Molecular insights into the benefits of nicotine on memory and cognition (Review)

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Abstract. The health risks of nicotine are well known, but there is some evidence of its beneficial effects on cognitive function. The present review focused on the reported benefits of nicotine in the brain and summarizes the associated underlying mechanisms. Nicotine administration can improve cognitive impairment in Alzheimer's disease (AD), and dyskinesia and memory impairment in Parkinson's disease (PD). In terms of its mechanism of action, nicotine slows the progression of PD by inhibiting Sirtuin 6, a stress-responsive protein deacetylase, thereby decreasing neuronal apoptosis and improving neuronal survival. In AD, nicotine improves cognitive impairment by enhancing protein kinase B (also referred to as Akt) activity and stimulating phosphoinositide 3-kinase/Akt signaling, which regulates learning and memory processes. Nicotine may also activate thyroid receptor signaling pathways to improve memory impairment caused by hypothyroidism. In healthy individuals, nicotine improves memory impairment caused by sleep deprivation by enhancing the phosphorylation of calmodulin-dependent protein kinase II, an essential regulator of cell proliferation and synaptic plasticity. Furthermore, nicotine may improve memory function through its effect on chromatin modification via the inhibition of histone deacetylases, which causes transcriptional changes in memory-related genes. Finally, nicotine administration has been demonstrated to rescue long-term potentiation in individuals with sleep deprivation, AD, chronic stress and hypothyroidism, primarily by desensitizing α_7 nicotinic acetylcholine receptors. To conclude, nicotine has several cognitive benefits in healthy individuals, as well as in those with cognitive dysfunction associated with various diseases. However, further research is required to shed light on the effect of acute and chronic nicotine treatment on memory function.

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Contents

1. Introduction

Nicotine, or 3-(1-Methylpyrrolidin-2-yl) pyridine, is an alkaloid that is found in the tobacco plant (1,2). Nicotine use can lead to a number of health complications, including heart and lung diseases, and increases the risk of cancer occurrence (3) and the susceptibility to several infectious diseases, including tuberculosis, pneumonia and sexually transmitted diseases such as chlamydia (4). However, increasing evidence suggests that nicotine also has beneficial health effects, particularly in terms cognitive function.

Nicotine acts as an agonist of nicotinic cholinergic receptors (nAChRs), which are found in both the central nervous system (CNS) and the peripheral nervous system (2,5,6). Each nAChR comprises five α or β subunits (7). There are nine potential α subunits and three β subunits, and different nAChR receptor subtypes possess varying compositions of these subunits (8,9). The most abundant receptor subtypes present in the human brain are $\alpha_4\beta_2$, $\alpha_3\beta_4$ (heterogenic) and α_7 (homomeric) (10). The $\alpha_3\beta_4$ nAChR is known to mediate the cardiovascular effects of nicotine (11), while the homomeric α_7 nAChR is speculated to be involved in synaptic transmission, as well as in learning and sensory gating (12,13). Stimulation of nAChRs in the CNS by

nicotine or acetylcholine regulates the release of a variety of neurotransmitters, such as dopamine, glutamate, serotonin, norepinephrine and γ-aminobutyric acid (14,15). Therefore, alterations in the expression or function of nAChRs, as a result of a disease, may alter the release of other neurotransmitters and, thus, affect brain function.

It is commonly known that long-term exposure to nicotine causes nAChR desensitization (16), leading to memory impairment in otherwise healthy individuals (17). Such nicotine-induced cognitive dysfunction is associated with several mechanisms, including activation of the phosphodiesterase-5 (PDE-5) signaling pathway and inhibition of estrogen biosynthesis (18,19). In particular, nicotine stimulates the expression of PDE-5 (19,20), which plays a role in cleaving cyclic guanosine monophosphate and cyclic adenosine monophosphate that activate downstream signaling pathways contributing to memory impairment (21-23). Nicotine also blocks estrogen synthase (aromatase) in the brain, which is important for estrogen biosynthesis (18,24). Estrogen activates estrogen receptors in the brain, which function as transcriptional factors and enhance the expression of several neurotransmitters (including glutamate, acetylcholine, serotonin and noradrenaline), and thus stimulate the neuronal circuits required for memory encoding (25). Therefore, alterations in estrogen biosynthesis due to nicotine (20,26), as well as the nicotine-induced elevation of PDE-5 levels, can lead to cognitive impairment in healthy individuals.

In contrast to these detrimental effects of nicotine on cognitive function, some studies report that nicotine also has beneficial effects on memory and learning processes. Thus, the present review summarizes the potential benefits of nicotine on cognition (Fig. 1).

2. Benefits of nicotine in Alzheimer's disease (AD)

AD is a neurodegenerative disease that primarily affects older adults and causes dementia (27). AD is characterized by the deposition of toxic amyloid-β (Aβ) and tau proteins in the brain (28,29). In particular, the accumulation of Aβ has been demonstrated to inhibit mitochondrial function, leading to increased reactive oxygen species formation and the stimulation of inflammatory processes (30). Indeed, several studies have revealed that Aβ deposition alters the physiological function of the brain and causes neuronal dysfunction (31,32). Unfortunately, there is still no cure for AD, and the disease is currently managed by slowing its progression with the administration of antioxidants and drugs such as cholinesterase inhibitors (33).

According to the cholinergic hypothesis, the cognitive decline in AD arises from deficiencies in central cholinergic neurotransmission due to the loss of acetylcholine (34). Therefore, cholinesterase inhibitors (such as donepezil and galantamine), which block the degradation of acetylcholine, remain the first-line approach to restore central cholinergic function in AD. Moreover, changes in the expression and density of α_7 nAChRs in the hippocampus have been observed in AD and appear to have the most impact on cognitive function (35). Such α_7 nAChRs have also been found to be co-localized with plaques in AD (36). Therefore, agonists of α_7 nAChRs, including nicotine, may be useful for treating AD.

The stimulation of nAChRs by nicotine also likely affects downstream signaling molecules, including protein kinases, which are important regulators of synaptic plasticity and memory (37). In particular, protein kinase B (also referred to as Akt) is a central molecule of the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway, which plays a vital role in the regulatory functions of neurons in the CNS, including neuronal survival (38-42), and learning and memory encoding (38,43,44). Therefore, it is hypothesized that the stimulation of nAChRs by nicotine or its analogs activates the PI3K/Akt signaling pathway, which, in turn, regulates learning and memory processes (42,45). Indeed, acute and chronic administration of nicotine was reported to improve cognitive impairment in patients with AD (46-48). Moreover, acute nicotine administration during electroencephalography (EEG) performed in patients with AD who received cholinesterase inhibitors was found to shift the EEG readings towards normal levels (49). Thus, nicotine administration may have a beneficial effect on the cognitive decline observed in AD.

3. Benefits of nicotine in Parkinson's disease (PD)

PD is the second most common neurodegenerative disorder after AD that affects older individuals (50). Although the exact cause of PD is still not fully understood, its pathogenesis involves the loss or degeneration of the dopaminergic neurons (dopamine-producing neurons) in the substantia nigra of the midbrain (51). This loss of dopaminergic neurons causes impairment of motor control, tremors, rigidity and bradykinesia, and cognitive impairment (52,53). Studies in animal models of PD have revealed that nicotine can protect the brain cells from damage (54,55). Smoking cigarettes is also reported to reduce the risk of PD occurrence (53), and nicotine may help improve some symptoms of PD, such as dyskinesia and memory impairments (55). Indeed, the neuroprotective effects of nicotine in PD have been examined *in vitro* and *in vivo*, and are hypothesized to be primarily due to its pro-survival effects on dopaminergic neurons (56).

In addition to activating pro-survival signaling pathways in the brain, such as the aforementioned PI3K/Akt pathway, nicotine may also slow the progression of PD by inhibiting Sirtuin 6 (SIRT6), an NAD^+-dependent class III deacetylase (57). This suppression of SIRT6 was found to reduce apoptosis and increase neuron survival (57). Consistently, several studies reported that the overexpression of SIRT6 impairs contextual fear memory formation (58,59). Despite this, another study found that loss of SIRT6 in the brain also causes memory impairment (60). Therefore, the downstream effects of nicotine on SIRT6 in PD require further investigation.

4. Benefits of nicotine on memory processes in patients with thyroid disease

Studies have revealed that thyroid hormones (61), including thyroxine (T4) and triiodothyronine (T3), regulate brain development, neurogenesis, synaptogenesis and myelination (62,63). T3 and T4 are synthesized in the thymus (64,65), released into

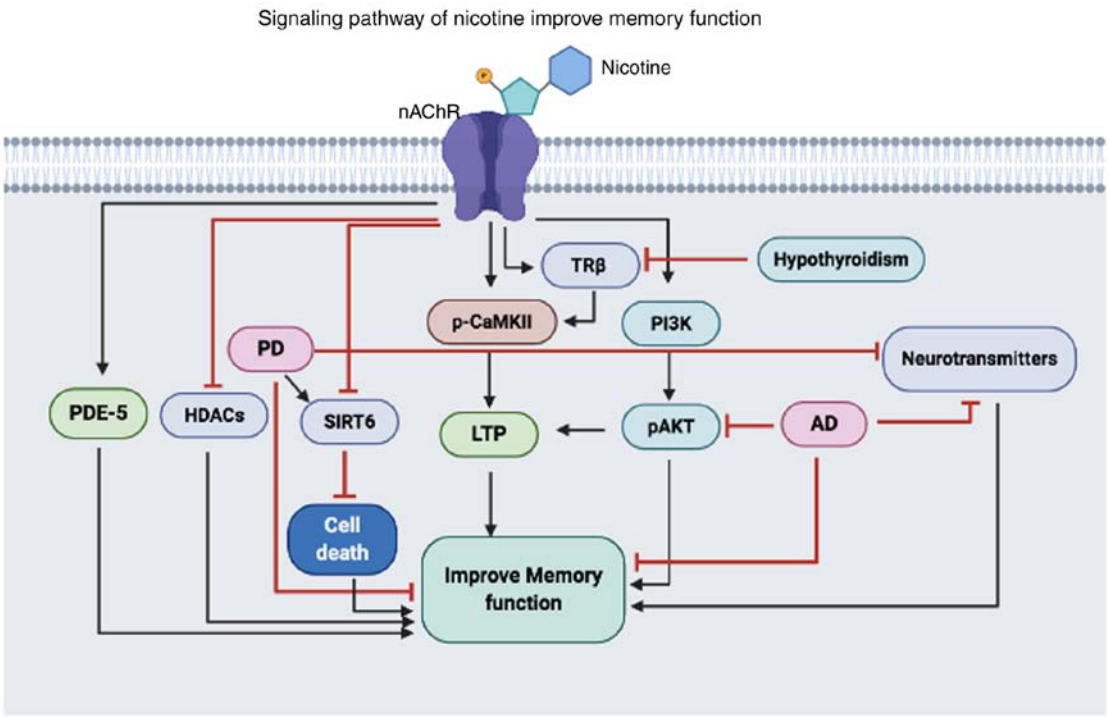

Figure 1. Illustration of the proposed mechanisms of nicotine in improving memory dysfunction. Nicotine activates nAChR, which can activate or inhibit the expression and functions of various proteins. Nicotine can activate PDE-5, TRβ and CaMKII, and activation of these proteins can lead to increased neuronal communication that ultimately improves memory function. In addition, nicotine activates the pro-survival PI3K/AKT pathway that increases LTP and improves memory dysfunction caused by AD. Also, nicotine can inhibit HDACs and SIRT6, which are increased in PD, thus reducing the activity of these proteins reduces neural apoptosis and improves memory dysfunction. PDE-5, phosphodiesterase-5; HDAC, histone deacetylases; PD, Parkinson's disease; SIRT6, Sirtuin 6; LTP, long-term potentiation; p-, phosphorylated; CAMKII, calmodulin-dependent protein kinase II; TRβ, thyroid receptor subunit β; PI3K, phosphoinositide 3-kinase; AD, Alzheimer's disease; nAChR, nicotinic cholinergic receptors.

the bloodstream, and eventually exert their effects by binding to a nuclear receptor termed the thyroid hormone receptor (TR), which is present in two different isoforms, α and β (66). The expression levels of these isoforms differ among tissues: The α1 receptor is primarily expressed in the heart and the skeletal muscle (67), whereas β1 is mainly expressed in the liver, kidney and brain (68).

TRs are also abundantly expressed in the hippocampus, which is the part of the brain that is responsible for memory formation (63). Therefore, in diseases such as hyperthyroidism, hypothyroidism and cretinism, in which abnormal thyroid hormone levels are present (69,70), hippocampal function may be affected, thus resulting in cognitive impairment (71). Indeed, neuroimaging studies have demonstrated that the structure and function of the hippocampus are altered in patients with hypothyroidism (72-74).

Of note, acute nicotine administration has been reported to activate TRs (particularly TRβ in the brain) and, thus, may enhance learning and memory processes in certain individuals (66). Furthermore, TRβ knockout in mice did not affect memory function following nicotine administration, confirming the role of TRβ in memory processes (75). In addition, memory impairment caused by hypothyroidism was revealed to be improved by nicotine via the modulation of calcineurin, which regulates the function of calmodulin-dependent protein kinase II (CaMKII) to improve synaptic plasticity (76). However, the precise underlying mechanisms of nicotine administration in improving cognitive impairments in patients with thyroid diseases require further investigation.

5. Effects of nicotine on cognitive function in healthy individuals

There is mounting evidence that nicotine administration may improve memory in otherwise healthy individuals. For example, research revealed that sleep deprivation causes memory impairment by downregulating the phosphorylation of CaMKII, which is an essential regulator of cell proliferation and synaptic plasticity (77-79). CaMKII was previously found to regulate the expression of glutamate receptor subunit-1 and its trafficking to the synaptic surface, which is necessary for normal brain function and memory formation (80). Consistently, acute nicotine administration was found to improve memory impairments caused by sleep deprivation by enhancing the phosphorylation of CaMKII (81). Therefore, nicotine may improve memory impairments caused by a lack of sleep in otherwise healthy individuals.

6. Nicotine-induced chromatin modifications may improve memory and learning

Some studies have indicated that nicotine affects chromatin in the cell nucleus (82-84). Chromatin is composed of four subunits, called histones, which can be modified via acetylation, methylation or phosphorylation (85), thereby regulating gene transcription (86,87). In particular, histone acetyltransferases and histone deacetylases (HDACs) play essential roles in the chromatin modifications involved in various cellular functions, including memory and synaptic

plasticity (88,89). For example, inhibition of HDACs can increase the expression of key genes involved in memory processes, which are regulated by the cAMP response element-binding protein (CREB)-CREB-binding protein transcriptional complex (89). In particular, HDAC4 has been demonstrated to be crucial for learning and memory processes (89,90). As cigarette smoking has been reported to modulate the regulation of chromatin by altering the functionality of HDACs, such as HDAC6, in the lungs (83), it may also have a similar effect in the CNS. Indeed, it has been revealed that nicotine can inhibit HDACs in the brain, and, thus, improve memory function (84). However, further study is required to investigate the effect of nicotine on cognitive function through chromatin modulation.

7. Electrophysiological effects of nicotine: Strengthening synapses

The neurons in the brain interconnect to form networks, which are organized according to function (91). Therefore, understanding these connections allows certain areas to be stimulated and recorded, to monitor neurotransmitter release and receptor response in particular regions of the brain. Long-term potentiation (LTP) is used to measure synaptic plasticity, and can provide a cellular model of learning and memory encoding. For example, an increase in the level of glutamate released from the presynaptic to the postsynaptic neurons was found to enhance excitatory postsynaptic potential in the hippocampus during spatial learning tasks (92). Previously, studies have reported that acute nicotine exposure rescues LTP in individuals with sleep deprivation (81). In addition, chronic administration of nicotine has been revealed to improve LTP in AD, chronic stress models and hypothyroidism models (74,93,94). There is also mounting evidence that the restoration of LTP due to nicotine exposure is related to the normalization of the phosphorylation of essential kinases, such as CREB and CaMKIV (48,78,95). Therefore, nicotine administration may strengthen synapses between two neurons, leading to improved memory in both healthy individuals and those with diseases such as AD or hypothyroidism.

8. Conclusions

The findings reported in the studies included in the present review article indicate that nicotine can stimulate memory function. Therefore, although nicotine is similar to other psychoactive substances, in that it can induce dependence or abuse, it also has certain beneficial effects, including enhancing cognitive function in healthy individuals and restoring memory function in patients with diseases, such as AD, PD and hypothyroidism.

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AA designed the review paper, performed the literature search and wrote the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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