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Review

Tobacco smoking, epilepsy, and seizures

Lingling Rong *, Alfred T. Frontera Jr., Selim R. Benbadis

Department of Neurology, University of South Florida, Tampa, FL 33612, USA

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ABSTRACT

Tobacco smoking is considered the greatest risk factor for death caused by noncommunicable diseases. In contrast to extensive research on the association between tobacco smoking and diseases such as heart attack, stroke, and cancers, studies on the association between tobacco smoking and seizures or epilepsy are insufficient. The exact roles tobacco smoking and nicotine use play in seizures or epilepsy have not been well reviewed.

We reviewed available literature and found that 1) there are vast differences between tobacco smoke and nicotine based on their components and their effects on seizures or epilepsy; 2) the seizure risk in acute active tobacco smokers, women who smoke during pregnancy, electronic cigarette smokers, and the role of smoking in sudden unexplained/unexpected death in epilepsy remain unclear; 3) seizure risks are higher in acute secondhand smokers, chronic active smokers, and babies whose mothers smoke; 4) tobacco smoke protects against seizures in animal models whereas nicotine exerts mixed effects in animals; and 5) tobacco smoking agents can be noneffective, proconvulsant, or anticonvulsant. Finally, the opportunities for future research on this topic is discussed.

1. Introduction

Smoking is a practice in which a substance is burned and the smoke is tasted or inhaled. The smoked substances include legal compounds such as tobacco as well as illegal recreational drugs. Tobacco remains the most popular smoked substance. Currently, there are more than one billion tobacco smokers in the world. About 8–14% of them regularly use nicotine replacement therapy when they cannot or are not allowed to smoke. Each year, approximately six million people die due to tobacco smoking. It is estimated that if the current trend continues, by 2030, tobacco smoking will kill more than eight million people worldwide annually [1]. Tobacco smoking predisposes people to many diseases including heart attack, stroke, cancers, COPD, and premature birth or birth defects [2–7]. Nevertheless, the distinct correlation between tobacco smoking or nicotine use and seizures or epilepsy is unclear, and this topic has not been well reviewed.

We aimed to review the available literature on the differences between tobacco smoke and nicotine, and their roles in causing, potentiating, or protecting against seizures in both animal models and human subjects. Effects of acute and chronic tobacco smoking on seizures or epilepsy in humans and animals, seizure risk in women who smoke, in children whose mothers smoke, in secondhand smokers, and in electronic cigarette smokers, the role of tobacco smoking or nicotine use in sudden unexplained death in epilepsy (SUDEP), as well as the effects of available smoking cessation agents in seizures/epilepsy were all reviewed. The opportunities for future research on this topic is also discussed.

2. Are there any associations between tobacco smoking or nicotine use and seizures or epilepsy?

2.1. Tobacco smoke versus nicotine

Tobacco is a product of dried leaves of plants in the genus of *Nicotiana*. Tobacco smoke differs from nicotine in many aspects: 1) tobacco smoke is a mixture of more than five thousand chemicals [8]. In March 2012, a long list containing 93 harmful and potentially harmful constituents (HPHCs) and an abbreviated list containing 18 HPHCs in tobacco products and tobacco smoke were established by the Food and Drug Administration (FDA) [9,10] (Table 1). In comparison, nicotine is a parasympathomimetic alkaloid which accounts for only 0.6–3% of the dry weight of tobacco; 2) the level of nicotine in a human's or animal's body varies based on the nicotine delivery method. When tobacco is smoked, levels of nicotine along with other chemicals fluctuate. When nicotine patches are used, the level of nicotine in the body remains relatively constant; 3) nicotine exerts its effects by binding to the nicotinic acetylcholine receptor (nAChR), whereas other chemicals in the tobacco smoke may have completely different mechanisms of action.

2.1.1. Evidence that tobacco smoke or nicotine is associated with seizures or epilepsy

Many components in tobacco smoke are associated with seizures or epilepsy. For example, nicotine, when overdosed, caused seizures in human subjects [11]. Carbon monoxide can cause seizures in both children and adults [12,13]. Seizures induced by carbon monoxide can be focal or generalized and can even present as status epilepticus [13–16]. Previously, it was thought that seizures only occur when carboxyhemoglobin (CO-Hb) levels equal or exceed 40%; however,

* Corresponding author at: 2134 Fletcher's Point Circle, Tampa, FL 33613, USA.
E-mail addresses: linglingrong@yahoo.com, lrong@health.usf.edu (L. Rong).

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Table 1
Abbreviated list of harmful and potentially harmful constituents [10].

HPHCs in cigarette smoke	HPHCs in smokeless tobacco	HPHCs in roll-your-own tobacco[a] and cigarette filler
Acetaldehyde	Acetaldehyde	Ammonia
Acrolein	Arsenic	Arsenic
Acrylonitrile	Benzo[a]pyrene	Cadmium
4-Aminobiphenyl	Cadmium	Nicotine (total)
1-Aminonaphthalene	Crotonaldehyde	NNK[b]
2-Aminonaphthalene	Formaldehyde	NNN[c]
Ammonia	Nicotine (total and free)	
Benzene	NNK[b]	
Benzo[a]pyrene	NNN[c]	
1,3-Butadiene		
Carbon monoxide		
Crotonaldehyde		
Formaldehyde		
Isoprene		
Nicotine (total)		
NNK[b]		
NNN[c]		
Toluene		

[10] http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm297752.htm.

[a] *Roll-your-own tobacco* is defined in section 900(15) of the FD&C Act to mean "any tobacco product which, because of its appearance, type, packaging, or labeling, is suitable for use and likely to be offered to, or purchased by, consumers as tobacco for making cigarettes." The term cigarette *filler* is not defined in the FD&C Act. For purposes of this draft guidance, we intend cigarette *filler* to mean the cut, ground, powdered, or leaf tobacco that is a component of a cigarette.

[b] 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.

[c] N-nitrosonornicotine.

more data support the idea that seizures may occur when the CO-Hb level is low. It was even suggested that there is no correlation between CO-Hb levels and the occurrence of seizures [16]. Other chemicals in tobacco smoke that can trigger seizures in humans or animals include ammonia, lead, hexane, toluene, cresol, arsenic, and acetone [17–23]. Besides these chemicals with proconvulsant effects, many other constituents in tobacco smoke have demonstrated anticonvulsant effects. It was reported that levels of selenium and zinc were low in patients with idiopathic intractable epilepsy [24]. Five percent carbon dioxide (CO_2) can function as a potent, fast-acting inhalation anticonvulsant in rats, macaque monkeys, and patients with drug-resistant partial epilepsy [25]. Toluene could reduce seizures by inhibiting NMDA receptors and enhancing $GABA_A$ receptor function [26]. Acetone has broad spectrum anticonvulsant effects in multiple seizure types including tonic–clonic seizures, typical absence seizures, complex partial seizures with secondary generalization, and atypical absence seizures associated with the Lennox–Gastaut syndrome [27]. Nickel chloride can reverse pentylenetetrazole-induced seizures in mice [28] (Table 2).

Specifically, nicotine, the addictive and proconvulsant chemical in tobacco, has also been found to have anticonvulsant effects in patients with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). Autosomal dominant nocturnal frontal lobe epilepsy was the first partial epilepsy syndrome described in humans that was shown to be caused by a single gene-mutation. The causative mutations occur in the nicotinic acetylcholine receptor (nAChR) gene subunits and result in pathological profiles for agonists such as nicotine or antiepileptic drugs [29]. Such mutations cause pathological profiles for agonists such as nicotine or antiepileptic drugs [30]. A single case report described that when a woman with medication-refractory epilepsy secondary to a mutation causing ADNFLE underwent an open and double-blind trial of nicotine dermal patches, her seizure frequency significantly decreased when she started to use the nicotine dermal patch [31]. Another case report described a woman who had long-standing and drug-refractory frontal lobe epilepsy and whose EEG revealed generalized frontal lobe-dominant epileptiform discharges. This patient also responded to transdermal nicotine patches both clinically and electroencephalographically. Following treatment with transdermal nicotine, her seizure frequency and intensity first decreased and subsequently resolved completely, and this corresponded to the resolution of the EEG abnormalities and an improvement in her cognition [32]. Although the patient's genetic testing was negative for mutations in CHRNB2 or CHRNA4, the common mutations found in ADNFLE, her positive family history of nocturnal frontal lobe epilepsy, and the characteristics of her seizures still made ADNFLE the most likely diagnosis. In addition to case reports, a study on patients admitted for video-EEG monitoring found that patients on nicotine patches, especially those with focal epilepsy, had, on average, one day longer hospital stays and fewer total seizure events compared with those who were not on nicotine patches [33]. The difference in the number of days of the hospital stay was statistically significant, but the difference in the total seizure events was not. This study had a small sample size. A larger, longitudinal study is anticipated. Interestingly, there was no difference in the length of hospital stay or total number of seizure-like events in patients with psychogenic nonepileptic attacks with or without nicotine patches [33].

The smoking habits in ADNFLE family members is of interest, and one study investigated twenty-two subjects from two families with ADNFLE α4 mutations and found that smokers had statistically significant longer seizure-free periods when compared with nonsmokers. Multiple smokers in both families reported increased seizure severity and frequency when they stopped smoking, but decreased seizure frequency and severity when they resumed tobacco smoking. One member, in particular, a nonsmoker in the past, had decreased seizure frequency and severity several months after she started transdermal nicotine patches [34]. What were or are the smoking habits or smoking status in the families where ADNFLE was originally found? Answering this question could help better understand tobacco smoking's possible beneficial role in this disorder.

The smoking habits and smoking status in families with sporadic NFLE were also examined. One study investigated a total of 434 individuals and found no significant difference in the distribution of tobacco use among the group with NFLE and controls, although there was a slightly higher trend of tobacco use in the former [35]. The power of the study was too small to make a conclusion even though the authors felt that there was no large difference between the two groups based on available results.

2.1.2. Effects of acute versus chronic tobacco smoking on seizures or epilepsy

2.1.2.1. Seizure risk during the act of smoking.

Whether the risk of having a seizure immediately increases, decreases, or is unchanged during the act of tobacco smoking remains unknown. As reviewed earlier, tobacco smoke is much more complex than nicotine alone. Many components in tobacco smoke have either unclear effects, proconvulsant effects, or anticonvulsant effects. Studies of immediate changes to seizure thresholds or latency in humans have not been done, but there is a small amount of data from animal models (see Section 4).

2.1.2.2. Effects of chronic tobacco smoking on seizures or epilepsy.

In chronic smoking, chemicals in tobacco smoke exert more prolonged and profound effects on multiple organs and systems.

2.1.2.2.1. Risks of seizures or epilepsy in chronic smokers.

In 2010, a group studied 116,363 female nurses aged 25 to 42 for a period of 15 years and found that after an adjustment for stroke and other potential confounding factors, smokers had double the risk of seizures when compared with nonsmoker controls with a relative risk of 2.60. The same study also found that past tobacco smokers had a modestly increased risk of epilepsy, but this did not reach statistical significance. For current smokers, the seizure risk was not related to the number of cigarettes they smoked per day, but the risk increased with pack-years of smoking. For people with a past history of smoking, there was no association between epilepsy risk and the number of cigarettes smoked daily, pack-years, or time since quitting smoking [36]. However, it is apparent that the group of patients with epilepsy was too small in this study. In 2012, another study found that current smoking was the only feature associated with seizures in patients with primary antiphospholipid