Published in final edited form as:

JAMA Neurol. 2016 January 1; 73(1): 13–14. doi:10.1001/jamaneurol.2015.2960.

Blood-brain Barrier Permeability and Gadolinium: Benefits and Potential Pitfalls in Research

Axel Montagne, PhD,

Zilkha Neurogenetic Institute, Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, 1501 San Pablo Street, Los Angeles, CA 90089, USA

Arthur W. Toga, PhD, and

Institute for Neuroimaging & Informatics, Department of Neurology, University of Southern California, 1501 San Pablo Street, Los Angeles, CA 90089, USA

Berislav V. Zlokovic, MD, PhD*

Zilkha Neurogenetic Institute, Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, 1501 San Pablo Street, Los Angeles, CA 90089, USA

The blood-brain barrier (BBB) normally prevents blood-derived products, pathogens and cells from entering into the brain¹. The BBB is disrupted in multiple neurological disorders resulting in entry and accumulation in neurons and the neuronal interstitium of several toxic molecules from blood. These include fibrinogen, thrombin, hemoglobin, iron-containing hemosiderin, free iron, plasmin (an extracellular matrix degrading enzyme), environmental toxins and metals, and possibly microbial pathogens, which have either direct neuronal toxic effects and/or can lead to oxidant stress, activation of pro-inflammatory microglia response and/or lead to disruption of neuronal matrix causing neuronal injury, neurodegenerative changes and/or neuronal loss¹. Additionally, the BBB breakdown leads to a loss of brain's immune privilege, which may result in the formation of auto-antibodies against different neuronal cell membrane proteins and/or axonal proteins.

Magnetic resonance imaging (MRI) with gadolinium-based contrast agents (GBCAs) have been used for more than 25 years in more than 100 million patients with a broad spectrum of the central nervous system (CNS) disorders with BBB breakdown, ranging from multiple sclerosis, stroke and infection to brain tumors, for both detection and therapeutic guidance². An improved dynamic contrast-enhanced MRI method (DCE-MRI) using GBCAs with an individual arterial input function curve has been developed for research purposes to measure the BBB permeability K_{trans} constant value in the normal brain and in patients with mild dementia, which typically have 10–100 times lower BBB permeability K_{trans} values compared to patients with brain tumors, stroke or infections³. This DCE-MRI method has

*To whom address correspondence should be directed. zlokovic@usc.edu.

Conflict of interest disclosure

None of the authors has conflict of interest.

Role of the Funder/Sponsor:

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

allowed us to determine the regional BBB permeability in different gray and white matter regions including subregions such as the dentate gyrus, CA1 and CA3 in the hippocampus. Moreover, this study revealed that a moderate age-dependent BBB breakdown during normal human aging begins in the hippocampus which is worsened in patients with mild dementia suggesting that BBB breakdown could play a role in etiology and/or pathogenesis of dementias, and is likely an important new diagnostic and therapeutic target for Alzheimer's disease and other dementias.

The extraordinarily positive safety record of GBCAs with serious adverse reactions only in the range of 0.03% of all administrations² has made possible research studies in humans to focus on pathologically relevant changes in the BBB permeability³. However, heavy metals such as gadolinium are also highly toxic to mammals and humans, which precluded using free Gd^{3+} as a human contrast agent. Several Food and Drug Administration (FDA) approved GBCAs have Gd^{3+} bound to a chelating molecule that renders GBCAs sufficiently safe for acute intravenous use in humans while preserving gadolinium's paramagnetic activity for MRI detection. Critical to the safety of any GBCAs is for free Gd^{3+} to remain tightly bound to its chelating agent as long as it remains in the patient's body. With normal kidney function, the biological half-life of GBCAs for CNS indications is between 90–120 min, which eliminates significant dissociation of Gd^{3+} from its chelating agent resulting in barely detectable release and accumulation of free toxic Gd^{3+} in the body fluids and tissues².

GBCAs were initially believed to be risk-free. However, findings in patients with renal insufficiency that developed nephrogenic systemic fibrosis (NSF) likely related to dechelation of toxic Gd^{3+} from some forms of GBCAs and deposition in the skin and internal organs², have changed this view. The cause of NSF is not yet fully understood, but the chemical structure of GBCAs, which determines their stability *in vivo*, and in human serum seems to play a key role. Namely, so-called macrocyclic forms of GBCAs compared to the linear forms have shown to be considerably more resistant to dechelation of toxic Gd^{3+} *in vivo*, which in turn correlated with clinical findings showing that NSF is predominantly associated with the linear form of GBCAs that more rapidly dissociate free toxic Gd^{3+} under stress². In addition to setting a new standard of care by incorporating patient renal function before screening, these studies suggest macrocyclic GBCAs is a likely safer variant.

Over the last year, a few new retrospective studies have been conducted to determine whether or not gadolinium accumulates in the brain after multiple GBCAs administrations for neurological indications in patients with normal renal function (Table 1). Retention of gadolinium in the globus pallidus and the dentate nucleus has been suggested based on T1-weighted (T1w) MR signal hyperintensity^{2,4,5}, although possible contributions of other deposits due to BBB breakdown were difficult to rule out. However, mass spectrometry (MS) analysis also suggested retention of gadolinium in some CNS regions in patients with brain tumors with significant BBB breakdown⁴, and the electron microscopy analysis of post-mortem brain tissue confirmed gadolinium deposits in the endothelial walls and the neuronal interstitium⁵, but not the neuropil itself, in these patients. The nature of gadolinium deposits and whether they contain toxic free Gd^{3+} or not, or mainly non-toxic gadolinium chelates remains unknown, but health adverse effects have not been reported so

far. Interestingly, gadolinium retention was found again associated mainly with the linear, chemically less-stable GBCAs agents, raising a question whether, similar to NSF, linear GBCAs carry a higher risk of gadolinium accumulation in the brain. In support of this concept, using both MR T1w and MS analysis two recent studies reported barely detectable or no deposition of gadolinium in the brain in patients with brain tumors, multiple sclerosis or cancer metastasis receiving multiple injections of two macrocyclic GBCAs^{2,6,7} (Table 1). Similar studies in rodents using MR and MS analyses⁸ and our unpublished data (not shown) also indicated that repeated injections of linear GBCAs, but not macrocyclic, led to significant gadolinium retention in the brain.

GBCAs have been extremely valuable to patients worldwide for decades. Their use, however, has been and should continue to be guided by the risk-benefit ratio. Last month the FDA launched an investigation on the risk of brain deposits following repeated use of GBCAs (<http://www.fda.gov/Drugs/DrugSafety/ucm455386.htm>)⁹. While the clinical world is awaiting first and foremost to see whether some adverse health effects will be reported, as none was reported so far, some intriguing research questions remain, for example **i)** which form of gadolinium deposits in the brain - toxic or non-toxic; **ii)** is there a safe number of gadolinium injections or time interval between the injections for patients with severe BBB breakdown for life saving indications such as brain tumors, metastasis, infections or active MS; and **iii)** does gadolinium remains in the brain of individuals with an intact BBB with no neurological disease or with only a moderate BBB breakdown due to mild dementia³ that is typically one order of magnitude lower than BBB breakdown in studied patients with brain tumors or stroke. To be on a safe side, the research studies should probably turn meanwhile to gadolinium preparation with a low risk for retention in the brain such as macrocyclic GBCAs reported in the recent studies⁶⁻⁸.

Acknowledgments

Funding/Support:

Dr. Zlokovic's research is supported by the National Institutes of Health (NIH) through grants R01AG023084, R01NS090904, R01NS034467, R01AG039452, 5P50AG005142-30, and the Cure for Alzheimer's Fund. Dr. Toga's research is supported by the NIH through grants P41EB015922, U01AG024904, and the Alzheimer's Association 003278.

References

1. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci.* 2011; 12(12):723–738. [PubMed: 22048062]
2. Kanal E, Tweedle MF. Residual or retained gadolinium: practical implications for radiologists and our patients. *Radiology.* 2015; 275(3):630–634. [PubMed: 25942418]
3. Montagne A, Barnes SR, Sweeney MD, et al. Blood-brain barrier breakdown in the aging human hippocampus. *Neuron.* 2015; 85(2):296–302. [PubMed: 25611508]
4. Kanda T, Ishii K, Kawaguchi H, et al. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology.* 2014; 270(3):834–841. [PubMed: 24475844]
5. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology.* 2015; 275(3):772–782. [PubMed: 25742194]

6. Kanda T, Osawa M, Oba H, et al. High signal intensity in dentate nucleus on unenhanced T1-weighted MR images: association with linear versus macrocyclic gadolinium chelate administration. *Radiology*. 2015; 275(3):803–809. [PubMed: 25633504]
7. Radbruch A, Weberling LD, Kieslich PJ, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. *Radiology*. 2015; 275(3):783–791. [PubMed: 25848905]
8. Robert P, Lehericy S, Grand S, et al. T1-weighted hypersignal in the deep cerebellar nuclei after repeated administrations of gadolinium-based contrast agents in healthy rats: difference between linear and macrocyclic agents. *Invest Radiol*. 2015; 50(8):473–480. [PubMed: 26107651]
9. US Food Drug Administration. FDA drug safety communication: FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI). <http://www.fda.gov/Drugs/DrugSafety/ucm455386.htm>. Accessed July 27, 2015

Table 1

Detection of blood-brain barrier permeability with gadolinium and brain deposition in neurological disorders.

Chelating Agent Chemical Structure	BBB Permeability	Brain Deposition	Method of Detection	Neurological Disorders	Number of Injections mean [range]	Interval between the First and Last MRI	References
Gadobenate dimeglumine <i>Linear</i>	YES	YES	MRI	Primary Brain tumors, Brain Metastasis, Multiple Sclerosis, Stroke	4.6 [3–11]	7.8 months	36 months
Gadopentetate dimeglumine <i>Linear</i>	YES	YES	MRI + MS		4.6 [2–11]	4.6 months	21 months
Gadodiamide <i>Linear</i>	YES	YES	MRI +MS + EM		6.4 [2–29]	7.0 months	45 months
Gadoterate meglumine <i>Macrocyclic</i>	YES	NO	MRI	Primary Brain Tumors, Brain Metastasis, Multiple sclerosis	7.1 [6]	5.8 months	41 months
Gadoteridol <i>Macrocyclic</i>	YES	NO	MRI + MS		2.6 [2–15]	8.1 months	21 months

BBB, Blood-Brain Barrier; MRI, Magnetic Resonance Imaging; MS, Mass Spectroscopy; EM, Electron Microscopy.