



### 溶解拡散

Fickの第一法則によりその透過量 ( $J$ ) は次式により表される。

$$J = \frac{DS}{L} (C_0 - C_1) \quad (1)$$

$D$  は膜の中の拡散係数 (cm<sup>2</sup>/secの単位を持つ),  
 $S$  は表面積,  $L$  は膜の厚さ

ここで  $C_0 - C_1$  は膜内での物質の濃度勾配であり, 膜の両側の濃度勾配 ( $C_1 - C_2$ ) に一致するとは限らない。これは物質の物性, すなわち, 膜/溶液の分配に依存するからである。そこで, 膜/水層でのみかけの分配係数\* partition coefficient を  $K_{app}$  とすると,

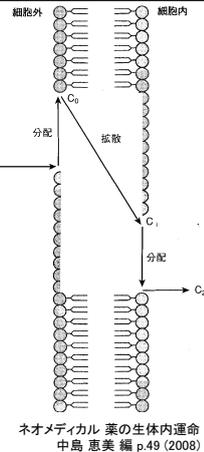
$$K_{app} = \frac{C_0}{C_1} = \frac{C_1}{C_2} \quad (2)$$

という関係から (1) 式は

$$J = D \cdot K_{app} \cdot S/L \cdot (C_1 - C_2) = P \cdot S \cdot (C_1 - C_2) \quad (3)$$

$$P = D \cdot K_{app}/L \quad (4)$$

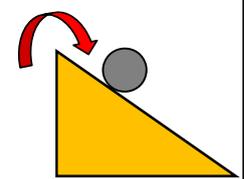
となる。ここで  $P$  は膜透過係数 permeability coefficient と呼ばれ物質の膜の透過しやすさの指標になる。



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### 促進拡散 (facilitated diffusion)

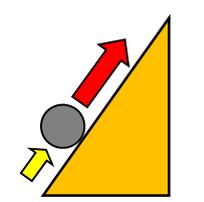
- 化学ポテンシャル差に従う輸送
- 担体を介する
- 輸送速度が速やか
- 飽和現象が見られる
- 類似物質によって阻害
- 代謝エネルギーは不要
- 濃度勾配に逆らった輸送は行われない



・・・担体を介する受動輸送

### 能動輸送 (active transport)

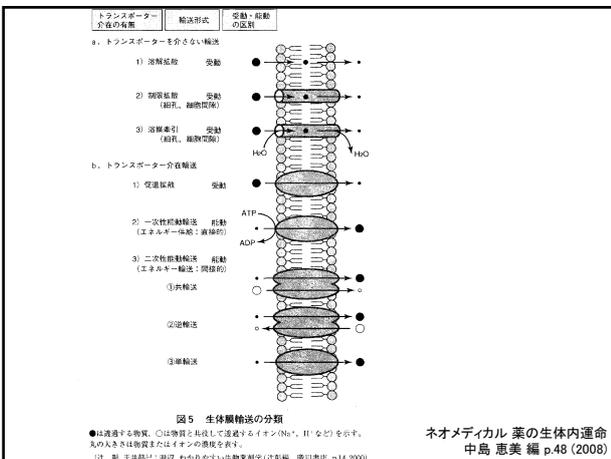
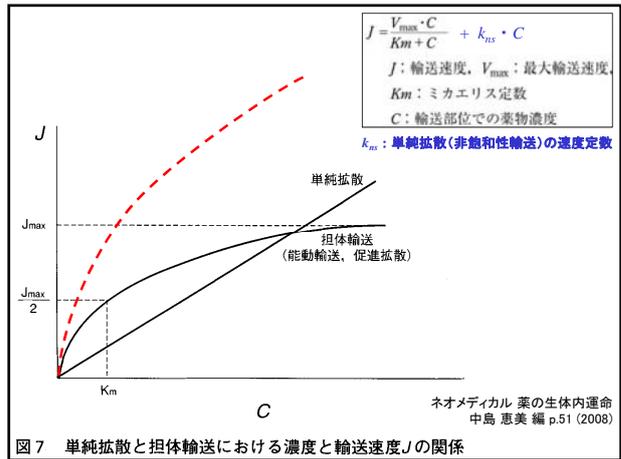
- 担体を介する
- 飽和現象がみられる
- 濃度勾配に逆らった輸送
- 代謝エネルギーが必要
- 代謝阻害剤で阻害
- 類似物質と競合阻害



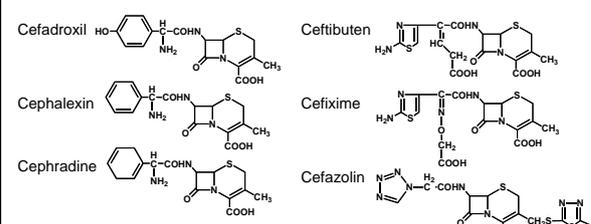
**一次性能動輸送**  
 ATP水解エネルギーと共役(直接の駆動力とする)

**二次性能動輸送**  
 一次性能動輸送で生じた化学ポテンシャル (Na<sup>+</sup>, H<sup>+</sup>等) を二次的に駆動力とする

- 共輸送
- 交換輸送 (逆輸送)

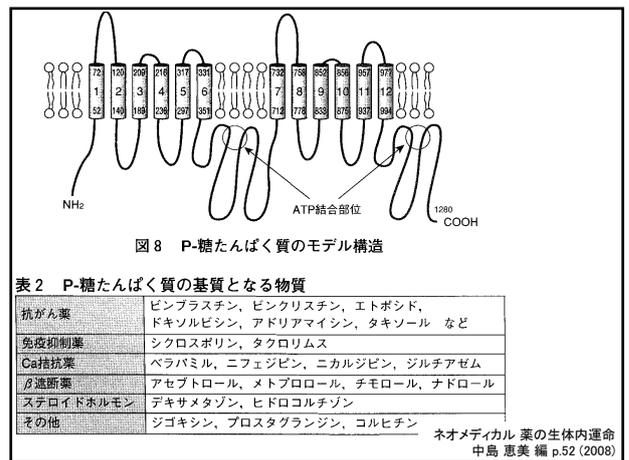
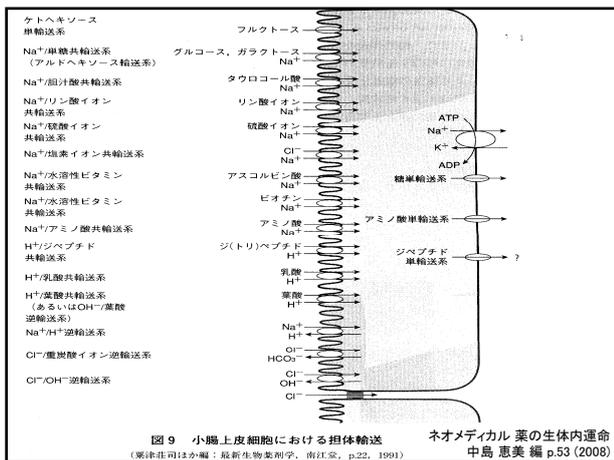
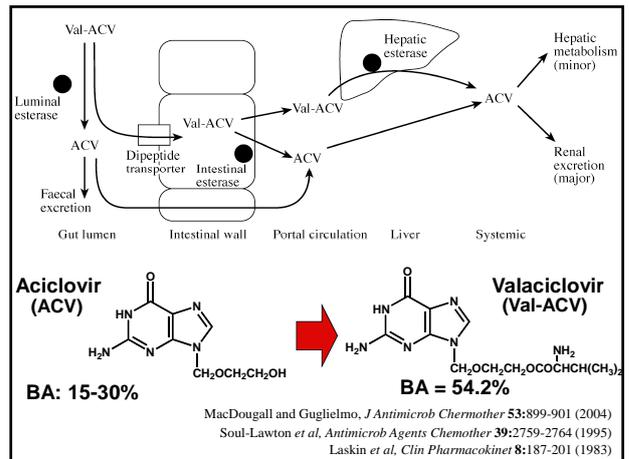
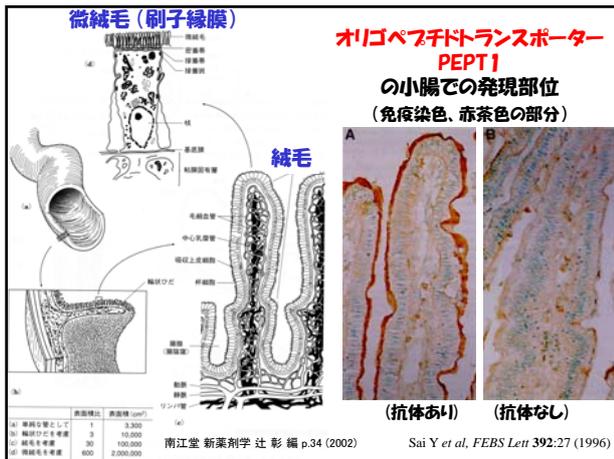


### セフェム系抗生物質の消化管吸収の違い



バイオアベイラビリティ	ラット	ヒト
Cefadroxil		90 - 100
Cephadrine	96	
Cephalexin		90
Cefbuten		84
Cefixime	27	45 - 52
Cefazolin		Low

Tsuji & Tamai, Pharm Res 13:963-977 (1996)



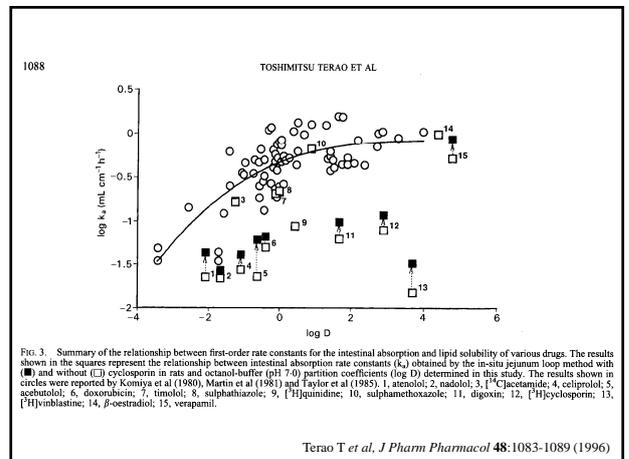
J. Pharm. Pharmacol. 1996, 48: 1083-1089  
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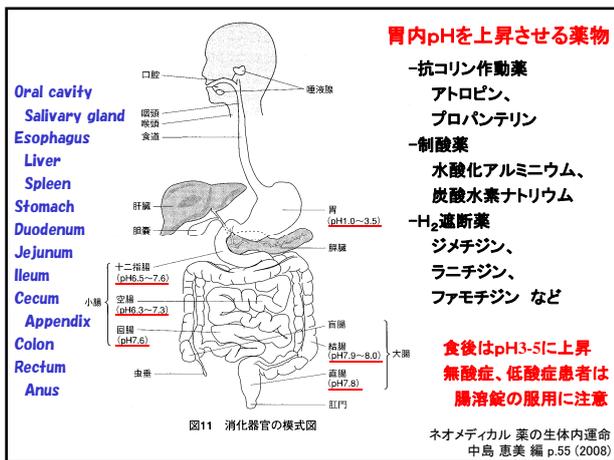
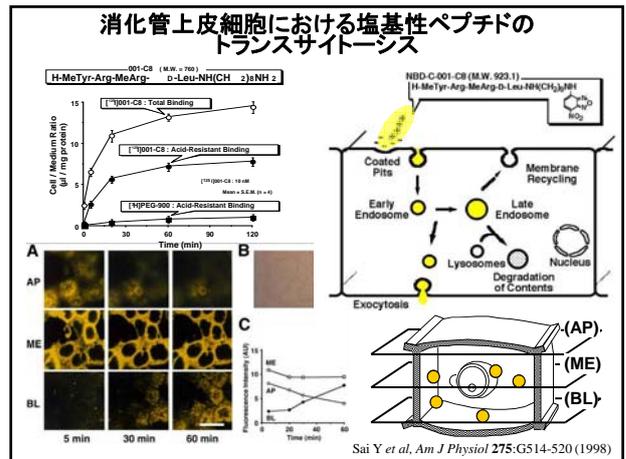
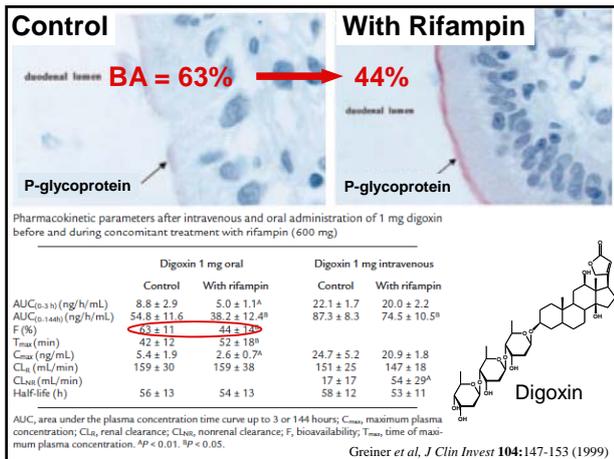
**Active Secretion of Drugs from the Small Intestinal Epithelium in Rats by P-Glycoprotein Functioning as an Absorption Barrier**

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**Abstract**  
 Because the significance of P-glycoprotein in the in-vivo secretion of  $\beta$ -blockers in intestinal epithelial cells is unclear, the secretory mechanism for  $\beta$ -blockers and other drugs has been evaluated. Uptake of the  $\beta$ -blockers acebutolol, celiprolol, nadolol and timolol, and the antiarrhythmic agent, quinidine by the multidrug-resistant leukaemic cell line variant K562/ADM was significantly lower than that by drug-sensitive K562 cells, suggesting that these  $\beta$ -blockers are transported by P-glycoprotein out of cells. The reduced uptake of acebutolol by the drug-resistant K562/ADM cells was reversed by treating the cells with anti-P-glycoprotein monoclonal antibody, MRK16, whereas no such alteration in uptake was observed for drug-sensitive K562 cells. Acebutolol uptake by K562/ADM cells was, moreover, markedly enhanced, in a concentration-dependent manner, in the presence of the specific P-glycoprotein inhibitors, MS-209 and cyclosporin. Caco-2 cells were used for evaluation of the role of P-glycoprotein in intestinal permeability to drugs in-vitro. Basolateral-to-apical transport of acebutolol was twice that in the reverse direction. A similar polarized flux was also observed in the transport of vinblastine, but not in that of acetamide or mannitol. When in-vivo intestinal absorption was evaluated by the rat jejunal loop method, with simultaneous intravenous administration of a P-glycoprotein inhibitor, cyclosporin, intestinal absorption of both acebutolol and vinblastine increased 2.4- and 2.2-fold, respectively, but no such enhancement was observed in the absorption of acetamide. The effect of cyclosporin on the intestinal absorption of several drugs was further examined, and the extent of the contribution of P-glycoprotein as an absorption barrier to those drugs was evaluated. ATP depletion by occlusion of the superior mesenteric artery resulted in a clear increase in epithelial permeability to vinblastine, but not to 3-O-methylglucose or acetamide, indicating that vinblastine is secreted by ATP-dependent P-glycoprotein into the lumen. These findings demonstrate that P-glycoprotein plays a role as an absorption barrier by transporting several drugs from intestinal cells into the lumen.

Terao T et al, *J Pharm Pharmacol* 48:1083-1089 (1996)

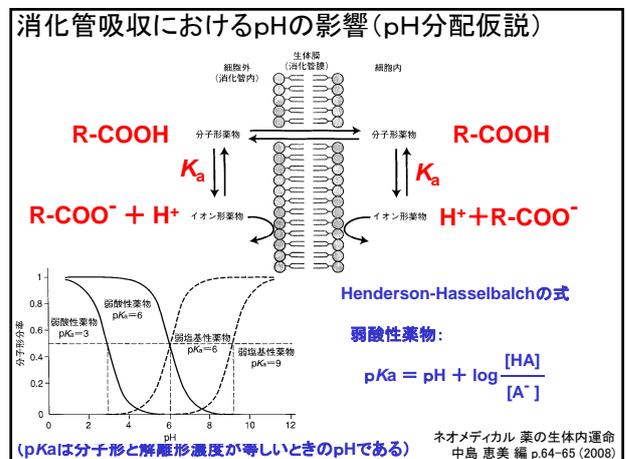
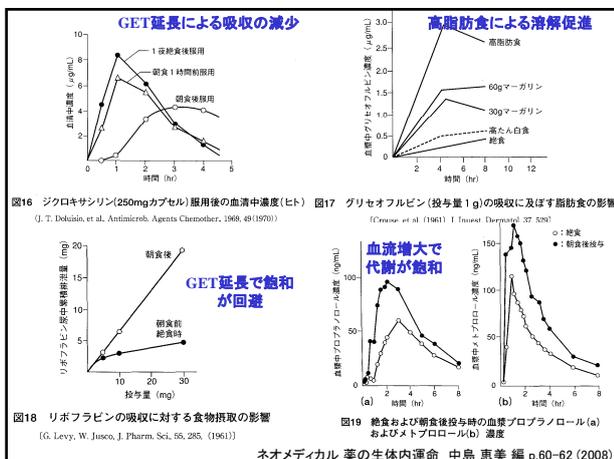




**表3 胃内容物排出時間に影響する要因**

時間を遅延させる	食物、脂肪食 高い浸透圧 (ショ糖、アミノ酸、高濃度の塩) 高い粘度 高い酸性度 精神作用の低下時 抗コリン作用薬、三環系抗うつ薬 抗ヒスタミン薬、麻薬性鎮痛薬、フェノチアジン系薬物
時間を短縮させる	空腹 不安、緊張 右側を下にする メトクロプラミド

ネオメディカル 薬の生体内運命 中島 恵美 編 p.61 (2008)



## 胃からの薬物吸収

表4 酸性薬物のラット胃からの吸収

薬物	pKa	吸収率 (%) (1時間)	
		0.1M HCl溶液	NaHCO <sub>3</sub> 溶液, pH 8
5-Sulfosalicylic acid (強酸)	0.3	0±0	0±0
Phenolsulfonphthalein (強酸)	2±2	2±1	2±1
5-Nitrosalicylic acid	2.3	52±3	16±2
Salicylic acid	3.0	61±7	13±1
Acetylsalicylic acid	3.5	35±4	—
Benzoic acid	4.2	55±3	—
Thiopental	7.6	46±3	34±2
p-Hydroxypropiphenone	7.8	55±3	—
Barbital	7.8	4±3	—
Secobarbital	7.9	30±2	—
Phenol	9.9	40±5	40±5

表5 塩基性薬物のラット胃からの吸収

薬物	pKa	吸収率 (%) (1時間)	
		0.1M HCl溶液	NaHCO <sub>3</sub> 溶液, pH 8
Acetanilide	0.3	36±3	—
Caffeine	0.8	24±3	—
Antipyrine	1.4	14±3	—
m-Nitroaniline	2.5	17±0	—
Aniline	4.6	6±4	56±3
Aminopyrine	5.0	2±3	—
p-Toluidine	5.3	0±0	47±4
α-Acetylmethadol	8.3	0±0	—
Quinine	8.4	0±0	18±2
Dextrophan, Levorphan	9.2	0±2	16±1
Ephedrine	9.6	3±3	—
Tolazoline	10.3	7±2	—
Mecamylamine	11.2	0±0	—
Darstine	強塩基	0±0	—
Procainamide ethobromide	強塩基	0±0	5±1
Tetraethylammonium	強塩基	0±1	—

(Schanke, et al. (1957) J. Pharmacol. Exptl. Ther. 120, 528)

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中島 恵美 編 p.66 (2008)

## 小腸からの薬物吸収

表6 有機酸性薬物のラット小腸からの吸収

薬物	pKa	1回経流のときの吸収率 (%)
Salicylic acid	3.0	60*
Acetylsalicylic acid	3.5	20±4
Benzoic acid	4.2	51±5
Phenylbutazone	4.4	65±7
Thiopental	7.6	55±6
Barbital	7.8	61±8

\*30例に実験で標準偏差±10%

(L. S. Schanke, et al.: J. Pharmacol. Exp. Ther. 123, 81, 1958より引用)

表7 有機塩基性薬物のラット小腸からの吸収

薬物	pKa	1回経流のときの吸収率 (%)
Acetanilide	0.3	42±5
Theophylline	0.7	28±1
Antipyrine	1.4	32±6
Aminopyrine	5.0	33±4
Ephedrine	9.6	7±3
Tolazoline	10.3	6±1
Procainamide ethobromide (強塩基)		<

(L. S. Schanke, et al.: J. Pharmacol. Exp. Ther. 123, 81, 1958より引用)

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