A DOUBLE-PEAKED QUANTITIVE STRUCTURE-ACTIVITY RELATIONSHIP (QSAR) IN A SERIES OF PARACETAMOL DERIVATIVES

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We recently (Dearden & O'Hara 1976) reported a parabolic QSAR for the analgesic potencies of a series of ring-substituted alkyl derivatives of paracetamol of low lipophilicity (log P < 1.8). On extending the range of compounds up to a log P value of 4.4, we were surprised to find a second peak of activity, as measured by the mouse abdominal constriction response test with p-phenylbenzoquinone as the challenge agent. This second peak can be described as follows:

$$\log(1/ED30) = 4.070 \log P - 0.612(\log P)^2 - 0.444I - 5.343 \qquad (1)$$
$$n = 8 \quad r = 0.906 \quad s = 0.248 \quad \log P_o = 3.33$$

where I is an indicator variable (I = 1 for absence of a 4-OH group).

It is possible that the second peak represents anti-inflammatory activity, for there is evidence (Collier et al 1968) that the abdominal constriction response contains an inflammatory component; furthermore, a number of lipophilic derivatives of paracetamol have been patented as anti-inflammatory agents (Passedouet et al 1969, Martin & Verge 1970), whilst paracetamol itself has negligible anti-inflammatory activity.

If this hypothesis is correct, then the compounds must be acting at one of two distinct receptor sites with quite different lipophilic binding requirements. In order to check whether such a situation could give rise to a double-peaked QSAR, we modified our mathematical model of drug transport and binding (Dearden & Townend 1976) by the inclusion of two side cells, one of which was made hydrophilic and the other lipophilic; the total "biological response" was taken as the sum of the drug concentrations in the two side-cells at any given time after "dosage". Such a model did indeed generate a double-peaked QSAR, and although the ordinate is arbitrary we have superimposed the curve on the experimentally determined results to show the qualitative agreement of theory and experiment (Fig.1).

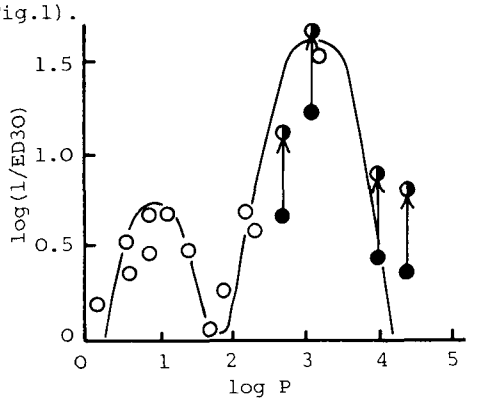

Fig. 1 Variation of potency with lipophilicity. The points marked (○) are observed potencies for compounds with a 4-OH group, and those marked (●) are observed potencies for compounds without a 4-OH group. The latter points are corrected thus (→◑) for the absence of a 4-OH group by adding 0.444 to the observed potencies, as required by equation (1)

The above hypothesis to account for the experimental results shown in Fig.1 is, we believe, more acceptable for this set of compounds than is that of Franke & Kühne (1978), which requires adjacent receptors with increasingly lipophilic molecules spilling over from one to the other receptor.

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