Année de publication : 2019

Nathalie Fretellier, Agnès Granottier, Marlène Rasschaert, Anne-Laure Grindel, Fannie Baudimont, Philippe Robert, Jean-Marc Idée, Claire Corot (2019 Feb 1)

Does Age Interfere With Gadolinium Toxicity and Presence in Brain and Bone Tissues?: A Comparative Gadoterate Versus Gadodiamide Study in Juvenile and Adult Rats.

Investigative radiology : 54 : 61-71 : DOI : 10.1097/RLI.0000000000000517

Résumé

Objectives

The main objective of the study was to assess the effect of age on target tissue total gadolinium (Gd) retention after repeated administration of gadodiamide (linear) or gadoterate (macrocyclic) Gd-based contrast agent (GBCA) in rats. The secondary objective was to assess the potential developmental and long-term consequences of GBCA administration during neonatal and juvenile periods.

Materials and Methods

A total of 20 equivalent human clinical doses (cumulated dose, 12 mmol Gd/kg) of either gadoterate or gadodiamide were administered concurrently by the intravenous route to healthy adult and juvenile rats. Saline was administered to juvenile rats forming the control group. In juvenile rats, the doses were administered from postnatal day 12, that is, once the blood-brain barrier is functional as in humans after birth. The tests were conducted on 5 juvenile rats per sex and per group and on 3 adult animals per sex and per group. T1-weighted magnetic resonance imaging of the cerebellum was performed at 4.7 T during both the treatment and treatment-free periods. Behavioral tests were performed in juvenile rats. Rats were euthanatized at 11 to 12 weeks (ie, approximately 3 months) after the last administration. Total Gd concentrations were measured in plasma, skin, bone, and brain by inductively coupled plasma mass spectrometry. Cerebellum samples from the juvenile rats were characterized by histopathological examination (including immunohistochemistry for glial fibrillary acidic protein or GFAP, and CD68). Lipofuscin pigments were also studied by fluorescence microscopy. All tests were performed blindly on randomized animals.

Results

Transient skin lesions were observed in juvenile rats (5/5 females and 2/4 males) and not in adult rats having received gadodiamide. Persisting (up to completion of the study) T1 hyperintensity in the deep cerebellar nuclei (DCNs) was observed only in gadodiamide-treated rats. Quantitatively, a slightly higher progressive increase in the DCN/brain stem ratio was observed in adult rats compared with juvenile rats, whereas no difference was noted visually. In all tissues, total Gd concentrations were higher (10- to 30-fold higher) in the gadodiamide-treated groups than in the gadoterate groups. No age-related differences were observed except in bone marrow where total Gd concentrations in gadodiamide-treated

juvenile rats were higher than those measured in adults and similar to those measured in cortical bone tissue. No significant treatment-related effects were observed in histopathological findings or in development, behavior, and biochemistry parameters. However, in the elevated plus maze test, a trend toward an anxiogenic effect was observed in the gadodiamide group compared with other groups (nonsignificant). Moreover, in the balance beam test, a high number of trials were excluded in the gadodiamide group because rats (mainly males) did not completely cross the beam, which may also reflect an anxiogenic effect.

Conclusions

No T1 hyperintensity was observed in the DCN after administration of the macrocyclic GBCA gadoterate regardless of age as opposed to administration of the linear GBCA gadodiamide. Repeated administration of gadodiamide in neonatal and juvenile rats resulted in similar total Gd retention in the skin, brain, and bone to that in adult rats with sex having no effect, whereas Gd distribution in bone marrow was influenced by age. Further studies are required to assess the form of the retained Gd and to investigate the potential risks associated with Gd retention in bone marrow in juvenile animals treated with gadodiamide. Regardless of age, total Gd concentration in the brain and bone was 10- to 30-fold higher after administration of gadodiamide compared with gadoterate.

M Schmidt-Cernohorska, I Zhernov, E Steib, M Le Guennec, R Achek, S Borgers, D Demurtas, L Mouawad, Z Lansky, V Hamel, P Guichard (2019 Jan 19)

Flagellar microtubule doublet assembly *in vitro* reveals a regulatory role of tubulin C-terminal tails.

Science (New York, N.Y.) : 363 : 285-288 : DOI : 10.1126/science.aav2567

Résumé

Microtubule doublets (MTDs), consisting of an incomplete B-microtubule at the surface of a complete A-microtubule, provide a structural scaffold mediating intraflagellar transport and ciliary beating. Despite the fundamental role of MTDs, the molecular mechanism governing their formation is unknown. We used a cell-free assay to demonstrate a crucial inhibitory role of the carboxyl-terminal (C-terminal) tail of tubulin in MTD assembly. Removal of the C-terminal tail of an assembled A-microtubule allowed for the nucleation of a B-microtubule on its surface. C-terminal tails of only one A-microtubule protofilament inhibited this side-to-surface tubulin interaction, which would be overcome in vivo with binding protein partners. The dynamics of B-microtubule nucleation and its distinctive isotropic elongation was elucidated by using live imaging. Thus, inherent interaction properties of tubulin provide a structural basis driving flagellar MTD assembly.

Viviana Barra, Glennis A Logsdon, Andrea Scelfo, Sebastian Hoffmann, Solène Hervé, Aaron Aslanian, Yael Nechemia-Arbely, Don W Cleveland, Ben E Black, Daniele Fachinetti (2019 Jan 13)

Phosphorylation of CENP-A on serine 7 does not control centromere function.
Nature communications : 175 : DOI : 10.1038/s41467-018-08073-1

Résumé

CENP-A is the histone H3 variant necessary to specify the location of all eukaryotic centromeres via its CENP-A targeting domain and either one of its terminal regions. In humans, several post-translational modifications occur on CENP-A, but their role in centromere function remains controversial. One of these modifications of CENP-A, phosphorylation on serine 7, has been proposed to control centromere assembly and function. Here, using gene targeting at both endogenous CENP-A alleles and gene replacement in human cells, we demonstrate that a CENP-A variant that cannot be phosphorylated at serine 7 maintains correct CENP-C recruitment, faithful chromosome segregation and long-term cell viability. Thus, we conclude that phosphorylation of CENP-A on serine 7 is dispensable to maintain correct centromere dynamics and function.

Année de publication : 2017

Laurence Vernis, Nadine El Banna, Dorothée Baïlle, Elie Hatem, Amélie Heneman, Meng-Er Huang (2018 Dec 28)
Fe-S Clusters Emerging as Targets of Therapeutic Drugs.
Oxidative medicine and cellular longevity : 3647657 : DOI : 10.1155/2017/3647657

Résumé

Fe-S centers exhibit strong electronic plasticity, which is of importance for insuring fine redox tuning of protein biological properties. In accordance, Fe-S clusters are also highly sensitive to oxidation and can be very easily alteredby different drugs, either directly or indirectly due to catabolic by-products, such as nitric oxide species (NOS) or reactive oxygen species (ROS). In case of metal ions, Fe-S cluster alteration might be the result of metal liganding to the coordinating sulfur atoms, as suggested for copper. Several drugs presented through this review are either capable of direct interaction with Fe-S clusters or of secondary Fe-S clusters alteration following ROS or NOS production. Reactions leading to Fe-S cluster disruption are also reported. Due to the recent interest and progress in Fe-S biology, it is very likely that an increasing number of drugs already used in clinics will emerge as molecules interfering with Fe-S centers in the near future. Targeting Fe-S centers could also become a promising strategy for drug development.