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Neurotoxicological outcome of a chemical and radiological co-exposure in rat: low dose gamma irradiation and inhalation of tungsten particles

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Background and Purpose

Toxicology studies gradually tend to consider the concept of exposome in their experimental design. Each individual is indeed exposed to a unique and wide range of stressors simultaneously, and these stressors might interact. Combining them therefore provides a more realistic representation of an individual's exposome and the toxicity they experience.

Nuclear industry workers integrate specific stressors in their occupational exposome, including external gamma irradiation. It is of particular interest due to uncertainties regarding its dose-response curve in the low dose range, some studies even reporting beneficial neuroprotective effects. Nuclear industry workers are also subject to particulate aerosol inhalation, a major cause of contamination. Our chemical stressor, Tungsten (W), is an emerging contaminant in the environment, used in various industrial or military settings due to its remarkable physical properties. More specifically, nuclear fusion reactors integrate a W shielding which is eroded by the plasma stream during normal operation. The W particles produced pose a risk of exposure of nuclear workers during maintenance, dismantling operations, or loss of vacuum accidents. Although W was initially considered an inert metal, recent national authorities report raise questions about its effective toxicity.

Our aim is to explore the differential neurotoxicological effects of a radiological and chemical co-exposure combining W particles inhalation and low dose gamma irradiation and study the mechanisms involved.

Methods

12-week-old male Sprague-Dawley rats were exposed to a polydisperse aerosol of metal W particles in a nose-only setting (80 mg.m⁻³, 30 minutes) and/or to a full body low dose gamma irradiation (50 mGy, 50 mGy.min⁻¹). 24 hours (24h) and 28 days (28d) post-exposure, biological samples were collected: whole brains, brain structures, olfactory epithelium, lung, kidney, and plasma. Processes of interest included neuronal integrity, cell survival, oxidative stress, and inflammation in the frontal cortex (FC) and olfactory bulb (OB).

Results

While no changes could be observed in OB or FC in apoptosis or proliferation with the markers used, histological studies did unveil statistically significant differences more often between co-exposed and control groups for several parameters, than groups exposed to stressors alone. We observed an

increase at 24h and 28d of total cellular density in FC. Microglial density increased at 24h and decreased at 28d in the FC, while activation phenotypes remained unchanged. In OB, both microglial density and activation increased after 28d in the co-exposed group. Analyzing a specific suffering phenotype in FC, we observed a decrease of the density of donut-like neurons at 24h, and an increase after 28d.

Gene expression analysis via RT-qPCR revealed a strong heterogeneity of response between FC and OB and the main significant differences were observed for the co-exposed group compared to control. A significant increase of the expression of antioxidant genes in the FC at 28d was observed in parallel with a decrease of these genes in OB. In terms of inflammation, we measured an increased expression of MCP1 in FC at 24h and a decreased expression of TNF α in OB at 28d.

Conclusions

Our goal was to determine whether differential effects could be observed on target processes involved in cerebral toxicity. Co-exposure appears to cause significant effects when compared to control and single stressor groups, hence our discussion and conclusion will focus on the co-exposed groups.

Although we see modulations of cell density for microglia and donut-like neurons, our findings do not suggest an increase in cell death or proliferation.

The temporal concordance between the microglial depletion in FC and the increase in density in OB at 28d suggests a potential migration of these cells from the FC to the OB in the time window considered. Similarly, the increase in microglial density in FC at 24h is probably caused by a microglial migration from deeper layers of the FC or neighboring microstructures. The changes observed in terms of cytokines gene analysis support the migratory hypothesis as MCP1 expression increases in FC at 24h. The decrease in TNF α gene expression in OB at 28d could reflect microglial activation towards anti-inflammatory phenotypes.

The antioxidant response appearing in FC at 28d could be the consequence of a disruption in the cerebral microenvironment caused by the microglial depletion. This unbalance in microenvironment could also be increasing the density of donut-like neurons at 28d in FC.

Overall, our results suggest heterogeneous responses among structures and an increased effect when combining our stressors. Ongoing experiments are investigating antioxidative mechanisms (transcription factor translocation) and hypoxia contribution. ICP-MS studies will determine the impact of irradiation on the biodistribution of W in our target organs. Additionally, the increase in total cell density observed in FC at both time points cannot be explained entirely by microglial density modulations. Other cell types will be considered in this process (progenitor cells, peripheral cell intrusion). As the modulations are still visible or reversed at 28d, studies should be undertaken beyond this time point to question their persistence.

Keywords: Co-exposure, Inhalation, Irradiation, Neurotoxicity, Rat