A theoretical model of two functionally opposite receptor populations

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A theoretical model is presented to describe 'antagonistic agonism', i.e. the interaction between an agonist and two functionally opposite receptor populations.

The interaction between agonist A and the opposite receptors $R_{(+)}$ and $R_{(-)}$ can be broken down into three steps:

1. Relationship between agonist concentration ([A]) and biological stimuli ($S_{(+)}$ and $S_{(-)}$ (see Ariëns, Simonis & van Rossum, 1964a):

$$S_{(+)} = \frac{\alpha_{(+)}[A]}{K_{A(+)} + [A]}; \quad S_{(-)} = \frac{\alpha_{(-)}[A]}{K_{A(-)} + [A]} \qquad (1)$$

where $\alpha_{(+)}$ and $\alpha_{(-)}$ are the intrinsic activities of A on $R_{(+)}$ and $R_{(-)}$ respectively; $K_{A(+)}$ and $K_{A(-)}$ are the dissociation constants for the drug-receptor complexes $AR_{(+)}$ and $AR_{(-)}$ respectively.

Summation of stimuli:

$$S_t = S_{(+)} - S_{(-)} \qquad (2)$$

where S_t is the total biological stimulus.

3. Relationship between total biological stimulus and effect (E):

$$E = S_t - S_t \frac{S_{tmax} - E_{max}}{S_{tmax}} \qquad (3)$$

where S_{tmax} is the maximum total stimulus, and E_{max} is the maximum observable effect. (Equation (3) is formally similar to the equation proposed by Ariëns, Simonis & van Rossum (1964b) to describe functional synergism.)

Theoretical concentration-effect curves can be calculated by substituting into equations (1), (2) and (3). As the relationship between the two opposite biological stimuli is determined by the relative values of $\alpha_{(+)}$ and $\alpha_{(-)}$, and of $K_{A(+)}$ and $K_{A(-)}$, five different cases of antagonistic agonism can be distinguished. *Case 1:* $\alpha_{(+)} = \alpha_{(-)}$, $K_{A(+)} = K_{A(-)}$ $E = 0$ for all values of [A]. *Case 2:* $\alpha_{(+)} = \alpha_{(-)}$, $K_{A(+)} < K_{A(-)}$; the result is a bell-shaped concentration-effect curve. *Case 3:* $\alpha_{(+)} > \alpha_{(-)}$, $K_{A(+)} = K_{A(-)}$; the result is a monophasic saturation curve. *Case 4:* $\alpha_{(+)} > \alpha_{(-)}$, $K_{A(+)} < K_{A(-)}$; the result is a monophasic curve which has a peak, and then declines to a plateau. *Case 5:* $\alpha_{(+)} > \alpha_{(-)}$, $K_{A(+)} > K_{A(-)}$; the result is a biphasic curve, consisting of a negative and a positive phase. The receptor population whose activation is reflected in the direction of the observed effect, may be called 'dominant', and the opposite receptor population may be called 'masked'.

A competitive antagonist acting at either or both receptors can change the relationship between the two component concentration-stimulus curves. Thus the blockade of masked receptors causes potentiation, and the blockade of dominant receptors causes reversal of the response. If both receptors are affected by the antagonist, either potentiation or antagonism can be observed depending on the concentrations of the agonist and antagonist.

This model is used to explain the unmasking of latent effects (Tamayo, Contreras & Quijada, 1974), bell-shaped dose-response curves (Okpako, 1972), biphasic dose-response curves (Spedding & Weetman, 1972), potentiation by antagonists (Ignarro & Titus, 1968), reversal by antagonists (Ignarro & Titus, 1968), and the dual action of antagonists (Burks & Cooper, 1967).

I am grateful to C.M. Bradshaw and P. Bevan for helpful discussions.

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