A novel pharmacological intervention to neuroinflammatory outcomes of air pollution: the gamma secretase modulator BPN-15606 attenuated microglial and amyloid induction by urban nano-particulate (nPM) in young male C57BL/6J mice.

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Background Urban traffic-derived nano-particulate matter (nPM) increases the levels of endogenous amyloid beta (Aβ) peptides in rodent brains (1,2). Amyloid-β peptides Aβ40 and Aβ42are generated from the amyloid precursor protein (APP) by β- and γ-secretases. γ-secretases generate the peptides. The γ-secretase modulators (GSMs) are novel drugs targeting the secretase enzyme complex of APP processing (3). The new GSM BPN-15606 selectively decrease Aβ42 levels in rodent brains (3,4).

Method To evaluate whether pharmacological inhibition of Aβ production during nPM exposure attenuates the amyloidogenic processing of APP and has impact on pathological AD hallmarks, we treated C57BL/6J mice with the γ-secretase modulator BPN-15606. 3 month old male mice were exposed 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 cortexes were analyzed by multiplex ELISA for Aβ40 and Aβ42 peptides and by immunohistochemistry for the microglial marker, Iba1.

Result Mice exposed to nPM and fed BPN-15606 had decrease of Aβ40 and 42 peptides by 35% and 45% respectively. Moreover, induction of the microglial marker Iba1, in hippocampal subfields by nPM was significantly attenuated by the GSM.

Conclusion The strong connection between microglia inflammatory responses due to nano-particulate exposure and Aβ peptides are consistent with a role of endogenous Aβ levels in cognitive impairments from air pollution. The efficacy of BPN-15606 in attenuating pro-inflammatory and pro-amyloidogenic effects of AAP suggest that the GSMs may have broader uses in AD prevention.

1, Levesque et al 2011, PMID 21864400; 2, Cacciottolo et al 2017, PMID 28140404; 3, Kounnas et al. 2010, PMID 20826309; 4, Wagner et al 2017, PMID 28416568.

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