J. Pharm. Pharmacol. 1998, 50 (Supplement): 106

Molecular properties and structure–permeation relations revisited

BERNARD TESTA

School of Pharmacy, BEP, University of Lausanne, Lausanne-Dorigny, CH-1015, Switzerland

Robust and predictive structure-permeation relationships (SPR) have become a sort of Holy Grail in drug research, one objective being to shorten the time-consuming development of active compounds ultimately doomed by hidden pharmacokinetic defects.

Structure-activity relationships and SPR use a variety of parameters to describe molecular structure and properties, e.g. lipophilicity, H-bonding and volume.

Lipophilicity is a molecular property of particular relevance in drug design and SPR. However, the intrinsic lipophilicity of ions remains a poorly explored field despite the fact that most drugs exist predominantly in ionized form under physiological conditions. Our laboratory relies extensively on novel methods such as two-phase titration to obtain reliable log P values for ions.

A large number of SPR studies have been published, with results that must be considered with care. Qualitative SPR, e.g. rules or decision trees, can reveal informative trends and give useful hints. Quantitative SPR have proven their great worth in drug design, but these statistical tools must be used in the careful observance of their rules and conditions to obtain robust and reliable models. Thus, the set of compounds must be as broad, diverse and as regularly distributed as possible. Intercorrelated variables and overfitting plague too many models which are misleading or at best have very limited predictive power despite their appeal.

Beyond these technical problems, there exist intrinsic limitations to our current knowledge which prevent us from developing truly general SPR models. One problem with parameters is that their values are the measured or calculated expression of molecular states that may not be biologically relevant. Molecular properties and structural attributes are not only interdependent, they also fluctuate, thus delineating an ensemble of molecular states which forms a property space. Such molecular states include conformation, ionization, electronic distribution and *virtual* lipophilicity. Their use in SPR remains an unsolved challenge (Testa, 1997).

Molecular modelling has done much to allow medicinal chemists to reach a better understanding of the dynamic behaviour of molecules. It has also revealed the significance of molecular fields as the main factors controling biochemical recognition. The molecular lipophilicity potential thus offers a 3D, time-dependent representation of recognition forces encoded in lipophilicity.

In SPR, membranes can be seen as fuzzy targets due to the diversity and fluctuation of their components. Hence various permeants may interact differently with membrane components, resulting in a poorly defined "activity". The expected result is a blurring of potential SPR.

References

Testa, B. (1997) Drugs as chemical messages: Molecular structure, biological context, and structure-activity relationships. Med. Chem. Res. 7: 340-365