Nicotine as a Health Risk

Background

Until well into the 1980s, tobacco consumption was socially acceptable and a habit that was not regarded as an addiction risk[88]. The word "addiction" was reserved for illegal drugs such as cocaine and heroin and the definition of addiction established by the WHO mainly focused on physical withdrawal symptoms which, back then, had not yet been investigated for tobacco[87,95]. In 1974, the theory of the addictive effect of nicotine was still considered an outsider's opinion[64,83]. Since then research has produced a large number of studies and the addictive effect of nicotine has meanwhile become a scientific consensus that made its way into a U.S. Surgeon General report (Fig. 1) in 1988.[84,87] The report in addition states that the pharmacologic and behavioral processes of nicotine addiction are similar to those of other drug addictions[84,87]. This notwithstanding, in the year 1994 seven CEOs of U.S. tobacco companies still declared under oath that they believe, cigarettes do not cause cancer and that nicotine is not addictive – against their better knowledge as now evidenced by formerly secret documents from the tobacco industry. Long before the public health institutions the tobacco industry was already aware of the addictive effect of nicotine. It had been secretly testing how tobacco cigarettes as an ideal vehicle for the release of nicotine acould accelerate consumer addiction.[42]

To date, 180 parties have bindingly committed to the first global public health treaty – the WHO Framework Convention on Tobacco Control, FCTC. These parties represent around 90 percent of the world's population[25]. In Germany, the Framework Convention came into force in early 2005. The aim of the convention is to "protect present and future generations from the devastating health, social, environmental and economic consequences of tobacco consumption and exposure to tobacco smoke [...]". In the Preamble, one of the motivations for the treaty states "that cigarettes and some

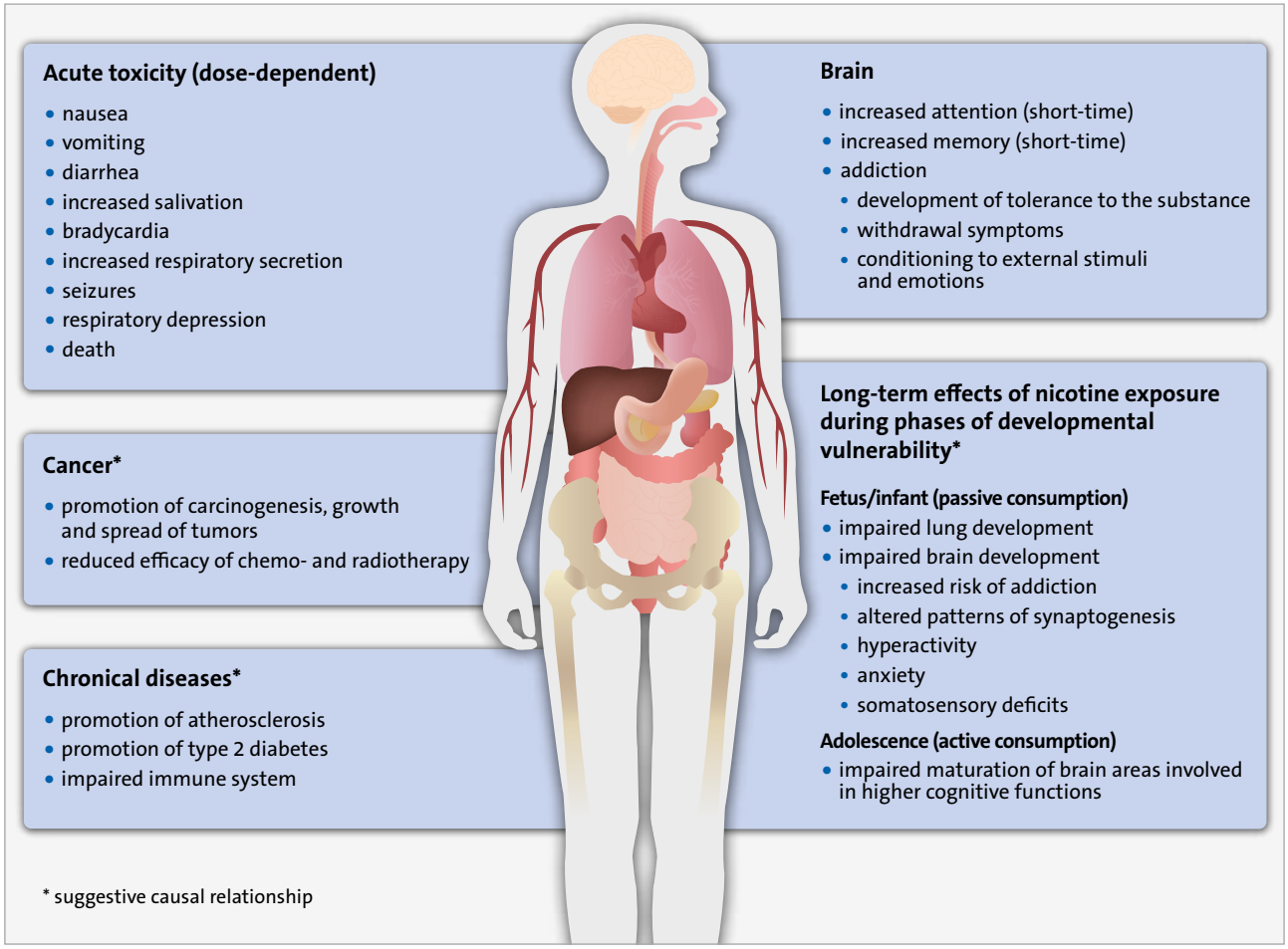

Figure 1: Effects of nicotine on the body and possible adverse effects and diseases. Sources: U.S. Department of Health and Human Services 2014[87], Sanner 2015[65], Grando 2014[35], Bruin 2010[13], Yuan 2015[101], England 2015[23]. Illustration: Unit Cancer Prevention, German Cancer Research Center.

other products containing tobacco are highly engineered so as to create and maintain dependence, and that many of the compounds they contain and the smoke they produce are pharmacologically active, toxic, mutagenic and carcinogenic, and that tobacco dependence is separately classified as a disorder in major international classifications of diseases."[20]

Uptake, distribution and metabolism of nicotine

Nicotine can be absorbed through the skin, the lung epithelium as well as the mucous membranes of the respiratory and digestive organs. The distribution of the substance in the body and its elimination rates depend on the route of administration[10]. Via the systemic circulation, nicotine is distributed throughout the body and activates the most diverse processes by binding to a certain receptor type. This nicotine-sensitive (nicotinic) receptor is found throughout the organism and is normally activated by the body's endogenous messenger substance acetylcholine (ACh): nicotinic ACh receptors are found on cells of the nervous system (neurones) in the same way as on muscle, kidney, skin, lung and immune cells and on cells of the lymphatic and vascular system[16,43,44].

In the brain, activation of nicotinic ACh receptors influences the signal transmission between nerve cells and, via complex mechanisms, contributes to the development of dependence and withdrawal symptoms. In non-neuronal cells, activation of nicotinic ACh receptors triggers processes affecting the differentiation, multiplication, survival and migration of the cells.

In the systemic circulation, nicotine has a half-life of two hours. This means that the nicotine level in the blood decreases by half every two hours as nicotine is quickly and efficiently metabolized in the liver. Regular smoking over six to eight hours nevertheless causes nicotine to accumulate in the organism. The metabolite of nicotine, cotinine, is metabolized much more slowly; it has a half-life of 17 to 19 hours and is therefore detectable for a much longer time. Cotinine can be detected in the blood, but also in urine and saliva and allows assessing how much nicotine was consumed.[5,8]

Intake by inhaling is the most efficient way of delivering nicotine: nicotine is absorbed via the extensive lung epithelium from where it directly enters the pulmonary venous circulation and reaches the brain within 10 to 20 seconds[8,9,62]. The faster nicotine is absorbed and reaches the brain, the greater the pleasant experience it gives and the faster the substance leads to addiction[9].

E-cigarettes are comparable to tobacco cigarettes regarding the delivery of nicotine: e-cigarette consumers inhale around 90 percent of the nicotine contained in the aerosol. Nicotine from e-cigarette aerosol is quickly absorbed in the lung: the maximum nicotine concentration in the blood can be reached just as fast and at the same level as that in the blood of smokers[79].

If nicotine is absorbed via the gastrointestinal tract instead of the lungs, around 80 percent of the nicotine are metabolized to cotinine in the liver before reaching the brain. Nicotine products used for smoking cessation work at an intake route between these two extremes. They deliver nicotine in such a way that it enters the blood in an effective concentration, but is absorbed slowly: the nicotine is absorbed via the oral and nasal mucous membranes with sprays, inhalers, gums and lozenges or via the skin with transdermal patches[81].

Health effects of nicotine

Nicotine and cognitive abilities

Animal tests show that nicotine-sensitive ACh receptors play an important role in processes that control the attention and related performances of the short-term and working memory. Studies with humans who were administered nicotine replacement therapy products evidence that nicotine increases the cognitive performance of adult non-smokers: in the short-term, it raises the attention and improves the memory (working memory and short-term memory).[87]

In dependent smokers, however, nicotine probably does not produce any enhancement of the cognitive performance, but merely provides relief from withdrawal symptoms. Typical withdrawal symptoms are negative affects (emotional disorders) such as anxiety and depression and a reduced memory performance as well as attention deficits. These attention deficits show as early as 30 minutes after the last cigarette and are potentially related to the negative affective symptoms.[87]

Dependence

The dependence results from the interaction of several factors and comprises a physical and a psychological element. According to the internationally accepted medical diagnosis system ICD-10 (International Statistical Classification of Diseases and Related Health Problems) tobacco dependence exists if at least three of the following six criteria occur jointly: strong craving (necessity), withdrawal symptoms caused by an interruption or reduction of consumption, uncontrolled consumption, evidence of tolerance, consumption despite negative physical consequences, changes in one's pace of life for the purpose of obtaining, using and recovering from consumption.[96]

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Physical dependence

The decisive factor for physical dependence is the effect of nicotine on the brain: it binds to nicotinic ACh receptors located, among others, on dopamine neurons in the ventral tegmental area (VTA) and stimulates the release of dopamine in the nucleus accumbens (NA), a critical component of the brain's reward system[11]. Dopamine is a neurotransmitter and enables interneuronal communication. The release of dopamine is supported by a nicotine-induced release of other neurotransmitters in these brain areas, in particular by GABA (gamma-aminobutyric acid) and glutamate[4,48]. The increased dopamine level in the reward system signals a pleasurable experience. This is the first step into dependency as this experience promotes further nicotine consumption[56] (Fig. 2). Repeated consumption causes the brain to get used to nicotine and develop a tolerance that leads to physical dependence and withdrawal symptoms. As a consequence of chronic nicotine intake the existing nicotinic ACh receptors become less sensitive (desensitization/inactivation)[6,11,90]. This makes it increasingly difficult to stimulate the reward system as only high nicotine levels can activate a desensitized or inactive receptor[24,56].

Acting against this tolerance is the upregulation (increase in number) of nicotinic ACh receptors[34]. This excess of nicotinic ACh receptors is dose-dependent and leads to withdrawal symptoms: as soon as a critical number of ACh receptors is no longer occupied by nicotine (around four to six hours after nicotine consumption) a stress hormone (corticotropin-releasing factor, CRF) is released[24,30,37]. This hormone activates the extended amygdala, a brain area that conveys symptoms that are typical for withdrawal such as irritability, lethargy, depressed mood, restlessness, and anxiety[11,46,49].

This means that, initially, the dependence is based on the craving for the quick pleasure caused by dopamine. Later, the predominant wish is to reinstate the normal condition and avoid physical withdrawal symptoms[29].

Psychological dependence

In parallel to the nicotine-induced release of dopamine in the nucleus accumbens, dopaminergic neurotransmissions stimulate an area in the prefrontal cortex that is involved in learning processes. The disastrous consequence: smoking and its perceived positive effect is associated with certain situations (a cup of coffee in the morning, a good meal or a conversation with friends, an evening at the pub) and actions connected to smoking (taking out the cigarette), sensory perceptions while smoking (smell, taste, feel of the smoke in the throat), and with affective conditions (stress, sadness). The repeated association modifies neuronal connections in the brain resulting in a long-lasting conditioning to these stimuli. This leads to psychological dependence and makes it so difficult to quit because certain stimuli and situations can elicit the craving for a cigarette.[11,61,85]

Increasing the addictive potential of nicotine by way of other substances in tobacco smoke

Tobacco additives can directly or indirectly increase the addiction potential of nicotine (Fig. 3). Ammonium, for example, enhances the biological availability of nicotine by raising the pH of the tobacco and thus of the smoke. At a higher pH, nicotine is increasingly found as a free, uncharged substance that is more easily absorbed by the cells and, consequently, increases the nicotine level in the blood. When the sugar contained in the tobacco is burnt, the combustion products are

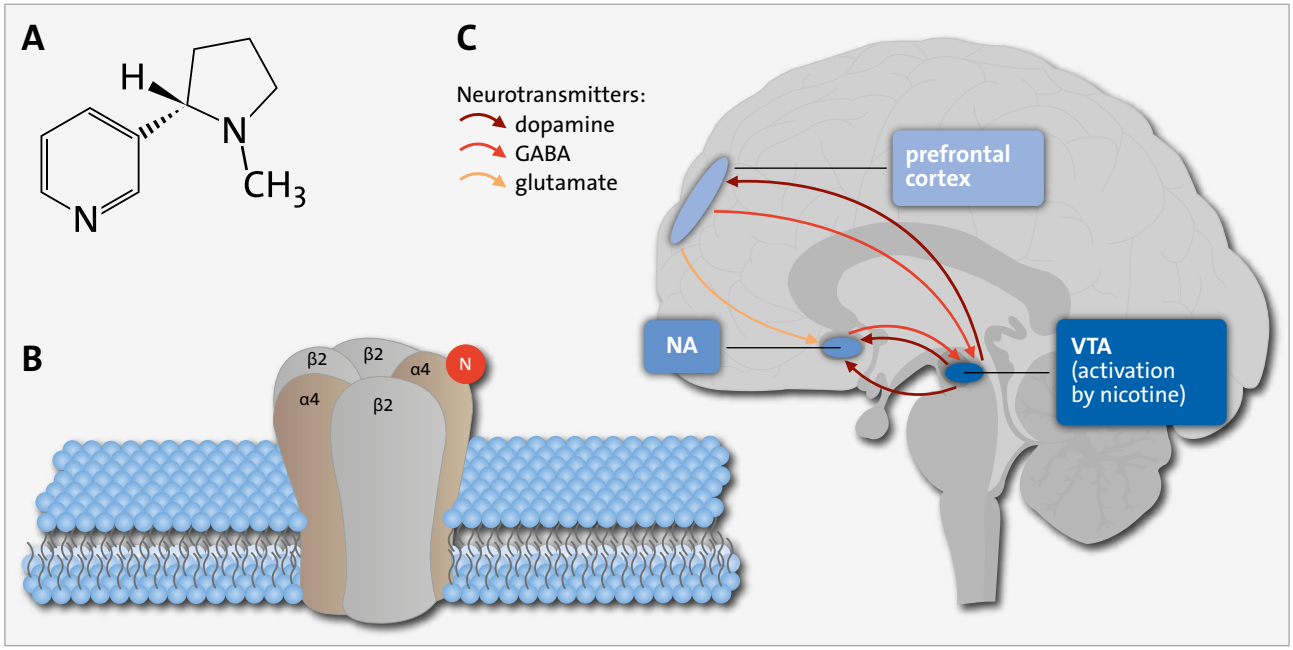

Figure 2: Nicotine, nicotinic acetylcholine receptor and nicotine addiction. A: Structural formula of nicotine; B: Schematic representation of a nicotinic acetylcholine receptor (nAChR); C: Nicotine binds to nAChRs in the ventral tegmental area (VTA) of the brain and induces a dopamine release in the nucleus accumbens (NA) and the prefrontal cortex. Further transmitter systems (GABA and glutamate) get involved. Activation of the prefrontal cortex and other brain areas associated with learning and memory lead to psychological addiction. Source: Benowitz 2010[11]. Illustration: Unit Cancer Prevention, German Cancer Research Center.

found in the smoke. One of these products is acetaldehyde. Animal testing evidenced that acetaldehyde increases the addiction potential of nicotine. The acetaldehyde presumably inhibits a protein in the brain (monoamine oxidase, MAO) that metabolizes dopamine and thus plays a role in regulating the dopamine level. Also the addition of tryptophan may potentially increase the effect of nicotine: tryptophan is suspected to react with the aldehydes contained in tobacco smoke and in the process form two substances, harman and norharman, that increase the addictive potential of nicotine by inhibiting monoamine oxidase. Other tobacco additives have an indirect influence on the addictive potential of nicotine: essential oils such as menthol or thymol have a slightly anesthetizing effect on the throat and mask the taste of tobacco. This leads to deeper inhalation of the smoke and thus to higher nicotine levels. Menthol is not only contained in menthol cigarettes, but also added to other cigarettes in small amounts so that the characteristic taste is not perceptible but the inhalation-enhancing effect remains[32]. Pyrazines, too, have a slightly anesthetizing effect on the throat[1]. The tobacco additive theobromine possibly has a bronchodilating effect and could thus facilitate the intake of nicotine.[67]

Nicotine and brain development

In sensitive phases of brain development, the connections between the nerve cells are increasingly established and specific neural circuits are formed. During this period, the brain undergoes major changes and is therefore particularly sensitive. One such sensitive phases is the fetal phase, others are puberty and early adulthood.[14,33]

Tobacco smoke contains more than 5,000 substances[63]. This makes it difficult to single out individual substances that are responsible for certain effects. Nevertheless, countless studies evidence that nicotine – the main psychoactive substances contained in tobacco smoke – has a detrimental effect on the developing brain that may lead to irreversible changes.[13,22,23,87,93,101]

Nicotine consumption during pregnancy

Around the world, about 10 to 23 percent of pregnant women smoke (in Germany, the figure is around 12 percent[47]). Of those who try to quit, only about half stay permanently nicotine-free.[94] There is growing evidence that not only the tobacco smoke, but also nicotine alone, has a longlasting and seriously adverse effect on the progression of pregnancy as

Tobacco additive	Effect in the tobacco product	Effect on nicotine metabolism and addiction
Ammonium	Increases pH of tobacco and tobacco smoke.	Increased pH leads to increased bioavailability of nicotine and thus higher nicotine uptake.
Sugars	When sugars in the tobacco product are combusted, various aldehydes (i.e. acetaldehyde) are generated. Acetaldehyde is claimed to increase addictiveness of nicotine in a synergistic way by inhibiting an enzyme that degrades transmitters involved in the addiction-metabolism.	Nicotine increases the levels of transmitters in certain brain areas. Transmitter levels stay elevated over a sustained period due to impaired metabolization of transmitters.
Tryptophan	Reacts with aldehydes and forms beta-carbolines. Beta-carbolines are claimed to increase addictiveness of nicotine in a synergistic way by inhibiting an enzyme that degrades transmitters involved in the addiction-metabolism.	Nicotine increases the levels of transmitters in certain brain areas. Transmitter levels stay elevated over a sustained period due to impaired metabolization of transmitters.
Essential oils (menthol, thymol, etc.)	Menthol and other essential oils have a cooling and anesthetic effect on mucosal surfaces of mouth and throat and cover the harshness and taste of tobacco smoke.	Harshness and irritating effect of tobacco smoke are reduced and thus inhalation of tobacco smoke is facilitated. This leads to deeper inhalation (inhalation of a larger volume) and thus higher nicotine uptake.
Pyrazines	Pyrazines have a cooling and anesthetic effect on mucosal surfaces of mouth and throat.	Harshness and irritating effect of tobacco smoke are reduced and thus inhalation of tobacco smoke is facilitated. This leads to deeper inhalation (inhalation of a larger volume) and thus higher nicotine uptake.
Theobromine	Theobromine is a bronchodilator.	Opened/Broadened airways lead to deeper inhalation (inhalation of a larger volume) and thus higher nicotine uptake.

Figure 3: Tobacco additives enhancing the addictiveness of tobacco products. Selection of substances in tobacco that enhance nicotine induced addiction. Sources: Alpert 2015[1], Giovino 2004[32], Scientific Committee on Emerging and Newly Identified Health Risks 2010[67]. Illustration: Unit Cancer Prevention, German Cancer Research Center.

Gateway theory: nicotine as a gateway for further drug addictions

In western societies, drugs are frequently consumed in a certain sequence, starting with nicotine and alcohol to marihuana to cocaine and other illicit drugs. The gateway theory states that this sequence of drug consumption is based on the fact that certain "soft" drugs such as nicotine precede more the use of "harder" drugs like cocaine. Another theory attributes the consumption of several drugs to a genetically and environmentally conditioned disposition for drug consumption and addiction.[89]

Various studies support the gateway hypothesis. By way of experiments, the research group around Denise Kandel – the originator of the gateway hypothesis – found a molecular mechanism by which nicotine acts as a gateway drug: in mice, nicotine loosens the DNA packaging system thereby enabling the transcription of a gene that is decisive for creating drug addiction. Mice who had been given nicotine via their drinking water for seven days reacted more strongly to a cocaine injection than mice whose water did not contain nicotine. This boosted response showed in the behavior, in the interneuronal communication of the nucleus accumbens, the amygdala and the hippocampus – brain areas connected to various aspects of drug addiction – and in the gene expression and enzyme activity in the nucleus accumbens. This effect is unidirectional: only nicotine boosts the effect of cocaine – not the other way around. Epidemiologic studies suggest that this mechanism also works in humans: cocaine addiction is most frequently found among those cocaine consumers who had already been smokers before they started consuming cocaine. Among those who started smoking after consuming cocaine, much fewer were addicted to cocaine.[45]

well as on the health of the unborn child and its cognitive performance later on in life.[13,22,23,55,87]

Pregnant women consume nicotine not only via cigarettes, but also via nicotine-replacement therapy products (nicotine patches, etc.) or via nicotine-containing products such as e-cigarettes.[93] Since, for ethical reasons, no studies on humans about the isolated effect of nicotine during pregnancy on the development of the unborn child and, later, of the infant/adolescent exist, most results in this context are based on animal tests. Also studies with pregnant women using nicotine-replacement therapy products to stop smoking are not able to exactly determine the effect of nicotine as many users at the same time continue consuming cigarettes[13]. Studies involving pregnant women consuming smokeless tobacco can exclude the substances contained in cigarette smoke, but not the substances contained in the tobacco.

Consequences for the unborn child and infants: studies on the use of nicotine-replacement therapy products during pregnancy could not evidence whether and to what extent nicotine contributes to the lower birth weight of babies of smoking mothers[13,93]. Studies conducted with women consuming smokeless tobacco during pregnancy indicate that nicotine also plays an important role in humans when it comes to processes leading to tobacco-related preterm birth and stillbirth[3,39,87,92].

A large number of animal studies show that nicotine has a neuroteratogenic effect during pregnancy, meaning that it affects the brain development of the unborn child[13,75]. The Sudden Infant Death Syndrome (SIDS) is the most frequent cause of death in babies during their first year of life and probably owed to an impairment of breathing control and waking reactions. Smoking during pregnancy causes increased breathing arrests while sleeping and a reduced waking response[58,66]. According to estimates, one third of all SIDS cases are attributable to maternal smoking[54]. Also the consumption of smokeless tobacco during pregnancy increases the risks of postnatal apnoea at a rate comparable to that of cigarette exposure. Extensive animal studies confirm the role of nicotine in SIDS[13,21,22,66,74,76].

Consequences for children and adolescents: smoking during pregnancy is associated with behavioral problems of children such as ADHS (attention-deficit/hyperactivity syndrome), learning disabilities, behavioral disorders and a higher risk of dependency[13]. Studies in humans about the long-term effects of nicotine exposure during pregnancy on the future development of children are not available. This impact has nevertheless been excellently documented by animal research. Rats and mice exposed to nicotine in the uterus show long-term health consequences that are also found in children of smoking mothers: a changed reaction to nicotine and other drugs, changed survival of neurons, disturbed formation of synapses, hyperactivity, anxiety, cognitive and somatosensory deficits[13,22,58]. The results of the animal tests strongly suggest that nicotine causes long-term disruptions that are associated with prenatal smoking[13,58,87].

Nicotine consumption during adolescence

The pubescent brain is subject to significant changes. At the beginning of the puberty period, the brain structures of the limbic system responsible for emotional processing undergo a hormone-induced maturation. As part of this maturation social behaviors and sexuality develop. The brain continues to mature rapidly also during early adolescence: structures that control higher cognitive performance mature independently of hormones, based on experience.[31,60,77] That is the reason why pubescent teenagers, while being exposed to strong emotions, still lack the cognitive skills of self-control and responsible decision-making. This imbalance explains characteristics that are typical for adolescents like emotional fluctuations, suggestibility to peer pressure and increased impulsive and risk-taking behavior which, all taken together, increase the probability that young people experiment with addictive substances.[28,57,78] Accordingly, most smokers start smoking in their youth[86].

In the adolescent, nicotine activates nicotinic ACh receptors on developing brain structures and can thereby affect the maturing of emotional and cognitive processes[22,33]. This can have long-term consequences: smoking at a young age is associated with irreversible cognitive impairments and

behavioral disorders relating in particular to the working memory and to attention. Animal research indicates that nicotine could be responsible for the effects observed in adolescents: in adolescent rats, nicotine leads to particularly strong changes of the neuronal genetic expression causing structural and functional changes in the brain and having a persistent effect on the behavior of the animals.[22,23,101]

Nicotine and lung development

Lung development begins at the embryonic stage and extends into young adulthood. Prenatal smoking damages the lung of the unborn child and thereby affects lung development into childhood and beyond.[13,87]

Studies on various animals – including rhesus monkeys whose lung development is similar to that of humans – indicate that the nicotine contained in cigarette smoke is co-responsible for the disrupted lung development in children exposed to tobacco smoke before birth[13]. In the lung of the unborn child, nicotine binds to the ACh receptors on various cells of the respiratory tract[59]. In unborn rhesus monkeys, the activation of such cells by nicotine results in changes to the elasticity of the lung[26,68,69,82]. The exact molecular mechanisms by which nicotine affects lung development are not yet clear.

Nicotine and the immune system

Some cells of the immune system (lymphocytes, macrophages and dendritic cells) carry nicotine-sensitive ACh receptors which are usually activated by endogenous acetylcholine, thereby regulating the response of the immune system. The release of endogenous acetylcholine into the circulatory system can be stimulated by nicotine. But nicotine can also assume the role of acetylcholine itself and directly activate immune cells.[53,71-73,91] Via the ACh receptors, nicotine affects both, the development of immature and the activation of mature immune cells. Over and beyond this, nicotine controls the number of ACh receptors on the cell surface and thus the sensitivity of the cell to acetylcholine and nicotine: the lymphocytes in the blood of smokers express more ACh receptors than the lymphocytes in the blood of non-smokers[18]. Animal tests have evidenced that nicotine is responsible for this[18]. Nicotine also affects the availability of the neurotransmitter serotonin in the blood. Serotonin, like acetylcholine, controls important immune response processes[17].

Across all these processes, nicotine can both stimulate and also suppress the immune response – depending on the quantity and frequency of use[17]. Despite the complex and contradictory effect of nicotine there is growing evidence that nicotine mainly has a negative impact on the cellular immune response: animals infused with nicotine are more vulnerable to viruses and bacteria. Smokers, too, are often more vulnerable to infections. However, it is difficult to prove to which extent nicotine contributes to a weakening of the immune system because the effect of a single substance on smokers cannot be isolated from the effect of other substances contained in cigarette smoke, and their interactions. In cell cultures, however, it was evidenced that nicotine reduces the production of cytokines.[2,17,80] Cytokines are messengers of the immune system and play an important role in inflammation processes. As a consequence of cytokine deficiency smokers suffer from abnormal inflammation processes that are potentially owed to a strongly increased susceptibility to infections of the respiratory tract[2,80].

Nicotine and cardiovascular diseases

Cardiovascular diseases represent the most common cause of death worldwide and account for about one third of all mortalities[97]. Most cardiovascular diseases are caused by atherosclerosis, i.e. a hardening and narrowing of arteries caused by plaque. The risk of a coronary heart disease and stroke for smokers is double to four times that of non-smokers.[85,87]

Nicotine is suspected to negatively impact the cardiovascular system in two ways: via the activation of the sympathetic nervous system and via the activation of the nicotinic ACh receptors on the cells that form the blood vessels.

The function of the sympathetic nervous system is to stimulate the body's reaction response in stress situations by adjusting the respiration, metabolism and digestion as well as the blood pressure. Nicotine activates the sympathetic nervous system and thereby increases the strength and frequency of the heart rate and the resistance of the coronary vessels. This can raise the speed of the blood flow and increase the blood pressure over the long term. These blood flow effects are found in humans after an intravenous administration of nicotine and after the use of nicotine patches or nicotine gums and are similar to the effect of smoking[7]. Long-term high blood pressure is a risk factor for atherosclerosis.

Nicotine does not only activate the sympathetic nervous system, but also acts directly on the blood vessels. Experiments with cell cultures and animals show that nicotine binds to the nicotinic ACh receptors of cells that form the blood vessels. Nicotine affects the proliferation, differentiation and survival of these cells as well as their migration within the blood vessels and the formation of new vessels. These processes, which are usually activated by the body's own acetylcholine, activate the development of new blood vessels (angiogenesis). The angiogenesis induced by nicotine is suspected to trigger and promote atherosclerosis. In this context, also the effect of nicotine on inflammation processes comes into play.[19,41,87,100,102]

It is difficult to prove the atherosclerotic effect of nicotine with studies on humans. Meta-analyses on the cardiovascular health of snus consumers (snus is a smokeless tobacco) show that these have a risk of heart attack comparable to that of people who do not consume any form of tobacco[12,40,51]. Since snus has a similar nicotine content as cigarettes, these results indicate that there is no relationship between nicotine and acute heart attacks. Nicotine patches do not have any influence on the risk of cardiovascular diseases either[36]. Even for smokers with a pre-existing cardiovascular condition no increased risk for cardiovascular diseases could be found that was attributable to the long-term use of nicotine gum or nicotine patches[15]. However, it must be borne in mind that nicotine-replacement therapy products are used by smokers to give up smoking or reduce cigarette consumption. In case of a simultaneous use of nicotine-replacement therapy products and cigarettes, the effects of smoking (i.e. of the nicotine and other substances contained in cigarette smoke) mask any potential effects of the nicotine contained in these

products[7]. Adequately designed studies on the effects of a long period of nicotine consumption on the health of former smokers and non-smokers would be informative, but are not available[70].
In animal tests, by contrast, nicotine is evidenced to initiate atherosclerosis and support its progression[41,50,102].

Nicotine and metabolic disorders: Type 2 diabetes and obesity

In type 2 diabetes, the cells become insensitive (resistant) to insulin and the pancreas loses its capability to produce sufficient insulin. As a consequence, the blood sugar level cannot be maintained. The cause for type 2 diabetes is probably found in the death or malfunctioning of the insulin-secreting cells (beta cells). Smokers run a significantly higher risk of developing type 2 diabetes.[85,87]
Nicotine appears to be the substance contained in cigarette smoke that is responsible for the strongly increased disease risk of smokers. ACh receptors are found on the insulin-producing cells that can be activated by nicotine[99]. In studies with humans and in animal studies it showed that both, the short-term and the long-term nicotine exposure negatively impacts the effectiveness of insulin and could thereby trigger insulin resistance[13,98]. Nicotine reduces the insulin release from beta cells in humans and animals. In animal tests, insulin was found to reduce the function of the beta cells – especially in the fetus or newly born – thereby promoting their cell death. Possibly, nicotine this way also contributes to the progressing insulin deficiency of type 2 diabetes in humans.[13,87]
The hypothalamus – the brain region which, besides other vital functions, also controls the appetite and weight regulation – contains many nicotinic acetylcholine receptors. Animal tests indicate that nicotine consumption during pregnancy negatively affects the prenatal development of the hypothalamus and may thereby lead to overweight and obesity during childhood.[13,87]

Nicotine and cancer

The formation of cancer (cancerogenesis) is a continuous and extremely complex process. This process is initiated by factors causing alterations in the genetic material (mutations) and stimulated by further factors that promote the growth of these altered cells and, eventually, the development of cancer. Cell culture tests, tissue and animal models demonstrate that nicotine can both cause and promote cancer. Adequate human studies are missing, however.[35,65,87]

Formation of cancer

In cell culture assays, nicotine in concentrations similar to those found in the blood of smokers was found to cause damage to the genetic material in isolated human white blood cells that is associated with a cancer risk. In addition, nicotine damages the genetic cell material of human salivary glands, nasal mucous membranes and bronchia. Nicotine contributes to cancerogenesis by disrupting cellular metabolic processes through activation of the ACh receptors, promotes the formation of oncogenes, and inactivates tumor suppressor genes. Oncogenes are genes that transform healthy cells into cancer cells under certain conditions; tumor suppressor genes are genes that protect the cell from this fate by inhibiting an uncontrolled cell reproduction. A nicotine concentration corresponding to that contained in the blood of smokers negatively regulates the programmed cell death, a mechanism that causes defective cells to destroy themselves, promotes the growth of cancer cells, and activates cell proliferation and cell migration – all these processes are associated with the onset of cancer. In addition, nicotine enhances the cells' mobility and triggers the transformation of a cell into a cancer cell that migrates into neighboring tissue (highly invasive carcinoma cell) and thereby potentially contributes to metastatic spread.[35,65,87]
A study on mice shows that nicotine can also cause cancer in living organisms: the majority of the mice that regularly received subcutaneous nicotine injections for a period of two years developed cancer (muscle sarcoma)[27]. The dose corresponded to the nicotine consumption of regular chewing tobacco users. This notwithstanding, other animal tests showed that the long-term intake of nicotine via drinking water does not promote the onset and growth of lung tumors in mice. The nicotine concentration in the blood of the mice corresponded to that of humans using nicotine-replacement therapy products. A study on humans did not find any correlation between the long-term consumption of nicotine-replacement products and cancer. However, this study was not designed to examine this aspect.[35,65,87]

Progression of cancer

Nicotine extends the life of cancer cells and promotes their proliferation and migration. In addition, nicotine creates a cancer-supporting environment. A tumor can only continue to grow if the tumor tissue has blood vessels through which it receives more nutrients and oxygen. Tumor cells produce molecules that promote the sprouting of existing blood vessels (angiogenesis). In tests conducted with tissues from lung, breast and colon cancer, nicotine was found to induce the angiogenesis and thereby double the growth rate of tumor tissue. In animal tests, nicotine raised the number and size of lung tumors (previously induced by a different substance) and promoted their proliferation metastasis. When implanting human tumor tissue in mice, nicotine was found to promote their growth rate and spread.[35]

Nicotine and cancer therapy

Tests with tumor cells indicate that nicotine negatively impacts the success of cancer therapies. Nicotine reduces the effectiveness of chemotherapeutic drugs in different cancer cell lines and enhances the survival of lung cancer cells subjected to radiotherapy. Also in animal tests nicotine was found to reduce the effectiveness of chemotherapy and radiotherapy.[65]

Acute toxicity of nicotine

The toxic effect of nicotine depends on a number of factors. These include the route of administration, a possible addiction, the development phase (child or adult) and the health condition of the consumer. Data on the acute toxicity of nicotine – i.e. the toxic effect that shows within a few seconds to several days after intake – for the human body originate from animal tests, poisoning case studies and from studies

on therapeutic applications of nicotine, like for example in tobacco cessation with nicotine patches. According to these data, nicotine may lead to mild poisoning symptoms ranging from nausea to vomiting and, in case of a stronger exposure, to diarrhea, increased salivation, deceleration of the heart rate (bradycardia) and increased formation of respiratory secretions. Serious poisoning symptoms are respiratory depression, epileptic seizures and death[5,87]. However, nicotine poisoning is only very seldom lethal as the oral intake of nicotine frequently causes vomiting and thus prevents the ingestion of a lethal dose. The widespread assumption that the lethal dose of nicotine for humans amounts to about 60mg is based on poorly documented self-experiments dating back to the 1850s. From the few incidents where people actually died as a consequence of an intentional or accidental ingestion of nicotine it can be derived that the lethal amount of nicotine for humans amounts to about 6.5 to 13mg per kilogram of body weight.[52] Accordingly, the lethal dose for an adult with a body weight of 60kg would be 390 to 780mg.

Key messages

- The fastest and most effective way to deliver nicotine to the body is via the lung (inhalation) after which it reaches the brain within just a few seconds.
- Nicotine acts on certain brain areas and leads to physical and psychological dependence.
- One important aspect of the psychological dependence is the conditioning to key stimuli that make it very difficult for smokers to quit.
- Smoking during pregnancy is associated with premature births and stillbirths as well as the Sudden Infant Death Syndrome. Animal tests show that nicotine plays a role in this context.
- Smoking during pregnancy negatively affects the brain development of the unborn child and is associated with behavioral disorders later on in life. Animal tests show that nicotine plays a role in this context.
- Smoking during pregnancy has a long-term negative effect on the lung development of the unborn child. Animal tests show that nicotine plays a role in this context.
- Smoking during puberty and early adulthood negatively affects brain maturation and is associated with behavioral disorders in adulthood. Animal tests show that nicotine plays a role in this context.
- Nicotine in many ways alters the immune response and is probably responsible for the increased susceptibility of smokers to infections.
- Smoking increases the risk of type 2 diabetes. Animal tests and cell culture tests show that nicotine plays a role in this context.
- In animal tests, nicotine consumption during pregnancy increases the obesity risk of the offspring.
- Nicotine activates the sympathetic nerve system and thereby increases the speed of the blood flow. In addition, nicotine initiates the sprouting of blood vessels. Via these two effects, nicotine probably causes atherosclerosis and contributes to its progression.
- In cell culture tests as well as in tissue and animal models nicotine was found to both initiate and also promote cancer.
- Cell culture and animal tests show that nicotine reduces the effectiveness of chemotherapy and radiotherapy.
- Nicotine is toxic. The acute poisoning symptoms for adults are dependent on the dose and range from nausea and vomiting to respiratory distress and epileptic seizures and (in rare cases) to death.

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