THE IMPACT OF PHYSICOCHEMICAL PROPERTIES OF COMPOUNDS ON THEIR ABSORPTION PROFILES IN VIVO

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There are some examples that consideration of physicochemical properties has been useful in the optimization of oral bioavailability or permeability. However, few studies have revealed the relationship between the physicochemical properties and the intestinal absorption profiles in vivo. We have previously reported a new screening method to estimate the intestinal absorption in vivo (19th Annual Meeting of JSSX, 18PE-18); the absorption properties of compounds could be predicted by one-point (5 min after oral administration) simultaneous sampling of portal and systemic blood in mice with pre-dose of ketoconazole. Using these screening results, we have investigated the correlation of physicochemical properties of in-house compounds and their in vivo absorption profiles. Total set of 557 compounds are classified absorbable (n=179), poorly absorbable (n=171) and intermediately absorbable (n=207) compounds. There are marked differences in mean molecular weight (M.W.) and clogP between absorbable compounds and poorly absorbable compounds. Other physicochemical properties such as PSA, hydrogenbond donors, hydrogen-bond acceptors, rotatable bonds of absorbable compounds are all significantly lower than those of poorly absorbable compounds. Next, we have categorized the compounds into four types by M.W. and clogP. Category 1 (M.W.<500, clogP<5.0) compounds show good absorption profiles; about 50% of compounds are absorbable. On the other hand, the fraction of absorbable compounds in category 4 (M.W. ≥500, clogP ≥5.0), falls to only 10%. These results demonstrate that the physicochemical properties of compounds affect considerably their intestinal absorption in vivo.

EFFECTS OF ACANTHOPANAX SENTICOSUS ON THE INTESTINAL DRUG TRANSPORTERS IN CACO-2 CELLS

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Acanthopanax senticosus (AS) is used as Chinese medicines and supplements in Japan. However, little is known about the drug interaction between AS and other drugs. In previous study, we demonstrated that MDR-1 function is suppressed by the addition of AS extract in Caco-2 cells (The Pharmaceutical Society of Japan, 126th Meeting, Sendai). We performed further studies to examine the effect of AS extract on the MDR-1 and the other transporters functions in Caco-2 cells. Caco-2 cells were cultured on culture dish and permeable membrane for 1-3 weeks. The basolateral-to-apical (B-to-A) transport of MDR-1 specific substrate, rhodamine 123 (Rho123) was significantly decreased by the addition of AS extract. By contrast, the apical-to-basolateral (A-to-B) transport of Rho123 was not altered. Furthermore, the intracellular Rho123 concentrations were significantly increased by the addition of AS extract in the efflux studies. We also examined the effects of AS extract on the transports of PEPT1 substrates, cephalaxin, cephradine and glycylsarcosine. The A-to-B transports of these substrates were significantly decreased by the addition of AS extract, but not B-to-A transport. These results suggest that the MDR-1 and PEPT1 functions are suppressed by the addition of AS extract. However, no effect on these functions was observed upon AS extract pretreatment for 7 days in Caco-2 cells. Now, we are further studying to clarify the inhibition mechanism of AS extract on MDR-1 and PEPT1 functions.