MECHANISTIC ANALYSIS FOR ENHANCING EFFECTS OF ACYLCARNITINES ON DRUG PERMEATION IN CACO-2 CELL MONOLAYERS
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INTRODUCTION: We have reported that for enhancing effects of lauroylcarnitine (LC) and palmitoylcarnitine (PC) on the intestinal membrane permeation of ranitidine, lucifer yellow, and FITC-dextran 4000 (FD-4) as paracellular markers, adding an excess of carnitine or metabolic inhibitors such as dinitrophenol (DNP) significantly inhibits the effects of LC and PC. These results suggest that the increase in paracellular marker permeation by LC and PC is apparently mediated by cellular uptake of acylcarnitines through energy requiring system, one of which shows substrate specificity for moiety of carnitine. In this study, we investigated relation between the intracellular concentration of LC or PC and the following two parameters in Caco-2 cell monolayers: (1) decrease in transepithelial electric resistance (TEER), and (2) the increase in permeation clearance of FD-40.

METHODS: TEER and permeation clearance of FD-40 was obtained by the diffusion chamber method. Intracellular carnitine concentration was determined by an enzymatic cycling method.

RESULTS AND DISCUSSION: In the presence of LC or PC, influx clearances of FD-40 were increased in a dose dependent fashion of LC or PC when compared with the control condition. The decrease in TEER by LC or PC was ameliorated by adding an excess amount of carnitine, tetraethylammonium (TEA) or metabolic inhibitors such as sodium azide. Addition of LC or PC in the apical side increased intracellular carnitine concentration in a dose dependent of LC or PC, but not in the basal side. These results suggest that as one of the paracellular enhancing mechanism of LC and PC, the opening of tight junction is mediated by cellular uptake of LC and PC.

TRANSNASAL DELIVERY OF PROSTAGLNDIN E₁ AND E₂ TO THE RAT CENTRAL NERVOUS SYSTEM
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Purpose: Prostaglandins (PGs) exhibit a variety of pharmacological potency on the central nervous system (CNS). For the clinical application of these potencies of PGs, two obstacles, i.e. rapid elimination in the systemic circulation and peripheral actions, must be overcome. It is well known that half-lives in the plasma clearance of PGs are very short, resulting in the degradation before the uptake of PGs by brain sufficient for the CNS potency. Additionally, a variety of peripheral action is unfortunately the side effect in this case. The nasal route of drug administration draws much attention recently as a new route enabling drug delivery to the CNS via cerebrospinal fluid (CSF). Since the stability of PGs in the CSF is expected much better than that in the systemic circulation, nasal route may allow both delivery to the CNS and the reduction of peripheral actions of PGs. In this study, in order to investigate the feasibility of delivery of PGs to the CNS through the nasal route, the levels of PG in plasma and CSF after intranasal (i.n.) and intravenous (i.v.) administration were examined and compared. Methods: PGE₁ and PGE₂ were administered nasally (50 µg/rat) or infused intravenously (125µg/rat/15min) to Male Wistar rats (200 - 250 g), and the concentrations in the blood and CSF were determined by the commercially available enzyme immunoassay kit. Results and Discussion: The total body clearances of PGE₁ and PGE₂ were 9.3 mL/min and 86.0 mL/min, with plasma half-lives of 28.2 sec and 23.8 sec, respectively. Following nasal application, the profiles of the concentration in the plasma showed the peak at 10 min for PGE₁ and at 5 min for PGE₂, and the concentration was decreased thereafter. The levels of PGs in CSF 15 min after i.n. administration were markedly higher than those after i.v. administration, suggesting the feasibility of transnasal delivery of PGs to the rat CNS. Improvement of delivery of PGs to the CSF, such as the use of phenylephrine (α₁ agonist) and acetazolamide (inhibitor of CSF secretion) is now under investigation and results will be shown at the presentation.