Air pollution nano-particulate matter, APP processing, and glutamate receptors

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USA

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Research Abstract
? DESCRIPTION (provided by applicant): Prior work has associated air pollution with accelerated atherosclerosis and with the incidence of stroke. Moreover, recent epidemiological

studies associate air pollution with accelerated cognitive decline of normal aging. Associations with Alzheimer disease are being studied, supported by postmortem findings that humans exposed to extreme urban pollution have premature brain inflammation and deposits of diffuse amyloid-beta (Abeta). Rodent models support these emerging associations of cognitive dysfunctions with air pollution. After exposure to various urban air pollutants, several rodent genotypes show synaptic changes and increased Abeta, as well as induction of TNFa and other inflammatory responses. Our model uses chronic exposure of mice to nano-scale PM (nPM) derived from urban traffic, which shows greater cytotoxicity than larger PM. Under controlled exposure by duration and dose (nPM density), mice show a 30% decrease of the hippocampal GluA1 AMPA receptor subunit, with little change in other AMPA receptor subunits, or in NMDA receptor subunits, while in vitro studies show that nPM exposure increases excitotoxic damage. Because of its role in fast excitatory transmission and in spatial memory, GluA1 decreases could contribute to cognitive decline in association with air pollutants. Another potential link to brain aging involves interactions of AMPA receptor subunits with Abeta. This proposal addresses key gaps in experimental models for epidemiological associations and postmortem findings: the impact of nPM exposure on hippocampal neuronal physiology associated with cognitive processes, and associations of pro-amyloidogenic amyloid precursor protein (APP) processing with GluA1 changes. These studies use C57BL/6 mice of both sexes, because gender effects of air pollution on brain functions are understudied. Aim 1: Effects of chronic nPM exposure on hippocampal-dependent learning and cellular correlates. After behavioral testing of chronic nPM exposed mice, hippocampal slices will be analyzed for changes in the AMPA GluA1 vs GluA2 receptor subunits at excitatory Schaffer-collateral hippocampal synapses and in long-term potentiation (LTP). Subcellular fractionation of cortical tissue will address alterations in AMPA receptor trafficking, which regulates synaptic plasticity. The processing of the APP will also be examined in relation to glutamate receptor function. Aim 2: Manipulation of APP processing in male mice with two drugs: a novel gamma secretase modulator (BPN-15606) and with memantine to test the role of endogenous Abeta in cognitive changes and down- regulation of GluA1 during chronic in vivo nPM exposure. Indications of glutamatergic involvement in responses to air pollution nPM are relevant to the epidemiological findings of cognitive impairment because of the role of glutamate receptors in learning and memory and because of AMPA receptor sensitivity to Abeta. Findings will enable deeper analysis of synaptotoxic mechanisms of air pollution, which are needed to identify therapeutic neuroprotection and to adjust permissible environmental limits of ultrafine PM.

Further information available at:

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