Cinti, D. L., Moldeus, P., Schenkman, J. B. (1972) Ibid 21: 3249–56

Dutton, G. J. Burchell, B. (1977) in: Bridges, J. W., Chassaud, L. F. (eds) Progress in Drug Metabolism, Wiley Interscience, Vol. 2, Chapter I.

Hems, R., Ross, B. D., Berry, M., Krebs, H. A. (1966) Biochem. J. 101: 284–292

Howie, M. B., Bourke, E. (1979) Clin. Sci. Mol. Med. 56: 9–14

Illing, H. P. A., Benford, D. (1976) Biochim. Biophys. Acta 429: 768–778

Leber, H. W., Streitzig, P., Kayser, M., Schütterle, G. (1972) in: Kluthe, R., Berlyne, G., Burton, B. (eds) Uraemia, Georg. Thieme, Stuttgart

Lichter, M., Black, M., Arias, I. M. (1973) J. Pharm. Exp. Ther. 187: 612–9

Lowry, O. H., Rosebrough, N. J., Farr, A. L., Randall, R. J. (1951) J. Biol. Chem. 193: 265–275

Maddocks, J. L., Wake, C. J., Harber, M. J. (1975) Br. J. Clin. Pharmacol. 2: 339–343

Takemori, A. E., Glowacki, G. A. (1962) Biochem. Pharmacol. 11: 867–870

Verity, M. A., Caper, R., Brown, W. J. (1964) Arch. Biochem. Biophys. 106: 386–393

Wardle, E. N. (1978) Kidney Int. suppl. 13:8, S13–14

Inhibition of peristalsis in rat jejunum by non-ionic surfactants

DAVID A. WHITMORE, LEONARD G. BROOKES*, KENNETH P. WHEELER†, *School of Biological Sciences, University of Sussex, Brighton BN1 9QG, U.K. and *Upjohn Ltd., Fleming Way, Crawley, Sussex, U.K.*

The non-ionic polyoxyethylene alkylether surfactants have been shown to exert both systemic and local anaesthetic effects (Zipf et al 1957, 1964; Benke et al 1977). They may also have an analgesic action (Schulz et al 1953). Recently this class of surfactants was shown to be toxic to goldfish, the compounds based on stearyl, oleyl and cetyl alcohol being much less potent than those derived from lauryl alcohol (Florence et al 1978). In this communication we report the inhibitory effects of some of the 'Brij' non-ionic surfactants on the peristalsis of sacs of rat jejunum in vitro.

Sacs, 4 cm long, were prepared from the lower jejunum of male Sprague-Dawley rats weighing about 350 g as described by Whitmore et al (1979) except that the sacs were not everted. Each sac was filled with 0·2 ml of Krebs' original Ringer phosphate buffer (Dawson et al 1969) at pH 6 and suspended in 5 ml of the same solution maintained at 37°C in a water bath and 'bubbled' with a mixture of O_2/CO_2 (95/5%). The top ligature on the sac was attached to an isometric transducer (Devices Instruments Ltd, Welwyn Garden City, Herts) and the output from the latter was fed through an amplifier to a X-T recorder. Peristalsis was initiated by application of a 4 g tension to the sac and monitored by the recorder. Brij 30 (polyoxyethylene$_4$ laurylether), Brij 35 (POE_{23} laurylether), Brij 58 (POE_{20} cetylether) and Brij 98 (POE_{20} oleylether) were used as received from Honeywill Atlas Ltd, Carshalton.

Fig. 1 shows a typical recording of the peristalsis. The first 20 min were used as a control and then samples (10 μl or less) of the text surfactant were added to the solution bathing the serosal surface at intervals of about 10 min. The surfactant was dissolved in the same buffer solution used for the bathing medium. In the example shown only one addition of Brij was made because the high concentration used was sufficient to cause complete inhibition of the peristalsis. The average amplitude of the pendular movement clearly decreased within 3 min of addition of the surfactant, although the frequency of the contractions did not change significantly. Thereafter the amplitude continued to decrease, with no change in frequency, until no movement was detectable (after about 15 min). Similar responses were recorded when lower concentrations of surfactant were added to other sacs, except that only partial inhibition of movement was produced—that is, the average amplitude decreased but remained measurable. The decrease in the inherent tone of the sac that is apparent in Fig. 1 was not consistently observed.

To quantify the results the average amplitude of the pendular movement during the appropriate periods of time was taken as an arbitrary measurement of peristalsis. The values thus obtained for different sacs were then normalized by conversion to relative peristalsis values:

$$\text{Relative peristalsis} = \frac{\text{Peristalsis in the presence of Brij}}{\text{Peristalsis during the control period}}$$

These relative values are plotted in Fig. 2 as a function of surfactant concentration. A value of 1 shows that peristalsis was unaffected and a value of zero indicates complete inhibition of movement. All four of the Brij compounds tested inhibited peristalsis but they were not

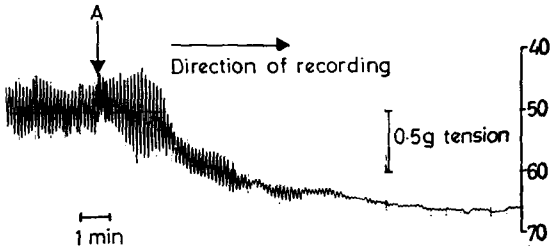

FIG. 1. Recording of isometrically transduced peristaltic movement. The experimental conditions are given in the text. Only the last 3 min of the control incubation period are shown and at the time marked A the surfactant (Brij 30) was added to the solution bathing the serosal surface, giving a final concentration above 20 μM.

† Correspondence.

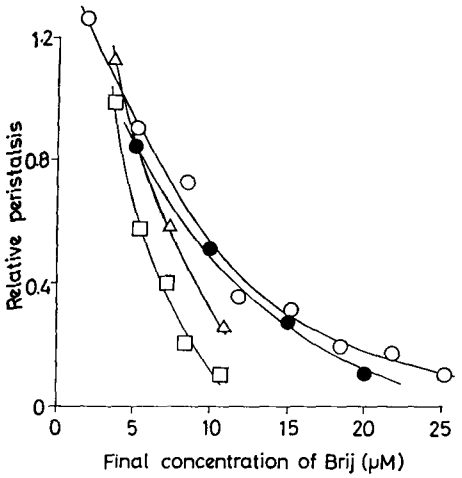

FIG. 2. Inhibition of peristalsis by non-ionic surfactants. Peristalsis was measured and quantified as described in the text in the presence of the indicated concentrations of ○-Brij 35, ●-Brij 30, △-Brij 58 and □-Brij 98.

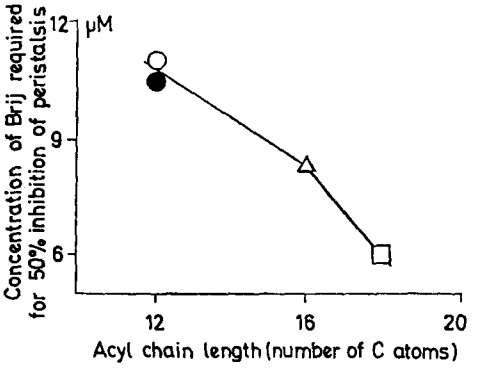

FIG. 3. Relationship between acyl chain length of the surfactants and their potency in inhibiting peristalsis. The concentrations of the Brijs that produced 50% inhibition of peristalsis (see Fig. 2) are plotted against their acyl chain lengths.

equally effective in terms of the concentration required to bring about a given inhibition. This finding is shown more clearly in Fig. 3, in which the concentrations of the surfactants required to produce 50% inhibition are plotted against the lengths of the acyl chains of each compound. The two derived from lauryl alcohol (POE_4 and POE_{23}) not only were least effective but also gave virtually identical results, showing that the chain length of the POE moiety was not important in determining the extent of inhibition. Instead it appears that the chain length of the acyl part of the compounds was the important factor because potency increased with increasing length of the acyl chains.

Extrapolation of the results in Fig. 3 might not be valid; but, at least within the limits tested, our findings suggest that there is a simple relationship between the hydrophobicity and the pharmacological effect of these non-ionic surfactants. This is most easily interpreted as indicating that interaction of the Brijs with cell membranes underlies their inhibition of peristalsis. Such an interpretation is in keeping with the anaesthetic effects mentioned above and it seems reasonable to expect that these compounds may affect a variety of cell responses mediated by their membranes. The contrasting observation that the C_{12} alkyl derivatives were most potent in the toxicity studies with goldfish (Florence et al 1978) suggests that the basis of that action was somewhat different—perhaps an interaction between surfactant and membrane surfaces rather than the hydrophobic interiors?

July 19, 1979

REFERENCES

Benke, G. M., Brown, N. M., Walsh, M. J., Drotman, R. B. (1977) Food Cosmet. Toxicol. 15: 309–318

Dawson, R. M. C., Elliott, D. C., Elliott, W. H., Jones, K. M. (eds) (1969) Data for Biochemical Research, 2nd Ed. p. 507

Florence, A. T., Walters, K. A., Dugard, P. (1978) J. Pharm. Pharamcol. 30: Suppl. 24P

Schulz, K. H., Harz, A., Soehring, K. (1953) Theor. Med. 7(3): 92

Whitmore, D. A., Brookes, L. G., Wheeler, K. P. (1979) J. Pharm. Pharmacol. 31: 277–283

Zipf, H. F., Wetzels, E., Ludwig, H., Fredrich, M. (1957) Arzneim.-Forsch. 7: 162

Zipf, H. F., Dittmun, E. Ch. (1964) Naunyn. Schmiedebergs Arch. Exp. Pathol. Pharmakol. 247: 544–557