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 Aβ42 are 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 cortices 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 nanoparticulate 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.


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