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Nicotine: from plants to people

Nikotin: od biljaka do ljudi

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Abstract

Nicotine is naturally present in many crops, including but not limited to tobacco, eggplant, and tomatoes. Only in the tobacco plant is nicotine present in high enough quantities (~2% of dry weight) to have pharmacological effects. People have recognized the stimulating effects of the smoke created by burning dried tobacco leaves for thousands of years, and cigarette smoking remains the most common form of nicotine uptake from tobacco. Decades of epidemiologic data show that smoking causes a number of serious diseases (including cardiovascular diseases, lung cancer, and chronic obstructive pulmonary disease [COPD]). Undoubtedly, the best way to avoid the harm from smoking is to never start. For current smokers, quitting smoking altogether is the most effective way to reduce the risk of harm and smoking-related disease.

Along with other aspects such as taste and ritual, nicotine is one of the reasons people smoke. Nicotine, while addictive and not risk-free, is not the primary cause of smoking-related diseases. Indeed, experts agree that smoking-related diseases are caused primarily by chronic exposure to the harmful constituents that are produced when tobacco is burning. Nevertheless, many people still mistakenly believe that nicotine is a major cause of tobacco-related diseases.

While nicotine-containing products should not be used by certain groups of people — such as minors, people with or at risk of heart disease, diabetes, epilepsy, or seizure, pregnant or breast-feeding women or women who think they may be pregnant — delivery of nicotine by less harmful means can support public health goals by encouraging smokers who would otherwise continue smoking to switch to less harmful products. It is, therefore, pivotal to address the biggest misconceptions about nicotine to empower smokers to make informed decisions.

In this article, we discuss basic facts about nicotine, its effects on the human body, as well as the risks related to nicotine consumption.

Key words: nicotine, tobacco, smoking

Apstrakt

Nikotin je prirodno prisutan u mnogim usevima, uključujući ali ne ograničavajući se na duvan, patlidžan i paradajz. Nikotin je jedino u biljci duvana prisutan u dovoljno velikim količinama (~ 2% suve mase) da bi postigao farmakološke efekte. Ljudi su prepoznali stimulativne efekte dima nastalog sagorevanjem osušenog lišća duvana pre hiljade godina, i pušenje cigareta ostaje najčešći oblik unosa nikotina iz duvana.

Decenije epidemioloških podataka pokazuju da pušenje uzrokuje brojne ozbiljne bolesti (uključujući kardiovaskularne bolesti, rak pluća i hroničnu opstruktivnu bolest pluća [HOBP]). Nesumnjivo, najbolji način da se izbegne šteta od pušenja je da nikada ne započnete. Za sadašnje pušače potpuno odvikavanje od pušenja je najefikasniji način smanjenja rizika od štete i bolesti povezanih sa pušenjem.

Zajedno sa drugim aspektima poput arome i rituala, nikotin je jedan od razloga zašto ljudi puše. Nikotin, iako izaziva zavisnost i nije bez rizika, nije primarni uzrok bolesti povezanih sa pušenjem. Zaista, stručnjaci se slažu da su bolesti povezane sa pušenjem uzrokovane prvenstveno hroničnim izlaganjem štetnim sastojcima koji nastaju kada duvan gori. Ipak, mnogi ljudi i dalje pogrešno veruju da je nikotin glavni uzrok bolesti povezanih sa pušenjem. Iako proizvode koji sadrže nikotin ne bi smele da koriste određene grupe ljudi – poput maloletnika, ljudi koji boluju ili sa rizikom od srčanih bolesti, dijabetesa, epilepsije ili napada, trudnice ili dojilje ili žene koje misle da bi mogle biti trudne – isporuka nikotina manje štetnim sredstvima može podržati ciljeve javnog zdravlja podsticanjem pušača koji bi inače nastavili da puše da pređu na manje štetne proizvode. Stoga je, presudno baviti se najvećim zabludama o nikotinu kako bi se pušači osnažili da donose utemeljene odluke.

U ovom članku, razmatramo osnovne činjenice o nikotinu, njegovim efektima na ljudsko telo, kao i rizicima povezanim sa konzumacijom nikotina.

Ključne reči: nikotin, duvan, pušenje

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Introduction

Quitting smoking is the best way to reduce the risk of smoking-related diseases, which includes certain types of cancer, cardiovascular diseases, and emphysema. Cigarette smoke stains teeth, causes bad breath, and ages the skin. **Despite being a well-known component of cigarettes, nicotine is not a primary cause of these harms.** It is many of the other so-called "harmful and potentially harmful constituents" (HPHC) in smoke that are the major cause of smoking-related health risks.

Unsurprisingly, there are many misconceptions about nicotine. How much do you really know about nicotine, and how much of that information is accurate? Read on to discover facts you may not have known about nicotine as well as its role in tobacco harm reduction research.

It starts with plants

Where does nicotine come from? The simple answer is: plants. More specifically, from plants of the Solanaceae family, commonly known as nightshade plants. This family includes tomatoes (~332 ng of nicotine in each fruit, on average), potatoes (~675 ng), and eggplants/aubergines (~525 ng) (1). To put this into perspective, a single cigarette contains ~12 mg of nicotine (1) — around 18 thousand times more nicotine than a potato, by mass. But only a fraction (<2 mg) of that nicotine is transferred into the smoke of a cigarettes, and thus, into the lungs of a smoker.

What does this mean? Nicotine is present in our diet in small doses. Research estimates that people eat about 1,400 ng of nicotine every day in ordinary food (2). But that does not explain why tobacco and other plants contain nicotine in the first place.

Nicotine is created in the plant's roots when two chemical compounds—pyridine and pyrrolidine—are linked together before being transported to the leaves. The genes behind this combination exist in all plants, but genetic duplications in the nightshade family are believed to have led to nicotine production (3).

Wild tobacco plants of the *Nicotiana* genus with higher concentrations of nicotine survived longer than sibling plants with lower concentrations (4). In other words: evolution. The chemical exists in these plants at greater concentrations because it benefits them. Although the primary purpose of the chemical in plants is not definitively known (4), studies have shown that at least one of its functions is to defend against attacking insects (4).

However, nicotine's effects in people are different from its function as an insect repellent. Since prehistorical times, people have recognized the stimulating effects of the smoke created by burning dried tobacco leaves (5). Since then, smoking has been the most common form of nicotine uptake from tobacco.

Into the brain

Commercially available products, including cigarettes, nicotine replacement therapies (NRT), smoke-free products, and others, contain high enough levels of nicotine to temporarily affect a person's brain function in a reversible way. But how does nicotine reach the brain in the first place?

Nicotine in various forms can be absorbed through the lungs, mouth, or skin. The route of uptake determines the speed and intensity of nicotine delivery. Once absorbed, nicotine enters the bloodstream and is distributed, at various concentrations, to all tissues and organs, including the brain.

It takes little time after starting product use for nicotine to reach the brain at a sufficient concentration to cause an effect. That time ranges from a few seconds, as with smoking, to up to an hour, as with a nicotine patch. Nicotine is also constantly being cleared from the body. It is metabolized mainly by the liver, at approximately 70% at each pass through the liver, and the metabolites are excreted via the kidneys (6).

Once inside the brain, nicotine binds to nicotinic acetylcholine receptors (nAChR), such as those located on the brain's nerve cells. These nAChRs are crucial receptors, involved in most communications not only between neurons in the brain, but also outside the nervous system, for example, between neurons and muscle cells. The natural signaling molecule for nAChRs is acetylcholine, which nicotine can imitate as it binds to these receptors. When it does, it causes the release of dopamine, gamma aminobutyric acid (GABA), glutamate, acetylcholine, and noradrenaline. As a result, nicotine may stimulate and ultimately affect short-term brain functions such as emotion, learning, and memory.

The action of nicotine in the brain can also trigger physiological effects outside the brain. For example, the messenger epinephrine is released into the bloodstream, leading to temporary narrowing of blood vessels, higher blood pressure, and increased heart rate.

After repeated nicotine stimulation, the brain adapts to the presence of nicotine, a process that is reversible when a person stops using nicotine-containing products. This process of nicotine stimulation can ultimately lend to the reason why someone chooses not to quit smoking.

Nicotine and addiction

It has been recognized that the addictive properties of cigarette smoking are due to a complex interaction of factors that enhance the action that would be caused by nicotine alone. Other factors also make smoking addictive: ritual, sensory experience, and social experiences all play a significant role. Exposure to nicotine and the extent of its effects can also be influenced by individual differences in smoking behavior, metabolism, body mass index, and genetic differences.

Once nicotine enters the brain, it modulates the reward systems by binding to specific nAChRs distributed in certain regions of the brain. Chronic exposure to nicotine results in tolerance, a *decreased* response of some kind to the same dose of nicotine. It also results in sensitization, which is an *increased* response of some kind to the same dose of nicotine. These changes in response underlie the development of dependence, and they can lead to temporary withdrawal symptoms, a reason why one chooses not to quit.

Regarding terminology, nicotine dependence is described by the World Health Organization as "a disorder of regulation of nicotine use arising from repeated or continuous use." (7) "Tobacco use disorder" is the relevant term described by the American Psychiatric Association in their Diagnostic and Statistical Manual of Mental Disorders (8).

Withdrawal symptoms—including difficulty concentrating, anxiety, and dysphoria (meaning distress or discomfort with life)—are another concern for about half of smokers when they initially quit smoking (9). Quitting smoking is very much possible, and millions of smokers quit every year. NRTs and other cessation products can help address withdrawal symptoms.

One critical factor in nicotine dependence is the dose and rate of nicotine delivery. Because smoking delivers nicotine to the brain very efficiently, products that rapidly deliver peak doses of nicotine, like sprays and inhalers, are more satisfying to smokers than those that slowly deliver nicotine at much lower doses, like gums and patches (10, 11).

Levels of nicotine in the blood: not all products are equal

Many people assign most of the addictiveness of cigarettes to the rapid absorption of nicotine through the lungs. When a person smokes a cigarette, their blood nicotine levels peak in about 6 to 10 min, after which the levels drop by about half every 2 h on average, as the body naturally clears the nicotine from its system (12). Most NRTs do not provide this same pharmacokinetic profile (13), which makes them less likely to be addictive, but also less likely to satisfy the smokers' desire for nicotine.

On the other hand, Philip Morris International's (PMI) heated tobacco product, the Electrically Heated Tobacco System (EHTS), creates a nicotine profile similar to that of a cigarette (14). In two studies in Japan, the peak concentration of nicotine in the blood occurred about 6 min after starting product use and reached more than 88% of the level reached with cigarettes. This likely comes even closer to 100% as the user becomes more familiar with the product; however, participants in this study had only used the product during a product trial at the start of the study and during the assessment of nicotine uptake. Subjectively, the people who used EHTS instead of a cigarette also found that the product reduced their urge to smoke in a manner similar to cigarettes.

In another study, the pharmacokinetic profile of *MESH*, PMI's e-vapor product, was very similar to the profile created upon smoking a cigarette or using the study subjects' preferred e-cigarette. Further, participants who used *MESH* instead of their own brand of e-cigarettes had reduced nico-

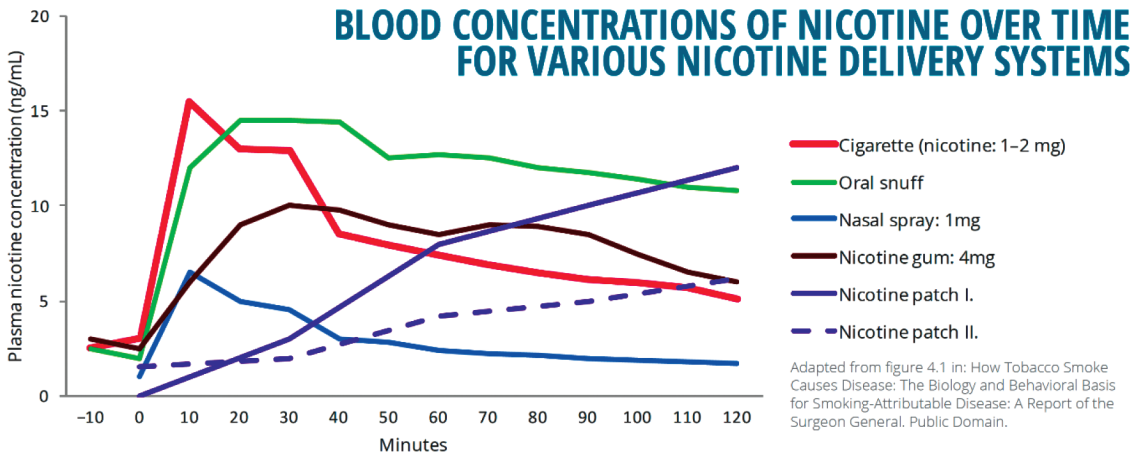

Figure 1. Blood concentration of nicotine over time with various nicotine delivery systems

tine craving over the next few hours after product use, comparable to the reduction achieved with the study subjects' preferred e-cigarette (15).

Comparing products while matching nicotine levels

It is important for us to have a quantitative way for comparing the effects of smoke-free product aerosols and cigarette smoke. For example, we know from our laboratory studies that EHTS aerosol is significantly less toxic than cigarette smoke. This statement means that, **at the same levels of exposure, EHTS aerosol and cigarette smoke cause different levels of toxicity.** But how can we know we are exposing our samples to the same levels of smoke and aerosol in our laboratory studies?

One approach is to focus on a single chemical present in both. Nicotine is an important part of why people use tobacco products. So, it serves as a meaningful point of comparison. This approach also helps us report our results in a way that other researchers can replicate.

Comparisons can also be made on a per-stick or per-cigarette basis. We do use this comparison in some cases where it makes sense, such as when participants in our clinical studies are using the product under consideration. But it is necessary to use equivalent nicotine doses in our cell culture and other toxicity studies, for example (16). A cell culture is exposed to a liquid containing an extract of cigarette smoke or smoke-free product aerosol at multiple matched nicotine levels. In other studies, cell cultures may be exposed to the smoke or aerosol directly, but, again, at matched nicotine levels. Doing so provides a clear way for comparing the effects of different products at the same nicotine exposure level, and it makes the experiment and results easier for other scientists to confirm independently. It also makes it easier to extrapolate the results to what a user of the product might experience.

Because a major part of that experience is the nicotine, smokers may try to compensate for the nicotine level in their blood by using more of the product or by intensifying the frequency and volume of puffs taken for a while after they first switch from cigarettes to EHTS or other smoke-free products. However, over the long-term use of EHTS, the compensation often remains incomplete. In other words, they end up maintaining a lower nicotine level in their blood (17).

In a recent PMI study, switching from mentholated cigarettes to the menthol EHTS resulted in an almost complete compensation (measured as urinary nicotine equivalents) within a period of 90 days (18). On the basis of these observations, comparing products on the basis of their nicotine content seems like the right approach.

Such comparisons can be made by using automated smoking machines, which collect cigarette smoke by puffing on the product. The smoke volume inhaled in a puff and the interval between puffs are some of the parameters that can be quantified. Under the ISO smoking regimen, we measure 0.672 mg nicotine per reference cigarette (19). The Health Canada Intense smoking regimen, with deeper puffs repeated more often yields 1.86 mg of nicotine per reference cigarette. These or other puffing regimens can be used to compare the levels of constituents in smoke-free product aerosols with those in cigarette smoke in a repeatable manner in a laboratory setting, though they do not accurately mimic real smoking behaviors.

Exploring the risks of nicotine

Nicotine is not risk-free. However, it is not the primary cause of smoking-related diseases. Researchers are currently exploring the potential benefits of nicotine when it is decoupled from smoking.

Nicotine alone is less harmful than the smoke generated by cigarettes that contain it, as can be seen in many studies on nicotine-containing products that are not cigarettes. For example, the United States (US) Surgeon General concluded that "*there is insufficient data to conclude that nicotine causes or contributes to cancer in humans*." (20) While the Surgeon General has acknowledged the possibility that nicotine might be a tumor promoter on the basis of animal and mechanistic studies, the current scientific consensus appears to be that nicotine does not initiate cancer and is far less harmful than many of the harmful and potentially harmful chemicals found in cigarette smoke (21, 22).

The Lung Health Study on the natural history and safety of prolonged use of medicinal nicotine gum indicated no evidence of an effect of NRT use on overall cancer (23) or COPD risk (24). Additionally, available evidence to date suggests that nicotine use likely does not increase the risk of cardiovascular events: Five out of six previous epidemiological studies did not detect any increased cardiovascular risk among snus users relative to never tobacco users (25). Nicotine-containing products should not be used by people who have or are at risk of heart disease, are diabetic, are epileptic, or are experiencing seizures. Nicotine-containing products should not be used by minors, by women who think they may be pregnant, during pregnancy or while breast-feeding.

What do public health representatives say?

"*Nicotine is the very same compound FDA has approved for over 30 years as a safe and effective medication. People are dying from the tobacco-related diseases from the smoke particles, not the nicotine… Can we start to take a different look at this?*" (26) as stated by Mitch Zeller, director of the US Food & Drug Administration's (FDA) Center for Tobacco Products back in 2014.

The Royal College of Physicians have said: "*Nicotine is not, however, in itself a highly hazardous drug… It is inherently unlikely that nicotine inhalation itself contributes significantly to the mortality or morbidity caused by smoking. The main culprit is smoke and, if nicotine could be delivered effectively and acceptably to smokers without smoke, most if not all of the harm of smoking could probably be avoided.*" (27)

We agree that the burning of tobacco, not the nicotine, is the biggest problem with cigarettes. This is why we develop and offer a portfolio of smoke-free nicotine-containing products that are a better choice for smokers than continuing to smoke cigarettes. Independent studies have shown how important it is to make better alternatives like these available to adult smokers who would otherwise continue to smoke (28–30).

Among the leaders of public change are public health organizations and regulatory bodies, whose opinions and decisions affect everyone involved. Most of these leaders agree that tobacco harm reduction is the right route to take. However, opinions still vary about what role alternative products should play in tobacco harm reduction.

Institutes like Public Health England (PHE) (31) and the FDA (32) see the potential of nicotine-containing products as smoking alternatives. For example, PHE states that "*e-cigarettes could be contributing to at least 20,000 successful new quits per year and possibly many more.*" (33) However, regions like Australia have heavier restrictions on nicotine. Under Australian Commonwealth law, nicotine-containing products are categorized as prescription-only (with nicotine patches, gums, or sprays being exceptions) or dangerous poisons (with the exception of their use in therapeutics or cigarettes).

PHE also weighs in on the public awareness of nicotine saying, "*there is much public misunderstanding about nicotine (less than 10% of adults understand that most of the harms to health from smoking are not caused by nicotine).*"

What do people think?

People deserve accurate and non-misleading information to let them know they have a choice about what products to use. And, choices like these add up to affect public health outcomes. This is one of the reasons why it is so important to combat public misperceptions about nicotine.

Many people still mistakenly believe that nicotine is a major cause of tobacco-related diseases. A literature review of 54 studies has shown that peoples' assumptions about nicotine vary and are often wrong (34). According to another review, these incorrect assumptions could alter the outcome or even the validity of smoking cessation trials (35).

Up to 73% of people mistakenly believe nicotine causes cancer, according to a US population study (36). It is, therefore, important to educate the public about nicotine and nicotine-containing products.

Conclusions

It is important for people to have a balanced perspective on nicotine. On the one hand, products containing nicotine should not be used by certain groups of people. On the other hand, other products than cigarettes containing nicotine can support public health by encouraging smokers who would otherwise not quit cigarettes to switch to smoke-free products, where nicotine is provided without the harmful chemicals produced during combustion.

It is time to decouple the discussions about nicotine from those on the dangers of smoking cigarettes. There is already plenty of information worth sharing about nicotine, and we look forward to seeing what new additions are made to the body of research that already exists on nicotine.

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