Drug transporters and toxicity

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By: Baan Aljasani
Bsc. Pharmacy, University of Basrah

Supervisor: Dr. Heather. M. Wallace
Division of applied medicine, University of Aberdeen, Aberdeen, Scotland, UK

Abstract

Interest in polyamine and the polyamine transport system increased after the discovery that polyamine intracellular content and the polyamine transporting activity are up regulated in cancer cells compared to normal ones. Thousands of investigations were done to identify the mammalian PTS. Disappointingly, the identity and nature of the mammalian PTS is still unknown. However, many of these studies were successful in identifying some of the general characteristic of the PTS, among which is the promiscuous nature in accepting compounds that are structurally different. Moreover, recent studies have verified the involvement of some well-known human permeases in transporting polyamine.

Based on these facts, this project hypothesised the possibility of drug – drug interactions with the loose nature of the PTS in accommodating diverse compounds and the capability of some established permeases to transport polyamine. Thus, the investigation was set to achieve three major aims; to examine the responsiveness of three cell lines (RCC26A, HK2, and HEK293) to the polyamine – anthracene conjugate (Ant 4,4), to compare between normal (HK2) and cancer (RCC26A) renal cell lines in the pattern of Ant 4,4 uptake into these cells, and to provide a preliminary data to characterise the transporter responsible for Ant 4,4 influx in each cell line, anticipating by that some of the potential drug – drug interactions at the level of the designated transporter in each cell line.

The investigations were carried out using an MTT cytotoxicity assay and an established transporter inhibitor (prazosin and furosemide) to examine the possibility

of the uptake of Ant 4,4 into the three cell lines by four known permeases (OCT1, OCT2, OCT3, and CCC9a).

The cell lines were found to be highly responsive to Ant 4,4, where the conjugate produced a statistically significant cytotoxic effect in all of the cell lines. The study also might have detected differences between normal and cancer cell lines in the uptake of Ant 4,4, in which the influx of Ant 4,4 into the cancer cell line was inhibited by prazosin, whereas the influx of Ant 4,4 into HK2 was not affected by prazosin inhibitory action. These results might indicate the involvement of OCT1 in the uptake of Ant4,4 into RCC26A cells, but not HK2 cells. The same inhibitory action was also seen with HEK293 cells. Moreover, the study have also revealed the possibility of the enrolment of an efflux transporter in exporting Ant 4,4 in HEK293 cells. Both mdr1, and ABCG2 multi resistant transporters were proposed to be responsible for Ant 4,4 efflux outside HEK293 cells, however its high likely to be ABCG2.

In conclusion, OCT1 might be involved in the uptake of Ant 4,4 in both RCC26A, and HEK293 cells, but not HK2 cells. An efflux transporter, most likely ABCG2 might be involved in the transportation of Ant 4,4 outside HEK293 cells. The uptake of Ant 4,4 into HK2 cells is most likely to be by a genuine PTS.