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An overview of SR121463, a selective non-peptide vasopressin V(2) receptor antagonist.

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Abstract

SR121463 is a selective, orally active, non-peptide antagonist of vasopressin (AVP) V(2) receptors with powerful aquaretic properties in various animal species and humans. SR121463 belongs to a new class of drugs, called aquaretics, which are capable of inducing free-water excretion without affecting electrolyte balance. SR121463 displays high affinity for animal and human V(2) receptors and exhibits a remarkably selective V(2) receptor profile. SR121463 and [(3)H]SR121463 are used, therefore, as selective probes for characterization and labeling of V(2) receptors. In various functional studies in vitro, SR121463 behaves as a potent antagonist. It inhibits AVP-stimulated human renal adenylyl cyclase and dDAVP (1-desamino, 8-D arginine-vasopressin)-induced relaxation of rat aorta. SR121463 also behaves as an inverse agonist in cells expressing a constitutively activated human V(2) receptor mutant. In vitro, SR121463 rescued misfolded V(2) AVP receptor mutants by increasing cell surface expression and restoring V(2) function. In normally hydrated conscious rats, dogs and monkeys, SR121463, by either i.v. or p.o. administration, induced a dose-dependent aquaresis with no major changes in urinary Na⁺ and K⁺ excretion (unlike classical diuretics). In cirrhotic rats with ascites and impaired renal function, a 10-day treatment with SR121463 totally corrected hyponatremia and restored normal urine excretion. In a model of diabetic nephropathy in rats, SR121463 strongly reduced albumin excretion. SR121463 was also effective at extrarenal V(2) (or V(2)-like) receptors involved in vascular relaxation or clotting factor release in vitro and in vivo. In the rabbit model of ocular hypertension, SR121463 by either single or repeated instillation, decreased intraocular pressure. After acute and chronic administration to rats, dogs or healthy human volunteers, SR121463 was well absorbed and well tolerated. In all species studied the drug produced pronounced aquaresis without any agonist effect. Thus, SR121463 is a potent, orally active and selective antagonist at V(2) receptors with powerful aquaretic properties. It is a useful tool for further exploration of function of renal or extrarenal V(2) receptors. Pure V(2) receptor antagonists are likely to be therapeutically useful in several water-retaining diseases such as hyponatremia, Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH), congestive heart failure, liver cirrhosis, and other disorders possibly mediated by V(2) receptors (e.g., glaucoma).

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