Cigarette Smoking: A Causal Factor for Alzheimers Disease?

Jason J Woods1, Kristy L Martin1, Elvis Freeman-Acquah2, Mickeely Smith1, Philip M Hansbro1, Jay C Horvat1, Daniel M Johnstone2 and Elizabeth A Milward1

1 School of Biomedical Sciences and Pharmacy, University of Newcastle, Australia
2 The Bosch Institute and Discipline of Physiology, University of Sydney, Australia

Corresponding author: Elizabeth A Milward, School of Biomedical Sciences and Pharmacy, The University of Newcastle, Australia, Tel: 61249215000; E-mail: liz.milward@newcastle.edu.au

Introduction

As detailed by the Alzheimer’s Association (http://www.alz.org) and elsewhere [1], Alzheimer’s disease (AD) is a neurodegenerative disease characterized clinically by loss of cognitive ability and histopathologically by amyloid-beta (Aβ) plaques and neurofibrillary tangles. Patients suffer debilitating symptoms such as progressive memory loss, difficulty performing complex tasks and temporal or spatial confusion (Alzheimer’s Association, 2013). Various factors are proposed to influence the risk of developing AD, including aging and education. Here we examine evidence for and against cigarette smoking as a modifiable risk factor for AD.

Human Studies Examining Relationships of Smoking and AD

There have been numerous contradictory studies on smoking in AD. Several studies have found no significant relations between smoking and AD [2-4]. For example, a pooled study of three Canadian case-control datasets by Tyas et al. [2] showed that, after adjustment for confounders, there was a consistent lack of association between smoking and AD in all three data sets analyzed, suggesting smoking had no significant relationship with the risk of developing AD. Other studies, including case control studies and population-based cohort studies (only a few examples will be given here), have proposed either that smoking may protect against AD [5-8] or that smoking increases the risk or severity of AD [9-13]. While failure to account for APOE genotype, the strongest known genetic risk factor for AD [7], might provide evidence that smoking modifies the relationship between smoking and AD risk, these studies have been performed in AD patients, including aging and education. Here we examine evidence for and against cigarette smoking as a modifiable risk factor for AD.

Animal Studies on Alzheimer’s Disease and Smoking

Some animal studies suggest direct nicotine administration causes changes in processing of the Aβ parent molecule, Aβ42 precursor protein (AβPP), to favour the non-amyloidogenic pathway [22,23]. Initial experiments were performed on wild-type rats which do not develop AD, but findings were replicated in an AD mouse model [24,25]. Suggested mechanisms include up-regulation of nicotinic acetylcholine receptors by nicotine, enhancing cognition [26], direct effects of nicotine, decreasing APP secretion and Aβ generation [22,23] and binding of nicotine to Aβ peptides resulting in conformational changes that prevent subsequent formation of amyloid plaques [27].

While the above studies appear to favor protective actions, such effects may not be relevant to the human disease. However, controlled studies on the relationship between smoking and AD risk in humans have been performed in AD patients, including aging and education. Here we examine evidence for and against cigarette smoking as a modifiable risk factor for AD.

Beside the reported industry bias, human epidemiological studies have other limitations; for example, it is difficult to draw valid conclusions.
disease and white matter damage, both often observed in AD, and this may contribute to neurodegenerative changes [1,32]. A third study from the same group is harder to interpret smoking was reported to modified not been confirmed to exhibit human AD pathology. The ‘Aβ’ species detected has not been confirmed to be amyloidogenic and should perhaps more correctly be called ‘Aβ-like’. More studies are required for valid interpretation of these results.

Perhaps the most conclusive findings to date have come from a well-designed study by Moreno-Gonzalez et al, providing more specific evidence that smoking increases AD pathology. This study examined effects of smoking in the APPswP53/Tg (B6C3) mouse model of AD using a plexiglass chamber passive smoking apparatus [28]. Both experimental and control mice were exposed to the apparatus, effectively reducing the confounding factor of stress. Smoking increased amyloid plaque density and maturation, tau phosphorylation and neuroinflammation [28].

Conclusion

There is ongoing controversy over whether smoking is a risk factor or a protective factor for AD and whether it enhances or reduces generation of amyloidogenic peptides or acts through mechanisms less specific for AD, for example through effects involving vascular or myelin damage. Further study is required to help understand the effects smoking has on brain pathology; this may pave the way for new understanding of the mechanisms underlying AD.

References

