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Effects of Prenatal Nicotine Exposure on Short-Term and Long-Term Memory: A Literature Review

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Abstract

Introduction: Maternal smoking impacts the health of both the mother and the baby. During gestation, nicotine can pass through the maternal-fetal blood interface in the placenta, accumulating in the fetal circulation and amniotic fluid. Because nicotine is a teratogenic agent, it can affect the development of the structures and functions in the brain of the fetus. Short-term and long-term memory are two areas of cognitive function that are affected. This literature review seeks to understand how prenatal nicotine exposure affects short-term and long-term memory, and how these effects will present in exposed individuals.

Methods: An extensive literature search was performed to find pre-clinical trials, clinical trials, and reviews on the effects of prenatal nicotine exposure on memory. The databases used for the search were PubMed, CINHL, and EMBASE. After removing duplicates and studies that did not meet inclusion criteria, 17 studies remained.

Results: 8 preclinical studies, 2 clinical studies, and 7 reviews that met inclusion criteria were included in this review. These studies found that exposed participants did not perform as well in memory and learning tests as compared to non-exposed control participants. Decreased integrity of structures in the brain, decreased function and size of neuronal structures, and low birth weight were noted in exposed subjects in multiple studies.

Discussion: Prenatal nicotine exposure impairs short-term and long-term memory by altering the development of structures and processes in the brain such as the hippocampus, prefrontal cortex, blood-brain barrier, cerebellum, and cholinergic functioning. Placental dysfunction associated with prenatal nicotine exposure can cause abnormal development of the brain and cerebral vasculature due to chronic hypoxia and fetal growth restriction. Due to the abnormal development of crucial systems used in short-term and long-term memory function, memory and learning deficits can be observed in adolescence and adulthood of individuals exposed to prenatal nicotine.

Conclusion: Information summarized in this literature review can be used to conduct future research and aid in public education on the negative effects of maternal smoking. Therapeutic strategies to lessen the effects of cognitive issues faced by individuals prenatally exposed to nicotine can be derived from future research on this subject.

Keywords: prenatal exposure; nicotine; short-term memory; long-term memory; fetal; hippocampus; blood-brain barrier; prefrontal cortex; addiction.

Introduction

Over the past decade, there has been an exponential rise in the use of electronic nicotine delivery systems, also known as vaporizers [1]. The rise in popularity of these devices can be attributed to the belief that electronic nicotine delivery systems are a safer alternative to smoking traditional tobacco cigarettes [1]. Some individuals may even switch to using electronic nicotine delivery systems during pregnancy as opposed to cigarette smoking due to the perceived harm reduction or choice to use both cigarettes and electronic nicotine delivery systems together [2]. This rise in the use of electronic nicotine delivery systems in pregnant users and the general population implicates the need for further research into the effects of prenatal nicotine exposure (PNE).

Throughout gestation, many harmful substances can enter the fetal circulation through the maternal-fetal interface in the placenta and cause an array of negative effects on development. While the placenta acts to protect the fetus from these harmful substances, many drugs can still pass through the maternal-fetal interface, resulting in developmental problems that last well beyond the perinatal period [3]. Nicotine is one such substance found in many tobacco and vaping products. When maternal smoking occurs, nicotine can pass through the maternal-fetal blood interface and accumulate in fetal blood and amniotic fluid.

This can alter placental development by disrupting cholinergic transmission [4]. Consequentially, this results in the calcification and impairment of regenerative tissues of the placenta, leading to further developmental issues [4]. As a teratogenic agent, nicotine has many negative effects on fetal well-being and overall cognitive function [5]. Memory is one area of cognitive function that is typically affected in individuals whose mothers smoked nicotine during pregnancy. Specifically, brain regions responsible for short- and long-term memory are affected during fetal brain development. When exposed to nicotine, many different structures and functions of the fetal brain, including areas that play a role in memory such as the dorsolateral and ventrolateral prefrontal cortices and the hippocampus can show altered development and function [6]. The blood-brain barrier can also be affected throughout development [1]. Damage to the fetal blood-brain barrier can cause fewer tight junction proteins within the structure and altered ion transport expression, hence increasing its permeability and affecting the barrier's integrity [1]. Ultimately, these harmful effects of nicotine on fetal brain development can lead to long-term deficits that continue to affect the brain as it develops into adolescence and adulthood.

Methods

This literature review aims to answer the question of how prenatal exposure to nicotine affects short-term and long-term memory. PubMed, EMBASE (Excerpta Medica Database), and CINAHL (Cumulative Index to Nurses and Allied Health Literature) were the databases searched for systematic reviews, meta-analyses, randomized control trials, and research studies published within the past 10 years. Using Boolean Operators (nicotine) AND (prenatal) AND (memory), 119 studies were found. After removing duplicates and studies that did not meet inclusion criteria, 17 studies remained. Exclusion criteria included studies that did not discuss the effects of PNE on structural integrity or cognitive function. Pre-clinical and clinical studies were included. A secondary search was conducted using Boolean operators (placenta) AND (nicotine) for additional information included in this review.

Table 1. Search Strategy

Databases Searched	Publication Date Ranges	Inclusion Criteria	Boolean Operators
PubMed (Medline), EMBASE, and CINAHL	2014-2024 (past 10 years)	English language, preclinical and clinical studies, prenatal nicotine use, effects on short or long-term memory and/or cognitive function	(nicotine) AND (prenatal) AND (memory) Secondary Search (placenta) AND (prenatal) AND (nicotine)

Results

Preclinical research studies (n = 8), clinical studies (n = 2), and literature reviews (n = 7) were found as part of the literature search. Preclinical studies using rodent models were included. The outcomes in these preclinical studies were measured using various cognitive and memory tasks. Findings from each study are found in Table 2. A preclinical study conducted by Li et al. used a rodent model to measure memory and learning performance in offsprings that were exposed to PNE using a Morris water maze test. Results found that PNE offsprings took longer to complete the task and that there was alteration in the expression of messenger RNA and protein of N -methyl- D -aspartic acid receptors, as well as a decreased volume of alpha 7 nicotinic acetylcholine receptor proteins in the hippocampus suggesting that working memory was affected by PNE [18].

The two clinical studies included measured memory performance in adults who were prenatally exposed to nicotine. One study recruited adults (with a mean age of 21 years), while the other clinical study examined effects in infants (aged 3-5 months). [8]. This study conducted by King et al. compared the brain responses of PNE infants to an auditory stimulus during the second stage of sleep to assess the difference in auditory processing and attention reorienting which are important for memory consolidation during sleep as compared to non-exposed infants [8]. This study also found that infants in this trial who were prenatally exposed to nicotine had an overall lower gestational age at birth as compared to the non-exposed control infants [8].

Seven literature reviews discussed the effects of PNE on different systems used in the development of the fetal brain and later in life into adolescence and adulthood. A theme found throughout many of these reviews was how nicotine interacts with different receptors during gestation such as nicotinic acetylcholine receptors (nAChRs), as well as how altered development can lead to deficits in many areas of the brain such as the hippocampus, prefrontal cortex, and the cerebellum [3,5,8,9,10,11,12]. Research has shown that the hippocampus plays a key role in short and long-term memory, however, the prefrontal cortex plays an important role in the regulation of attention, short-term, or working memory, and behavior [13,16,17]. Reviews found the effects of PNE on the blood-brain barrier to play a large role in the alteration of memory processes as well [1,3].

Table 2. Summary of Findings from Preclinical Studies

Authors and Year Published	Study Models	Nicotine Exposure Duration	Findings
Al-Sawala et al. (2020) [13]	Adult Wistar male rats.	Prenatal exposure, maternal exposure until post-natal day 21 during lactation.	Impaired long-term memory and increased activity of superoxide dismutase in the hippocampus associated with PNE.
Archie et al. (2023) [1]	Adult CD1 female and male mice.	Gestational day 5 until postnatal day 7 via lactation	Reduced expression of tight junction proteins (Claudin-5, ZO-1, Occludin, GFAP, AQP4, NeuN, GLUT1) in the blood-brain barrier.
Feuntes-Cano et al. (2020) [14]	Adult albino bALB/c female and male mice.	10 days pre-gestation until lactation ceased	Delay in the acrophase for short-term memory recall and decreased long-term memory recall associated with PNE. Development of both the cholinergic signals and neural circuits involved in cognitive control showed alteration (hippocampus and prefrontal cortex).
Zhang et al. (2018) [7]	Adult C57Bl/6 female and male mice	Prenatal exposure until 3 weeks postnatal	Significant deficits in spatial working memory and attention in male offspring but none noted in female offspring.
Polli et al. (2020) [15]	Adult NMRI female and male mice	1 week prior to gestation until the end of gestation	PNE mice displayed cognitive deficits in the hippocampal-dependent rCPT, as differences in learning, attention, and impulsive behavior were detected.
Kalejaiye & Gondré-Lewis (2016) [16]	Adult Sprague–Dawley female and male rats.	Gestational day 7 until the gestational day 21.	Disruption of synaptic processing associated with the hippocampal CA3 subregion, PNE can disrupt glutamatergic receptor stoichiometry during neurodevelopmental periods.
Mcarthy et al. (2022) [17]	Adult female and male C57BL/6 or Swiss Webster mice	Prenatal exposure models and pre- and post-natal exposure models used.	Spatial working memory deficits, locomotor hyperactivity attention deficit, decreased frontal cortical dopamine tissue content, frontal cortical GABA to non-GABA ratio, reduced microstructural integrity of dorsal striatum, cerebellum, and prefrontal cortex.
Li et al. (2014) [18]	Adult female and male rats	Prenatal exposure from day 4 of gestation until the end of gestation	Fetal growth restriction in the offspring, developmental issues in learning and memory in the offspring suggesting that α7 nAChR and NMDAR1 in the hippocampus might be affected by prenatal nicotine exposure associated with memory impairment.

Table 3. Summary of Findings from Clinical Studies

Authors & Year Published	Study Models	Sample Size	Significant Findings
Longo et al. (2014) [6]	Mean age = 21 years	n = 6 exposed, n = 6 non-exposed controls	Increased activity in the middle frontal gyrus, the precentral gyrus, the superior parietal lobe, and the cingulate gyrus, alteration in the neural circuitry when given tasks of verbal working memory.
King et al. (2017) [8]	Mean age = 3-5 months, singleton births only	n = 24 exposed, n = 24 non-exposed controls	Decreased neural responses to auditory information, a reduced ability in sensory gating of repeated auditory stimuli in sleep.

The Effect of Prenatal Nicotine Exposure on Short-term Memory

Short-term memory is the process of how information is stored for short periods of time as well as the ability to quickly recall that information [19]. Two main branches of short-term memory are typically implicated when it comes to prenatal nicotine exposure: working memory and sensory memory. These short-term memory subtypes aid in the cognitive function and manipulation of stored memory, as well as the visual and acoustical processing of information before it processes into short-term memory [19]. As an individual develops into adolescence and adulthood, these processes are all crucial to the overall cognitive function of the human brain. Prenatal nicotine exposure can affect areas of the brain such as the hippocampus, prefrontal cortex, middle frontal gyrus, the precentral gyrus, the superior parietal lobe, and the cingulate gyrus [6]. The hippocampus is especially important for short-term memory as it plays an important role in encoding new memories [16]. Disruption of the synaptic processes during the development of this area of the brain has been associated with long-term deficits in working memory associated with PNE [16]. The cholinergic system plays a large role in the development and daily function of the hippocampus and many other areas of the brain as well. Cholinergic activity in the brain has been observed as early as the gastrulation phase in gestation [9]. As nicotine activates the nAChRs in the hippocampus in utero, this disrupts cholinergic functioning and affects development throughout gestation [11]. Abnormal development of these structures leads to issues with short-term memory as the brain continues to mature.

The Effect of Prenatal Nicotine Exposure on Long-Term Memory

Long-term memory is responsible for storing an infinite amount of information long-term and is used to perform skills and actions, as well as aid in maintaining general knowledge [19]. Areas of the prefrontal cortex and the cerebellum are associated with procedural long-term memory [17]. As prenatal exposure to nicotine has been shown to decrease the structural integrity of these areas, their function in long-term memory can be further impacted. The blood-brain barrier is another area that is shown to have a decreased structural integrity resulting in increased permeability of the membrane when exposed to PNE [1]. Increased permeability of the blood-brain barrier due to a decrease in tight junction proteins can cause issues with motor function, learning, and memory [1]. Additional harmful substances may pass through the blood-brain barrier due to the increased permeability, putting the individual at a higher risk of further impairment and declining cognitive abilities. While the exact role of the blood-brain barrier in memory is unknown, the breakdown and increased permeability of this structure have been associated with loss of cognitive function [1]. The reduced structural integrity of the cerebellum due to PNE may affect procedural long-term memory (i.e., “muscle memory”) [17]. Nicotine alters the integrity of brain regions responsible for long-term memory.

Discussion

Study Designs

Preclinical studies gave PNE rodents memory and learning tests to see how they performed as compared to their non-exposed control counterparts [1,7,13,14,15,17,18]. All studies included adhered to ethical standards and practices. The results of these studies all showed some form of impaired cognitive function due to PNE in the rodentss when completing the assigned tasks [1,7,13,14,15,17,18]. The two clinical studies were different in the age ranges of their sample [6,8]. These two clinical studies show the effects of PNE on different stages of maturation of the brain. Limitations of this review are the differences between rodent and human brain development as rodent models are not identical to human cognitive development and function. A limited number of clinical studies are available on this subject as well.

Nicotine and Fetal Growth Restriction

Research has shown how nicotine affects the etiology of fetal brain development due to pathophysiological changes in the placenta, different compensatory mechanisms in the fetal brain, and fetal growth restriction resulting in small gestational age at birth [4,10,12,18].

When there is placental dysfunction, chronic fetal hypoxia leading to fetal growth restriction can occur [4]. Because blood flow is compromised, the body attempts to protect the fetal brain by using a mechanism known as brain sparing [12, 20]. This mechanism redirects more cardiac output toward the left ventricle of the fetal heart to supply the brain with more oxygenated blood to prevent further injury. However, in doing so it fails to support normal brain development if this process is prolonged into the second stage of brain sparing, due to alteration of the cerebral vasculature. Fetal growth restriction may lead to an increased risk of preterm delivery, resulting in further risk to cognitive development as low birth weight can result in a decreased volume of total brain matter, white brain matter, and grey brain matter [12]. Fetal growth restriction can ultimately lead to neurobehavioral problems, motor learning, and cognitive issues which are often present in school-aged children as areas of the brain responsible for attention and learning are affected during development [12, 20]. However, there are still disparities throughout the literature on the exact mechanism of injury that occurs during this process known as brain sparing as at certain stages of gestation autoregulation of cerebral perfusion pressure can occur, while at other stages it may not [20].

Behavior and Memory Performance

The effects of PNE on the development of brain structures and synaptic processes can continue to affect the exposed individual throughout their lifetime. While these effects can present at many different stages of development, they most often present for the first time in school-aged children [12]. School-aged children who were exposed to nicotine prenatally can present with disorders such as attention deficit hyperactive disorder, behavioral issues, and overall lower academic performance [12, 15, 17]. Because certain structures of the brain such as the prefrontal cortex and the hippocampus are impacted during development, there is an increased risk of developing disorders such as attention deficit hyperactive disorder in individuals exposed to prenatal nicotine. [7, 12, 15, 17].

Sex Differences

Research shows that in male rodents, prenatal nicotine exposure has more prominent effects on spatial working memory and is associated with hyperactivity and attention deficits [7]. Mild spatial memory deficits were still noted in females as well but due to this, preclinical trials mainly focus on effects on male rodents. However, females were noted to be at a higher risk of developing nicotine dependency than males [9]. This can be explained as gonadal hormones play a role in the modulation of behaviors such as memory, reward, and reinforcement as they interact with ligand-gated ion channel receptors [9]. As females and males have varying levels of sex hormones, nicotine can interact with them differently, which could explain the differences in behaviors observed [9]. The exact mechanism behind observed sex differences in the etiology of PNE is still unknown in current literature. As attention deficit disorders are more diagnosed in school-aged males than in school-aged females, there is a need for further research [12].

Conclusions

Prenatal nicotine exposure has many negative effects on the development and function of different parts of the brain associated with short-term and long-term memory. Alteration of structures in utero implicated in short and long-term memory such as the hippocampus, prefrontal cortex, blood-brain barrier, cerebellum, and cholinergic functioning can have lasting developmental effects on cognitive function and capacity [1, 6, 13, 14, 15, 16, 17]. Fetal growth restriction due to PNE can greatly impact the development of these structures, impacting the function of short-term and long-term memory, and increasing the risk of developing attention deficit disorders postnatally [12]. Due to these developmental alterations, learning and memory tasks can be more difficult for exposed individuals to complete [6]. This information can be used for public education on the risks of maternal smoking, as well as aid in further research to potentially help lessen the effects experienced by those prenatally exposed to nicotine. Gaps in the literature on differential sex effects implicate the need for further research as well.

List of Abbreviations Used

PNE: orenatal nicotine exposure
nAChR: nicotinic acetylcholine receptors
EMBASE: Excerpta medica database
CINAHL: cumulative index for nursing and allied health literature

Conflicts of Interest

The author declares that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

This study did not require ethics approval and/or participant consent as it was a review.

Authors' Contributions

SMM: was the sole author and was responsible for database search, data collection and interpretation, design of the study, writing of the manuscript, and final approval for the results to be published.

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