THE ROLE OF PHOSPHATIDYLCHOLINE IN REDUCING THE TOXICITY OF BILE SALTS TO MEMBRANES

Gary P. Martin and Christopher Marriott*. Schools of Pharmacy, Portsmouth Polytechnic, King Henry I St., Portsmouth, PO1 2DZ and *Brighton Polytechnic, Moulsecoomb, Brighton, BN2 4GJ.

Bile salts and lysophosphatidylcholine (LPC) have previously been demonstrated to be toxic to goldfish (Marriott and Kellaway 1977), to damage mucus structure (Martin and others 1978) and to cause leakage of hydronium ions from the gastric lumen, resulting in the initiation of gastric ulceration (Rhodes et al 1969; Johnson and McDermott 1974). However, although these lipids are secreted in the bile, no extensive disruption of the intestinal mucosa is apparent until the bile salts reach the site of active absorption in the ileum, where the mucosal cells have the shortest life span (Fry and Staffeldt 1964). Phosphatidylcholine (PC), another natural component of bile, forms mixed micelles in the duodenum with both bile salts and LPC. However, little work has been published demonstrating that such micelles are any less toxic so it is the purpose of this study to examine the possible role of PC in preventing membrane damage by sodium deoxycholate (SDC) and LPC; the consequences of this protective action on quinalbarbitone absorption have also been examined.

Goldfish weighing 3-5 g were immersed in 100 ml Tris buffer (pH 7.4) containing a range of surfactant concentrations and the overturn time, T (min), was obtained for 3 to 9 fish. A plot of SDC concentration against T^{-1} exhibited a maximum below 5mM, above which concentration the relationship was linear. When the experiments were repeated in the presence of 5mM PC the minimum threshold concentration necessary to produce overturn was increased from less than 1mM to approximately 3mM. Overturn times were significantly increased ($p < 0.05$) in the presence of PC at all of the SDC concentrations examined. For example, the presence of 5mM PC in 5mM SDC, increased T from 11.46 to 51.54 minutes. In contrast the addition of 2.5mM of LPC to SDC solutions increased the toxicity of the bile salt, as indicated by shortened overturn times.

Goldfish were "pretreated" with 1mM SDC either alone or in conjunction with 1mM PC for time periods ranging from 5-40 mins. The fish were then transferred to a solution of quinalbarbitone sodium (100 mg l^{-1}) and the overturn times, T_Q (min), noted. In contrast to a previous study (Gibaldi and Nightingale 1968), T_Q was found to decrease with increasing SDC exposure time, up to 20 minutes. Extension of the exposure time to 30 minutes produced an identical value of T_Q whereas 40 minutes exposure to 1mM SDC was directly toxic to the goldfish membrane and overturn occurred before immersion in the barbiturate solution. Pretreatment with 1mM SDC in the presence of PC, reduced the subsequent rate of quinalbarbitone sodium induced turnover and the curve of T_Q^{-1} against exposure time was linear up to the 40 minute maximum exposure time used.

These results suggest that the integrity of the intestinal membrane is preserved as a direct result of mixed micelle formation between PC and other more toxic lipids. After bile reflux into the stomach, PC is hydrolysed to LPC and presumably the mixed micelles breakdown; allowing the free bile salts (and LPC) to initiate the processes that lead to gastric ulceration.

Fry, R.J.M., Staffeldt, E. (1964) Nature 203: 1396-1398
Gibaldi, M., Nightingale, C.H. (1968) J.Pharm.Sci. 57: 1354-1357
Johnson, A.G., McDermott, S.J. (1974) Gut 15: 710-713
Marriott, C., Kellaway, I.W. (1977) J.Pharm.Pharmac. 29: 508-509
Martin, G.P., Marriott, C., Kellaway, I.W. (1978) Gut 19: 103-107
Rhodes, J., Barnado, D.E. et al (1969) Gastroenterology 57: 241-252