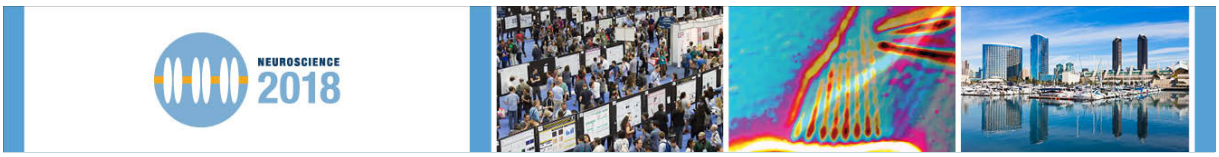

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474.11 / S16 - Effects of a novel gamma secretase modulator on traffic-related air pollution exposure: Implication in the amyloidogenic processing of APP and cognitive impairment

November 6, 2018, 8:00 AM - 12:00 PM | SDCC Halls B-H

Presenter at Poster
Tue, Nov. 6, 2018, 10:00 AM - 11:00 AM

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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 (Cacciotttolo et al 2017). TRAP exposure increases the levels of endogenous amyloid beta (Aβ) peptides in rodents after chronic exposure (Levesque et al. 2011). Multiple evidences suggest that accumulation or overproduction of Aβ peptides is one of the main cause of Alzheimer disease (AD) (Zhang et al. 2011). Amyloid-β peptides are generated following a proteolytic processing of the amyloid precursor protein (APP) by β- and γ-secretases. γ-secretases generates the most abundant Aβ40 and Aβ42 isoforms and the latest is considered to be the key pathogenic species in AD. γ-secretase modulators (GSMs) are the last generation drugs that target Amyloid peptides (Kounnas MZ et al. 2010). Among them a novel soluble γ-secretase modulator (BPN-15606) has been shown to strongly and selectively decrease Aβ42 levels (Wagner SL et al 2017). To evaluate whether pharmacological inhibition of Aβ production during exposure to a nano-scale subfraction of TRAP (nPM) attenuates the amyloidogenic processing of APP and has impact on pathological AD hallmarks, we treated C57BL/6JN mice with the γ-secretase modulator BPN-15606. 3 months old male mice were exposed to nPM for 8 weeks, 3day/w, 5hr/d and fed with regular diet or 10 mg/kg GSM in the chow for 1 week before and during exposure to air pollution. Cerebral cortices were collected and analyzed by MSD multiplex ELISA for the quantification of Aβ40 and Aβ42 peptides. Mice exposed to nPM had elevated levels of Aβ40 and 42 peptides, which were reduced by 35% and 45%, in mice exposed to both nPM and GSM. Moreover, nPM induction of the microglial marker Iba1, in

hippocampal subfields by nPM was significantly attenuated by the GSM. The strong connection between microglia inflammatory responses due to nano-particulate exposure and Aβ peptides confirm the possible role of endogenous Aβ levels in cognitive changes. Our data suggest that cognitive impairment due to air pollution exposure might be ameliorated through the manipulation of the APP processing and the novel γ-secretase modulator drugs could be the lead on this path.

Abstract Citation