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MEETING ABSTRACT

A1.6

Vascular toxicity risk assessment of MC18 and MC70, novel potential diagnostic tools for *in vivo* PET studies

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Background: The P-glycoprotein (P-gp) inhibitor MC18 has recently been proposed as a valuable PET tracer to measure P-gp expression *in vivo* [1]. The aim of this study was to evaluate the toxic hazard towards the vasculature of MC18 along with the structurally related and more potent P-gp inhibitor MC70 [2].
Methods: Their effects on A7r5 and human endothelial EA.hy926 cell viability, on the mechanical activity of fresh and cultured rat aorta rings, as well as on $Ca_V1.2$ channel current ($I_{Ca1.2}$) of A7r5 cells were analysed [3].
Results: At concentrations >10 µM, MC18 and MC70 decreased cell viability causing evident morphological changes. In fresh rat aorta rings, both compounds antagonized phenylephrine-induced contractions in a concentration-dependent manner with IC_{50} values in the range 2.44–14.5 µM, whereas only MC18 caused a concentration-dependent decrease of the responses induced by 60 mM K^+ (K60). In rings cultured for 7 days in the presence of tested compounds, 10 µM MC70 significantly reduced, while 10 µM MC18 completely prevented the contractile response to both phenylephrine and K60. MC18 and MC70 inhibited $I_{Ca1.2}$ in a concentration-dependent manner with IC_{50} values of 16.81 and 32.13 µM, respectively. The effects of the two compounds on the induction of endothelial-mesenchymal transition in EA.hy926 cells are currently under investigation.
Discussion: These findings demonstrate that MC18-induced vascular effects take place at concentrations that are at least three orders of magnitude higher than those allowing in vivo measurement of P-gp expression (≤10 nM). Thus, MC18, and possibly MC70, can be considered promising PET tools for *in vivo* P-gp quantification.
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