Modifications of Cerebral Cholesterol Metabolism in Rats Following Internal Contamination by Depleted Uranium

R. Racine[a], Y. Gueguen[a], P. Gourmelon[b] and M. Souidi[a]

[a] *IRSN, DRPH/ SRBE, LRTOX, BP n° 17, 92262 Fontenay aux Roses, France;* [b] *IRSN, DRPH, BP n° 17, 92262 Fontenay aux Roses, France*

maamar.souidi@irsn.fr

The occurrence of uranium in the environment results from both natural and human origins. Its enrichment in nuclear power plants produces two compounds: enriched uranium (EU) and depleted uranium (DU). The dispersion of uranium in the environment sets human populations at risk of being contaminated mainly through ingestion. After entering the body, uranium builds up in several organs including the brain, where it can induce behaviour disorders after chronic contamination. Brain is the most lipidic organ of the body: half of its weight is due to phospholipids and it contains about 25% of the body's cholesterol. Cholesterol is essential to brain function due to its various roles, ranging from membrane structure and myelin sheath constitution to synthesis of active molecules such as neurosteroids. Moreover, it is well known that some disruptions in cholesterol metabolism are involved in neurological pathologies, such as Alzheimer's disease or Niemann-Pick C disease. Considering the importance of cerebral cholesterol and the susceptibility of brain to uranium exposure, we studied the effect of uranium contamination on cerebral cholesterol metabolism. Therefore, rats were exposed during 9 months to DU through drinking water at a concentration of 40 mg/l (twice the highest environmental level, equivalent to 1 mg/rat/day). After DU contamination, the HDL-cholesterol level in plasma decreased (25%) whereas plasma level of 27-hydroxycholesterol increased (200%). The mRNA levels of several proteins involved in cerebral cholesterol metabolism were modified. Gene expression of CYP46A1, involved in cholesterol catabolism, was increased by 39%. HMGCoA Synthase (HMGS) mRNA levels rose from 91%. Gene expression of three proteins involved in cholesterol transport was also modified: SR-B1 (+34%), ABC A1 (+34%) and Apo E (+75%). Finally, mRNA levels of nuclear receptors PPAR? and PPAR? were increased (46% and 36% respectively). Conversely, gene expression of RXR was reduced by 29%. DU contamination enhances at the same time pathways that increase the cholesterol pool in the cell (uptake and synthesis) and pathways that lead cholesterol out of the cell (detoxification and efflux). This would lead to an overall balanced cholesterol pool in the brain: whatever pathways are primarily altered by DU, the compensatory pathways are also activated. Besides, it is noteworthy that the modification of HDL-cholesterol and 27-hydroxycholesterol plasma levels might foreshadow a disruption of cholesterol metabolism at body level.

Article published by EDP Sciences and available at http://www.radioprotection.org or http://dx.doi.org/10.1051/radiopro:2008585