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Poster 32

Gadoteric acid and gadolinium exposure – what is the impact on kidney gene expression?

Susana Coimbra [1,2,ǂ,*], Susana Rocha [1,ǂ], Sofia D. Viana [3,4,5,6], Rute Rebelo [1], Maria João Valente [7], Cristina Catarino [1], Luís Belo [1], Elsa Bronze-da-Rocha [1], Flávio Reis [3,4] and Alice Santos-Silva [1]

[1] UCIBIO i4HB, Laboratório de Bioquímica, Faculdade de Farmácia, Universidade do Porto, 4050-313 Porto, Portugal
[2] UCIBIO i4HB, Translational Toxicology Research Laboratory, University Institute of Health Sciences (1H-TOXRUN, IUCS-CESPU), Avenida Central de Gandra 1317, 4585-116 Gandra, Portugal
[3] Institute of Pharmacology & Experimental Therapeutics, & Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, 3000-548 Coimbra, Portugal
[4] Center for Innovative Biomedicine and Biotechnology (CIBB), University of Coimbra, 3000-548 Coimbra, Portugal
[5] Polytechnic Institute of Coimbra, ESTESC-Coimbra Health School, Pharmacy, 3046-854 Coimbra, Portugal
[6] H&TRC- Health and Technology Research Center, Coimbra Health School, Polytechnic University of Coimbra, 3046-854 Coimbra, Portugal
[7] National Food Institute, Technical University of Denmark, 2800 Kgs Lyngby, Denmark
[ǂ] these authors contributed equally to this work

* Correspondence: carla.coimbra@ipsn.cespu.pt

Abstract

Background: The nephrotoxicity of gadolinium [Gd (III)] has been reported, raising concerns about the safety of gadolinium-based contrast agents (GBCA). Gd (III) exposure, in renal tubular cells (HK-2), causes apoptosis, and leads to upregulation of genes related to lipogenesis/lipolysis and to signaling pathways related to inflammation/hypoxia [1]. Gadoteric acid (Gd-DOTA), a macrocyclic GBCA, appears to be one of the more stable. Recently, we reported that, in healthy rats exposed to a single dose of Gd (III) or Gd-DOTA, the kidneys' transcriptome, compared to controls, presented distinct differential gene expression patterns [2]. **Objective:** To evaluate the short- and long-term effects of exposure to Gd (III) and Gd-DOTA on the kidney's gene expression of genes specifically related to apoptosis, inflammation, hypoxia and lipid metabolism. **Methods:** In short- and long-term studies (2 days and 20 weeks after exposure, respectively), male Wistar rats were divided in 3 groups/study (*n*=10/group) and exposed to a single dose (0.1 mmol/kg) of Gd (III), Gd-DOTA or vehicle (control). At the end of the protocols, renal tissue was collected to evaluate the kidney gene expression of *casp3, bcl2*, *spp1*, *sqstm1*, *nfkb1, nfe2, nlrp3, il6, tgfb1, il1b, hif1a, acaca* and *cpt1a,* through qPCR. **Results:** Two days after exposure, Gd (III) group presented higher levels of gene expression of *il6*, *tgbf1*, *nfkb1* and *hif1a* than the controls and, compared to Gd-DOTA group, *tgbf1* and *acaca* mRNA levels were increased; the Gd-DOTA group presented increased levels of *il6* and *cpt1a,* compared to the control group. Twenty weeks after exposure, Gd (III) group presented decreased gene expression of *tgbf1* and *acaca* compared to the controls; the Gd-DOTA group presented lower *tgbf1* mRNA levels than the control group. **Conclusions:** Short-term exposure to free Gd (III) was associated with upregulation of genes related to hypoxia and inflammation, while exposure to Gd-DOTA was only associated with upregulation of *il6* (encoding interleukin-6) and *cpt1a*, which encodes for carnitine palmitoyltransferase 1A, an enzyme involved in fatty acid oxidation. Over time, these alterations seem to reduce or even revert for both compounds, since in the long term, only gene expression downregulation was observed. Gd-DOTA revealed a safer profile, however, further studies are warranted to evaluate its true safety, especially in cases of repeated exposures and/or pre-existing renal function impairment.

Keywords: inflammation; hypoxia; apoptosis; lipid metabolism

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