Distribution of brain Gd relative to other trace metals

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Conflicts of Interest

No conflicts of interest reported.

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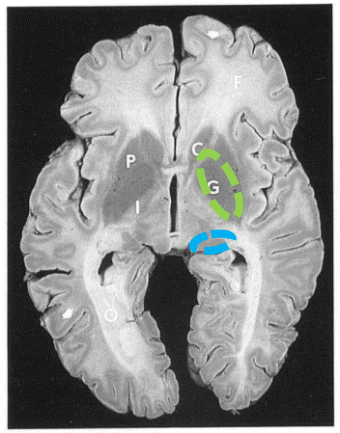
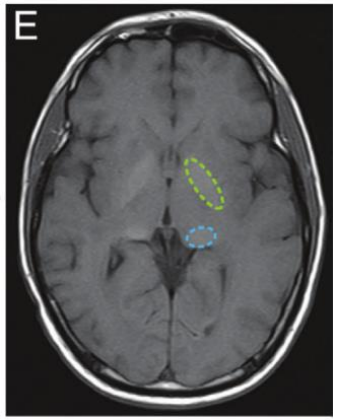
Apparent Iron Correlation

Stain of Fe^{3+} in brain



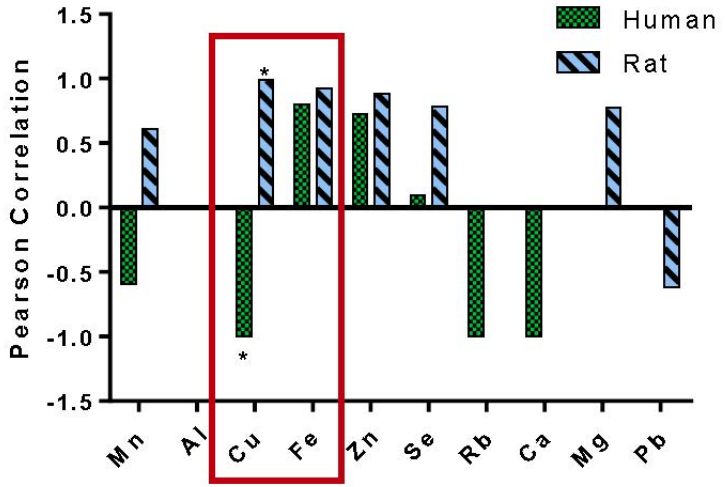
MRI of Gd^{3+} in brain



Globus pallidus
Thalamus

Image sources: J Neurol Sci. 2003;207(1-2):99–102. | Radiology. 2015;275(3):150025.

Significant, Paradoxical Copper Correlation



P < 0.10 by Sidak-adjusted T-test of Pearson correlation
GBCA Human/Rat data: Gadobutrol

Data sources:
Physiol Rev. 1987;67(3):858-901.
Toxicol Appl Pharmacol. 1981;61(2):227-33.
Science. 1977;197(4309):1187-9.
Biol Trace Elem Res. 1996;52(2):181-92.
Biol Trace Elem Res. 1987;13(1):1-17.
J Neurol Sci. 1997;146(2):153-66
Brain Res. 1982;251(1):180-2.
J Neurochem. 1989;52(6):1830-6.
J Neurochem. 1994;62(3):1097-101.
Invest Radiol. 2017;52(7):396-404
Invest Radiol. 2016;51(7):447-53.

Findings from Cu transport/deposition in the brain can inform Gd research

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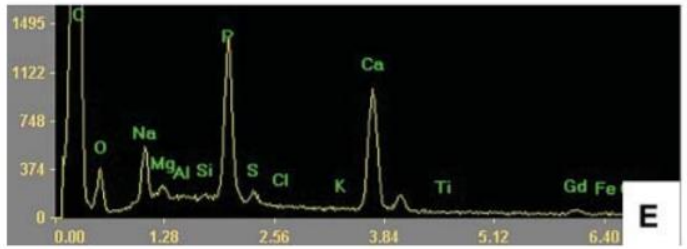
Gd brain protein binding

Minimal Data

Associated with Ca/P Insoluble Particles



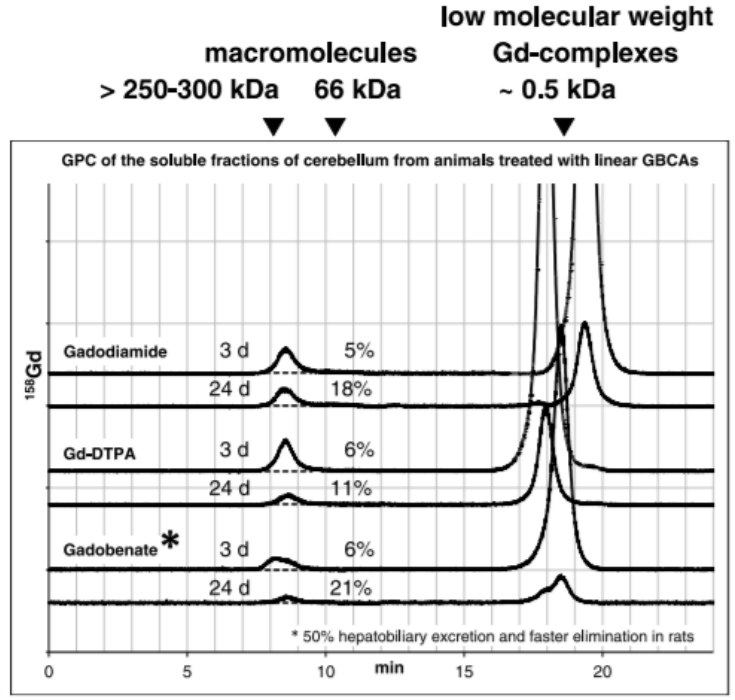
Acta Radiol. 2010;51(10):1126-36.

and with 60-300 kDa Soluble Pa

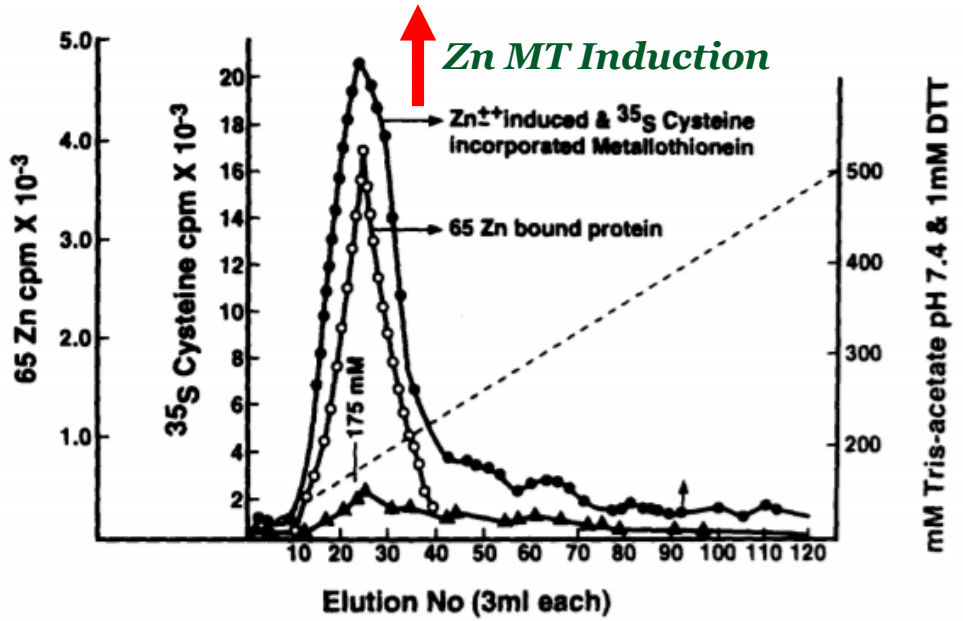
Invest Radiol. 2017;52(7):396-404.

Iron comparison: primarily stored/solubilized by ferritin

Copper comparison: stored wi metallothionein (MT)



MT-binding metals induce MT-production:



Neurochem Int. 1995;27(1):1-22.

Gd-binding proteins in rats may be MT-based, and different than in humans

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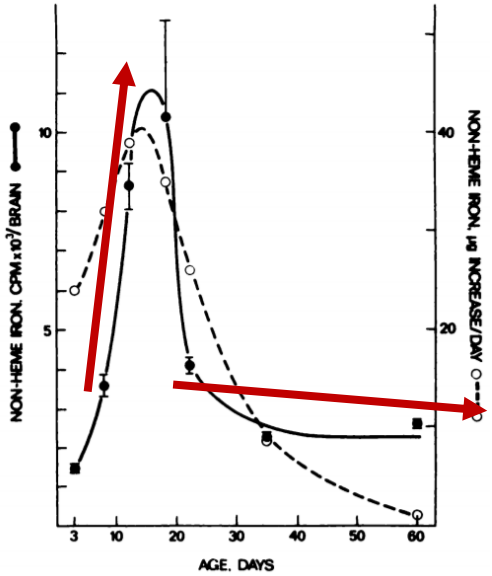
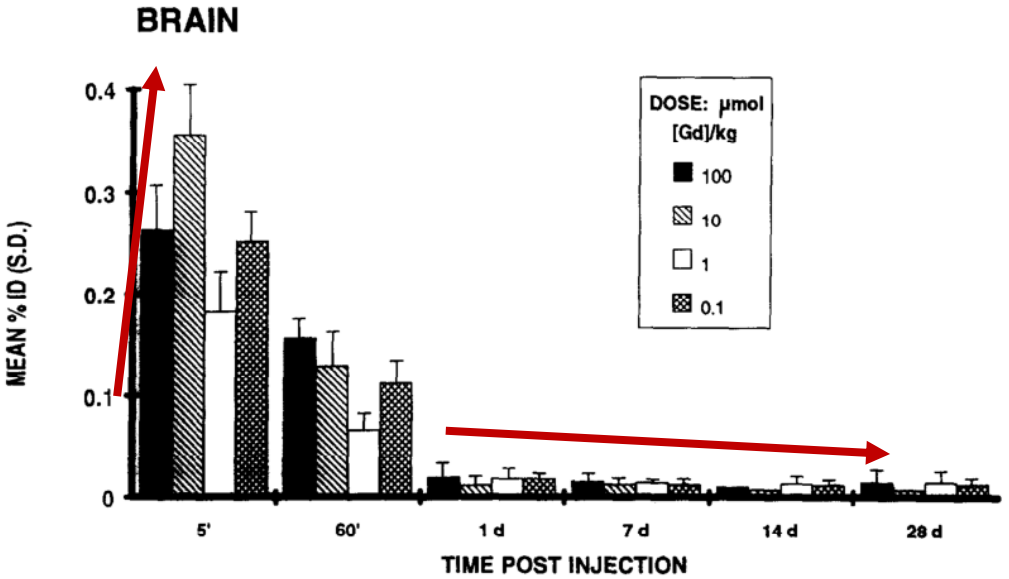
Fe/Cu Brain Transport Relative to Gd

Fe uptake by transferrin, and *very slow* turnover:



J Nutr. 1977;107(6):1075-81.



Nucl Med Biol. 1993;20(5):679-91.

No Δ from ~1 m-1 yr for linear GBCAs

FDA MIDAC Meeting Sept 2017. Bayer Healthcare

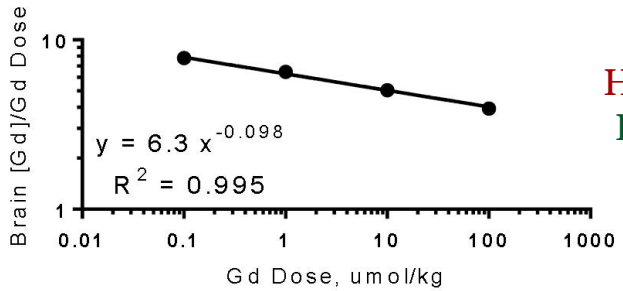
Cu uptake/efflux by ATP7A. Efflux is dependent on Cu-status:

Brain elimination half-life:

Cu-deficient	Cu-adequate
6930 d	457 d

Anal Biochem. 1994;221(2):243-9.

Higher [Cu] ➡ Faster Brain CL
Lower [Cu] ➡ Lower Brain CL



Adapted from: Nucl Med Biol. 1993;20(5):679-91.

High Gd Dose ➡ High Brain CL
Low Gd Dose ➡ Low Brain CL

Gd brain PK similar to both Fe and Cu

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