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Letter to the Editor

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Basolateral transport of the uraemic toxin *p*-cresyl sulfate: a role for organic anion transporters?

Sir,

The article by Miyamoto *et al.*[1] recently published in this journal describes the role of organic anion transporters (OATs) in the uptake of *p*-cresyl sulfate (PCS) in rat renal cortical slices and a human proximal tubule cell model, *viz.* HK-2 cells. In this study, uptake of PCS in both model systems could be inhibited by several OAT inhibitors including probenecid and *p*-aminohippuric acid. As mentioned by the authors, specificity of PCS transport was investigated using well-known substrates for OATs at a concentration of 1 or 10 mM in renal slices or HK-2 cells, respectively. As these concentrations are much higher compared to their inhibitory potencies reported [2], it could be argued that the affinity of PCS for OATs is very low in both models. Moreover, such concentrations are hardly soluble in an aqueous solution at physiological pH and highly influence cell viability [3].

In our opinion, it is more likely that HK-2 cells have only little or no OAT expression at all. Functional transport by OATs is generally studied using heterologous expression in cultured cells or *Xenopus leavis* oocytes [2]. These systems are used because there are no stable cell lines known to date that highly express functional endogenous OATs and, to our knowledge, no publications are available for functional OAT transport in HK-2 cells. Moreover, functional expression of OATs in primary human proximal tubule cells can only be sustained for a limited time in culture [4]. In the study from Miyamoto *et al.*, protein expression of OATs was solely demonstrated by an unconvincing western blot. Previously, it has been reported that OATs can become non-functional upon culturing due to internalization [2]. These findings indicate that, although protein expression seems to be present, multiple assays are required to demonstrate functionality of transporters.

How can the uptake of PCS as observed by Miyamoto *et al.* be explained? Another kidney-specific basolateral transporter demonstrated to be involved in the removal of uraemic toxins is the organic anion transporting polypeptide 4C1 (SLCO4C1) [5]. Note that the lack of inhibition by digoxin, as demonstrated by Miyamoto *et al.*, is not conclusive for the involvement of this transporter [5]. Using quantitative PCR, we indeed demonstrated the expression of SLCO4C1 in human kidney homogenates and HK-2 cells (C_t: 29 ± 0.06 and 22 ± 0.05; C_t GAPDH: 26 ± 0.5 and 15 ± 0.1, respectively), whereas gene expression levels of OAT1 and OAT3 were undetectable in the cell line.

Taken together, the low affinity of PCS as demonstrated together with the absence of OATs in the HK-2 model suggest that the mechanism of PCS excretion in the kidney is more complicated than postulated by Miyamoto *et al.*, and the possible contribution of SLCO4C1 warrants further investigation.

Conflict of interest statement. None declared.

Editorial Note: Dr Miyamoto *et al.* had been invited to reply to this letter but we did not receive a response.

[1]Department of Pharmacology and Toxicology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
[2]Department of Physiology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
[3]Department of Pediatrics, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
E-mail: r.masereeuw@pharmtox.umcn.nl

Henricus A. M. Mutsaers[1,2]
Martijn J. G. Wilmer[1]
Lambertus P. van den Heuvel[3]
Joost G. Hoenderop[2]
Rosalinde Masereeuw[1]

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