

Vasopressin Receptors and Drugs: A Brief Perspective

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Abstract: Objective: In the last decade, knowledge of vasopressin receptors has expanded enormously. It is the purpose of this review to present the current status of our knowledge of vasopressin receptor and drugs acting on them. The goal is to provide a brief perspective as a context for our current understanding and to highlight the gaps in our current understanding. From a pharmacological perspective, it should permit the development of very selective drugs with relatively few side effects. Method A comprehensive review of scientific articles published that address vasopressin receptor subtypes, agonist and antagonist was carried out. Results: There are three subtypes of vasopressin receptor V_1 (V_{1A}), v_2 and V_3 (V_{1B}). vasopressin receptor agonists are found to be effective in septic shock hypothalamic diabetes insipidus, nocturnal enuresis, some kinds of urinary incontinence, hemophilia, von Willebrand's disease and as antiproliferative. vasopressin receptor agonists are found to be effective in SIADH, postoperative hyponatremia, CHF, cirrhosis, polycystic kidney disease and Nephrogenic diabetes insipidus. In Conclusions though vasopressin receptor agonists and antagonists have effect on various organs only few drugs are available in the market and certain available drugs use are limited due to adverse effects. This can be overcome by doing further research and developing new drugs with fewer side effects.

Key words: Vasopressin • Receptor • Subtypes • Agonist • Antagonist

INTRODUCTION

Vasopressin, also called the anti-diuretic hormone or ADH, is an important part of regulation in the circulatory system and is integral to the balance of water in the body. As a fundamental part of hormonal control in the body, it is implicated in many different conditions.

This review will briefly summarize the Vasopressin receptor subtypes, agonist, antagonist and their uses.

Subtypes of Vasopressin Receptors: There are three subtypes of vasopressin receptor:

- V_{1A} (V_1),
- V_{1B} (V_3) and
- V_2 .

All three are G-protein coupled receptor.

These three vasopressin receptors have unique tissue distributions (Table 1). V_{1A} are expressed in vascular smooth muscle cells, hepatocytes, platelets, brain cells and uterus cells. V_{1B} are expressed in cells of the anterior pituitary and throughout the brain, especially in the pyramidal neurons of the hippocampus. V_2 are expressed in the kidney tubule, predominantly in the distal convoluted tubule and collecting ducts, in fetal lung tissue and lung cancer. V_2 is also expressed in the liver where stimulation releases a variety of clotting factors into the bloodstream. In the kidney, V_2 's primary function is to respond to arginine vasopressin by stimulating mechanisms that concentrate the urine and maintain water homeostasis in the organism. When the function of V_2 is lost, the disease Nephrogenic Diabetes Insipidus (NDI) results [1].

Table 1: Distribution, signaling pathway and functions of vasopressin receptors

Receptor	Signaling pathway	Location	Function
V ₁ (V _{1A})	G protein-coupled, phosphatidylinositol/calcium	Vascular smooth muscle, platelet, hepatocytes, myometrium	Vasoconstriction, myocardial hypertrophy, platelet aggregation, glycogenolysis, uterine contraction
V ₂	Adenylyl cyclase/cAMP	Basolateral membrane of collecting duct, vascular endothelium and vascular smooth muscle cell	Insertion of AQP-2 water channels into apical membrane, induction of AQP-2 synthesis, releases von Willebrand factor and factor VIII, vasodilation
V ₃ (V _{1B})	G protein-coupled, phosphatidylinositol/calcium	Anterior pituitary gland	Releases ACTH, prolactin, endorphins

Vasopressin Receptor Agonists:

- V_{1A} - Arginine-vasopressin
Terlipressin
- V_{1B} - 1-Deamino-4-cyclohexylalanine-arginine vasopressin
d[Leu4,Lys8]vasopressin
- V₂ - OPC-51803
- V_{1B} & V₂ - 1-Desamino-8-D-arginine vasopressin (Desmopressin)

Arginine-Vasopressin: A V₁ receptor agonist is a potent alternative to vasoconstrictors in the treatment of fluid and catecholamine-refractory septic shock [2].

Terlipressin: Recent experimental and clinical studies on Terlipressin showed it to be the clinically available, most selective V₁ receptor agonist and may be more potent than arginine-vasopressin in restoring catecholamine refractory septic shock [2].

1-Deamino-4-Cyclohexylalanine-Arginine Vasopressin: Potent and selective human vasopressin V_{1B} receptor agonist stimulates ACTH and corticosterone secretion and exhibits negligible vasopressor activity *in vivo* [3].

D[Leu4,Lys8]vasopressin: Selective vasopressin V_{1B} receptor agonist displays weak antidiuretic, vasopressor and *in vitro* oxytocic activities [4].

OPC-51803: OPC-51803 is a V₂ selective agonist that produces a significant antidiuretic action after single and multiple oral dosing in AVP-deficient and normal AVP states. The data suggest that OPC-51803 is a useful therapeutic drug in the treatment of hypothalamic diabetes insipidus, nocturnal enuresis and some kinds of urinary incontinence [5].

Desamino-d-Arginine-Vasopressin: Synthetic vasopressin analog, that acts as an agonist at V_{1B} and V₂ receptors. Prevents polycystic kidney disease

formation and exhibits antidiuretic, antiproliferative, hemostatic and hypotensive activity *in vivo*. Also used in the management of bleeding in individuals with some forms of hemophilia and von Willebrand's disease [6-8].

Mechanism of Action of Vasopressin Agonists:

Vasopressin binds to specific autoreceptors to trigger an influx of Ca(2+) and this response involves both phospholipase C (PLC) and adenylyl cyclase (AC) pathways that, in the periphery, are activated by V₁ (V_{1A} and V_{1B}) and V₂-type receptors. The [Ca(2+)](i) increase and vasopressin release induced by the V(1a) agonist were strongly inhibited by a PLC blocker, an IP(3) receptor antagonist and a PKC blocker. An AC inhibitor did not affect the V(1a) response, while PKA inhibitors significantly reduced the V_{1A} induced [Ca(2+)](i) and release responses. The [Ca(2+)](i) increase and vasopressin release elicited by the V₂ agonist were attenuated not only by AC pathway blockers, but also by PLC inhibitors. Surprisingly, the V_{1B} agonist showed no [Ca(2+)](i) or vasopressin release response. In conclusion, the V_{1A} agonist activates both PLC and AC pathway, confirming the functional expression of a V_{1A} vasopressin receptor on vasopressin neurones. The V₂ agonist activation of both PLC and AC pathways could result from an action on the PLC-linked unknown receptor and/or the AC-linked dual angiotensin II-vasopressin receptor [9].

Vasopressin Receptor Antagonists

Tetracyclines: Demeclocycline

Vaptans: A new class of medication, the "vaptan" drugs, act by inhibiting the action of vasopressin on its receptors (V_{1A}, V_{1B} and V₂). These receptors have a variety of functions, with the V_{1A} and V₂ receptors are expressed peripherally and involved in the modulation of blood pressure and kidney function respectively, while the V_{1A} and V_{1B} receptors are expressed in the central nervous system.

The vaptan class of drugs contains a number of compounds with varying selectivity, which is either already in clinical use or in clinical trials [12-14].

Unselective (mixed V_{1A}/V_2)

- Conivaptan

V_{1A} selective (V_1RA)

- Relcovaptan
- SR 49059
- (D (CH₂)₅₁, TYR (Me)₂, Arg₈)- Vasopressin

V_{1B} selective (V_3RA)

- Nelivaptan

V_2 Selective (V_2RA)

- Lixivaptan
- Mozavaptan
- Satavaptan
- Tolvaptan

Demeclocycline: A tetracycline antibiotic, is sometimes used to block the action of vasopressin in the kidney in hyponatremia due to inappropriately high secretion of vasopressin (SIADH), when fluid restriction has failed [10].

Uses of Vaptans

Hyponatremia: V_2R antagonists have become a mainstay of treatment for euvoletic (i.e., SIADH [1], postoperative hyponatremia) and hypervolemic hyponatremia (i.e., CHF and cirrhosis) [15]. V_2RA s predictably cause aquaresis leading to increased $[Na^+]$ in majority of patients with hyponatremia due to SIADH, CHF and cirrhosis. The optimum use of VRAs has not yet been determined, but some predictions can be made with reasonable certainty. For hyponatremia in hospitalized patients, who are unable to take medication orally or for those in whom a more rapid correction of hyponatremia is desired, conivaptan (V_1/V_2R antagonist) will likely be the preferred agent. Selective V_2R antagonists such as tolvaptan, lixivaptan etc. will likely be useful in patients for whom oral therapy is suitable and for more chronic forms of hyponatremia [15].

Congestive Heart Failure: Neurohormonal activation characteristic of CHF, including increased renin, angiotensin, aldosterone and catecholamines, contributes to progression of CHF. It has been suggested that cardiovascular mortality may be reduced by selective V_2RA such as tolvaptan in the higher risk group with kidney function impairment or severe congestive findings [15]. But until FDA indication is granted for use in CHF with or without accompanying hyponatremia, VRAs are not recommended in patients with CHF [15].

Cirrhosis: V_2RA may be particularly beneficial in the treatment of patients with advanced liver cirrhosis and ascites [16]. Blockade of V_2R will induce an effective aquaresis and inhibition of V_2 -mediated vasodilation. This aquaresis, in combination with a diuresis, may provide a potential therapy for patients with resistant ascites. V_2 receptor antagonism increases plasma vasopressin concentration, which may cause unopposed hyperstimulation of the vasoconstrictor V_1 receptor. Given the potential hyperstimulation of V_1R , V_2RA may have additional secondary preventative benefits in patients with cirrhosis through a reduction in portal pressure and a decreased risk of variceal bleeding [16].

Polycystic Kidney Disease: Polycystin defects increase intracellular cAMP, secondary messenger for vasopressin acting at V_2R , leading to cyst development [15]. cAMP-dependent genes promote fluid secretion into developing renal cysts and increase cell proliferation. Studies in several animal models of polycystic kidney disease have shown a reduction in kidney size and cyst volume after treatment with specific V_2 receptor antagonist [15]. Full-scale therapeutic trials of V_2RA s in patients with autosomal dominant polycystic kidney disease are currently ongoing [15].

Nephrogenic Diabetes Insipidus: Congenital Nephrogenic diabetes insipidus (NDI) may result from V_2R or aquaporin-2 (AQP2) mutations. Exogenously administered V_2R antagonists can bind to misfolded intracellular V_2R and improve transport of V_2R to the cell membrane [15]. Clinical studies in patients with X-linked NDI showed that the selective V_1R antagonist relcovaptan significantly increased urine osmolality and decreased 24-hour urine flow [15]. Thus V_1R and/or V_2R antagonists may serve as molecular chaperones to mitigate misfolding defects in selected patients with type 2 NDI [15].

CONCLUSION

A major message of this review is that Vasopressin receptors are distributed in wide range of organs and their agonist and antagonists have numerous indications. The identification of multiple receptor subtypes for the major types of vasopressin receptors has obvious implications for drug therapy. It is to be expected that more and better selective drugs for the various subtypes will be developed in the near future. A major impediment at the current time to the development of better therapeutic agents is a paucity of knowledge as to which functions are mediated by which receptor subtypes. This is an area that clearly needs immediate attention. Current studies under way on the localization of the various subtypes in various tissues and regions of tissues may help to correlate receptor subtype with function. It appears that receptor subtype- specific antibodies may be developed in the near future and this will also be an important tool. Another important area in the next few years will be a study of subtype- specific regulation of the protein and mRNA level. Further in the future it seems reasonable to expect that it may be possible to regulate levels of receptors and G proteins in order to produce therapeutic effects, rather than regulating the degree of receptor occupancy by the agonist as is currently done.

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