Goldschmidt 2021 Abstract
https://doi.org/10.7185/gold2021.5623

Using copper stable isotopes in the detection of Alzheimer's Disease

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Alzheimer's disease (AD) is a leading cause of death in high-income countries, and afflicts one out of ten people 65 or older worldwide. One of the major physiological features of AD is the formation of senile plaques associated with extracellular deposition of metal-rich (e.g. Cu, Zn) amyloid β (Aβ) fibrils and the accumulation of tau proteins. The natural stable isotopic composition of metals such as Zn, Cu and Fe vary between bodily organs and show very limited natural variations. They are therefore powerful tracers of metal inbalance in the body. In particular, blood is isotopically distinct in Zn, Cu and Fe from the brain. The speciation (bonding) of metals in Aβ fibrils is different to that in the healthy brain, and this can modify the isotopic distribution of metals between the brain and body fluids. Here we will present serum and brain Cu isotopic compositions of (i) APPswe/PSEN1dE9 transgenic mice (a model of AD), (ii) wild-type (WT) controls for 3, 6, 9 and 12-month-old mice, (iii) human brain tissues including both AD and healthy patients (Moynier et al. 2020) , and (iv) AD-afflicted and healthy human cerebropinal fluids (work in progress). We find that AD-afflicted brains of mice and humans are isotopically lighter for Cu than brains of healthy mice and patients. We suggest that this reflects an increase of Cu(I) associated with the formation of Aβ fibrils and accumulation of tau proteins. In the mice, the Cu isotopic composition of the brains and serum were correlated, implying copper transport between these two reservoirs, in particular a transfer of Cu(I) from the brain to the serum. These data suggest that the Cu stable isotopic composition of body fluid(s) may have the potential to be used as detection tools for the formation of Aβ fibrils in the brain.

Moynier et al. A&D dadm, 2021 doi: 10.1002/dad2.12112