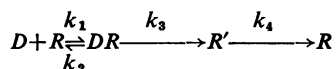


**Drug receptor inactivation: a new kinetic model**

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The following hypothesis is examined:



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  $k_2 \gg k_3 \ll k_4$ . 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 ( $\epsilon$ ) 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  $k_3$ s and the other by small  $k_4$ s. 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

than the residual lifetime, because all the molecules on the tissue have already been adsorbed for some time at  $t=0$ . Yet it has been stated that the mean lifetime would also be 10 min. How is this paradox resolved?

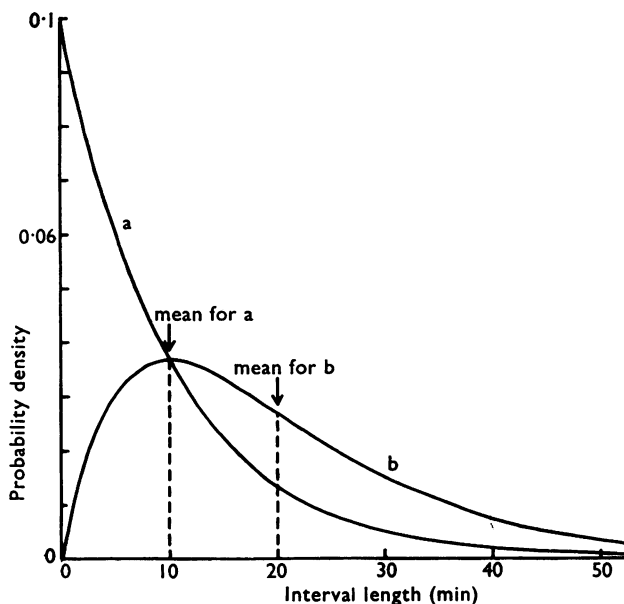


FIG. 1. (a) Distribution of lifetimes for all complexes. (b) Distribution of lifetimes for complexes in existence at  $t=0$ . The distribution of residual lifetimes for these complexes is identical with curve (a).

The key to the explanation lies in the realization that the drug-receptor complexes in existence at a specified arbitrary moment of time (such as  $t=0$ ) are not typical of all complexes, in the sense that there is a better chance of catching the long-lived complexes in existence than there is of catching the short-lived ones. The lifetimes are said to be sampled by a length-biased method (Cox, 1962). Figure 1, curve (a), shows the distribution of the lifetimes of all drug-receptor complexes. The mean is 10 min. Curve (b) shows the distribution of lifetimes for those complexes which are in existence at a specified moment,  $t=0$ , only. Short lifetimes are seen to be relatively rare, and the mean lifetime for these complexes is 20 min, twice that for all complexes. Now there is an equal chance that  $t=0$  will fall anywhere within the 20 min mean lifetime, so, at  $t=0$ , molecules will on average have been adsorbed already for 10 min and, on average, their residual lifetime until desorption will also be 10 min, the same as the mean total lifetime for all complexes.

These results are further discussed and proved by Colquhoun (1970).

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