Reviewer's report

Title: Impaired endocytosis in proximal tubule by subchronic exposure to cadmium involves angiotensin II type 1 receptor.

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Reviewer: Isabelle RUBERA

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In this study, the authors investigated the role of the megalin and the AT1 receptor in Cd-induced microalbuminuria. The major finding of this study is that losartan (an inhibitor of AT1 receptor) reduced microalbuminuria in Cd-treated rats without any change in expression of megalin.

Major Compulsory Revisions

-intoxication protocol / cadmium accumulation in the kidney / kidney damage.

1) It would be interesting to compare and discuss the results of this study with others, concerning the route of administration (oral), the duration of treatment and the Cd content in the kidney. In the literature, subcutaneous or intraperitoneal injections of lowest dose of Cd have been shown to induce highest Cd concentration in kidney and kidney failure. Likewise, how an equivalent amount of Cd (around 5-7 µg/g) in the kidney can induce different kidney damage phenotype? (for example, Jacquillet et al., Am J Physiol Renal Physiol. 2006 Jan;290(1):F127-37)

2) Microalbuminuria is the only renal parameter tested affected in those Cd-treated animals. The authors may provide additional studies and test an early biomarker of Cd-induced proximal tubule injury such as Kim-1.

-oxidative stress parameters.

3) In the Table 2 lipid peroxidation index is diminished in LOS-treated and Cd-treated groups. The authors need to explain.

4) Upregulation of the expression of pro-oxidant enzyme NADPH oxidase has been reported in several models of Cd intoxication. The authors may enrich the discussion to explain how NADPH activity is inhibited in Cd+LOS group and only in this group.

Page 20 line 19. What is the reason to cite Reference 48 (Renugadevi et al., Toxicology. 2009 Feb 4;256(1-2):128-34) here in the discussion as no NADPH oxidase activity has been studied in this paper.

-megalin expression/ tubular endocytosis.

5) The megalin-independent Cd-induced microalbuminuria is an interesting observation but it need to be followed up and the involvement of cubulin has to be tested in the current study.
- 6) Legend of Figure 3 and description of Figure 3 in Results section correspond to Figure 4 and vice versa.

Minor Essential Revisions:
- Page 18 line 16: correct the sentence “however, receptor-mediated endocytosis was affected as evidenced by the presence of microalbuminuria” suggested instead of evidenced; no experiments have been performed for receptor-mediated albumin endocytosis
- Page 18, latest line: define MT1/2
- Page 20, latest line: correct “we used a Losartan (AT1 receptor antagonist);”
- Page 21 line 2: other studies instead of others studies
- the authors may add and discuss a new paper recently published “Effect of angiotensin II type 1 receptor blocker on renal function, arterial blood pressure and parathyroid hormone related protein over expression in cadmium induced nephrotoxicity in adult male rats” Int J Physiol Pathophysiol Pharmacol 2013;5(2):109-119 by Marwa A Ahmed.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests