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REVIEW ARTICLE

Differential Effects of Nicotine Exposure on the Hippocampus Across Lifespan

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Abstract: ***Background*:** Nicotine exposure affects the hippocampus through activation of hippocampal nicotinic acetylcholine receptors (nAChRs), which are present throughout excitatory and inhibitory hippocampal circuitry. The role of cholinergic functioning in the hippocampus varies across developmental stages so that nicotine exposure differentially affects this region depending upon timing of exposure, producing developmentally distinct changes in structure, function, and behavior.

***Methods*:** We synthesize findings across literature in this area to comprehensively review current understanding of the unique effects of nicotine exposure on the hippocampus throughout the lifespan with a focus on hippocampal morphology, cholinergic functioning, and hippocampus-dependent learning and memory.

***Conclusions*:** Chronic and acute nicotine exposure differentially affect hippocampus structure, functioning, and related learning and memory in the perinatal period, adolescence, and aging. Age-related differences in sensitivity to nicotine exposure should be considered in the research of nicotine addiction and the development of nicotine addiction treatments.

Keywords: Hippocampus, nicotine, development, prenatal, adolescence, aging.

1. INTRODUCTION

While the brain retains a degree of plasticity throughout the lifespan, the potential for synaptic modification varies between brain regions and across developmental periods. For this reason, the brain's sensitivity or resilience to environmental teratogen exposure largely depends upon its developmental state. Nicotine-containing tobacco product exposure has consistently been shown to exert neurotoxic effects across the lifespan, with the most adverse effects associated with early exposure [1]. However, the unique effects of nicotine, the primary psychoactive component of tobacco products, on specific brain regions and during distinct developmental periods have recently been identified. Potential consequences of prolonged nicotine exposure are of particular concern with the escalating popularity of tobacco-free nicotine products, which are often presumed to be a safe alternative to tobacco products. Use of tobacco-free, nicotine containing e-cigarettes has dramatically risen among adolescents, and pregnant and lactating women are increasingly replacing traditional tobacco consumption with nicotine replacement therapy alternatives [2, 3].

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The hippocampus is a temporal lobe brain structure uniquely associated with memory, emotion, and adult neurogenesis. This region appears to be distinctly sensitive to the effects of drugs of abuse, and its drug-induced activation is theorized to play a central role in the development and perpetuation of addictions [4]. Nicotine exposure affects the hippocampus directly through activation of hippocampal nicotinic acetylcholine receptors (nAChRs), a family of ionotropic neuronal receptors that regulate hippocampal activity throughout the lifetime. The hippocampal formation is divided into a number of functionally distinct but interconnected subregions that differentially express nAChRs, and, consequently, are differently sensitive to nicotine exposure. Broadly, the hippocampal formation includes the neighboring perirhinal and entorhinal cortices as well as the hippocampal dentate gyrus (DG), subiculum, and *Cornu Ammonis* regions CA1 and CA3. The perirhinal and entorhinal cortices richly innervate hippocampal field CA1 to form the direct temporoammonic pathway input to the hippocampus. The trisynaptic pathway input to the hippocampus consists of entorhinal and perirhinal innervation of the DG, whose mossy fibers terminate in region CA3. CA3 Schaffer axon collaterals innervate region CA1, which extends its own axons to limbic and cortical brain regions [5, 6] Interneurons situated throughout this circuitry as well as additional innervation from cortical and subcortical regions, such as cho-

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linergic projections extending from the medial septal nuclei, further modulate the activity of these pathways [7]. Multimodal sensory information converges onto the perirhinal and entorhinal cortices, which funnel this information through hippocampal circuitry in processes known to be involved in the formation and storage of memories [8]. nAChRs are located at nearly every synaptic level within this system such that nicotinic activation of these receptors induces broad alterations of hippocampal processing [9, 10].

nAChRs are pentameric proteins composed of varying combinations of α and β subunits, and receptor subunit composition determines its conductive properties and affinity for ligands. nAChRs are endogenously activated by acetylcholine, a neurotransmitter metabolite of the molecule choline. Choline and acetylcholine stores are typically established through balanced dietary intake, and optimal levels ensure normal cholinergic neurotransmission in healthy individuals [11]. However, nicotine, an exogenous nAChR agonist at most nAChR subtypes, bypasses this pathway to directly activate nAChRs at acetylcholine binding sites, dysregulating cholinergic functioning in the developing hippocampus [12, 13]. Low affinity, calcium- and sodium-permeable α7, which have relatively high calcium permeability, and high affinity, sodium- and calcium-permeable α4β2 nAChRs, which have lower calcium permeability [14], are the most prominently expressed nAChR subtypes in the hippocampus [1,15]. Neuronal nAChR activation triggers ion channel gating and influxes of depolarizing current, which can stimulate a range of effects depending upon the affected population of cells. Receptor activity induced by nicotine binding can trigger neural plasticity mechanisms that ultimately result in altered expression of receptor proteins [16]. Thus, in addition to affecting downstream efferents of nAChR-expressing cells, nicotine exposure directly influences receptor expression by altering cellular patterns of activity and triggering compensatory upregulation or downregulation of receptor expression and function [17, 18]. Particularly when exposure occurs during early development and/or chronically, its consequences can persist long after the removal of nicotine, resulting in lasting changes in hippocampal function, structure, and related behavior [1].

The hippocampus is especially sensitive to disruption of cholinergic activity during early development (prenatal and early postnatal), during which cholinergic signaling modulates hippocampal circuit development [19]. During adolescence, the hippocampus undergoes substantial maturation, again sensitizing this region to nicotine-induced disruptions of these developmental plasticity mechanisms [20-22]. On the other hand, the aging hippocampus is sensitive in that it experiences reductions in plasticity and neurogenesis, and, despite conflicting evidence regarding its neuroprotective potential, nicotine has been offered as a buffer against age-related cognitive decline [23]. Here, we review current understanding of the effects of nicotine exposure on hippocampal morphology, cholinergic functioning, and related cognitive processes throughout the lifespan.

2. HIPPOCAMPAL DEVELOPMENT AND CHOLINERGIC SIGNALING

Human hippocampal neuronal formation begins prenatally, with distinct CA1-CA3 subregion pyramidal cell layers visible by gestational week 15. Formation and migration of CA1-CA3 pyramidal, entorhinal cortex, and subicular cells are complete by the 24th gestational week. Generation of the granule cells of the dentate gyrus is slightly delayed, beginning around gestational week 11 and completing formation by gestational week 28. Dentate gyrus cells continue migration throughout the first postnatal year, and the dentate gyrus subgranular zone retains the ability to generate new neurons throughout the lifespan [24, 25]. Neural connections mature into late childhood, and substantial pruning and remodeling of these circuits occurs during adolescence [26]. In addition to the subgranular zone's potential for adult neurogenesis, hippocampal plasticity in the form of synaptic potentiation and related mechanisms continues throughout the lifespan. The aged hippocampus experiences declines in receptor binding/functioning, synaptic complexity, cell density, and plasticity [23, 27, 28].

Hippocampal development in other mammals follows a similar course, adjusted to the gestational conditions and lifespan of these species [25]. For instance, rodents are born in an undeveloped state, and the first few postnatal days correspond to the third trimester of gestational human development [1]. The rodent *Cornu Ammonis* pyramidal cells complete formation and migration during the gestational period, and dentate gyrus granule cells mature postnatally [29, 30]. Broad similarities between human and rodent hippocampal development and functioning allow for the utilization of animal models to study the general effects of teratogen exposure on this brain region.

In addition to their later role in mature neural functioning, cholinergic systems are important regulators of early neural development [31]. Cholinergic signaling plays an especially prominent role in prenatal and postnatal development of hippocampal circuitry. In rodents, basal forebrain cholinergic projections arrive at the hippocampus by gestational day 15 and are functional by postnatal day 2 [32, 33]. Hippocampal subpopulations of nAChRs are transiently up- and down-regulated throughout the gestational and early postnatal period in accordance with hippocampal developmental needs [34, 35]. For instance, upregulated expression of highly calcium permeable α5 and α7 subunit-containing nAChRs coincides with periods of oscillatory hippocampal activity crucial to appropriate hippocampal synaptic wiring. During this time, cholinergic signaling regulates glutamatergic activity and modulates giant depolarizing potentials driven by GABAergic activity, which are crucial for proper formation of hippocampal excitatory synapses [36, 37]. Subsequently, nicotinic cholinergic activity allows for the critical switch from excitatory to inhibitory GABAergic interneuron signaling in the young hippocampus [1, 38]. The adolescent hippocampus exhibits unique nAChR binding and expression patterns relative to other developmental periods [38-40]. During this sensitive period of growth, cholinergic signaling modulates the synaptic plasticity responsible for hippocampal maturation [20]. Finally, reductions in cholinergic functioning have long been associated with cognitive decline in healthy aging individuals as well as cognitive dysfunction associated neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease [41, 42]. These include reductions in hippocampal nAChR binding

and subunit expression as well as imbalances in metabolic acetylcholine synthesis pathways [43, 44].

Throughout the lifetime, cholinergic signaling in the hippocampus is a critical regulator of hippocampal synaptic plasticity, and, consequently, of hippocampus-dependent learning and memory [15, 45]. Nicotine exposure disturbs these systems to produce physiological and behavioral changes that are highly dependent upon developmental state. Prolonged nicotine exposure during prenatal development, when the hippocampus is just forming, or in adolescence, when the hippocampus begins the process of adult maturation, is associated with persistent modifications to hippocampal circuitry. The effects of nicotine exposure in adulthood and aging differ in terms of their qualitative and temporal characteristics, generally presenting as more transient and producing differential modulation of hippocampus-dependent cognition. Comprehensive understanding of the unique effects of nicotine exposure at each life stage is integral to informed and successful construction of health interventions, whether they involve nicotine product usage cessation efforts or the utilization of nicotine as a therapeutic agent.

3. METHODOLOGICAL CONSIDERATIONS

As Dwyer *et al*. [1] discuss in more detail, several methodological difficulties must be considered when extrapolating findings from nicotine exposure studies utilizing animal models to human issues. Most problematic of these concerns include baseline biological differences between species and differences in dosage levels and administration routes between studies. As will be discussed in the context of each section below, developmental periods analogous to those observed in humans have not been distinctly delineated in rodents and other animals and must be surmised according to secondary behavioral or biological observations. For instance, as rodent studies for which nicotine exposure occurs during the early postnatal period (postnatal day 1 to 11) roughly mimic human fetal exposure during the third gestational trimester, these results will be discussed in the context of human prenatal considerations. Studies examining the effects of controlled prenatal and early postnatal nicotine exposure in rodent models often utilize maternal miniosmotic pump implantation or regular maternal nicotine injection, indirectly exposing unborn or young pups to nicotine (through placental perfusion or nursing). Other early postnatal controlled exposure paradigms include intermittent or continuous gastric intubation, during which nicotine is dissolved in milk formula and administered to pups intermittently or as the sole source of nutrition, respectively. Adolescent and aging nicotine exposure studies utilize similar methodologies, most often with single injections mimicking acute exposure and daily injections or prolonged osmotic minipump administration representing chronic exposure. Finally, studies focusing on the effects of nicotine self-administration often expose animal cages (housing maternal dams in the case of prenatal exposure) to ad-libitum nicotine in drinking water. Controlled nicotine exposure studies in animal models most closely simulate human nicotine patch administration, whereas ad libitum nicotine administration resembles unrestricted tobacco use in humans. However, well-designed controlled exposure models resulting in nicotine plasma levels similar to those produced in tobacco users are useful for studying the effects of specific levels of exposure. This review attempts to account for methodological and conceptual discrepancies to provide a comprehensive and converging account of the effects of nicotine exposure on the hippocampus throughout the lifespan.

4. EFFECTS OF PRENATAL NICOTINE EXPOSURE ON THE HIPPOCAMPUS

4.1. Hippocampal Morphology

Chronic prenatal nicotine exposure is associated with structural changes in the developing hippocampus, which can be observed in examinations of gross hippocampal morphology as well as in measures of molecular markers of cellular distribution. Although prenatal nicotine exposure broadly affects brain structure, the hippocampus appears to exhibit a unique response that varies in its breadth and duration in an age-dependent manner. The prenatal and postnatal maturation of this region is extended relative to other brain regions, hypersensitizing it to environmental neurotoxin exposure [25]. Nicotine exposure is especially damaging to the prenatally developing hippocampus, as cholinergic activity regulates migration and composition of nascent hippocampal circuitry [46]. The broad structural changes associated with prenatal nicotine exposure likely reflect perturbation of these processes, and the consequences of these disturbances are manifested in tests of neuronal function and behavior in later life, most notably in measures of cholinergic functioning and hippocampus-dependent learning and memory tasks, as will be discussed in the following sections.

Prenatal nicotine exposure differentially affects hippocampal regions and cell types, although the interconnected nature of the hippocampus means that changes to one region can go on to influence the structure or function of others. For instance, DG interneuron development is affected by prenatal nicotine exposure, and, as interneurons modulate hippocampal circuit activity, disturbances of their activity at this developmental stage can alter granule cell differentiation and DG efferents. Ohishi *et al*. [47] found a transient, sex- and dose-dependent change in glutamic acid decarboxylase (GAD 67) interneuron distribution, so that higher doses of maternal nicotine self-administration were associated with increased interneuron count in the DG of males. It should be noted that, although sex-dependent effects of nicotine exposure on the hippocampus are more often associated with nicotine exposure in puberty or beyond, neural sexual differentiation begins in utero and may explain differential effects of prenatal exposure in males and females [48]. Alterations in interneuronal functioning in the DG could go on to affect the development of interconnected hippocampal regions, either producing or exacerbating the effects seen in these regions. However, changes in any one region likely do not fully explain morphological alternations throughout the hippocampus, as is evinced in studies finding effects in both sexes.

In CA1, prenatal nicotine exposure is associated with increases in dying neuron density and glial fibrillary acidic protein (GFAP), whose elevated expression is associated

with cellular damage [49]. In structural observations of hippocampi of prenatally exposed rats, Sankar Roy and Sabherwal [50] and Sankar Roy, Seidler, and Slotkin [51] found that the DG showed decreased neuronal cell area and a corresponding increase in cell packing density, with the latter study also noting that decreased cell layer thickness in the juvenile DG was reversed in adolescence; however, this compensation did not ameliorate the observed decrease in neuronal size and increase in cell packing density. Although alterations of neuronal size and packing are an interesting and apparently consistent consequence of perinatal nicotine exposure, the behavioral significance of these changes has not been conclusively determined. Similar findings were reported for CA3 and CA1, with more persistent effects in CA3 and smaller, more transient changes in CA1. Interestingly, Sankar Roy and Sabherwal [50] noted that, in CA3, apical dendritic spine complexity on pyramidal cells was significantly reduced, while dendritic spine density was increased on basal and terminal pyramidal cell dendrites, as well as on DG basal granule cell dendrites and CA1 basal pyramidal cell dendrites. In support of these findings, Abreu-Villaça, Seidler, Tate & Slotkin [52] found an overall increase in hippocampal cell count following prenatal nicotine exposure. On the other hand, these authors also observed a sex-dependent effect on cell size, with molecular markers suggesting decreased cell size in males and increased cell size in females relative to controls. Additionally, Wang and Gondré-Lewis [53] found no change in cell number across regions, decreased cell packing density in the DG, and an increase in CA1 volume. Other studies utilizing similar routes of administration have found no changes in neuronal density or numbers in the hippocampi of prenatally exposed rats, but differences in length of nicotine exposure or methods of regional analysis, as well as exclusion of sex difference analyses could account for lack of a detectable effect [54]. Across the majority of studies in this area, however, prenatal nicotine exposure is consistently associated with marked and persistent morphological alterations to the hippocampus, highlighting nicotine's potent potential as a modulator of early neural development.

In sum, prenatal nicotine exposure broadly alters hippocampal morphology at the level of cellular structure, circuit arrangement, and regional structure. These modifications are a product of nicotine's activation of hippocampal nAChRs, the consequences of which are additionally manifested as pronounced, lasting shifts in cholinergic functioning.

5. HIPPOCAMPAL CHOLINERGIC FUNCTIONING

Nicotine exposure during early development disrupts endogenous activity in the developing hippocampus by acting as a ligand at nicotinic acetylcholine receptors, often resulting in compensatory adjustments to hippocampal receptor expression and function [17, 18]. EEG (electroencephalography) and ERP (event-related potential) recordings from adult rodents exposed to nicotine during the postnatal period show altered activity in the hippocampus, a change that may be driven by permanent rewiring of hippocampal cholinergic systems [55, 56]. Perinatal nicotine exposure studies consistently report associations between prenatal and postnatal nicotine exposure and altered nAChR expression and function [4, 16, 57]. Receptor expression and functioning can be inferred through measurements of subunit protein mRNA levels, ligand binding assays, and subunit protein density assays [58, 59]. However, it is important to note that many of these analyses are indirect measurements of these parameters; thus, each assay speaks to slightly different dimensions of hippocampal receptor characteristics, and differences in assay choice may produce disparate findings between studies. For instance, measures of mRNA levels do not take into account rates of translation of these transcripts into protein, while binding assays can reflect either receptor density or receptor functioning [60, 61]. Notwithstanding these limitations, considerable convergence between findings in this area suggest that prenatal nicotine exposure produces relatively consistent hippocampal functional detriments.

Prenatal nicotine exposure is associated with persistent dysregulation of hippocampal α7 and α4β2 nAChRs. α4 subunit expression surges transiently following prenatal nicotine exposure, with corresponding returns to normal or subnormal levels during adulthood. nAChR β2 subunits seem to be similarly affected, indicating that α4β2 nAChRs function irregularly in the prenatally exposed hippocampus [62-64]. Epibatidine and cytisine (selective α4β2 ligands) binding assays further confirm these results, showing transiently increased binding postnatally and a return to normal binding levels in later life [65-68]. α4β2 nAChRs are important regulators of excitatory signaling during early development, and chronic nicotinic hyperactivation of these receptors can result in desensitization and compensatory up- or down-regulation of their expression and functioning. Further, hippocampal α7 subunit protein expression is subnormal in the adult hippocampus of prenatally exposed rats [16]. In addition to their regulatory roles during early development, calcium-gating α7 nAChRs can trigger amplified depolarization currents and calcium-dependent second messenger cascades, which are implicated in synaptic plasticity and long term memory mechanisms. Persistent reductions in cholinergic transporters involved in delivering choline to acetylcholine-synthesizing cells and in enzymes involved in acetylcholine synthesis pathways have also been identified, in addition to abnormalities in muscarinic receptor density [66, 69, 70]. Together, these outcomes suggest that prenatal nicotine exposure has the potential to permanently alter hippocampal cholinergic systems.

As Wang *et al*. [68] note, nicotine availability in the prenatal period followed by withdrawal thereafter appears to produce an initial overshoot in hippocampal cholinergic functioning during early development and a subsequent lifelong downregulation of these systems. For instance, sustained circulation of nicotine during the perinatal period hyperactivates nAChRs, resulting in upregulation of receptor expression and functioning as well as premature synaptic activation and growth [71]. These compensations are not sustained once nicotine is removed, and, in early adulthood, synaptic pruning and receptor downregulation result in near normal or slightly subnormal hippocampal functioning. Abnormal downregulation continues into adulthood, bringing about increasingly severe deficits. It should be noted, however, that these effects are still expected, perhaps to a greater magnitude, with nicotine exposure extending into adoles-

cence. Indeed, combined prenatal and adolescent exposure appears to produce an effect approximately equal to the sum of exclusively prenatal or exclusively adolescent exposure [72].

Hyperactivation of hippocampal cholinergic systems during the prenatal period and resultant persisting modifications to hippocampal circuitry and structure produce lasting disruption of hippocampal molecular mechanisms of synaptic plasticity. These processes are intimately involved in the brain's processing of emotion, learning, and memory [73-75]. Prenatally exposed animals exhibit deficits in hippocampus-dependent learning and memory tasks. The extent of these biological and behavioral adaptions is discussed in the following section.

6. HIPPOCAMPAL PLASTICITY AND ASSOCIATED LEARNING AND MEMORY

Perhaps the most striking of prenatal nicotine exposure's consequences are its distinct and wide-ranging effects on hippocampus-dependent learning and memory. The hippocampus plays an established role in the formation and retrieval of declarative, spatial, and emotional memories, and cholinergic projections modulate hippocampal molecular learning and memory mechanisms [4, 76, 77]. Memory formation is thought to rely upon adjustments to synaptic connectivity mediated by potentiation (strengthening) or depression (weakening) of synapses [78]. Long-term synaptic changes require modifications to synaptic excitability, which are dependent upon calcium-induced changes in protein phosphorylation state and protein expression. Glutamate-activated, calcium-gating *N*-methyl-D-aspartate receptors (NMDARs) receptors, abundantly expressed in the hippocampus, allow for significance and coincidence detection in memory storage, as their magnesium open-channel block is only dislodged to admit calcium following strong and persistent depolarization of the postsynaptic membrane. NMDARs are co-expressed with glutamate-activated, sodium-gating α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARS) at hippocampal synapses, so that persistent AMPAR activation produces depolarization sufficient to dislodge the NMDAR Mg^{2+} channel block and induce calcium-dependent molecular cascades [79]. NMDARs and AMPARs mediate multiple forms of long lasting memory processing in the hippocampus [80, 81].

nAChRs are well-placed to modulate memory processes within the hippocampus; when they are located presynaptically, nAChRs can modulate neurotransmitter release, and postsynaptic nAChRs can either facilitate depolarization through sodium influx or admit calcium and directly induce synaptic modification mechanisms [9, 82, and see 77 for review] Further, chronic prenatal nicotinic activation of nAChRs appears to affect NMDAR and AMPAR expression in the hippocampus throughout the lifespan, with subunits of both receptors exhibiting a pattern of upregulated expression in the early postnatal period, near normal expression in early adulthood (PND 60-90), and downregulated expression in later adulthood (7 months postnatally) [16, 68]. AMPAR-mediated depolarizing currents showed decreased frequency and intensity of excitatory postsynaptic potentials, and AMPAR functional binding was reduced in the young adult hippocampus of rats prenatally exposed to nicotine, indicating that functioning of these receptors show impairment even when expression levels are near normal [53, 83].

Synaptic potentiation and depression, referred to as long-term potentiation (LTP) and long-term depression (LTD) when the effects are persistent, are induced following calcium-dependent protein kinase activation, which triggers a series of downstream effects that vary based on the nature of the stimulation. Following prenatal nicotine exposure, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is transiently upregulated in the early postnatal period and subsequently downregulated in adulthood [68]. This kinase facilitates the insertion of readily-available AMPAR into the postsynaptic membrane, increases the conductance of AMPARs present in the membrane, and activates downstream effectors, including extracellular signal–regulated kinases 1 and 2 (ERK1/2) [84]. ERK1/2, known to stimulate transcriptional regulation of protein synthesis, is downregulated in the adult hippocampus of rats prenatally exposed to nicotine [85].

Targets of kinases and transcriptional regulation could include synaptic vesicular and scaffolding proteins, which optimize synapses for neurotransmitter release and reception. Postsynaptic density protein 95 (PSD-95), which anchors AMPARS to the postsynaptic membrane, and synaptosomal-associated protein (SNAP25), a vesicular docking protein, are transiently upregulated postnatally and normalize in early adulthood in rats prenatally exposed to nicotine [53]. Interruption of normal synaptic functioning can disrupt the critically regulated balance of synaptic excitability and inhibition in the hippocampus. In rats exposed to nicotine during the gestational period, synapses are transiently sensitized to excitatory input such that the threshold for LTP is lowered [86]. Again, this is followed by pronounced depression of synapses, a heightened threshold for LTP, and a lowered threshold for LTD in the adult hippocampus [85, 87]. On the other hand, hippocampi of young adult rats exposed in the early postnatal period, analogous to the final gestational trimester in humans, exhibit enhanced excitability and LTP relative to controls, possibly reflecting differential consequences of early versus late gestational exposure or a delayed appearance of the same effects [88-90]. LTP and LTD in the hippocampus are implicated in the formation of episodic memories, and each of these processes acts to balance the actions of the other so that information is stored in the activity of both potentiated and depressed synapses [91]. An inclination toward excitation or inhibition, as promoted by early nicotine exposure, can produce consequences ranging from apparently enhanced retention of fear memories (associated with PTSD and other anxiety disorders) to memory attenuation and loss [4, 92].

In adult rodents, withdrawal from chronic nicotine exposure is associated with deficits in hippocampus-dependent learning tasks; however, these deficits are markedly transient, lasting only a few days [93]. In contrast, learning and memory deficits induced by prenatal nicotine exposure emerge early and often persist into adulthood. Prenatally and early-postnatally exposed rats exhibit impaired object recognition and spatial memory deficits in adulthood independently of changes in locomotor and anxiety-related behaviors

[16, 87, 94, 95], as well as deficits in both cued and contextual fear learning tasks [62, 83]. However, some low-dose postnatal exposure studies have shown no direct association between postnatal nicotine exposure and performance in a spatial memory task [96]. This suggests a threshold for toxic effects.

In all cases, behavioral deficits paralleled the alterations to hippocampal functioning and morphology discussed above. Although few studies have specifically investigated the effects of human maternal nicotine or tobacco use on hippocampus-dependent learning and memory tasks, maternal smoking is associated with a range of learning and memory deficits in offspring throughout the lifetime, some of which may be hippocampus-specific [97, 98].

Prenatal nicotine exposure disrupts early formation of the hippocampus, setting the stage for lifelong dysfunction in hippocampal regulation of learning and memory. Adolescent nicotine exposure, acting during a second sensitive period of development, similarly produces long-lasting but generally less pronounced deficits in hippocampal functioning and hippocampus-dependent behavior.

7. EFFECTS OF ADOLESCENT NICOTINE EXPOSURE ON THE HIPPOCAMPUS

In humans, adolescence is a period of rapid biological and psychological growth during which the highest incidence of initial exposure to tobacco and other nicotine products occurs [99, 100]. Initiation of tobacco and nicotine product use in adolescence is associated with greater likelihood of regular usage into adulthood, and tobacco users who first use tobacco products during adolescence are more prone to relapsing following cessation attempts [101, 102]. Although the neurological changes coinciding with the onset of puberty prepare the adolescent brain for the trajectory toward adulthood, the developmental plasticity mechanisms set in action to allow this development sensitizes it to environmental teratogens that act on these processes [21]. Further, sexually and socially dichotomous development in males and females differentially predisposes them to the effects of drug exposure [103, 104].

Sex differences in hippocampal functioning and structure, and, consequently, in nicotine's effects on the hippocampus, become especially pronounced at puberty, when gonadal maturation allows for elevated sex-hormone release [105]. Estrogen receptors are densely expressed in the hippocampus, and testosterone levels have been found to be related to hippocampal structure and development [106]. Both estrogen and testosterone act as regulators of cell proliferation and synaptic plasticity in the adolescent and adult brain [39, 107-109]. In human adolescents, nicotine product usage correlates with stage of male and female pubertal development [110, 111]. Adolescent male and female rats exhibit different anxiolytic responses to nicotine [112]. Further, the male and female hippocampi mature at slightly temporally shifted developmental trajectories and remain structurally and functionally distinct in adulthood [113-116] Thus, males and females are differentially sensitive to the effects of nicotine exposure particularly during puberty and beyond.

Human adolescence is traditionally thought to begin before or with the onset of puberty (typically between the ages of 8-15). In rodents, the onset of puberty and an analogous adolescent period appears to occur during postnatal days 21-45, with adolescent rodents exhibiting novelty-seeking, impulsivity, and neurological maturation, changes similar to those observed in humans [117, 118]. The adolescent brain undergoes substantial structural modification; thus, adolescent humans and rodents are distinctly susceptible to nicotine exposure [102, 119]. As with prenatal nicotine exposure, the effects of adolescent nicotine exposure on the hippocampus qualitatively differ from those associated with adult exposure in terms of morphology, functioning, and related cognition.

8. HIPPOCAMPAL MORPHOLOGY

Adolescent nicotine exposure disrupts hippocampal development to produce distinct changes to neuronal and glial cell packing, structural integrity, and dendritic morphology [120]. Chronic nicotine exposure during adolescence differentially affects structure between hippocampal regions, perhaps due to variable distribution of nAChR subtypes between these regions [121]. In young adult rodents exposed to nicotine during adolescence, dendritic branching in the DG increased in length and complexity [122], while the opposite effect was observed in CA1 [123]. Additionally, total hippocampal cell packing density and neuritic projection are reduced and cell size is increased in adolescent rodents chronically exposed to nicotine [53, 124, 125]. Interestingly, Bhatti, Hall, Ma, Tao, and Isgor [126] found that persistent nicotine-induced increases in DG mossy fiber volume and terminal field size were dependent upon nicotine sensitivity phenotype. That is, morphological differences were only present in rats exhibiting high locomotive behavior in response to a nicotine challenge. In humans and rodents, degree of vulnerability to nicotine addiction is moderated by genotype, and variants of genes encoding nAChR proteins have been found to predict nicotine addiction phenotype (for review, see [127]). Thus, the effects of nicotine exposure are moderated by genotype, which can confer resistance or vulnerability to the effects of nicotine.

Although nicotine associated morphological hippocampal modifications resulting from adolescent exposure are less severe than those observed following prenatal nicotine exposure, the presence of persistent structural deterioration and accompanying cholinergic dysfunction suggest dramatic dysregulation of hippocampus-modulated processes. Findings related to adolescent nicotine exposure's effects on cholinergic functioning, molecular mechanisms of learning and memory, and behavioral markers of learning and memory confirm the presence of lasting hippocampal deficits.

9. HIPPOCAMPAL CHOLINERGIC FUNCTIONING

Changes in hippocampal structure produced by adolescent nicotine exposure are mediated by nicotine's activation of hippocampal nAChRs. Distribution and functioning of nAChRs in the hippocampus differs between adolescents and adults [39], possibly allowing for or moderating heightened synaptic plasticity and reward evaluation during adolescence [128]. Adolescents also appear to more rapidly metabolize nicotine, so that nicotine reaches its effectors at an age-dependent rate [129]. As with prenatal nicotine exposure, exposure in adolescence is associated with persistent as op-

posed to transient alterations to hippocampal cholinergic functioning as seen in adulthood.

Nicotine administration in adolescence was associated with increases in hippocampal nAChR binding to cytisine, a nAChR partial agonist, in adulthood with no concurrent change in nicotine binding [40, 130]. As cytisine binding assays indicate general nAChR binding site functionality, while nicotine binding assays indicate nicotine binding to nAChRs, these findings may suggest specific alteration of responses to nicotine, a biological mechanism that may be related to heightened vulnerability to lifelong nicotine dependence in smokers initiating use in adolescence. In other words, while both cytisine and nicotine exhibit affinity to the nAChR ligand-binding site, changes in receptor responsivity exclusive to nicotine may indicate a nicotine-specific compensatory adjustment. However, nicotine exposure during adolescence appears to impact hippocampal metabolic cholinergic synthesis pathways as well, with elevations in choline acetyltransferase activity and reductions in high-affinity choline transporter binding [52]. Therefore, nicotine-response specific receptor adjustments may be insufficient to compensate for prolonged nicotine exposure in adolescence, although this idea requires further empirical exploration.

As cholinergic activity regulates the functioning of other neurotransmitter systems in the hippocampus, persistent disturbances of these systems might be expected following adolescent nicotine exposure. Indeed, adolescent nicotine exposure is correlated with pronounced abnormalities in hippocampal noradrenergic and serotonergic neurotransmitter systems as well as in hippocampal endocannabinoid and opioid receptor distribution and function [131-133]. Variations in the functionality of serotonergic, adrenergic, and endogenous opioid systems are associated with a number of mental disorders, including addiction, depression, and anxiety disorders [134, 135]. In humans, nicotine exposure in adolescence predicts nicotine dependence and alcohol consumption in adulthood, and, in both humans and in animal models, adolescent exposure is associated with anxiety and depression [101, 102, 123, 135-138]. Learning and memory deficits can be exacerbated by mental disorder or serve to perpetuate their symptoms [92, 139, 140]. Thus, the behavioral consequences of perturbations to hippocampal cholinergic functioning extend beyond deficits in learning and memory.

10. HIPPOCAMPAL PLASTICITY AND ASSOCIATED LEARNING AND MEMORY

It is theorized that the cellular and behavioral changes in learning and memory changes induced by nicotine exposure are partially responsible for the addictive potency of nicotine [141]. In adolescence, neural systems begin to mature, undergoing substantial remodeling in preparation for adult functioning. This reorganization requires a magnified potential for synaptic plasticity to allow for "pruning" (depression) of unneeded circuitry and growth (potentiation) of active or important connections. The mechanisms responsible for this plasticity are identical to those involved in learning and memory processes and modulated by nAChR activation [4, 142]. During adolescence, the hippocampus and other brain regions become particularly sensitive to the influence of environmental teratogens, a vulnerability that is reflected in the lifelong learning and memory deficits associated with chronic adolescent nicotine exposure [119]. These prolonged cognitive deficits may contribute to difficulties in attempted cessation of nicotine product usage in adulthood [4, 143, 144, and see 145 for review].

Changes in learning-related cell signaling cascades may mediate the effects of adolescent nicotine exposure on learning and cognition. In support, adenylyl cyclase, a regulatory enzyme present in most cells, plays an important role in calcium-dependent learning and memory cascades. Adenylyl cyclase activity is enhanced in the hippocampi of rats chronically administered nicotine in adolescence, an effect that persists into adulthood in females; notably, however, even transient disturbances of intracellular molecular cascades during adolescence can disrupt adult plasticity mechanisms [133]. In contrast, the transcription factor cAMP response element-binding protein (CREB) is reduced following chronic nicotine exposure in mouse adolescent hippocampi, but not following identical nicotine administration in adults [129]. Moreover, AMPAR GluR2/3 glutamate receptor subunits are under-expressed in the hippocampus of male and female adult mice exposed to chronic nicotine during adolescence, an effect that does not appear with nicotine exposure exclusively in adulthood [146]. Glutamate receptor subunit composition determines the regulatory role of these receptors in hippocampal synaptic plasticity processes [147, 148]. Thus, prolonged nicotine exposure during adolescence may disrupt hippocampal learning and memory by altering the molecular cascades and cell signaling associated with memory formation and storage; multiple studies have shown altered learning.

The effects of chronic nicotine on learning and memory are different in animals exposed to nicotine during adolescence compared to those exposed during adulthood. For example, it has been shown that chronic low-dose nicotine exposure in adolescent rats enhances cued fear conditioning in adulthood, while equivalent exposure in adulthood does not affect cued fear conditioning [137]. Further, adolescent mice are less sensitive to the immediate impairing effects of withdrawal from a higher dose of chronic nicotine on contextual fear conditioning [129]. However, adolescents chronically exposed to nicotine at a dose producing a plasma nicotine level similar to that obtained in human smokers exhibited contextual learning deficits in adulthood; adult nicotine exposure did not produce similar deficits. [129, 149]. Adult spatial memory appears to be affected by adolescent nicotine exposure, as female mice chronically exposed to nicotine in adolescence exhibit spatial learning impairments in adulthood. The reason for a lack of effect in males is unclear, although it is possible that sex differentially moderates the effects of nicotine exposure on learning and memory depending on learning task [150]. Human fMRI studies indicate that, during adolescence, a switch from hippocampus-independent response-based navigational strategies to hippocampus-dependent spatial navigational strategy occurs, and drug use may disrupt this process. Interestingly, smokers who reported greater numbers of cigarettes smoked over a lifetime (most initiating use during adolescence) were more likely to use a response-based navigational strategy than a spatial navigational strategy relative to smokers who re-

ported fewer cigarettes smoked over a lifetime [151]. Together, these findings indicate that chronic nicotine exposure in adolescence is strongly associated with long-lasting learning and memory impairments.

As with chronic nicotine exposure, acute nicotine has differential effects on adolescent learning and memory relative to adults. For example, acute nicotine administration more effectively enhances hippocampus-dependent contextual learning in early adolescent mice (PND 23) relative to adult mice [129]. Interestingly, late adolescent mice (PND 38) required higher doses of nicotine for the enhancement effects suggesting a right-ward shift of dose response and decreased sensitivity to acute nicotine's effects in late adolescent mice relative to adults. In contrast, studies investigating the rewarding effects of nicotine have reported that acute nicotine administration produced a conditioned place preference in adolescent rats but not in adult rats [152-156], while others found that nicotine induced conditioned place preference at lower doses in adolescents than the dose required for adults [157, 158]. These results suggest either enhanced drug-context associative learning or greater sensitivity to nicotine's rewarding effects in adolescence. Thus, it is possible that increased sensitivity to nicotine's cognitive enhancing effects and rewarding properties may contribute to the acquisition of nicotine dependence in adolescence (see ref. [4, 159] for review).

Adolescence is a period of distinct susceptibility to the effects of nicotine exposure on learning and memory. Across species, puberty and adolescence are periods of substantial biological growth and behavioral maturation, during which plasticity mechanisms contribute to significant neural development. Nicotine exposure during adolescence activates hippocampal nAChRs during this sensitive period, disturbing these mechanisms to produce persistent morphological, functional, and behavioral hippocampal dysfunction. Along with lifelong deficits in memory processing, these changes may contribute to the development or exacerbation of addictions and other mental disorders in nicotine product-using adolescents.

11. EFFECTS OF NICOTINE EXPOSURE ON THE AGING HIPPOCAMPUS

In humans and other animals, aging is accompanied by a decline in cognitive function. Cholinergic system declines are tightly linked with deficits in learning and memory during dementia as well as in healthy aging [160-162]. In the hippocampus, aging is associated with decreases in nAChR binding, reduced DG subgranular zone neuronal precursor cell proliferation, and reductions in neurite complexity [44, 163]. Basal forebrain projections, including those extending to the hippocampus, are selectively deteriorated in the brains of Alzheimer's disease patients, and nAChR activation has been offered as a potential treatment to alleviate the effects of neurodegeneration [162, 164]. The range for senescent aging has not been well defined in rodents, as rodent lifespans vary widely between strains and housing conditions [165]. However, studies of the effects of nicotine on aging rodents generally utilize animals that are 18 months of age (around the age of reproductive senescence) or beyond [166]. Behaviorally, healthy aging animals and humans exhibit deficits in hippocampus-related learning and memory tasks relative to younger adults, and nicotine administration has been reported to alleviate or reverse these deficits. However, findings in this area are sometimes contradictory and dependent upon methodological differences [23], and the long-term implications of supposedly enhanced molecular learning and memory mechanisms in the aging brain have not fully been elucidated. Further, while the benefits of acute and chronic nicotine administration on cognitive performance in patients suffering from neurodegenerative disorders have been well-documented, impacts of its therapeutic use within the healthy aging population are unknown.

12. HIPPOCAMPAL MORPHOLOGY & CHOLINERGIC FUNCTIONING

As in other developmental periods, nicotine exposure during aging is associated with a number of physiological adjustments; however, these changes are less distinct, and their connection with concurrent behavioral modifications are unclear. For instance, the DG subgranular zone experiences age-related reductions in neuronal precursor cell proliferation that parallel cognitive decline, but nicotine administration has no effect on these changes [163]. It should be noted, though, that nicotine administration in adult rodents reduces DG neurogenesis and induces apoptosis of hippocampal progenitor cells [167-171]. Thus, the aging hippocampus may be resistant to nicotine-induced cell death, as apoptosis or morphological changes are not generally associated with aged nicotine exposure. However, general hippocampal cellular decline may mask morphological modifications resulting from nicotine exposure in the aged hippocampus. While it is possible that shifts in hippocampal neurogenesis are inconsequential in aging individuals already experiencing a general decline in neurogenesis [172], studies finding a relationship between increased neurogenesis and enhanced learning suggest that hippocampal neurogenesis may be an important modulator of cognitive decline in aging [173-175]. Nevertheless, the relationship between DG neurogenesis and cognitive decline in aging individuals is ambiguous [23, 176].

Chronic nicotine exposure in aging rodents increases nAChR binding in the DG, while in younger adult rodents, nAChR upregulation occurs across the hippocampus [77, 177]. CA1 pyramidal neurons in the aged hippocampus are more sensitive to nicotine-triggered excitation than those of young adults [178] and, as with adult rats, acute and chronic nicotine exposure facilitate LTP in the aged hippocampus, an effect possibly reflecting receptor upregulation following nicotine treatment [179, 180]. Abundance of high-affinity hippocampal nAChRs gradually declines with aging, and upregulation of these receptors by chronic nicotine administration may compensate for this loss, allowing for nAChR-mediated heightened synaptic excitability and alleviating age-related cognitive decline [180]. Crucially, however, while chronic nicotine exposure in adult mice produces immediate improvements in cognitive tasks, marked learning and memory deficits emerge in the nicotine withdrawal period [179, 181-183]. The precise effects of nicotine withdrawal on the aging hippocampus have not been detailed; therefore, as will be discussed in the following section, nico-

Table 1. Effects of nicotine exposure on behavioral learning and memory paradigms across lifespan.

Age	Length of Exposure	Type of Learning			
		Contextual Fear Conditioning	**Cued Fear Conditioning**	**Spatial Learning Tasks**	**Conditioned Place Preference**
Perinatal exposure	*Chronic*	Long-term impairment [62]	Long-term impairment [83]	Long-term impairment [86, 87, 94, 95] or no effect (low dose) [96]	
Adolescent exposure	*Acute*	Enhanced [129]	No effect [129]		Enhanced [152-156]
	Chronic	Long-term impairment [129, 149]	Enhanced (low dose) [136]	Long-term impairment in females [150]	
Aged exposure	*Acute*			Enhanced [41, 187, 188]	
	Chronic			Enhanced [186, 187]	

tine therapies purported to treat cognitive decline in aging individuals should be met with caution until further work is conducted in this area.

13. HIPPOCAMPAL PLASTICITY AND ASSOCIATED LEARNING AND MEMORY

In younger adult rodents, acute nicotine administration enhances hippocampal learning and memory, with this effect disappearing when nicotine is chronically administered. Subsequently, withdrawal from chronic nicotine exposure produces distinct but transient cognitive deficits. These effects are mirrored in adult human smokers, whose withdrawal-associated cognitive deficits encourage continued nicotine administration [184, 185]. On the other hand, in aging rodents, both acute and chronic nicotine administration facilitate hippocampal LTP and produce immediate improvements in spatial memory tasks [186-189]. With these promising outcomes in mind, nicotine administration has been suggested as a therapeutic option for alleviating cognitive declines associated with Alzheimer's disease and other neurodegenerative disorders, especially as nicotine has additionally been found to reverse accumulation of beta-amyloid (Aβ) peptides in rodent models of Alzheimer's disease [189]. Indeed, preclinical human trials have found that relatively short-term nicotine patch exposure improved learning and memory that persisted into the patch removal period in patients with probable Alzheimer's disease [190]. Notably, however, it has been suggested that nicotine-generated improvements in attentional abilities (rather than direct improvements in memory encoding or retrieval) may be responsible for enhanced memory formation in both human and animal models [191, 192].

Despite nicotine's potential for treating the symptoms of age-related neurodegenerative disorders, recommendations for use to alleviate cognitive decline associated with healthy aging should be treated with caution. Existing work regarding nicotine's potential as a cognitive enhancer in aging individuals has rarely addressed the potential consequences of nicotine withdrawal in this population. Furthermore, that these benefits refer to nicotine's effects *in isolation* should be strongly emphasized. If nicotine therapy does confer some benefits for individuals suffering from neurodegenerative disorders, any pairing of nicotine with tobacco consumption surely counteracts them. Indeed, lifelong smoking is associated with greater decreases in cognitive ability in aging, and smoking-linked cardiovascular disease is associated with dementia in aging [193, 194]. Moreover, for younger smokers, improved hippocampal memory task performance is often discussed in the context of its implications in nicotine addiction and anxiety disorders: enhanced memory for nicotine administration context triggers cravings and relapse during cessation attempts, and enhanced fear memories can perpetuate feelings of anxiety [4, 195]. Some work has shown that administration of other, less addictive nAChR agonists is sufficient to ameliorate learning and memory deficits [186]. Thus, further research should be conducted with special consideration of addictive potential and mental health in healthy aging adults.

CONCLUSION

Nicotine's effects on the hippocampus are age-dependent, with unique morphological, functional, and behavioral outcomes associated with exposure in the prenatal period, adolescence, and aging. Nicotine induces hippocampal cholinergic activity and modulates cholinergic regulation of hippocampus-dependent cognitive processes. Nicotine exposure in the prenatal period and during adolescence disrupts hippocampal development and produces lifelong structural and functional hippocampal modifications that translate to persistent hippocampus-dependent cognitive deficits that may contribute to subsequent mental disorder susceptibility. On the other hand, studies of nicotine's effects on the aging hippocampus suggest that activation of cholinergic systems during this period may have neuroprotective effects, resulting in improved cognitive functioning in individuals suffering from neurodegenerative disorders; however, potential consequences of the use of nicotine as a therapeutic agent for individuals suffering from cognitive decline have not been extensively studied. See Table **1** for a summary of nicotine's effects on learning and memory paradigms across the lifespan. Comprehensive understanding of nicotine's unique effects at different stages of the lifespan is integral to informed and successful construction of health interventions,

whether they involve nicotine product use cessation efforts or the utilization of nicotine as a therapeutic agent. Future research should work to more specifically elucidate effects unique to each developmental period as well as their links to cognition, addiction, and mental health.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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