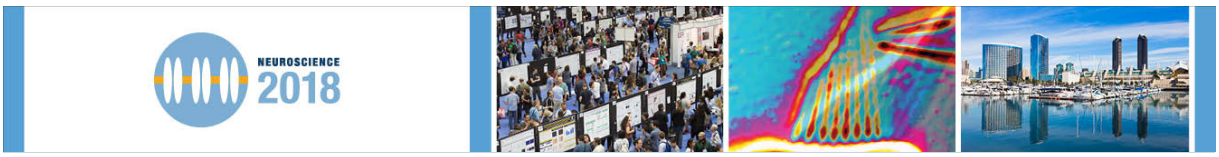

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474.12 / S17 - Lipid rafts as novel target of traffic related air pollutant exposure: Evidence from *in vivo* and *in vitro* models

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Abstract
Traffic-related air pollution (TRAP) is increasingly documented as a risk factor for Alzheimer Disease (AD) onset and for accelerated cognitive decline. Mouse models exposed to a nano-scale subfraction of TRAP (nPM) showed increased brain amyloid levels, concurrently with oxidative damage, as possible mechanism of neurotoxicity (Cacciotttolo et al 2017). Additionally, cell production of Aβ is also increased by oxidative stress. Brain cell oxidative responses to nPM are also shown in *in vitro* models of hippocampal slices and primary brain cell cultures with increased NO (nitric oxide) production and lipid oxidation (4-HNE) (Davis et al 2013; Cheng et al 2016). Air pollutants may affect multiple steps in APP processing. In neurons, APP undergoes an endoproteolytic cleavage mediated by the 'secretases' in which the initial cleavage by α- or β-secretase determines the level of Aβ production. Subsequently, the γ-secretase yields soluble APP fragments (sAPPα and sAPPβ), then processed for Aβ peptides of 38-43 residues. We investigated subcellular lipid rafts, which are the main site of pro-amyloidogenic processing of APP by BACE 1 and γ-secretase catalytic subunit PS1 with J20 mice and N2a cells transgenic for hAPP/Swe (familial AD). Exposure of J20 mice for 150 hours to nPM increased lipid oxidation (4-HNE) and increased proamyloidogenic processing of APP on lipid raft subcellular fractions. The lipid raft responses to nPM were regionally selective, arising in cerebral cortex, but not in cerebellum, which parallels the regionality of Aβ deposits in transgenic mice and humans. *In vitro,* N2a-APP/Swe cells modeled brain responses to nPM, with dose-dependent production of NO, oxidative damage (4-HNE, 3-NT), and lipid raft alterations of APP that increased Aβ peptides. The anti-oxidant n-acetyl-cysteine (NAC) attenuated oxidative damage and lipid raft alterations of APP processing. These novel findings identify neuronal lipid rafts as targets of oxidative damage in the proamylodogenic effects of air pollution.

Abstract Citation