6. Residence Time of the Drug-Receptor Complex

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Ten years after Robert A. Copeland and colleagues (2006; Copeland, 2016) suggested that the key determinant of *in vivo* pharmacological activity, and its duration, was not the affinity of a drug for its receptor, but rather the lifetime of the drug-target complex, it seemed timely to define and discuss here the concept of **residence time of the drug–receptor complex**. *Stricto sensu*, as originally defined (Copeland et al., 2006), the residence time of a drug on its target (receptor, enzyme) is the reciprocal of the dissociation rate constant (k_{off}, k_{-1}), that is: $\tau = 1/k_{off}$.

According to this model, pharmacological activity (at least for antagonists and enzyme inhibitors) would depend on the binding of the drug to its intended target, with activity persisting only while the drug remains bound. Thus, there may be particular interest in compounds with a long residence time, especially if this exceeds the plasma half-life (Copeland, 2016), making it an important factor for understanding the pharmacokinetic/pharmacodynamic (PK/PD) relationship of these drugs. As an example supporting this idea, Guo and colleagues (2012) showed that there was no relationship between efficacy and affinity for a series of adenosine A2A receptor agonists, whereas a good correlation was found between efficacy and residence time.

On the other hand, a shorter residence time may be beneficial to avoid continuous receptor blockade, as in the case of clozapine at the dopamine D2 receptor. Indeed, the "fast-off" theory proposes that atypical antipsychotics bind weakly to synaptic D2 receptors and are therefore rapidly released, which would explain their lower propensity to induce extrapyramidal side effects and hyperprolactinemia, both consequences of prolonged receptor blockade (Kapur and Seeman, 2000).

Accordingly, this concept may change one of the paradigms in the evaluation of new compounds during the drug discovery process, which has traditionally been based on binding affinity measurements under thermodynamic equilibrium conditions, conditions that are not fully valid in the context of an open system where drug concentrations at the biophase change according to pharmacokinetic processes (Copeland, 2016; Swinney et al., 2015). It is noteworthy that since the first descriptions of this model, numerous compounds have progressed to clinical trials based on efforts to incorporate the concept of drug-target residence time as a key factor in lead optimization (Copeland, 2016).

Finally, it is important to emphasize that this pharmacodynamic parameter, **residence time** (of the drug on the receptor), has nothing to do with the pharmacokinetic parameter **mean residence time**, which estimates the average time a drug remains in the body.

References

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