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Poster 73

Evaluation of P-glycoprotein activity mediated by fiscalin derivatives at the rat intestinal barrier

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Abstract

Background: P-glycoprotein (P-gp) is an active efflux pump that reduces xenobiotics' accumulation inside cells, and which activity can be modulated by inhibitors, inducers and activators [1,2]. The first ones have been used to counteract the multidrug resistance (MDR) phenomena and the inducers and activators have been proposed as a therapeutic approach in intoxication scenarios. In fact, P-gp binds several unrelated hydrophobic drugs and its activity can be changed in order to increase or decrease drugs intracellular accumulation. Previous *in vitro* studies showed that fiscalins, marine-derived compounds, are able to alter P-gp transport activity in differentiated neuronal SH-SY5Y cells. Interestingly, some fiscalin derivatives showed to act as inhibitors, whether others were activators of P-gp expressed in SH-SY5Y cells [3]. **Objective:** Considering the fact that P-gp is a major efflux pump expressed in barrier tissues, influencing xenobiotics' pharmacokinetics and bioavailability, the main purpose of this study is to investigate the modulatory effects of two fiscalin derivatives, FISC 1 and FISC 2, on P-gp activity in the rat intestinal barrier, using *ex vivo* approaches. **Methods:** The study was performed at the distal portion of the rat ileum, using everted intestinal sacs as an *ex vivo* model, aiming to evaluate the potential immediate effects of the fiscalin derivatives on P-gp transport activity, as a result of a direct inhibition or activation of this pump. P-gp activity was evaluated in rat everted intestinal sacs after a direct and short contact of the tested fiscalin derivatives (5 µM), in the presence and absence of ZOS (5 µM). A fluorescent P-gp substrate widely used in these assays is rhodamine 123 (RHO 123), which allows for the direct evaluation of P-gp activity by measuring RHO 123 fluorescence in samples of mucosal medium, determined by spectrofluorometry. **Results and Conclusions:** The findings revealed that FISC 1 is able to activate P-gp activity at rat intestinal barrier, highlighting the pharmaco(toxico)kinetic relevance of this efflux protein.

Keywords: fiscalin derivatives; P-glycoprotein; inhibition; activation; *ex vivo*; rat intestine

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