Drug receptor inactivation: a new kinetic model

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The following hypothesis is examined:

$$D+R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} DR \xrightarrow{k_3} R' \xrightarrow{k_4} R$$

In this scheme DR represents the combination of a receptor (R) with a drug (D). The complex (DR) is converted irreversibly to inactive receptor (R'). R' cannot react with D but can be reactivated to generate R. Stimulus for the effector and the response intensity at any moment are assumed to be proportional to the rate of formation of R' ($=k_3[DR]$). Thus the model is a modified occupation theory and becomes identical to the classical occupation theory whenever $k_2>>k_3<<k_4$. In contrast, when k_3 is much larger than the other three rate constants, the model becomes formally equivalent to the Paton rate theory. Therefore the occupation theory and rate theory represent special cases of the present proposal.

In general, this model possesses most of the dynamic (transient state) characteristics of the rate theory. For example, overshoot and fade are often encountered, but highly damped oscillations are predicted to occur under some circumstances. In the steady state the intrinsic efficacy (ϵ) can be represented by $k_3 \cdot k_4(k_3+k_4)$. If every drug tends to generate a unique R' with characteristic values of k_3 and k_4, then there must exist two classes of antagonists, one typified by small k_3s and the other by small k_4s. General properties of the new model are examined for agonists, antagonists and combinations thereof.

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How long does a molecule stay on the receptor? Explanation of a paradox

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When an atropine-treated tissue is transferred to a large volume of drug-free solution, the proportion of receptors occupied by atropine will fall according to an exponential curve (if the receptors are identical and independent, and the rate is dissociation-controlled). The time constant (half-life/0·693) for this exponential desorption was found to be about 10 min for longitudinal muscle from the guinea-pig ileum by Paton & Rang (1965).

Molecules stay on the receptors for a random length of time, and it can be shown that the mean lifetime (defined as the length of time from the moment of adsorption to the moment of desorption) of a drug-receptor complex is the time constant for desorption. After transferring the tissue to drug-free solution, at $t=0$ say, some molecules will desorb almost straight away, others not for a long time. The experimental method clearly measures the mean length of time from $t=0$ until the moment of desorption. This interval (measured from $t=0$) is called the residual lifetime of the molecule on the receptor. Suppose its mean value is 10 min as above. Now obviously the lifetime (measured from the moment of adsorption) must be longer