

In vitro and in vivo pharmacological characterisation of the potent and selective vasopressin V_{1A} receptor antagonist 4-[4-(4-Chloro-phenyl)-5-[1,2,3]triazol-2-ylmethyl-4H-[1,2,4]triazol-3-yl]-piperidin-1-yl-(3,5-difluoro-phenyl) methanone (PF-00738245)

The pathophysiological consequences of deregulated Arginine vasopressin (AVP) AVP secretion have been studied in a many systems as for example, in polycystic kidney disease, where elevated AVP is hypothesized to stimulate accumulation of cAMP, triggering epithelial cell growth and fluid secretion culminating in renal cyst formation (Torres et al., 2004). Additionally, primary dysmenorrhoea is a common gynaecological complaint, characterized by cyclical cramping pelvic pain. Vasopressin levels appear to be raised in women with dysmenorrhoea both prior to and during menstruation (Ekstrom et al., 1992, Hauksson et al., 1987, Hauksson et al., 1988), the effects of which appear to increase myometrial smooth muscle contraction.

The aim of present study is to describe the pharmacologic profile of PF-00738245, potent, non-peptide vasopressin V_{1A} receptor antagonist, in rats.

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Summary:

The dysregulation of AVP release and activation of vasopressin receptors plays an important role in disease conditions including polycystic kidney disease, congestive heart failure and dysmenorrhoea. The development of potent and selective vasopressin receptor ligands is needed to help dissect the function of the specific subtypes in disease pathogenesis. Here we report the pharmacological characterisation of PF-00738245 in in vitro binding and functional assays using cells expressing vasopressin V_{1A}, V_{1B} or V₂ receptors. PF-00738245 inhibited AVP binding to the recombinant human vasopressin V_{1A} receptor ($K_i=2.85$ nM) and blocked AVP-induced rat aortic ring and human myometrial contraction ($pK(B)=7.35$ and 8.62 respectively). PF-00738245 was selective for the vasopressin V_{1A} receptor by demonstrating minimal binding to vasopressin V_{1B} (3.6% inhibition at 10 μ M) or functional activity at vasopressin V₂ receptors (8.1% agonist and -8.4% antagonist activity at 10 μ M) as well as the oxytocin receptor (46.3% antagonist activity at 10 μ M). The in vivo pharmacological properties were tested orally in the rat and PF-00738245 dose dependently blocked the effect of AVP on a capsaicin-induced cutaneous flare response. Taken together the data support the use of PF-00738245 as a potent and selective vasopressin V_{1A} receptor antagonist which may have utility in the treatment of disease conditions which are propagated by elevation in vasopressin V_{1A} receptor signalling.

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