

ELUCIDATION OF THE INITIAL MOLECULAR INTERACTIONS OF THE AGONISTS WITH THE ADRENOCEPTOR IN RELATION TO THE FUNCTIONAL PHARMACOLOGIC 'EFFICACY'

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The terms 'affinity' and 'intrinsic activity' were introduced by E.J. Ariens et al. to describe the quantitative pharmacologic parameters of agonists and antagonists molecules on the isolated organs¹. The antagonist molecules lack intrinsic activity. Subsequently, R.P. Stephenson, M. Nickerson pointed out that organs contain spare receptors and structurally different molecules may produce equal pharmacologic responses by activating different proportions of receptors. Such molecules may differ in intrinsic receptor mediated activity or 'efficacy'. Furchgott and co-investigators on the isolated organ reduced the spare receptors to the optimum fraction by irreversible blockers². Under these conditions two agonists with unequal efficacy produced unequal pharmacologic effects. The method for calculating relative intrinsic efficacy was developed. Currently the secondary biochemical cascades after the activation of α or β -adrenoceptor leading to the mechanical responses are well described. The quantitation of the initial molecular events in the activation of the receptor and related conformational changes are methodologically limiting. From studies based on stereoisomers of sympathomimetic catecholamines, catechol imidazolines and their desoxy analogues, we propose³⁻⁵ that 'efficacy' is mainly encoded in the mode of activation of the adrenoceptor. Intracellular events amplify the process leading to the mechanical effect. It is deduced that for α -adrenoceptor activation the charged amino group in extended transconformation must initiate the disruption of the proposed salt bridge constraint⁶, and the phenyl-catechol group must interact with the second site(s). Finally the benzylic hydroxy group in the correct steric orientation appears to intensify the conformational change for the optimum efficacy of the potent enantiomer. The receptor site for the latter is speculative. Thus in contrast to affinity, the efficacy parameter is related to the rate and the sequence in which chemical groups interact with the α -adrenoceptor⁴. In some imidazolines, there are mainly two functionally important groups which sequentially activate the receptor. Two charged nitrogens of the imidazoline moiety which are equally reactive may produce "interaction hesitancy"⁷ or partial-conformational change leading to the partial agonist activity. In order to understand the initial molecular events in the activation of the adrenoceptors, a structure-based molecular modeling is proposed. The α -adrenoceptor structure will be modeled based on the bovine rhodopsin crystal structure (PDB ID 1F88) and in consistency with existing experimental data. Representative agonists of the catecholamine and imidazoline type will be docked to the proposed binding site near Asp113 on helix III. Binding affinities of both enantiomers will be calculated and compared to the experimental ones. The hypotheses of "interaction hesitancy" of some imidazolines and "two-site sequential interaction" of tolazolines will be tested via molecular dynamics simulation. Their interaction with Ser204, Ser207 and Phe290 will be monitored throughout. The conformational changes upon the agonist interaction will be simulated to relate to their enantiomeric intrinsic efficacy differences, in consistency with existing CD spectral and/or pharmacologic efficacy data.

References:

1. Ariens EJ and De Groot, WM (1954) *Arch Int Pharmacodyn Ther.* 99(2): 193.
2. Furchgott, RF and Bursztyn, P. (1967) *Ann NY Acad Sci.* 144: 882.
3. Patil, PN, Miller, D. and Trendelenburg, U. (1974) *Pharmacol Rev.* 26(4): 323.
4. Patil, PN., Feller, D. and Miller, D. (1991) *J Neural Transm Suppl.* 34: 187.
5. Patil, PN., Fraundorfer, P. and Dutta, P. (1996) *Chirality* 8(7): 463.
6. Porter, JE., Hwa, J. and Perez, DM (1996) *J Bio Chem.* 271(45), 28318.
7. Patil, PN., 1st IUPHAR Conference on Receptor Mechanisms: Principles of Agonism, poster-abstract, P.17, July 23-25, 1998, Merano, Italy.