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El Hassen Mokrani, Abderrahmane Bensegueni, Ludovic Chaput, Claire Beauvineau, Hanane Djeghim, Liliane Mouawad (2019 Feb 7)

Identification of New Potent Acetylcholinesterase Inhibitors Using Virtual Screening and *In Vitro* Approaches.

Molecular informatics : Early view : DOI : 10.1002/minf.201800118

Résumé

Acetylcholinesterase (AChE) is currently the most favorable target for the symptomatic treatment and reduction of Alzheimer's disease (AD). In order to identify new potent inhibitors of this enzyme, we describe herein a new structure-based virtual screening (SBVS) using the Institut Curie-CNRS chemical library (ICCL), which contained at the screening date 14307 compounds. The strategy undertaken in this work consisted of the use of several docking programs in SBVS calculations followed by the application of a consensus method (vSDC) and a scrupulous visual analysis. It allowed us to obtain a high degree of success, with a yield of almost 86 %, since 12 hits were identified among only 14 molecules tested *in vitro*. Still more remarkably, 6 of these hits were more active than galantamine, the reference inhibitor. These hits were predicted to have good ADMET properties. The two most promising compounds can serve as leads for AD treatment.

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.

Larissa Mourao, Guillaume Jacquemin, Mathilde Huyghe, Wojciech J Nawrocki, Naoual Menssouri, Nicolas Servant, Silvia Fre (2019 Jan 31)

Lineage tracing of Notch1-expressing cells in intestinal tumours reveals a distinct population of cancer stem cells.
Scientific reports : 888 : DOI : 10.1038/s41598-018-37301-3

Résumé

Colon tumours are hierarchically organized and contain multipotent self-renewing cells, called Cancer Stem Cells (CSCs). We have previously shown that the Notch1 receptor is expressed in Intestinal Stem Cells (ISCs); given the critical role played by Notch signalling in promoting intestinal tumourigenesis, we explored Notch1 expression in tumours. Combining lineage tracing in two tumour models with transcriptomic analyses, we found that Notch1+ tumour cells are undifferentiated, proliferative and capable of indefinite self-renewal and of generating a heterogeneous clonal progeny. Molecularly, the transcriptional signature of Notch1+ tumour cells highly correlates with ISCs, suggestive of their origin from normal crypt cells. Surprisingly, Notch1+ expression labels a subset of CSCs that shows reduced levels of Lgr5, a reported CSCs marker. The existence of distinct stem cell populations within intestinal tumours highlights the necessity of better understanding their hierarchy and behaviour, to identify the correct cellular targets for therapy.

Maria Duda, Natalie J Kirkland, Nargess Khalilgharibi, Melda Tozluoglu, Alice C Yuen, Nicolas Carpi, Anna Bove, Matthieu Piel, Guillaume Charras, Buzz Baum, Yanlan Mao (2019 Jan 30)
Polarization of Myosin II Refines Tissue Material Properties to Buffer Mechanical Stress.
Developmental cell : 245-260.e7 : DOI : S1534-5807(18)31088-8

Résumé

As tissues develop, they are subjected to a variety of mechanical forces. Some of these forces are instrumental in the development of tissues, while others can result in tissue damage. Despite our extensive understanding of force-guided morphogenesis, we have only a limited understanding of how tissues prevent further morphogenesis once the shape is determined after development. Here, through the development of a tissue-stretching device, we uncover a mechanosensitive pathway that regulates tissue responses to mechanical stress through the polarization of actomyosin across the tissue. We show that stretch induces the formation of linear multicellular actomyosin cables, which depend on Diaphanous for their nucleation. These stiffen the epithelium, limiting further changes in shape, and prevent fractures from propagating across the tissue. Overall, this mechanism of force-induced changes in tissue mechanical properties provides a general model of force buffering that serves to preserve the shape of tissues under conditions of mechanical stress.