Current literature highlights – September 2001

Endothelin receptor antagonists

Endothelin (ET-1) is a potent vasoconstrictor consisting of 21 amino acids. This peptide and two other structurally and functionally related vasoconstricting peptides, termed endothelin-2 and endothelin-3, interact with two known G-protein coupled receptors ET_A and ET_B and induce vasoconstricting effects. ET_A, ET_B, and more recently discovered ET_C are tissue specific and are displayed preferentially in varying proportions on different cell types. ET_A is found in vascular smooth muscle tissue and is mainly responsible for vasoconstriction of smooth muscle cells, while ET_B, which is found in nonvascular smooth muscle tissues, has been implicated in the release of endothelial-derived relaxing factors. Elevated levels of endothelin are found in patients suffering from a variety of diseases including hypertension, pulmonary hypertension, and cerebral vasospasm, and evidence is accumulating that newer ET antagonists may not only provide a novel therapy for the treatment of such diseases but also help in understanding the precise physiological roles of endothelins.

In an effort to discover new ET antagonists, a small library of 15 peptoid compounds was synthesised in solution (Peptoids as endothelin receptor antagonists, F. Dasgupta et. al., Bioorg. Med. Chem. Lett., 11, (2001), 555-557). Screening of these compounds revealed their affinity for endothelin receptors in terms of their ability to competitively inhibit ET. One of the most potent compounds discovered was (1) with an IC_{50} value of 660 nM against ET_B and 13-fold selectivity over ET_A. This library has been successful in providing novel peptoids possessing a range of ET_A and ET_B receptor affinities. Future work may be directed at comparing biophore mapping of this series with the energy minimised 3-D model of other active compounds from the literature which may aid in the design of further compounds with improved activity.

\[ \text{Structure (1)} \]

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Dopamine D4 receptor partial agonists
Recent advances in molecular cloning techniques have led to the characterisation of a number of dopamine receptor subtypes which can be divided into the D1-like and D2-like families. Whereas the D1-like family comprises D1 and D5 subtypes, the D2-like family consists of D2, D3 and D4 receptors. Due to the preferred expression of messenger RNA for dopamine receptors in the frontal cortical and mesolimbic areas, considerable interest has been focused on selective D4 antagonists. According to recent neuropathological and genetic studies (Evidence that the dopamine D4 receptor is a susceptibility gene in attention deficient hyperactivity disorder, S. L. Smalley et. al., Mol. Psychiatry, (1998), 3, 427-430), selective dopamine D4 receptor agonists, partial agonists or antagonists, might be of interest for the treatment of neuropsychiatric disorders including attention-deficient hyperactivity, mood disorders and Parkinson's disease (Cyanoidole derivatives as highly selective dopamine D4 receptor partial agonists: solid-phase synthesis, binding assays, and functional experiments, P. Gmeiner et. al., J. Med. Chem., 43, (2000), 4563-4569). A small library of 13 compounds was synthesised on solid phase. One of the most potent compounds isolated was (2) which possessed a Kᵢ value for human D4 affinity of 0.52 nM, and 25000-, 6000-, 550-, and 3300-fold selectivity over the bovine D1, human D2long, human D2short, and human D3 receptors respectively. This library has been successful in generating highly potent and selective D4 receptor binding compounds. In the future, selective D4 partial agonists could serve as interesting tools for the treatment of neuropsychiatric disorders such as attention-deficient hyperactivity.