The Pharmacology of CP-154,526, a Non-Peptide Antagonist of the CRH1 Receptor: A Review

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ABSTRACT

Since CRH has been shown to mediate stress-induced physiological and behavioral changes, it has been hypothesized that CRH receptor antagonists may have therapeutic potential in disorders that involve excessive CRH activity. CP-154,526 and its close analog antalarmin are potent, brain-penetrable, selective nonpeptide CRH1 receptor antagonists that were discovered in an effort to develop compounds with efficacy in CNS disorders precipitated by stress. Since its discovery many investigators have used CP-154,526 as a tool to study the pharmacology of CRH and its receptors and to evaluate its therapeutic potential in a variety of CNS and peripheral disorders. Systemically-administered CP-154,526 has been demonstrated to antagonize CRH- and stress-induced neuroendocrine, neurochemical, electrophysiological, and behavioral effects.

These findings support the hypothesis that CRH1 receptor antagonists may have therapeutic utility in a number of neuropsychiatric disorders. CP-154,526, as well as other CRH1 receptor antagonists that have since been discovered, have also shown activity in several preclinical models of anxiety, depression, and substance abuse, while having little effect on locomotor activity and motor function. Although these effects are on occasion inconsistent among different laboratories, clinical evaluation of CRH1 antagonists appears justified on the basis of these and clinical data implicating the involvement of CRH in several CNS disorders. The effects of CRH1 antagonists on cognition, neurodegeneration, inflammation, and the gastrointestinal system have not been as extensively characterized and additional studies will be necessary to evaluate their therapeutic potential in these areas.