Effects of oxidative stress and inflammation induced by ultrafine particles on Alzheimer disease onset

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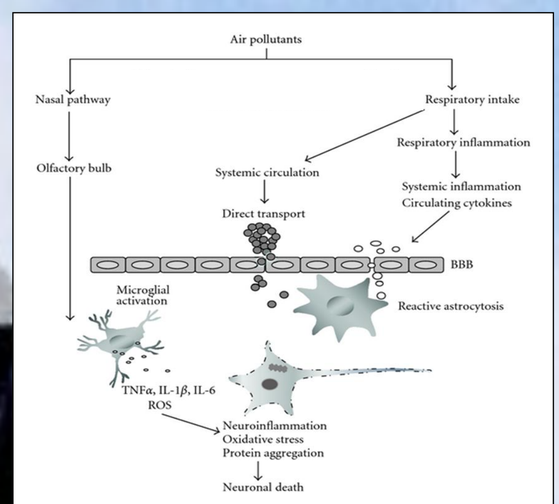
BACKGROUND

Alzheimer's disease (AD) is a neurodegenerative illness affecting the elderly population, characterized by plaques of Aβ42 aggregates, neurofibrillary tangles and neuronal loss (Allsop, 2000). Several epidemiological studies propose that air pollution may exert adverse effects on central nervous system (CNS) functions and that these effects are chronic, as they begin during childhood and may take time to result in a pathological outcome. Particulate matter (PM) is a heterogeneous mixture that includes chemicals, metals and soils, and its sources comprise motorized vehicles, diesel-powered equipment, industrial and residential fuel combustion, and other industrial processes. Ultrafine particles (UFPs, d_{ae} < 100nm), which seems to be able to reach the brain through alternative ways including olfactory bulb and peripheral circulation, cause the greatest health effects (Block and Calderón-Garcidueñas, 2009; Genc et al., 2012). Inflammation and oxidative stress have been suggested as underlying mechanisms by which PM exerts its harmful action on CNS (Genc et al., 2012).

OBJECTIVE

The aim of this work was to evaluate the activation of oxidative stress and inflammation in CNS of mice exposed to UFPs and to elucidate putative physiopathological correlations with neurodegeneration.



(Modified from Genc et al., 2012)

MATERIALS AND METHODS

UFPs derived from two different anthropogenic sources were used: DEP, from EURO 4 diesel engine emission, and BC, from pellet boiler biomass emission (ENEA). Male BALB/c mice were submitted to single or repeated intratracheal instillation of BC and DEP (50µg); in parallel, control mice were always considered (sham). Cortex, cerebellum and hippocampus from sham and treated mice were screened for markers of inflammation and oxidative stress (iNOS, HO-1), endoplasmic reticulum stress (Hsp70), a putative pro-carcinogenic marker (Cyp1B1) and markers related to the onset of Alzheimer Disease (AD) (P-APP, APP, BACE1, Tau, P-Tau Ser199).

RESULTS

After single BC and DEP instillation, we observed an increase in HO-1, Hsp70 and iNOS levels in all brain districts, while Cyp1B1 and markers of neurodegeneration did not show significant alteration (**Fig 1**). After repeated BC and DEP instillations, the induction of Hsp70 and iNOS was maintained in all districts. HO-1 seemed to turn back to control levels in cortex, while in cerebellum and hippocampus it remained activated. Moreover, Cyp1B1 showed a significant increase, especially after DEP treatment. Interestingly, after repeated UFPs treatments we observed an increase in P-APP/APP ratio and in BACE-1 levels, the latter with the exception of cerebellum (**Fig 2**). The analyses of Tau total protein and Tau phosphorylation on Ser 199 did not show significant alteration.

Single Intratracheal instillation

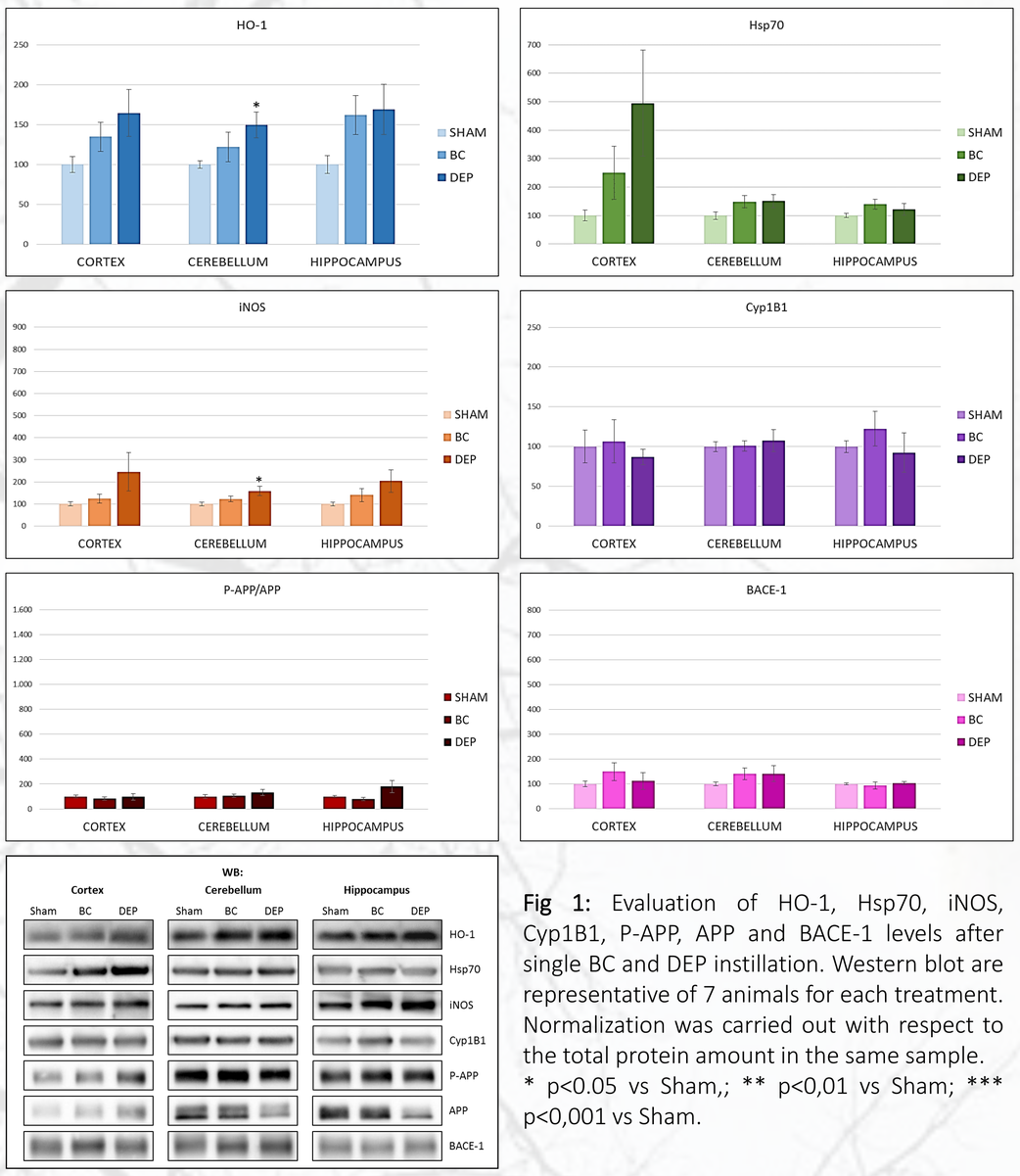


Fig 1: Evaluation of HO-1, Hsp70, iNOS, Cyp1B1, P-APP, APP and BACE-1 levels after single BC and DEP instillation. Western blot are representative of 7 animals for each treatment. Normalization was carried out with respect to the total protein amount in the same sample.
* p<0.05 vs Sham,; ** p<0,01 vs Sham; *** p<0,001 vs Sham.

Repeated Intratracheal instillations

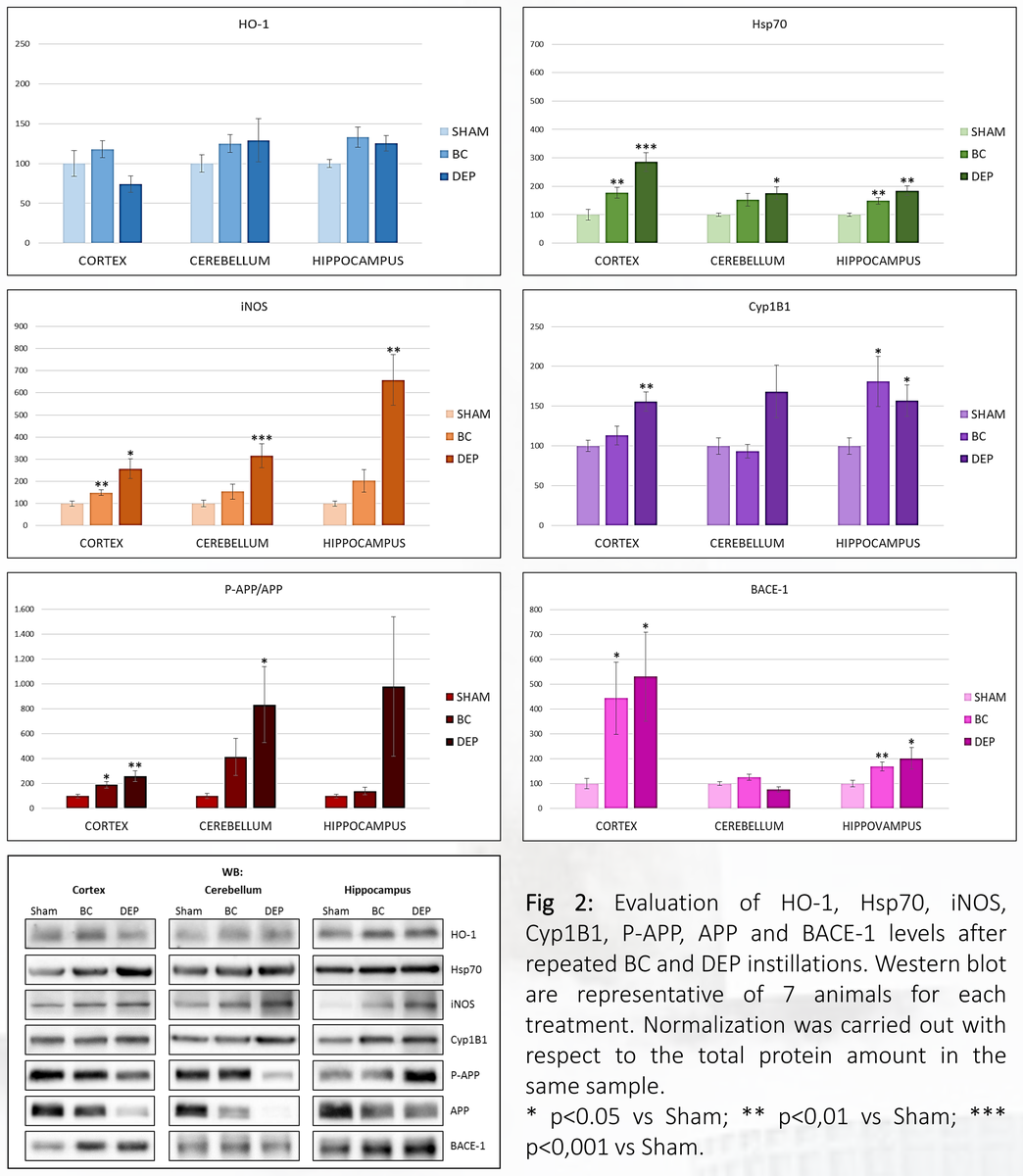


Fig 2: Evaluation of HO-1, Hsp70, iNOS, Cyp1B1, P-APP, APP and BACE-1 levels after repeated BC and DEP instillations. Western blot are representative of 7 animals for each treatment. Normalization was carried out with respect to the total protein amount in the same sample.
* p<0.05 vs Sham; ** p<0,01 vs Sham; *** p<0,001 vs Sham.

DISCUSSION

Our results suggested that single BC and DEP instillation induce in mouse brain oxidative stress, endoplasmic reticulum stress and inflammation, while typical Alzheimer disease related proteins seemed not affected. The repeated instillation was able to sustain oxidative stress and inflammation, and it also induced increase of Cyp1B1 and BACE-1 levels and changes in APP total levels and phosphorylation. Moreover, BC seemed to be less effective than DEP.

In conclusion, we can hypothesize that UFPs or inflammatory mediators produced in lungs can translocate to the brain after both acute and repeated BC and DEP treatment. When the exposure to UFPs occurs in chronic, the effects observed could promote neuronal damage and AD onset, as inflammation and oxidative stress are considered common denominators of neurodegenerative disease.

References:
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