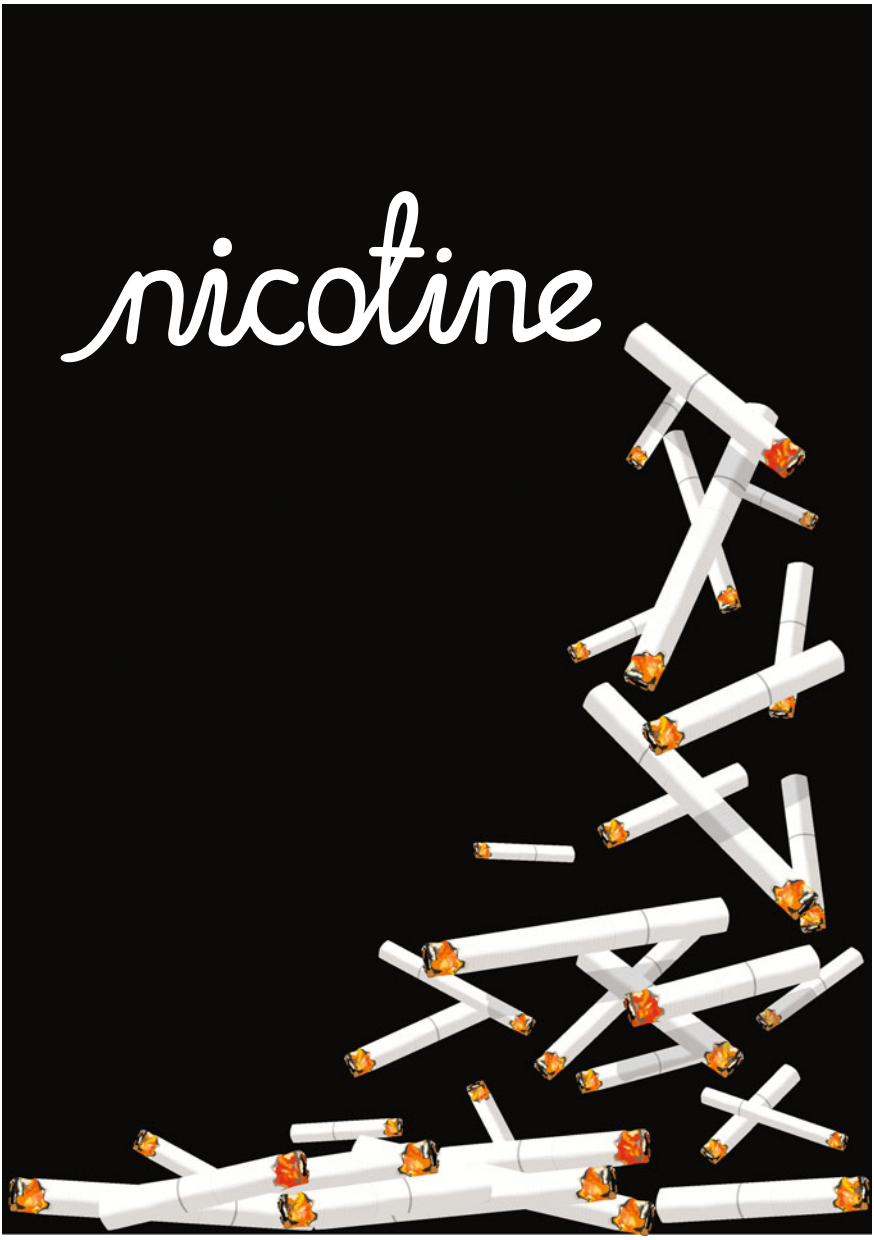
nicotine

Nicotine

Lorenza S. Colzato and Iris Spruit

Introduction

Nicotine is an alkaloid found in tobacco leaves that are processed and smoked. Nicotine is known for its addictive nature and, according to the World Health Organization, six million tobacco smokers die annually as a result of smoking (World Health Organization 2016). In 2015, over 1.1 billion people in the world smoked tobacco (World Health Organization 2016). Smoking occurs more in men than in women. Globally, smoking decreased from 41.2% in 1980 to 31.1% in 2012 in men and from 10.6 to 6.2% in women (Ng et al. 2014). In the United States 16.8% of the adults aged 18 years and older smoke cigarettes of which 18.8% is male and 14.8% is female (Jamal et al. 2015). Smoking is most prevalent in adults aged 25–44 years (20.0%) and least in adults over 65 years (8.5%). Furthermore, American Indians and Alaska Natives smoke the most (29.2%) and American Asians the least (9.5%). Also, smoking is more prevalent among individuals with a low education than high education and more prevalent among individuals that live below the poverty level (26.3%) than above the poverty level (15.2%; Jamal et al. 2015).

Recently a new phenomenon in nicotine delivery has come to light: electronic cigarettes (e-cigarettes). E-cigarettes are electronic delivery systems physically similar to cigarettes, but functionally different. Instead of burning tobacco leaves and producing tar, e-cigarettes aerosolize liquid nicotine from a disposable

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container. The absence of tar from the aerosol has two main advantages. First, many of the dangerous chemicals incorporated in tobacco cigarettes are supposedly absent. Second, the different composition of particulate matter implies that nicotine delivery is slowed, reducing the addiction potential. Accordingly, e-cigarettes have been considered a safe alternative to smoking. However, while the levels of perilous chemicals are indeed largely minimized in e-cigarettes, a recent review of 48 studies suggests there is no evidence for a decreased addiction potential (Grana et al. 2014). Therefore, e-cigarettes seem to be a helpful harm-reduction agent, but not a cure for nicotine addicts.

In the brain nicotine promotes the function of acetylcholine (ACh), because it binds on nicotinic acetylcholine receptors (nAChRs; Briley and Changeux 1977). The cholinergic system plays a major part in various cognitive functions, including learning, memory, and attention (Everitt and Robbins 1997). Nicotine administration increases nicotine blood plasma concentration and nicotine concentration in the brain. It binds on nAChRs and thereby facilitates the release of several neurotransmitters critical for cognitive functioning such as dopamine (dos Santos Coura and Granon 2012). The effects nicotine exerts on cognition has been studied extensively over the past few decades (for extensive reviews see Newhouse et al. 2004; Swan and Lessov-Schlagger 2007). Reports of the acute effect of nicotine are abundant, but inconsistent. The chronic (long-term) effects of nicotine have been less studied. The goal of chapter is to give an overview of the studies that investigated the effect of nicotine on cognition in healthy humans in order to get a better understanding under which conditions nicotine can enhance cognition and to elucidate whether nicotine can function as a cognitive enhancer.

In this chapter we will first explain how nicotine administration affects the cholinergic system. Then, we will review the studies that investigated the acute effects of nicotine. Finally, we will outline studies that examined the long-term effect of nicotine on cognition. The studies show that nicotine at short term can potentially enhance attentional and memory processes, but only in poor performers. Nicotine at long term can also enhance cognition, mainly attention, but only in the elderly with cognitive deficits.

Mechanism of Action

In the brain, nicotine binds to nicotinic acetylcholine receptors (nAChRs) that are ordinarily activated by the neurotransmitter acetylcholine (Briley and Changeux 1977; Poorthuis et al. 2009). Nicotine inhaled through smoking is rapidly absorbed into the lungs, which results in high concentrations of nicotine in the blood that leaves the heart and this blood reaches the brain within 8–10 s (Matta et al. 2007). Nicotine blood levels are highest after a cigarette is smoked and then drop quickly over the next 20 min. The elimination half-life of nicotine is about 2 h. There are several methods of nicotine administration for experimental purposes, but the ones most used in the literature seem to be transdermal exposure through nicotine

patches or nicotine gum. The nicotine patch Nicoderm results in peak levels of nicotine within 4 h of administration, while other patches result in peak levels after 6–9 h (Gore and Chien 1998). When chewing nicotine gum, nicotine levels rise increasingly over 15–30 min and, important to note, only about half of the nicotine in the gum is absorbed (Shiffman et al. 2002). After administration, nicotine is transported across the blood–brain barrier (see Fig. 1). In the brain, nicotine binds to nAChRs, which can be found widespread throughout the brain including the prefrontal cortex, thalamus, hippocampus, and monoamine-containing nuclei such as the substantia nigra, raphe nuclei, locus coeruleus, and ventral tegmental area. nAChRs consist of unique combinations from at least 12 subunits (α2–α10, β2–β4; Wu and Lukas 2011). The receptors are either heteromeric (e.g., α4β2) or homomeric (e.g., α7). The α4β2 receptor is the most common in the mammalian brain and because this receptor is highly sensitive to nicotine, it desensitizes at low concentrations of nicotine that correspond to blood concentrations in smokers (Millar and Gotti 2009; Wu et al. 2006). The saturation of nAChRs is dose-dependent. Smoking one cigarette (1.2–1.4 mg of nicotine) results in nearly complete occupation of α4β2 receptors (88%) 3.1 h after smoking and it is thought that smokers maintain an almost full α4β2 nAChR saturation (96–98%) throughout the day (Brody et al. 2006). Smoking only three puffs resulted in 75% of α4β2 occupancy 3.1 h after smoking (Brody et al. 2006).

Short-Term Effects of Nicotine

Although numerous studies investigated the acute effect of nicotine on cognition, the results are mixed. In this section, we will give an overview of the recent findings involving the acute effects of nicotine and explain which factors may cause the contradictory results.

Nicotine seems to enhance cognition in several domains, but mainly attention and memory. This was demonstrated by Heishman et al. (2010), who performed a meta-analysis on 41 studies published from 1994 to 2008. These studies all used a double-blind, placebo-controlled design and the participants consisted of healthy nonsmoking or smoking adults who were not or minimally deprived from tobacco (≤ 2 h). Studies with participants who were nicotine-deprived were excluded from the analysis due to the reversed-withdrawal effect. This means that when deprived smokers are administered nicotine, the enhanced cognitive performance is only due to the reversal of performance deficits caused by withdrawal. The authors found enhancing effects of nicotine limited to attention (alerting and orienting), and memory (episodic and working memory). Nevertheless, some studies published after this meta-analysis show no cognitive enhancing effects of nicotine. Grundey et al. (2015) assessed the effect of nicotine, in the form of a nicotine patch releasing 15 mg over 16 h, on working memory, which was measured with the n-back task, and attention, which was measured with the Stroop task in nonsmokers and nicotine-deprived smokers. Compared to nonsmokers, nicotine-abstinent smokers

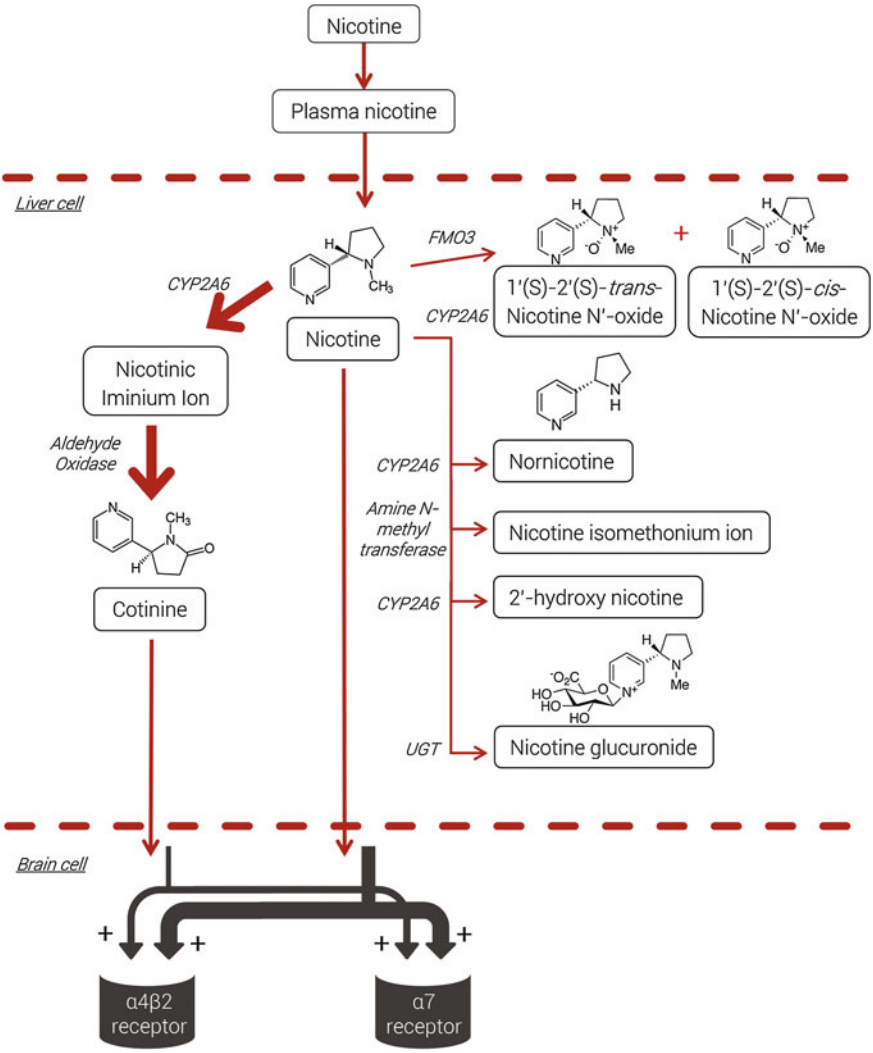

Fig. 1 Schematic representation of nicotine metabolism. When nicotine enters the liver through circulation it is metabolized into 6 primary metabolites, primarily cotinine (70–80%) through the intermediary metabolite nicotinic iminium ion. Nicotine not metabolized crosses the blood–brain barrier and binds agonistically to nicotinic acetylcholine receptors (nAChR's) in the brain. Cotinine also binds to nAChR's agonistically but with lower affinity than nicotine. The α4β2 and α7 receptors shown here represent 90% of nAChR's in the mammalian central nervous system, but 13 other types are known. Metabolism in the liver occurs mostly through the enzyme cytochrome P450 2A6 (CYP2A6). Other enzymes include Flavin-containing monooxygenase 3 (FMO3), uridine diphosphate-glucuronosyltransferase (UGT), amine *N*-methyltransferase and aldehyde oxidase

showed deficit in working memory and attentional control. However, the intake of nicotine improved performance of both cognitive processes in smokers, but performance worsened in nonsmokers. This effect was especially clear for working memory performance. However, these findings are not in line with findings of another study. Fisher et al. (2012) found that nicotine did not improve working memory. In this placebo-controlled study, nonsmoking healthy adults received 6 mg of nicotine gum. Nicotine did not affect response speed or accuracy on the n-back task, which, using different loads, measures the ability to update and monitor task-relevant information in working memory. The contradictory results of these two studies may be explained by the different doses of nicotine employed. Indeed, in order to get some nicotine-facilitated neurotransmitter responses, a sufficient level of nicotine is necessary (Balfour 2004).

Even though an adequate dose of nicotine is crucial to get a beneficial effect, high nicotine doses can have an adverse effect on cognition. Poltavski et al. (2012) investigated the effect of different doses, administered through nicotine patches (7, 14, and 21 mg), on cognitive performance and found an inverted u-shaped relationship between different doses of nicotine and cognitive performance. Indeed, as previously pointed out by Newhouse et al. (2004), moderate nicotine intake can produce optimal performance, whereas low or high nicotine intake can impair performance. The idea is that only suboptimal performing individuals can benefit from nicotine administration. However, if individuals are already performing optimally, nicotine administration will impair performance as in the case of the nonsmokers in the study by Grundey et al. (2015) previously discussed. This idea is supported by studies showing the nicotine can act as cognitive enhancer in low-performing clinical populations such as Alzheimer's disease, schizophrenia or attention deficit hyperactivity disorder (ADHD) (see Newhouse et al. 2004 for a review). In a seminal study Potter and Newhouse (2008) investigated how acute nicotine administration, in the form of a nicotine patch (7 mg, administered for 45 min), affects several cognitive functions in 15 nonsmoking young adults diagnosed with ADHD. After nicotine administration, the participants showed improvement in behavioral inhibition and a tendency, even if not significant, of improvement in recognition memory.

Another factor that contributes to mixed results in the literature may be the genetic predisposition. Indeed, Ahrens and colleagues (2015) showed that the individual variability in the effects of nicotine on cognition could be explained by variation in dopaminergic (DRD2) and cholinergic (CHRNA4) genes. In this study, employing a within-subject, double-blind, placebo-controlled crossover design, nicotine was administered to healthy nonsmoking adults in the form of a nicotine patch (7 mg, administered for 1 h). The participants performed a visual search task with different load conditions and distractors. The results pointed to the conclusion that the effects of nicotine on distractor interference are moderated jointly by cholinergic and dopaminergic genetic variations (Ahrens et al. 2015).

In conclusion, acute nicotine administration promotes cognition but this effect seems to be limited to the domains of attention and memory. Further, this effect seems to differ depending on the dose of nicotine, the genetic predisposition, and the individual baseline performance level. At short term, nicotine acts as a cognitive enhancer in low-performing, but not in already optimally performing individuals.

Long-Term Effects of Nicotine Across the Life Span

In this section we will outline studies that investigated the chronic effects of nicotine across the life span. Several animal studies suggest that prenatal exposure to nicotine has adverse effects on cognitive functioning. For instance, the offspring of rat dams that were injected with 2 mg/kg of nicotine a day showed memory deficits compared to a control group (Levin et al. 1996). The effect of prenatal nicotine exposure on cognition in humans is less clear. In one study, 10-year old children (n = 593), of which little over half was prenatally exposed to smoking, were assessed on measures of learning, memory, and problem solving. After controlling for several maternal characteristics, such as other prenatal substance use and sociodemographic variables, the authors found that prenatal exposure to smoking was related to impairments in learning and memory (Cornelius et al. 2001). On the other hand, another study could not replicate this outcome. Kafouri et al. (2009) investigated the association between prenatal exposure to cigarettes and cognition in 503 adolescents, aged 12–18 years. Nicotine-exposed participants were matched with nonexposed participants by education of the mother and school attended. Several cognitive functions were measured, including visuospatial skills, verbal and visual memory, processing speed and inhibition. No effect of prenatal cigarette exposure on cognitive abilities was found. As suggested by Clifford et al. (2012) in their review, the reductions in cognitive performance due to prenatal nicotine exposure are generally small and can sometimes at least in part be attenuated by maternal characteristics, such as IQ, education, and other factors.

Given that many smokers started smoking during adolescence, several researchers have focused their interest in investigating the chronic effect of smoking on cognitive functioning during adolescence. One study found that adolescent smokers, aged 14–18 years, showed poorer performance in working memory and divided attention than nonsmokers, while both groups were comparable in age, gender, and education (Jacobsen et al. 2005). Furthermore, they found that performance was worse in smokers that started smoking on an earlier age, than in smokers that started on a later age. These findings concur with another study in which it was found that smokers who started smoking during adolescence performed worse on a working memory task (as indexed by the n-back task) than nonsmokers (Ernst et al. 2001). No difference was found between smokers and nonsmokers in visual attention or logical reasoning. Another study examined the prefrontal attentional network function using functional magnetic resonance imaging in smokers and nonsmokers (aged 18–25 years) while they performed an oddball task (Musso et al. 2007). Although they found no difference in reaction time between smokers and nonsmokers, activity in the prefrontal attentional network was lower in smokers than in nonsmokers. Moreover, smoking duration was associated with the degree of reduced attentional network activity. Note that these studies did not assess the effect of nicotine alone. Cigarette smoke (both mainstream and sidestream) consists of various other substances, such as tar, that could possibly influence the brain (Fowles and Dybing 2003). Furthermore, although the

previously mentioned studies controlled for several possibly confounding variables like age, gender, and education, it is still possible that other variables such as social environment and genetic variability might have impacted the results. Nevertheless, it has been suggested that during adolescence nicotine can induce changes in gene expression and neuronal morphology in the prefrontal cortex, which not surprisingly, could explain the negative repercussion on cognition in adulthood (Poorthuis et al. 2009). Further evidence that exposure to nicotine during adolescence may have long-lasting effects on cognition comes from a study with rats (Counotte et al. 2009). In this study, male rats were infused with either nicotine (0.4 mg/kg three times daily) or saline for 10 days during adolescence. Attentional performance was assessed 5 weeks after the last injection. Rats that received nicotine during adolescence showed reduced attentional performance, while rats that received nicotine during adulthood showed normal attentional performance.

Although nicotine exposure during adolescence seems to have a negative effect on cognition, long-term nicotine exposure can ameliorate cognitive deterioration in the elderly population. Nicotine seems to have a positive effect on attention in individuals with Alzheimer's disease. In a double-blind, placebo controlled, crossover study, 8 participants with Alzheimer's disease (mean age = 77) wore a nicotine patch for 4 weeks with doses of 5 mg/day during week 1 and 4, and 10 mg/day during week 2 and 3 (White and Levin 1999). Nicotine significantly enhanced attentional performance, which was assessed with Conners continuous performance test (CPT), whereas there was no significant effect on motor or memory performance. Nicotine also seems to have a positive effect on cognition in the mildly cognitive impaired elderly population. In a double-blind clinical study, 67 nonsmoking participants (age > 55) with mild cognitive impairments received either a nicotine patch (15 mg a day) or placebo patch for 6 months (Newhouse et al. 2012). Attentional performance and several other cognitive functions were assessed using the CPT and the cognitive drug research computerized battery. Nicotine treatment improved performance in attention, memory, and mental processing tasks. White and Levin (2004) also found an improvement in attention and memory due to long-term nicotine exposure. In their double-blind, placebo-controlled, crossover study, 11 nonsmoking participants with age-associated memory impairment (mean age = 75) wore nicotine patches during a 4-week period with the following doses: 5 mg/day during week 1 and 4, and 10 mg/day during week 2 and 3. Outcomes of the clinical global impression scale showed a significant improvement in memory symptoms when participants were treated with nicotine compared to placebo. Also attention performance improved as measured by the CPT.

In sum, long-term nicotine exposure seems to have different effects across the life span. Prenatal nicotine exposure possibly impairs cognition in later life and adolescent exposure to nicotine seems to negatively affect memory and attention in adulthood. Nicotine exposure later in life, however, shows promising effects on attention and possibly memory.

Conclusion

As it binds to nAChRs, nicotine has the potential to influence primarily the cholinergic system and secondarily other neurotransmitters critically relevant for cognitive functioning such as dopamine. Even though more research is necessary to further elucidate the effect of nicotine on cognition, at short- term, nicotine seems to improve mainly memory and attention and this effect seems to be restricted to low-performing individuals. This might be due to an inverted u-shaped relationship between nicotine and cognitive performance. Therefore, future studies that investigate the cognitive enhancing effects of nicotine should consider individual variations in performance.

Long-term nicotine exposure has different effects across the life time. Prenatal nicotine exposure seems to have slight adverse effects on cognition, although more research is necessary to disentangle the effects of nicotine from factors like social environment and genetics. In adolescence, nicotine exposure seems to also exert adverse effects on cognition and this might be due to changes in gene expression and neural morphology in the prefrontal cortex. Only in elderly population nicotine has the potential to enhance cognition, specifically attention. Accordingly, nicotine may be a promising tool for cognitive enhancement in restoring cognitive decline in aging.

Future studies should further investigate the neurological basis underlying the cognitive enhancing effect of nicotine. As studies have shown that genetic variability may have a modulatory effects on the nicotine-induced effects (Ahrens et al. 2015), genetic variability should be taken into account. Future studies could investigate whether individuals with genetic variability associated with suboptimal level of acetylcholine and dopamine will indeed benefit from nicotine administration.

In sum, although more research is needed and keeping in mind that six million tobacco smokers die annually as a result of smoking, we conclude that nicotine may have the potential to enhance attention and memory in low-performing individuals and individuals showing cognitive decline. Especially for the elderly and cognitively impaired population nicotine might offer cognitive benefits.

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