Biochemical Pharmacology – Invited Review

The impact of cocaine on adult hippocampal neurogenesis: potential neurobiological mechanisms and contributions to maladaptive cognition in cocaine addiction disorder

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Abstract: After discovering that addictive drugs alter adult neurogenesis, the potential role of adult-born hippocampal neurons in drug addiction has become a promising research field, in which cocaine is the most frequently investigated drug. Although a substantial amount of pre-clinical evidence has accumulated, additional studies are required to reveal the mechanisms by which cocaine modulates adult hippocampal neurogenesis (AHN) and determine whether these adult-born neurons have a role in cocaine-related behaviors, such as cocaine-mediated cognitive symptoms. First, this review will summarize the cocaine-induced alterations in a number of neurobiological factors (neurotransmitters, neurotrophins, glucocorticoids, inflammatory mediators) that likely regulate both hippocampal-dependent learning and adult hippocampal neurogenesis after cocaine exposure. A separate section will

provide a detailed review of the available literature that challenges the common view that cocaine reduces adult hippocampal neurogenesis. In fact, cocaine has a short-term anti-proliferative role, but the young adult-born neurons are apparently spared, or even enhanced, following certain cocaine protocols. Thus, we will try to reconcile this evidence with the hippocampal-dependent cognitive symptoms that are typically observed in cocaine addicts, and we will propose new directions for future studies to test the relevant hypothesis. Based on the evidence presented here, the regulation of adult hippocampal neurogenesis might be one of the many mechanisms by which cocaine sculpts hippocampus-dependent learning.

Keywords: vulnerability, associative memory, conditioned place preference, withdrawal, relapse

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1. A focus on the hippocampus to explain the aberrant cognition induced by cocaine

Cocaine is a psychostimulant and euphoria-inducing drug that is widely used around the world [1, 2]. Some casual users (~20 %) with certain environmental and/or biological risk factors will progress from recreational cocaine consumption to an addiction disorder [3]. Once an addiction is established, cocaine use is no longer explained by the will to experience its reinforcing properties but becomes a compulsion or 'habit' that the person can no longer control [4]. Uncontrollable drug intake may be then triggered by internal or external factors, such as experiencing stressful life events or stimuli previously associated with the effects of the drug. Therefore, exposure to a cocaine-associated stimuli (e.g., visiting a place or context where cocaine was usually administered) may elicit an intense desire for the drug ('*craving*') and precipitate drug use and relapse, contributing to the chronic nature of addiction [4]. Since memories of the cocaine-stimuli associations are highly persistent and resistant to extinction and forgetting, cocaine addiction has been considered as a learning and memory disease [5]. However, the potent memories of drug-stimuli associations paradoxically contrast with the cognitive decline caused by repeated cocaine use [6]. Approximately 30 % of cocaine-dependent individuals show global cognitive impairment (affecting attention, working memory, declarative memory and executive functions [6, 7]) that hampers the treatment of cocaine addiction and predicts treatment drop-out and relapse [8-10]. Therefore, different cognition-related events have been distinguished in cocaine addiction disorder, including 1) the formation of engrained memories of cocaine-stimuli associations that may be established at the initial experiences with the drug and precipitate relapse when a drug-paired stimulus is presented; and 2) a global cognitive impairment that emerges after chronic cocaine exposure, persists during abstinence and contributes to relapse by disrupting the acquisition of new adaptive information (i.e., 'cognitive inflexibility' [5]) and by impeding engagement in behavioral therapy that requires a considerable cognitive effort to change maladaptive behavioral patterns [11].

The recent emphasis on the learning components of cocaine addiction has directed a focus towards the hippocampus [5, 12], the main brain region involved in declarative and associative memory. The hippocampus is anatomically and functionally integrated into the 'cocaine addiction brain circuit' and establishes reciprocal connections with the main addiction-related areas [12]. Notably, a cocaine infusion boosts hippocampal neuronal activity [13, 14] and enhances hippocampal long-term potentiation (LTP) and synaptic plasticity (although LTP may be reduced at high cocaine doses) [5], which may result in an acutely strengthening of hippocampus-dependent function by cocaine, including enhanced memory consolidation [15]. Moreover, the hippocampus is clearly required for the acquisition, consolidation, recall and update (reconsolidation or extinction) of cocaine-stimuli associations. This requirement is illustrated by numerous experiments in rodents that used the cocaine-induced conditioned place preference (CPP) or the cocaine self-administration paradigms to study cocaine-induced associative memory (reviewed in [12]) and by clinical studies of cocaine addicts showing increased hippocampal activity (associated with craving feelings) when these individuals are presented a cocaine-associated cue [16-18]. On the other hand, the global cognitive decline reported after chronic cocaine use and withdrawal reflects the emergence of a blunted hippocampal function after extended cocaine exposure. Both cocaine addicts [6, 7] and cocaine-withdrawn rodents [19, 20] show deficits in their performance on hippocampus-dependent memory tasks for months after abstaining from cocaine. This effect is concomitant with persistent neuroadaptations in the hippocampus that affect its functional activity, connectivity, structure and neurochemistry (in rodents: [19, 21]; in addicts: [22-24]; **Section 2**).

The involvement of the hippocampus in cocaine addiction cannot be completely understood without considering a role for adult hippocampal neurogenesis (AHN), a key neuroplastic phenomenon required for both the formation and updating of hippocampal-dependent memories [25, 26]. This manuscript does not aim to detail AHN dynamics, which are reviewed elsewhere [25, 27]. However, the reader should consider that adult-born

hippocampal neurons are continuously generated in the subgranular zone of the dentate gyrus (DG) from a pool of proliferating neural progenitor cells with radial astrocyte-like properties, which generate neuroblasts by asymmetric division. These neuroblasts differentiate into mature granular neurons in approximately 4 weeks [25, 27] **(Fig. 2)**. This process occurs in a complex and sensitive microenvironment ('neurogenic niche') that receives numerous molecular inputs from neurotransmitters, hormones, neurotrophins, growth factors and inflammatory mediators that modulate AHN in response to environmental demands or disease states [28] **(Figs. 1 and 2)**. Importantly, cells at each maturational stage (proliferating neural progenitor cell > proliferating neuroblast > immature neuron > mature neuron) exhibit unique electrophysiological properties, expression patterns of receptors and degrees of synaptic integration [25, 27]; therefore, the events of proliferation, differentiation/maturation and survival may be regulated by independent pathways as they concern different cell types. The most important link between AHN and cocaine addiction was revealed in several pre-clinical experiments showing that cocaine, as well as other drugs of abuse, inhibit cell proliferation in the DG (reviewed in [12]), and that animals with reduced AHN exhibit an increase cocaine self-administration behaviors [29, 30]. Thus, the scientific community has proposed that reduced AHN is a potential mechanism by which cocaine establishes and maintains addiction [12, 31]. However, according to recent data (summarized in the **Table 1**), the young neurons generated *before* cocaine exposure are usually spared, or even exhibit enhanced maturation and functional integration in animals that learn cocaine-stimuli associations (**Section 3.1**). In addition, the reduction in DG cell proliferation induced by repeated cocaine administration is only transient and rarely yields a reduction in AHN during cocaine withdrawal (**Section 3.2**).

Although AHN could certainly have different roles in cocaine addiction, such as blunting the reinforcing value of cocaine [30] or reducing stress and negative mood [32], this review will focus on the cognitive domain, given the prominent role of AHN in learning. An effort will be made to reconcile the available data regarding the regulation of AHN by cocaine with the two

main cognitive events observed in cocaine addiction that involve the hippocampus: the strong memories of cocaine-stimuli associations and the blunted learning of new or updated memories. In summary, we propose that acute cocaine administration takes advantage of the hippocampal mechanisms that are normally involved in learning to recruit immature neurons to encode and update cocaine-related memories. On the other hand, a dysregulation of these learning systems by prolonged cocaine intake and withdrawal disrupts the neurogenic niche, probably resulting in impairments in learning-related regulation of the newly generated neurons and subsequent cognitive decline.

2. Neurobiological mechanisms by which cocaine regulates AHN: overlap with the hippocampal learning and memory systems

Once cocaine reaches the bloodstream from any of its administration routes, its amphiphilic properties [33] allow the drug to cross the blood-brain barrier and rapidly penetrate the brain. The peak uptake of cocaine in the human brain occurs approximately 4-7 minutes after the injection of this drug, and the half peak clearance occurs 17-29 minutes after administration, depending on the brain region [34]. Although the highest density of cocaine-binding sites corresponds to the richest monoamine reuptake sites, the dorsal and ventral striatum, the hippocampus is one brain region that shows intermediate cocaine binding and clearance rates [34]. Repeated administration of a high cocaine dosage does not obviously parallel neurotoxicity in the hippocampus *in vivo* [35], but cocaine triggers the apoptotic death of human neuroblasts *in vitro* by increasing oxidative stress and the inflammatory response [36] and inhibiting the proliferation of neural progenitors by downregulating cyclin A [37]. Therefore, cocaine may directly impact adult-born hippocampal neurons and progenitor cells **(Fig. 2)**.

Nevertheless, many ‘indirect’ mechanisms by which cocaine could regulate AHN have been identified. The notable actions of cocaine on the whole brain include increasing or decreasing neuronal activity in many addiction-related and limbic regions that are anatomically or functionally connected with the hippocampus [12, 13]. As a result, cocaine widely modulates

hippocampal neurotransmission and even complex physiological functions, such as the stress or immune responses, thus changing the inputs that reach the neurogenic niche **(Fig. 2)**. This section (with no intention of being exhaustive) will discuss some of the neurobiological mechanisms that are likely to contribute to regulating AHN in response to cocaine administration. Notably, few studies have provided direct evidence of the events underlying the effects of cocaine on AHN. Therefore, we will address a number of factors that are important regulators of AHN under normal conditions and that are notably altered by cocaine. Interestingly, all these factors that regulate the AHN share a common trait: they are important for hippocampus-dependent learning, usually including cocaine-associated memories.

2.1. Neurotransmitters and neuromodulators

2.1.1. Amino acids (glutamate and GABA)

The hippocampus is primarily composed of glutamatergic excitatory neurons, and glutamate is the main neurotransmitter involved in hippocampal function, including LTP, a key form of plasticity that involves the strengthening of glutamatergic synapses and is the basis of hippocampal learning and memory [38]. In the DG, glutamatergic neurons are densely packed granule cells that receive a prominent glutamatergic input from the entorhinal cortex (perforant path) and project axons to the cornu ammonis 3 area (mossy fibers path) [39]. Interestingly, the DG also directly receives glutamate and gamma-amino butyric acid (GABA) released from mesohippocampal neurons in the ventral tegmental area, a key region involved in the reward/addiction brain system [40]. On the other hand, hippocampal excitability is locally regulated by several inhibitory GABAergic interneuron types that comprise approximately 10 % of the neuron population of the DG [41].

Based on its role in learning-related neuroplasticity, glutamate and GABA crosstalk is critical for the experience-dependent differentiation and functional integration of adult-born neurons. Neural progenitor cells, neuroblasts and immature neurons express both GABAA and

GABAB receptors [42, 43] that allow a tonic response to ambient GABA. Importantly, this response is excitatory until neurons reach approximately 3 weeks of age [25, 27]. This unique electrophysiological feature defines a 'critical period' in which the immature neurons are highly capable of adapting their structure and function in response to environmental inputs [25, 44]. During this period, GABA depolarization through the GABAA receptor drives differentiation, migration and dendritic development [45, 46] and is responsible for the synaptic integration of the immature neurons into the DG circuitry by unsilencing glutamatergic N-methyl-D-aspartate (NMDA) receptor-dependent synapses in an activity-dependent manner [47]. Upon the initiation of glutamatergic synaptic transmission at approximately the third to fourth week, the adult-born neurons will have greater chances of long-term survival in the DG circuitry [44], where they will develop features of mature granule neurons, including an inhibitory GABA response [25, 27] **(Fig. 2)**. Moreover, both ambient glutamate and GABA modulate AHN at its early proliferative stage through receptors in neural progenitor cells. GABA acts a 'stop' signal for cell proliferation by binding to both GABAA and GABAB receptors [42, 43], whereas glutamate may both promote (through metabotropic mGlu3 and mGlu5 receptors) or inhibit (through NMDA receptors) proliferation [48-50].

Cocaine uses hippocampal glutamatergic transmission to enhance memory formation. Cocaine-mediated facilitation of LTP depends on hippocampal metabotropic glutamate receptors [51], and hippocampal glutamatergic signaling is involved in the acquisition and retrieval of cocaine-stimuli associative memories [52-55]. After chronic administration, cocaine disrupts the excitatory/inhibitory balance in the brain [56]. Repeated cocaine administration may not change basal hippocampal glutamate levels [57], but cocaine depresses GABA-induced currents in isolated hippocampal neurons [58] and dysregulates the expression of receptor genes in the rodent hippocampus and DG (i.e., the expression of NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and GABAA receptor subunits are differentially regulated, altering the receptors' composition; the expression of

mGlu5 receptors and GABAB receptor subunits typically increases) [59-64]. Remarkably, post-mortem studies of cocaine addicts support a profound dysregulation of the expression of hippocampal genes involved in glutamatergic and GABAergic transmission, including genes encoding both GABA and glutamate receptor subunits and the GABA-synthesizing enzymes; the expression of genes implicated in glutamate synthesis were not evaluated [23, 24, 65]. These persistent synaptic changes may explain the aberrant activity of the hippocampal neurons observed after chronic cocaine use and withdrawal (in rodents: [19] specifically in the DG; in cocaine addicts: [16-18, 22]), suggesting that glutamate/GABA neurotransmission in the neurogenic niche is disrupted and likely impairs the functional integration of adult-born hippocampal neurons.

2.1.2. Monoamines (dopamine, serotonin, and noradrenaline)

Monoamines play an important role in hippocampal plasticity and function as they modulate the activity of both hippocampal glutamatergic neurons and GABAergic interneurons that express monoaminergic receptors [66-68]. Notably, monoamines are involved in the emotional enhancement of memory, as they boost the efficacy of LTP, whereas a lack of monoamine signaling impairs LTP and leads to deficits in hippocampus-dependent memory [68-71].

The DG receives a diffuse monoaminergic projection from the ventral tegmental area (which releases dopamine; DA) and prominent inputs from the raphe nucleus (which releases serotonin; 5-HT) and the locus coeruleus (which releases noradrenaline; NA) **(Fig. 2)** [39, 72]. The monaminergic fibers are located in close proximity to proliferating cells and young neurons (DA [73, 74]; 5-HT [75]); thus, monoamines may directly innervate the adult-born cells to modulate their response to glutamate and GABA inputs [74, 76]. Monoamines mainly regulate AHN by modulating cell proliferation, which is reduced if monoamine levels are depleted (DA [73]; 5-HT [77]; NA [78, 79]), -although some divergent results have been reported- (DA [80]; 5-HT [81]). In particular, D1, 5-HT1A and β-adrenergic receptors are

expressed in hippocampal neural progenitor cells [76, 82, 83] and are responsible for the pro-proliferative effects of monoamines, whereas other monoamine receptors may not induce these effects or may even inhibit proliferation (DA [84]; 5-HT [83, 85]; NA: [82, 86]). Finally, dopamine and serotonin (but not noradrenaline; [78, 79]) also enhance the differentiation and survival of adult-born hippocampal neurons through D1 [84] and 5-HT1A [83, 87] signaling.

Monoamines, particularly dopamine, have received considerable attention in cocaine addiction research because they are responsible for the rewarding and psychostimulant properties of cocaine [88]. Cocaine enhances monoamine activity in the extracellular space by blocking the membrane transporters responsible for monoamine reuptake at the presynaptic terminals (DA transporter (DAT) for DA, serotonin transporter (SERT) for 5-HT and norepinephrine transporter (NET) for NA; to which cocaine binds with similar affinity) [89, 90]. Transporter-independent mechanisms have also been described; for example, cocaine may enhance dopamine release from the ventral tegmental area [91]. Based on pre-clinical research, dopaminergic activity in the hippocampus is required for the cocaine-induced increase in glutamatergic LTP [92, 93] and potentiates both the acquisition and retrieval of memories of cocaine-stimuli associations through D1-like receptors (but it impairs late memory consolidation). [94-96]. Although less frequently investigated, both hippocampal serotoninergic (mainly through 5-HT1A/1B receptors) and noradrenergic (through β-adrenergic receptors) activity also participate in retrieving memories of cocaine-context associations [97, 98]. Long-lasting alterations in the total hippocampal levels of monoaminergic neurotransmitters have not been observed following chronic cocaine exposure [99], but their turnover rate is increased [100] and the expression of the hippocampal monoamine receptors is altered (e.g., hippocampal D1 and D2 receptors are upregulated: [101, 102]; but the 5HT1A receptor is downregulated in the DG [103]).

The monoaminergic system has been postulated to mediate cocaine-induced regulation of AHN. Interestingly, the systemic administration of a 5-HT1A receptor antagonist (WAY 100635) prevented the reduction in the numbers of an immature DG neuron population

(expressing the polysialylated neuronal cell adhesion molecule, PSA-NCAM) observed after the acute administration of cocaine and protected against cocaine-induced depletion of LTP [104]. This finding appears to contradict the pro-proliferative effect that has usually been reported for hippocampal 5-HT1A receptors [83], but the many neurobiological systems impacted by cocaine are likely to interact, yielding a complex regulatory mechanism. For example, systemic WAY 100635 administration results in reduced corticosterone secretion [105], which could preserve AHN under conditions with high glucocorticoids levels, such as the acute administration of cocaine [106] (**Section 2.3**).

2.1.3. Other neurotransmitters and neuromodulators

In addition to the amino acids and monoamines, hippocampal function and AHN are also regulated by many neurotransmitters and neuromodulators, such as acetylcholine, nitric oxide, neuropeptides or endocannabinoids [28, 107], which may be 'hijacked' by cocaine [108-112]. Among these factors, a preliminary study has examined the role of the endocannabinoid system in mediating cocaine-induced regulation of AHN. Endocannabinoid signaling has been observed in both the central and peripheral nervous systems and is mainly mediated by the endogenous endocannabinoid ligands 2-arachidonoylglycerol and anandamide, the latter of which is a member of the N-acyl-ethanolamine family (reviewed in [113]). The endocannabinoid ligands are systemically synthetized in tissues such as the kidney and the liver [114, 115] and centrally synthesized by neurons [116] (**Fig. 2**). Cannabinoid receptors CB1 (presynaptic) and CB2 (postsynaptic) are widely expressed in hippocampal neurons, and they suppress or stimulate excitatory neuronal transmission, respectively [117, 118]. In addition, the CB1 receptor is located in hippocampal interneuron terminals, reducing GABA release [119]. Both DG granule neurons and DG interneuron populations that express calcium-binding proteins also express cannabinoid-synthesizing and -degrading enzymes, as well as the receptor for N-acylethanolamines, peroxisome proliferator-activated receptor alpha (PPARα) [120, 121]. Endocannabinoid signaling exerts a number of contrasting effects on AHN that are predominantly pro-neurogenic [122]. Both the

CB1 and CB2 receptors expressed in the neural progenitor cells drive proliferation [123, 124], and CB1 promotes both the basal and activity-dependent differentiation and survival of adult-born immature neurons [125, 126]. Nevertheless, endocannabinoids frequently worsen hippocampal memory [127]. Without excluding other possible explanations for this apparent contradiction, the impairment of the hippocampal functions that are usually associated with AHN (e.g., reference memory consolidation) seems to be induced by the acute actions of endocannabinoids [127] and likely involve fast synaptic mechanisms independent of the mechanisms regulating AHN. The hippocampal impairment induced by chronic cannabinoid exposure is primarily a working memory deficit [127]. Working memory may depend on the hippocampus but does not seem to be enhanced by elevated AHN [25].

Repeated cocaine exposure widely dysregulates the expression of endogenous proteins involved in endocannabinoid signaling in the rodent hippocampus [128, 129]. In long-abstinent cocaine addicts, circulating levels of endocannabinoid-related lipids (N-acyl-ethanolamines) are increased and associated with comorbid anxiety and mood disorders, whereas plasma 2-acyl-glycerol levels are reduced [113, 130]. Interestingly, circulating endocannabinoid levels have been shown to influence the motivation for cocaine in pre-clinical models, where systemic pharmacological agonism of the endocannabinoid system increases cocaine self-administration in abstinent rats, but a CB1 receptor antagonist prevents relapse [131]. In contrast, repeated co-administration of systemic antagonists of either CB1 or CB2 receptors (rimonabant and AM630, respectively) with cocaine protects the brain from both the cocaine-induced inflammatory response and the cocaine-induced reduction in DG cell proliferation, and impedes the acquisition of cocaine-conditioned locomotion through an as yet undefined mechanism [132]. Thus, the cannabinoid system could support a pathway by which cocaine regulates both AHN and the acquisition of memories of cocaine-stimuli associations, a hypothesis that should be examined in future studies. Notably, other lipid signaling molecules, such as lysophosphatidic acid, are also

potent regulators of AHN [133, 134] and candidates for involvement in cocaine addiction [60, 135].

2.2. Neurotrophins and growth factors

The neurotrophin that has received the most attention in cocaine addiction research is brain-derived neurotropic factor (BDNF). BDNF modulates glutamatergic transmission through tropomyosin receptor kinase B (TrkB) receptors in hippocampal glutamatergic neurons [136]. Under learning-related conditions, the hippocampus secretes BDNF in an activity-dependent manner to induce and maintain LTP [137], which is required for the acquisition, consolidation and extinction of hippocampus-dependent memories, including contextual/associative memories [137]. In particular, engaging in hippocampal contextual learning selectively and rapidly increases hippocampal BDNF levels [138]. Other sources of BDNF in the hippocampus include astrocytes [139] and probably the circulation, where BDNF is primarily produced by platelets [140] and could directly modulate hippocampal plasticity after crossing the blood-brain barrier [141, 142] **(Fig. 2)**.

Both central and peripheral BDNF are involved in regulating AHN [142-144]. Among adult-born hippocampal neurons, the TrkB receptor is expressed at high levels in neural progenitor cells and at low levels in proliferating neuroblasts; however, TrkB expression progressively increases in the young neurons as they progress towards maturity [136]. Accordingly, BDNF has been closely linked to the survival, differentiation and functional integration of young neurons [142-144], although some studies have shown that BDNF also stimulates proliferation [143].

According to pre-clinical research, cocaine increases BDNF expression in the regions of the brain related to addiction, where BDNF signaling is required for cocaine-induced behaviors (reviewed in [145, 146]). In the hippocampus, BDNF levels are not readily modified either after acute or repeated cocaine administration [147], but BDNF levels increase in all

hippocampal regions (including the DG) when animals are submitted to withdrawal [21, 147], which parallels the reduction in hippocampal TrkB receptor expression [147]. Hippocampal BDNF has also been shown to be involved in associative memory [148] although, unfortunately, this function has not yet been tested for cocaine-stimuli associative memories. Regarding cocaine-dependent individuals, the peripheral BDNF is more accessible for investigation. Importantly, blood BDNF also regulates AHN [142] and reflects the BDNF levels in the hippocampus across species [149]. The clinical research on circulating BDNF levels is consistent with the results of animal studies supporting the differential regulation of this neurotrophin depending on the phase of addiction that is assessed, and BDNF levels are specifically increased during short-term cocaine abstinence. Although serum BDNF levels are either reduced [150, 151] or unaltered [152] in chronic cocaine users who are consuming cocaine, circulating BDNF levels increase during early cocaine abstinence (i.e., during the first days or weeks of abstinence) [150, 151, 153-155], predicting cocaine craving behaviors and future relapse [150, 154]. After prolonged cocaine abstinence (i.e., approximately one year of abstinence) plasma BDNF levels appear to return to control levels but are reduced in addicts with comorbid anxiety and mood disorders [156]. Therefore, the hippocampal neurogenic niche is likely to suffer from altered BDNF signaling, particularly during early cocaine withdrawal periods.

Notably, other AHN regulators, such as the neurotrophins and growth factors NGF (nerve growth factor), VEGF (vascular endothelial growth factor) and IGF-1 (insulin-like growth factor 1), seem relevant to cocaine addiction [155-157], although these investigations are in a very early stage.

2.3. Glucocorticoids

Glucocorticoids (mainly corticosterone in rodents and cortisol in humans) are the principal hormones involved in the stress response. In the presence of a stressor, the hypothalamus delivers the neurohormone corticotropin-releasing hormone (CRH) that stimulates the

pituitary gland to release the adrenocorticotropic hormone (ACTH), which in turn stimulates the liberation of glucocorticoids from the adrenal glands to the bloodstream (reviewed in [158]). In addition to acting on many organs in the body, glucocorticoids readily pass the blood-brain barrier due to their lipophilic nature and bind to the hippocampus **(Fig. 2)**, one of the brain areas that provides inhibitory feedback to the hypothalamus-pituitary-adrenal (HPA) axis to inhibit glucocorticoid production [158]. Accordingly, the hippocampus is enriched in the two types of glucocorticoid receptors (glucocorticoid receptor (GR) and mineralocorticoid receptor (MR)) that are located in the principal hippocampal neurons to enhance glutamate release [158, 159]. Acute glucocorticoid stimulation modulates hippocampal-dependent memory through an *inverted U-shaped* relationship (i.e., only moderate levels of glucocorticoids potentiate memory [160]), whereas chronic administration of glucocorticoids widely impair hippocampal memory performance [161]. Chronic glucocorticoid stimulation also induces a profound remodeling of hippocampal plasticity and morphology that includes down-regulation of AHN, since glucocorticoids normally suppress cell proliferation, differentiation and survival [158, 162] and chronically stressed animals show reduced AHN [158]. In this regard, glucocorticoids may exert direct effects on AHN, since the GR receptor is expressed in progenitor cells and young neurons at most maturational stages, and MR receptor expression increases progressively as the new neuron matures [163].

Although glucocorticoids probably have a role in the acquisition and consolidation of cocaine-related memories (since they modulate both normal hippocampal learning and the effects of cocaine on hippocampal LTP [106]), this aspect has not been thoroughly investigated. Animals submitted to stressful experiences have been shown to establish stronger cocaine-stimuli associative memories [164-166] and both corticosterone and stress reinstate cocaine-conditioned behaviors in response to cocaine-associated cues [167, 168]. These effects, however, may be better explained by the enhanced reward properties of cocaine and cocaine cravings than by the modulation of the associative learning mechanisms. Nevertheless, acute or repeated cocaine administration has clearly been shown to increase

peripheral glucocorticoid levels and inhibit the inhibitory feedback of the HPA axis in pre-clinical studies [169-171]. Plasma corticosterone levels become progressively normalized during cocaine withdrawal, but dysregulation of the expression of stress-related genes has been observed in the hippocampus, including increased GR and MR expression in the DG [172]. In clinical studies, cocaine addiction usually occurs concomitantly with an altered emotional state [130, 156], and studies of cocaine addicts have confirmed a strong dysregulation of the HPA axis. Both acute cocaine intake and exposure to cocaine-associated cues notably increase circulating cortisol and ACTH levels in dependent individuals [173-175]. Under basal conditions, cocaine addicts who are using the drug or have abstained for short periods frequently display hypercortisolemia compared to non-user controls [9, 176, 177]; and these individuals are particularly sensitive to stress-inducing situations [178]. Notably, elevated cortisol levels in cocaine addicts are associated with a worse prognosis, including comorbid depressive symptoms [177, 179], increased cocaine cravings [180], poorer hippocampal-dependent cognitive performance [9] and increased relapse outcomes [181, 182].

Overall, considering the well-known deleterious effects of glucocorticoids on AHN and the profound impact of cocaine on the stimulation and dysregulation of the HPA axis, these molecules are likely to downregulate AHN in patients with a cocaine addiction. Indeed, the acute effect of cocaine on reducing the numbers of an immature DG neuron population (expressing PSA-NCAM) is prevented by depleting circulating corticosterone levels or by the systemic administration of the GR antagonist mifepristone (but not by the administration of the MR antagonist spironolactone). Therefore, the GR receptors expressed in these young neurons may mediate the inhibitory effect of cocaine [106]. In any case, the relationships among cocaine, AHN and glucocorticoids require further investigation, because rewarding experiences that activate the HPA axis (e.g., physical exercise, sexual activity or learning) stimulate AHN, despite the elevated glucocorticoid levels [183]. Thus, glucocorticoids may

have pro-neurogenic actions, depending on the presence of modulators such as neurotransmitters, neurotrophic factors or inflammatory molecules [183].

2.4. Inflammatory mediators

Finally, cocaine increases inflammation in the body and brain [184, 185]. The main cells responsible for the immune response in the brain are glial cells, such as astrocytes and microglia, which trigger inflammation in response to both brain and systemic insults (since peripheral pro-inflammatory molecules access the brain and activate resting microglia to engage in inflammation) [186] **(Fig. 2)**. Once 'activated', microglia secrete inflammatory mediators, such as the pro-inflammatory cytokines interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNFα) and chemokines, among others, and clears the microenvironment by phagocytosis [187, 188]. Under physiological conditions, basal levels of neuroimmune signaling are required for normal hippocampal functions, whereas the pathological overexpression of immune factors results in memory impairments that persist even after the inflammation is resolved [188, 189]. This impairment occurs because cytokines and chemokines regulate synaptic function in the hippocampus. For example, under pathological conditions, these factors inhibit LTP and alter the expression of both glutamate and GABA receptors in hippocampal neurons [187, 188, 190]. Reduced AHN is another frequent outcome of inflammation [186]. Chronic exposure to IL-1β, IL-6 or TNFα usually decreases AHN by downregulating proliferation, differentiation and survival [189, 191], and this effect is partially mediated by the IL-1 receptors expressed in the neural progenitor cells, whose stimulation causes cell cycle arrest [192]. Accordingly, AHN is frequently reduced in different animal models of inflammation, concomitant with memory deficits [186].

The pro-inflammatory actions of cocaine are evident. The exposure of microglial cells to cocaine elicits microglial activation [193], and rodents that are administered cocaine express inflammation-related markers in the brain [185]. Regarding the hippocampus, both acute and

repeated cocaine administration induces gliosis in the DG [132], and, interestingly, rats exposed to cocaine during adolescence show a notable hippocampal inflammatory response that persists into adulthood and involves gliosis and increased hippocampal levels of IL-1β, IL-6 and TNFα [21]. Cocaine users display high basal circulating levels of pro-inflammatory cytokines (IL-1β, IL-6, TNFα; whereas the levels of the anti-inflammatory cytokine IL-10 may be reduced or increased) compared to non-using individuals [184, 194, 195]. Thus, an elevated inflammatory state may be present in the cocaine-addicted brain, which has been confirmed by a post-mortem study [196], but has not yet been confirmed *in vivo* [197]. On the other hand, in long-abstinent cocaine addicts (i.e., approximately one year of abstinence), plasma levels of pro-inflammatory plasma cytokines and chemokines are normalized or even reduced [130, 198], suggesting that the immune system is also regulated by extended drug withdrawal.

3. AHN modulation as a potential mechanism by which cocaine regulates cognition in the addicted brain

As introduced in the previous section, acute and chronic cocaine administration modulates and hampers a number of neurobiological mechanisms that are involved in learning and regulating AHN in the normal brain, suggesting that AHN is profoundly dysregulated after cocaine exposure. Unfortunately, evidence of AHN in a cocaine addict population is still lacking, probably because human post-mortem samples that are suitable for immunohistochemistry are difficult to obtain and the current technology does not allow researchers to detect AHN *in vivo* [199] -although remarkable advances are being made in this field [200]-. Nevertheless, based on abundant pre-clinical evidence in rodents (mostly from studies focused on cell proliferation), AHN is regulated by cocaine (reviewed in [12]; **Table 1**). The available studies on AHN and cocaine will be summarized in this section in an attempt to reconcile the results with the aberrant cognition induced by cocaine.

3.1. Role of AHN in the acquisition and maintenance of memories of cocaine-stimuli associations

The majority of the studies (reviewed in [12]) have systemically administered cocaine in 'resting', non-stimulated rodents (i.e., in their home cage), usually rats, and analyzed AHN within the first 24 hours after the administration of the last cocaine dose. According to these studies, a single cocaine dose may not inhibit DG cell proliferation [201-203], but it reduces the numbers of an immature neuron population expressing PSA-NCAM [104, 106, 204]**.** However, if cocaine administration is repeated (usually for ~7 days or more), then DG cell proliferation is most likely reduced ([201-203, 205-208], although one report showed increased cell proliferation [209]) (**Table 1**). Accordingly, DG cell proliferation is also reduced in rats after the completion of a cocaine self-administration protocol that extended across several days [210, 211], and experiments that did not report this reduction used fewer self-administration sessions or a lower cocaine dosage [211, 212]. In conclusion, although several modulatory factors should be considered (including the animals' ages and genetic backgrounds [201]), DG cell proliferation has been consistently shown to be reduced immediately after a repeated cocaine treatment if the animals were exposed to a sufficient amount of drug (**Table 1**, reviewed in [12]). Interestingly, this effect does not appear to be specific to the DG, as the few studies that have investigated the other main adult neurogenic locus, the subventricular zone/olfactory bulb, observed a reduction in cell proliferation in this region after cocaine administration [210, 213].

Nevertheless, an acute reduction in DG cell proliferation or in neurons that are a few days old is not expected to impair hippocampus-dependent learning. In fact, engaging in normal hippocampal learning is usually associated with reduced cell proliferation, since the proliferating cells are removed to ensure that they will not compete for inputs with the neurons involved in the task [214, 215]. Although proliferating cells may modulate hippocampal plasticity by releasing growth factors in the neurogenic niche [216], they are not thought to directly participate in memory, as they lack synaptic integration [25, 27]. The role

of AHN in learning seems to be supported by either the adult-born neurons that have reached maturation [217] or, mainly, by the young immature neurons aged ~1-3 weeks that are in the 'critical period' of enhanced plasticity ([25, 44], **Section 2.1.1**). When these immature neurons are exposed to proper hippocampal stimulation (i.e., the formation of a new memory), they are 'rescued' from death and undergo an experience-specific functional integration; thus, these cells will become incorporated in DG circuits and are activated in response to events that are relevant to the memory for which they were recruited [44, 218]. Specifically, hippocampus-dependent associative learning (trace eye blink conditioning) recruits neurons aged 1-2 weeks at the time or training, whereas it removes younger proliferating neurons [25, 219]. Overall, immature neurons aged ~1-3 weeks at the time of learning are required for the initial acquisition and consolidation of a hippocampus-dependent memory [220-222], as well as for its subsequent retrieval [223, 224] and updating, including reversal [222], extinction [223] and re-consolidation [225].

Because memories of cocaine-stimuli associations are a form of hippocampal learning (**Section 1**), a main question is whether AHN participates in these memories in a similar manner as it does for other forms of hippocampus-dependent cognition. Therefore, in addition to studying the effect of cocaine on the pool of proliferating cells, researchers must investigate how cocaine impacts the population of ~1-3-week-old immature neurons that may support the acquisition and future processing of the associative memory. Experiments in which animals were administered cocaine in their home cages suggest that both the survival and maturation of the hippocampal cells generated *prior* to cocaine exposure are spared ([206, 207, 226]; in [201, 227], the number of these cells was reduced, but exclusively in highly vulnerable rats; **Table 1**). Nevertheless, since AHN is only expected to be involved in response to certain learning demands [25], these neurons should be examined in rodents that establish complex cocaine-context associative memories than in animals that are passively exposed to the drug. Mice trained to learn cocaine-context associations in a CPP paradigm show normal survival of neurons aged 1-3 weeks before training [128, 228], but,

interestingly, these neurons exhibit enhanced maturation compared to saline-treated animals [128]. Moreover, the maturing hippocampal neurons show functional integration in response to cocaine CPP, as they are specifically activated when rodents revisit the context they associated with cocaine administration [228] **(Fig. 3A)**. The mice trained in the cocaine CPP paradigm did not show evident alterations in DG cell proliferation [128], possibly because the learning activity counteracted some of the actions of cocaine or simply because proliferation was assessed three days after the administration of the last cocaine dose and not within a ~24 h period, as in the aforementioned studies.

Further evidence supporting the involvement of AHN in the acquisition and subsequent processing of the cocaine-stimuli associative memories was derived from the manipulation of the numbers of adult-born hippocampal neurons. Intriguingly, strategies that either increase or reduce AHN compared to the basal levels observed *before* cocaine CPP learning may lead to an enhanced cocaine CPP memory. On one hand, if animals are submitted to pro-AHN manipulations, such as voluntary exercise or environmental enrichment, the subsequently acquired cocaine-context associative memories are stronger and more resistant to extinction ([229-232] but see [233]) **(Fig. 3B)**. Based on abundant pre-clinical evidence, a greater neurogenic capacity (due to experimental manipulations, age or genetic background) usually correlates with better performance on hippocampal tasks (reviewed in [25]). Notably, a recent study using a *knock-in* mouse model showed that hippocampal spatial memory acquired after a gain of AHN notably extended its long-term persistence over time [234]. Therefore, increased AHN indicates that more young neurons are potentially available for recruitment during cocaine CPP learning, yielding a stronger encoding and representation of the cocaine memory within the DG network **(Fig. 3B)**, which would explain why more effort is required for subsequent updating, extinction or forgetting of this memory trace.

On the other hand, when AHN is reduced by DNA alkylating agents or irradiation, rodents apparently acquire cocaine CPP normally [128, 235, 236], but the learned cocaine memory is

more resistant to extinction and more likely to be reinstated [236] **(Fig. 3C)**. One explanation for this outcome is that the DG triggers changes in numerous compensatory networks after AHN is reduced in an attempt to restore plasticity [237]. For example, the hippocampal cells born immediately before neurogenesis is suppressed exhibit increased survival, and hippocampal LTP becomes progressively normalized [237]. Supporting the existence of alternative neurobiological mechanisms, mice that learned the cocaine CPP task in the context of reduced AHN engaged different functional circuits in the brain for expression of the CPP than normal mice [236]. Thus, the cocaine-associated memory might be encoded in the absence of new hippocampal neurons, probably by recruiting the older (and less plastic) DG granule cells **(Fig. 3C).** However, this memory would be less sensitive to further manipulation. This effect has been described for other forms of hippocampal memories, since contextual fear associations learned in the context of reduced AHN are subsequently more difficult to extinguish [223, 238]. In addition to memory modulation, reduced AHN may contribute to addiction vulnerability by increasing cocaine reward and the motivation for cocaine, since rats with reduced AHN have been shown to self-administer greater quantities of this drug [30].

The hippocampal neurons generated *after* a memory is acquired may also influence its maintenance. The mechanism by which the newly born neurons remodel the DG circuits contributes to clear previously learned associative and spatial information, thus contributing to 'forgetting' [26, 239]. This mechanism also seems valid for the cocaine-contextual memories. Animals that learned a cocaine CPP and were then exposed to environmental enrichment or running to stimulate AHN show diminished CPP retrieval and/or reinstatement ([230, 240, 241], but see [242]); **(Fig. 4)**. Consistent with this finding, strategies that reduce the generation of new neurons during cocaine withdrawal enhance both the long-term retention and reinstatement of the previously learned cocaine CPP memory [128] **(Fig. 4)**.

In summary, cocaine exerts an acute anti-proliferative effect on the DG with an unclear functional significance, but learning is not expected to be impaired and may even be

potentiated by a short-term reduction in the number of proliferating cells. In addition, a pool of immature neurons has been postulated to be recruited by cocaine for the acquisition and future processing (retrieval, extinction and reinstatement) of cocaine-associated memories. Thus, strategies that either increase or decrease AHN compared to the normal physiological levels observed *before* acquisition result in vulnerability to establish stronger memories of cocaine-stimuli associations. On the other hand, new neurons generated *after* a cocaine-stimuli association is learned exert beneficial effects on rejuvenating the DG circuits and 'erasing' the previous cocaine memory. Additional, more specific studies are certainly needed to further describe how AHN is regulated by and involved in cocaine-stimuli associative memories. Nevertheless, we have no *a priori* reason to believe that the establishment and processing of cocaine-stimuli associative memories would be governed by very unique rules in terms of AHN, at least at the initial experiences with the drug. As discussed above, the potential implications of AHN on cocaine CPP memories resemble other forms of hippocampus-dependent learning. This hypothesis is particularly compelling because the acquisition of cocaine-stimuli associative memories is achieved by stimulating the normal hippocampal learning-related mechanisms, including the neurotransmission responsible for the activity-dependent functional integration of the immature hippocampal neurons (**Section 2.1; Fig. 3A**).

3.2. Role of AHN in the cognitive decline induced by chronic cocaine administration

Another common cognitive feature of cocaine addicts is a notable impairment in hippocampus-dependent memory (concomitant with impairments in other cognitive domains) that emerges after chronic cocaine use [6, 7] (**Section 1**). This cocaine-induced cognitive decline is associated with the amount of cocaine consumed and lasts for several months after the individual ceases using cocaine, but reverses within one year of abstinence if the individual completely ceases using the drug [6]. The detection and alleviation of blunted cognition during cocaine withdrawal periods are important because they predict an increased likelihood of relapse [8-10].

In addition, because AHN is required for the acquisition, retention and updating of hippocampus-dependent memories ([25]; **Section 3.1**), a persistent reduction in AHN induced by cocaine may certainly account for the observed cognitive impairment. However, this hypothesis is not supported by the pre-clinical experiments that repeatedly administered cocaine and assessed AHN during drug withdrawal. Most studies conclude that the anti-proliferative effect of cocaine is not long-lasting, as DG proliferation becomes normalized during abstinence, even a few days after the administration of the last cocaine dose (cocaine administered in the home cage: [19, 202-204, 207-209]; open-field: [132]; CPP: [128, 242]; self-administration: [212]; **Table 1**). Although only a few studies have examined the long-term survival or maturation of the neurons generated during or after cocaine administration [29, 202, 203, 210], they have not revealed evident alterations in these processes. In fact, a transitory increase in the number of proliferating cells or immature neurons has been observed at certain times during cocaine withdrawal (home cage: [204, 208]; self-administration: [29, 210]), which may be a compensatory mechanism by which the DG overcomes the reduction in cell proliferation [25, 215]. These mixed results regarding the regulation of AHN during cocaine withdrawal (reporting either normalized, reduced or increased numbers) partially resemble the evidence on the circulating levels of AHN-modulating factors that seem to be differentially regulated in cocaine addicts at different points of abstinence (**Section 2**).

In summary, strong evidence for a persistent reduction in AHN upon cocaine withdrawal is not currently available. One could argue that the protocols for repeated cocaine exposure that are frequently used in rodents (that usually last ~2 weeks) are insufficient to model a life-long addiction, resulting in a transitory and low level AHN impairment. However, these same cocaine protocols are indeed valid for inducing other long-lasting neuroadaptations in the hippocampus (including bizarre neuronal morphologies, increased BDNF secretion, enhanced inflammation, increased glucocorticoid receptor gene expression and dysregulation of the expression other neuroplasticity-related genes [19, 21] (**Section 2**), as

well as hippocampal-dependent memory deficits [19-21]) of rodents that have been withdrawn from cocaine for 1-2 months. Thus, a feasible answer is that the current literature has not assessed the appropriate AHN phenomenon that is altered during cocaine abstinence. The wide dysregulation of AHN-modulating systems observed during this period (**Section 2**) may preserve the numbers of adult-born hippocampal neurons but prevents new neurons from receiving appropriate inputs for experience-dependent integration. A recent study from our laboratory [19] supports this hypothesis. Mice that were withdrawn from cocaine for 45 days were submitted to a behavioral test battery that included a number of hippocampus-relevant stimuli (exploration of novel contexts, mild anxiogenic and inescapable situations and learning activities), and the hippocampal tissue was examined 73 days after the administration of the last cocaine dose. The numbers of adult-born hippocampal neurons (proliferating and young neurons) in the cocaine-withdrawn mice that were left undisturbed in their home cage were apparently normal. But, interestingly, the experience-dependent regulation of AHN was impaired. The cocaine-withdrawn mice that underwent the behavioral training showed fewer proliferating cells in the DG compared to control mice submitted to behavioral training, and their young neurons displayed a more immature-like morphology. This defective AHN occurred concomitant with other alterations in the neurogenic niche, such as increased basal DG neuron activity and altered numbers of GABAergic neuron populations [19]. Thus, the cocaine-withdrawn DG becomes less responsive to new learning and hippocampus-related experiences. Therefore, future studies should focus not only on the basal numbers of adult-born hippocampal neurons but also on whether these neurons are capable of modulating their maturation and survival in response to the environmental demands, retaining the ability to be ‘sculpted’ and functionally integrated into the DG to support new hippocampal memories during cocaine abstinence.

Finally, another unexplored topic that deserves investigation is whether strategies that manipulate AHN levels during cocaine withdrawal have consequences on the cocaine-induced cognitive decline. Strategies that increase AHN are known to exert a pro-cognitive

effect on the ability of rodents to learn new information [243, 244], whereas strategies that reduce AHN yield the opposite outcome [245], but this effect has not yet been shown for cocaine. We can only speculate that this logic is valid for the cocaine-induced cognitive decline and postulate that a treatment that increases AHN during cocaine withdrawal would ameliorate hippocampal function. In humans, physical exercise improves memory under both healthy and pathological conditions [246-248] and is a commonly used intervention for drug addicts, although cocaine studies have mainly focused on the benefits of exercise in reducing cravings and relapse and have rarely focused on the cognitive domain [249].

4. Concluding remarks

This review summarizes the available pre-clinical evidence showing that cocaine regulates AHN, with a special focus on reconciling the AHN data with the notorious impact of cocaine on hippocampus-dependent learning and memory that maintains the cycle of addiction (**Fig. 1**).

On one hand, acute cocaine administration hyperstimulates the hippocampal learning systems to form strong memories of cocaine-stimuli associations, as evidenced by the ability of cocaine to facilitate hippocampal LTP and glutamatergic transmission by enhancing dopamine signaling. However, other neurobiological systems are probably involved in this effect and likely to interact with hippocampal pathways. The learning-related inputs are critical for regulating the experience-dependent synaptic integration of the immature DG neurons. Based on recent data (as evidenced for other forms of hippocampal-dependent memory), the formation of cocaine-stimuli associative memories recruits immature adult-born hippocampal neurons that are incorporated into the DG and have a functional role in retrieving and updating the cocaine memory. The requirement for AHN in cocaine-stimuli association processing should ideally be corroborated by more sophisticated methodologies. For example, current genetic approaches allow researchers to tag specific populations of adult-born neurons and silence/eliminate them either at the time of learning or after learning

is acquired [224, 250]. Furthermore, the addition of appropriate controls (i.e., animals that receive cocaine non-contingent to discriminative cues) would also allow researchers to confirm whether cocaine exerts different effects on the adult-born hippocampal neurons, depending on the learning of cocaine-stimuli associations.

On the other hand, repeated cocaine administration and withdrawal induce a hippocampus-dependent cognitive decline, although this aspect of addiction has been less frequently addressed by pre-clinical studies than the processing of cocaine-stimuli associative memories. Chronic cocaine exposure leads to persistent neuroadaptations in the hippocampal neurotransmitter learning systems and dysregulates peripheral plasticity-related factors, such as the circulating levels of BDNF, glucocorticoids or inflammatory mediators, during different stages of cocaine withdrawal. Regarding AHN, repeated cocaine administration exerts a prominent anti-proliferative effect on the DG, but this effect is transient and rodents that are withdrawn from cocaine show overall normal numbers of adult-born hippocampal neurons. Thus, a reduced number of adult-born hippocampal neurons does not apparently account for the long-lasting cocaine-induced cognitive decline, at least in the pre-clinical models. However, although cocaine withdrawal apparently preserves the generation of adult-born neurons, further investigations are required to determine whether these neurons are indeed 'functional' and retain their ability to mature and become integrated into the hippocampal circuits in response to learning experiences. Thus, AHN should be tested in 'resting', cocaine-withdrawn animals before and after they have received relevant hippocampal-dependent stimulation.

Finally, the research field evaluating the consequences of altered AHN levels on cocaine-related behaviors is promising. An abnormally reduction in AHN either before or after learning cocaine-stimuli associations potentiates the formation and maintenance of these memories, and a low level of AHN during withdrawal presumably aggravates the cognitive decline. In contrast, strategies that increase AHN during cocaine abstinence would be beneficial in erasing previous cocaine memories and may also boost the ability of the

hippocampus to acquire new memories. Ideally, pre-clinical investigations in this field should utilize methodologies that allow specific manipulations of AHN and not unspecific approaches (such as voluntary exercise) that exert many additional effects on the brain. Neurogenesis-enhancing clinical manipulations may comprise either pharmacological (e.g., antidepressants drugs [251]) or behavioral interventions. For example, mental and physical activity (MAP) training combines exercise (which increases the numbers of new hippocampal neurons produced) with cognitive learning (which increases the survival of new neurons) and is assumed to generate greater AHN levels than either these interventions alone; thus, MAP training is more beneficial to mental health [252].

The AHN-enhancing manipulations may be valuable adjuncts to popular cocaine addiction therapies. Therefore, strategies that increase cognitive abilities by modulating AHN could allow the individual to reach the goals of a cognitive-behavioral therapy by learning new behavioral or difficult skills to recognize and manage his/her addictive behaviors [11]. In a cue-exposure therapy, the individual is exposed to cocaine-associated stimuli in a drug-free environment [11]. Under these conditions, AHN may help the individual acquire new 'extinction' learning indicating that the stimuli no longer predicts the drug. Furthermore, even if the person is not exposed to cocaine-associated cues, strategies that increase AHN may help restructure the hippocampal circuits in a way that previous addiction-related memories are weakened or forgotten. In summary, the renewal and remodeling of the hippocampal networks induced by AHN would provide the addicts an increased capacity to form new, adaptive memories that replace the old memories. These potential therapeutic effects of AHN on cognition-related events may complement other effects of AHN, such as reducing the motivation for cocaine or regulating mood [12].

In conclusion, the investigation of AHN and cocaine has generated notable interest in the scientific community, but it is still in an early stage. No strong conclusions have been established regarding the particular mechanisms by which cocaine modulates AHN or the functional role of these neurons in supporting hippocampus-dependent behaviors in

response to cocaine administration. Nevertheless, the rapidly accumulating pre-clinical evidence suggests that AHN has relevant roles in cognition in the cocaine-addicted brain, and the manipulation of adult-born hippocampal neurons may yield important therapeutic consequences for cocaine addiction.

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TABLE 1 LEGEND

Table 1: Effects of cocaine on adult hippocampal neurogenesis, as evidenced by pre-clinical studies. The hypothesis that cocaine usually reduces AHN is mainly valid for cells generated during or shortly after cocaine withdrawal. Cells generated before cocaine exposure are rarely studied and they generally seem to be spared by cocaine; these cells even exhibit an increase in their maturation/functional integration in rodents that learn cocaine-stimuli associations. When AHN is assessed during cocaine withdrawal, the effects are highly mixed (either unchanged, increased or decreased) and apparently transient.

Data are presented based on the moment at which the studied adult-born hippocampal cells were *generated*: before cocaine exposure, during/immediately after cocaine treatment, during cocaine withdrawal (e.g., a study that labelled proliferating cells while cocaine was administered, but assessed them weeks later, would fall within the 'during cocaine treatment' category). For a different version of this table that shows the data organized according to the

neurobiological process studied (proliferation, survival, and maturation), the reader may refer to our previous review [12].

Abbreviations: BC: before cocaine; d: day(s); h: hours; i.p.: intraperitoneal injection; s.c.: subcutaneous injection; W: withdrawal.

Symbols: (↑): increase; (↓): decrease; (=): no changes; (-): not evaluated. (=,↓) or (=,↑): mixed results (e.g., depending on the cell marker analyzed or the time until perfusion).

[#]Due to the cell marker used (i.e., expressed by immature neurons up to few weeks after birth) and the design of the experiment, the moment when the cells were generated is difficult to determine.

FIGURE LEGENDS

Fig. 1. A reciprocal relationship among cocaine, cognition and AHN. Cocaine dysregulates learning and memory related-mechanisms in the brain **(Section 2)** and affects behavior. Both the learning-related neurobiological systems and the behavioral experiences are potent regulators of AHN. In turn, AHN is a key process involved in hippocampal function, including both hippocampus-dependent cognition and the hippocampal modulation of other addiction-related brain regions and neurobiological processes [12]. This complex interaction results in two cognitive events that are linked to the hippocampus: 1) the formation of strong memories for cocaine-stimuli associations that may be established during the initial experiences with the drug and 2) the global cognitive decline that emerges after chronic cocaine exposure and impedes the acquisition of new and beneficial information. These maladaptive cognitive events promote relapse in cocaine users, thus contributing to the maintenance of the addiction cycle.

Fig. 2. Both acute and chronic cocaine administration potentially impacts AHN by modulating learning-related neurobiological mechanisms. The proliferation, survival and maturation of the adult-born hippocampal neurons are highly dependent on the neurochemical inputs in the

neurogenic niche of the DG. Cocaine strongly dysregulates central AHN-regulating mediators, such as neurotransmitter and neuromodulator systems (amino acids, monoamines, endocannabinoids and others), as well as hippocampal neurotrophic and inflammatory factors that may be locally synthetized and released in the DG. Circulating levels of peripheral AHN-regulating molecules (neurotrophins, glucocorticoids, inflammatory factors, endocannabinoids, etc.) are also altered following cocaine administration and may reach the neurogenic niche through the bloodstream. Finally, cocaine may exert a direct effect on the adult-born hippocampal neurons since circulating cocaine readily penetrates the brain.

Legend: 5-HT: serotonin; BDNF: brain-derived neurotrophic factor; CA: cornu ammonis; DA: dopamine; DG: dentate gyrus; EC: endocannabinoids; Ent: entorhinal cortex; GC: glucocorticoids; IF: inflammatory factors; LC: locus coeruleus; NA: noradrenalin; RN: raphe nucleus; SGZ: subgranular zone; VTA: ventral tegmental area.

Fig. 3. Proposed roles of AHN in establishing and maintaining memories of cocaine-stimuli associations, based on the available pre-clinical results from the cocaine-induced CPP paradigm.

(A) As shown for other forms of hippocampus-dependent memory, the immature hippocampal neurons generated before cocaine CPP conditioning show learning-dependent maturation [128] and functional integration [228], whereas cell proliferation is apparently unaltered after this task [128]. The adult-born hippocampal neurons that are recruited for learning are presumably involved in the acquisition and maintenance of the CPP memory.

(B) If cocaine CPP conditioning is conducted in animals with increased numbers of adult-born hippocampal neurons (e.g., after the animals were exposed to environmental enrichment or exercised), more young neurons might be recruited for CPP learning. This finding would explain why the cocaine-stimuli associative memory is more strongly acquired under this condition [229-232] and is more resistant to extinction and tends to be reinstated after subsequent cocaine re-exposure [230].

(C) If cocaine CPP conditioning is conducted in animals with reduced AHN (e.g., after an anti-mitotic pharmacological treatment or brain irradiation), the initial acquisition of the CPP memory is apparently normal [128, 235]. However, the absence of AHN involves alternate or compensatory functional brain circuits [128] that ultimately lead to impaired extinction of the CPP memory and enhanced cocaine-induced reinstatement [128].

In this figure, 'normal' refers to the typical result observed in animals with basal AHN levels (i.e., not submitted to experimental manipulations of AHN).

Fig. 4. Proposed role for the adult-born hippocampal neurons generated *after* the establishment of cocaine-stimuli associative memories, based on the available pre-clinical results from the cocaine-induced CPP paradigm.

Importantly, newly generated adult-born hippocampal neurons are able to modify the DG circuitry to influence previously acquired hippocampus-dependent memories.

Although cocaine withdrawal may either increase or decrease AHN, no changes in the newly generated adult-born hippocampal neurons have been described after cocaine CPP training (**Table 1**). However, strategies that increase the generation of hippocampal neurons after cocaine CPP acquisition (by environmental enrichment, running or pharmacological treatments) result in reduced CPP memories [230, 240, 241]. In contrast, the CPP memory is strengthened if cell proliferation is reduced after CPP conditioning [128]. Thus, the adult-born hippocampal neurons that are generated after learning cocaine-stimuli associations play a role in memory maintenance.

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Figure1

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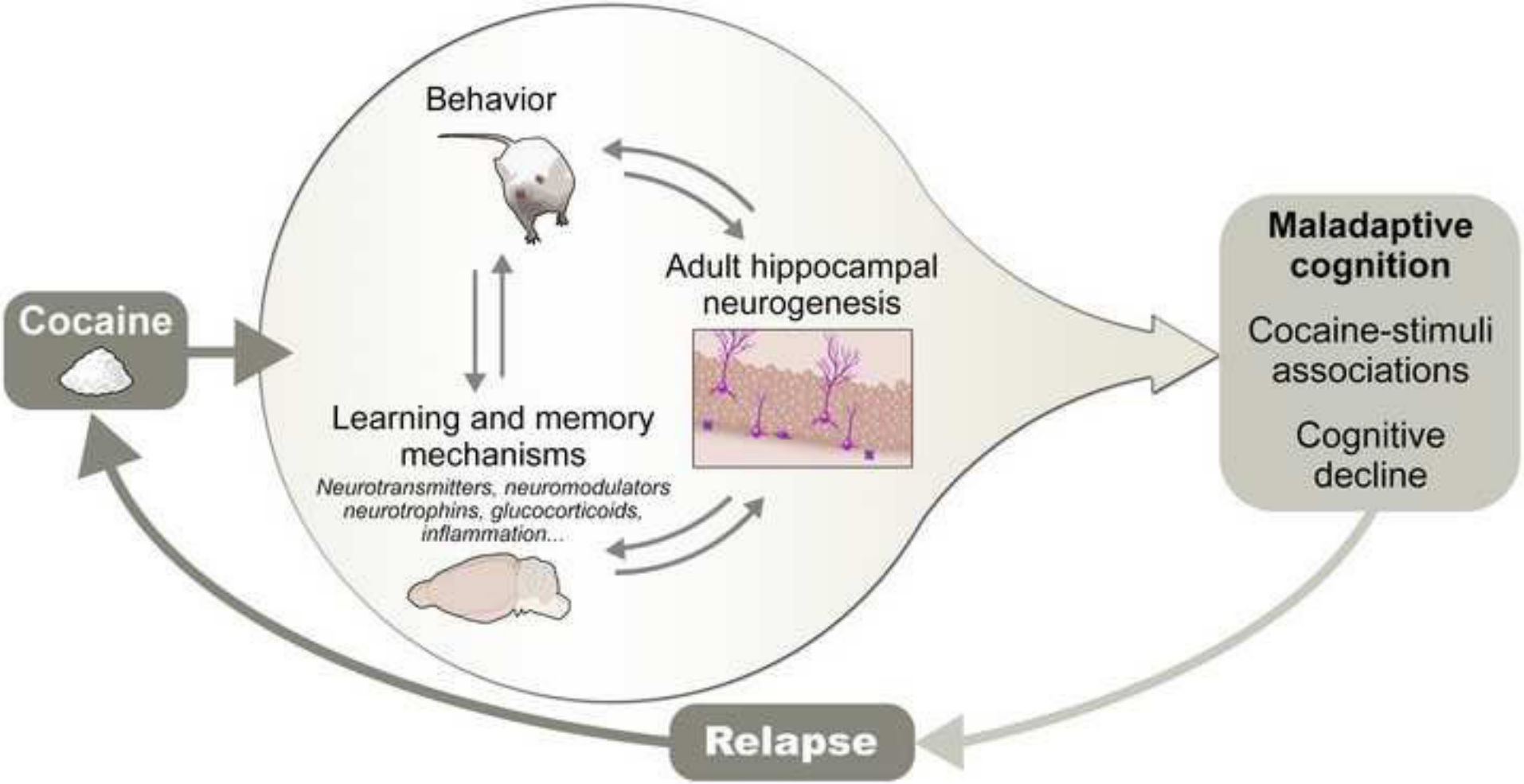

Figure2

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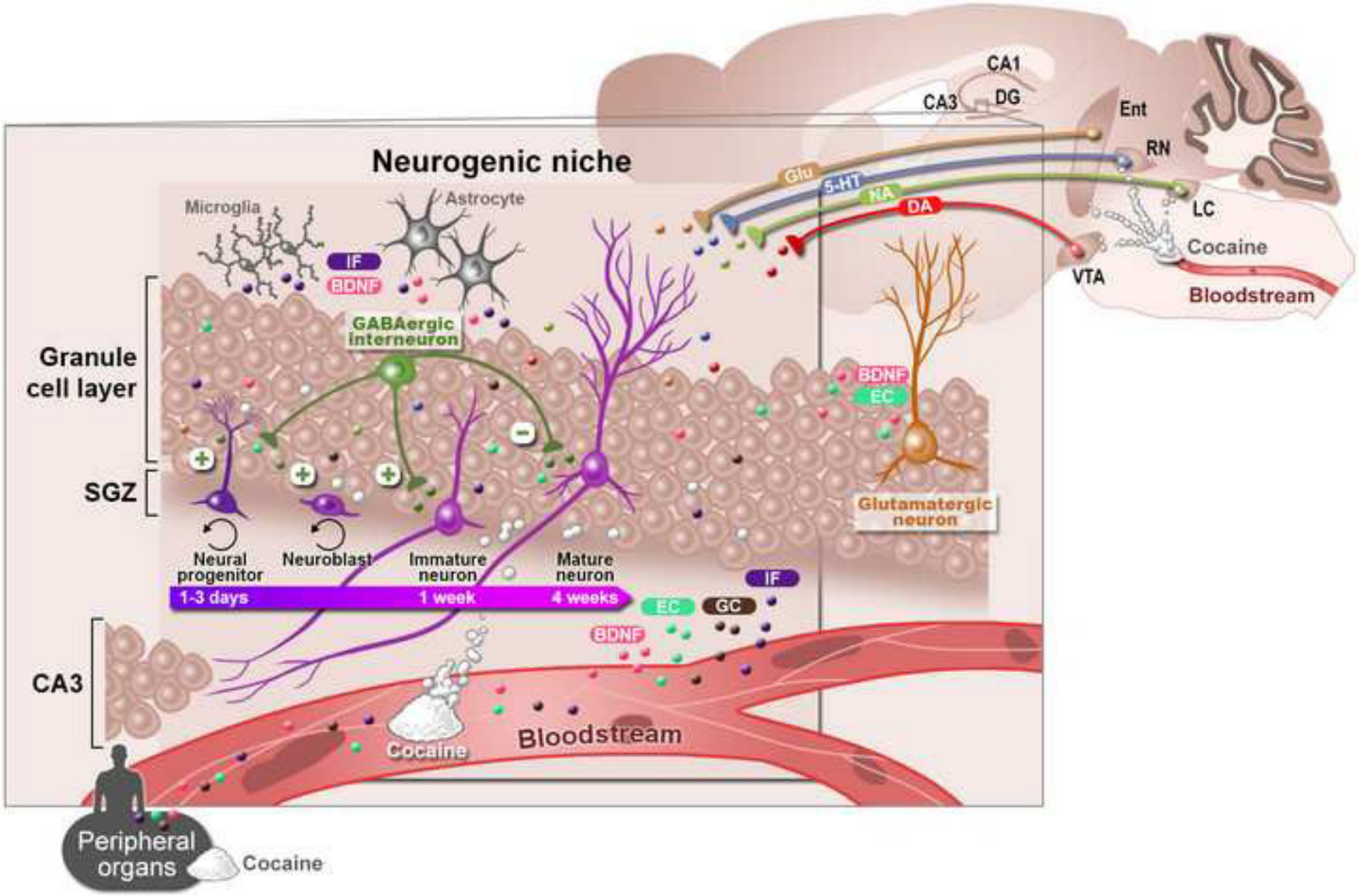

Figure3

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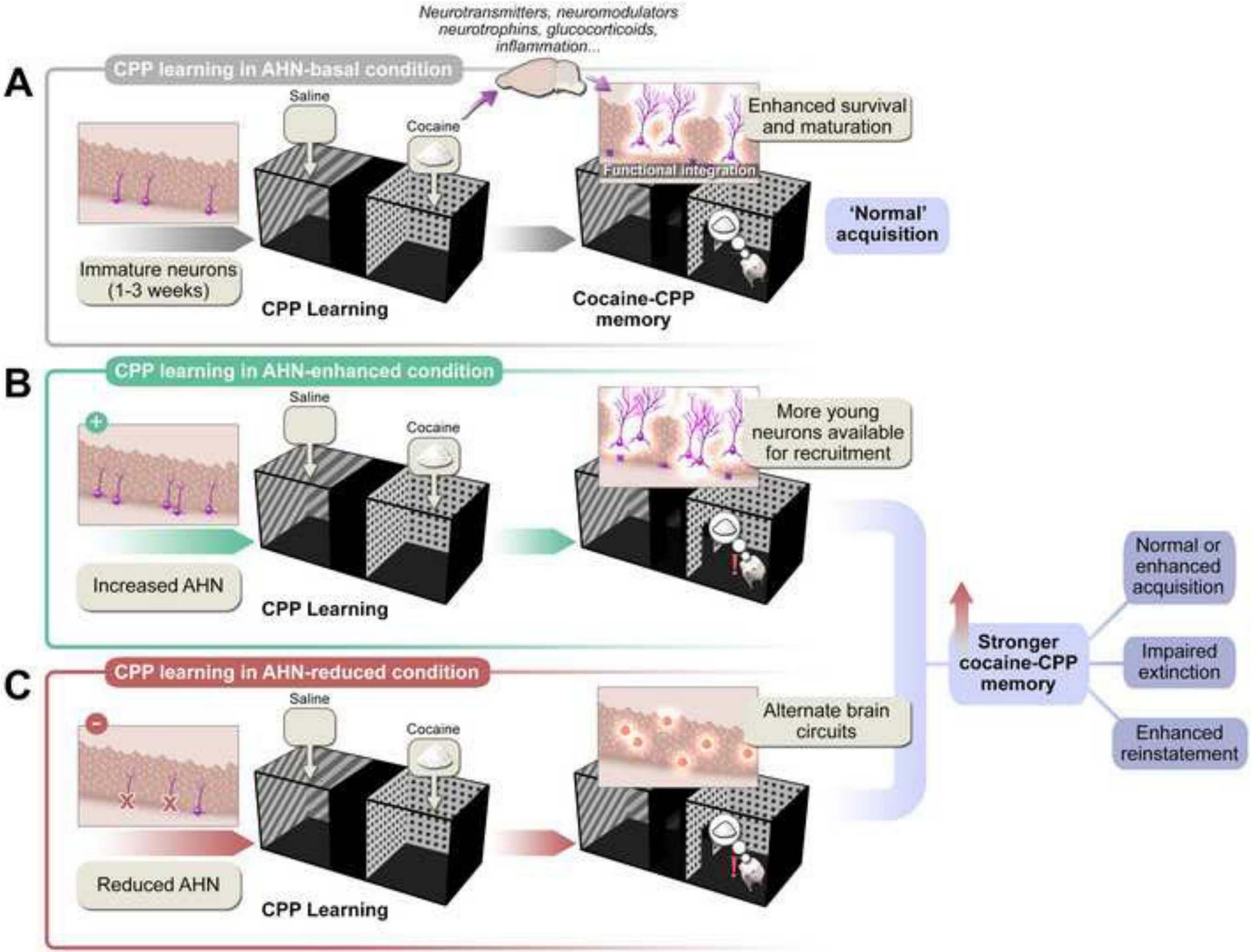

Figure4

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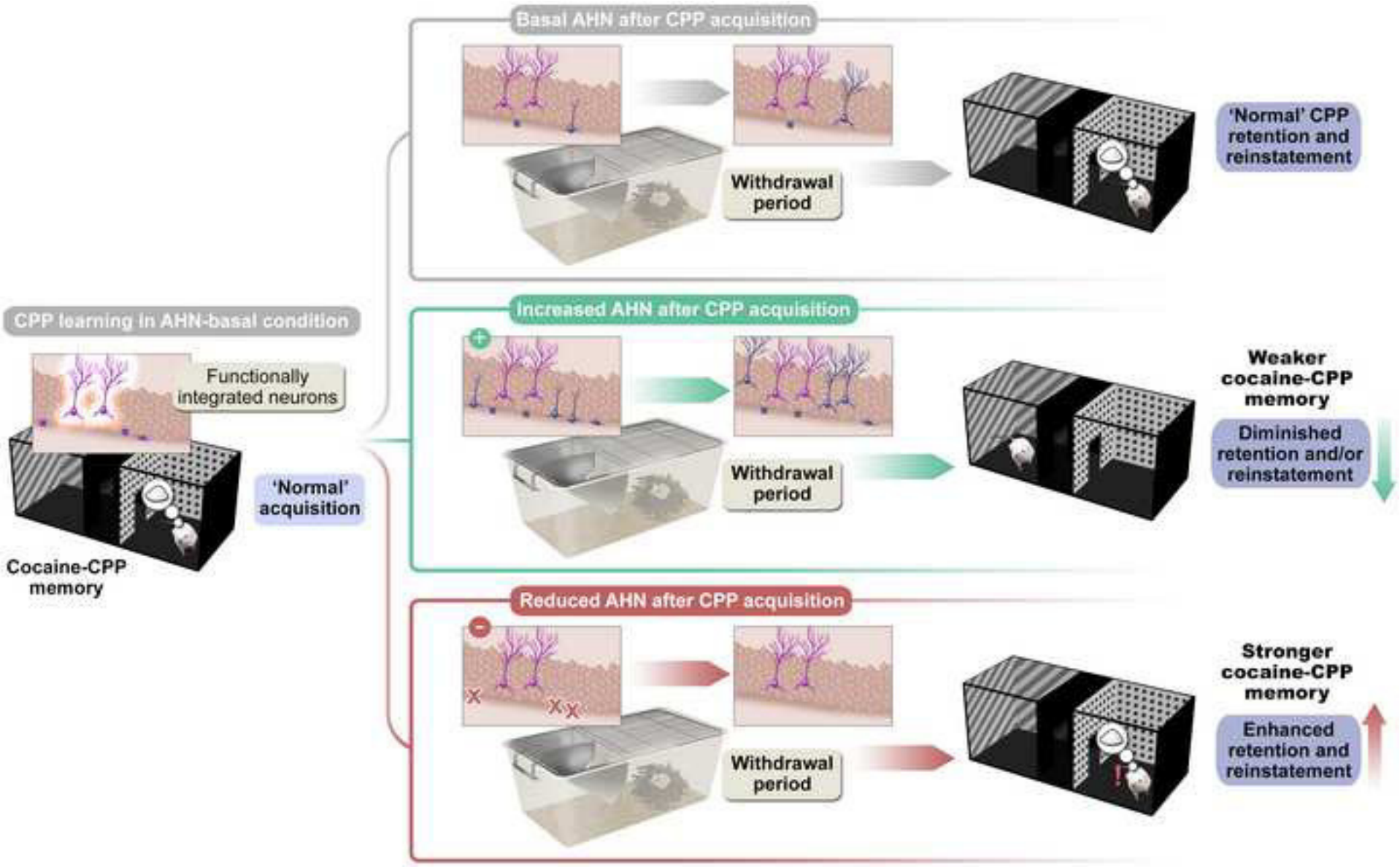

Table1

Reference	Animals	Cocaine exposure protocol	Cells generated BEFORE cocaine exposure	Cells generated during/short after (~24 h) cocaine exposure	Cells generated during cocaine withdrawal
HOME CAGE COCAINE ADMINISTRATION					
Andersen et al. 2007 [205]	Rat (Wistar)	7 mg/kg (i.p.) 12 weeks (3 times/week)	-	↓	-
Dominguez-Escriba et al. 2006 [206]	Rat (Wistar)	20 mg/kg (i.p.) 8 or 24 days	= (cells aged 1 d old BC)	=,↓	-
Garcia-Cabrerizo et al. 2015 [207]	Rat (Sprague Dawley)	15 mg/kg (i.p.) 7 days	= (cells aged 5-8 d old BC)	=,↓ *Depending on rat's age	= (25 d W)
		14 days	= (cells aged 5-8 d old BC)	-	= (25 d W)
Garcia-Fuster et al. 2010 [201]	bLR rat (Sprague Dawley, breed for low novelty response)	15 mg/kg (i.p.) 1 day	-	=	= (3 d W)
		7 days	= (cells aged 1 week old BC)	↓	= (3 d W), ↓ (14 d W)
	bHR rat (Sprague Dawley, breed for high novelty response)	15 mg/kg (i.p.) 1 day	-	=	= (3 d W)
		7 days	↓ (cells aged 1 week old BC)	=	= (3 d W), = (14 d W)
Garcia-Fuster et al. 2017 [227]	bLR rat-adolescent	15 mg/kg (i.p.) 7 days	↓ (cells aged 4-7 d old BC)		↓ (38 d W)
	bHR rat-adolescent	15 mg/kg (i.p.) 7 days	= (cells aged 4-7 d old BC)		= (38 d W)
Grzegorzewska et al. 2010 [104]	Rat (Wistar)	15 mg/kg (i.p.) 1 day	-	↓#	-
Hernández-Rabaza et al. 2010 [227]	Rat (Long-Evans)	15 mg/kg (i.p.) 3 days (a dose every 6 h)	= (cells aged 1-2 d old BC)	-	= (17 d W) #
Ladrón de Guevara-Miranda et al. 2017 [19]	Mice (C57BL/6J)	20 mg/kg (i.p.) 12 days	-	-	=, ↓ (73 d W) *Normal basal numbers, but blunted experience-induced plasticity
Loyd et al. 2010 [209]	Mice (C57BL/6J)	20 mg/kg (s.c.) 28 days	-	=,↑	-
Mackowiak et al. 2008 [106]	Rat (Wistar)	15 mg/kg (i.p.) 1 day	-	=,↓#	= (2 d W)
Mackowiak et al. 2005 [204]	Rat (Wistar)	15 mg/kg (i.p.) 1 day	-	↓#	↓ (2-6 d W) #, = (10 d W) #
		5 days	-	=	↑ (2-4 d W) #, = (6-10 d W) #
Yamaguchi et al. 2004; 2005 [202,203]	Rat (Sprague Dawley)	20 mg/kg (i.p.) 1 day	-	=	-
		14 days	-	↓	= (7 d W)
Xie et al. 2010 [208]	Mice (Aquaporin 4 wild type)	20 mg/kg (i.p.) 14 days	-	↓	= (7 d W), ↑ (14 d W), = (21-28 d W)
OPEN-FIELD COCAINE ADMINISTRATION					
Blanco-Calvo et al. 2014 [132]	Rat (Wistar)	20 mg/kg (i.p.) 1 day	-	↓	-
		4 days	-	=	-
COCAINE SELF-ADMINISTRATION PARADIGM					
Deschaux et al. 2014 [29]	Rat (Wistar)	0.5 mg/kg/infusion ~55 sessions	-	=, ↓	-
		~35 sessions + extinction	-	=	↑ (~20 days W)
García-Fuster et al. 2011 [212]	Rat (Wistar)	0.5 mg/kg/infusion 14 days (5 h/session)	-	=	↓ (14 d W), = (28 d W)
Noonan et al. 2008 [210]	Rat (Sprague Dawley)	0.5 mg/kg/infusion 3 weeks (5 days/week, 4 h/session)	-	=#,↓	↑ (28 days W)
		7 weeks (5 days/week, 4 h/session)	-	=,↑#	-
Sudai et al. 2011 [211]	Rat (Sprague Dawley)	0.5 mg/kg/infusion 2 weeks (1 h/session)	-	=	-
		1.5 mg/kg/infusion 2 weeks (1 h/session)	-	↓	-
COCAINE CONDITIONED PLACE PREFERENCE (CPP) PARADIGM					
Barr et al. 2015 [228]	Rat (Sprague Dawley)	20 mg/kg (i.p.) 7 days	= (cells aged 3 week old BC), ↑ (immature neurons #; up to 3-4 weeks) *Functional integration		-
Castilla-Ortega et al. 2016 [236]	Mice (C57BL/6J)	20 mg/kg (i.p.) 5 days	↑ (cells aged 3 week old BC) *Maturation	-	= (3 d W)
Mustroph et al. 2011 [230]	Mice (C57BL/6J)	20 mg/kg (i.p.) 4 days	= (cells aged 20-30 d old BC)	=	= (1-10 d W)

Table 1.

*Graphical Abstract (for review)

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