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Cigarette Smoking: A Causal Factor for Alzheimers Disease?

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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 account in part for discrepancies, data on how APOE genotype modifies the relationship between smoking and AD risk also appear inconsistent, with some studies associating the APOE ε4 allele with decreased risk of AD in smokers [7,11] and others the reverse [9,10], suggesting other factors must also considered.

A recent meta-analysis controlled for tobacco industry affiliation of both cohort and case-control human studies [14]. Of the studies included in the analysis, 26% had tobacco industry affiliation and only 27% of these affiliated studies disclosed their affiliation. Controlling for this, the analysis suggested smoking is a significant risk factor (relative risk 1.72; 95% CI 1.33-2.12) [14]. It has been noted that industry sponsored research is more likely to produce outcomes favourable to the sponsor and to be subject to publication bias and data withholding [15]. There have also been concerns raised about tobacco industry affiliated research suggestions that smoking protects against other diseases such as schizophrenia [16]. A more recent meta-analysis also suggests smoking increases AD risk [17].

Besides the reported industry bias, human epidemiological studies have other limitations; for example, it is difficult to draw conclusions with regard to causation and mechanism from such studies. However MRI and post-mortem studies also report that cigarette smoking may have harmful effects on the human brain. For example, chronic smoking has been reported to reduce cerebral perfusion, causes white matter lesions and accelerates cerebral atrophy [18,19]. Longstreth et al. found smoking increases age-associated brain atrophy [20] and a study of a chronic smoking cohort by Durazzo et al. found increased rates of atrophy in regions specifically vulnerable to pre-clinical AD [21].

Yet difficulties controlling variables, performing experimental manipulations, obtaining post-mortem tissue and other restrictions all limit the usefulness of human studies for investigating the nature of the relationship, if any, between smoking and AD or the mechanisms involved. Although animal models do not always completely represent human disease processes, animal studies still offer many advantages for studying molecular and cellular mechanisms involved in AD pathogenesis. Mice age over a short period and transgenic mouse models of AD can develop neuropathological lesions within 5-6 months or less, facilitating study of AD pathology in reasonable time-frames. The ability to manipulate experimental design in animal studies, for example by regulating cigarette smoke intake, also means variation of confounders can be better controlled.

Animal Studies on Alzheimer's Disease and Smoking

Some animal studies suggest direct nicotine administration causes changes in processing of the Aβ parent molecule, Aβ 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 favour protective actions, to our knowledge, industry-related bias in animal studies has not been examined and other studies have again shown opposing effects [28-31]. A set of studies of passive, 'second hand' smoking in wild type AJ mice (not genetically modified to exhibit human AD pathology) report effects potentially relating to myelin damage and white matter lesions [29-31]. Passive cigarette smoking exposure inhibited expression of genes needed for myelin synthesis and maintenance [31]. Cigarette smoking-mediated white matter degeneration was proposed to be associated with lipid peroxidation, protein oxidative injury and altered myelin lipid composition [30]. This is biologically plausible, since as reviewed elsewhere smoking has been implicated in both vascular

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 affect insulin and insulin-like growth factor (IGF) signaling pathways, accompanied by molecular abnormalities relevant to AD such as increased levels of amyloid-beta Aβ peptide and its parent AβPP [29]. However the study was performed in wild type AJ mice not genetically modified 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 APPswe/PS1dE9 (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.

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