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Mini Review

# Cigarette smoke – an aging accelerator?

David Bernhard [a,*], Christina Moser [b], Aleksandar Backovic [a], Georg Wick [a]

[a] *Vascular Biology Group, Division Experimental Pathophysiology and Immunology, Biocenter, Innsbruck Medical University, Fritz-Pregl-Str. 3/4. OG. 6020 Innsbruck, Austria*
[b] *General Hospital, Kufstein, Endach 27, A-6330 Kufstein, Austria*

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**Abstract**

Cigarette smoking reduces life span by an average of 7 years, and tobacco consumption accounts for a shortening of disease free life by 14 years. The exact mechanisms by which smoking causes disease and death are generally not well understood, but evidence continues to mount that cigarette smoking exhausts cellular defense and repair functions, leading to an accumulation of damage e.g. mutations and malfunctioning proteins. In this review, we make an attempt to ascribe many of the deleterious effects of smoking on human health to a general principle, namely the acceleration of aging processes by cigarette smoke chemicals.


*Keywords:* Senescence; Extrinsic aging; Intrinsic aging; Smoking; Cigarette smoke; Tobacco; Cardiovascular; Endothelial; Oxidants; Radicals; Mutagens; Osteoporosis; Cancer; Skin; In vitro; Pre-mature; Cellular; Aging; Ageing

## 1. Introduction

At the moment approximately 1.25 billion people in the world are smokers. Half of those who smoke today will be killed by tobacco related diseases, making smoking one of the most relevant health problems. It is estimated that by the year 2020, 8.4 million human lives per year will be extinguished by cigarette smoking. Calculations show that chronic smoking reduces the life span of humans by an average of 7 years (WHO, 2004). The early death of smokers is usually classified as "pre-mature" death which is of course correct. However from a scientific point of view there is evidence that smokers show patterns of accelerated aging, and that the biological age at death may well be the same as of non-smokers who die 7 years later. Similarly, diseases free life is reduced by up to 14 years due to smoking (WHO, 2004). The most relevant diseases that cause this increase in morbidity are classical age-related diseases like osteoporosis, cancers, macular degeneration, and cardiovascular diseases. As in the normal aging process, the individual genetic background determines which organs are most sensitive to damage and consequently become diseased. This review should be seen as a collection of data in support of the hypothesis that cigarette smoking accelerates the aging process of the human body. We highlight chemicals and pathophysiologically relevant mechanisms underlying smoking- and aging-related diseases, and point at analogies between both phenomena.

## 2. Chronic smoking and aging at the molecular level

### 2.1. Smoke chemicals

Cigarette smoke contains more than 4000 different chemicals, most of which are generated during the combustion process in the cigarette (Burns, 1991). This cocktail of chemicals is then inhaled by the smoker (for an overview see (Bernhard and Wick, 2006)). Consequently, the first organs that come into contact with noxious agents are the oral and nasal cavities followed by the upper respiratory tract and the lung. Hydrophobic compounds (the tar fraction of cigarette smoke) that precipitate in the oral

* Corresponding author. Tel.: +43 512 9003 70968; fax: +43 512 9003 73960.
*E-mail address:* David.Bernhard@i-med.ac.at (D. Bernhard).

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cavity are swallowed and thereby reach the digestive system from the luminal side. Inhaled compounds are further "filtered" by precipitation on the surfaces of the respiratory tract. Since hydrophobic agents, like polycyclic aromatic hydrocarbons (PAHs) can diffuse across cellular membranes and cell layers, precipitate-contained chemicals can penetrate the mucosal linings and reach the circulation, and consequently all organs of the body, including the skin. The volatile, mainly hydrophilic, fraction reaches the alveoli and either diffuses directly across the extremely complex lung–blood barrier is transported through the lung–blood barrier, or is retained in the lung. After having entered the circulation, smoke chemicals (hydrophilic and hydrophobic) enter biochemical (albumin) and cellular (erythrocytes) transport systems, or are dissolved in serum (Bernhard and Wick, 2006). Accordingly, many of these agents can enter organs, deposit, and cause damage. Cigarette smoke contained Cadmium (Cd) for example, is deposited in the vasculature (intima and media) and in renal tubules (Bernhard et al., 2005). This process occurs physiologically with aging because Cd is also a constituent of normal nutrients. However, tobacco smoke – the most important source for Cd – accelerates this process which may lead to atherosclerosis and reduced renal function (Bernhard et al., 2005, 2006). Further cigarette smoke chemicals come into contact with detoxification systems such as the enzymes of the cytochrome P450 family or oxidant detoxification systems (hemeoxygenase (HO), superoxide dismutase (SOD), or paraoxonase) (Beckman and Koppenol, 1996). In the case of PAHs, the body's detoxification systems (cytochrome P450) may convert these compounds into even more dangerous and mutagenic agents (Thirman et al., 1994).

### 2.2. Processes in cigarette smoke-accelerated aging

Radical- and oxidant-mediated modification of proteins, nucleic acids, lipids, sugars, and consequent damage of cells play crucial roles in the genesis of a large number of age-related diseases. This accumulation of (oxidative) damage constitutes per definition a major principle in most models for aging. Analyses of cigarette smoke reveals that tar contains $>10^{17}$ long lived radicals per gram, and the volatile fraction contains $>10^{15}$ short lived reactive radicals per gram (Pryor and Stone, 1993; Pryor et al., 1998). By delivering a broad range of different – mainly carbon and nitrogen centered – radicals and oxidants to the human body, smoking accelerates the pace of oxidative damage. This modification of biological molecules towards a malfunctioning state reflects a typical aging process, fitting into the definitions of extrinsic aging. Prolonged consequences of these biomolecular modifications result from mutations that "memorize" the damage, and relay the damaged (i.e. aged) information to descending cell generations. As a result, malfunctioning proteins are produced that may, for example, induce tumor development.

The body has evolved a range of defense mechanisms that counteract alterations of the physiological state occurring in the course of aging. Cigarette smoke chemicals interfere with these mechanisms in a twofold fashion. First, smoke chemicals increase the number of repairs required from the defense machinery by increasing the number of damaged sites. Second, smoke chemicals interfere with the defense machinery itself, and reduce its efficiency. For example, the concentration of factors like serum selenium and zinc, which play vital roles in oxidant-defense, are reduced by smoking (Chiba and Masironi, 1992; Kafai and Ganji, 2003). Cigarette smoke exhausts physiological "anti-aging" systems via these two principles, and thereby also increases the pace of aging.

Typical reactions via which cigarette smoke chemicals modify biomolecules include oxidation-reactions (e.g. oxidation of low density lipoprotein and glycoxidation of extracellular matrix), as well as the formation of bulky adducts (e.g. PAHs attaching to DNA). This results in defective cellular signaling, the accumulation of adversely functioning proteins, the deposition of these proteins both intra and extracellularly (Heitzer et al., 1996; Dickerson and Janda, 2002). In an experiment where we analyzed the effects of cigarette smoke chemicals on vascular endothelial tissue (see Fig. 1), we were able to observe a browning of vascular tissue in response to the treatment. This reaction could be inhibited by applying the anti-oxidant *N*-acetyl cystein, indicative of a direct chemical modification (oxidation) of the tissue. This browning reaction (the so called Maillard reaction) also occurs during the normal aging process in, for example, cartilage tissue. In a similar experiment, we directly tested for the formation of

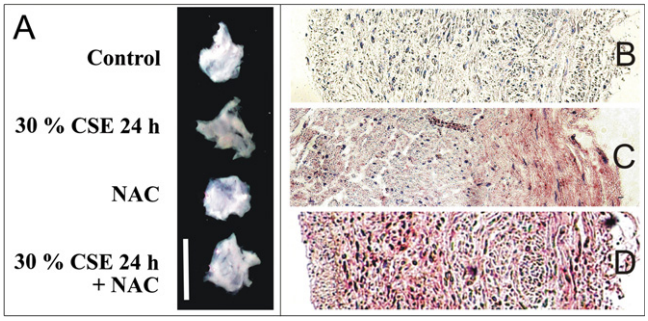


Fig. 1. Maillard reaction and AGE-formation caused by cigarette smoke chemicals in vascular tissue. The left panel (A) shows an experiment where a human umbilical vein was cut into pieces and immobilized on a silicone surface with the endothelial side up. The venous fragments were incubated for 30 min with or without 1 mM *N*-acetyl cystein (NAC) and consequently for an additional 24 h with or without cigarette smoke extract (CSE). The white bar indicates 0.5 cm. The images on the right side show an immunohistochemical staining of advanced glycation endproducts (polyclonal anti-AGE antibody, Abcam, UK) of human umbilical artery tissue treated with or without 8% CSE for 24 h. Subsequently, the tissue was embedded into paraffin and sections were prepared. Sections were immobilized and stained with hematoxylin (nuclei), and isotype antibodies (B) or the anti-AGE antibodies (C and D). Image B, isotype control; image C, AGE-staining of control treated artery; image D, AGE-staining of CSE treated artery. Representative images are shown.

advanced glycation endproducts in arterial tissue (Fig. 1 images B–D). This experiment showed that cigarette smoke chemicals clearly induce the formation of advanced glycation endproducts, representing aged proteins.

Apart from altering biomolecular structures, cigarette smoke chemicals were shown to increase the number of cell divisions of non-transformed cells (Yu et al., 2006). This characteristic of cigarette smoke may promote tumor-development and also lead to accelerated aging by causing cellular senescence. The earlier onset of cellular senescence is underlined by the ex vivo observation of reduced telomere length in lung cells and lymphocytes of smokers compared to non-smokers (Morla et al., 2006).

## 3. Chronic smoking and age-related diseases

### 3.1. Skin aging

Although the appearance of wrinkles is not considered a disease, they are a paradigmatic sign of skin aging. Cigarette smoking has clearly been shown to cause pre-mature skin aging (Frances, 1998). Skin aging, however, is thought to account for a considerable number of deaths, as various tumors of the skin e.g. squamous cell carcinoma, and reduced wound healing are results of skin aging (Frances, 1998; Freiman et al., 2004). Smoking reduces wound healing – similar to other effects of cigarette smoke – via a range of different mechanisms (Silverstein, 1992). This observation was made for the first time in 1966 and has since been extensively documented. The most important mechanism was ascribed to the reduction of the blood flow in the skin, resulting in a reduced supply of the wound with oxygen and nutrients, leading to a prolonged healing period (Freiman et al., 2004; Roppo et al., 1966). The pathophysiologies underlying skin cancer development are not entirely clear but more than 300 different carcinogens found in cigarette smoke as well as the massive amount of oxidants and radicals are likely to account for these effects (Demarini, 2004). An interesting but not clearly answered question is whether skin cancer is caused by chemicals that are inhaled or whether passive smoke chemicals induce cancer development. An interesting study by Mohtashamipur et al. (1990) sheds some light on this issue by reporting that collected side stream smoke chemicals bear a much higher carcinogenic potential than main stream smoke chemicals when applied to mouse skin.

### 3.2. Cancers

Cigarette smoke contains a large number of mutagenic compounds including oxidants, radicals, and PAHs (Burns, 1991; Demarini, 2004). The mechanisms by which individual compounds exert their DNA damaging activity are diverse, but have in common the alteration of gene sequences to induce cellular proliferation, inhibit apoptosis, and to promote immune evasion. Accumulation of mutations in the nuclear and mitochondrial genome also occurs during the normal aging process (Kang and Hamasaki, 2005) by exposure of individuals to naturally occurring mutagens like radioactivity, UV-light, nutrition-contained mutagens, and environmental as well as endogenously generated oxidants/radicals. As outlined above, smoking increases the rate of mutations over time which not only accounts for the carcinogenic activity of cigarette smoke but also reduces the functionality of enzymes, cells, and organs. Mutations in the mitochondrial genome are, for example, thought to result in defective activity of the respiratory chain, which in turn leads to increased intracellular oxidative stress and damage (Sastre et al., 2003). These processes which are accelerated by cigarette smoke mutagens play a central role in most models for aging. As mentioned earlier, yet unknown cigarette smoke chemicals induce cellular proliferation (although probably not by causing mutations) (Yu et al., 2006). This increased proliferative capacity will allow already mutated cells to increase their replication rate (clonal expansion), which will increase the probability of acquiring further transformation-causing mutations.

### 3.3. Cardiovascular diseases (CVD)

Among the classical age-related diseases which are CVDs the leading cause of death in developed countries (WHO, 2004). The pathophysiologies of the various CVDs are extremely complex, and most risk factors promote CVD development via a range of different activities. Cigarette smoking per se is a very complex risk factor which alone accounts for approximately 11% of all deaths from CVDs (Ezzati et al., 2005). The mechanisms of action are not entirely understood but more and more data suggest that smoking causes CVD via several activities and at different time-points throughout diseases progression. Importantly, a major principle in vascular damage caused by cigarette smoke chemicals is the exhaustion of defence mechanisms, and the reduction of vasomotor function (Ambrose and Barua, 2004; Benowitz, 2003).

Nitric oxide (NO) is an important regulator of vascular tone. Cigarette smoke contains superoxide radicals $O_2^{\cdot -}$ – which are also increasingly generated in aged cells – that interact with NO to form peroxynitrite (ONOO). As a result, NO pools are decreased and vasomotor function is reduced reflecting a less responsive, i.e. an aged, endothelium. Decreased endothelial responsiveness, also termed endothelial dysfunction, is thought to constitute a major principle in atherogenesis (Kojda and Harrison, 1999). As a result of accelerated vascular aging by cigarette smoke, individuals suffer earlier from vascular associated events/diseases, like myocardial infarction, stroke, peripheral arterial diseases, erectile dysfunction, and vascular dementia.

### 3.4. The lung

The lung is an organ that is especially exposed to the environment. In contrast to skin, pulmonary tissue has to

allow for an extremely high flux of chemicals from the environment into the body (and the other way round) and has therefore a vast surface area. The functionality of the lung as a selective filtering system is maintained by a complex system of maintenance, repair, and cleaning functions. Cigarette smoke interferes with all of these systems. Cigarette smoke contains a high amount of particulate matter, including small sized particles below 2.5 μm that can reach the alveoli (Burns, 1991). Particulate matter is a part of normal air and the body has evolved efficient removal systems (surfactant, lung macrophages, and cilia). The amount of particles deposited per time period is increased in smokers, and thereby the cleaning functions are burdened. Consequently, the performance of a smokers lung is reduced. Apart from high exposure to particles, cigarette smoke contains agents that induce a senescence-like phenotype in lung fibroblasts characterised by reduced proliferation and upregulation of senescence markers, including β-galactosidase (Nyunoya et al., 2006). Since fibroblast proliferation is vital for lung repair and homeostasis aging of lung fibroblasts by cigarette smoke may significantly contribute to age-related lung diseases.

### 3.5. The endocrine system and smoking

Cigarette smoking massively perturbs the endocrine system (Kapoor and Jones, 2005). An aging-relevant phenomenon is the decrease of total estrogen activity in smokers. By promoting 2-hydroxyestrogen production, smoking reduces estrogenic activity and contributes to the clearance of estrogen from the circulation (Michnovicz et al., 1986). Reduced estrogen production may contribute to an earlier onset of menopause which is associated with several age-related diseases like mammary carcinoma, cardiovascular events, and osteoporosis.

### 3.6. Osteoporosis

Osteoporosis is a classical age-related disorder, characterized by a loss of bone mass, which is caused by a deregulated balance between bone assembly and disassembly. Several factors contribute to osteoporosis. As mentioned above, smoking reduces estrogenic activity. Since estrogens are important regulators of bone metabolism, smoking also contributes to osteoporosis (Raisz, 2005). Similarly, smoking contributes to osteoporosis by interfering with calcium (Ca) and vitamin D homeostasis, which are vital for bone metabolism (Kapoor and Jones, 2005). Further, it has been shown that oxidative stress (as caused by smoking) inhibits the differentiation of osteoblastic cells, resulting in reduced bone formation (Mody et al., 2001). In a recent study, from our group we could show that young smokers show increased serum levels of strontium (Sr). Since Sr is biochemically similar to Ca, these data provide evidence for a reduced incorporation of Ca/Sr into bone and/or an increased release of Ca/Sr from bone already early in life, mimicking the status in aged individuals (Bernhard et al., 2006).

### 3.7. Fertility

The loss of fertility is associated with aging in both males and females. Cigarette smoking accelerates this process, and contributes to an early loss of fertility. Cigarette smoking delays the time of conception, reduces fertility, and smoking women show a 1–4 years earlier onset of menopause (Practice Committee, 2004). It is thought that cigarette smoke chemicals accelerate follicular depletion which is mediated by alterations in hormone production (e.g. young smokers show up to 66% increased levels in FSH) (Cooper et al., 1995). The data on male infertility by smoking are not entirely clear, but by causing vascular aging, cigarette smoke contributes to male impotence by causing erectile dysfunction (Korenman, 2004).

### 3.8. The retina

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in Western countries (Schmier et al., 2006). Currently, there is no cure or medication for slowing disease progression, and the only risk factor known to clearly contribute to AMD is smoking. The precise mechanisms and the agents involved are yet not identified, but besides a genetic predisposition, oxidative, and inflammatory processes appear to play crucial roles (Guymer and Chong, 2006). By causing continuous cellular damage, cigarette smoking contributes to a chronic systemic inflammatory status, which – apart from other detrimental effects – also damages the retina.

### 3.9. The brain

Similar to the retina, cigarette smoke chemicals also contribute to aging of the brain. An important principle by which smoking contributes to age-related brain diseases is the causation of cerebrovascular dysfunction. The reduced supply of nutrients and oxygen is thought to directly account for cell demise associated with reduced mental performance (vascular dementia) (Roman, 2005). In addition, smoking-caused cerebrovascular diseases have been also shown to accelerate degenerative dementias such as Alzheimer's disease (Roman, 2005). Elevated levels of C-reactive protein (CRP) were recently found to constitute a risk factor for dementia. Since smoking causes inflammation and increased levels of CRP, smoking-mediated inflammation is also likely to contribute to brain aging.

## 4. Conclusions

Aging is a very complex process and a precise definition of aging is difficult. Accordingly, it is not easy to clearly define smoking as an aging accelerator. Nevertheless, as outlined above there are a number of similarities between smoking-induced changes of the physiological state and the natural aging process. In detail, the natural aging process itself is not a uniform program but is highly dependent

on the individuals' genes in combination with the environment. Different natural aging-inducers act in different ways, and do not cause homogenous aging of the whole human body. In that way, smoking is likely to affect human health by inducing "real aging". Frequent smoking-associated diseases, like lung cancer, indicate that smoking does not cause homogenous aging of the human body, but rather affects a subset of organs, like UV-light causes a specific aging of the skin. However, as outlined above (and the list is not complete) cigarette smoke chemicals contribute to the aging of a large number of organs, making cigarette smoke a "broad range" aging accelerator.

Still, cigarette smoking could be seen as a chronic toxication, rather than an aging accelerating process. In our opinion both ideas are not mutually exclusive since the natural aging process itself fulfills criteria of a chronic toxication. The toxins that cause aging are naturally occurring compounds that accumulate in the soma and/or lead to an increase of damage with time that finally results in organ failure and death. Cigarette smoke contains more than 4000 different chemicals, and a large number of those can reach organs within the human body. Although some single compounds act rather specifically (e.g. PAHs) many health-threatening agents, especially oxidants and radicals, do not. Therefore, and because of the large number of different agents, cigarette smoke is in general a rather unspecific noxa that leads to an accumulation of damage and thereby causes aging.

Although a number of aspects may argue against accelerated aging by cigarette smoke chemicals being the only principle via which smoking reduces the life span and causes diseases, it is certainly an important feature. In conclusion, we think that if aging is defined as "the deterioration of a system with time" smoking clearly accelerates the aging process of the system man, by affecting molecules, cells, and organs.

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