult neurogenesis [2–4, 27].

Potential functions of adult hippocampal neurogenesis

The recognition of adult neurogenesis in the hippocampus and olfactory bulb has raised the following critical questions: 1) Are the neurons born during adulthood functional? and 2) What roles do these new neurons serve in the adult brain? To answer the first question, a retrovirus-mediated birth-dating and labeling approach was combined with electrophysiological analysis to demonstrate that newborn neurons in the adult brain are capable of firing action potentials and receiving functional GABAergic and glutamatergic synaptic inputs within 1 month after their birth [28–31]. Imaging analysis using c-fos or Arc, two activity-induced genes, further supported the notion that newly generated neurons are actively involved in hippocampal and olfactory functions [28–31]. Morphological analysis also has shown extension of newborn granule cell axons to their putative target regions [32–34]; however, direct electrophysiological evidence that new neurons make functional synaptic outputs in the adult brain remains lacking.

Does the synaptic integration of newly generated neurons in the adult contribute to cognition? In their initial discovery of adult neurogenesis, Altman and colleagues hypothesized that adult neurogenesis is involved in learning and memory [35]. The first evidence to support this hypothesis came from studies in songbirds [36, 37]. New neurons were shown to be recruited into existing circuits and to respond to sound stimulation; ablation of these new neurons affected song learning. Recent ablation experiments in rodents using antimitotic compounds and localized irradiation have revealed impairment in several specific cognitive processes, including fear conditioning, spatial learning and spatial memory [38–41]. However, potential side effects of these treatments on other physiological processes, including toxicity to mature cell types or induction of inflammation responses within the CNS, preclude definitive conclusions about the role of neurogenesis in mammalian cognition. As discussed below, additional studies have provided correlative evidence for a reciprocal relationship between adult neurogenesis and learning and memory [42–45]. Overall, although definitive demonstration of the exact function in mammals is still lacking, accumulative evidence supports the view that adult hippocampal neurogenesis plays an important role in learning and memory [8, 9, 44] and contributes to the maintenance of cognitive function [46, 47].

Regulation of adult hippocampal neurogenesis

Adult neurogenesis is a developmental process that includes proliferation and fate specification of adult neural progenitors, maturation, migration, targeting, synapse formation and survival of neuronal progeny (Fig. 1). Both intrinsic and extrinsic factors have been shown to regulate various steps of adult hippocampal neurogenesis [1–4, 48, 49]. One of the intrinsic factors with a significant impact on adult neurogenesis is the genetic background in mice [50]. Recently, a panel of inbred mouse strains was analyzed and showed significant differences in neural precursor cell (NPC) proliferation, differentiation and survival of newborn neurons in the adult hippocampus. These phenotypic data were then correlated with microarray-based whole-brain gene expression analysis to identify a set of 190 genes whose expression covaries with alterations in specific phases of development of newly generated dentate granule cells [51]. Such approaches will likely lead to a better understanding of the intrinsic genetic influences on hippocampal neurogenesis and serve to delineate how changes at the molecular level (expression patterns of genes) translate into

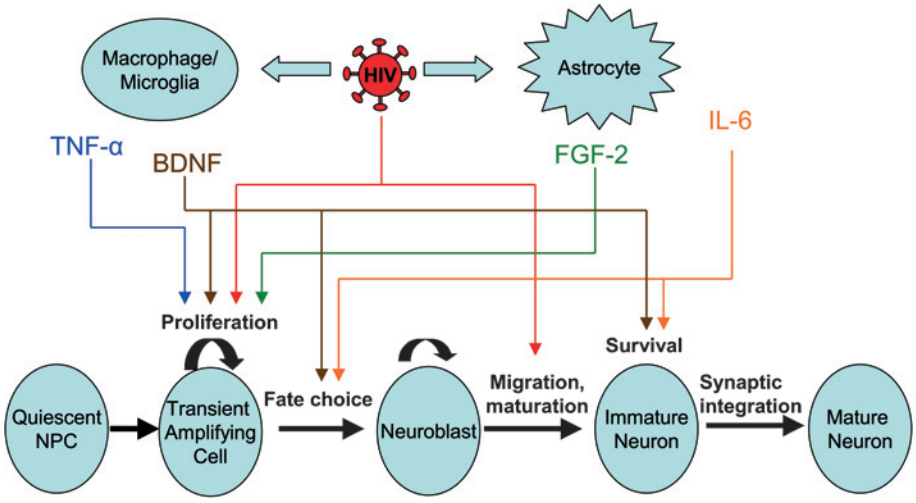

Figure 1. Potential mechanisms by which HIV affects adult hippocampal neurogenesis.

changes in the cellular underpinnings of neurogenesis (as measured by proliferation, survival, differentiation and function of newly generated cells).

A range of environmental stimuli, including learning, environmental enrichment and stress, have profound effects on proliferation and differentiation of neural progenitors as well as survival of their progeny in the adult dentate gyrus [3, 52]. For example, training rats with specific hippocampal dependent tasks, such as fear conditioning or spatial learning, leads to increases in the number of newborn cells in the dentate gyrus [42–44]. Physical exercise also promotes hippocampal neurogenesis [53, 54], possibly through changes in vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) levels [55, 56]. Importantly, exercise-induced increases in adult hippocampal neurogenesis were correlated with enhanced long-term potentiation in the dentate gyrus and improved spatial learning [54].

A variety of hormones and drugs also regulate adult hippocampal neurogenesis [3]. For example, corticosteroids decrease subgranule zone neurogenesis likely through activation of either the glucocorticoid receptor or the mineralocorticoid receptor, and increasing levels of this hormone during aging or stress may mediate the reductions in neurogenesis [57, 58]. On the other hand, several psychotropic drugs, including serotonin selective and norepinephrine selective reuptake inhibitors, increase neurogenesis, at least in part through increases in VEGF and BDNF levels [59]. Such increases in adult hippocampal neurogenesis occur over several weeks, paralleling the onset of the antidepressant action of these drugs [59]. The molecular mechanisms by which many of these external stimuli affect neurogenesis are not well understood, and this remains an active area of current research.

Adult hippocampal neurogenesis is also altered under a variety of pathological conditions. Epilepsy, for example, is associated with a marked increase in proliferation of hippocampal NPCs [60, 61]. The resulting newly generated granule cells exhibit abnormal migration and accelerated integration, which may participate in aberrant networks that contribute to seizure development or recurrence [60, 61]. On the other hand, reduction in hippocampal neurogenesis due to inflammation, aging and stress is hypothesized to contribute to the cognitive decline observed in these settings [3, 7, 62]. Below, we discuss emerging evidence suggesting that both HIV and drugs of abuse also modulate adult hippocampal neurogenesis, thereby potentially contributing to cognitive dysfunction.

Modulation of neurogenesis by HIV: potential molecular mechanisms

Much of the effort to understand how HIV affects the CNS has been focused on the deleterious effects of viral infection on mature neurons. Although HIV does not productively infect neurons, extensive neuronal loss in many brain areas has been widely demonstrated in HIV dementia [63–65]. Neuronal loss is accompanied by a variety of other histopathological changes, including activation of astrocytes and microglia, demyelination and dendritic pruning [66, 67]. Perivascular macrophages and microglia are a major target of HIV infection within the brain, leading to the hypothesis that the observed neurotoxicity is an indirect effect of HIV-infected cells [68]. Indeed, infected macrophages and activated astrocytes secrete

a variety of inflammatory mediators, including interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and monocyte chemoattractant protein 1 (MCP-1), that have been hypothesized to play a major role in HIV neurotoxicity [69]. In addition, HIV proteins alone can cause neurotoxicity. Of these, the HIV envelope protein gp120 and the transcriptional activator Tat have emerged as likely mediators of viral neurotoxicity, both *in vitro* and *in vivo* [70].

Despite significant progress in understanding the molecular mechanisms underlying HIV infection-induced neurotoxicity, few studies have directly examined how adult hippocampal neurogenesis is affected during the course of HIV infection, and whether such alterations may contribute to HIV-associated neurologic dysfunction. In one recent autopsy-based study, immunohistochemical analysis of hippocampal tissue demonstrated a reduction in proliferating hippocampal NPCs in patients with HIV-associated dementia as compared to non-demented HIV-infected patients and controls [71]. Although this decrease may reflect general pathogenic mechanisms arising in the setting of late-stage dementia rather than specific effects of HIV on neurogenesis, emerging evidence suggests that adult hippocampal neurogenesis is affected by altered expression of cytokines or growth factors [72–77], several of which are modulated by HIV infection (Fig. 1). In addition, HIV may have direct effects on NPCs either via interaction between HIV proteins and NPC surface receptors, or by infection of NPCs themselves [78, 79].

SDF-1/CXCR4 signaling

Chemokines, small secreted proteins that signal through the activation of G-protein-coupled receptors, are grouped into four families based upon structural motifs [80]. Studies of knockout mice suggest that the chemokine stromal derived factor-1 (SDF-1) serves as a chemoattractant and signals through its receptor CXCR4 to regulate embryonic neuronal development. Deletion of either gene leads to abnormalities in the embryonic development of the cerebellum [81, 82], hippocampus [83, 84], and neocortex [85], manifested largely by defects in NPC proliferation and migration of immature neurons. In the adult brain, SDF-1 is expressed in the dentate granule cell layer, and expression of CXCR4 was detected in the subgranular zone [84, 86]. CXCR4 is also prominently expressed by adult mouse and human NPCs in culture [78, 87]. Such a close juxtaposition between NPCs expressing CXCR4 and mature neurons expressing SDF-1 suggests that granule cells may influence NPC proliferation and migration in the adult hippocampus [88].

How might HIV interfere with the SDF-1/CXCR4 interaction? T-cell tropic strains of HIV, which use CXCR4 as a co-receptor along with CD4 as the principal receptor for viral entry, are found in the brains of infected patients [89]. *In vitro* studies using mouse NPCs demonstrate that the HIV envelope protein gp120, when complexed with human CD4 (hCD4), interacts with CXCR4 on the surface of NPCs. The hCD4/gp120 complex induces calcium fluxes and activates the MAP kinase pathway in a similar fashion to SDF-1 [79]. However, gp120 does not mimic the chemoattractive or proliferative effects of SDF-1 on NPCs [90]. Instead, hCD4/gp120 blocks SDF1-mediated NPC chemoattraction and proliferation, through mechanisms distinct from receptor antagonism [79]. These studies raise the possibility that the HIV gp120 protein may directly inhibit SDF1-mediated NPC proliferation and migration through interaction with the CXCR4 receptor during adult neurogenesis.

Inflammatory cytokines

Inflammatory cytokines are known to regulate various steps of adult neurogenesis. Cytokines such as interleukin-4 and interferon-γ, for example, may potentiate neuronal differentiation through effects on microglia [91]. HIV infection alters expression of several cytokines in the CNS, including MCP-1, IL-6, and TNF-α [69]. Here, we focus on the potential for altered expression of the latter two cytokines to affect adult neurogenesis in the setting of HIV infection.

Interleukin-6

IL-6 is expressed by CNS astrocytes predominantly under pathological circumstances and exerts multiple effects, either beneficial or detrimental, on mature neurons [92]. The effects of IL-6 on NPCs have only recently been investigated. *In situ* hybridization studies revealed high expression of the IL-6 receptor complex in the hippocampal subgranular zone [93]. *In vitro,* IL-6 may either inhibit or promote neurogenesis, likely depending upon levels of cytokine and culture conditions [94, 95]. *In vivo* studies with transgenic mice chronically overexpressing IL-6 in astrocytes showed decreased proliferation, survival, and neuronal differentiation of adult hippocampal NPCs [75]. Different from gliogenic effects of IL-6 on embryonic precursor cells *in vitro* [96], no increase in hippocampal gliogenesis was noted.

Several studies on HIV-infected patients have demonstrated increased levels of IL-6 in both cerebrospinal fluid (CSF) and brain parenchyma [97–100]. CSF IL-6 is detected more frequently and at higher concentrations in patients with advanced HIV infection as compared to those at early stages [97]. In a

simian immunodeficiency virus (SIV)-macaque model of HIV encephalitis, CNS IL-6 is upregulated in acute SIV encephalitis [101], and remains elevated in the post-acute and chronic phases of the disease [102]. How might HIV infection lead to increases in CNS IL-6? One mechanism may be via the effects of HIV proteins, since both gp120 and Tat can stimulate the production of IL-6 [103, 104]. Indeed, transient Tat exposure causes sustained increases of IL-6 from astrocytes; interestingly, such increases are exacerbated in the presence of drug of abuse, such as opiates [103, 105]. Thus, it is possible that both acute and chronic HIV infection may affect adult hippocampal neurogenesis in part through upregulation of IL-6 within the CNS.

Tumor necrosis factor-α

TNF-α is a proinflammatory cytokine produced in the CNS predominantly by activated microglia [106], and exerts either toxic and protective effects on neurons depending upon the receptor subtypes with which it interacts [107]. TNF-Receptor 1 (TNF-R1) contains an intracellular 'death domain' and can contribute to neuronal death, while signaling through TNF-Receptor 2 (TNF-R2) can be neuroprotective [108]. Several *in vivo* studies have demonstrated a complex role for TNF-α in adult hippocampal neurogenesis (Fig. 1). Lipopolysaccharide-induced inflammation, which results in high levels of TNF-α in plasma and CNS, impairs adult hippocampal neurogenesis, likely by decreasing neuronal differentiation and survival [109]. In an acute stroke model in rats, post-stroke infusion of an antibody against TNF-α resulted in reduced survival of newly generated dentate neuroblasts, possibly through interaction with TNF-R2 [110]. More definitive evidence of the differential effects of TNF-R signaling on adult hippocampal neurogenesis came from studies of TNF-R knockout mice [72]. Adult hippocampal NPC proliferation was increased in TNF-R1$^{-/-}$ or TNF-R1/R2$^{-/-}$ mice both under basal conditions and after status epilepticus. TNF-R2$^{-/-}$ mice, on the other hand, exhibited decreased proliferation after status epilepticus. Overall, these results suggest that signaling through TNF-R1 negatively regulates neurogenesis, while signaling through TNF-R2 may enhance adult hippocampal neurogenesis, particularly after pathologic insult.

Does HIV affect the expression of either TNF-α or its receptors? Immunohistochemical analysis of brains from patients with AIDS does demonstrate an increased expression of CNS TNF-α [98]. TNF-R1 and TNF-R2 are also upregulated, but predominantly in activated macrophages and microglial cells [98]. Application of HIV to primary rat brain cells causes increased expression of TNF-α, likely from astrocytes and microglia [111]. Since rat glial cells, unlike human glia, are not productively infected by HIV, these results suggest that interaction of CNS cells with HIV proteins may be sufficient for the induction of TNF-α. Indeed, HIV gp120 induces the expression and secretion of TNF-α in mouse astrocytes [112] and human brain cell cultures [104]. Furthermore, injection of HIV Tat into the mouse hippocampus results in increased expression of TNF-α [113]. Although these studies demonstrate that HIV induces TNF-α expression in the CNS, the potential effects of such induction on neurogenesis remain unclear given the complex nature of TNF-R signaling. It will be of interest to determine whether specific TNF-R subtypes are induced by HIV, and whether such induction affects adult hippocampal neurogenesis.

Growth factors and neurotrophins

Expression and/or signaling of a number of growth factors and neurotrophins, including glial-derived neurotrophic factor (GDNF), nerve growth factor (NGF), basic fibroblast growth factor (FGF-2), and brain-derived neurotrophic factor (BDNF), is altered during HIV infection [114–118]. Among these factors, FGF-2 and BDNF are known to exert significant effects on adult hippocampal neurogenesis (Fig. 1), and will be further discussed here.

Basic fibroblast growth factor

FGF-2 has long been recognized to have pleiotropic effects on NPCs [119]. FGF-2 serves as a mitogen to maintain proliferating multipotent NPCs *in vitro* [120, 121]. FGF-2 also promotes neuronal production from adult NPCs *in vitro* at lower concentrations [122, 123]. Surprisingly, targeted deletion of the FGF-2 gene in mice does not affect basal neurogenesis rates in the adult hippocampus [76]. Increases in neurogenesis normally seen after insults, such as stroke, kainic acid injection, or traumatic brain injury, however, are diminished in FGF-2 knockout mice [76, 77]. Furthermore, intracerebral delivery of FGF-2 in these knockout mice resulted in an increase in post-injury neurogenesis. Taken together, these experiments suggest an important role for FGF-2 in adult hippocampal neurogenesis, particularly after brain injury.

Data on effects of HIV infection on CNS FGF-2 levels are conflicting. In one study, cerebrospinal fluid (CSF) samples from patients with HIV, human T cell leukemia virus-1 (HTLV) and Creutzfeldt-Jacob disease (CJD), as well as healthy controls were analyzed by quantitative enzyme-linked immunosorbent assay (ELISA) [114]. The patients with HIV, all of whom had motor and cognitive dysfunction, had significantly lower levels of CSF FGF-2 than the other three groups. However, in an earlier autopsy study in the

brains of patients with HIV dementia, FGF-2 messenger RNA (mRNA) levels were increased, as was immunoreactivity against FGF-2 protein [115]. Reasons for this discrepancy are unclear, but may include differences in translational regulation of FGF-2 or in the stage of HIV-mediated neurological dysfunction. Additionally, FGF-2 may be synthesized in focal areas of the brain or may not have access to the CSF compartment, resulting in differences in measurements of this growth factor. In any case, alterations in FGF-2 levels may have both direct effects on neurogenesis through interaction with FGF receptors as well as indirect effects through downregulation of CXCR4 expression [124], further affecting neurogenesis in the setting of HIV infection (see above).

Brain-derived neurotrophic factor

A variety of environmental stimuli that increase adult hippocampal neurogenesis, including kainic acid administration, environmental enrichment and dietary restriction, are associated with increased levels of hippocampal BDNF [125–127]. *In vitro* BDNF promotes survival and neuronal differentiation of adult hippocampal NPCs [128]. In $BDNF^{+/-}$ mice, both NPC proliferation and survival of newborn cells in the dentate gyrus are decreased as compared to wild-type animals [73, 74]. Taken together, these studies suggest an important role of BDNF in adult hippocampal neurogenesis.

BDNF expression in the CNS appears to be altered in the setting of HIV infection. In an autopsy-based study, the intensity of BDNF immunoreactivity in the neocortex tended to be higher in post-mortem brains of patients with AIDS and HIV encephalitis as compared to controls [129]. On the other hand, CSF samples from patients with HIV showed significantly lower levels of BDNF than samples from healthy controls as measured by quantitative ELISA [114]. In a rodent model of HIV neurotoxicity when gp120 was injected into the rat striatum, BDNF levels were found to be rapidly decreased and continued to be decreased for up to 4 days by immunohistochemistry [117]. Since BDNF is produced by a variety of cell types, including neurons, astrocytes and macrophage/microglia, it may be not surprising that discrepancies are present in the assessment of CNS BDNF levels as described above. It is quite possible that levels of CNS BDNF vary depending upon the degree of neuronal loss, microglial activation and reactive astrocytosis, which in turn depend upon the stage of HIV encephalitis. Therefore, either increases or decreases in BDNF levels, with concomitant effects on neuronal differentiation and survival, may occur during the course of HIV infection.

Direct infection of NPCs by HIV

Can HIV directly infect NPCs, thereby affecting NPC function? Primary human neuroblasts derived from olfactory tissue, as well as neuroblastoma cell lines, can be infected by both macrophage- and T cell-tropic strains of HIV [130, 131]. Infection occurs in a CD4-independent manner, since these cells do not express the primary HIV receptor on their cell surface. In addition, immature neurons of different subtypes support HIV infection to variable degrees, suggesting that lineage- or differentiation-dependent factors may be important for productive infection [131]. Recently, it has been shown that a small subset of self-renewing, nestin-positive, multipotent human NPCs was infected by HIV [78]. Peak virus production from these NPCs occurs within the first several days and decreases rapidly after 3–6 days. Importantly, as late as 5 weeks after initial infection, virus production from NPCs was stimulated by TNF-α, suggesting that latent infection can be reactivated in NPCs [78]. Whether active or latent HIV infection of NPCs affects their function remains to be determined.

Modulation of adult neurogenesis by drugs of abuse: cellular mechanisms

Exposure to drugs of abuse results in specific neurotoxic and neuroadaptive changes that may influence behavior [132–134]. Recently, attention has focused on understanding how drugs of abuse may affect hippocampal neurogenesis for several reasons. First, drug-induced dysfunction of hippocampal neurogenesis may provide a basis for the cognitive dysfunction often observed in drug abusers. Second, alteration of hippocampal neurogenesis may play a role in the development of addiction-related behaviors [27]. Investigating effects of drugs of abuse on neurogenesis in animal models can be challenging, as many factors must be taken into account in the design of such studies. Factors such as route of administration, dosing paradigms, species/strain of animal studied, method to determine the neurogenesis rate, and potential effects of drug withdrawal must be carefully considered. Despite these challenges, there has been some success in characterizing the effects of several drugs of abuse on the cellular mechanisms of adult hippocampal neurogenesis using rodent models of substance abuse (Table 1). In most of these studies, detection of exogenously administered BrdU, a nucleotide analog incorporated into DNA during the S phase of the cell cycle, has been employed to identify proliferating cells in the hippocampus. This method allows for assessment of NPC proliferation rate, determination of the fate of these cells and their survival. Ethanol, for instance, impairs the survival of NPCs, possibly through

Table 1. *In vivo* effects of drugs of abuse on adult hippocampal neurogenesis.

Drug	Species	Duration of drug exposure	Effects	Study
Cocaine	rat	acute	proliferation n.c.	Yamaguchi et al., 2004, 2005
	rat	short-term	proliferation ↓	Dominguez-Escriba et al., 2006
	rat	chronic	proliferation ↓	Yamaguchi et al., 2004, 2005 Dominguez-Escriba et al., 2006
METH	gerbil	acute	proliferation and/or survival ↓	Teucherdt-Noordt et al., 2000
Amphetamine	rat	acute	proliferation n.c.	Mao et al., 2001
Morphine	rat	acute	proliferation n.c.	Eisch et al., 2000
	rat	short-term	proliferation and survival ↓	Eisch et al., 2000, Kahn et al., 2005
	mouse	short-term	proliferation ↓	Mandyam et al., 2004
Heroin	rat	chronic*	proliferation ↓	Eisch et al., 2000
Alcohol	rat	chronic	proliferation n.c., survival ↓	Herrera et al., 2003
		chronic	proliferation, survival, and neuronal differentiation ↓	He et al., 2005
	rat	abstinence**	proliferation and neuronal differentiation ↑	Nixon and Crews, 2004
	mouse	chronic*	proliferation and neuronal differentiation ↑	Aberg et al., 2005

Acute: <3 days. Short-term: 3–7 days. Chronic: >7 days
* Self administration.
** Abstinence after chronic administration.

induction of oxidative or nitrosative stress [135]. NPC proliferation and neuronal differentiation may also be suppressed during chronic ethanol administration, but are increased following an abstinent period [136–138]. Here, we will focus our discussion on the effects of cocaine and opiates on adult hippocampal neurogenesis, since these drugs are often abused by HIV-infected individuals.

Effects of cocaine on neurogenesis

Of the psychostimulants, cocaine, amphetamines, and methamphetamines have been studied in relation to effects on hippocampal neurogenesis (Table 1). *In vitro,* cocaine inhibits proliferation and promotes differentiation of human fetal NPCs [139]. In adult rats, acute cocaine exposure did not alter proliferation of hippocampal NPCs, as measured by BrdU incorporation [140, 141], although decreased expression of PSA-NCAM, a cell surface molecule expressed by immature neurons, was noted in the dentate gyrus for several days after acute cocaine administration in another study [142]. On the other hand, chronic exposure to cocaine in rats resulted in a significant decrease in BrdU incorporation in the dentate gyrus, without influencing cell differentiation. Importantly, in the same study, BrdU incorporation returned to control levels 1 week after cocaine withdrawal, suggesting that effects on NPC proliferation may be reversible [140, 141]. A decrease in BrdU incorporation of similar magnitude was also seen in mice [143]. No changes in survival of NPCs exposed to cocaine as detected by terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL), and no significant changes in dendritic arborization or synaptic architecture of newly generated neurons were noted [143]. Thus, chronic cocaine exposure appears to lead to decreases in NPC proliferation without significantly affecting NPC survival or differentiation.

Effects of opiates on neurogenesis

Similar to cocaine, chronic, but not acute, administration of morphine decreases NPC proliferation as measured by BrdU incorporation in both adult rats and mice [144–146]. These effects are robust (~40 % reduction), independent of the route of opiate delivery (subcutaneous pellet vs. intraperitoneal injection), and occur during settings of both forced- and self-administration (Table 1) [144, 146]. Importantly, the effects of opiates on adult hippocampal NPC proliferation appear to be independent of stress-induced effects on glucocorticoids, as adrenalectomized rats continued to demonstrate opiate-induced decreases in BrdU incorporation [144]. Survival of newborn cells also appears to be reduced by morphine, albeit to a smaller extent than proliferation [144]. In addition, the reduction in proliferation appears to translate into fewer newly generated mature neurons [144], reflecting a true reduction in neurogenesis. Conversely, knockout of the *mu* re-

ceptor resulted in increased survival of adult mouse hippocampal NPCs [147]. Taken together, these studies suggest that chronic opiate stimulation results in decreases in both proliferation and survival of hippocampal NPCs.

What is the cellular mechanism underlying the effects of morphine on adult hippocampal NPCs? Since BrdU labeling only identifies cells in the S phase of the cell cycle, a recent study employed immunohistochemistry with antibodies directed toward proliferating cell nuclear antigen (PCNA), which is most abundant from G1 to early S phases, and pHisH3, which is most abundant from G2 through M phases [145]. This approach, combined with a morphological analysis of mitotic cells to determine whether cells were in prophase, metaphase, anaphase or telophase, suggested that morphine results in a shortening of G2/M phase. The finding of premature mitosis induced by morphine appears to be paradoxical, since faster progression through the cell cycle might be expected to lead to increases, rather than decreases, in proliferation. However, the authors posit that premature mitosis may impact cell cycle checkpoint-specific proteins or even induce cell death, thereby potentially leading to decreased proliferation or survival [145].

Conclusions and future directions

Over the past several years, an appreciation for the variety of pathogenic processes that affect hippocampal neurogenesis has emerged. HIV infection results in a number of molecular changes that are known to affect neurogenesis, while drugs of abuse can impact several cellular parameters, including NPC proliferation and survival of their neuronal progeny. However, a number of challenges remain. In the case of HIV, it has not been possible to determine with confidence which molecular mechanisms contribute to altered hippocampal neurogenesis during HIV infection, because of a lack of detailed characterization of HIV-induced cellular changes in neurogenesis. Therefore, a major challenge will be to develop both *in vitro* models of HIV neurotoxicity and effective animal models (e.g. pseudotyped viral infection [148], mice transgenic for HIV viral proteins gp120 or Tat [149, 150], or direct injection of viral proteins and/or viral protein-producing cells [151]). For example, a recent report showed that implantation of either uninfected or HIV-infected monocyte-derived macrophages into brains of immunodeficient mice results in fewer proliferating NPCs and altered morphology of newly generated hippocampal neurons, thus implicating a role for factors secreted by activated macrophage/microglial cells in modulating neurogenesis [152]. Such studies will likely serve as a basis for a more thorough understanding of the cellular mechanisms of neurogenesis affected by HIV.

In the case of drugs of abuse, a growing number of studies have begun to document the effects of various substances on hippocampal NPC proliferation, neuronal differentiation and survival. Both psychostimulants and opiates, when administered chronically, may lead to decreases in proliferation and survival, with concomitant reduction in adult hippocampal neurogenesis. A major challenge will be to identify specific developmental stages and processes [153] that are influenced by the various drugs of abuse. Using transgenic mice lines in which expression of a fluorescent reporter protein is driven by the nestin promoter, it has been possible to pinpoint that selective serotonin reuptake inhibitors (SSRIs) influence neurogenesis through effects on the transient amplifying cells [154]. A further challenge will be to understand which of the multitude of molecular changes induced by drug abuse underlie alterations in neurogenesis.

Although it appears that both HIV and drugs of abuse can negatively impact adult hippocampal neurogenesis, the functional consequences of such disruption and its relation to neurological deficits in affected patients remain unclear. Attempts so far to lesion newly generated hippocampal neurons have likely affected other biological processes in addition to neurogenesis, clouding the interpretation of such studies. Currently, genetic strategies are being developed in an attempt to specifically manipulate hippocampal neurogenesis. Such systems will be pivotal to determine the role of continued neurogenesis in hippocampal function and in cognition and addictive behavior. Combined with a better understanding of how HIV and drug abuse affect the molecular and cellular mechanisms of adult hippocampal neurogenesis, such approaches may contribute to the development of specific therapies that preserve hippocampal neurogenesis, protect cognitive function and limit addictive behavior in HIV-infected and drug-abusing populations.

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