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Mechanisms underlying cognitive impairment induced by prenatal nicotine exposure: a literature review

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Abstract. – Human and animal studies have conclusively shown that prenatal nicotine exposure alters fetal brain development and causes persistent impairment in the cognitive function of offspring. However, the mechanisms underlying the effect of prenatal nicotine exposure on cognitive function in offspring are still unclear. The objective of this review is to discuss the published studies on the mechanisms underlying the effects of prenatal nicotine exposure on cognitive impairment and discuss the potential mechanisms of action. The findings of the reviewed studies show that the main mechanisms involved are alteration in the composition of nicotinic acetylcholine receptor subunits, increase in surface expression of the glutamate receptor subunit GluR2, a reduction in neurogenesis, alteration of Akt and ERK1/2 activity, and mitochondrial dysfunction in the hippocampus and cortex. These pathways could shed light on future molecular markers and therapeutic targets for the prevention and treatment of cognitive dysfunction induced by prenatal nicotine exposure.

Key Words:
Nicotine, Prenatal nicotine exposure, Neurogenesis, Cognitive impairment.

Introduction

Nicotine is an alkaloid found in the tobacco plant. Nicotine consumption is highly addictive and can cause several serious systemic side effects, such as heart and lung diseases, and it is associated with an increased risk of cancer[1] and certain infectious diseases[2]. Importantly, there is a lot of evidence to show that long-term nicotine exposure causes cognitive impairment in both humans and animals, especially in the offspring of smoking mothers[3]. Nicotine crosses the blood-brain barrier and the placental barrier easily and has been detected in human fetal circulation[4,5]. In fact, the levels of nicotine in fetal blood were found to exceed maternal concentrations by 15%, and the nicotine concentrations in amniotic fluid were 88% higher than that in maternal plasma[4,6,7]. This is especially concerning given the rates of smoking among pregnant women, which was reported to be 9.4% among pregnant women in the United States in a recent study[8].

Experimental studies[9,10] on rodents have shown that cognitive function is impaired in the offspring of animals exposed to nicotine during pregnancy based on behavioral tasks. Similarly, the offspring of pregnant rats exposed to nicotine showed cognitive impairment in spatial memory tasks[11]. In accordance with the findings of these studies on experimental animals, clinical studies in humans have also observed changes in cognitive function (based on parameters such as the IQ score) in the children of smoking women[12]. Further, in New Zealand, it was reported that children born of smoking mothers were more likely to have depression than children born of non-smoking mothers[13]. These studies together indicate that maternal smoking can alter neurobehavioral development in offspring and, importantly, nicotine-induced cognitive impairment may be initiated during the embryonic development stages.

This review discusses the recent studies that have provided insights into the mechanisms by which prenatal nicotine exposure causes cognitive impairment in offspring. These mechanisms include the effects of nicotine on memory impairment, mitochondrial function, synaptic plasticity, neurogenesis, and protein kinases (Figure 1). The aim of this review is to improve our understanding of the mechanisms underlying the cognitive effects of prenatal nicotine exposure from the

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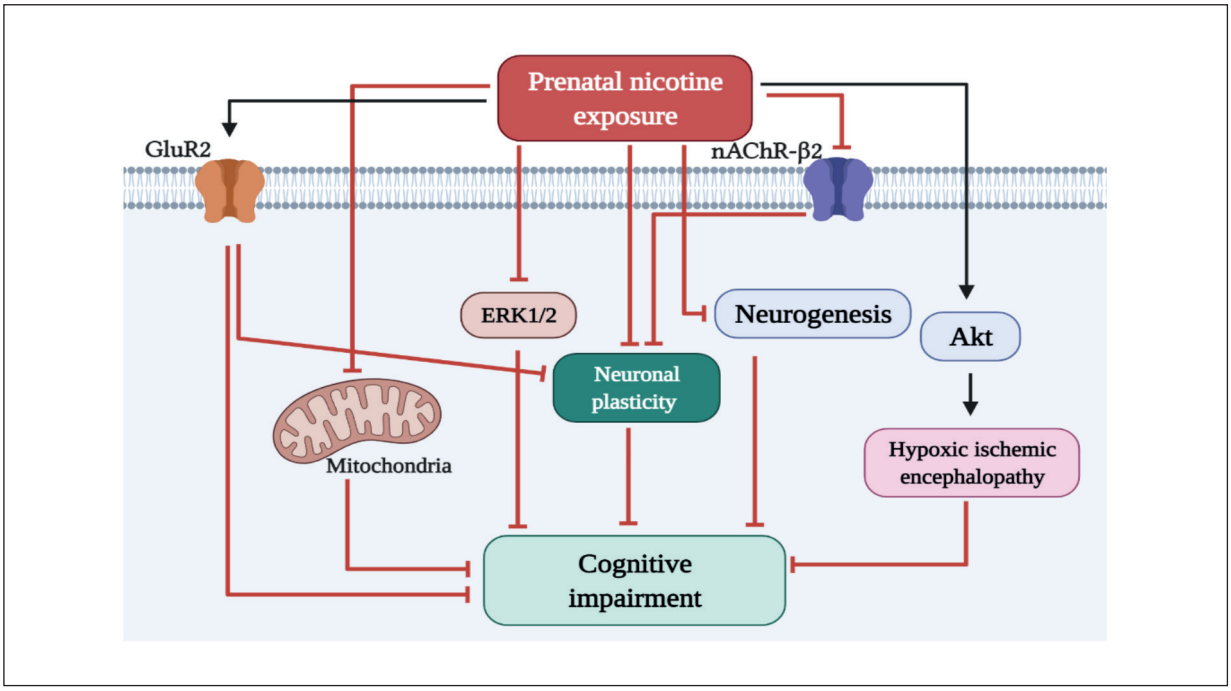

Figure 1. Schematic diagram of the mechanisms of cognitive impairment induced by prenatal nicotine exposure.

perspective of developing preventive strategies to ameliorate the adverse effects of prenatal nicotine exposure in children.

Prenatal Nicotine Exposure and Nicotinic Receptors

Nicotinic receptors play an important role in the regulation of general brain functions, including learning processes and memory consolidation[14,15]. Additionally, nicotinic receptors have been reported to play an important role in brain development, as they are expressed and begin to function from day 10 of the embryonic phase[16]. Nicotine binds to nicotinic acetylcholine receptors (nAChRs) in the central nervous system (CNS)[17], as well as nicotinic cholinergic receptors in peripheral tissues such as autonomic ganglia, neuromuscular junctions, and the adrenal medulla, as well as tissues in the CNS[17-19]. nAChRs are expressed throughout the CNS, with the expression being predominant in the hippocampus, prefrontal cortex, cerebellum, thalamus, hypothalamus, brainstem, basal ganglia, ventral tegmental area, amygdala, the retina, cochlea, and nucleus accumbens[20,21].

Nicotine-induced activation of nAChRs on glutamatergic and dopaminergic neurons appears to stimulate the release of neurotransmitters such as glutamate and dopamine in the CNS[22]. Accordingly, in experimental animal models, nicotine administration has been shown to increase the release of glutamate and dopamine[23,24]. Moreover, intermittent subcutaneous nicotine administration has also been found to increase the mRNA expression of dopamine receptor D1 in the prefrontal cortex of rats[25]. On the other hand, reduction in the activation of nicotine receptors has been linked to behavioral changes via deregulation of certain neurotransmitters, such as glutamate, dopamine, and gamma-aminobutyric acid[21,24]. However, it has been reported that long-term use of nicotine causes a decrease in dopamine release in the nucleus accumbens[26], and it was also shown that dopamine synthesis capacity is decreased in nicotine-dependent smokers[27]. It is not clear whether these effects of nicotine are brought about via its effects on dopamine receptors. In one study, repeated nicotine treatment was found to inactivate dopamine receptors in the rat basal ganglia[28], but another study[29] on mice showed that neither chronic nicotine administration nor nicotine withdrawal after chronic administration affected dopamine D1 and D2 receptors in the striatum. Importantly, the effects of prenatal nicotine exposure on dopaminergic receptors in the fetal brain are unclear.

nAChRs are composed of five subunits, and they can be classified into various types based on the composition of their subunits[30]. There are nine α subunits (α2-α10) and three β subunits (β2-β4), and the number of these subunits varies widely between the different receptor types[31,32]. The most common receptor subtypes found in the brain are heterogenic receptors, such as α4β2 and α3β4, and homomeric receptors, such as α7[33]. These receptors play an important role in the regulation of various functions. For instance, the α3β4 nAChR mediates the cardiovascular effects of nicotine[10], and the homomeric α7 nAChR is involved in synaptic transmission and facilitates the learning and memory processes[34,35]. In fact, changes in nAChR expression in transgenic animals have been found to impair memory function[36,37]. Nicotine mainly binds to Type 2 nAChRs, which are composed of β2/α4 subunits in most brain regions[38]. Additionally, α5 nAChRs were also found to be involved in nicotine-mediated behaviors specific to the development of nicotine dependence[39].

Both the peripheral and central nervous system also express another type of acetylcholine receptor called muscarinic acetylcholine receptors (mAChRs). These receptors specifically bind muscarine, and there is no conclusive evidence to show that prenatal nicotine exposure might have an effect on mAChRs. For example, one study[40] in a rat model showed that nicotine exposure in the early gestation period led to a decrease in the mRNA expression of muscarinic receptors and restricted fetal brain growth. However, another study[41] showed that in the offspring of rats that were exposed to nicotine in the early postnatal period, impairment of hippocampus-dependent memory was associated with the disruption of nicotinic cholinergic systems rather than muscarinic cholinergic systems. Thus, the effects of nicotine on muscarinic receptors are a topic that requires further investigation.

Prenatal Nicotine Exposure and Mitochondrial Function

The mitochondria are the power source for cells, and they are involved in many cellular processes such as oxidative phosphorylation, ATP production, β-fatty acid oxidation, Kreb's cycle, and apoptosis[42,43]. Mitochondria contain mitochondrial DNA (mtDNA), which is important for the enzymes and pathways needed for energy production within the mitochondria[44,45]. Studies[46,47] have reported that nicotine exposure during pregnancy can cause methylation of mitochondrial DNA in the fetus. Increase in nicotine exposure during pregnancy results in an increase in mtDNA methylation[47], which is associated with mitochondrial dysfunction. Additionally, it has been reported that prenatal nicotine exposure could impair cognitive function through alteration of the activity of mitochondrial complex I and mitochondrial complex IV[10]. Therefore, an increase in mtDNA methylation and decrease in the activity of mitochondrial complex I and mitochondrial complex IV could be potential mechanisms underlying cognitive impairment in the offspring of smoking mothers.

Prenatal Nicotine and Synaptic Plasticity

The hippocampus is the part of the brain that is responsible for learning processes and memory consolidation, which occur as a result of alteration in the synaptic structure, also known as synaptic plasticity[48,49]. Synaptic plasticity represents the cellular levels of synaptic neuron communication during memory formation based on their ability to modify their shape and structure[50,51]. Long-term potentiation (LTP) and long-term depression are used as measures of synaptic plasticity[52,53]. The response of the synapse is based on neuronal presynaptic release of neurotransmitters and receptor response on postsynaptic neurons[54]. Alteration in the presynaptic release of neurotransmitters or the response of receptors in the postsynaptic neurons can reduce or abolish LTP[55,56]. The link between synaptic change and memory formation has been investigated through *in vitro* and *in vivo* electrophysiological studies[45,57,58], which show changes in synaptic activity in the hippocampus following behavioral tasks. Such studies have shown that prenatal nicotine exposure results in a reduction in LTP in the offspring[59]. In one such study that used a theta burst stimulation protocol, prolonged synaptic recording showed that LTP is persistently reduced in offspring with prenatal nicotine exposure[11]. These studies indicate that the cognitive effects of nicotine may be brought about via a reduction in synaptic plasticity.

Prenatal Nicotine and Neurogenesis

Neurogenesis is the process by which new neurons are born, and it occurs from the embryonic period until adulthood in brain regions such as the hippocampus and dentate gyrus[60]. Neurogenesis is important for the proliferation of neural stem cells and differentiation of these cells into

mature neurons, which are then integrated into hippocampal circuitry[61]. Neurons are known to communicate with other neurons through synapses[62]. Formation of new synaptic connections between neurons in the hippocampus, dentate gyrus, and cerebral cortex is very important in acquired learning and memory consolidation, and new neuron generation plays an important role in the formation of new aspects of memory[63]. Previous studies[64-66] have revealed that reduction in hippocampal neurogenesis impairs memory function. In addition, it has been reported that neurogenesis is reduced in the hippocampus of offspring with prenatal nicotine exposure[11,67]. Thus, one of the mechanisms underlying cognitive impairment associated with prenatal nicotine exposure might be a reduction in neurogenesis.

Prenatal Nicotine and Protein Expression and Activity

Several proteins, such as receptors and protein kinases, present in the brain are involved in various functions such as the structure of the cells, metabolism, differentiation, and learning and memory[68,69]. In memory formation, these proteins mediate signal transduction through the activation of different protein kinases via receptors that are involved in different mechanisms, such as alteration of channel properties, alternation of ion channel density in synapses, and regulation of gene expression and protein synthesis[70-72]. For example, the levels of protein kinase B (PKB or Akt) and extracellular signalregulated kinase 1 and 2 (ERK1/2) phosphorylation are increased in the hippocampus following behavioral tasks that are dependent on the hippocampus[73,74]. However, in the offspring of rats exposed to nicotine in the prenatal period, the levels of PKB/Akt protein expression and ERK1/2 phosphorylation in the brain were reduced[11]. Thus, the cognitive effects of nicotine may be brought about via changes in these two kinases.

Most receptors consist of different subunits, and the number and structure of these subunits in the receptor affects their function[75]. For instance, the glutamate α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor is a tetramer that is assembled in different combinations of four subunits, namely, GluR1, GluR2, GluR3, and GluR4[76]. When the GluR2 subunit is present in the receptor, it causes calcium impermeability[77,78]. During development, GluR2 is present in the brain in its pre-transcriptional form that includes a glutamine residue; however, after birth, post-transcription modification results in the glutamine residue being replaced with an arginine residue to make the AMPA receptor impermeable to calcium[79]. It has been reported that GluR2 surface expression is increased in the hippocampus of offspring born of rats exposed to nicotine and alcohol during the prenatal period; therefore, cognitive dysfunction in the offspring of such rats may be associated with the overexpression of GluR2[10]. In addition, alterations in the subunit composition of other receptors also lead to changes in cognitive function[80]. For instance, prenatal nicotine exposure was found to cause a decrease in the level of the β2 subunit in nAChRs, and this was associated with cognitive dysfunction in the offspring[11].

PKB (also known as Akt) is a downstream protein of phosphoinositide 3-kinase (PI3K), and is expressed in almost all cells in the body[81]. In the brain, Akt plays an essential role in the development and general functions of neurons[82]. The PI3K/Akt pathway has been identified as a pro-survival pathway in cells[83]. Akt phosphorylation can also regulate the expression and function of other proteins that regulate cell survival, proliferation, learning and memory encoding, and apoptosis[45,84]. When nAChRs are stimulated, they activate PI3K, which leads to the phosphorylation of Akt and subsequent modifications in downstream signaling pathways that ultimately enhance memory formation[85]. However, over-phosphorylation of the Akt protein was found to cause hypoxic ischemic encephalopathy, which altered brain development in rat models of prenatal nicotine exposure[86]. Therefore, according to these findings, nicotine exposure during pregnancy could decrease cognitive function in offspring *via* over-activation of Akt protein activity.

ERK1/2 belongs to the mitogen-activated protein kinase family[87]. ERK1/2 mediates several biological functions, including protein synthesis, which is important for many functions such as cell proliferation, differentiation, neurogenesis, synaptic plasticity, and memory consolidation[88,89]. It is well established that activation of nAChRs can activate ERK1/2, which then plays a role in memory formation, retrieval, and reconsolidation[15,90]. Accordingly, studies have shown that inhibition or decreased activation of ERK1/2 can lead to impaired memory function[89,90]. A recent study[11] revealed that ERK1/2 expression is reduced in the hippocampus of rat models of prenatal nicotine exposure. Therefore, it is speculated that reduction in ERK1/2 activity is

one of the mechanisms underlying the memory dysfunction associated with prenatal nicotine exposure. On the contrary, another study revealed that ERK1/2 phosphorylation was increased on prenatal nicotine exposure, and the offspring exhibited memory impairment based on an increase in anxiety-like behavior in the open-field test[67]. Despite their differences, both studies showed that prenatal nicotine exposure resulted in cognitive impairment and reduction in hippocampal neurogenesis. The differences in ERK1/2 activity could be attributable to differences in the route of administration, as nicotine was orally administered in Liu et al[67] and subcutaneously administered in the Parameshwaran et al[11].

Conclusions

Prenatal nicotine exposure has been found to cause cognitive impairment in humans and experimental models, and it is important to understand the underlying mechanisms for the prevention and treatment of nicotine-induced cognitive dysfunction. The findings of the studies reviewed here show that nicotine affects cognitive development by altering the expression and function of nAChR subunits, altering ERK1/2 activity, increasing Akt activity, and increasing GluR2 surface expression, as well as decreasing neurogenesis, synaptic plasticity, and mitochondrial dysfunction in the hippocampus and cortex. In the future, these pathways could be further investigated to identify treatment targets and molecular markers of the risk of cognitive dysfunction.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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