Laser Raman Spectroscopy and Circular Dichroism Studies of the Peptide Hormones Mesotocin, Vasotocin, Lysine Vasopressin, and Arginine Vasopressin

CONFORMATIONAL ANALYSIS*

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Peptide backbone, disulfide bond conformations, and other salient structural features of the naturally occurring neurohypophyseal hormones mesotocin, vasotocin, arginine vasopressin, and lysine vasopressin were examined by laser Raman and circular dichroism spectroscopy. Judging from the amide I and III in-plane peptide bond vibrational bands of their Raman spectra, these naturally occurring peptide hormones all have similar peptide backbone conformations. The circular dichroism results also indicate that the gross conformational features of these compounds are similar but further indicate that some increased relative rigidity in the backbone obtains for the vasopressins and at lower pH for all the compounds due to local intramolecular interactions. The conformations about the disulfide bond of all of the native hormones examined are similar, giving a major S-S stretching band at ~510 cm⁻¹ in their Raman spectra, and in some cases a minor band at 534 cm⁻¹. A gauche-gauche-gauche conformation of the C-C-S-S-C-C moiety is possible, but contributions from other conformations are apparent. This is further indicated by the circular dichroism spectra of these compounds which under a variety of conditions show substantial contributions from the disulfide n→π* transition at wavelengths greater than 290 to 300 nm, indicating contributions from conformations of the C-S-C moiety with dihedral angles ±120° (or less likely ±60°).

The intensity of the tyrosine doublet lines at 850 and 830 cm⁻¹ indicate that all four neurohypophyseal hormones examined have tyrosine aromatic side chain exposed to the outside of the 20-membered ring of the hormone molecule, as was found for oxytocin.

The similarities of the conformational properties of the oxytocin-like and vasopressin-like hormones is briefly discussed in terms of their biological and pharmacological activities.

Oxytocin and vasopressin are neurohypophyseal hormones with similar structural features, each possessing a 20-membered disulfide-containing ring and a tripeptide side chain as shown:

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† The abbreviations used are: AVT, arginine vasotocin; MT, mesotocin; OT, oxytocin; AVP, arginine vasopressin; LVP, lysine vasopressin; Pen, half-penicillamine. The abbreviations used for amino acids are the standard abbreviations recommended by the IUPAC-IUB Commission on Biochemical Nomenclature.
Spectroscopic Methods

Laser Raman Spectroscopy—The Raman systems used in the investigation are similar to those described previously (1, 2). The Raman spectra were obtained with 514.5 nm line excitation (Spectra-Physics, model SP-164 argon ion laser) with a green interference filter and were recorded on a Spex Ramalog 5. Lyophilized powder was used for the spectra. For deuteration, the samples were dissolved in D2O and allowed to stand for 1 hr or more, after which the sample was lyophilized. This procedure was repeated twice for complete deuterium exchange. The spectra were obtained by placing the deuterated samples in a sealed glass container saturated with D2O vapor.

In some samples (mesotocin, vasotocin), there was considerable fluorescence background. The intensity of fluorescence can frequently be reduced by baking the sample with laser radiation for several hours. For mesotocin and vasotocin, the samples were exposed to the laser beam overnight. However, from 900 to 1200 cm\(^{-1}\) regions, the fluorescence background remains undesirably high even though the spectra are good enough for analysis (Figs. 1 and 2) of the important bands. Fortunately, there is very little fluorescence background above 1200 cm\(^{-1}\); thus, the peptide conformation analysis based on the amide II band frequency. However, judging from the amide I frequencies of mesotocin, vasotocin, and arginine vasopressin at 1662 to 1672, 1668 to 1674, and 1676 (1676) cm\(^{-1}\), respectively, the possibility of any a conformation can be excluded (Table I, Figs. 1 to 4). The amide III band originates from “in-plane” vibration of the peptide bond, but the main contribution comes from the bending motion of an -NH. Thus, the exchange of hydrogen with deuterium should shift the amide III by a factor of \(\sqrt{2}\) while the amide I should not significantly change its frequency. For instance, the amide

### Table I

Comparison of characteristic Raman lines of neurohypophysial hormones

<table>
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<tr>
<th>Compounds</th>
<th>Amide I</th>
<th>Amide III</th>
<th>(\theta_\text{m}), Reference</th>
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<td>516 (m) This paper</td>
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<td>534(s)</td>
<td></td>
</tr>
<tr>
<td>[Gly(^4)]Oxytocin</td>
<td>1670</td>
<td>1270</td>
<td>510 (m) This paper, 3</td>
</tr>
</tbody>
</table>

* m, main peak; s, shoulder.

RESULTS

Laser Raman Spectra—The frequencies of the amide I and III bands are most frequently used for the determination of peptide backbone conformation. The amide I band arises from the coupled C=O stretching vibrations of the peptide bond. The \(\alpha\) conformation normally appears in the region of 1650 to 1658 cm\(^{-1}\); random coil, at 1643 to 1666 cm\(^{-1}\); and \(\beta\) sheet conformation, in the region of 1665 to 1680 cm\(^{-1}\) (13, 14). With sea snake neurotoxins which contain both \(\beta\) sheet and \(\alpha\) turn structure, the amide I appears at 1672 cm\(^{-1}\) (15-17). Oxytocin contains a 20-membered ring, and in aqueous solution probably possesses a reverse turn structure with no intramolecular hydrogen bonds. Both oxytocin and [Gly\(^4\)]oxytocin have very high amide II bands at 1663 to 1670 cm\(^{-1}\) (1, 2). The amide I originates from the coupled C=O stretching vibrations of peptide bonds. Oxytocin and [Gly\(^4\)]oxytocin, by virtue of their 20-membered cyclic ring moieties, possess a reverse turn structure, but there is no evidence that they possess intramolecular hydrogen bonds in aqueous solution (18, 21, 45). [Pen\(^4\)]Oxytocin\(^1\) (50), an oxytocin antagonist, possesses two 1 → 3 turns with intramolecular hydrogen bonds in aqueous solution and has a different conformation than oxytocin (21, 45). [Pen\(^4\)]-Oxytocin also possesses a high amide I frequency at about 1666 to 1668 cm\(^{-1}\) (2). Apparently, turn structures tend to give high amide I frequencies comparable to \(\beta\) sheet structures and, thus, it is difficult to differentiate various reverse turn structures from \(\beta\) sheet structures on the basis of the amide I band frequency. However, judging from the amide I frequencies of mesotocin, vasotocin, lysine vasopressin, and arginine vasopressin at 1662 to 1672, 1668 to 1674, and 1676 (1676) cm\(^{-1}\), respectively, the possibility of any a conformation can be excluded (Table I, Figs. 1 to 4).

Frequencies of 516, 516, and 510 cm\(^{-1}\), respectively. Apparently, all of these compounds have C-C-S-S-C-C conformation and [Gly\(_4\)]oxytocin. Maxfield and Scheraga (3) obtained similar results for LVP. MT, AVT, and AVP also give very similar 

III band of sea snake neurotoxin which occurs at 1240 to 1248 cm\(^{-1}\) shifted to 970 cm\(^{-1}\) when —NH was exchanged to —ND (15, 16). The amide III shifted by the factor of 1.30 which is close to the theoretical value of \(\sqrt{2}\). Mesotocin, vasotocin, AVP, and LVP have major bands at 1278, 1278, 1274, and 1275 cm\(^{-1}\), respectively, in the Raman, with other bands also apparent in the region of the amide III band. When these compounds were deuterated, the major peaks disappeared and new peaks at 1254, 1263 and 1240, 1263 and 1248, and 1249 cm\(^{-1}\), respectively, appeared for the compounds mentioned. These results support the assignment of 1278, 1278, 1274, and 1275 cm\(^{-1}\) bands, respectively (Table I), to the amide III for the above compounds. Normally, a \(\beta\) sheet conformation gives a low amide III frequency of 1231 to 1240 cm\(^{-1}\), random coil conformation, at 1242 to 1251 cm\(^{-1}\); and the \(\alpha\) helix conformation gives very high values of 1261 to 1295 cm\(^{-1}\) (13, 14). From NMR, CD, and Raman (1, 2, 18-21) studies, it has been suggested that in aqueous solution, oxytocin and [Gly\(_4\)]oxytocin have no strong intramolecular hydrogen bonds but probably possess reverse turn structures. These compounds give a high amide III frequency of 1266 and 1270 cm\(^{-1}\) (2). Snake neurotoxins known to have both \(\beta\) sheet and reverse turn structure also give high amide III frequencies (15-17). The high frequency amide III found for the compounds studied here suggest that they all contain structures quite similar to that in oxytocin.

Raman spectroscopy has been used extensively for the conformational study of the disulfide bond (2, 3, 92-25). LVP gives an S-S stretching vibrational frequency of 510 cm\(^{-1}\) (Table I, Fig. 4) which is about the same as that of oxytocin and [Gly\(_4\)]oxytocin. Maxfield and Scheraga (3) obtained similar results for LVP, MT, AVT, and AVP also give very similar frequencies of 516, 516, and 510 cm\(^{-1}\), respectively. Apparently, all of these compounds have C-C-S-S-C-C conformation which are very similar to that of oxytocin. MT and AVP also contain a small shoulder at ~534 cm\(^{-1}\). According to the simple interpretation of Sugeta and Miyazawa (22), an S-S band at ~540 cm\(^{-1}\) indicates the presence of a trans-gauche-trans form for these compounds in addition to the gauche-gauche gauche form of the other compounds. However, as Van Wart and Scheraga (23-25) and Maxfield and Scheraga (3) have discussed, a type A conformation (A-S-S-C-C ~20-30°) is likely in the latter two cases, and a contribution from a trans conformation cannot be excluded in the other cases.

It is well known that the relative intensities of the Raman lines at 850 and 830 cm\(^{-1}\) are related to the environment of the tyrosine side chain (25, 26). This interesting and important doublet line originates from the Fermi resonance between the ring-breathing vibration and the overtone of an out-of-plane ring bending vibration of the \(\beta\) substituted benzene (27). All four compounds investigated have 1 tyrosine residue within a ring. The important question is whether the tyrosine side chain is folded inward into the ring or exposed to the outside of the ring. All four compounds (Figs. 1 to 4) show a much higher Raman intensity at 850 cm\(^{-1}\) than at 830 cm\(^{-1}\). This indicates that the tyrosine side chains of all four compounds are exposed to the outside.

**Ultraviolet Spectra**—The ultraviolet absorbance spectra of mesotocin, arginine vasotocin, lysine vasopressin, and arginine vasopressin were determined and the results are summarized in Table II. All of the above compounds have an aromatic tyrosine residue in position 2 of the hormone, and LVP and AVP also have a phenylalanine residue in position 3. In all cases, the spectra above 220 nm are dominated by the \(\pi-\pi^*\) transitions of the aromatic ring in tyrosine at about 275 nm. All of the other chromophores which are expected to be UV-active and thus be observable, namely the phenyl group of the phenylalanine residue in AVP and LVP, the very weak (electric dipole forbidden) \(n-\pi^*\) absorptions at ~230 nm (28) of the disulfide moiety found in all the compounds, and the amide band, are not observed as distinct maxima or even as shoulders in the UV spectra of MT, AVT, LVP, or AVP. Contributions from these chromophores, however, are apparent from the intensity of the bands at lower wavelengths.

**Circular Dichroism**—The circular dichroism spectra for aqueous solutions of mesotocin, vasotocin, lysine vasopressin, and arginine vasopressin. At a number of pH values are shown in Figs. 5 to 7, and the data for the major observed transitions are summarized in Table II. The results can be compared with the published CD spectra of oxytocin (29-31), arginine vasopressin (32), and other related neurohypophysial hormone analogs (2, 29-34). The assignments for the major transitions can be made with the aid of these previous investigations. Since mesotocin closely resembles oxytocin in its structure (Ile is substituted for Leu in position 8), the CD of this compound will first be discussed. AVT will be presented next since it possesses the same ring moiety as oxytocin and the same tripeptide side chain as AVP. AVP and LVP then will follow.

As expected, the CD spectra of mesotocin (Fig. 5) are very similar to that of oxytocin under conditions where comparisons can be made (29-31). The strong negative band found at ~210 nm at all pH values is due primarily to the \(\pi-\pi^*\) transition of the amide groups (31), with perhaps some small contribution from the tyrosine chromophore. Since this band is not significantly affected by pH changes, it suggests that the backbone conformation of the peptide is not fundamentally affected by pH changes. The large positive band at ~225 nm at neutral pH is a composite band which includes the tyrosine \(\pi-\pi^*\) transition and the amide \(n-\pi^*\) transition (2, 29, 31). The presence of the tyrosine \(\pi-\pi^*\) transition is clearly seen in the red shift of this peak to ~242 nm at basic pH. A weak positive
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Table II
Circular dichroism and ultraviolet spectral data for mesotocin, vasotocin, lysine vasopressin, and arginine vasopressin

*sh, shoulder.
Laser Raman and CD for oxytocin and especially Leu-Oxytocin (2), this is a significant contributor in these compounds is obtained from observations on the breadth of this band (cf: Refs. 2 and 3), especially its significant molar ellipticity above 300 nm at acid pH. As in oxytocin (3) and various analogs (29, 31), the neutral and acidic pH values. This is the case for mesotocin where the ellipticity above 300 nm is greater than in oxytocin. The pK, of the tyrosine group in oxytocin (31), and in the CD of oxytocin (29) and mesotocin (Fig. 5), the band at 280 to 290 nm becomes positive. This probably results from a change in the optical activity of the ionized tyrosine residue, but a change in the disulfide transition as a result of a charge on the tyrosine residue cannot be ruled out.

There are many qualitative similarities in the CD spectrum of arginine vasotocin (Fig. 6) and mesotocin (Table II), especially at pH 7.4 to 7.5 where the spectra are virtually identical. At this pH, the negative composite band at 280 nm due to the disulfide n-\sigma* and the tyrosine \pi-\pi* transitions, and the positive 250-nm band, seen at 247.5 nm and assigned to the disulfide n-\sigma* transition, are about 3 times more intense than the comparable bands found in mesotocin (Table II) or in oxytocin (31). Though the overall features of the CD spectrum of AVT and MT are apparent, several quantitative differences should be noted. In the first place, at acid pH, especially pH 2.0, the intense positive band at 225 nm due to the tyrosine \pi-\pi* and the peptide backbone amide n-\pi*, has significantly greater molar ellipticity. This suggests, as previously discussed for oxytocin and its analogs (2, 31), that the protonation of the \alpha-amino group in position 1 of oxytocin leads to an attractive interaction between the positive charge of the amino group and the \pi-electron system of the aromatic ring, which results in a decrease in the conformational flexibility of the hormone, and an increase in molar ellipticity due to conformational stabilization of the tyrosine residue and peptide backbone in the vicinity of the tyrosine. Of special note also is the increased intensity of the long wavelength negative band at -280 nm in AVT relative to that in MT, and most other oxytocin analogs (29-34). The intensity of this band is generally about 3 times that in MT or oxytocin. This appears to be due to an increased negative contribution of the disulfide n-\sigma* contribution. This is seen not only by the substantial ellipticity of these bands above 300 nm at neutral and acidic pH values. This is the case for mesotocin where the ellipticity above 300 nm is greater than in oxytocin. As in oxytocin (3) and various analogs (2, 29, 31, 34), the disulfide n-\sigma* transition in mesotocin appears to have a negative ellipticity. This is suggested by the observation that the intensity of the negative band at neutral and acid pH is slightly greater than that of the positive band observed at basic pH (in oxytocin which has a negative disulfide n-\sigma* transition at -280 nm, the positive band at pH 10.6 at 290 nm is much more intense than the native band at -280 nm at neutral or acidic pH). The pK, of the tyrosine group in oxytocin derivatives occurs at -9.7 (35), and in the CD of oxytocin (29) and mesotocin (Fig. 5), the band at 280 to 290 nm becomes positive. This probably results from a change in the optical activity of the ionized tyrosine residue, but a change in the disulfide transition as a result of a charge on the tyrosine residue cannot be ruled out.
band in oxytocin (29, 31). As previously discussed by Fríč et al. (32) for AVP and several of its analogs, this band is a composite band of the tyrosine π-σ* transition and of the amide n-σ* transition. This is particularly clear at pH 10.5 where the tyrosine π-σ* transition is shifted to ~245 nm, but a residual band remains at 225 nm. The increased intensity of this band can be ascribed to interaction of the Tyr-2 and Phe-3 aromatic groups in these molecules at neutral and acid pH (32), as has been observed in proton magnetic resonance studies (36). This interaction should cause an increased rigidity of the side chains in these 2 residues and of the peptide backbone in this vicinity leading to an increased intensity. Similar enhancement of these transitions by more rigid structures in this vicinity have been previously noted (2, 30-31). The broad, long wavelength band centered at about 280 to 285 nm in LVP (AVP contains contributions from both the tyrosine and phenylalanine π-σ* transitions, and from the disulfide n-σ* transitions (32). Although analysis of the disulfide contribution is difficult due to the other chromophores which contribute to this band, the results obtained under certain conditions provide some new insight. For example, at pH 3.5, the LVP spectra (Fig. 7) show a distinct shoulder at ~300 nm which can only be due to the disulfide n-σ* chromophore (as shown by Fríč et al. (32), the Tyr chromophore has essentially no rotatory contribution above 290 nm). Significant negative molar ellipticities are seen above 290 nm for LVP under the other neutral and acidic conditions. Similar results are seen for AVP, and at pH 10.5 a weak negative band is observed at 315 nm which can only be due to the disulfide n-σ* transition. These results add support to the suggestions of Maxfield and Scheraga (3) that contributions to the disulfide band come from conformations with a dihedral angle >120° or <60°. Since these transitions are the long wavelength transitions for the disulfide n-σ*, a quadrant rule applies (37, 38) which predicts a relationship of the sign of the longest wavelength transition and the chirality (left- or right-handedness) and dihedral angle (38, 39) of the C-S-S-C moiety. Assuming a dihedral >120°, a right-handed chirality is predicted for the negative band observed, and vice versa if the dihedral angle is <60°. However, the latter is unlikely since disulfide dihedral angles less than 75° are rare even in proteins (see Ref. 23 (Table IV) and Ref. 24 (Fig. 3)).

DISCUSSION

Previous investigations of the conformational and dynamic properties of oxytocin (18-22, 40-47) and the vasopressins (43, 44, 47, 48) in aqueous solution using primarily NMR studies have indicated that these compounds possess similar average conformations and considerable conformational flexibility with a possible turn structure in the cyclic moiety, but no intramolecular hydrogen bonds. To further investigate similarities and differences in the conformational properties of these and related natural hormones, we have utilized laser Raman in conjunction with CD spectroscopy and examined mesotocin which is nearly identical with oxytocin (Ile-8 replaces Leu-8), and AVP and LVP. To help in the analysis of the structural differences of these hormones, we have examined another neutral hormone, AVT, which possesses the 20-membered ring moiety of oxytocin and mesotocin, but differs in the triple peptide side chain of AVP.

The Raman and CD spectroscopic studies reported here support the idea that the overall conformational properties of the native hormones examined here are quite similar, but somewhat different than some neurohypophysial hormone inhibitors (2, 21). Thus, for example, the amide I and amide III bands, and the S-S stretching vibrations are all very similar to those found previously for oxytocin (1-3), but the latter two bands are quite different from those found in certain antagonists (2). In regard to Fs-S, our Raman results for the major peak in LVP are in agreement with those reported earlier (3), and we also find some indication for the small shoulder at ~525 cm⁻¹, which they report. However, this latter peak (shoulder) is seen much more clearly in MT and AVP (see Figs. 1 and 3) than in LVP. These results suggest that the conformation about the disulfide moiety is essentially the same in all of these native hormones, and the similarity of the amide III band in all of these compounds also suggests that their peptide backbone structures are very similar. The circular dichroism results also indicate that the gross conformational features of the oxytocin-like and vasopressin-like compounds are the same, although certain subtle conformational differences are apparent from these studies.

In corroboration of the suggestions of Maxfield and Scheraga (3), our results indicate that disulfide dihedral angles substantially different from 90° can obtain for at least some contributing conformations in aqueous solution of MT, AVT, LVP, and AVP. Additional evidence is presented here that a substantial contribution from disulfide dihedral angles of about 120° with a right-handed chirality exists for all of these compounds. The major difference between oxytocin-like compounds, such as AVP and LVP, is in the increased local rigidity about the tyrosine-2 residue of the latter two compounds, which apparently has its origin in the interaction of the aromatic rings of the Tyr-2 and Phe-3 residues (36). Further work with appropriately substituted oxytocin and vasopressin analogs will be necessary to evaluate more completely these differences.

The similarities in the conformational properties of oxytocin- and vasopressin-like molecules is reasonable from a biological point of view since, although these molecules have different physiological roles, there is considerable overlap in their biological and pharmacological activities (for a review see Ref. 49). The complementary nature of laser Raman and spectroscopy methods in conformational and structural studies indicate that these physical methods will be useful in further studies of peptide hormone agonists and antagonists.

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3278 Laser Raman and CD of Mesotocin, Vasotocin, and Vasopressins


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Conformational analysis.

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