SHORT RESEARCH ARTICLE

Rapid doubling of Alzheimer's amyloid- β 40 and 42 levels in brains of mice exposed to a nickel nanoparticle model of air pollution [version 1; peer review: 3 approved]

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Abstract

Background: Over 20 genetic risk factors have been confirmed to associate with elevated risk for Alzheimer's disease (AD), but the identification of environmental and/or acquired risk factors has been more elusive. At present, recognized acquired risks for AD include traumatic brain injury, hypercholesterolemia, obesity, hypertension, and type 2 diabetes.

Methods: Based on reports associating various inhalants with AD pathology, we investigated the possibility that air pollution might contribute to AD risk by exposing wild-type mice to a standard air pollution modeling system employing nickel nanoparticle-enriched atmosphere for 3 hr.

Results: Mice exposed to air pollution showed 72-129% increases in brain levels of both amyloid- β peptides A β 40 and A β 42, as well as A β 42/40 ($p < 0.01$).

Conclusions: These effects on elevation of brain A β exceed those associated with trisomy 21, a known risk for early onset AD pathology, raising the possibility that clinical importance might be attached. Further work is required to establish the molecular and physiological basis for these phenomena. The rapid, dramatic effect, if verified, would suggest that inhalant exposures should be evaluated for their possible roles in contributing to the environmental risk for common forms of AD.

Keywords

air pollution

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Approval Status

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Any reports and responses or comments on the article can be found at the end of the article.

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Competing interests: S.G. holds research grant support from Amicus Pharmaceuticals and Baxter Pharmaceuticals; he is a consultant to Balance Pharmaceuticals and Diagenic; and he is a member of the Data and Safety Monitoring Board for the Pfizer-Janssen Alzheimer's Immunotherapy Alliance.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Introduction

One common neurodegenerative disease, Parkinson's disease, has been linked to exposure to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and to inhaled manganese^{1,2}. Similarly, inhaled aluminum dust has been associated with neurotoxic effects and pre-clinical cognitive impairment³. Certain inhalation anesthetics have also been implicated in elevating AD risk, possibly by exacerbating the neurotoxic oligomerization of the amyloid- β (A β) peptide⁴. The early involvement of the olfactory cortex in AD has caused long-time speculation that some inhaled agent might play a role in AD risk⁵.

Recently, AD pathology was identified in young people living in areas with high levels of air pollution^{6,7}. Furthermore, impaired cognition has been recently attributed to air pollution exposure in some populations⁸. These converging lines of evidence led us to analyze brain levels of A β 40 and A β 42 in mice exposed to an inhaled particulate matter (nickel nanoparticle; Ni NP) model of air pollution.

Methods

All procedures involving animals were conducted in compliance with guidelines for ethical animal research and approved by the New York University School of Medicine Animal Care and Use Committee. Two-month-old male and female FVBN mice (Taconic Farm, Hudson, NY) were randomly assigned to Ni NP inhalation (count median diameter 54 nm, at 1 mg/m³, which is the current Occupational Safety and Health Administration's Permissible Exposure Limit for nickel hydroxide [http://www.osha.gov/pls/os-haweb/owadisp.show_document?p_table=standards&p_id=9992]) ($n = 16$ per group) or control filtered air ($n = 5$ per group) for 3 hours in a nose-only exposure chamber. This protocol has been established as a model for air pollution toxicity in pulmonary disease⁹, atherosclerosis¹⁰, and insulin resistance¹¹. Twenty-four hours post exposure, mice were given pentobarbital, bled out via the vena cava, and then their brains were harvested, snap frozen and stored at -80°C until assay. For measurement of endogenous mouse brain A β 40 and A β 42, we employed the Schmidt method¹² and human/rat A β 1–40/1–42 ELISA kits (Wako, Richmond, VA). Statistical analysis was performed via Mann-Whitney test. #8 Ni NP is excluded from the analysis due to being more than 2 SD's away from mean or closest value.

Results

Both endogenous A β 40 and A β 42 were elevated in the brains of mice following Ni NP exposure (Figure 1). A β 40 was increased by 1.72-fold ($P = 0.0011$, Mann-Whitney test), and A β 42 was increased by 2.29-fold ($P = 0.0005$, Mann-Whitney test). A β 42/40 ratio was also increased in the Ni NP-exposed group compared to the filtered air control group (0.27 ± 0.01 and 0.21 ± 0.007 , respectively; $P = 0.0093$, Mann-Whitney test). Both male and female mice responded similarly to Ni NP exposure (male vs. female for A β 40 and A β 42 levels; $P > 0.1$, Mann-Whitney test).

Figure 1. Exposure to air pollution increases amyloid- β (A β) levels in the mouse brain. Elevated endogenous mouse brain A β 40 and A β 42 in mice exposed to nickel nanoparticles (count median diameter 54 nm, at 1 mg/m³) ($n = 16$ per group) versus filtered air ($n = 5$ per group) for 3 hours in a nose-only exposure chamber. Data presented as mean + SEM. ** $P < 0.01$, *** $P < 0.001$ (Mann-Whitney test).

Raw data table for endogenous mouse brain A β 40 and A β 42 levels in mice exposed to nickel nanoparticles versus filtered air

1 Data File

<http://dx.doi.org/10.6084/m9.figshare.105158>

Discussion

These data add credence to the proposal⁴ that one or more inhaled neurotoxin(s) might increase the risk for AD by elevating levels of brain A β . We have not identified whether this accumulation occurs at the level(s) of transcription, translation, or post-translational processing. It is tempting to speculate that the well-known links between inhaled toxins and brain inflammation, and other links between brain inflammation and AD established by Griffin and colleagues¹³ may underlie these phenomena.

The changes that we observed were dramatic, rapid, and unexpected. Human A β is more aggregatable than murine A β , making it conceivable that the effect on A β levels in human brain could be even greater. While elucidating the genesis and molecular underpinnings will be an important next step, an even more important step will be a rigorous application of environmental toxicology and epidemiology to determine whether the elevated brain A β caused in mice by this air pollution model corresponds to any situation of authentic human inhalation exposure that is linked to an increased risk for AD.

Author contributions

S.H.K., E.M.K., E.L.S. and A.K.C. designed the experiments with L.C.C. and S.G. S.H.K., E.L.S., A.K.C. and M.P. performed the experiments. E.M.K. analyzed the data. S.G. wrote the manuscript. All authors commented on the manuscript. L.C.C. and S.G. supervised the project.

Competing interests

S.G. holds research grant support from Amicus Pharmaceuticals and Baxter Pharmaceuticals; he is a consultant to Balance Pharmaceuticals and Diagenic; and he is a member of the Data

and Safety Monitoring Board for the Pfizer-Janssen Alzheimer's Immunotherapy Alliance.

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Ottavio Arancio

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This is an intriguing observation that might potentially have important relevance to the etiopathogenesis of Alzheimer's Disease.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 23 January 2013

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George Perry

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Linkage of environmental air toxicity from nanoparticles leading to Alzheimer-like changes in the brain of mice opens a new avenue to understanding the development of brain diseases. These findings are consistent with prior work showing particulate air pollution can affect the brains of human as well as dogs living in polluted cities.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to confirm that it is of an acceptable scientific standard.

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Neurodegenerative consequences are a looming possibility with the current increased burden of air-borne pollutants. Many studies have suggested an association between anesthesia administered to older adults and cognitive decline and development or progression of Alzheimer's disease (AD). A number of studies have already established links between air-borne pollutants and risk for development of systemic disorders several of which, like AD are inflammatory in nature. Gandy and his colleagues have taken a purposeful step toward more directly connecting air-pollution to increased risk for development of AD in a study of wild type mice exposed to a toxin at the OSHA permissible level for an 8h human exposure. The results are very convincing, showing that a one-time 3h exposure to nickel hydroxide nanoparticles at the "permissible" level doubled brain levels of A β 40 and A β 42 within 24h—increases that are similar to levels reported in younger adults with Down's syndrome. Interestingly, as noted by the authors, and in accord with systemic inflammatory consequences reported following exposure to air-borne pollutants, neuroinflammatory changes that drive Alzheimer neuropathological change may also be elicited by such exposure. This may be particularly important as we necessarily inhale air that appears to be "clean," but which contains permissible levels of agents that may have adverse effects on the brain, especially in persons with genetic risk factors and or co-morbid conditions that already predispose them for development of AD.

Competing Interests: No competing interests were disclosed.

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