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An Overview of SSR149415, a Selective Nonpeptide Vasopressin V_{1b} Receptor Antagonist for the Treatment of Stress-Related Disorders

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ABSTRACT

Vasopressin (AVP) and corticotropin-releasing factor (CRF) are key mediators in the organism's neuro-adaptive response to stress. Through pituitary and central vasopressin V_{1b} receptors, AVP participates in the control of the hypothalamic-pituitary-adrenal axis (HPA) and is involved in various emotional processes. SSR149415 is the first selective, orally active vasopressin V_{1b} receptor antagonist yet described. It is a competitive antagonist with nanomolar affinity for animal and human V_{1b} receptors and displays a highly selective profile with regard to a large number of receptors or enzymes. *In vitro*, SSR149415 potently antagonizes functional cellular events associated with V_{1b} receptor activation by AVP, such as intracellular Ca^{2+} increase or proliferation in various cell systems. Pharmacological studies, performed by measuring ACTH secretion induced by various stimulants such as hormones (AVP or AVP + CRF) or physical stress (restraint or forced swimming stress and dehydration) in conscious rats or mice, confirm the antagonist profile of SSR149415 and its efficacy in normalizing ACTH secretion *in vivo*. SSR149415

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is active by the oral route, at doses from 3 mg/kg, it potentiates CRF effect and displays a long-lasting oral effect in the different models. At 10 mg/kg p.o. its duration of action is longer than 4 h. This molecule also decreases anxiety and exerts marked antidepressant-like activity in several predictive animal models. The anxiolytic effects of SSR149415 have been demonstrated in various Generalized Anxiety Disorders (GAD) models (four-plate, punished drinking, elevated plus-maze, light dark, mouse defense test battery, fear-potentiated startle and social interaction tests). It is as effective as the benzodiazepine diazepam in the acute stress exposure test. SSR149415 has similar efficacy to the reference antidepressant drug, fluoxetine, in acute (forced-swimming) and chronic (chronic mild stress and subordination stress) situations in rodents. SSR149415 also reduces offensive aggression in the resident-intruder model in mice and hamsters. Depending on the model, the minimal effective doses are in the range of 1–10 mg/kg i.p. or 3–10 mg/kg p.o. SSR149415 is devoid of adverse effects on motor activity, sedation, memory or cognitive functions and produces no tachyphylaxis when administered repeatedly. It is well-tolerated in animals and humans and exhibits an adequate ADME profile. Thus, SSR149415 is a new dual anxiolytic/antidepressant compound, which appears to be free of the known side effects of classical anxiolytic/antidepressant drugs. Clinical trials are in progress, they will hopefully demonstrate its therapeutical potential for treating stress-related disorders.