Nicotine in E-cigarette smoke: cancer culprit?

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Abstract

Tobacco smoke's harmful effects are well-known; the harmful effects of tobacco smoke have been well-investigated. Nicotine in tobacco smoke contributes to the pathogenesis of various conditions, such as lung cancer, coronary artery disease and asthma. A decade ago, a seemingly safer alternative to tobacco cigarettes was introduced- the E-cigarette. However, studies have found that E-cigarette smoke (ECS) not only induces DNA damage but also reduces DNA repair activity via BER and NER pathways. Further research conducted with cells damaged by Ultra-Violet (UV) light or hydrogen peroxide (H₂O₂) indicates that ECS can function as a comutagen; nicotine can amplify mutagenic activity by merging with other mutagens. The downstream metabolites derived from nicotine found in ECS put E-cigarette smokers at a higher risk for developing lung or bladder cancers or heart disease than their non-smoking counterparts. Overall, these findings are instrumental in our understanding of the harmful effects of ECS.

Keywords Nitrosamines · Nitrosamine ketones · DNA damage · Mutagen · DNA repair · Lung injury

For many years, humans have smoked tobacco as a pastime; however, the advent of E-cigarettes has started a new revolution in the world of smoke inhalation. Directly smoking tobacco cigarettes can lead to lung cancer while passive inhalation of the smoke can lead to the development of conditions such as coronary artery disease and asthma (Ciaccio and Gentile 2013; Furrakh 2013; Naeem 2015). Since E-cigarettes deliver nicotine in an aerosol state without burning tobacco, they appear less harmful (Farsalinos and Polosa 2014). While the harmful effects of tobacco smoke (TS) are known, the effects of E-cigarette smoke (ECS) have not been thoroughly examined thus far (Callahan-Lyon 2014; Cooke et al. 2015). Despite the unknown long-term effects of E-cigarette smoking, roughly 18 million individuals in the USA still use E-cigarettes, especially individuals seeking to substitute tobacco cigarettes with an alternative source of nicotine (Drummond and Upson 2014; Farsalinos and Polosa

2014; Lee et al. 2018). Due to this widespread usage of E-cigarettes, it is of utmost importance that the effects of ECS be understood.

In a recent issue of *PNAS*, Lee et al. (2018) present novel data regarding the effects of ECS. Sanner and Grimsrud (2015) determined that the nicotine in TS that plays an important role in the pathogenesis of many diseases associated with tobacco cigarette smoking. They also urged future research to determine nicotine's role in ECS (Sanner and Grimsrud 2015). In accordance with this call to action, Lee et al. determined that the derivatives of the nicotine in ECS were carcinogenic by examining DNA damage caused by nitrosamines derived from nicotine (Lee et al. 2018).

The nitrosation of nicotine forms nitrosamine ketones (NNK) which metabolize into methyldiazohydroxide (MDOH) and aldehydes, which may induce O⁶-methyl-deoxyguanosine (O⁶-medG) adducts and γ-OH-1,N²-PdG (γ-OH-PdG) adducts, respectively. By extracting genomic DNA from tissues and using the immunochemical slot blot hybridization method, Lee et al. (2018) determined that ECS can induce DNA damage in the form of O⁶-medG and γ-OH-PdG adducts in the lung, bladder and heart tissues of mice and cultured human bronchial epithelial and urothelial cells.

In addition to investigating the DNA damage induced by ECS, Lee and his colleagues (2018) explored the effect of ECS on DNA repair activity. They used an in vitro DNA

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damage-dependent repair synthesis assay with mouse lung, heart and bladder tissues to assess the activity of a couple of major DNA repair pathways- nucleotide excision repair (NER) and base excision repair (BER). Lee et al. (2018) found a decrease in NER and BER activity in ECS-exposed mouse lung tissue, supporting the claim that ECS can impair DNA-repair activity. Similar results were discovered after the same experiment was performed using human lung and bladder epithelial cells. It was further determined that DNA-repair activity is impaired due to modifications and proteosomal or autophagosomal degradation of DNA-repair proteins, such as XPC and hOGG1/2, by the metabolites of ECS, most notably, aldehydes. Overall, the authors found that the metabolism of nicotine can occur in mouse lung, heart and bladder tissues and human bronchial epithelial and urothelial cells and these metabolites have a profound effect not only on inducing DNA damage, but also on reducing DNA repair activity.

In order to examine the comutagenic qualities of ECS, Lee et al. (2018) induced mutagenesis in a plasmid containing the *supF* gene (encoding tyrosine suppressor tRNA) by exposing it to Ultra-Violet (UV) light or treating it with hydrogen peroxide (H₂O₂). They then transfected the plasmid into human lung and bladder epithelial cells with or without pretreatment of nicotine and NNK. The high frequency of mutations observed in cells treated with nicotine and NNK and transfected with a damaged plasmid allowed the authors to ascertain that ECS can function as a comutagen; in the presence of another mutagen, nicotine and NNK amplify mutagenic activity. The authors then conducted an anchorage-independent soft-agar growth assay and discovered that nicotine and NNK induce growth of human lung and bladder cells that is anchorage-independent, a quality that is characteristic of tumorigenic cells.

This study by Lee et al. (2018) is among the first studies to indicate that the nitrosamines and downstream metabolites derived from nicotine found in ECS put E-cigarette smokers at a higher risk for developing lung or bladder cancers or heart disease than their non-smoking counterparts. These novel findings will have far-reaching implications for further studies on ECS, especially regarding its long-term effects. Additionally, although studies on the interaction between TS and ECS are necessary as individuals often use E-cigarettes when attempting to quit smoking tobacco cigarettes, the inquiry into the

comutagenic nature of ECS by Lee et al. (2018) provides a strong foundation for further studies (Drummond and Upson 2014). The limited information detailing the effects of ECS has led to a divide in opinions regarding the regulation of E-cigarettes (Tremblay et al. 2015). The compelling evidence provided by Lee et al. (2018) will thus not only have a significant impact on future research but will also be instrumental in the regulation of E-cigarettes.

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