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Nitrogen oxides induced neurodegeneration as examined by nuclear magnetic resonance

Abstract

Nitrogen oxides pollutants in ambient air are potential source of neurodegenerative disorders, including Alzheimer's and Parkinson's diseases. Routes by which inhaled nitrogen oxides can impose neuronal defects pass through the olfactory bulb, nasal epithelium and the lungs via diffusion or capture and carriage by red blood cells across the blood-brain-barrier. Pulmonary inflammation releases cytokines that reach the brain via the same routes. Ultimately, nitrogen oxides and cytokines activate microglia to upregulate the expression of inducible and neuronal nitric oxide synthase, which results in increased oxidative stress and neurotoxicity and neurodegeneration. Metabonomic studies with the nuclear magnetic resonance allow identification of neurodegenerative diseases using N-acetylaspartate as a biomarker as well as identification of new biomarkers.

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Nitrogen oxides and neurodegeneration

Air pollutant gases include ground-level ozone, carbon monoxide, sulfur dioxides and nitrogen oxides, particulate matter, organic compounds, including polycyclic aromatic hydrocarbons and endotoxins, and metals.[1] Nitrogen is released during fuel combustion and combines with oxygen atoms in the atmosphere to produce nitric oxide and other nitrogen oxides, which can be inhaled by the upper respiratoy tract. Nitrogen oxides are a source of neurotoxin; thus, minimizing exposure and detecting its levels in the brain is pertinent. Nitrogen oxides have been shown to be associated with dementia, such as Alzheimer's disease (AD) and Parkinson's disease (PD). NO2 inhalation by C57BL/6J mice with amyloid precursor protein and presenilin 1 mutations aggravated β-amyloid accumulation, caused deterioration of spatial learning and memory and induced pathological abnormalities and cognitive defects related to AD compared to naïve control mice.[2] Furthermore, nitrogen oxides were associated with increased dementia risk in two clinical cohort studies.[3] One was a 15-year study of 1806 healthy men and women in Sweden,[4] and another was a 10-year study of nearly 30,000 individuals in Taiwan.[5]

Mechanisms of nitrogen oxide induced neurodegeneration

Inhaled nitrogen oxides can access the brain via multiple routes. They can enter the brain through the olfactory bulb or disrupt the nasal epithelium. It has been reported that olfactory dysfunction due to ambient airborne pollutant exposure is associated with neurodegenerative diseases.[6] The nasal epithelium is also vulnerable to damage by air pollutants, and there is a correlation with increased deposition of apolipoprotein E and neurofibrillary tangles.[7] Nitrogen oxides can be inhaled into the lung, where it induces the expression of inflammatory cytokines.[8] Nitrogen oxides and cytokines either diffuse to the brain (as they can diffuse easily across a broad volume and unconstrained by cell membranes)[9] or scavenged by hemoglobin in red blood cells, thereby entering the peripheral vasculature and crossing the blood-brain-barrier (BBB) into the cerebral vasculature.[10]

Once reached the brain, nitrogen oxides and cytokines can activate the resident innate immune system via microglial cells, the macrophages of the central nervous system (CNS). Microglial cells represent a major cell type involved in nitrogen oxide induced neuropathogenesis. Cultures treated with diesel exhaust particles (DEP) showed microglial activation with changes in morphology and increased in superoxide production.[11] Of note, DEP combustion leads to nitrogen oxide release. Only in the presence of microglia did DEP induce dopaminergic neurotoxicity, suggesting that microglia mediated the neuronal damage. In addition, microglia exposed to ambient air pollution*in vitro*resulted in an upregulation of IL-1β and TNFα mRNA.[12] In neurodegenerative conditions and aging, microglia enter a hyperactive state, in which they produce abundant neurotoxic pro-inflammatory mediators, including iNOS (inducible nitric oxide synthase, which results in excessive inflammatory NO), cytokines and chemokines, prostaglandins, cyclo-oxygenase and free radicals that all aggravate the inflammatory response. iNOS mRNA in the cerebral hemisphere and pituitary was increased 24 hours after a 4-hour exposure to ozone inhalation in Fischer-344 rats.[13] In addition, 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) exposure, from burning of organic material, induced a time- and dose-dependent increase in nNOS expression, which results in high levels of NO production.[14] Nitrogen oxides can directly activate microglia and the induced cytokines can also activate microglia, which lead to increased reactive oxygen species (ROS) that mediates neurotoxicity.[8] Additionally, the cytokines can directly induce neuronal death.

Using metabonomics to detect neuro degeneration

Metabonomics is the analysis of low molecular mass metabolites found in cells, tissues or biofluids of organisms in response to external stress.[15] Nuclear magnetic resonance (NMR) based metabolomics is a common method that generates reproducible data, results in no sample destruction, allows high throughput measurements and requires minimal sample preparation steps.[16] N-acetylaspartate (NAA) is a metabolic neuronal marker that is synthesized under normal conditions by neuronal mitochondria.[17] Correspondingly, a decline of NAA is suggestive of neurodegeneration. AD transgenic mice with mutant amyloid precursor protein showed decreased NAA in the NMR spectra of brain tissue extract.[18] Thus, clinical applications include disease identification and treatment progress monitoring. For preclinical applications, in addition to NAA, NMR of brain tissue extracts allows elucidation of new biomarkers that could be used for disease identification, treatment progress monitoring as well as new drug targeted discovery.

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Conflict of interest

None.

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