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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?

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

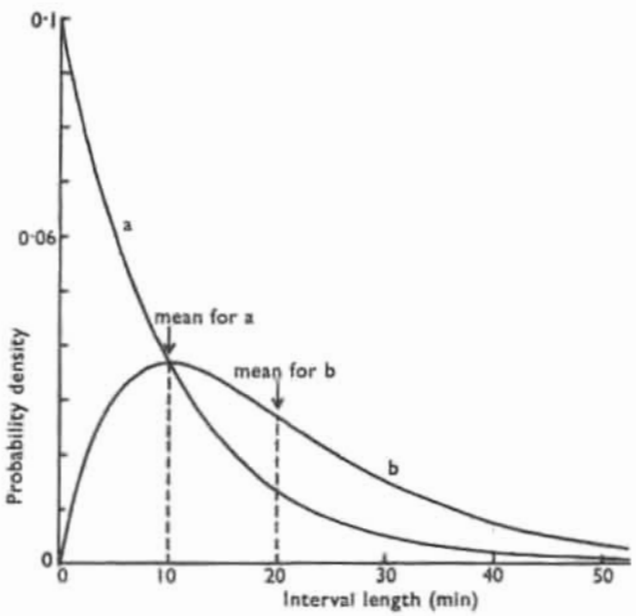

FIG. 1. (a) Distribution of lifetimes for all complexes. (b) Distribution of lifetimes for complexes in existence at $t=0$. The distribution of residual lifetimes for these complexes is identical with curve (a).

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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