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Gadolinium and gadoteric acid single exposure – long-term impact on the kidney's gene expression

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Abstract

Background: In gadolinium-based contrast agents (GBCAs), gadolinium [Gd (III)] is chelated to prevent its toxicity. Gadoteric acid (Gd-DOTA), a macrocyclic GBCA with a more stable structure, is commonly used in magnetic resonance imaging [1]. The kidney is one of the major targets of Gd (III), since renal excretion is the main elimination route for most GBCAs [2]. In healthy rats exposed to a single dose of Gd (III) or Gd-DOTA, the kidney transcriptome, compared to controls, showed different gene expression patterns [3]. **Objective:** This study aims to evaluate the long-term effects of Gd (III) or Gd-DOTA single exposure on kidney gene expression. **Methods:** Male Wistar rats were divided into 3 groups *(n*=10 each) and exposed to a single dose (0.1 mmol/kg) of Gd (III), Gd-DOTA or vehicle (control); 20 weeks after exposure, renal tissue was collected to evaluate differential gene expression of its transcriptome (RNASeq), followed by Gene Set Enrichment Analysis (GSEA) of all the identified differentially expressed genes. **Results:** Compared to controls, the Gd (III) group showed an up-regulation of *Ly6al* (Lymphocyte Antigen 6 Complex, Locus A-like), *Snap91* (Synaptosome Associated Protein 91) and *Fosfb (*FosB proto-oncogene, AP-1 transcription factor subunit) genes; and Gd-DOTA group showed an upregulation of *Ly6al*, *Snap91* and *Ugt2b7* (UDP-glucuronosyltransferase family 2 member B7) genes, and a down-regulation of *Cyp26b1* (Cytochrome P450, family 26, subfamily b, polypeptide 1) gene. Gd-DOTA, compared to the Gd (III) group, showed an upregulation of *Ly6al* and *Ugt2b7* genes, and downregulation of *Cyp26b1* and *Fosfb* genes. GSEA analysis for Gd-DOTA showed values of reasonable enrichment (>2) in all the studied genes, while for Gd (III), only *Cyp26b1* and *Fosfb* were altered. **Conclusions:** Single exposure to free Gd (III) or Gd-DOTA induced distinct transcriptional responses in the kidney, showing that Gd-DOTA had a unique profile of gene expression, compared to free Gd (III). Moreover, the GSEA results imply a possible alternative biological pathway(s) activation for each compound. Gd (III) or Gd-DOTA exposure induced long-term disturbances in the expression of genes associated with immunity and xenobiotic metabolism. Further confirmatory studies (qPCR assays) are necessary to validate our gene expression results, allowing the exploration of our data for new insights about Gd (III) impact on kidney function, and Gd-DOTA safety, as *Fosfb* appears to be involved in acute kidney injury [4].

Keywords: nephrotoxicity; kidney transcriptome; next-generation sequencing analysis; RNAseq

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References

1. Seithe, T. et al. Diagnostic efficacy and safety of gadoteric acid MR mammography in 1537 patients. *Eur J Radiol* **2016**, *85*, 2281-2287, doi:10.1016/j.ejrad.2016.10.013.
2. Richter, H. et al. Gadolinium tissue distribution in a large-animal model after a single dose of gadolinium-based contrast agents. *Radiology* **2021**, *301*, 637-42, doi:10.1148/radiol.2021210553.
3. Coimbra, S. et al. Gadoteric acid and gadolinium: exploring short- and long-term effects in healthy animals. *J Xenobiot* **2025**, *15*, 34, doi: 10.3390/jox15020034.
4. Tang, X. et al. Network expression analysis identifies and experimentally validates the involvement of Fosb in acute kidney injury**.** *FASEB Bioadv* **2025**, *7*, e70002, doi: 10.1096/fba.2024-00201.

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