2-B1-10-2

ENHANCEMENT OF ZIDOVUDINE UPTAKE BY DHEAS IN CD4(+) T LYMPHOCYTE MODEL, MOLT-4 CELLS
Tomohiro Nishimura, Yoshiaki Seki, Masatoshi Tomi, Jun Tanaka, Yoshimichi Sai and Emi Nakashima
Faculty of Pharmacy, Keio University, 1-5-30 Shibakoen, Minato-ku, Tokyo 105-8512, Japan

[Purpose] Zidovudine (3'-azidothymidine, AZT) is a well-known nucleoside reverse transcriptase inhibitor and widely used for antiretroviral therapy. We previously showed that the uptake of AZT in TR-TBT 18d-1 cells, a placental cell line, was transporter-mediated and that it was enhanced by the addition of a certain type of estrogen sulfate. In the present study, we aimed to clarify that the uptake of AZT in CD4(+) T lymphocyte, a pharmacological target of AZT, is also enhanced by the addition of dehydroepiandrosterone sulfate (DHEAS).

[Methods] Molt-4 cells was used as a model for CD4(+) T lymphocyte. Radiolabelled drug uptake in Molt-4 cells was performed by silicone layer centrifugation method. The uptake was measured in the presence and absence of a specific enhancer.

[Results and Discussion] [3H]AZT and [3H]thymidine uptake was increased in a time-dependent manner and the presence of 1 mM DHEAS increased [3H]AZT uptake but decreased [3H]thymidine uptake. Michaelis-Menten equation revealed K_m values of 2.6 μM and 1.2 μM for [3H]AZT uptake in the absence and presence of DHEAS, respectively. These results indicate that DHEAS improves the affinity of AZT transport system, similar to the TR-TBT 18d-1 cells. [3H]DHEAS uptake in Molt-4 cells was measured to characterize the relationship between substrate and enhancer, however, [3H]DHEAS uptake was not increased in the presence of 1 mM AZT.

[Conclusions] [3H]AZT uptake by Molt-4 cells was enhanced in the presence of DHEAS by changing transport affinity. The increased uptake of AZT and the decreased uptake of thymidine may simultaneously give work towards antiretroviral therapies.

2-B1-10-3

PROFOUND ACCUMULATION OF CAMPTOTHECIN DERIVATIVE IN CANCER CELLS POSSIBLY THROUGH AN AMINO ACID TRANSPORTER
Eun-Young Kwak¹, Won-Sik Shim², Dae-Duk Kim², Suk-Jae Chung³, Chang-Koo Shim⁴
¹National Research Laboratory of Transporters Targeted Drug Design, College of Pharmacy, Seoul National University, San 56-1, Silim 9-dong, Seoul, Korea

[Purpose] Cancer cells often pump out anti-cancer agents through various efflux transporters, the process known as “multi drug resistance”. Blocking this efflux process is ideally a best way to increase the potency of anti-cancer drugs, but it still is a difficult task to inhibit or even control the nature of drugs to be effluxed. It is then wise to increase the influx of anti-cancer agents in cancer cells. One way to achieve this is to take advantage of various amino acid transporters, because cancer cells hunger for plenty of amino acids for their proliferation. Therefore, in the present study, we prepared an amino acid analogue of camptothecin (CA) to increase the accumulation in cancer cells. Furthermore, we examined which transporters are responsible if the accumulation of CA is enhanced. [Methods] CA was treated on HEK293T or MCF7 cell lines and their accumulations were investigated. Inhibitors of some transporters were also used to see if they are involved. Sodium dependency was tested by replacing NaCl with NMDG Semi-quantitative PCR for more than 15 candidate transporters was done in order to confirm their presence and contribution. [Results and Discussion] The accumulation of CA was much higher in HEK293T (15-fold) and MCF7 (6-fold) compared to its parent molecule (C). The accumulation rate of CA was reduced by 40% in HEK293T cell when sodium is replaced with NMDG indicating that the enhanced accumulation is sodium-dependent process, which is found when amino acid transporters are involved. However, it turned out that amino acid transporters such as SLC6A14, SLC7A5 are not responsible for the enhanced accumulation. Furthermore, CA still is a substrate of various efflux transporters such as P-gp, MRP1, and BCRP. Although further studies are necessary, it is likely that SLC38A1 or yet unknown transporter might be involved in the enhanced uptake process of CA. [Conclusions] CA showed increased accumulation in cancer cells compared to C, suggesting that CA may enhance its cytotoxic effect on cancer cells. Furthermore, the present study proposes one way to enhance the uptake of anti-cancer drugs via amino acid transporters by adding amino acid moiety to the parent drug molecules.