

Hippocampal Neurogenesis: Effects of Psychedelic Drugs

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Abbreviations

5,7-DHT	5,7-Dihydroxytryptamine
5-HT	Serotonin
BDNF	Brain-derived neurotrophic factor
BrdU	Bromodeoxyuridine
CA	Cornu ammonis
cAMP	Cyclic adenosine monophosphate
CBD	Cannabidiol
CNS	Central nervous system
DA	Dopamine
DG	Dentate gyrus
DOI	2,5-Dimethoxy-4-iodoamphetamine
EC	Entorhinal cortex
HPA	Hypothalamic–adrenal–pituitary axis
HPC	Hippocampus
HPPC	4-(4-Hydroxypiperidino)-4-phenylcyclohexanol
IGF-1	Insulin growth factor 1
IP₃	Inositol triphosphate
KO	Knockout
LSD	Lysergic acid diethylamide
LTP	Long-term potentiation
MDMA	3,4-Methylenedioxymethamphetamine
MFB	Medial forebrain bundle
MWM	Morris water maze
NE	Norepinephrine
NMDA-R	<i>N</i> -methyl-D-aspartate receptor
PCHP	1-(1-Phenylcyclohexyl)-4-hydroxypiperidine
PCP	Phencyclidine
PKC	Protein kinase C
PLC	Phospholipase C
PPC	4-Phenyl-4-(1-piperidinyl)cyclohexanol
PSOP	Psilocybin, 4-phosphoryloxy- <i>N,N</i> -dimethyltryptamine
RAWM	Radial arm water maze
RN	Raphe nucleus
SSRI	Selective serotonin uptake inhibitor
SGZ	Subgranular zone
SVZ	Subventricular zone
THC	Δ^9 -Tetrahydrocannabinol
VEGF	Vascular endothelial growth factor

DISCOVERY OF ADULT NEUROGENESIS

The idea of new neurons forming in the adult central nervous system (CNS) is a relatively new one. In the 1960s Joseph Altman published the first evidence of neurogenesis, or the birth of new neurons, in the adult mammalian brain (Altman, 1962). Utilizing the tritiated thymidine method, Joseph Altman was able to demonstrate that the subventricular zone (SVZ) of the lateral ventricles and the dentate gyrus (DG) of the hippocampus (HPC) produce new neurons throughout the life span (Altman, 1962). For years following Altman's discovery scientists acknowledged the possibility of the generation of new glial cells in the adult brain but rejected the concept of newborn neurons. With the advent of new technologies such as the bromodeoxyuridine (BrdU) method of birth-dating cells and double labeling using immunofluorescence, adult neurogenesis has been identified in many mammalian species, including mice, rats, hamsters, tree shrews, nonhuman primates and humans (Eriksson et al., 1998; Gould, McEwen, Tanapat, Galea, & Fuchs, 1997; Kempermann, Kuhn, & Gage, 1998). Peter Eriksson's discovery of new neurons in the human HPC changed the perception of neurogenesis in the scientific community, so now the fact that new neurons are produced in the adult brain is firmly established.

THE ANATOMY OF HIPPOCAMPAL NEUROGENESIS

The HPC is divided into four areas: the DG (also called area dentate or fascia dentata), cornu ammonis (CA, further divided into CA1, CA2, CA3, and CA4), presubiculum, and subiculum. This anatomical description of the HPC has been confirmed by both gene expression and fiber connections. The DG and CA areas form a trisynaptic circuitry within the HPC (see Figure 1). Neurons in the entorhinal cortex (EC) project to dendrites of the granule cells in the DG forming the perforant pathway. The granule cells extend their axons to pyramidal neurons in area CA3, forming the mossy fiber tract. CA3 pyramidal neurons project to the contralateral (via the associational commissural pathway) and the ipsilateral CA1 region, forming the Shaffer collateral pathway. Pyramidal neurons in CA1 extend

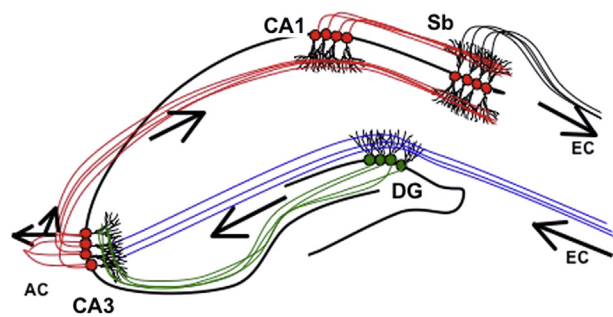


FIGURE 1 Anatomy of the hippocampus (HPC). The HPC forms a trisynaptic pathway with inputs from the entorhinal cortex (EC) that project to the dentate gyrus (DG) and CA3 pyramidal neurons via the perforant pathway. Granule cells in the DG project to CA3 via the mossy fiber pathway. Pyramidal neurons in CA3 project to both the contralateral (associational commissural pathway) and the ipsilateral CA1 region via the Schaffer collateral pathway. CA1 pyramidal neurons send their axons to the subiculum (Sb), which in turn projects out of the HPC back to the EC.

axons to the subiculum and from the subiculum back to the EC (for detailed descriptions of hippocampal circuitry see Witter, 1993).

Under normal physiological conditions, neurogenesis that occurs in the HPC is found only in the DG and results in the generation of new granule cells. Within the DG, progenitor cells reside in a narrow band between the DG and the hilus (also called CA4 or plexiform layer) called the subgranular zone (SGZ), which is approximately two or three cells thick (20–25 μm) (see Figure 2). Neural progenitor cells (1) divide and (2) form clusters of proliferating cells. (3) Proliferating cells exit from the cell cycle and begin to differentiate into immature neurons. (4) The immature granule cell forms sodium currents and extends dendrites and an axon to make connections with other cells and form synapses to become a mature neuron. The SGZ contains many cell types, including astrocytes, several types of glial and neuronal progenitor cells, and neurons in all stages of differentiation and maturation (Alvarez-Buylla, Garcia-Verdugo, & Tramontin, 2001).

REGULATION OF NEUROGENESIS IN THE DG

The proliferation and survival of neural progenitors in the adult HPC can be influenced in positive and negative manners by a variety of factors (see Table 1). Stimuli as diverse as stress; odors; neurotrophins; psychoactive drugs such as antidepressants, psychedelics, opioids, and alcohol; electroconvulsive therapy; environmental enrichment; learning; seizures; ischemia; cranial irradiation; physical activity; hormones; and age, among many others, have been linked to the regulation of neurogenesis (Kempermann et al., 1998; Malberg & Duman, 2003; Malberg, Eisch, Nestler, & Duman, 2000; van Praag, Christie, Sejnowski, & Gage, 1999; Tanapat, Hastings, Rydel, Galea, & Gould, 2001). Some of these factors have been studied extensively and their role in the regulation of neurogenesis is well defined. For example, environmental enrichment and physical activity are strong positive regulators of neurogenesis (Kempermann, Kuhn, & Gage, 1997; van Praag et al., 1999), whereas stress and aging appear to be negative regulators of neurogenesis (Cameron, Woolley, & Gould, 1993; Kempermann et al., 1998).

The first report of any factor increasing neurogenesis in the mammalian brain was an enriched environment. In an experimental setting a rodent enriched environment typically consists of a large cage, a large number of animals, toys, and a tunnel system. To maintain the enrichment aspect novel toys are introduced and the tunnel system is rearranged on a regular basis. Rodents living in an enriched environment exhibited a strong upregulation of cell proliferation and neurogenesis in the DG of the HPC (Kempermann et al., 1997). The proneurogenic effects of environmental enrichment can be increased further depending on the age of the animal when exposure occurs. When late adolescent/young adult animals live in an enriched environment it enhances the ability of environmental enrichment to upregulate cellular proliferation and neurogenesis in the DG. In fact, when the morphology of the HPC was examined later in life, a greater number of absolute granule cells was observed (Kempermann et al., 1997). In aged animals (typically 18 months or older in rodents) lower levels of neurogenesis have been observed; however, living in an enriched environment counteracts the effects of aging (Kempermann et al., 1998). Kempermann et al. (1998) demonstrated that environment enrichment during aging increases cell proliferation and neurogenesis in the DG. Furthermore, if animals live in an enriched environment during middle age, basal levels of neurogenesis increase as much as fivefold in old age.

When experimentation with environmental enrichment began, novel foods were included as a part of the environmental enrichment experience. When similar food was given to mice living in either an enriched or a control environment, the effect of environmental enrichment was still present. One type of diet, however, has been found to have positive effects on neurogenesis specifically, caloric restriction (Lee, Duan, Long, Ingram, & Mattson, 2000). As an experimental manipulation caloric restriction usually consists of limiting the amount of food an animal can eat by a third. Caloric restriction is the only factor that has been shown experimentally to increase the life span of animals and it is thought that caloric restriction actually acts as a mild stressor. It is of interest to note that while environmental enrichment is a strong positive regulator of adult hippocampal neurogenesis, it does not affect adult neurogenesis in the olfactory system (Brown et al., 2003).

Exposure to an enriched environment increases neurogenesis in the DG of adult rodents; however, environmental enrichment typically includes a running wheel and increased physical activity. Physical activity is known to upregulate cell proliferation and neurogenesis in the DG. Rodents will take full advantage of the opportunity to exercise on a running wheel during the active phase of their day. Mice have been reported to run between 3 and 8 km per night on a running wheel (van Praag et al., 1999). Voluntary physical activity has been shown to increase the number of progenitor cells and new neurons in the DG of the HPC (van Praag et al., 1999). The effect of running on neurogenesis is acute, so that running must continue, to affect neurogenesis, and once the animal no longer uses the running wheel the effect on neurogenesis will decline. The upregulation of adult neurogenesis by physical activity also increases long-term potentiation (LTP) in the DG and enhances performance on the Morris water maze (MWM), a behavioral task that assesses memory and learning (van Praag et al., 1999).

The mechanisms underlying the increase in neurogenesis by physical activity are not completely known. However, growth factors such as insulin growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and brain-derived neurotrophic factor (BDNF) have

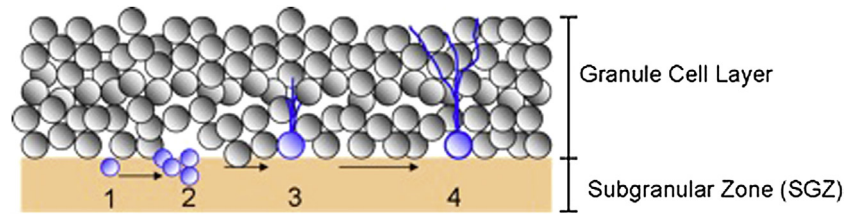


FIGURE 2 Neurogenesis in the dentate gyrus of the hippocampus. Neural stem cells exist in the subgranular zone of the dentate gyrus; these cells then divide, differentiate, and mature into their phenotypic fate. Neural progenitor cells (1) divide and (2) form clusters of proliferating cells. (3) Proliferating cells exit from the cell cycle and begin to differentiate into immature neurons. (4) The immature granule cell forms sodium currents and dendrites and extends an axon out to make connections with other cells and form synapses to become a mature granule cell.

TABLE 1 Regulation of Neurogenesis in the Dentate Gyrus

Regulation of Hippocampal Neurogenesis	
+	–
Environmental enrichment	Stress
Learning	Depression
Physical activity	Aging
Ischemia	Irradiation
Seizures	Alcohol
Electroconvulsive therapy	Psychostimulants
Antidepressants	Opiates
Neurotrophins	MDMA
Cannabinoids	PCP

The proliferation and survival of neural progenitors in the adult hippocampus can be influenced in positive (left) and negative (right) manners by a variety of factors. Stimuli such as environmental enrichment, learning, physical activity, ischemia, seizures, electroconvulsive therapy, antidepressants, neurotrophins, and cannabinoids have all been shown to increase neurogenesis in the hippocampus. In contrast, factors such as stress, depression, aging, irradiation, alcohol, psychostimulants, opiates, 3,4-methylenedioxymethamphetamine (MDMA) and phencyclidine (PCP) all reduce hippocampal neurogenesis.

been strongly implicated. IGF-1 levels are increased in the HPC of running animals, and running stimulates cellular proliferation and neurogenesis (Carro, Nunez, Busiguina, & Torres-Aleman, 2000). This increase in neurogenesis is blocked by scavenging circulating IGF-1 and absent in IGF-1 mutants (Carro et al., 2000). VEGF is necessary for the effects of running on adult hippocampal neurogenesis. Blocking peripheral VEGF abolished the running-induced induction of neurogenesis; however, there were no detectable effects on baseline neurogenesis in nonrunning animals. Quantitative polymerase chain reaction analysis revealed that BDNF mRNA levels are significantly increased in the DG of running rats. BDNF is a key factor involved in modulating neuroplasticity including LTP and neurogenesis. Infusions of BDNF into the lateral ventricles induced neurogenesis originating in the SVZ, and BDNF-knockout (KO) mice have diminished levels of neurogenesis in the DG. Like environmental enrichment, physical activity upregulates adult hippocampal neurogenesis; however, it does not affect adult neurogenesis in the olfactory system (Brown et al., 2003).

Stress severely impairs hippocampal neurogenesis. One of the first studies to link stress to hippocampal neurogenesis was conducted by Gould, Cameron, Daniels, Woolley, and McEwen (1992). They found that stress increased the number of dying cells in the HPC but that the total number of granule cells in the dentate was not different from that in nonstressed controls and concluded that neurogenesis must be occurring to maintain cellular balance (Gould et al., 1992). They postulated that the stress hormone, cortisol in humans and corticosterone in rodents, mediates the stress effect on neurogenesis and went on to discover that adrenalectomy (removing the adrenal gland and hence the source of endogenous corticosterone) led to an upregulation of neurogenesis and that exogenous corticosterone downregulated cellular proliferation and neurogenesis in the DG (Cameron et al., 1993). Since these early experiments, severe stress has been shown to downregulate cell proliferation and consecutive stages of neuronal development using many different paradigms. Prenatal stress caused learning deficits and had detrimental effects on neurogenesis that lasted well into adulthood. The effects of psychosocial stress on neurogenesis were demonstrated using the resident–intruder model of territorial tree shrews (Gould et al., 1997). Tree shrews are extremely territorial and guard their environment so the introduction of an intruder into the resident's cage is extremely stressful. The territorial tree shrews compete for dominance, and soon after the introduction of an intruder a dominant–subordinate relationship is established resulting in elevated cortisol and decreased neurogenesis in the subordinate tree shrew (Gould et al., 1997). Predator odor triggered a stress response in prey and had detrimental effects on cell proliferation. In rodent models, fox odor has been shown to decrease cell proliferation and neurogenesis in the DG (Tanapat et al., 2001). Both acute and chronic restraint stress have been shown to affect the rate of adult hippocampal neurogenesis. Pham, Nacher, Hof, and McEwen (2003) demonstrated that 6 weeks of daily restraint stress suppressed cell proliferation and attenuated survival of the newly born cells, resulting in a 47% reduction in granule cell neurogenesis. Not only is neurogenesis affected by environmental stimuli, but the absence of stimuli, such as social isolation, negatively regulates neurogenesis. Young rats reared in social isolation for 4–8 weeks showed decreased performance on the MWM and decreased hippocampal neurogenesis. In the learned helplessness model of depression, animals are exposed to an inescapable foot shock using avoidance testing. Exposure to inescapable shock decreased cell proliferation in the HPC, extending previous studies demonstrating downregulation of neurogenesis by exposure to acute stressors (Malberg & Duman, 2003).

The key mechanism underlying the negative impact that stress has on neuroplasticity appears to be stress hormone (glucocorticoid) secretion (Cameron et al., 1993). Acute, severe, and sometimes traumatic stress leads to chronically high levels of glucocorticoids and alters the functioning of the hypothalamic–adrenal–pituitary (HPA) axis, resulting in dysregulation of glucocorticoid secretion and receptor expression. Depression is an example of a clinical condition associated with disturbed regulation of the HPA axis, which upsets the circadian rhythm of hormone secretion, resulting in chronically elevated glucocorticoid levels and decreased neurogenesis.

Aging is another factor known to have a strong negative influence on neurogenesis, a fact known since the discovery of adult neurogenesis by Altman and Das in 1962. In the original study a progressive decrease in the levels of neurogenesis was observed after puberty and continued into old age (Altman & Das, 1965), and this finding has since been replicated in rats (Cameron & McKay, 1999), mice (Kempermann et al., 1998), and humans (Eriksson et al., 1998). The highest levels of adult neurogenesis occurred in young adulthood and steadily decreased over the life span. In old age (typically 18 months or older in rodents) baseline levels of neurogenesis are extremely low; however, there are ways to enhance neurogenesis in the aging HPC. Environment enrichment during aging increases cell proliferation and neurogenesis in the DG; however, the effect of an enriched environment is more robust in young animals (Kempermann et al., 1998). Animals that lived in an enriched environment starting at middle age had fivefold increases in basal levels of neurogenesis in old age (Kempermann et al., 1998). Cortisol (or corticosterone in rodents) levels are elevated in aging, which probably reduces baseline proliferation and neurogenesis. Adrenalectomy in aged animals restored adult neurogenesis in the DG to a level comparable to that of a much younger age, demonstrating that corticosterone is at least in part responsible for the decline in neurogenesis observed in aging (Cameron & McKay, 1999). IGF-1 levels are increased in the HPC of running animals and running induced increases in cellular proliferation and neurogenesis (Carro et al., 2000). Similarly, aged animals were administered exogenous IGF-1 to restore endogenous IGF-1 levels to those of a younger age, which induced neurogenesis above controls and thus counteracted the negative effect of aging on neurogenesis.

SEROTONERGIC INNERVATION IN THE DG

5-HT is a modulatory neurotransmitter in the CNS that plays an important role in the regulation of vital brain functions such as feeding, thermoregulation, sleep, and aggression. In psychopathological states such as depression, eating disorders, and anxiety, serotonergic signaling is disturbed.

In the mammalian brain 5-HT is produced by neurons in the raphe nucleus (RN), which project to many areas of the brain via the medial forebrain bundle. Neurons from the RN innervate virtually all brain areas, with dense innervation occurring in the HPC, cerebral cortex, striatum, hypothalamus, thalamus, septum, and olfactory bulb (Jacobs & Azmitia, 1992). The innervation of serotonergic fibers to areas within the HPC is variable (Moore & Halaris, 1975). The DG is innervated with serotonergic fibers in both the molecular layer and the hilus, with particularly dense innervation projecting to the SGZ, where they synapse with interneurons (Halasy & Somogyi, 1993).

5-HT activates 15 known receptors, many of which are expressed in the DG (el Mestikawy et al., 1989). Most of the 5-HT receptors interact with G proteins except for the 5-HT_{3A} receptors, which are ligand-gated ion channel receptors. The 5-HT₃ receptors (subtypes 5-HT_{3A} and 5-HT_{3B}) are ligand-gated Na⁺ ion channels and their activation leads to the depolarization of neurons (Barnes & Sharp, 1999). The 5-HT₁ family of receptors (including subtypes 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}) are coupled to the G_i protein, which, when activated, decreases the activity of adenylyl cyclase, thus decreasing the rate of formation of cyclic adenosine monophosphate (cAMP). Activation of 5-HT₁ receptors can lead indirectly to the opening of K⁺ channels, therefore increasing the conductance of the cell membrane for K⁺ ions. Activation of 5-HT₄, 5-HT₆, and 5-HT₇ receptors is coupled to G_s proteins, which have the opposite effect. They increase the activity of adenylyl cyclase, increase the rate of cAMP formation, and decrease K⁺ conductance (Thomas, Matli, Hu, Carson, & Sutcliffe, 2000). The 5-HT₂ receptors (including subtypes 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}) are coupled to G_q proteins and activate phospholipase C, increasing the rate of formation of inositol triphosphate and diacylglycerol, leading to the increased formation of protein kinase C (PKC) (Kurrasch-Orbaugh, Parrish, Watts, & Nichols, 2003).

SEROTONIN AND NEUROGENESIS IN THE DG

While several factors regulate the rate of generation of new cells in the adult DG, one of the most important known factors is 5-HT. Malberg and colleagues found that increased levels of 5-HT resulted in an increased rate of proliferation of neural progenitors in the DG (Malberg et al., 2000). Administering 5,7-dihydroxytryptamine (5,7-DHT), a serotonergic neurotoxin, into the RN caused the destruction of axons and serotonergic cells and resulted in a decrease in the number of BrdU-labeled cells in the DG (Brezun & Daszuta, 1999). The 5,7-DHT lesion resulted in around a 60% depletion of the serotonergic innervation to the DG, which lasted for 1 month. After 2 months, reinnervation to the DG was observed, with the sprouting of serotonergic axons, so that by the third month there was no observable difference between the 5,7-DHT and the vehicle treatments in newly generated cells or serotonergic innervation (Brezun & Daszuta, 2000).

Many serotonergic receptors have been implicated in the regulation of neurogenesis in the DG. In vitro, when the 5-HT_{1A} receptor agonist 8-OH-DPAT was added to a medium in which cultured fibroblasts transfected with the 5-HT_{1A} receptor were present, the rate of cell divisions increased (Varrault, Bockaert, & Waeber, 1992). In vivo, 5-HT_{1A} receptor antagonists (NAN-190, *p*-MPPI, and WAY-100635) decreased the number of progenitors in the DG by approximately 30% (Radley & Jacobs, 2002) and injections of 5-HT_{1A} receptor agonists increased the number of BrdU-positive cells in the DG (Santarelli et al., 2003). Similarly, Banasr and colleagues showed that various 5-HT₁ receptor agonists increase the number of BrdU-labeled cells in the subgranular layer. Acute administration of the 5-HT_{2A/C} receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI), 5-HT_{2C} receptor agonist RO 600175, and 5-HT_{2C} receptor antagonist SB 206553 had no effect on cell proliferation in the HPC, whereas the 5-HT_{2A/C} receptor antagonist ketanserin produced a 63% decrease in BrdU incorporation.

A 2008 study found that acute ketanserin decreased proliferation, whereas chronic ketanserin increased proliferation in the DG (Jha, Rajendran, Fernandes, & Vaidya, 2008). No effect on proliferation in the DG was observed after DOI or lysergic acid diethylamide (LSD) was administered, either acutely or once daily for 7 consecutive days (chronic) (Jha et al., 2008).

The 5-HT_{2A} receptor is involved in the regulation of BDNF in the HPC (Vaidya, Marek, Aghajanian, & Duman, 1997). DOI alone and in combination with selective 5-HT_{2A} and 5-HT_{2C} receptor antagonists decreased the expression of BDNF mRNA in the HPC. Interestingly, the decrease in BDNF mRNA expression was blocked by the 5-HT_{2A} receptor antagonist but not the 5-HT_{2C} receptor antagonist, implicating the 5-HT_{2A} receptor in the regulation of BDNF expression. In addition, the stress-induced reduction in BDNF expression in the HPC was blocked by a 5-HT_{2A/C} receptor antagonist (Vaidya et al., 1997).

EFFECTS OF PSYCHEDELIC DRUGS ON HIPPOCAMPAL NEUROGENESIS

Psychedelic drugs (from the Greek words for “mind manifesting”) are substances that alter cognition and perception. Psychedelics are part of a wider class of psychoactive drugs known as hallucinogens, a class that also includes mechanistically unrelated substances such as dissociative anesthetics (*N*-methyl-D-aspartate receptor (NMDA-R) antagonists like ketamine) and deliriants (anticholinergic drugs like atropine, scopolamine, and hyoscyamine).

Psilocybin

Psilocybin (PSOP; 4-phosphoryloxy-*N,N*-dimethyltryptamine) is the main active agent in “magic mushrooms” and is categorized as an indole hallucinogen. First isolated from *Psilocybe mexicana*,

a mushroom from Central America, by Albert Hofmann in 1957, PSOP was then produced synthetically in 1958 (Hofmann, Heim, Brack, & Kobel, 1958). PSOP is converted into the active metabolite psilocin (4-hydroxy-*N,N*-dimethyltryptamine), which may produce some of the psychoactive effects of PSOP. The chemical structures of PSOP (C₁₂H₁₇N₂O₄P) and the metabolite, psilocin (C₁₂H₁₆N₂O), are similar to that of 5-HT (C₁₀H₁₂N₂O), the main neurotransmitter that they affect (see Figure 3).

PSOP exerts psychoactive effects by altering serotonergic neurotransmission by binding to 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, and 5-HT_{2C} receptor subtypes (Passie, Seifert, Schneider, & Emrich, 2002). PSOP binds to the 5-HT_{2A} receptor (*K*_i=6 nM) with high affinity and to a much lesser extent to the 5-HT_{1A} receptor subtype (*K*_i=190 nM) (McKenna, Repke, Lo, & Peroutka, 1990). However, PSOP has a lower affinity for 5-HT_{2A} and 5-HT_{2C} receptors compared to LSD, a similar indole hallucinogen (Nichols, 2004). In contrast to LSD, PSOP has a very low affinity for dopamine (DA) receptors and only extremely high doses affect norepinephrine (NE) receptors. PSOP has been shown to induce schizophrenia-like psychosis in humans, a phenomenon attributed to the action of PSOP through 5-HT_{2A} receptor action. Specifically, human volunteers were pretreated with ketanserin, an antagonist of the 5-HT_{2A/C} receptor, and then orally administered 0.25 mg/kg PSOP, and the psychotomimetic effects of PSOP were completely blocked (Vollenweider, Vollenweider-Scherpenhuyzen, Babler, Vogel, & Hell, 1998). Because blocking the 5-HT_{2A} receptor prevented the psychotropic effects of PSOP, it appears as though the actions of PSOP are mediated via the activation of 5-HT_{2A} receptors. Repeated daily administration of PSOP selectively downregulated 5-HT_{2A} receptors in the rat brain (Buckholtz, Zhou, Freedman, & Potter, 1990). PSOP binds to the 5-HT_{2A} receptor and stimulates arachidonic acid and, consequently, the phosphatidylinositol (PI) pathway resulting in the activation of PKC (Kurrasch-Orbaugh et al., 2003).

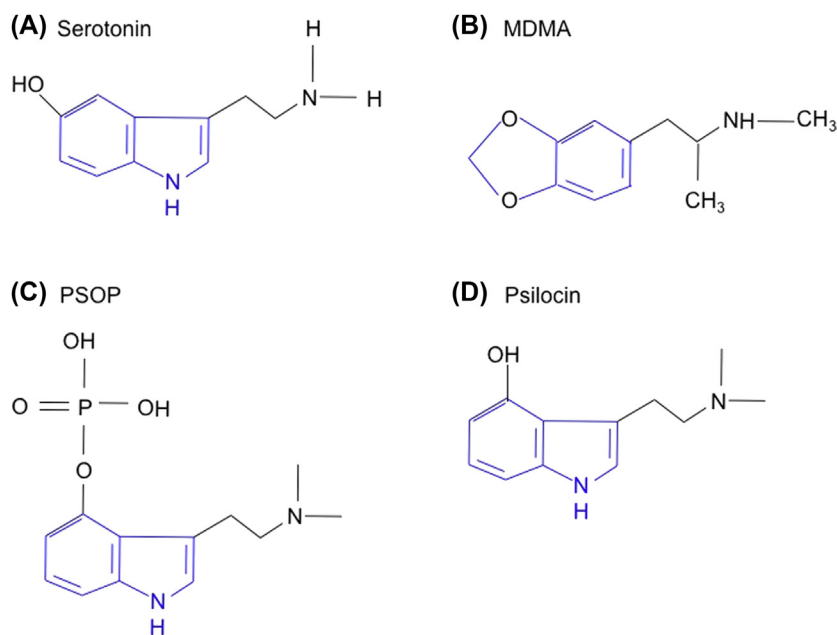


FIGURE 3 Chemical structures of serotonin, 3,4-methylenedioxymethamphetamine (MDMA), psilocybin (PSOP), and psilocin. The chemical structure of (A) the neurotransmitter serotonin is very similar to those of (B) MDMA, (C) PSOP, and (D) the metabolite of PSOP, psilocin.

In 2013, our laboratory reported that acute administration of PSOP produces alterations in hippocampal neurogenesis (Catlow, Song, Paredes, Kirstein, & Sanchez-Ramos, 2013). Specifically, we observed a biphasic response in hippocampal neurogenesis, with the low dose (0.1 mg/kg) producing a trend toward an increase in neurogenesis and the high dose (1.0 mg/kg) significantly decreasing neurogenesis (Catlow et al., 2013). In addition, we administered PSOP using a repeated intermittent paradigm that consisted of once-weekly administration for 4 weeks. This repeated administration paradigm was designed to avoid rapid tolerance and selective 5-HT_{2A} receptor downregulation that results from repeated daily exposure (Buckholtz et al., 1990). We found that 1.5 mg/kg PSOP significantly increased the number of newborn neurons in the DG and that ketanserin (5-HT_{2A/C} antagonist) decreased neurogenesis (see Figures 4 and 5).

3,4-Methylenedioxymethamphetamine (Ecstasy)

3,4-Methylenedioxymethamphetamine (MDMA) is an empathogenic and psychostimulant drug commonly referred to as ecstasy. It was first patented by Merck KGaA in 1914 and used in conjunction with psychotherapy by psychiatrists before it was classified as a Schedule I controlled substance in the United States in 1985. MDMA has been reported to increase one's capacity for introspection and intimacy while attenuating the neurophysiological fear response to emotional threats (Grinspoon & Bakalar, 1986). It produces these effects by altering monoamine reuptake and promoting presynaptic release of 5-HT, NE, and DA and binds 5-HT₁, 5-HT₂, DA, muscarinic M₁, α_2 -adrenergic, and histamine H₁ receptors (Lyon, Glennon, & Titeley, 1986). The long-term use of MDMA has been reported to damage 5-HT axon terminals in the striatum, HPC, and prefrontal cortex in animal models (Battaglia et al., 1987). However, it remains unclear whether the "damage" represents permanent cytotoxicity to serotonergic nerve terminals or a reversible pharmacological effect similar to actions of methamphetamine on dopaminergic terminals (Volkow et al., 2001).

There are few studies that have investigated the effects of MDMA on hippocampal neurogenesis. Hernandez-Rabaza and colleagues used a "binge" paradigm that consisted of administering 5 mg/kg MDMA every 6 h for 2 days to investigate the effects of MDMA on hippocampal neurogenesis. They quantified the number of BrdU-positive cells in the DG and found that the binge MDMA administration had no effect on proliferation, but significantly reduced the survival of hippocampal precursors (Hernandez-Rabaza et al., 2006). The authors further analyzed the morphological features of doublecortin-positive neuroblasts and found no developmental differences between binge MDMA administration and control (Hernandez-Rabaza et al., 2006). Our laboratory found that at a rewarding dose of MDMA (2.5 mg/kg), assessed by conditioned place preference, there was no effect of MDMA on proliferation or survival (Catlow et al., 2010). However, as the dose of MDMA was increased to 5 mg/kg, an increase in proliferation and subsequent reduction in survival and neurogenesis was observed (Catlow et al., 2010). In addition, the effects of in utero MDMA exposure on adult neurogenesis in offspring were assessed and no differences in proliferation or neurogenesis were observed (Canales & Ferrer-Donato, 2014). However, when

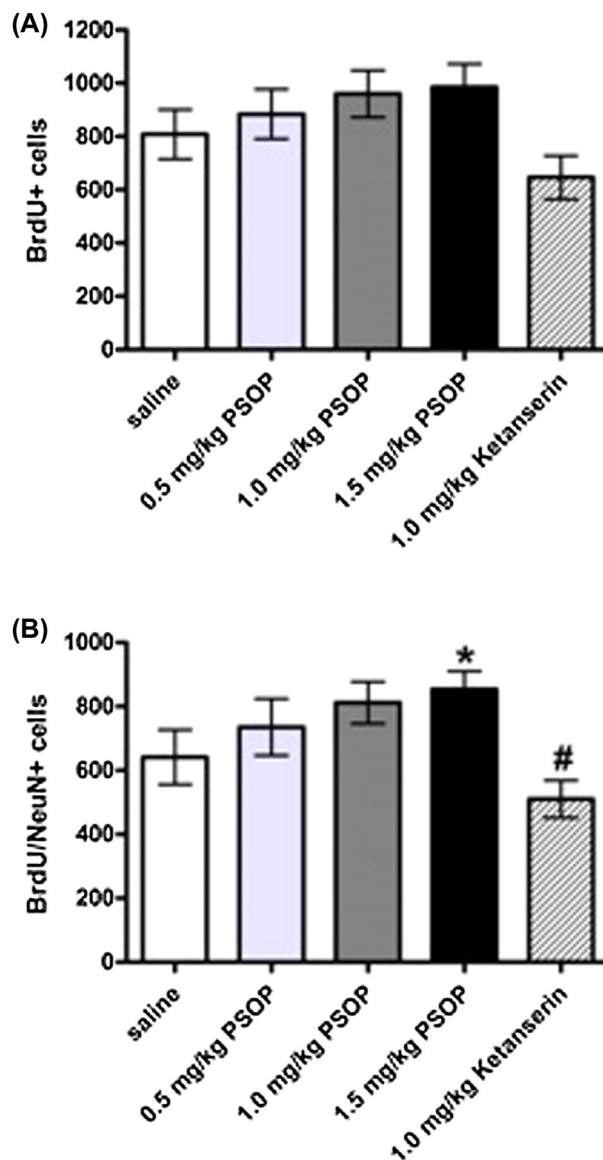


FIGURE 4 The effects of chronic psilocybin administration on hippocampal neurogenesis. Mice ($n=6$ or 7 per condition) were injected with psilocybin (PSOP) (0.5, 1.0, or 1.5 mg/kg), 1.0 mg/kg ketanserin, or saline once weekly for 4 weeks. Each day following drug administration, the mice were administered 75 mg/kg BrdU, and they sacrificed 2 weeks after the last drug injection. (A) The total number of BrdU+ cells ($\pm$ SEM) in the dentate gyrus did not differ as a result of chronic drug treatment; however, a trend toward a decrease in the number of surviving cells was observed after ketanserin administration. (B) Chronic administration of 1.5 mg/kg PSOP significantly increased the number of BrdU/NeuN+ cells compared to saline, whereas the 5-HT_{2A} antagonist ketanserin significantly decreased the number of BrdU/NeuN+ cells compared to 1.5 mg/kg PSOP ($p<0.05$). These data suggest that chronic administration of PSOP, a 5-HT_{2A} agonist, upregulates neurogenesis, and the 5-HT_{2A} antagonist ketanserin downregulates neurogenesis in the dentate gyrus of the hippocampus. * indicates a significant difference from saline and # indicates a significant difference from 1.5 mg/kg PSOP.

MDMA was combined with alcohol in utero, there was a significant reduction in both proliferation and neurogenesis in the DG (Canales & Ferrer-Donato, 2014).

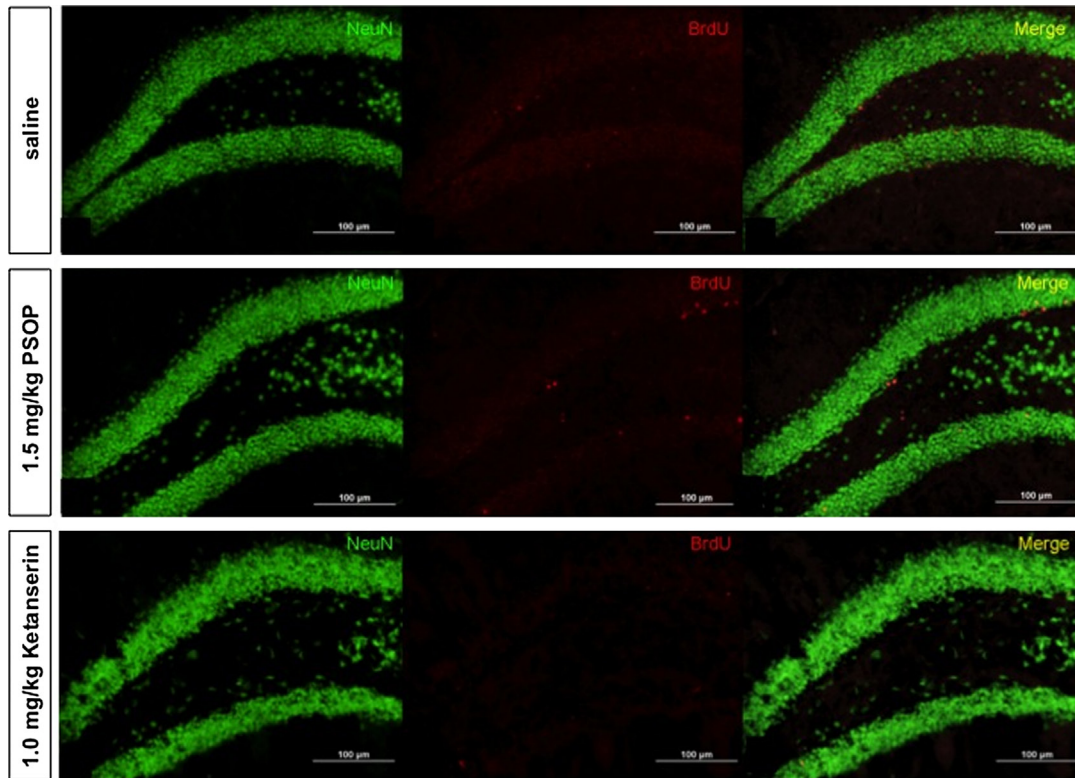


FIGURE 5 Representative photomicrographs showing the effects of chronic PSOP or ketanserin administration on neurogenesis in the dentate gyrus. NeuN+ cells (left), BrdU+ cells (center), and NeuN/BrdU+ cells (right). Saline (top), 1.5 mg/kg PSOP (middle), and 1.0 mg/kg ketanserin (bottom). Scale = 100 µm.

Cannabinoids

Cannabinoids are chemical compounds that produce psychoactive, anticonvulsive, analgesic, and neuroprotective effects. More than 85 cannabinoids have been isolated from the *Cannabis sativa* plant, commonly known as marijuana, with the major constituents being Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) (El-Alfy et al., 2010). These two cannabinoids have varying effects; THC is the primary psychoactive compound in cannabis, whereas CBD is a potent antioxidant with neuroprotective and anticonvulsive effects, but is not psychoactive.

The mechanism of action of cannabinoids is through CB₁ and CB₂ receptors. CB₁ receptors are highly expressed in various brain regions, including the cerebral cortex, substantia nigra, globus pallidus, entopenduncular nucleus, striatum, and HPC (Mailleux & Vanderhaeghen, 1992). Within the HPC, dense CB₁ receptor expression has been reported in the molecular layer of the DG, dendritic layers of CA3, and interneurons (Mailleux & Vanderhaeghen, 1992). CB₂ receptors were initially thought to be expressed only in peripheral tissues derived from the immune system, but more recently they have been shown to be expressed in neurons, astrocytes, and microglia of the CNS in the following regions: olfactory tubercle, islands of Calleja, cerebral cortex, striatum, thalamic nuclei, amygdala, substantia nigra, periaqueductal gray, paratrochlear nucleus, paralemniscal nucleus, red nucleus, pontine nuclei, inferior colliculus, and the parvocellular portion of the medial vestibular nucleus (Gong et al., 2006).

There is evidence to suggest that the cannabinoid system is involved with the regulation of neurogenesis. Specifically, activation of CB₁ and CB₂ receptors by cannabinoids enhances hippocampal neurogenesis (Jiang et al., 2005; Kim et al., 2006; Palazuelos et al., 2006; Wolf et al., 2010). CB₁ agonists, including CBD, WIN55,212-2, and HU210, have been reported to enhance hippocampal neurogenesis (Jiang et al., 2005; Kim et al., 2006; Wolf et al., 2010). Further evidence demonstrating the specificity of the proneurogenic effect of the CB₁ receptor is the inability of CB₁ agonists to stimulate neurogenesis in CB₁ receptor-KO mice (Kim et al., 2006; Wolf et al., 2010). In addition, CB₂ receptor agonists significantly increase neural progenitor proliferation in the HPC and deficits are observed in mice lacking the CB₂ receptor (Palazuelos et al., 2006). The pharmacological targeting of the CB₂ receptor to alter neurogenesis is of interest because of the lack of psychoactive effects. Researchers have begun to investigate how cannabinoids alter neurogenesis during development. Abboussi, Tazi, Paizanis, and El Ganouni (2014) investigated the effects of chronic exposure to the cannabinoid agonist WIN55,212-2 during adolescence and found that WIN55,212-2 blocked the increase in neurogenesis that has been observed during adolescence (Abboussi et al., 2014).

Phencyclidine

Phencyclidine (PCP; 1-(1-phenylcyclohexyl)piperidine) was first developed in 1926 by Parke–Davis and Company and was placed

on the market during the 1950s under the name *Sernyl*. The drug was noted for its anesthetic properties: patients could receive laparotomies using PCP alone (Greifenstein, Devault, Yoshitake, & Gajewski, 1958). Its use was discontinued in humans, however, when its side effects became apparent. Healthy volunteers experienced poor muscle relaxation, uncontrollable eye movements, memory loss, mania, and intense hallucinations (Greifenstein et al., 1958). PCP was eventually listed as a Schedule II drug under the U.S. Controlled Substances Act in the 1970s. The behavioral and cognitive effects brought on by PCP injection limited its use to research as a model for schizophrenia: administering PCP to healthy volunteers mimics positive and negative symptoms of schizophrenia and, in schizophrenic patients, worsens their psychotic and cognitive deficits (Itil, Keskiner, Kiremitci, & Holden, 1967). More recently, ketamine, a drug with a pharmacological profile similar to that of PCP, has been shown to produce a rapid, long-lasting antidepressant effect in subjects with major depression (Zarate et al., 2006). In addition, a comparison of the antidepressant effects of PCP with ketamine in a rodent model of depression revealed PCP to be a weaker antidepressant than ketamine (Hillhouse, Porter, & Negus, 2014).

Structurally, PCP is classified as an arylcyclohexylamine. It contains benzene and piperidine rings attached to the same carbon atom on a cyclohexane ring. PCP is metabolized by the liver into 1-(1-phenylcyclohexyl)-4-hydroxypiperidine, 4-phenyl-4-(1-piperidinyl)cyclohexanol, and 4-(4-hydroxypiperidino)-4-phenylcyclohexanol. In the brain, PCP exerts its effects as a noncompetitive NMDA-R antagonist and has been shown to act on the HPC, cervical spinal cord, hypothalamus, caudate nucleus, frontal cortex, cerebellum, medulla, and amygdala (Zukin & Zukin, 1979). Increases in extracellular DA and glutamate in the prefrontal cortex and nucleus accumbens are caused by PCP binding to the NMDA-R (Adams & Moghaddam, 1998). DA-related behaviors associated with chronic PCP use, such as increased stereotypy and locomotion, are indeed characterized by such an increase in DA levels in the prefrontal cortex and nucleus accumbens (Liu et al., 2006).

PCP exhibits particular effects on neurogenesis. In mice, chronic 7.5 mg/kg PCP administration has been shown to decrease progenitor cell proliferation in the SVZ as well as the DG by 23% (Liu et al., 2006). In addition, this effect is dose dependent, with 1 mg/kg chronic PCP not altering proliferation and 10 mg/kg significantly decreasing proliferation and neurogenesis in the DG (Maeda et al., 2007). Interestingly, after chronic PCP treatment the levels of proliferation returned to normal within 1 week and neurogenesis was not altered at later time points (2 and 4 weeks) (Liu et al., 2006). Furthermore, evidence suggests PCP does not affect the morphology, distribution, or phenotype of proliferating cells such as neurons or glia (Liu et al., 2006). The PCP-induced decreases in neurogenesis can also be mitigated by clozapine (D_2 and 5-HT₂ receptor antagonist) and D-serine and glycine (coactivators of NMDA-R), providing further evidence for PCP's effects through inactivation of the NMDA-R (Maeda et al., 2007). Interestingly, the attenuation in proliferation and neurogenesis caused by chronic PCP varies depending on the developmental period of administration. When administered to pregnant dams for 2 weeks PCP induces neurogenesis by as much as 77% in the granule cell layer of the dentate in the offspring of pregnant dams (Tanimura et al., 2009). Pups in this experiment displayed a sharp decline in

locomotion as well, in contrast to the exaggerated motor activity seen in animals given PCP directly (Tanimura et al., 2009).

THE NEUROBIOLOGICAL SIGNIFICANCE OF ALTERED HIPPOCAMPAL NEUROGENESIS INDUCED BY PSYCHEDELIC DRUGS

The functional significance of hippocampal neurogenesis in the human adult brain is not completely understood. As reviewed above, hippocampal neurogenesis is strongly influenced by behavior, stress, hormones, and drugs. Conversely, changes in hippocampal neurogenesis have an impact on subsequent behaviors. The difficulty in defining the function of new neurons in the HPC reflects incomplete understanding of hippocampal function. The capacity to form new synaptic connections (and to prune old synapses) between neurons in DG and afferent and efferent fibers from cerebral cortex is important for the acquisition of new associations (learning) and recall of those associations (memory). Hippocampal neurogenesis has been shown to play a critical role in some aspects of learning, especially regarding temporal encoding of episodic memory (Shors et al., 2001). Ablation of hippocampal neurogenesis with a potent chemotherapeutic agent has been shown to impair acquisition of HPC-dependent learning such as the conditioned eyeblink or fear conditioning (Shors et al., 2001). Moreover, interference with hippocampal neurogenesis will increase the propensity for depression, and enhanced neurogenesis is highly correlated with remission of depression following treatment with selective serotonin uptake inhibitor (SSRI) antidepressants (Santarelli et al., 2003). So the dose-dependent effects of psychedelic drugs on hippocampal neurogenesis may result in either enhanced learning or forgetting. The practical utility of such a medication might be to facilitate extinction of a conditioned fear response and might be used as an adjunctive pharmacotherapy in the treatment of posttraumatic stress disorder (PTSD).

SUMMARY

HPC neurogenesis occurs throughout adult life and is strongly influenced by many factors including behavior, stress, hormones, and drugs. Conversely, changes in HPC neurogenesis have an impact on subsequent behaviors. However, the functional significance of HPC neurogenesis in the human adult brain is not completely understood. The difficulty in defining the function of new neurons in the HPC reflects the incomplete understanding of hippocampal function. The capacity to form new synaptic connections (and to prune old synapses) between neurons in the DG and afferent and efferent fibers from the cerebral cortex is important for the acquisition of new associations (learning) and recall of those associations (memory). Hippocampal neurogenesis has been shown to play a critical role in some aspects of learning, as in spatial learning of a water maze task (van Praag et al., 1999). Other forms of learning, as in a conditioned eyeblink response or conditioned fear, also appear to require HPC neurogenesis. Moreover, interference with HPC neurogenesis will increase the propensity for depression, and enhanced neurogenesis is highly correlated with remission of depression following treatment with SSRI antidepressants (Santarelli et al., 2003). The dose-dependent effects of psychedelic drugs on HPC

neurogenesis may enhance learning or forgetting. It can be speculated that PSOP medication might be used to facilitate extinction of conditioned fear responses as an adjunctive pharmacotherapy for treatment of PTSD. PSOP and other similar drugs may be helpful in attenuating drug-seeking behavior in opiate-dependent persons who experience conditioned withdrawal responses triggered by stimuli associated with previous abstinence episodes. Some psychedelic drugs might also be useful for the treatment of depression. More clinical research will be needed to determine optimal psychedelic drug doses and procedures to use for treatment of specific conditions including depression, anxiety, PTSD, and drug dependence.

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCE MISUSE

1. PSOP, the active ingredient in “magic mushrooms,” has shown promise as a treatment for alcohol addiction when paired with psychotherapy. This study, led by Dr. Rick Strassman, was published in 2015 in the *Journal of Psychopharmacology* and demonstrates in 10 patients with alcohol dependence that PSOP is an effective drug to increase abstinence from alcohol use.
2. PSOP has a mechanism of action similar to that of another psychedelic drug, LSD, by binding to the 5-HT_{2A} receptor. An article published in the *Quarterly Journal of Studies on Alcohol* in 1959 showed that 40 patients with an “extremely unfavorable prognosis” of alcoholism responded to the therapeutic use of LSD for the treatment of alcoholism.
3. In addition to alcohol addiction, PSOP is effective for the treatment of tobacco addiction, which was demonstrated by a group of researchers led by Dr. Roland Griffiths from Johns Hopkins University and was published in the *Journal of Psychopharmacology* in 2014.
4. Another psychedelic compound called ibogaine is being used to treat addiction to opiates, which are commonly prescribed painkillers.
5. Psychedelics as a class of compounds are beneficial for treating addiction particularly because they are not themselves addictive and do not require years of treatment with daily medication use; often treatment occurs with an acute dosage.
6. Most psychedelics are classified as Schedule I controlled substances, by law rendering them with high abuse potential and no established medical use. However, many scientific papers have shown that psychedelics have low addictive potential and have medical uses beyond treating addiction, including depression, anxiety, and PTSD.

DEFINITION OF TERMS

- 3,4-Methylenedioxymethamphetamine** This is a psychostimulant drug commonly referred to as “ecstasy,” which induces emotional openness.
- Cannabinoids** These are chemical compounds that produce psychoactive, antiseizure, pain-relieving, and neuroprotective effects.
- Depression** This is a mental disorder that involves low mood, low self-esteem, and loss of interest in normal activities.
- Growth factors** These are proteins produced in the body that are involved in the growth and survival of cells.

Hippocampus This is a brain region that plays a critical role in short-term to long-term memory consolidation and spatial navigation.

Hypothalamic–pituitary–adrenal axis The HPA is a loop of feedback interactions between endocrine glands that regulate the levels of stress hormones and reactions to stress.

Neurogenesis This is the formation of new neurons from neural stem cells.

Neuroplasticity This is the ability of the brain’s synapses and pathways to change based on changes in thinking and emotions, the environment, or behavior.

Neurotransmitters These are chemicals produced in the brain that transmit signals from one neuron to another via the synapse.

Phencyclidine PCP is a dissociative drug, also known as “angel dust,” which causes hallucinations.

Posttraumatic stress disorder This is a disorder that can develop after a person experiences a serious trauma, which involves persistent fear and helplessness and prevents the individual from living a normal life.

Proliferation Proliferation, or cell growth, refers to the division of a “mother cell” to produce two “daughter cells.”

Psilocybin This is a naturally occurring substance in hallucinogenic mushrooms.

Psychedelic drug Also known as hallucinogens, psychedelic drugs are substances with psychoactive effects that alter cognition and perception.

Receptor This is a protein embedded in the plasma membrane of the cell that receives chemical messages from outside the cell.

KEY FACTS OF PSYCHEDELIC DRUGS AND HIPPOCAMPAL NEUROGENESIS

- Neurogenesis is the birth of new neurons and occurs throughout the life span in specific regions in the mammalian brain, including the HPC. Neurogenesis occurs at higher rates in early years and declines with aging.
- Hippocampal neurogenesis is critical in forming new memories. In fact, studies have shown that decreasing neurogenesis in the HPC severely impairs learning and memory tasks that are dependent on the HPC.
- Many factors, including psychedelic drugs, can alter neurogenesis in the HPC. Physical exercise is one way to boost neurogenesis, whereas stress is one of the most potent ways to reduce neurogenesis.
- Psychedelic drugs have potential therapeutic use in the treatment of specific conditions including depression, anxiety, PTSD, and drug dependence.

SUMMARY POINTS

- This chapter focuses on hippocampal neurogenesis, which occurs throughout the human life span.
- The process of neurogenesis involves proliferation of neural stem/progenitor cells and their differentiation into mature neurons, followed by integration into the hippocampal circuitry.
- Many factors regulate neurogenesis, including stress, physical exercise, hormones, and drugs.
- Psychedelic drugs have a dose-dependent impact on hippocampal neurogenesis.

- The functional significance of hippocampal neurogenesis is not completely understood but is important in various aspects of learning.
- In light of abundant preclinical data and the loosening of governmental restrictions on psychedelic drug research, these agents should be explored for their therapeutic potential in depression, PTSD, and drug dependence.

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