Conopressin-T from Conus tulipa Reveals an Antagonist Switch in Vasopressin-like Peptides
Sébastien Dutertre, Daniel Croker, Norelle Daly, Åsa Andersson, Markus Muttenthaler, Natalie Lumsden, David Craik, Paul Alewood, Gilles Guillon, Richard Lewis

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We report the discovery of conopressin-T, a novel bioactive peptide isolated from Conus tulipa venom. Conopressin-T belongs to the vasopressin-like peptide family and displays high sequence homology to the mammalian hormone oxytocin (OT) and to vasotocin, the endogenous vasopressin analogue found in teleost fish, the cone snail’s prey. Conopressin-T was found to belong to the vasopressin-like peptide family and displays high sequence homology to the mammalian hormone oxytocin (OT). Surprisingly, replacing Gly9 with Val9 in OT and vasopressin converted these peptides from full agonist to full antagonist at the V1a receptor, whereas conopressin-G was first isolated from Conus geographus venom but later found in Conus imperialis venom as well as in tissue extracts of the nonvenomous slayms Lymnea stagnalis and Aplysia californica. The vasopressin (AVP) and oxytocin (OT) peptides were originally discovered and identified as neurohypophysial hormones in mammals (1). In humans, AVP acts via three receptors in mammals (1): V1aR, V1bR, and V2R, whereas OT acts via one OT receptor (OTR). All targets are members of the G protein-coupled receptor family (2). Peripherally, they regulate water balance, the control of blood pressure, and contraction of uterine smooth muscle and mammary myoepithelium (3). Centrally, these peptides affect levels of aggression, depression, and young parent bonding (4–6). Endogenous analogues of OT and AVP have been reported in nonmammalian vertebrates, annelids, molluscs, and insects, suggesting an old lineage for these peptides (7). Surprisingly, two variants were also found in the venom of predatory cone snails. The original discovery of these two AVP analogues, named conopressins, was based on the characteristic “scratching” effect observed upon intracerebral injection into mice (8). Although the sequences of conopressins are similar to vasopressin itself, they have an additional positive charge in position 4, which is only found in two other endogenous vasopressin analogues, cephalotocin (Octopus vulgaris) and anetocin (Eisenia fetida). Conopressin-S was isolated from Conus striatus, whereas conopressin-G was first isolated from Conus geographus venom but later found in Conus imperialis venom as well as in tissue extracts of the nonvenomous slayms Lymnea stagnalis and Aplysia californica. Molluscs of the genus Conus produce bioactive peptides in a combinatorial fashion. As demonstrated for the snake toxins (12), most conotoxins or conopeptides are believed to be derived from an endogenous structural template (13). Because conopressin-G is widely distributed, it may represent the endogenous hormone in Gastropods and Annelids. However, a role in prey capture has also been proposed (14).

In this study, we report the discovery of conopressin-T isolated from Conus tulipa venom. Pharmacological characterizations of Con-T across human receptors revealed that it is a selective V1a antagonist, with partial agonist activity at the OT receptor and no detectable activity at V1b and V2 receptors. The exocyclic tripeptide segment of conopressin-T shows unusual sequence divergence. L7P-Con-T had increased affinity at the V1a receptor but minimal effect on the selectivity profile across all human receptors compared with Con-T. Interestingly, replacing Gly9 with Val9 in OT and AVP converted these peptides from full agonist to full antagonist at the V1a receptor, demonstrating the role of position 9 as an antagonist switch in these peptides. Finally, the NMR structures of conopressin-T and its L7P analogue provide new templates for the design of novel pharmacological agents with enhanced activity at the V1a receptor.
EXPERIMENTAL PROCEDURES

Materials—t-Butoxycarbonyl-protected amino acids and reagents used during chain assembly and HPLC purification (dimethylformamide, dichloromethane, acetonitrile, and trifluoroacetic acid) were peptide synthesis grade purchased from Auspep (Melbourne, Australia) and Novabiochem (San Diego, CA). 4-methylbenzhydramine-NH₂ resin was obtained from Auspep (Melbourne, Australia), Costar 96-well white polystyrene plate (containing [tyrosyl-2,6-3H]oxytocin; 40 Ci/mmol), 125I-linear vasopressin (Amersham, Buckinghamshire, UK), and CHO-K1 cells from the American Type Culture Collection.
by homogenization with a Polytron homogenizer and centrifugation at 100 × g for 10 min at 4 °C. Supernatants were recovered and centrifuged at 22,000 × g for 1 h at 4 °C. Membrane pellets were resuspended in 0.5 ml of ice-cold assay buffer A (50 mM Tris-HCl, pH 7.4, 5 mM MgCl₂, 0.1% bovine serum albumin, containing 10% glycerol and aliquots stored at −80 °C until use.

Receptor Binding Studies—Receptor binding assays were performed using FlashBlue™ GPCR scintillation beads. FlashBlue™ GPCR beads are 3-μm polystyrene scintillating beads with wheat germ agglutinin covalently attached on the surface. These beads allow development of a homogeneous GPCR radioligand binding assay using cellular membranes. Briefly, FlashBlue™ GPCR SPA binding assays were performed in 96-well white polystyrene plates with clear flat bottoms (Costar). Radioligand (OTR [³H]OT (2 nM), V₁a [¹³⁵I]-labeled linear V₁a antagonist (21 pM), Vₙb [³H]AVP (0.5 nM), V₂ [³H]AVP (0.85 nM)) was added to each membrane preparation, followed by the addition of various concentrations of competing compounds (1 pM to 10 μM) in a total volume of 80 μl containing assay buffer A or B (50 mM Tris-HCl, pH 7.4, 0.1% bovine serum albumin, and either 5 mM MgCl₂ (A) or 10 mM MgCl₂ (B)) (OT and V₂ assay, buffer A; V₁a and V₁b assay, buffer B). The final reaction volume per well comprised 20 μl of compound/buffer, 20 μl of FlashBlue™ GPCR beads (OTR, V₁a, and V₂, 100 μg; V₁b, 200 μg), and 20 μl of membrane, and the assay was initiated by the addition of 20 μl of radioligand. The plate was then sealed with TopSeal-A sealing film and incubated with shaking for 1 h at room temperature. Radioligand binding was then assessed for 30 s/well on a 1450 Microbeta scintillation counter (Wallac).

All binding data were analyzed using GraphPad PRISM (GraphPAD Software, Inc., San Diego, CA). Each data point was performed in triplicate and derived from at least three separate experiments. The inhibitory dissociation constant (Kᵢ) was calculated using the following formula: 

\[ Kᵢ = IC₅₀/[1 + [L]/K_d] \]

where [L] is the concentration of radioligand present, and K_d is the dissociation constant of radioligand (17).

Inositol Phosphate Assays—Inositol phosphate accumulation was determined as previously described (18). Briefly, CHO cells stably transfected with AVP/OT receptors were plated at 100,000 cells/well. Cells were grown for 24 h in their respective culture medium (see above) and further incubated for another 24-h period in a serum- and inositol-free medium supplemented with 1 μCi/ml [³¹P]inorganic phosphate. Cells were then washed twice with Hanks' buffered saline medium, incubated for 15 min in this medium supplemented with 20 mM LiCl, and further stimulated for 15 min with increasing concentrations of analogues to be tested. The reaction was stopped by adding perchloric acid (5%, v/v). Total inositol phosphates (IPs) accumulated were extracted and purified on a Dowex AGI-X8 anion exchange chromatography column and counted.

NMR Spectroscopy—Samples for ¹H NMR measurements contained ~1 mM peptide in 95% H₂O, 5% D₂O (v/v) at pH ~3. Spectra were recorded at 290 K on a Bruker AVANCE-600 spectrometer. Two-dimensional NMR spectra were recorded in phase-sensitive mode using time-proportional phase incrementation for quadrature detection in the t₁ dimension (19, 20). The two-dimensional experiments consisted of a TOCSY using a MLEV-17 spin lock sequence with a mixing time of 80 ms, DQF-COSY, and NOESY with mixing times of 200–300 ms. Solvent suppression was achieved using a modified WATERGATE sequence. Spectra were acquired over 6024 Hz with 4096 complex data points in F2 and 512 increments in the F1 dimension. ³¹PHN-H coupling constants were measured from a one-dimensional spectrum or from the DQF-COSY spectrum. Spectra were processed on a Silicon Graphics Indigo work station using XWINNMR (Bruker) software. The t₁ dimension was zero-filled to 1024 real data points, and 90° phase-shifted sine bell window functions were applied prior to Fourier transformation.

Structure Calculations—Preliminary structures were calculated using a torsion angle simulated annealing protocol within the program DYANA (21). Final structures were calculated using simulated annealing and energy minimization protocols within CNS version 1.1 (22). The starting structures were generated using random (φ,ψ) dihedral angles and energy-minimized to produce structures with the correct local geometry. A set of 50 structures was generated by a torsion angle simulated annealing protocol (19, 20). This protocol involved a high temperature phase comprising 4000 steps of 0.015 ps of torsion angle dynamics, a cooling phase with 4000 steps of 0.015 ps of torsion angle dynamics during which the temperature was lowered to 0 K, and finally an energy minimization phase comprising 500 steps of Powell minimization. Structures consistent with restraints were subjected to further molecular dynamics and energy minimization in a water shell, as described by Linge and Nilges (23). The refinement in explicit water involved the following steps. First, heating to 500 K via steps of 100 K, each comprising 50 steps of 0.005 ps of Cartesian dynamics. Second, 2500 steps of 0.005 ps of Cartesian dynamics at 500 K before a cooling phase where the temperature was lowered in steps of 100 K, each comprising 2500 steps of 0.005 ps of Cartesian dynamics. Finally, the structures were minimized with 2000 steps of Powell minimization. Structures were analyzed using PROMOTIF (24) and PROCHECK-NMR (25).

RESULTS

Isolation and Sequencing of Conopressin-T—A peptide with a monoisotopic mass of 1107.54 Da was purified from C. tulipa venom (Fig. 1, A–C). The Tris(2-carboxyethyl)phosphine-reduced peptide displayed a mass of 1109.5 Da, suggesting the presence of one disulfide bond (data not shown). N-terminal sequencing produced the sequence CYIQNCLRV with a calculated mass of 1110.53 Da, consistent with one disulfide bond (−2 Da) and C-terminal amidation (−1 Da). A BLAST search revealed that this sequence belonged to the vasopressin peptide family characterized by a disulfide-containing ring (residues 1–6) and a short exocyclic C-terminal tripeptide (residues 7–9). Conopressin-T had 7 of 9 residues identical to vasotocin (AVT), including the first six residues also found in oxytocin (OT), and mesotocin, and Arg₈ known to be essential for the pressor activity in vasopressin. However, two highly conserved residues, Pro₇ and Gly₉, found in other vasopressin-like peptides as well as conopressin-G and conopressin-S are modified to Leu₇ and Val₉ in conopressin-T. De novo mass spectrometry
Conopressin-T and L7P-Conopressin-T Are Selective V1a Receptor Antagonists—Con-T and L7P-Con-T were tested for their ability to displace radioligand from human AVP and OT receptors expressed in HEK and CHO cells (Fig. 2A and Table 1). Con-T showed the highest affinity for human OTR ($K_i = 108 \text{ nm}$) and $V_{1b}$R ($K_i = 319 \text{ nm}$) and no detectable activity at $V_{1b}$ and $V_2$ receptors at up to $10 \mu M$ peptide. In contrast, L7P-Con-T was 8-fold more potent than Con-T at the $V_{1b}$R ($K_i = 37 \text{ nm}$) but had similar affinity for OTR ($K_i = 132 \text{ nm}$). L7P-Con-T was also found to have a weak effect at $V_2$R ($K_i = 1.8 \mu M$), whereas no displacement of radioligand was detected at the $V_{1b}$R at up to $10 \mu M$ peptide. For comparison, we also tested the activity of conopressin-S (Con-S) across these receptors. Con-S does not bind to $V_2$R (up to $10 \mu M$ peptide), has similar affinity for OTR ($K_i = 175 \text{ nm}$) but is less potent at $V_{1a}$R ($K_i = 827 \text{ nm}$). In contrast to Con-T and L7P-Con-T, Con-S binds with high affinity to $V_{1b}$R ($K_i = 8.3 \text{ nm}$), although the displacement of specific [$^3H$]AVP binding was incomplete (a 30–40% resistant component remained; see Fig. 2A). Therefore, conopressin-T, -S, and -L7P have distinct pharmacological profiles on human receptors, with the lack of effect of Con-T on radioligand binding to both $V_{1b}$ and $V_2$ receptors being unique (supplemental Fig. 1).

The functional properties of Con-T and L7P-Con-T were investigated on CHO cells expressing human receptors (Fig. 2B and Table 2). Con-T did not stimulate phospholipase C activity in cells expressing $V_{1a}$R at $<10 \mu M$ peptide. However, Con-T at $10 \mu M$ showed partial agonist activity at the $V_{1b}$R and OTR, producing 9 and 22% of AVP and OT maximal activity, respectively. L7P-Con-T displayed a similar profile, with no agonist activity at the $V_{1a}$R at $<10 \mu M$ and partial agonist activity at the $V_{1b}$R and OTR (4 and 28% of AVP and OT maximal activity, respectively) at $10 \mu M$ peptide. In contrast, both Con-T and L7P-Con-T induced a potent and concentration-dependent inhibition of AVP-stimulated IP production in CHO cells expressing $V_{1b}$R, with $K_{\text{inact}}$ values of 329 and 90 nm, respectively (Table 2). These values correlated well with the binding affinities. Thus, both peptides are full antagonists at the human $V_{1a}$R subtype and weak partial agonists for the $V_{1b}$R and OTR (Fig. 2B). Due to the absence of significant binding to $V_2$R, the functional activity of Con-T and L7P-Con-T was not investigated on this subtype.

Gly$^9$ → Val Replacement in OT and AVP Acts as an Antagonist Switch at the $V_{1a}$ Receptor—L7P-conopressin-T and vasotocin differs only at position 9, yet L7P-conopressin-T acts as a full antagonist at the $V_{1a}$ receptor (Fig. 2B), whereas the closely related vasotocin is known to function as an agonist (29). To investigate if the Val$^9$ modification in conopressin-T could switch agonist to antagonist activity in related peptides, we tested this modification in OT and AVP. First, the binding properties of these analogues were assessed on human receptors (Fig. 3A and Table 1). G9V-AVP was equipotent at $V_{1a}$R and $V_{1b}$R ($<25 \text{ nm}$) and 5–7-fold less potent at the OTR and $V_{1b}$R (114 and 170 nm, respectively). Compared with AVP, G9V-AVP affinity ranged from 5-fold less at $V_{1b}$R to 2000-fold less at the OTR and $V_{1a}$R ($<10 \mu M$ and partial agonist activity for the $V_{1b}$R and OTR (Fig. 2B), due to the absence of significant binding to $V_2$R, the functional activity of Con-T and L7P-Con-T was not investigated on this subtype.
and Table 2). Both peptides failed to stimulate phospholipase C activity in cells expressing V1aR at ≤ 10 μM peptide. However, G9V-AVP and G9V-OT both acted as partial agonists at the OTR, eliciting ~5–10% and ~25–30% of OT maximal activity, respectively. In contrast, both peptides induced a potent and concentration-dependent inhibition of AVP-stimulated IP in CHO cells expressing V1aR. The affinities (K_i) of G9V-AVP (40 nM) and G9V-OT (391 nM) correlate well with the binding data at the V1a receptor (25 and 466 nM, respectively). Clearly, the G9V replacement shifted the activity of both AVP and OT from full agonist to full antagonist at the V1aR, supporting the hypothesis that position 9 can act as a functional switch at the V1a receptor.

**Solution Structure of Con-T and L7P-Con-T**—NMR spectral assignments of both peptides were made using established techniques (26). The chemical shifts in the amide region are well dispersed, and restraints derived from the NOESY spectra allowed determination of well defined structures. Analysis of the nuclear Overhauser effects indicated that the proline residue in L7P-Con-T is predominantly in a trans conformation based on the strong nuclear Overhauser effects between the Hα of Cys6 and the Hδs of Pro7. In addition, there is evidence of a minor conformation in the L7P-Con-T spectra, including a second proline spin system. However, this minor conformation could not be assigned because of its low intensity and missing peaks. It is not uncommon for small peptides to have prolines adopting mixed cis/trans conformations, which probably explains the second spin system observed.

The three-dimensional structures of conopressin-T and its L7P analogue were calculated using a simulated annealing protocol in CNS. The resulting families of structures had good structural and energetic statistics, as shown in Table 3. An ensemble of the 20 lowest energy structures for each peptide is shown in Fig. 4A. Analysis of the structures of each peptide with PROSOTIF (24) indicated that the major structural feature is a β-turn between residues 4 and 7. The structures of conopressin-T and L7P overlaid well over the defined regions of the structure (root mean square deviation for the backbone atoms of residues 1–6 is 0.52 Å). Although the C-terminal residues are disordered, the directions of the C-terminal tails clearly differ between the two structures as shown in Fig. 4, B and C.

**DISCUSSION**

Con-T isolated from *C. tulipa* venom is a novel vasopressin-like peptide. Investigation of its biological activity on human receptors revealed that Con-T acted selectively at V1a and OT receptors. Functional studies demonstrated that Con-T was a full antagonist at V1aR and a partial agonist at OTR. The pharmacological profile of an L7P analogue was similar but for increased affinity for the V1aR. The partial agonist activity of both peptides at OTR indicates incomplete signaling through
the associated G protein (Gq/11, Gi/0) perhaps because they bind and trap the OT receptor in a conformation that is unable to signal fully. Similarly, OT and AVP act as partial agonists on vasopressin and oxytocin receptors, respectively (27).

The sequence of Con-T differs significantly from the previously reported conopressin-G and Con-S. First, the additional positively charged residue at position 4, which was thought to be characteristic of conopressins, is absent in Con-T. Interestingly, and probably ecologically and evolutionarily relevant, Con-T has 7 of 9 residues (including the disulfide containing ring) identical to vasotocin, the teleost fish equivalent. In light of our pharmacological results, and since C. tulipa preys on fish, Con-T might specifically target teleost AVT receptors. So far, the only cloned receptor in teleost fish appears to be pharmacologically comparable with the mammalian V1a and oxytocin receptors (28). This receptor controls the arterial-venous flows and is particularly important in gill hemodynamics and consequently respiration. However, conopressin-G and Con-S were found to be only moderately active on fish vasotocin receptor (29). Animal toxins usually shut down vital functions by blocking membrane receptors rather than by activating them, and although Con-T is yet to be tested on this fish receptor, it may act as an antagonist as demonstrated here for the human V1a receptor. Alternatively, Con-T may also act synergistically with other lethal peptides present in the venom and/or modify the behavior of the fish to reduce the risk of injury to the cone snail. Interestingly, specific localization of staining for vasotocin in the brain of zebrafish was found to correlate with aggressive behavior (dominant versus subordinate social status) (30), and an antagonist might be expected to reduce such behavior. Other conopeptides are known to act centrally in fish, which have a leaky blood-brain barrier (31).

Recently, an unusual γ-carboxyglutamate at position 8 in the sequence of conopressin-Vil from the venom of Conus villepinii...
has been reported, but its biological activity was not determined (32). The discovery of multiple conopressin sequences supports the theory that the scaffold of the original vasopressin-like endogenous peptide in Conus has evolved for more specialized use in the venom (14).

Finally, the exocyclic tripeptide of Con-T has a Leu in position 7 and a Val in position 9. To our knowledge, Con-T is the first naturally occurring vasopressin-like peptide with substitutions at these positions (Table 4). Although substitutions within the tocin ring and at position 8 have been largely investigated over the past 50 years using natural and nonnatural amino acids, there has been limited study on positions 7 and 9, probably because of their absolute conservation in this peptide family. AVT acts as an agonist on AVP receptors (33), and since L7P-Con-T differs from AVT only at position 9 and acts as a V1a antagonist, it appears that modification at this position alone can switch peptide activity from agonist to antagonist. In support of this hypothesis, the modification G9V in OT and AVP indeed switched their activity to a full antagonist at the V1a receptor. Thus, all endogenous peptides in the AVP-like family have a Gly9 (see Table 4) and act as agonists on their respective receptors, whereas

![Figure 4. Three-dimensional structures of Con-T (left; BMRB code 2007) and L7P-Con-T (right; BMRB code 2008). A, superimposition of the 20 lowest energy structures. B, ribbon representation showing the backbone trace and cysteine connectivity (yellow). C, stick representation for each representative structure.](http://www.jbc.org/)

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Conopressin-T</th>
<th>L7P-Conopressin-T</th>
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<tr>
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<td>5</td>
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<td>i – j</td>
<td>&lt; 4)</td>
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<td>Long range (</td>
<td>i – j</td>
<td>&gt; 5)</td>
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<tr>
<td>Δ restraints</td>
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<td><strong>Structure Statistics</strong></td>
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<td>Distance constraints (Å)</td>
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<td>Maximum dihedral angle violation (degrees)</td>
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<tr>
<td>Maximum distance constraint violation (Å)</td>
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<td>Deviations from idealized geometry</td>
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<td>Bond lengths (Å)</td>
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<td>Bond angles (degrees)</td>
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<td>Improper (degrees)</td>
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<td>Average pairwise root mean square deviation* (Å)</td>
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<tr>
<td>Heavy atoms (residues 1–6)</td>
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* Pairwise root mean square deviation was calculated among 20 refined structures.
Con-T, L7P-Con-T, G9V-OT, G9V-AVP, and a synthetic OT analogue with a Tyr\(^{\beta}\) (34) act as antagonists. In contrast, all Val\(^{\gamma}\)-containing peptides investigated here acted as partial agonists at the OT receptor.

The three-dimensional structures of conopressin-T and its L7P analogue were determined using NMR spectroscopy. Although the peptides are only 9 residues in length, well defined structures were determined for residues 1–6, presumably as a result of the constraints imposed by the disulfide bond between Cys\(^{1}\) and Cys\(^{9}\). The C-terminal regions are disordered but are oriented differently between the two peptides, indicating that Leu\(^{7}\) has a significant influence on the overall structure of conopressin-T. This structural shift probably contributes to the relatively poor solubility of Con-T. Given that the orientation of the exocyclic residues is influenced by Pro\(^{7}\), it appears that this relatively short stretch of peptide acts independently to determine peptide activity, since the pharmacological profiles of Con-T and L7P-Con-T are somewhat similar.

Comparison of the Con-T and L7P-Con-T structures with oxytocin and vasopressin highlights the similarity between all of the structures (supplemental Fig. 2). In particular, the loop between the two cysteine residues is structurally similar, with root mean square deviations of less than 1.5 Å for all structures. The C-terminal tails of Con-T and L7P-Con-T, although somewhat disordered, do not overlay well with the tail region of vasopressin or oxytocin. The proline residue in L7P-Con-T is in a trans conformation, but there is evidence for a minor conformation that may originate from a cis proline isomer. The proline geometry in OT and AVP has been extensively studied, with small percentages (~10%) of cis isomers in the solution conformations of these molecules (35). This finding is consistent with the current study as the population of the minor conformation of L7P-Con-T is ~7% based on relative peak intensities. Previous studies have shown that a cis/trans conformational change plays a role in OT receptor binding and activation (36), but significant differences are not observed for the affinity of Con-T and L7P-Con-T for the OTR, suggesting that cis/trans isomerization is less important for the affinity of these peptides.

The V\(_{1a}\) receptor was recently reported to play a major role in spatial memory (37), heart hypertrophy (38), and hyperfiltration (39). Selective inhibition of this receptor subtype may therefore have important therapeutic applications. The antagonist action of conopressin-T, as well as the determination of its three-dimensional structure, offer novel insights into the structure-activity relationship within the vasopressin peptide family that may guide the synthesis of novel analogues modified at positions 7 and 9 toward the design of highly selective V\(_{1a}\) antagonists.

Acknowledgments—We thank Vera Boulay for technical assistance (IGF, France), Andreas Brust and Barbara Colless (Xenome Ltd., Brisbane, Australia) for the HF cleavage and analytical HPLC peptide quantification of the synthetic peptides, Marion Loughnan for the preparation and fractionation of Conus tulipa crude venom, Alun Jones for the MS-MS experiments, and Jin Ai-Hua and Gene Hopping for fruitful discussions.

REFERENCES


| Table 4: Vasopressin-like peptide family |

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<tr>
<th>Name</th>
<th>Sequence</th>
<th>Species or phylum</th>
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<td>CYQRNCPTG*</td>
<td>C. tulipa</td>
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<td>Glumitocin</td>
<td>FLQQRNCPTG*</td>
<td>Cartilaginous fishes</td>
</tr>
<tr>
<td>Valitocin</td>
<td>FLQQRNCPTG*</td>
<td>Cartilaginous fishes</td>
</tr>
<tr>
<td>Aspargtocin</td>
<td>FLQQRNCPTG*</td>
<td>Cartilaginous fishes</td>
</tr>
<tr>
<td>Phasvatocin</td>
<td>FLQQRNCPTG*</td>
<td>Cartilaginous fishes</td>
</tr>
<tr>
<td>Mesotocin</td>
<td>FLQQRNCPTG*</td>
<td>Lungfishes, marsupials</td>
</tr>
<tr>
<td>Isotocin</td>
<td>FLQQRNCPTG*</td>
<td>Osteichthyes</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>FLQQRNCPTG*</td>
<td>Mammals</td>
</tr>
</tbody>
</table>

* An asterisk indicates an amidated C-terminal. A represents a γ-carboxylglutamate.
SAR of Conopressin-T


Membrane Transport, Structure, Function, and Biogenesis:
Conopressin-T from Conus tulipa Reveals an Antagonist Switch in Vasopressin-like Peptides

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