Cell. Mol. Life Sci. 63 (2006) 1766–1779
1420-682X/06/151766-14
DOI 10.1007/s00018-006-6054-2

Cellular and Molecular Life Sciences

Drugs of the future: Review

Vasopressin antagonists

R. Lemmens-Gruber* and M. Kamyar

Department of Pharmacology and Toxicology, University of Vienna, Althanstr. 14, 1090 Vienna (Austria),
Fax: +43 1 4277 9553, e-mail: rosa.lemmens@univie.ac.at

Received 3 February 2006; received after revision 16 March 2006; accepted 26 April 2006
Online First 23 June 2006

Abstract. Effects of vasopressin via V1a- and V2-receptors are closely implicated in a variety of water-retaining diseases and cardiovascular diseases, including heart failure, hyponatraemia, hypertension, renal diseases, syndrome of inappropriate antidiuretic hormone secretion, cirrhosis and ocular hypertension. As vasopressin receptors are found in many different tissues, vasopressin antagonists may benefit the treatment of disorders such as cerebral ischaemia and stroke, Raynaud's disease, dysmenorrhoea and tocolytic treatment. V1b selective vasopressin antagonists are discussed in terms of their usefulness in the treatment of emotional and psychiatric disorders. The vaptans are vasopressin receptor antagonists with V1a (relcovaptan) or V2 (tolvaptan, lixivaptan) selectivity or non-selective activity (conivaptan) which may be advantageous in some disorders. The V1a/V2 non-selective vasopressin antagonist conivaptan is the first vaptan which is approved by the FDA for the treatment of euvolaemic hyponatraemia.

Keywords. Vasopressin antagonists, vaptans, conivaptan, relcovaptan, lixivaptan, tolvaptan, SSR149415, SR121463.

Introduction

The biological effects of vasopressin are mediated by the vasopressin receptor subtypes V1a (vascular), V1b (V3, pituitary) V2 (renal) [1–6], and oxytocin receptors [7]. The V1a-receptor subtype is located in vascular smooth muscle cells, cardiomyocytes, hepatocytes and platelets. It mediates vasoconstriction, vascular smooth muscle cell proliferation [8], glycogen metabolism, platelet aggregation, positive inotropy, hypertension and coronary vasospasm. Furthermore, the V1a-receptor promotes hypertrophic growth of myocardial cells [9–10]. Antagonism of V1a-receptors may result in increased cardiac output, reduced total peripheral resistance, reduced mean arterial blood pressure and inhibition of vasopressin-induced protein synthesis of cardiomyocytes.

The V1b receptor subtype is present in the anterior pituitary, Langerhans islets of the pancreas, adrenal medulla, phaeochromocytoma and the kidney inner medullary collecting duct [11]. This receptor subtype mediates the release of adrenocorticotropin [12–13], glucagon secretion and cell proliferation [14]. The vasopressin V1b receptor is located in the central nervous system, and animal experiments point to a role for vasopressin in the modulation of emotional processes via the V1b receptor.

The V2 subtype is located in the collecting tubules of the kidney, and regulates the antidiuretic action of vasopressin. Blockade of V2-receptors results in aquaresis, with increased serum sodium concentration and reduced cardiac preload. Thus, V2-receptor antagonists may be beneficial in the treatment of water-retaining diseases of various pathogeneses.

In the following chapters the mode of action of vasopressin and vasopressin antagonists is briefly reviewed in order to present the rationale for the pharmacotherapy of various diseases with vasopressin antagonists. In the section 'Binding sites', interspecies selectivity and its consequences for the interpretation of results from animal experiments are

* Corresponding author.

briefly discussed. Furthermore, the chemical structure of potent vasopressin antagonists is listed. The main part of the paper deals with the numerous indications for vasopressin antagonists, which were evaluated in animal models and clinical studies. Finally, we review completed and ongoing clinical trials with vasopressin antagonists.

Mode of action

The vasopressin receptors belong to the GTP-binding G-protein-coupled receptor family. Both the V1a and V1b receptors activate phospholipases via Gq/11 [15]. The activated phospholipase Cβ promotes hydrolysis of phosphatidylinositol(4,5)-biphosphate, thereby increasing the intracellular concentration of diacylglycerol and inositol(1,4,5)-triphosphate. The latter stimulates calcium release from the endoplasmatic reticulum. In addition, the emptying of calcium stores activates calcium influx via divalent cationic channels. This rise in intracellular calcium concentration initiates the cascade of calcium-mediated effects such as vasoconstriction.

In ventricular myocytes of the guinea pig, a vasopressin-induced increase in $[Ca^{2+}]_i$ originates from an increase in the open-state probability of the L-type calcium channel. This effect is due to an increased number of channel openings and increased open times [16]. In isolated guinea pig papillary muscles, this vasopressin-induced activation of calcium influx causes a slowly developing positive inotropic effect and an increase in resting tension. These vasopressin effects were antagonized by the V1-receptor antagonist OPC-21268, but not by the V2-receptor antagonist OPC-31260 [17, 18], indicating that the V1a-receptor is responsible for the positive inotropic action of vasopressin. In cultured rat hippocampal neurons, vasopressin-induced increase of $[Ca^{2+}]_i$ is due to an influx of calcium through V1-vasopressin receptor-coupled N-type calcium channels. The increase of $[Ca^{2+}]_i$ was inhibited by OPC-21268 [19] and other V1 antagonists.

In contrast to the V1a and V1b receptors, the V2-receptor activates adenylyl cyclase by interacting with Gs [15]. Stimulation of Chinese hamster ovary (CHO) cells expressing the human V2-receptor resulted in accumulation of cyclic AMP (cAMP) [9]. The increase in cAMP activates protein kinase A and the insertion of the preformed aquaporin channel into the apical membrane of cells in the kidney collecting duct [15], which contribute to the regulation of water homeostasis. Vasopressin-induced cAMP production of cultured renal epithelium cells was significantly blocked by the non-selective V1a/V2 antagonist conivaptan [20], but was not inhibited by the selective V1a antagonist YM218 [21].

Vasopressin also exerts a mitogenic action; several kinases are phosphorylated, DNA synthesis is increased, S- and G2-M phases of the cell cycle progress, and cell proliferation is increased. These effects are initiated by V1-receptor activation, and are mediated by calcium mobilization, coupling to a G (q) protein. Simultaneously, several kinases are activated; in particular, calcium/calmodulin-dependent kinase II, phosphatidylinositol-3-kinase, protein kinase C and p42/p44 mitogen-activated protein kinase [22, 23]. When added to growth-arrested vascular smooth muscle cells, the non-selective V1a/V2-receptor antagonists conivaptan and YM471 prevented the vasopressin-induced hyperplasia and hypertrophy of these cells [8, 24]. The selective V1a antagonist relcovaptan exerts a potent antiproliferative effect since it completely blocked vasopressin-stimulated 3T3 cell growth from G1/G0 into the S/G2-M phase, and it inhibited vasopressin-induced DNA synthesis [25].

Binding sites

The residues responsible for vasopressin binding have been identified, and a different mechanism of vasopressin binding to the V2-receptor as compared with the V1a-receptor has been proposed [26]. Isolation of the complementary DNAs (cDNAs) encoding the V1a and V1b receptor subtypes explained the tissue variability of V1 antagonist binding, whereas identification of the cDNA and gene encoding the V2-receptor provided information to identify the mutations responsible for the X-linked nephrogenic diabetes insipidus [15, 27].

Binding properties of potent vasopressin antagonists were studied using cloned human vasopressin receptors stably expressed in CHO cells, and human uterine smooth muscle cells expressing oxytocin receptors. Specific binding of H^3-labelled vasopressin was measured [9, 21]. After binding to the V1a-receptor, vasopressin receptor antagonists potently and concentration-dependently inhibit the vasopressin-induced increase in intracellular free calcium concentration, and activation of mitogen-activated protein kinase.

Site-directed mutagenesis experiments were performed in CHO cells, stably transfected with the human vasopressin receptor sybtypes. Molecular modelling of the results of these experiments revealed that non-peptide antagonists establish key contacts with a few amino acid residues of the receptor subtypes. For example, residue Phe225, which is located in transmembrane domain V, participates in the binding of the V1a-selective vasopressin antagonist relcovaptan [28]. The major component for binding of OPC-21268 to the rat V1a-receptor [29] was found to be the amino acid residue Ala-342 in domain VII. In contrast, Thibonnier et al. [30] identified Ala-337 as the important residue for OPC-21268 binding in a docking model. These amino acid residues for antagonist binding, however, are different from those involved in agonist binding [31].

The interactions of the vasopressin antagonists with the amino acid residues are species-specific. A few residues

in the amino acid sequence of the rat and human vasopressin receptor control interspecies selectivity [30]. The V1-receptor antagonist OPC-21268, for example, showed a markedly higher affinity for the rat V1a-receptor than for the human V1a-receptor. For the V2-receptor antagonist SR121463, however, similar binding affinities were found for the human V2-receptor and the V2-receptor of several animal species [32]. For the human V1b receptor, selectivity by four amino acids, located in distinct membrane helices (fourth, fifth, and seventh), were found to be responsible for antagonist binding [33].

Not only do distinct amino acid residues seem to determine drug binding, but binding pockets also play a role in specificity. Mutagenesis data point to significant differences in the shape of the V1 and V2-receptor antagonist-binding pockets. The most important factor determining the specificity of non-peptide antagonists seems to be the shape of the binding pocket on the receptor [34].

Chemical structure and selectivity of *in vivo* and *in vitro* tested vasopressin antagonists

No structure-activity relationship for receptor selectivity could be found for vasopressin antagonistic compounds. For example, benzazepines may act as selective V2 (Table 1), non-selective V1a/V2 (Tables 1, 2) or selective V1a antagonists (Table 2). Some of the oxindoles exert selective antagonistic activity to V2-receptors (Tables 1, 2). However, some of them do show selectivity for V1b receptors (Table 1). Most of the compounds were characterized by receptor binding assays, and a few have already

Table 1. Vasopressin antagonists which were tested in animal models and in human trials.

Receptor subtype	Antagonist	Structure	Lab where developed	References	Studies
Selective V1a	relcovaptan (SR49059)	pyrrolidine	Sanofi-Synthelabo	[90, 100, 104, 105, 112, 113, 115, 116]	clinical trials
				[35, 103, 106, 107, 108, 111]	animal models
	OPC-21268	quinolinone	Otsuka	[36, 102, 114]	animal models
Selective V1b (V3)	SSR149415	oxindole	Sanofi-Synthelabo	[37–39, 119]	animal model
				Sanofi	clinical trial
Selective V2	tolvaptan (OPC-41061)	benzazepine	Otsuka	[74, 75, 77, 78, 79]	clinical trials (ACTIV in CHF [77], EVEREST [78])
				[87, 88, 99]	animal models
	lixivaptan	benzodiazepine	Wyeth-Ayerst,	[85, 86, 93]	clinical trials
	(VPA-985)		CardioKine	[12, 40]	animal models
	SR121463	N-arylsulfonyl-oxindole	Sanofi-Synthelabo	[42]	clinical trials
				[42, 95]	animal models
	OPC-31260	benzazepine	Otsuka	[89]	clinical trial
				[99, 103]	animal model
Non-selective V1a/V2	conivaptan (YM087, Vaprisol)	benzazepine	Yamanouchi, Astellas	[70, 71, 84]	clinical trials (ADVANCE [71])
				[20, 43, 44, 65–69, 72, 73, 91]	animal models

Table 2. Compounds which receptor selectivity was tested by receptor-binding assays or other *in vitro* models.

V1a-selective	V1b-selective	V2-selective	Non-selective V1a/V2
Benzazepine-furanilides (YM218) [46]	oxindoles [37–39]	2,5-disubstituted benzothiazepines [50]	benzodiazepines [52, 55]
		indoloazepines [51]	benzodiazepine ring fused to a bridged bicyclic amine [53]
Benzazepine-benzanilides [48]		benzodiazepine ring fused to a bridged bicyclic amine [53]	benzoazepines [22, 45, 47, 55, 56]
N-Methylbenzanilides [49]		quinoxaline (vp-343) [54]	thienoazepines [41]
Triazoles [49]			thiazepines and thiazines [57, 58]

being tested in clinical trials (Table 1). Only one of the agents has been approved recently by the U.S. Food and Drug Administration (FDA). The structures of the vaptans are shown in Figure 1.

Indications for vasopressin receptor antagonists

Early peptide vasopressin receptor antagonists proved expensive, difficult to formulate for oral consumption and to have limited efficacy. The non-peptide vasopressin antagonists, however, are promising agents in the treatment of various diseases.

Vasopressin mediates vasoconstriction, platelet aggregation and coronary vasospasm via the V1a-receptor. Thus, blockade of this receptor subtype should contribute to the beneficial effect of V1a antagonists in the treatment of vascular diseases such as cardiac heart failure, Raynaud's disease, myocardial infarction, cerebral vasospasm and stroke as well as dysmenhorroea and preterm labour.

The vasopressin V1b receptor in the central nervous system plays a role in the modulation of emotional processes and psychiatric disorders. Experimental data suggest a therapeutic impact of selective V1b antagonists.

The V2-receptor has a prominent function in the regulation of water homeostasis. Effects of vasopressin via the V2-receptors are closely implicated in a variety of water-retaining diseases and cardiovascular diseases, including heart failure, hyponatraemia, renal diseases, syndrome of inappropriate antidiuretic hormone secretion (SIADH), cirrhosis and ocular hypertension.

The treatment of the above-mentioned diseases in which vasopressin is involved is presented and discussed below, beginning with heart failure, which can be treated with V1/V2 or V2 antagonists, and followed by disorders positively responding to V2, V1a and V1b antagonists.

Congestive heart failure

Congestive heart failure (CHF) is the state of reduced myocardial performance. Its most common causes are coronary heart disease, hypertension, valvar defects, cardiomyopathies and also extracardiac diseases. The sample of patients admitted with acute decompensated heart failure is heterogeneous. During cardiac dysfunction, activation of the sympathetic nervous system, vasopressin and the renin-angiotensin-aldosterone system (RAAS) occurs to maintain cardiac output and blood supply to vital organs. In recent large trials [59–62], angiotensin-converting enzyme inhibitors and β-adrenoceptor antagonists have been shown to improve mortality in chronic heart failure patients.

Newer approaches for the therapy of CHF, such as antagonists to a number of neurohumoral targets, are promising. The release of the neurohormones adrenaline, angiotensin II, endothelin-1, tumour necrosis factor, natriuretic peptide and vasopressin increases as patients become symptomatic. The levels of these hormones correlate with mortality [63]. However, recent clinical trials, using endopeptidase inhibitors, endothelin antagonists or cytokine antagonists, suggest that selective inhibition of neurohormonal systems may not be advantageous [64].

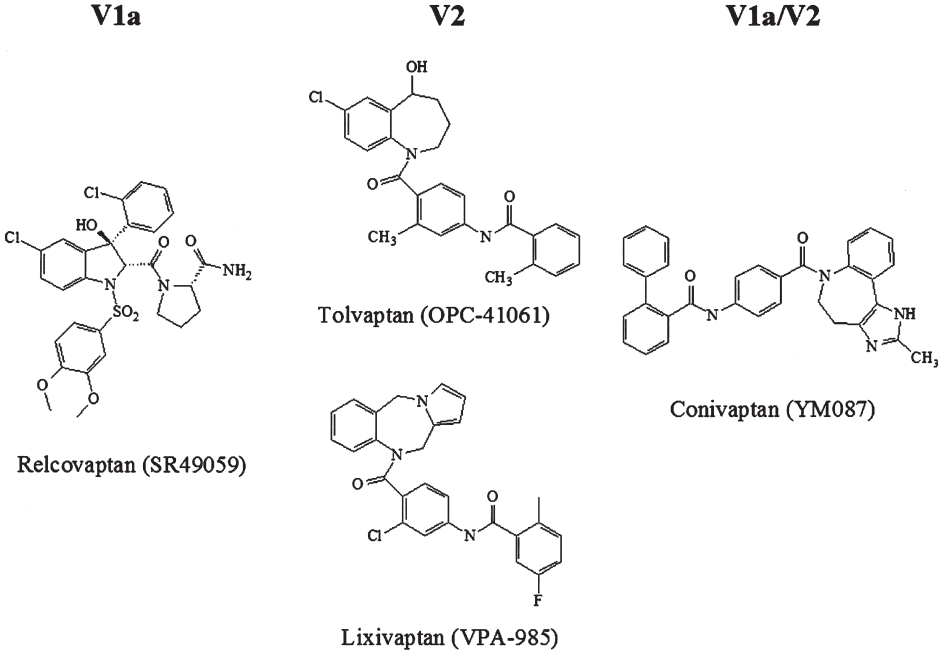

Figure 1. Chemical structure of vaptans.

Conivaptan has been characterized as a V1a/V2-receptor antagonist [65]. In an open-label, crossover study, conivaptan was administered to six healthy normotensive subjects in both oral and intravenous formulations [43]. The blockade of the V2-receptors in the renal collecting tubules results in aquaresis with minimal effects on electrolytes. In addition, V1a-receptors are also blocked by conivaptan, which results in vasodilation of vascular smooth muscle leading to increased cardiac output and lower systemic vascular resistance. A further beneficial effect of V1a blockade in patients with CHF is the prevention of vasopressin-caused coronary artery vasoconstriction. These effects were evaluated in animal models [10, 20, 44, 66–69] and humans [70].

A randomized, prospective, placebo-controlled trial was performed on 142 patients with CHF of NYHA class III (92%) and class IV (8%). The patients received conivaptan intravenously at a single dose of 10, 20 or 40 mg. In these patients with advanced heart failure, vasopressin antagonism with conivaptan resulted in favourable changes in haemodynamics and urine output without affecting blood pressure or heart rate. The urine output was dose-dependently and significantly increased at 3 h after administration, while the pulmonary capillary wedge pressure was decreased by 20 and 40 mg of conivaptan [70].

In a double-blind, multi-centre trial (ADVANCE trial) 345 patients with heart failure received placebo or one of three doses of conivaptan for 12 weeks. These results indicate progress in the therapy of vasoconstriction and volume overload in patients with CHF, although long-term safety and efficacy remain to be determined [71].

In a rat model of CHF, the effects of conivaptan in the presence or absence of the ACE inhibitor captopril was studied. Conivaptan treatment alone reduced body weight by loss of free water, and in combination with captopril, blood pressure, plasma natriuretic peptide, left and right ventricular mass, and lung mass also decreased [67, 72].

Results from animal experiments suggest that dual vasopressin V1a- and V2-receptor antagonists provide greater benefit than selective V2-receptor antagonists in the treatment of CHF [73]. Wada et al. [73] investigated the effects of intravenously administered conivaptan, a dual V1a- and V2-receptor antagonist, on cardiac function in rats with CHF following myocardial infarction, and compared the results with those for the selective V2-receptor antagonist SR121463A. Although the aquaretic and pre-load reducing effects of SR121463A were similar to those of conivaptan, the V2-receptor antagonist failed to improve the pressure in the left ventricle. These results suggest that dual vasopressin V1a- and V2-receptor antagonists provide greater benefit than selective V2-receptor antagonists in the treatment of CHF. The positive effect of dual V1/V2 antagonists is probably due to the inhibitory effect on both vasoconstriction and water retention.

Tolvaptan is an oral, specific V2-receptor antagonist which induces aquaresis in animals and humans [12, 74, 75, 76]. In a double-blind, placebo-controlled trial on 254 patients with CHF NYHA class II and III, tolvaptan was administered orally at doses of 30, 45 or 60 mg once daily for 25 days [77]. In addition to standard therapy, tolvaptan significantly increased urine output, reduced body weight, and improved clinical signs and symptoms of CHF. Normalization of serum sodium and reduction of oedema were observed in patients with hyponatraemia only in the tolvaptan-treated group, but not in the placebo group. Haemodynamic parameters and renal function were not changed. Dry mouth, thirst and polyuria were described as unwanted side effects.

The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure trial (ACTIV in CHF) was a multi-centre, randomized, double-blind, placebo-controlled, parallel-group trial with 319 patients suffering from acute exacerbation of CHF [78]. Patients were administered tolvaptan at doses of 30, 60 or 90 mg/day orally for 60 days in addition to standard therapy. Haemodynamic parameters and renal function were not altered as reported in the other trial. After 60 days, no significant differences in outpatient outcome of worsening CHF were observed between the tolvaptan and placebo groups, although event-free survival was longer for the tolvaptan group, and total mortality was lower in patients with elevated blood urea nitrogen levels and severe systemic congestion. In the EVEREST study (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) the effect of tolvaptan on mortality is currently being evaluated on mortality in hospitalized patients with heart failure [79].

The vaptans are promising agents for the symptomatic treatment of CHF. However, long-term studies are required to demonstrate their role in the outcome and quality of life of these patients.

Hyponatraemia

Hyponatraemia is estimated to affect up to 4% of hospitalized patients in the United States each year [80]. While many patients with hyponatraemia have no symptoms, severe cases are medical emergencies that can result in swelling of the brain, respiratory arrest and death. Hyponatraemia is primarily due to excessive or inappropriate vasopressin secretion that occurs in response to non-osmotic stimuli. Vasopressin secretion increases free-water absorption, thereby increasing intravascular volume and diluting the sodium concentration. These effects often occur in patients with CHF due to excessive vasopressin-induced water retention, but also during diuretic therapy. An increase in total body water with little increase in sodium is also often observed in patients with cancer, hypothyroidism, advanced kidney failure, chronic high blood

pressure, pulmonary disorders, and drug regimens such as the use of some antidepressants [81]. Hyponatraemia in CHF is associated with increased morbidity and mortality, underlining the importance for adequate correction of this electrolyte imbalance. The current treatment options for hyponatraemia are only moderately effective, and their use is limited by serious side effects [82]. The vaptans are a new class of aquaretic agents that increase water excretion while maintaining the level of sodium and other electrolytes. Especially, V2-receptor-antagonists may be advantageous in the treatment of hyponatraemia, because they induce diuresis without promoting sodium excretion and without activating the RAAS. Conivaptan, lixivaptan and tolvaptan are three such aquaretic drugs, which may redefine the treatment of heart failure-related hyponatraemia [83].

The V1a/V2-receptor antagonist conivaptan was effective in the treatment of chronic symptomatic hyponatraemia due to the syndrome of inappropriate antidiuretic hormone secretion [84].

Lixivaptan is an orally active V2-receptor antagonist which is effective in hyponatraemia in animals [12] and humans [85, 86]. The study included 33 patients with cirrhosis, 6 with CHF, and 5 with SIADH [85]. Patients received 25, 125 or 250 mg of lixivaptan or placebo twice daily for 7 days. Fluid intake was adjusted according to the urine output of the previous day. Lixivaptan increased free-water clearance, serum sodium levels, and serum osmolality significantly and in a concentration-dependent manner. At day 7 the plasma level of the antidiuretic hormone increased significantly at the two higher doses. In the group with the regimen of 250 mg of lixivaptan twice daily, significant dehydration occurred, so that dosage had to be reduced. In the second lixivaptan trial [86], the effects were evaluated in 60 patients with cirrhosis and dilutional hyponatraemia who received 100 or 200 mg/day of lixivaptan or placebo for 7 days. In this study fluid intake was restricted to 1 l/day. The serum sodium concentration was normalized concentration-dependently, but not in the placebo group.

In animal models, analogous to the hyponatraemia forms seen in humans, tolvaptan presents exciting therapeutic implications for the management of patients with severe hyponatraemia [87]. In the presence of furosemide, tolvaptan produced further diuresis without activating the RAAS, and it elevated serum sodium levels in rat [88]. Similar results were found when OPC-31260 was co-administered with furosemide [89].

Liver cirrhosis and ascites

The main pathophysiological states associated with high plasma vasopressin concentrations are cirrhosis, cardiac failure and SIADH secretion. Water retention in cirrhosis is a common problem, leading to ascites, peripheral oedema and hyponatraemia. Selective V2-receptor antagonists are effective in inducing aquaresis in humans and rats with cirrhosis, hyponatraemia and water retention [90]. Blockade of V1a-receptors could aggravate cardiocirculatory function in decompensated cirrhosis. The dual V1a/V2-receptor antagonist conivaptan was given to rats with CCL_4-induced cirrhosis, ascites and severe water retention. The data suggest that V1a/V2 antagonists may be therapeutically useful for the treatment of water retention in human cirrhosis [91].

In the lixivaptan trial [86] in which the effects were evaluated in 60 patients with cirrhosis and dilutional hyponatraemia, serum sodium concentration was normalized, and body weight and urine osmolality were reduced. An increase in serum creatinine, a sign of renal impairment, was observed only in 2 patients in each group. No other serious adverse effects were detected. These results were confirmed by several other research groups [85, 92, 93].

Ocular hypertension

V1a-receptors are present in the iris, and V1a-receptor antagonists can decrease the intraocular pressure without miosis [94]. In the rabbit model of ocular hypertension, either a single or repeated instillation of the selective V2-receptor antagonist SR121463 caused a decrease in intraocular pressure [42, 95].

Nephrogenic diabetes insipidus

In most cases, nephrogenic diabetes insipidus results from mutations in the V2 vasopressin receptor gene, which causes intracellular retention of improperly folded receptors. Relcovaptan and conivaptan act as pharmacological chaperones that rescue folding, trafficking and the function of several V2-receptor mutants [96, 97].

Polycystic kidney diseases

Polycystic kidney diseases (PKDs) are a group of genetic disorders. Approximately 12.5 million patients with PKD are estimated worldwide. In persons suffering from PKD, fluid-filled cysts progressively grow on their kidneys, often leading to renal failure and death. Cyst formation originates from proliferating renal tubular epithelial cells and epithelial-to-myofibroblast transition, which contributes to the progressive loss of renal function [98]. Dialysis and transplantation are the only options, as no other treatments are effective. Since cAMP plays a major role in cystogenesis in that it stimulates B-Raf/ERK activation and proliferation of cyst-derived cells in a Ca^{2+}-inhibited, Ras-dependent manner, vasopressin antagonists theoretically could interfere with this mechanism. The V2-receptor antagonists OPC-31260 and tolvaptan were shown to lower renal cAMP, and to inhibit renal disease develop-

ment and progression in animal models orthologous to human cystic diseases. The V2-receptor antagonists inhibit Ras/mitogen-activated protein kinase signalling in polycystic kidneys [99].

Hypertension

A recent study investigated the effects of the V1a-selective vasopressin antagonist relcovaptan on uterine contraction in non-pregnant women. This study showed a marked reduction of diastolic blood pressure, which indicates an inhibition of vascular vasopressin receptors by relcovaptan [100]. However, in a double-blind cross-over-versus-placebo study with 24 essential hypertensive patients at stage I or II, who received a single oral dose of 300 mg of relcovaptan 2 h before stimulation of vasopressin secretion, relcovaptan only caused a transient vasodilation. This effect was not associated with a sustained blood pressure reduction, but with a significant reduction of vasopressin-induced aggregation of blood platelets [101]. Furthermore, in animal models OPC-21268 [102], and in healthy volunteers, relcovaptan failed to demonstrate clinical efficacy in lowering blood pressure [90].

Myocardial infarction

After myocardial infarction, the load on the uninvolved myocardium increases, and forward heart failure develops due to diminished contractility. Heart failure induces a number of compensatory mechanisms that are primarily directed at restoring cardiac output and blood pressure. Most important in this is an increased sympathetic tone together with greater release of noradrenaline and adrenaline. As a result, renal perfusion is reduced, leading to activation of the RAAS, and to increased release of vasopressin. Angiotensin II and vasopressin have a vasoconstrictor effect. In coronary and mesenteric vessels of rats the vasoconstrictor responses to vasopressin are mediated by the V1a-receptor, as the effects were more susceptible to the V1a-selective antagonist relcovaptan than to the V2-selective antagonist OP-31260 [103]. Relcovaptan was shown to have potent cardioprotective effects in a conscious rabbit model. The increase of the T-wave amplitude, which was a significant index of coronary vasoconstriction-induced cardiac ischaemia, was prevented by relcovaptan, as well as bradycardia [35].

Raynaud's disease

Relcovaptan was found to be a potent and specific V1-receptor antagonist which blocks vasopressin-induced vasoconstriction [104]. In a single-centre, double-blind, placebo-controlled, randomized crossover study, favourable effects on finger systolic pressure and temperature recovery after cold immersion were found in patients suffering from Raynaud's phenomenon [105].

Cerebral vasospasm

It has been suggested that vasopressin and inflammation are involved in the development of cerebral vasospasm after subarachnoid haemorrhage (SAH). Relcovaptan significantly reduced cerebral vasospasm after SAH induction in rats. Inhibition of 5-lipoxygenase attenuated the vasopressin-induced contraction of basilar arterial strips in both control and SAH groups. The results suggest that cerebral vasospasm in SAH rats is at least partly due to endogenous vasopressin, and may involve an increase in 5-lipoxygenase activity. Relcovaptan may represent a potential therapeutic strategy for the treatment of cerebral vasospasm [106]. Although relcovaptan is not able to enter brain tissue from the peripheral circulation, it does bind specifically to regions devoid of blood-brain barrier and known to be involved in autonomic regulations [107].

Stroke

Cerebral oedema develops very early after the onset of focal cerebral ischaemia and may be a major factor in early disability after an acute ischaemic stroke. Relcovaptan was shown to be a potent neuroprotective agent when used early after the onset of arterial occlusion in an embolic focal ischaemia model in rats [108]. Vasopressin antagonists might also be advantageous in neuroprotection. Since vasopressin contributes to impaired ATP-sensitive and calcium-sensitive potassium channel function after brain injury, vasopressin may blunt ATP-sensitive and calcium-sensitive potassium channel-mediated cerebrovasodilation [109].

Dysmenorrhoea and tocolytic treatment

Both oxytocin and vasopressin cause potent and long-lasting vasoconstriction of uterine arteries of several species, including humans. The resulting ischaemia is thought to be involved in the pathogenesis of primary dysmenorrhoea. In women with primary dysmenorrhoea, the plasma concentration of vasopressin is elevated. The *in vivo* effect of vasopressin on uterine activity in non-pregnant women is about five times more pronounced than that of oxytocin, and it increases premenstrually. Correspondingly, the density of vasopressin V1a and oxytocin receptors was found to vary to the same degree, and a premenstrual rise of V1a-receptors was observed [110].

Relcovaptan could antagonize vasopressin- and oxytocin-induced vasoconstriction in rat uterus, and it was shown that V1a-receptors are responsible for vasoconstriction

[111]. A therapeutic effect of relcovaptan in the prevention of dysmenorrhoea was shown [112, 113]. In 16 non-pregnant women pre-treatment by relcovaptan caused a dose-related reduction of intrauterine pressure for vasopressin, but not for oxytocin. The much higher potency of vasopressin compared with oxytocin on uterine activity in non-pregnant women at menstruation was confirmed [100].

The V1-vasopressin receptor antagonist OPC-21268 inhibits oxytocin- and vasopressin-induced contractions of myometrial strips from rats and from full-term pregnant women [114]. Conivaptan not only binds to V1a and V2 vasopressin receptors, but also binds to OT receptors in the rat uterus, although with weaker affinity [24].

At the onset of labour preterm and at term, there is a tendency for an increase in the density of oxytocin and vasopressin V1a-receptors. The importance of oxytocin and vasopressin in mechanisms of preterm labour is confirmed by the therapeutic effect of the oxytocin and vasopressin V1a-receptor blocking oxytocin analogue, atosiban [110]. When relcovaptan was administered at a single dose of 400 mg to women with preterm labour [115], the frequency of uterine contractions significantly decreased in the relcovaptan group, but not in the placebo group. However, it has to be kept in mind that moderate amounts of relcovaptan are transferred from the maternal to foetal circulation [116].

ACTH-secreting tumours

V1b (V3)-receptor agonists and antagonists could be valuable additions to the diagnosis, imaging, localization, and medical treatment of adrenocorticotropic hormone-secreting tumours [33].

Emotional diseases/psychiatric indications

Vasopressin modulates many social and non-social behaviours, including emotionality. V1a, V1b and V2-receptors are located in the central nervous system, and thus are molecular targets for the treatment of particular psychiatric disorders [117]. Using site-specific injections of a V1a vasopressin receptor-specific antagonist, it could be demonstrated that the lateral septum of mice, but not the medial amygdale, is critical for social recognition [118].

The vasopressin V1b receptor antagonist SSR149415 was tested in a variety of classical and atypical rodent models of anxiety, and in two models of depression. SSR149415 improved the degradation of the physical state, anxiety, despair and the loss of coping behaviour produced by stress. These findings point to a role for vasopressin in the modulation of emotional processes via the V1b receptor, and suggest that its blockade may represent a novel possibility for the treatment of affective disorders [37, 38]. The antidepressant-like potential of SSR149415 and the anxiolytic effect were confirmed in the Flinders Sensitive Line rat, which is a selectively bred animal model of depression [39]. The blockade of aggressive behaviour in hamsters with SSR149415 was also reported [119].

Drugs under clinical investigation

In the following section, clinically tested V1a, V1b, V2 and V1/V2 vasopressin antagonists are presented in more detail, giving an overview about the state of experimental and clinical testing.

V1a-receptor antagonists

Relcovaptan

A therapeutic effect of relcovaptan in the prevention of dysmenorrhoea was shown in a placebo-controlled, double-blind, crossover trial with non-pregnant women [112], and in a double-blind, randomized, placebo-controlled, crossover trial in complete block design [113]. In a placebo-controlled, double-blind, parallel-group, four-dose comparison, the inhibitory effect of relcovaptan on oxytocin- and vasopressin-induced uterine contractions in 16 non-pregnant women was investigated [100].

In a double-blind study, relcovaptan was administered at a single dose of 400 mg to 12 women with preterm labour in pregnancy weeks 32–36, and six women received placebo [115]. The frequency of uterine contractions significantly decreased in the relcovaptan group, whereas in the placebo group, a decrease was only observed in women receiving rescue tocolytic treatment, i.e. beta-adrenoceptor stimulating drug.

A single-centre, double-blind, placebo-controlled, randomized crossover study investigated the effect of 300 mg of relcovaptan once daily in two 7-day periods, separated by 21 days of washout. Beneficial effects on finger systolic pressure and temperature recovery after cold immersion were found in patients suffering from Raynaud's phenomenon [105].

V1b receptor antagonists

SSR149415

In animal studies, the selective V1b-receptor antagonist SSR149415 showed beneficial effects in psychiatric disorders [37–39, 119]. Thus a phase I trial has been started to investigate the efficacy of SSR149415 in the treatment of depression and anxiety (Sanofi-Synthelabo).

V2-receptor antagonists

SR121463

The V2-receptor antagonist SR121463 has been studied in a phase IIb trial on patients (n = 27/group) with hyponatraemia at doses of 5, 12.5 and 25 mg once daily. In another phase IIb trial, SR121463 was tested on patients with cirrhotic ascites (n = 36) at doses of 30 and 75 mg once daily, in comparison to spironolactone. In both studies, SR121463 induced significant diuresis and an increase in plasma sodium.

In a double-blind comparison and a long-term, open-label study in patients with SIADH (in total 34) at doses of 25 and 50 mg, the drug showed good efficacy in the correction of the sodium serum concentration. SR121463 was well tolerated, and as the most common adverse side effect, thirst was reported. As positive effects were observed, SR121463 entered a phase III trial for the investigation of its efficacy in hyponatraemia. In the placebo-controlled study on 75 patients with SIADH of any cause, long-term effects have been monitored (Sanofi-Synthelabo).

Tolvaptan

The selective V2 vasopressin antagonist tolvaptan was investigated in the ACTIV in CHF [78] and the EVEREST trial [79]. The EVEREST study was a multi-centre, randomized, double-blind, placebo-controlled study on approximately 3600 patients with the goal to evaluate the long-term efficacy and safety of oral tolvaptan tablets in subjects hospitalized with worsening CHF. The ACTIV in CHF study was a multi-centre, randomized, double-blind, placebo-controlled, parallel-group trial with 319 outpatients suffering from acute exacerbation of CHF [78]. Patients were administered tolvaptan at doses of 30, 60 or 90 mg/day orally for 60 days in addition to standard therapy. However, haemodynamic parameters and renal function were not altered. No significant differences were observed between the tolvaptan and placebo groups. However, event-free survival was longer, and total mortality was lower for the tolvaptan group.

Another multi-centre, randomized, double-blind, placebo-controlled study (SALT 1) is now investigating the effect of tolvaptan on hyponatraemia in euvolaemic or hypervolaemic patients with CHF, SIADH or cirrhosis.

The ECLIPSE study is a multi-centre, randomized, double-blind, placebo-controlled trial which evaluates the effects of a single oral tolvaptan tablet on haemodynamic parameters in subjects with CHF.

As tolvaptan was effective in polycystic kidney disease development in the PCK rat model [99], phase II human trials followed, and they are almost complete. Thus, enrolment for phase III trials has begun in order to investigate whether tolvaptan is also able to inhibit cyst growth in humans (Otsuka).

Lixivaptan

As the selective V2 antagonist showed efficacy in hyponatraemia and cirrhotic ascites [85, 86, 92, 93], the company CardioKine is planning phase III clinical trials to achieve FDA approval. Lixivaptan is effective in hyponatraemia in animals [12] and humans [85, 86]. The study included 33 patients with cirrhosis, 6 with CHF, and 5 with SIADH [85]. Patients received 25, 125 or 250 mg of lixivaptan or placebo twice daily for 7 days. Lixivaptan increased free-water clearance, serum sodium levels and serum osmolality.

In another trial [86], the effects of lixivaptan were evaluated in 60 patients with cirrhosis and dilutional hyponatraemia who received 100 or 200 mg of lixivaptan once daily or placebo for 7 days. The serum sodium concentration was normalized in 27 and 50% of patients, respectively, but in none of the placebo group.

Non-selective V1/V2-receptor antagonists

Conivaptan

Vaprisol (investigational name: YM087, generic name: conivaptan hydrochloride injection) is a nonpeptide, dual V1a/V2-receptor antagonist. The FDA recently approved Vaprisol for the management of potentially life-threatening sodium/water imbalance. It is the first drug specifically indicated for the treatment of euvolaemic hyponatraemia in hospitalized patients. Thus, this compound will be described in more detail, based on the label information by the FDA. Vaprisol was discovered by Yamanouchi Pharmaceutical Co., Ltd., Japan, and was further developed by Astellas Pharma US, Inc., USA.

The affinity of conivaptan for the human V1a- and V2-receptors *in vitro* is in the nanomolar range. The predominant effect of conivaptan in the treatment of hyponatraemia is through V2 antagonism of vasopressin in the renal collecting ducts, resulting in free-water excretion, which is generally accompanied by increased net fluid loss, increased urine output and decreased urine osmolality [43, 70].

The pharmacokinetics of conivaptan has been investigated in healthy subjects [43], special populations and patients following both oral and intravenous dosing regimens. The inter-subject variability of conivaptan pharmacokinetics is high. 99% of conivaptan is bound to human plasma proteins over a wide plasma concentration range. The cytochrome P450 isoenzyme responsible for conivaptan metabolism was found to be CYP3A4. Four metabolites have been identified. They showed some pharmacological activity, but only contribute minimally to the clinical effect. The major part of administered conivaptan is excreted with the faeces.

Elimination of conivaptan in patients with hepatic or renal impairment has not been systematically evaluated,

but after oral administration, the systemic conivaptan concentration rose significantly in patients with cirrhosis and moderate hepatic impairment or renal dysfunction. This suggests caution when administered to patients with hepatic and/or renal diseases.

In clinical trials with oral conivaptan hydrochloride, two cases of rhabdomyolysis occurred in patients who were also receiving a CYP3A4-metabolized 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor. The co-administration of oral conivaptan (40 mg twice daily) combined with 0.5 mg of digoxin, which is a P-glycoprotein substrate, resulted in a marked reduction in the clearance of digoxin, and a significant increase of C_{max} and AUC (area under the curve) values.

In a double-blind, placebo-controlled, randomized, multicentre study, 56 patients with euvolaemic hyponatraemia of different aetiology were treated with conivaptan or placebo for 4 days. Vaprisol was administered intravenously at a loading dose of 20 mg intravenously over 30 min, followed by a continuous infusion of 40 or 80 mg/day. After 4 days, the normal serum sodium concentration of ≥135 mEq/l was achieved in 67% of patients with 40 mg/day conivaptan hydrochloride, hand in hand with a significant aquaretic effect.

In an open-label study with 104 patients suffering from euvolaemic hyponatraemia, an intravenous loading dose of 20 mg over 30 min was followed by a continuous infusion of 20 or 40 mg/day conivaptan hydrochloride. The results are in accordance with the outcome of the previously described study.

Vaprisol is indicated for the treatment of euvolaemic hyponatraemia in hospitalized patients, but it is contraindicated in patients with hypovolaemic hyponatraemia. To date conivaptan is not indicated for the treatment of CHF, but a randomized, double-blind, placebo-controlled, dose-ranging phase II trial for CHF has been completed (Astellas Pharma US, Inc.). The role of conivaptan in the treatment of acute and chronic heart failure was reviewed recently [120, 121].

In animal experiments it was shown that conivaptan can cross the placenta, and due to slow clearance, foetal accumulation is possible. Conivaptan shows adverse effects on the foetus at doses that are below the therapeutic dose. No well-controlled studies in pregnant women are available. Thus, Vaprisol is classified to category C, i.e. it should only be used in pregnant women if the potential benefit justifies the potential risk to the foetus.

Conivaptan delayed delivery in rats at doses which are equivalent to therapeutic doses. This effect is probably due to conivaptan's activity on the oxytocin receptor in rats [20]. The relevance to humans is unclear, and no studies on labour and delivery in humans are available. Conivaptan is excreted in milk of lactating rats, but no data are available which show excretion of conivaptan in human milk. Nonetheless, caution is necessary if conivaptan is administered to lactating women.

The most common adverse reaction was infusion site reaction (20.2%), infusion site phlebitis (15.8%) and infusion site pain (7.7%). However, in most cases, these infusion site reactions were mild. Further adverse effects were headache (12%), hypokalaemia (9.8%), thirst (9.8%), vomiting (6.6%), pollakiuria (6.0%), peripheral oedema (5.5%), diarrhoea (5.5%) and orthostatic hypotension (5%). At high doses, adverse effects occurred more frequently, in particular hypotension and thirst.

Conclusion

Advantageous effects of vasopressin antagonists have been identified in animal models as well as in human studies. This new class of therapeutics has promising features for the treatment of numerous disorders. However, the long-term clinical efficacy and benefit still has to be evaluated for these agents. Due to the wide distribution of vasopressin receptors in human tissue [90], a variety of adverse side effects cannot be excluded and may limit their clinical use. Nonetheless, this is an exciting field of research which may open new therapeutic possibilities for the treatment of diseases such as hyponatraemia, which cannot be managed satisfactorily by conventional drugs or which cannot be treated pharmacologically at present, such as PKD.

1 Birnbaumer, M., Seibold, A., GilBert, S., Ishido, M., Barberis, C., Antaramian, A., Brabet, P. and Rosenthal, W. (1992) Molecular cloning of the receptor for human antidiuretic hormone. Nature 357, 333–335.

2 Lolait, S. J., O'Carroll, A. M., McBride, O. W., Konig, M., Morel, A. and Brownstein, M. J. (1992) Cloning and characterization of a vasopressin V2-receptor and possible link to nephrogenic diabetes insipidus. Nature 357, 336–339.

3 Morel, A., O'Carroll, A. M., Brownstein, M. J. and Lolait, S. J. (1992) Molecular cloning and expression of a rat V1a arginine vasopressin receptor. Nature 356, 523–526.

4 De Keyzer, Y., Auzan, C., Lenne, F., Beldjord, C., Thibonnier, M., Bertagna, X. and Clauser, E. (1994) Cloning and characterization of the human V3 pituitary vasopressin receptor. FEBS Lett. 356, 215–220.

5 Sugimoto, T., Saito, M., Mochizuki, S., Watanabe, Y., Hashimoto, S. and Kawashima, H. (1994) Molecular cloning and functional expression of a cDNA encoding the human V1b vasopressin receptor. J. Biol. Chem. 269, 27088–27092.

6 Thibonnier, M., Auzan, C., Madhun, Z., Wilkins, P., Berti-Mattera, L. and Clauser, E. (1994) Molecular cloning, sequencing, and functional expression of a cDNA encoding the human V1a vasopressin receptor. J. Biol. Chem. 269, 3304–3310.

7 Thibonnier M., Conarty D. M., Preston J. A., Wilkins, P. L., Berti-Mattera, L. N. and Mattera, R. (1998) Molecular pharmacology of human vasopressin receptors. Adv. Exp. Med. Biol. 449, 251–276.

8 Tahara, A., Tomura, Y., Wada, K., Kusayama, T., Tsukada, J., Ishii, N., Yatsu, T., Uchida, W. and Tanaka, A. (1997) Effect of YM087, a potent nonpeptide vasopressin antagonist, on vasopressin-induced hyperplasia and hypertrophy of cultured

vascular smooth-muscle cells. J. Cardiovasc. Pharmacol. 30, 759–766.
9 Tahara, A., Saito, M., Sugimoto, T., Tomura, Y., Wada, K., Kusayama, T., Tsukada, J., Ishii, N., Yatsu, T., Uchida, W. and Tanaka, A. (1998) Pharmacological characterization of the human vasopressin receptor subtypes stably expressed in Chinese hamster ovary cells. Br. J. Pharmacol. 125, 1463–1470.
10 Tahara, A., Tomura, Y., Wada, K., Kusayama, T., Tsukada, J., Ishii, N., Yatsu, T., Uchida, W. and Tanaka, A. (1998) Effect of YM087, a potent nonpeptide vasopressin antagonist, on vasopressin-induced protein synthesis in neonatal rat cardiomyocyte. Cardiovasc. Res. 38, 198–205.
11 Saito, M., Tahara, A., Sugimoto, T., Abe, K. and Furuichi, K. (2000) Evidence that atypical vasopressin V(2) receptor in inner medulla of kidney is V(1B) receptor. Eur. J. Pharmacol. 401, 289–296.
12 Thibonnier, M. (2003) Vasopressin receptor antagonists in heart failure. Curr. Opin. Pharmacol. 3, 683–687.
13 Lee, C. R., Watkins, M. L., Gattis, W., O'Connor, C. M., Gheorghiade, M. and Adams, K. F. Jr. (2003) Vasopressin: a new target for the treatment of heart failure. Am. Heart J. 146, 9–18.
14 Folny, V., Raufaste, D., Likovic, L., Pouzet, B., Rochard, B., Pascal, M. and Serradeil-Le Gal, C. (2003) Pancreatic vasopressin V1b receptors: characterization in In-R1-G9 cells and localization in human pancreas. Am. J. Physiol. Endocrinol. Metab. 285, E566-E576.
15 Birnbaumer, M. (2000) Vasopressin receptors. Trends Endocrinol. Metab. 11, 406–410.
16 Zhang, S., Hirano, Y. and Hiraoka, M. (1995) Arginine vasopressin-induced potentiation of unitary L-type Ca^{2+} channel current in guinea pig ventricular myocytes. Circ. Res. 76, 592–599.
17 Yamaguchi, H., Uemura, H., Saito, T., Masuda, Y. and Nakaya, H. (1995) Vasopressin V_1-receptor stimulation produces a positive inotropic response without affecting pH_i in guinea pig papillary muscles. Jpn. J. Pharmacol. 68, 217–221.
18 Fujisawa, S. and Iijima, T. (1999) On the inotropic actions of arginine vasopressin in ventricular muscle of the guinea pig heart. Jpn. J. Pharmacol. 81, 309–312.
19 Mihara, T., Tarumi, T., Sugimoto, Y., Chen, Z. and Kamei, C. (1999) [Arg8]-vasopressin-induced increase in intracellular Ca^{2+} concentration in cultured rat hippocampal neurons. Brain Res. Bull. 49, 343–347.
20 Tahara, A., Tomura, Y., Wada, K., Kusayama, T., Tsukada, J., Takanashi, M., Yatsu, T., Uchida, W. and Tanaka, A. (1997) Pharmacological profile of YM087, a novel potent vasopressin V1a- and V2-receptor antagonist, *in vitro* and *in vivo*. J. Pharmacol. Exp. Ther. 282, 301–308.
21 Tahara, A., Tsukada, J., Tomura, Y., Kusayama, T., Wada, K., Ishii, N., Taniguchi, N., Suzuki, T., Yatsu, T., Uchida, W. and Shibasaki, M. (2005) Effects of YM218, a non peptide vasopressin V1a-receptor-selective antagonist, on human vasopressin and oxytocin receptors. Pharmacol. Res. 51, 275–281.
22 Thibonnier, M., Conarty, D. M. and Plesnicher, C. L. (2000) Mediators of the mitogenic action of human V(1) vascular vasopressin receptor. Am. J. Physiol. Heart Circ. Physiol. 279, H2529-H2539.
23 Berrada, K., Plesnicher, C. L., Luo, X. and Thibonnier, M. (2000) Dynamic interaction of human vasopressin/oxytocin receptor subtypes with G-protein-coupled receptor kinases and protein kinase C after agonist stimulation. J. Biol. Chem. 275, 27229–272237.
24 Tahara, A., Tsukada, J., Tomura, Y., Kusayama, T., Wada, K., Ishii, N., Yatsu, T., Uchida, W., Taniguchi, N. and Tanaka, A. (2002) Effect of YM471, an orally active non-peptide arginine vasopressin receptor antagonist, on human vascular smooth muscle cells. J. Hypertens. 20, 1807–1814.
25 Serradeil-Le Gal, C., Bourrie, B., Raufaste, D., Carayon, P., Garcia, C., Maffrand, J. P., Le Fur, G. and Casellas, P. (1994) Effect of a new, potent, non-peptide V1a vasopressin antagonist, SR 49059, on the binding and the mitogenic activity of vasopressin on Swiss 3T3 cells. Biochem. Pharmacol. 47, 633–641.
26 Ślusarz, M. J., Gieldon, A., Ślusarz, R. and Ciarkowski, J. (2006) Analysis of interactions for vasopressin binding to human neurohypophyseal hormone receptors-molecular dynamics study of the activated receptor-vasopressin-G (alpha) systems. J. Pept. Sci. 12, 180–189.
27 Rosenthal, W., Seibold, A., Antaramian, A., Lonergan, M., Arthus, M. F., Hendy, G. N., Birnbaumer, M. and Bichet, D. G. (1992) Molecular identification of the gene responsible for congenital nephrogenic diabetes insipidus. Nature 359, 233–235.
28 Tahtaoui, C., Balestre, M. N., Klotz, P., Rognan, D., Barberis, C., Mouillac, B. and Hibert, M. (2003) Identification of the binding sites of the SR49059 nonpeptide antagonist into the V1a vasopressin receptor using sulfhydryl-reactive ligands and cysteine mutants as chemical sensors. J. Biol. Chem. 278, 40010–40019.
29 Shinoura, H., Take, H., Itoh, S., Hirasawa, A., Inoue, K., Ohno, Y., Hashimoto, K. and Tsujimoto, G. (2000) Key amino acids of vasopressin V1a-receptor responsible for the species difference in the affinity of OPC-21268. FEBS Lett. 466, 255–258.
30 Thibonnier, M., Coles, P., Conarty, D. M., Plesnicher, C. L. and Shoham, M. (2000) A molecular model of agonist and nonpeptide antagonist binding to the human V(1) vascular vasopressin receptor. J. Pharmacol. Exp. Ther. 294, 195–203.
31 Thibonnier, M., Coles, P., Thibonnier, A. and Shoham, M. (2002) Molecular pharmacology and modelling of vasopressin receptors. Prog. Brain Res. 139, 179–196.
32 Serradeil-Le Gal, C., Raufaste, D., Double-Cazanave, E., Guillon, G., Garcia, C., Pascal, M. and Maffrand, J. P. (2000) Binding properties of a selective tritiated vasopressin V2-receptor antagonist, [H]-SR 121463. Kidney Int. 58, 1613–1622.
33 Derick, S., Pena, A., Durroux, T., Wagnon, J., Serradeil-Le Gal, C., Hibert, M., Rognan D and Guillon, G. (2004) Key amino acids located within the transmembrane domains 5 and 7 account for the pharmacological specificity of the human V1b vasopressin receptor. Mol. Endocrinol. 18, 2777–2789.
34 Macion-Dazard, R., Callahan, N., Xu, Z., Wu, N., Thibonnier, M. and Shoham, M. (2006) Mapping the binding site of six nonpeptide antagonists to the human V2-renal vasopressin receptor. J. Pharmacol. Exp. Ther. 316, 564–571.
35 Serradeil-Le Gal, C., Villanova, G., Boutin, M., Maffrand, J. P. and Le Fur, G. (1995) Effects of SR 49059, a non-peptide antagonist of vasopressin V1a-receptors, on vasopressin-induced coronary vasoconstriction in conscious rabbits. Fundam. Clin. Pharmacol. 9, 17–24.
36 Yamamura, Y., Ogawa, H., Chihara, T., Kondo, K., Onogawa, T., Nakamura, S., Mori, T., Tominaga, M. and Yabuuchi, Y. (1991) OPC-21268, an orally effective, nonpeptide vasopressin V1-receptor antagonist. Science 252, 572–574.
37 Griebel, G., Simiand, J., Serradeil-Le Gal, C., Wagnon, J., Pascal, M., Scatton, B., Maffrand, J. P. and Soubrié, P. (2002) Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. Proc. Natl. Acad. Sci. USA 99, 6370–6375.
38 Serradeil-Le Gal, C., Derick, S., Brossard, G., Manning, M., Simiand, J., Gaillard, R., Griebel, G. and Guillon, G. (2003) Functional and pharmacological characterization of the first specific agonist and antagonist for the V1b receptor in mammals. Stress 6, 199–206.
39 Overstreet, D. H. and Griebel, G. (2005) Antidepressant-like effects of the vasopressin V1b receptor antagonist SSR149415

in the Flinders Sensitive Line rat. Pharmacol. Biochem. Behav. 82, 223–227.
40 Albright, J. D., Reich, M. F., Delos Santos, E. G., Dusza, J. P., Sum, F. W., Venkatesan, A. M., Coupet, J., Chan, P. S., Ru, X., Mazandarani, H. and Bailey, T. (1998) 5-Fluoro-2-methyl-N-[4-(5H-pyrrolo[2,1-c]-[1,4]benzodiazepine-10(11H)-yl-carbonyl)-3-chlorophenyl]benzamide (VPA-985): an orally active arginine vasopressin antagonist with selectivity for V2-receptors. J. Med. Chem. 41, 2442–2444.
41 Albright, J. D., Delos Santos, E. G., Dusza, J. P., Chan, P. S., Coupet, J., Ru, X. and Mazandarani, H. (2000) The synthesis and vasopressin (AVP) antagonist activity of a novel series of N-Aroyl-2,4,5,6-tetrahydropyrazolo-[3,4-*d*]thieno[3.2-*b*]azepines. Bioorg. Med. Chem. Lett. 10, 695–698.
42 Serradeil-Le Gal, C. (2001) An overview of SR121463, a selective non-peptide vasopressin (2) receptor antagonist. Cardiovasc. Drug Rev. 19, 201–214.
43 Burnier, M., Fricker, A. F., Hayoz, D., Nussberger, J. and Brunner, H. R. (1999) Pharmakokinetic and pharmacodynamic effects of YM087, a combined V1/V2 vasopressin receptor antagonist in normal subjects. Eur. J. Clin. Pharmacol. 55, 633–637.
44 Yatsu, T., Tomura, Y., Tahara, A., Wada, K., Kusayama, T., Tsukada, J., Tokioka, T., Uchida, W., Inagaki, O., Iizumi, Y., Tanaka, A. and Honda, K. (1999) Cardiovascular and renal effects of conivaptan hydrochloride (YM087), a vasopressin V1a- and V2-receptor antagonist, in dogs with pacing-induced congestive heart failure. Eur. J. Pharmacol. 376, 239–246.
45 Matsuhisha, A., Tanaguchi, N., Koshio, H., Yatsu, T. and Tanaka, A. (2000) Nonpeptide arginine vasopressin antagonists for both V1A and V2-receptors: synthesis and pharmacological properties of 4-(1,4,5,6-tetrahydroimidazo[4,5-d] [1]benzoazepine-6-carbonyl)benzanilide derivatives and 4′-(5,6-dihydro-4H-thiazolo[5,4-d][1]benzoazepine-6-carbonyl)benzanilide derivatives. Chem. Pharm. Bull. 48, 21–31.
46 Tsukada, J., Tahara, A., Tomura, Y., Kusayama, T., Wada, K., Ishii, N., Taniguchi, N., Suzuki, T., Yatsu, T., Uchida, W. and Shibasaki, M. (2005) Pharmacological properties of YM218, a novel, potent, nonpeptide vasopressin V1a-receptor-selective antagonist. Vasc. Pharmacol. 42, 47–55.
47 Matsuhisa, A., Tanaka, A., Kikuchi, K., Shimada, Y., Yatsu, T. and Yanagisawa, I. (1997) Nonpeptide arginine vasopressin antagonists for both V1A and V2-receptors: synthesis and pharmacological properties of 2-phenyl-4′-[2,3,4,5-tetrahydro-1H-1-benzazepin-1-yl)carbonyl]benzanilide derivatives. Chem. Pharm. Bull. 45, 1870–1874.
48 Shimada, A., Akane, H., Taniguchi, N., Matsuhisa, A., Kawano, N., Kikuchi, K., Yatsu, T., Tahara, A., Tomura, Y., Kusayama, T., Wada, K., Tsukada, J., Tsunoda, T. and Tanaka, A. (2005) Preparation of highly potent and selective non-peptide antagonists of the arginine vasopressin V1a-receptor by introduction of a 2-Ethyl- 1*H*-1-imidazolyl group. Chem. Pharm. Bull. 53, 764–769.
49 Kakefuda, A., Suzuki, T., Tobe, T., Tsukada, J., Tahara, A., Sakamoto, S. and Tsukamoto, S. (2002) Synthesis and pharmacological evaluation of 5-(4-biphenyl)-3-methyl-4-phenyl-1,2,4-triazole derivatives as a novel class of selective antagonists for the human vasopressin V(1A) receptor. J. Med. Chem. 45, 2589–2598.
50 Urbanski, M. J., Chen, R. H., Demarest, K. T., Gunnet, J., Look, R., Ericson, E., Murray, W. V., Rybczynski, P. J. and Zhang, X. (2003) 2,5-disubstituted 3,4-dihydro-2*H*-benzo[b][1,4]thiazepines as potent and selective V2 arginine vasopressin receptor antagonists. Bioorg. Med. Chem. Lett. 13, 4031–4034.
51 Matthews, J. M., Greco, M. N., Hecker, L. R., Hoekstra, W. J., Andrade-Gordon, P., de Garavilla, L., Demarest, K. T., Ericson, E., Gunnet, J. W., Hageman, W., Look, R., Moore, J. B. and Maryanoff, B. E. (2003) Synthesis and biological evaluation of novel indoloazepine derivatives as non-peptide vasopressin V2-receptor antagonists. Bioorg. Med. Chem. Lett. 13, 753–756..
52 Matthews, J. M., Hoekstra, W. J., Dyatkin, A. B., Hecker, L. R., Hlasta, D. J., Poulter, B. L., Andrade-Gordon, P., de Garavilla, L., Demarest, K. T., Ericson, E., Gunnet, J. W., Hageman, W., Look, R., Moore, J. B., Reynolds, C. H. and Maryanoff, B. E. (2004) Potent nonpeptide vasopressin receptor antagonists based on oxazino- and thiazinobenzodiazepine templates. Bioorg. Med. Chem. Lett. 14, 2747–2752.
53 Dyatkin, A. B., Hoekstra, W. J., Hlasta, D. J., Andrade-Gordon, P., de Garavilla, L., Demarest, K. T., Gunnet, J. W., Hageman, W., Look, R. and Maryanoff, B. E. (2002) Bridged bicyclic vasopressin receptor antagonists with V_2-selective or dual V_{1a}/V_2 activity. Bioorg. Med. Chem. Lett. 12, 3081–3084.
54 Naito, A., Ohtake, Y., Hasegaw, H., Fukaya, A. Y., Kurasawa, T., Naito, K., Matsukawa, H., Oguma, T., Ezure, Y., Tsuriya, Y., Tanaka, H., Koike, K. and Shigenobu, K. (2000) Pharmacological profile of VP-343, a novel selective vasopressin V2-receptor antagonist, in rats. Biol. Pharm. Bull. 23, 182–189.
55 Aranapakam, V., Albright, J. D., Grosu, G. T., Delos Santos, E. G., Chan, P. S., Coupet, J., Ru, X., Saunders, T. and Mazandarini, H. (1999) 5-fluoro-2-methyl-N-[5-(5H-pyrrolo[2,1-c][1,4]benzodiazepine-10(11H)-yl carbonyl)-2-pyridinyl]benzamide (CL-385004) and analogs as orally active arginine vasopressin receptor antagonists. Bioorg. Med. Chem. Lett. 9, 1737–1740.
56 Tsukada, J., Tahara, A., Tomura, Y., Wada, K., Kusayama, T., Ishii, N., Aoki, M., Yatsu, T., Uchida, W., Taniguchi, N. and Tanaka, A. (2002) Pharmacological characterization of YM471, a novel potent vasopressin V(1A) and V(2) receptor antagonist. Eur. J. Pharmacol. 446, 129–138.
57 Galanski, M. E., Erker, T., Studenik, C. R., Kamyar, M., Rawnduzi, P., Pabstova, M. and Lemmens-Gruber (2005) Synthesis and pharmacological profile of non-peptide vasopressin antagonists. Eur. J. Pharm. Sci. 24, 421–431.
58 Galanski, M. E. Erker, T., Handler, N., Lemmens-Gruber, R., Kamyar, M. and Studenik, C. R. (2006) Studies on the chemistry of thienoanellated O,N- and S,N-containing heterocycles. Part 30: Synthesis and pharmacological properties of thieno[2,3-b][1,4]thiazines with potential vasopressin receptor antagonistic activity. Bioorg. Med. Chem. 14, 826–836.
59 CIBIS-II Investigators and Committees (1999) The cardiac insufficiency Bisprolol study II (CIBIS-II): a randomized trial. Lancet 353, 9–13.
60 Hjalmarson, A., Goldstein, S. and Fagerberg, B. (2000) Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients in heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA 283, 1295–1302.
61 Pfeffer, M. A., Braunwald, E., Moye, L. A., Basta, L., Brown E. J. Jr, Cuddy, T. E., Davis, B. R., Geltman, E. M., Goldman, S. and Flaker, G. C. (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N. Engl. J. Med. 327, 669–677.
62 Packer, M., Fowler, M. B., Roecker, E. B., Coats, A. J., Katus, H. A., Krum, H., Mohacsi, P., Rouleau, J. L., Tendera, M., Staiger, C., Holcslaw, T. L., Amann-Zalan, I. and DeMets, D. L. (2002) Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study. Circulation 106, 2194–2199.
63 Levine, T. B., Francis, G. S., Goldsmith, S. R., Simon, A. B. and Cohn, J. N. (1982) Activity of the sympathetic nervous

system and rennin-angiotensin system assessed by plasma hormone levels and their relation to hemodynamic abnormalities in congestive heart failure. Am. J. Cardiol. 49, 1659–1666.
64 Gheorghiade, M., De Luca, L. and Bonow, R. O. (2005) Neurohormonal inhibition in heart failure: insights from recent clinical trials. Am. J. Cardiol. 96, 3L-9L.
65 Risvanis, J., Naitoh, M., Johnston, C. I. and Burrell, L. M. (1999) *In vivo* and *in vitro* characterisation of a nonpeptide vasopressin V1a- and V2-receptor antagonist (YM087) in the rat. Eur. J. Pharmacol. 381, 23–30.
66 Yatsu, T., Tomura, Y., Tahara, A., Wada, K., Tsukada, J., Uchida, W., Tanaka, A. and Takenaka, T. (1997) Pharmacological profile of YM087, a novel nonpeptide dual vasopressin V1a- and V2-receptor antagonist, in dogs. Eur. J. Pharmacol. 321, 225–230.
67 Naitoh, M., Risvanis, J., Balding, L. C., Johnston, C. I. and Burrell, L. M. (2002) Neurohormonal antagonism in heart failure; beneficial effects of vasopressin V1a- and V2-receptor blockade and ACE inhibition. Cardiovasc. Res. 54, 51–57.
68 Wada, K., Tahara, A., Arai, Y., Aoki, M., Tomura, Y., Tsukada, J. and Yatsu, T. (2002) Effect of the vasopressin receptor antagonist conivaptan in rats with heart failure following myocardial infarction. Eur. J. Pharmacol. 450, 169–177.
69 Yatsu, T., Kusayama, T., Tomura, Y., Arai, Y., Aoki, M., Tahara. A, Wada, K. and Tsukada, J. (2002) Effect of conivaptan, a combined vasopressin V1a- and V2-receptor antagonist, on vasopressin-induced cardiac and hemodynamic changes in anaesthetised dogs. Pharmacol. Res. 46, 375–381.
70 Udelson, J. E., Smith, W. B., Hendrix, G. H., Painchaud, C. A., Ghazzi, M., Thomas, I., Ghali, J. K., Selaru, P., Chanoine, F., Pressler, M. L. and Konstam, M. A. (2001) Acute hemodynamic effects of conivaptan, a dual V1a and V2 vasopressin receptor antagonist, in patients with advanced heart failure. Circulation 104, 2417–2423.
71 Russell, S., Selaru, P., Pyne, D. A., Ghazzi, M. M., Massey, K. D., Pressler, M., Serikoff, A. and Coats, A. J.S. (2003) Rationale for use of an exercise end point and design for the ADVANCE (A Dose evaluation of a Vasopressin Antagonist in CHF patients undergoing Exercise) trial. Am. Heart J. 145, 179–186.
72 Clair, M. J., King, M. K., Goldberg, A. T., Hendrick, J. W., Nisato, R., Gay, D. M., Morrison, A. E., McElmurray, J. H. III, Krombach, R. S., Bond, B. R., Cazaubon, C., Nisato, D. and Spinale, F. G. (2000) Selective vasopressin, angiotensin II, or dual receptor blockade with developing congestive heart failure. J. Pharmacol. Exp. Ther. 293, 852–860.
73 Wada, K., Fujimori, A., Matsukawa, U., Arai, Y., Sudoh, K., Yatsu, T., Sasamata, M. and Miyata, K. (2005) Intravenous administration of conivaptan hydrochloride improves cardiac haemodynamics in rats with myocardial infarction-induced congestive heart failure. Eur. J. Pharmacol. 507, 145–151.
74 Hauptman, P. J., Zimmer, C., Udelson, J., Shoaf, S. E., Mallikaar jun, S., Bramer, S. L. and Orlandi, C. (2005) Comparison of two doses and dosing regimens of tolvaptan in congestive heart failure. J. Cardiovasc. Pharmacol. 46, 609–614.
75 Costello-Boerrigter, L. C., Smith, W. B., Boerrigter, G., Ouyang, J., Zimmer, C. A., Orlandi, C. and Burnett J. C. Jr, (2006) Vasopressin-2-receptor antagonism augments water excretion without changes in renal haemodynamics or sodium and potassium excretion in human heart failure. Am. J. Physiol. Renal Physiol. 290, F273-F278.
76 Sanghi, P., Uretsky, B. F. and Schwarz, E. R. (2005) Vasopressin antagonism: a future treatment option in heart failure. Eur. Heart J. 26, 538–543.
77 Gheorghiade, M., Niazi, I., Ouyang, J., Czerwiec, F., Kambayashi, J., Zampino, M., Orlandi, C., for the Tolvaptan Investigators (2003) Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation 107, 2690–2696.
78 Gheorghiade, M., Gattis, W. A., O'Connor, C. M., Adams, K. F. Jr, Elkayam, U., Barbagelata, A., Ghali, J. K., Benza, R. L., McGrew, F. A., Klapholz, M., Ouyang, J. and Orlandi, C., for the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) Investigators (2004) Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. JAMA 291, 1963–1971.
79 Gheorghiade, M., Orlandi, C., Burnett, J. C., Demets, D., Grinfeld, L., Maggioni, A., Swedberg, K., Udelson, J. E., Zannad, F., Zimmer, C. and Konstam, M. A. (2005) Rationale and design of the multicenter, randomized, double-blind, placebo-controlled study to evaluate the Efficacy of Vasopressin antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST). J. Card. Fail. 11, 260–269.
80 Tierney, W. M., Martin, D. K., Greenlee, M. C., Zerbe, R. L. and McDonald, C. J. (1986) The prognosis of hyponatremia at hospitalized admission. J. Gen. Intern. Med. 1, 380–385.
81 Goh, K. P. (2004) Management of hyponatremia. Am. Fam. Physician. 69, 2387–2394.
82 Goldsmith, S. R. (2005) Current treatments and novel pharmacological treatments for hyponatremia in congestive heart failure. Am. J. Cardiol. 95, 14B-23B.
83 Sica, D. A. (2006) Hyponatremia and heart failure – treatment considerations. Congest. Heart Fail. 12, 55–60.
84 Decaux, G. (2001) Long-term treatment of patients with inappropriate secretion of antidiuretic hormone by the vasopressin receptor antagonist conivaptan, urea, or furosemide. Am. J. Med. 110, 582–584.
85 Wong, F., Blei, A. T., Blendis, L. M. and Thuluvath, P. J. (2003) A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: a multicenter, randomized, placebo-controlled trial. Hepatology 37, 182–191.
86 Gerbes, A. L., Gulberg, V., Gines, P., Decaux, G., Gross, P., Gandjini, H., Djian, J., VPA Study Group (2003) Therapy of hyponatremia in cirrhosis with vasopressin receptor antagonist: a randomized double-blind multicenter trial. Gastroenterology 124, 933–939.
87 Miyazaki, T., Yamamura, Y., Onogawa, T., Nakamura, S., Kinoshita, S., Nakayama, S., Fujiki, H. and Mori, T. (2005) Therapeutic effects of tolvaptan, a potent, selective nonpeptide vasopressin V2-receptor antagonist, in rats with acute and chronic severe hyponatremia. Endocrinology 146, 3037–3043.
88 Hirano, T., Yamamura, Y., Nakamura, S., Onogawa, T. and Mori, T. (1999) Effects of the V_2-receptor antagonist OPC-41061 and the loop diuretic furosemide alone and in combination in rats. J. Pharmacol. Exp. Ther. 292, 288–292.
89 Shimizu K. (2003) Combined effects of vasopressin V2-receptor antagonist and loop diuretic in humans. Clin. Nephrol. 59, 164–173.
90 Ferguson, J. W., Therapondos, G., Newby, D. E. and Hayes, P. C. (2003) Therapeutic role of vasopressin receptor antagonism in patients with liver cirrhosis. Clin. Sci. 105, 1–8.
91 Fernandez-Varo, G., Ros, J., Cejudo-Martin, P., Cano, C., Arroyo, V., Rivera, F., Rodes, J. and Jimenez, W. (2003) Effect of the V1/V2-AVP receptor antagonist, conivaptan, on renal water metabolism and systemic hemodynamics in rats with cirrhosis and ascites. J. Hepatol. 38, 755–761.
92 Guyader, D., Patat, A., Ellis-Grosse, E. J. and Orczyk, G. P. (2002) Pharmacodynamic effects of a nonpeptide antidiuretic hormone V2 antagonist in cirrhotic patients with ascites. Hepatology 36, 1197–1205.
93 Decaux, G. (2001) Difference in solute excretion during correction of hyponatremic patients with cirrhosis or syndrome of inappropriate secretion of antidiuretic hormone by oral va-

sopressin V2-receptor antagonist VPA-985. J. Lab. Clin. Med. 138, 18–21.
94 Naito, A., Kurasawa, T., Ohtake, Y., Toyoda, Y., Ezure, Y., Koike, K. and Shigenobu, K. (2002) The effects of several vasopressin antagonists on normal intraocular pressure and the intraocular distribution of vasopressin receptor subtypes. Biol. Pharm. Bull. 25, 251–255.
95 Lacheretz, F., Barbier, A., Serradeil-Le Gal, C., Elena, P. P., Maffrand, J. P. and Le Fur, G. (2000) Effect of SSR121463, a selective non-peptide vasopressin V2-receptor antagonist, in a rabbit model of ocular hypertension. J. Ocul. Pharmacol. Ther. 16, 203–216.
96 Bernier, V., Lagace, M., Lonergan, M., Arthus, M. F., Bichet, D. G. and Bouvier, M. (2004) Functional rescue of the constitutively internalized V2 vasopressin receptor mutant R137H by the pharmacological chaperone action of SR49059. Mol. Endocrinol. 18, 2074–2084.
97 Bernier, V., Morello, J. P., Zarruk, A., Debrand, N., Salahpour, A., Lonergan, M., Arthus, M. F., Lapierre, A., Brouard, R., Bouvier, M. and Bichet, D. G. (2006) Pharmacologic chaperones as a potential treatment for X-linked nephrogenic diabetes insipidus. J. Am. Soc. Nephrol. 17, 232–243.
98 Schieren, G., Ramberger, B., Klein, M., Kreutz, C., Wilpert, J., Geyer, M., Faller, D., Timmer, J., Quack, I., Rump, I. C., Walz, G. and Donauer, J. (2006) Gene profiling of polycystic kidneys. Nephrol. Dial. Transplant., in press.
99 Wang, X., Gattone, V. 2nd, Harris, P. C. and Torres, V. E. (2005) Effectiveness of vasopressin V2-receptor antagonists OPC-31260 and OPC-41061 on polycystic kidney disease development in the PCK rat. J. Am. Soc. Nephrol. 16, 838–839.
100 Steinwall, M., Bossmar, T., Gaud, C. and Akerlund, M. (2004) Inhibitory effects of SR49059 on oxytocin- and vasopressin-induced uterine contractions in non-pregnant women. Acta Obstet. Gynecol. Scand. 83, 12–18.
101 Thibonnier, M., Kilani, A., Rahman, M., DiBlasi, T. P., Warner, K., Smith, M. C., Leenhardt, A. F. and Brouard, R. (1999) Effects of the nonpeptide V(1) vasopressin receptor antagonist SR49059 in hypertensive patients. Hypertension 34, 1293–1300.
102 Fraser, T. B., Turner, S. W., Wen, C., Li, M., Burrell, L. M. and Whitworth, J. A. (2000) Vasopressin V1a-receptor antagonism does not reverse adrenocorticotrophin-induced hypertension in the rat. Clin. Exp. Pharmacol. Physiol. 27, 866–870.
103 Langhuizen, I. M., van Veghel, R., Saxena, P. R. and Schoemaker, R. G. (2000) [Arg8]-vasopressin-induced responses on coronary and mesenteric arteries of rats with myocardial infarction: the effects of V1a- and V2-receptor antagonists. J. Cardiovasc. Pharmacol. 36, 38–44.
104 Weber, R., Pechere-Bertschi, A., Hayoz, D., Gere, V., Brouard, R., Lahmy, J. P., Brunner, H. R. and Burnier, M. (1997) Effects of SR49059, a new orally active and specific vasopressin V1-receptor antagonist, on vasopressin-induced vasoconstriction in humans. Hypertension 30, 1121–1127.
105 Hayoz, D., Bizzinin, G., Noel, B., Depairon, M., Burnier, M., Fauveau, C., Rouillon, A., Brouard, R. and Brunner, H. R. (2000) Effect of SR49059, a V1a vasopressin receptor antagonist, in Raynaud's phenomenon. Rheumatology 39, 1132–1138.
106 Trandafir, C. C., Nishihshi, T., Wang, A., Murakami, S., Ji, X. and Kurahashi, K. (2004) Participation of vasopressin in the development of cerebral vasospasm in a rat model of subarachnoid haemorrhage. Clin. Exp. Pharmacol. Physiol. 31, 261–266.
107 Tribollet, E., Raufaste, D., Maffrand, J. and Serradeil-Le Gal, C. (1999) Binding of the non-peptide vasopressin V1a-receptor antagonist SR-49059 in the rat brain: an *in vitro* and *in vivo* autoradiographic study. Neuroendocrinology 69, 113–120.
108 Shuaib, A., Wang, C. X., Yang, T. and Noor, R. (2002) Effects of nonpeptide V1 vasopressin receptor antagonist SR-49059 on infarction volume and recovery of function in a focal embolic stroke model. Stroke 33, 3033–3037.
109 Salvucci, A. and Armstead, W. M. (2000) Vasopressin impairs K(ATP) and K(Ca) channel function after brain injury. Brain Res. 887, 406–412.
110 Akerlund, M. (2002) Involvement of oxytocin and vasopressin in the pathophysiology of preterm labor and primary dysmenorrhea. Prog. Brain Res. 139, 359–365.
111 Chen, Y. L., Shepherd, C., Spinelli, W. and Lai, F. M. (1999) Oxytocin and vasopressin constrict rat isolated uterine resistance arteries by activating vasopressin V1a-receptors. Eur. J. Pharmacol. 376, 45–51.
112 Bossmar, T., Brouard, R., Doberl, A. and Akerlund, M. (1997) Effects of SR 49059, an orally active V1a vasopressin receptor antagonist, on vasopressin-induced uterine contractions. Br. J. Obstet. Gynaecol. 104, 471–477.
113 Brouard, R., Bossmar, T., Fournie-Lloret, D., Chassard, D. and Akerlund, M. (2000) Effect of SR49059, an orally active V1a vasopressin receptor antagonist, in the prevention of dysmenorrhoea. BJOG 107, 614–619.
114 Atke, A., Vilhardt, H., Hauzerova, L., Barth, T. and Andersen, L. F. (1995) Effects of the non-peptide inhibitor OPC-21268 on oxytocin and vasopressin stimulation of rat and human myometrium. Eur. J. Pharmacol. 281, 63–68.
115 Steinwall, M., Bossmar, T., Brouard, R., Laudanski, T., Olofsson, P., Urban, R., Wolff, K., Le-Fur, G. and Akerlund, M. (2005) The effect of relcovaptan (SR 49059), an orally active vasopressin V1a-receptor antagonist, on uterine contractions in preterm labor. Gynecol. Endocrinol. 20, 104–109.
116 Lagrange, F. J., Brun, J. L., Clot, P. F., Leng, J. J., Saux, M. C., Kieffer, G. and Bannwarth, B. G. (2001) Placental transfer of SR49059 in human dually perfused cotyledon *in vitro*. Placenta 22, 870–875.
117 Ring, R. H. (2005) The central vasopressinergic system: examining the opportunities for psychiatric drug development. Curr. Pharm. Design 11, 205–225.
118 Bielsky, I. F., Hu, S. B., Ren, X., Terwilliger, E. F. and Young, L. J. (2005) The V1a vasopressin receptor is necessary and sufficient for normal social recognition: a gene replacement study. Neuron 47, 503–513.
119 Blanchard, R. J., Griebel, G., Farrokhi, C., Markham, C., Yang, M. and Blanchard, D. C. (2005) AVP V1b selective antagonist SSR149415 blocks aggressive behaviours in hamsters. Pharmacol. Biochem. Behav. 80, 189–194.
120 Schwarz, E. R. and Sanghi, P. (2006) Conivaptan: a selective vasopressin antagonist for the treatment of heart failure. Expert Rev. Cardiovasc. Ther. 4, 17–23.
121 Gheorghiade, M., De Luca, L. and Bonow, R. O. (2005) Neurohormonal inhibition in heart failure: insights from recent clinical trials. Am. J. Cardiol. 96, 3L–9L.