

GASTRIC ABSORPTION IN THE PRESENCE OF SODIUM TAUROCHOLATE: INTERPRETATION OF ITS ULCEROGENIC EFFECT.



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Objective

To confirm, from a biophysical viewpoint, the structural features of the gastric mucosal surface and to study the influence of sodium taurocholate (NaTch) on gastric absorption as well as the mechanism involved in its ulcerogenic activity

Materials and Methods

In situ gastric absorption rate constants determined in rat for a homologous series of seven phenylalkylcarboxylic acids in free solution (k_a) and in the presence of NaTch at its critical micellar concentration (CMC), k_o , were correlated with n-octanol distribution coefficients P , pH=3.00). The fitting equations were:

$$k_a = \frac{C \cdot P^d}{1 + E \cdot P^d}$$

where C, d, E, a, B and km are the fitting parameters

$$k_o = \frac{k_m \cdot P^a}{B + P^a}$$

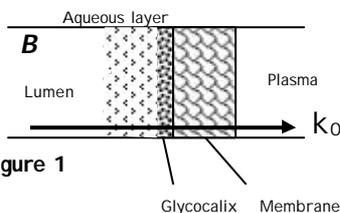
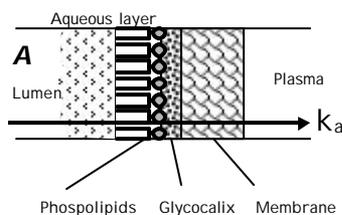


Figure 1

Results and Conclusions

The lipophilicity indexes (P) and the absorption rate constants obtained in the two conditions, k_a and k_o are listed in the Table1.

Table 1.

Tested Acid	P*	k_a (h^{-1})	k_o (h^{-1})
Phenylacetic	25.9±0.1	0.96±0.16	1.46±0.06
Phenylpropionic	71.1±0.6	1.30±0.16	1.71±0.27
Phenylbutyric	207±91	1.37±0.10	1.82±0.24
Phenylvaleric	499±43	1.66±0.15	2.02±0.38
Phenylcaproic	1866±14	1.91±0.33	2.30±0.22
Phenylheptanoic	4307±86	2.09±0.33	2.43±0.34
Phenylcaprilic	12383±601	1.87±0.18	2.57±0.29

* from reference (1), P: Distribution coefficient pH=3.00.

This lipid lining of natural amphiphiles protects the gastric mucosal surface against its acid environment. In presence of Sodium Taurocholate the correlation becomes hyperbolic. This is consistent with the existence of two resistances in series (aqueous stagnant layer that remain unaffected by NaTch (2) and lipoidal membrane). A statistically significant increase in the absorption rate constant is also found for all the compounds. Both features suggest the possibility that the hydrophobic lining is disrupted by NaTch, leaving the gastric membrane exposed to the aggressive surrounding medium as can be seen in Figure 1B. This could also explain the ulcerogenic activity of NaTch.

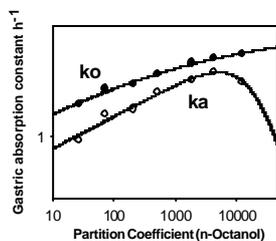


Figure 2

As can be seen in Figure 2 a bilinear correlation is obtained between k_a and P . This type of correlation is indicative of heterogeneous barrier systems and it seems in agreement with the approaches of Hills and coworkers that described a lipid lining of natural amphiphiles that protects gastric mucosae (1,3). The above structure must act as a heterogeneous system to xenobiotic diffusion. This system is represented in Figure 1A (stagnant aqueous layer (hydrophilic), phospholipids (lipophilic), Glycocalyx (hydrophilic), lipid bilayer (lipophilic) and aqueous plasma sink) and produces the bilinear correlation.

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References

- Garrigues TM, Pérez-Varona AT, Climent E, Bermejo MV, Martín-Villodre A, Plá Delfina JM. Gastric absorption of acidic xenobiotics in the rat: Biophysical interpretation of an apparently atypical Behaviour. *Int. J. Pharm* 64:127-138. 1990
- Bermejo MV, Pérez-Varona AT, Segura-Bono MJ, Martín-Villodre A, Plá Delfina JM, Garrigues TM. Compared effects of synthetic and natural bile acid surfactants on xenobiotic absorption. *Int. J. Pharm* 69: 221-231. 1991
- Hills BA. Gastric surfactant and the hydrophobic mucosal barrier. *Gut* 39:621-624. 1996