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SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry 14 (2006) 896–897
Bioorganic & Medicinal Chemistry

Perspective

The benefits of the multi-target approach in drug design and discovery

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Received 28 July 2005; revised 5 September 2005; accepted 6 September 2005
Available online 3 October 2005

Abstract—Promiscuous binding has been considered to be a problem in the design and development of new drugs against a given disease. However, promiscuity in molecular recognition is not all bad news, and scientists are currently taking advantage of the emerging 'promiscuous binding' or 'multi-target approach' in medicinal chemistry.

In living cells, where a pool of proteins can easily bind to a great variety of ligands, including ions, small organic and inorganic molecules and macromolecules, 'promiscuity' becomes a problem in drug design and discovery efforts. For many years, pharmaceutical companies and research laboratories around the world have been struggling to discover and develop highly specific compounds against a particular target—the one-probe-one-target approach. However, what would happen if a single molecule can selectively bind to multiple, but limited, targets?

Let us consider the case of Alzheimer's disease. It is known that the malfunction of different, but related, biochemical pathways causes the disease. The disease involves several complex pathways in which many different proteins play an important role in the pathogenesis of the disease.[1] To address this problem, in a recent study Weaver and co-workers performed an evaluation of common structural motifs on 43 Alzheimer's disease-related proteins.[2] They found that 27 out of these 43 proteins share a 'common' binding site. It was also found that this common site could bind a fragment of a polysulfonated disaccharide of heparin. In other words, a single molecule could selectively bind to more than one disease-related protein. Then, this 'common' site could be used for developing new 'promiscuous' drugs with higher therapeutic effectiveness by employing the novel one-probe-multiple-target approach.

Molecules exist in a range of dynamic populations around their native state. In the process of binding, different conformers of multiple targets and a given ligand may fit in one of the most favorable energetic states. Therefore, viewing targets and ligands as dynamic distributions, which present to the incoming ligands a range of different binding site shapes, illustrates how multiple-targets' binding sites can bind a single ligand. Considering the dynamic nature of both proteins and ligands, and that binding is not a static but a dynamic process that depends on the constant molecular dynamics of the molecules in the cell,[3,4] we can hypothesize that a common site of different proteins is certainly not a hole containing a specific arrangement of amino acids. Instead, it is a space driven by different energetic states and determined by its interaction with a given probe (Espinoza-Fonseca, unpublished work). Thus, the existence of these energetic spaces leads to promiscuous binding in biological systems. This hypothesis is better illustrated in Figure 1.

A 'promiscuous drug' is not a mixture of different molecules that *selectively* act on multiple receptors implicated in a given disease (combination therapy), but rather a single drug molecule that *selectively* targets multiple receptors. In addition, a promiscuous drug may present several advantages: (a) different pathways of the disease could be efficiently targeted by using only one molecule, thus increasing its therapeutic effectiveness; (b) for a single molecule, it is possible to improve not

Keywords: Drug design; Promiscuous drug; Cancer; Alzheimer's disease.
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doi:10.1016/j.bmc.2005.09.011

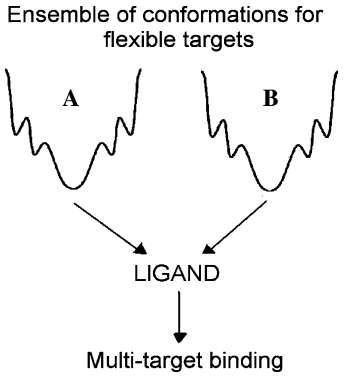

Figure 1. Representation of the multi-target binding process. A and B are two independent, unrelated targets that share similar energetic states. During the dynamic process, similar energetic states allow a single ligand to bind to both targets, leading to the multi-target approach.

only its biodisponibility in the cell, but also its ability to be efficiently eliminated after its therapeutic action is completed because the delivery and excretion systems are highly promiscuous; (c) related to (b), promiscuity does not necessarily mean that the drug will be toxic; and (d) promiscuous drugs do not necessarily over-suppress or over-activate a given pathway or network.

Fortunately, promiscuity in molecular recognition is not all bad news. There are several cases in which promiscuity becomes a virtue in drug design: the best well-known case is aspirin. Its therapeutic effect has gone beyond the area of pain relief, and now it is widely used to reduce platelet aggregation, for prevention of preeclampsia and cancer, and as an anti-arthritic, among other uses. Its effect involves several pathways that have been studied and discussed in depth, and reported in several papers. Besides, this approach has also started to be applied to the treatment of cancer, and promiscuous drugs such as SU11248 (developed by Pfizer, Inc.) and BAY 43-9006 (Bayer Pharmaceutical Corp.) have been shown to be promising multi-target drugs.[5] SU11248, a small molecule that inhibits tyrosine kinase activity, interacts with the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and FLT3 receptor tyrosine kinases; BAY 43-9006, which inhibits a variety of kinase receptors such as VEGF and PDGF, also targets the RAF/MEF/ERK signaling pathway (inhibition of cell proliferation) and the VEGFR-2/PDGFR-β signaling cascade (inhibition of tumor angiogenesis).

The novel concept of beneficial promiscuity in molecular recognition represents a promising alternative not only for drug-design efforts. Promiscuous binding of small drugs will also allow us to explore biological networks by systematically analyzing the interface between chemical and biological space: a single small molecule able to target a great diversity of receptors would reveal both local and global properties of chemical and biological interface and therefore understand certain biological phenomena.

In summary, promiscuity has potentially beneficial effects and we can take advantage of it not only in drug-design efforts, but also to better understand the structural and energetic keys involved in the promiscuous binding mechanism in drug delivery and excretion.[6] At this point, one thing is clear: the multi-target approach represents a new challenge for medicinal chemists, pharmacologists, toxicologists, and biochemists. With much more work, the multi-target approach could be an important deviation from the classical drug-design efforts.

Acknowledgments

The author thanks the referees for their useful comments and suggestions, and Asya Varbanova for the review of the manuscript draft. The author's research is supported by a research stipend granted by the Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota.

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