

Affinity of a Drug for and Residence Time at its Target

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Introduction

A major problem in drug designing and development is the difficulty in predicting efficacy in humans from *in vitro* data. For a long time, it was thought that an important contributor to the efficacy of a drug is its affinity for the target. This traditional view was challenged by accumulative evidence suggesting that thermodynamic equilibrium constants, such as K_d or K_p , in most cases do not reflect potency *in vivo*. A new concept was, therefore, introduced in 2006; the drug-residence time (t_R) concept [1]. This has arisen from the fact that a drug can elicit its action as long as it remains bound to its target. The drug-residence time, which is the reciprocal of the rate constant for dissociation of the binary drug-target complex (k_{off}), was suggested as an alternative perspective on drug optimization, with superior predictability for the duration of pharmacological effect and target selectivity. Nevertheless, recent studies revealed that long t_R has predictability value only when k_{off} is slower than the elimination rate of the drug from the target vicinity [2]. Therefore, pharmacokinetics as well as other factors, such as selectivity of targeting, biodynamics of the target, and endogenous ligands and signaling should be taken into account.

Defining the Appropriate Predictors for Lead Optimization

The efforts for development of new drugs have been often oriented to approaches aiming to exploit the thermodynamic control of the drug-target interaction. In a closed experimental system, such as a cell-free system or a cell culture in which potency is measured at fixed drug concentrations, drug and target are at equilibrium, and thus affinity constants precisely quantify the concentration of the binary complex between drug and target that in turns relates with the drug potency. However, *in vivo* systems are open systems in which drug concentration, endogenous ligands and the target itself fluctuate over time [3]. Therefore, it seems better to consider the lifetime of the drug-target complex, since each drug exerts its biological effect only when it encounters its target [1]. The significance of t_R value is highlighted by the fact that a large number of drugs, being in clinical practice, behave as slow-binding agents and are characterized by long residence time at their targets, ranging from hours to days [4,5]. However, the lifetime of a drug-target complex except for dissociative events, also depends on possible efflux of the drug from the vicinity of the target as well as on target clearance. There by, both effects, as dictated by pharmacokinetics of the drug and biodynamics of the target (desensitization, internalization, recycling), set the boundaries for when and whether t_R , as defined by thermodynamics terms, can reflect the *in vivo* target coverage. To be t_R a good predictor of the *in vivo* drug efficacy, recent studies suggest that k_{off} must be below the elimination rates that influence the local drug and target concentrations [2]. Experimental approaches for t_R optimization have been already published [3,6]. Nevertheless, the fact that many drugs have slower elimination rates than k_{off} is a strong evidence that t_R has a smaller role in the *in vivo* target coverage than was previously hypothesized [2].

Beyond the above weaknesses and limitations of residence time concept, other investigators argue that drug rebinding, i.e. the consecutive binding of dissociated drug molecules to the original target and/or adjacently placed targets, can be influential *in vivo* as well [7]. Finally, in certain cases long drug-target residence time may result in unfavorable outcomes [8]. For instance, for dopamine D2

receptors, mechanism-based toxicity can occur, if they are occupied by antipsychotics for prolonged time [9]. According to our opinion, even in the latter cases, knowledge of t_R will be critical in designing drugs with improved safety.

Conclusions

The *in vivo* target coverage by a drug and its relation with thermodynamic and pharmacokinetic properties requires a detailed analysis in a relevant context. One needs to avoid generalizations or oversimplifications. Using, for instance, healthy animals in preclinical studies may not adequately predict toxic effects in humans, given that species-specific differences may exist and that drugs are designed to be used in patients. As reviewed by Kenakin and Williams [10], substitution of human cellular systems for animal testing may better predict human efficacy and possible toxicity. However, special attention should be paid on that a cellular system is a closed system and that many cell lines often used to study drug-target interactions *in vitro* have lost their original phenotype. There are also other issues that must be addressed. In-depth knowledge of the target biology is of paramount importance, given that natural substrates or signaling molecules implicated in the function of the target may act as competing ligands. Moreover, target response may be changed by oligomerization or modifications that often result in different sensitivity against binders and cytoplasmic signaling. Last, a drug with a given affinity and efficacy for one target may, at higher concentrations, cause secondary effects on other target(s). In conclusion, the high complexity of biological systems requires special attention when one is aiming to understand and predict *in vivo* drug activity.

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Received February 04, 2014; Accepted February 07, 2014; Published February 10, 2014

Citation: Kalpaxis DL (2014) Affinity of a Drug for and Residence Time at its Target. *J Community Med Health Educ* S2: e001. doi:10.4172/2161-0711.S2-e001

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This article was originally published in a special issue, **Management and Prevention of Chronic Disease and Disability: a Global Challenge** handled by Editor. Dr. Syeda Zakia Hossain, University of Sydney, Australia