

Vasopressin and Oxytocin Receptors

Key References

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Overview

The pituitary hormones arginine vasopressin (AVP) and oxytocin (OT) are structurally related cyclic nonapeptides that act as hormones and neurotransmitters. Both peptides are synthesized in neurons in the hypothalamus that project to the posterior pituitary from which they are released into the circulation. In addition, OT and AVP neurons innervate various regions of the brain and spinal cord. Their amino acid sequences differ only in two of the nine amino acids, but despite this similarity they exhibit distinct biological activities. All of the currently known AVP/OT receptor subtypes (V_{1a}, V_{1b}, V₂, OT) have been cloned from rat and human tissues and characterized. They are members of the G protein-coupled superfamily of receptors and show significant structural homology to one another. The receptor selectivity of OT and AVP for their own receptors is not absolute and significant cross-talk can occur with OT at AVP receptors (and vice versa) at higher concentrations.

A primary physiological role of AVP involves regulation of cardiovascular function where its contractile actions on vascular smooth muscle, via V_{1a} receptors, maintain peripheral resistance under certain adverse conditions such as hemorrhage, and its antidiuretic actions on kidney, via V₂ receptors, correct fluctuations in blood osmolality. Binding of AVP to the V_{1a} receptor subtype also stimulates glycogenolysis in the liver and promotes platelet aggregation. In addition, V_{1a} receptors are present in the CNS where they may be involved in certain behaviors such as learning and memory. Activation of the recently discovered V_{1b} (also known as V₃) receptor by hypothalamic AVP causes adrenocorticotrophic hormone release from the anterior pituitary and is believed to mediate various stress-related behavioral responses.

OT binds to receptors in the uterus and mammary gland to mediate important functions in parturition such as contraction of the uterine myometrium during labor and the mammary myoepithelium postpartum to elicit milk letdown. In addition, OT receptors are located in a variety of other peripheral tissues as well as the brain where OT may have physiological effects on cardiovascular, renal, endocrinological and behavioral functions. In particular, OT has been shown to promote maternal, sexual and affiliative-type behaviors in various animal species including nonhuman primates. At present, only one OT receptor subtype has been identified pharmacologically or structurally.

The diverse functions of OT and AVP give rise to a number of possible therapeutic opportunities based on the modulation of their receptor activity. Two examples of current therapeutics are OT itself, for the promotion of labor and delivery, and desmopressin (dDAVP), a V₂ agonist for the treatment of diabetes insipidus in which there is a deficiency of circulating AVP. Nonpeptide V₂ agonists such as OPC 51803 have recently been described. Nonpeptide OT agonists have also been disclosed and are being explored for possible utilities in sexual function and affiliative disorders such as social phobias and obsessive-compulsive behavior. The OT antagonist atosiban, has recently been approved and launched (Tractocile®) in Europe for the treatment of preterm labor. Blockade of vascular V_{1a} receptors with OPC 21268, atosiban or YM471 may have utility in hypertension and dysmenorrhea, whereas an aquaretic response (water diuresis) caused by antagonism of renal V₂ receptors with OPC 41061(tolvaptan) or SSR121463A could be useful in counteracting fluid reten-

tion and hypo-osmolality resulting from a variety of conditions. A V₂ antagonist may also be useful in the treatment of congestive heart failure, particularly in combination with a V_{1a} antagonist or, with simply, a compound exhibiting both properties such as YM471 and conivaptan (YM087), recently filed in the U.S. for the treatment of hyponatremia. Selective V1b antagonists such as SSR149415 are being investigated for possible utility in various stress-related disorders such as depression and anxiety.

Vasopressin and Oxytocin Receptors

CURRENTLY ACCEPTED NAME	V _{1a}	V _{1b}	V ₂	OT
ALTERNATE NAME	V ₁	V ₃	—	—
STRUCTURAL INFORMATION	418 aa (human)	424 aa (human)	371 aa (human)	391 aa (human)
PREFERRED ENDOGENOUS LIGAND	Vasopressin (V9879 , V0377)	Vasopressin(V9879 , V0377)	Vasopressin (V9879 , V0377)	Oxytocin (O6379)
SELECTIVE AGONISTS	[Phe ² ,Orn ⁸]VT	deamino-[D-3'-(pyridyl)-Ala ²]AVP, d[Cha ⁴]AVP	dDAVP (V1005), dVDAVP (V2013), VDAVP, OPC 51803 (non-peptide)	[Thr ⁴ ,Gly ⁷]OT (O6380), Compound 39 (nonpeptide)
SELECTIVE PEPTIDE ANTAGONISTS	desGly ⁹ -d(CH ₂) ⁵ AVP, d(CH ₂) ⁵ -[Tyr(Me) ₂] AVP, HO-Phaa-D-Tyr(Me)-Phe-Gln-Asn-Arg-Pro-Arg-(NH ₂)	dP[Tyr(Me) ₂] AVP	d(CH ₂) ₅ -[D-Ile ² ,Ile ⁴] AVP, desGly(NH ₂) ⁹ -d(CH ₂) ⁵ [D-Ile ² ,Ile ⁴] AVP	desGly(NH ₂) ⁹ d(CH ₂) ⁵ [Tyr(Me) ² Thr ⁴]OVT, Atosiban (A3480), ANTAG III
SELECTIVE NON-PEPTIDE ANTAGONISTS	OPC 21268, SR 49059	SSR149415	OPC 31260, SR 121463, OPC 41061(Tolvaptan)	L-368,899, L-372,662, SSR126768A
SIGNAL TRANSDUCTION MECHANISMS	G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG)	G _s (increase cAMP)	G _{q/11} (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	[³ H]-AVP, [³ H]-d(CH ₂) ⁵ -[Tyr(Me) ₂] AVP, [³ H]-SR 49059	[³ H]-AVP	[³ H]-AVP, [³ H]-desglycinamide-d(CH ₂) ⁵ [D-Ile ² ,Ile ⁴]AVP	[³ H]-OT, [¹²⁵ I] d(CH ₂) ⁵ [Tyr(Me) ₂ -Thr ⁴ -Tyr(NH ₂) ⁹] OVT
TISSUE EXPRESSION	Vasculature	Pituitary, CNS	Kidney	Uterus, mammary gland, CNS
PHYSIOLOGICAL FUNCTION	Smooth muscle contraction	ACTH release, behavior	Antidiuresis	Smooth muscle contraction, maternal, sexual behavior
DISEASE RELEVANCE	Hypertension, congestive heart failure	Anxiety, depression	Hyponatremia, congestive heart failure	Preterm labor, sexual dysfunction

Abbreviations

ANTAG III: β,β-(3-Thiapentamethylene)-β-mercaptopropionic acid1,D-Trp²,penicillamine⁶,Arg⁸-OT

AVP: Arginine vasopressin

dDAVP: [des-amino D-Arg⁴]Vasopressin

dVDAVP: [des-amino Val⁴,D-Arg⁸]Vasopressin

Compound 39: Pitt, et al., *Bioorg. Med. Chem. Lett.*, **14**, 4385-4589 (2004).

L-362,662: 1-(1-[4-[1-(2-Methyl-1-oxidopyridin-3-ylmethyl)piperidin-4-yloxy]-2-methoxybenzoyl]piperidin-4-yl)-1,4-dihydrobenz[d][1,3]oxazin-2-one

L-368,899: 1S(-)-7-(7-Dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)butyramido)-bicyclo(2.2.1)-heptan-1-yl)methanesulfonyl-4-(2-methylphenyl)piperazine

LVP: Lysine vasopressin

OPC 51803: (5R)-2-[1-(2-chloro-4-(1-pyrrolidinyl)benzoyl)-2,3,4,5-tetrahydro-1H-1-benzazepin-5-yl]isopropylacetamide

OPC 31260: (+)-5-Dimethylamino-1-(4-[2-methylbenzoylamino]benzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

OPC 41061: 7-Chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine

OPC 21268: 1-(1-[4-[3-Acetylamino-propoxy]benzoyl]-4-piperidyl)-3,4-dihydro-2(1H)-quinolinone

OT: Oxytocin

OVT: [Orn⁸]Vasotocin

Phaa: Phenylacetic acid

SR 121463A: (1-[4-(N-Tert-butylcarbonyl)-2-methoxybenzene sulfonyl]-5-ethoxy-3-spiro-[4-(2-morpholinoethoxy)cyclohexane]indol-2-one

SSR149415: ((2S,4R)-1-[5-Chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-4-hydroxy-N,N-dimethyl-2-pyrrolidinecarboxamide

SR 49059: ((2S)-1-[(2R,3S)-(5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxybenzene-sulfonyl)-3-hydroxy-2,3-dihydro-1H-indole-2-carbonyl]-pyrrolidine-2-carboxamide

SSR126768A: (4-Chloro-3-[(3R)-(+)-5-chloro-1-(2,4-dimethoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-N-ethyl-N-(3-pyridylmethyl)-benzamide

VDAVP: [Val⁴,D-Arg⁸]Vasopressin

VT: Vasotocin

YM087: 4'-[(2-Methyl-1,4,5,6-tetrahydroimidazo[4,5-d][1]benzazepin-6-yl)-carbonyl]-2-phenylbenzamide

YM471: ((Z)-4'-[4,4-Difluoro-5-[2-(4-dimethylaminopiperidino)-2-oxoethylidene]-2,3,4,5-tetrahydro-1H-1-benzazepine-1-carbonyl]-2-phenylbenzamide

FOOTNOTES

The information in the Table refers largely to data obtained with rat receptors although some data exist for human receptors as well. It should be noted that substantial species differences in the affinities can exist between the pharmacology of rat and human receptors. For example, OPC 21268 is a high affinity antagonist ligand at rat, but not human receptors, and atosiban is a selective OT antagonist in rats, but has V_{1a} selectivity at human receptors. Also, for several cases for the compounds in the Table, compounds that are selective for certain AVP receptor subtypes have not been evaluated fully for OT receptor affinity. It is recommended that the reader go to the literature of a given compound before making assumptions of affinity and degree of selectivity within and across species.