

Similarities between the binding sites of SB-206553 at serotonin type 2 and alpha7 acetylcholine nicotinic receptors: Rationale for its polypharmacological profile

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Evidence from systems biology indicates that promiscuous drugs, i.e. those that act simultaneously at various protein targets, are clinically better in terms of efficacy, than those that act in a more selective fashion. This has generated a new trend in drug development called polypharmacology. However, the rational design of promiscuous compounds is a difficult task, particularly when the drugs are aimed to act at receptors with diverse structure, function and endogenous ligand. In the present work, using docking and molecular dynamics methodologies, we established the most probable binding sites of SB-206553, a drug originally described as a competitive antagonist of serotonin type 2B/2C metabotropic receptors (5-HT_{2B/2C}Rs) and more recently as a positive allosteric modulator of the ionotropic $\alpha 7$ nicotinic acetylcholine receptor (nAChR). To this end, we employed the crystal structures of the 5-HT_{2B}R and acetylcholine binding protein as templates to build homology models of the 5-HT_{2C}R and $\alpha 7$ nAChR, respectively. Then, using a statistical algorithm, the similarity between these binding sites was determined. Our analysis showed that the most plausible binding sites for SB-206553 at 5-HT_{2C}Rs and $\alpha 7$ nAChR are remarkably similar, both in size and chemical nature of the amino acid residues lining these pockets, thus providing a rationale to explain its affinity towards

both receptor types. Finally, using a computational tool for multiple binding site alignment, we determined a consensus binding site, which should be useful for the rational design of novel compounds acting simultaneously at these two types of highly different protein targets. Copyright: © 2015 Möller-Acuña et al.