AN AMBIGUITY IN RECEPTOR THEORY

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Two expressions for calculating receptor occupancy by antagonist in competitive drug antagonism are contrasted.

The following problem may arise when calculating receptor occupancy by an antagonist from standard 'occupation' theory (Gaddum, 1937) of competitive drug antagonism.

If A and B represent concentrations of agonist and antagonist, K_1 and K_2 their respective affinity constants, y and z their respective occupied receptor fractions and x the dose-ratio, the equation $z = (x - 1)/x$ (1) is often used to determine the receptor fraction occupied by the antagonist. Equation (1) was originally formulated in respect of rate theory (Paton, 1961), but when the same equation is applied to arguments based on occupation theory the following difficulty arises.

It is possible to derive equation (1) by combining $K_2B = x - 1$ (2) and $z = K_2B/(K_2B + 1)$ (3), but equation (1) contradicts $z = (1 - y)(x - 1)/x$ (4) which follows from $K_1 = y/(1 - y)A = y/(1 - y - z)Ax$. However, the above derivation of equation (1), insofar as it applies to occupation theory, is based on premises which are inconsistent since (2) refers to the situation where both agonist and antagonist are present and in equilibrium with receptors (Schild, 1949) whilst (3) refers to the situation in which only the antagonist is present and in equilibrium with receptors. By contrast, the derivation of (4) assumes the presence at equilibrium of both agonist and antagonist.

It would seem thus that, in terms of standard occupation theory, estimates of antagonist receptor occupancy by equation (1) do not represent the actual occupancy in a given experiment which is given by equation (4). However, (4) is difficult to evaluate because of the term containing y. Equation (1) could, however, be regarded as indicating receptor occupancy by antagonist if no agonist was present. Of course the results obtained by (1) and (4) could be very close, since the two equations converge when y becomes small, as is the case when an agonist of high efficacy acts on a preparation with abundant spare receptors. In such cases equation (1) is a very useful approximation to the result obtained from standard occupation theory.

I would like to thank Dr D.H. Jenkinson and Professor J.W. Black for discussion.

References

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