Secretory pattern of vasopressin in plasma and cerebrospinal fluid of patients with dementia and of two control groups

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Since the description of its antidiuretic effect in 1913, a variety of functions have been attributed to vasopressin, one of the most controversial throughout the years probably being its effect on memory processes. In an attempt to study the actual secretory rhythm of vasopressin in humans with demonstrated impaired memory, the plasma and cerebrospinal fluid levels of the peptide have been examined during 24 h in a group of patients with dementia, and their values compared with two healthy control groups of young and elderly volunteers. Patients with dementia had higher circulating levels of vasopressin in plasma than the healthy participants and the differences were statistically significant when compared with the healthy elderly (p = 0.003). This difference is not age-related because both groups were in the same age range. A possible explanation could be the higher plasma osmolality measured in the patients with dementia, despite the fact that their levels were within the normal ranges. The different results could not be attributed to changes in electrolytes or blood pressure because these parameters were similar in all groups (p = NS). But more interesting, perhaps, is the secretory pattern found in all three groups. The pattern is biphasic, with two significant peaks: at 16.00 h (p = 0.032) and at night (p = 0.002). This pattern was similar in all cases and in all groups. The total nocturnal secretion of vasopressin is higher than the diurnal secretion (p = 0.02) only in the plasma because the cerebrospinal fluid values were higher during the day. In contrast to plasma, no significant difference was found in the levels of vasopressin in cerebrospinal fluid between patients with dementia and the healthy groups. Furthermore, the correlation between plasma and cerebrospinal fluid levels was, as a whole, rather poor in our material but better in the healthy young volunteers. It seems evident, in view of these results, that the postulated relationship between vasopressin and memory cannot depend on an inadequate concentration of the hormone in the cerebrospinal fluid because all our groups showed similar values. Several hypotheses are given to explain the secretory pattern found in our material as well as for the differences in plasma between the patients with dementia and the control groups.

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Although the antidiuretic effects of extracts obtained from the posterior pituitary gland were described as early as 1913 (1), the structure of vasopressin (AVP) remained unknown for more than 40 years (2). Since then, while maintaining its paramount role as an antidiuretic hormone, many properties other than its primary endocrine function have been suggested. It is also used in the treatment of certain bleeding disorders (3) and nocturnal enuresis (4). Vasopressin as coadjuvant therapy in some forms of headache (5) and postural hypotension (6) also has been postulated. Although it is used in schizophrenia (7) and dementia (8), its role is questionable. Implication of AVP in learning processes and memory functions are even more controversial. The subject has been studied extensively; whilst several reports indicate improvement in memory (9-12) and partial reversal of retrograde amnesia (13), others have failed to confirm such results (14-18). Confusion may have arisen because none of these studies measured AVP levels. Furthermore, the blood–cerebrospinal barrier seems to be practically impermeable to AVP (19).

In an attempt to find out if patients with disturbed memory function present irregular secretion of AVP, we have studied the 24-h secretory rhythm of AVP in plasma and cerebrospinal fluid (CSF) in 10 elderly patients with dementia and compared the findings with those of 11 age-matched healthy elderly volunteers. To determine the effects of ageing on the secretory pattern, we have studied also a group of nine healthy young volunteers.

Materials and methods
The participants in the first group were nine young, healthy volunteers (seven males and two females).
None of them had a history of metabolic, endocrine or psychological disturbance and their familial antecedents also were negative in this respect. They were recruited from hospital personnel, they were all non-smokers and they had not undergone any form of pharmacological treatment in the last 6 months. Their age ranged between 19 and 45 years (mean 28 years).

The second group comprised 11 healthy elderly volunteers (three males and eight females) aged 67–86 years (mean 75 years). As in the previous group, their personal and family medical history was negative and the physical examination previous to the study showed no pathology. All of them were retired, non-smokers and free of medication.

The third group comprised 10 hospitalized patients (three males and seven females) with dementia from our Psychogeriatric Unit, aged 63–83 years (mean 77 years). None of them had any medication that could influence AVP secretion, and their state of hydration was considered normal as assessed by clinical examination, plasma osmolality and electrolyte levels.

Blood pressure (supine and after 5 min of rest) was considered normal in all groups.

All healthy participants received oral and written information previous to the study and were perfectly aware of the nature and purpose of signing a written consent. In the case of the patients with dementia, their legal representatives received the same information and gave written consent. The study was approved by the ethics committee of the hospital.

All ambulatory participants were admitted to the hospital the evening before the day of the test. During the test they were allowed to move freely but rested in a recumbent position for at least half an hour before every extraction. Meals were served at the same time of the day but from midnight until the end of the test neither meals nor fluids were allowed.

Sampling methods

Blood and liquor samples were taken simultaneously at 4-h intervals, starting at 08.00 h (08.00, 12.00, 16.00, 20.00, 24.00 and 04.00 and 08.00 h). An 18-gauge catheter (Brown-Melsungen, Germany) was inserted intrathecally via the L3–L4 interspace at 07.00 h on the day of the test for the liquor sampling. Blood samples were obtained from an antecubital vein. The liquor samples were frozen in dry ice immediately after extraction and stored at −80°C. Blood samples were centrifuged at +4°C within 30 min of their collection and the separated plasma was also frozen at −80°C until assayed. Blood samples for the determination of osmolality and sodium and potassium levels were taken at 08.00 h, 24.00 h and again at 08.00 h.

Vasopressin determinations

Plasma samples were extracted with acetone/petroleum ether before analysis according to Standard Operating Procedures 340-502, version 2 (Ferring Pharmaceuticals, Malmö, Sweden). The recovery of AVP from spiked EDTA–plasma was 50.8% at 2.50 ng AVP/l and 61.3% at 7.50 ng AVP/l. The minimum quantifiable concentration (MQC) was 0.50 ng AVP/l plasma. Liquor samples were extracted in the same way. The recovery of AVP from spiked 0.9% sodium chloride with 0.01% human serum albumin was 52.9% at 2.50 ng AVP/l and 58.9% at 7.5 ng AVP/l. The MQC was 0.50 ng AVP/l liquor.

Statistical methods

The results were compared by means of repeated measurements MANOVA. The correlation between plasma and CSF levels was studied by means of Pearson’s correlation coefficient. A linear model (Y = a + bX) was used for regression analysis.

Results

The concentrations of plasma vasopressin (P-AVP) in the three groups studied are presented in Table 1 and the CSF concentrations (L-AVP) in Table 2. The plasma osmolality and the Na/K ratio are given in Table 3. The osmolality/AVP ratio is shown in Table 4 and the Na/AVP ratio in Table 5.

Plasma AVP

All groups presented a similar secretory pattern with two peak levels, the first at 16.00 h and the second during the night. The levels measured at 16.00 h were significantly higher than those at 12.00 h (p = 0.03).

Table 1. Plasma vasopressin levels (mean ± sem) in healthy young (group 1), healthy elderly (group 2) and in patients with dementia (group 3).

<table>
<thead>
<tr>
<th>Time</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>08.00 h</td>
<td>1.56 ± 0.24</td>
<td>1.61 ± 0.29</td>
<td>3.09 ± 0.49</td>
</tr>
<tr>
<td>12.00 h</td>
<td>1.53 ± 0.20</td>
<td>1.77 ± 0.36</td>
<td>2.90 ± 0.87</td>
</tr>
<tr>
<td>16.00 h</td>
<td>2.18 ± 0.34</td>
<td>3.30 ± 0.64</td>
<td>4.49 ± 1.15</td>
</tr>
<tr>
<td>20.00 h</td>
<td>2.03 ± 0.43</td>
<td>2.35 ± 0.36</td>
<td>3.27 ± 0.74</td>
</tr>
<tr>
<td>24.00 h</td>
<td>2.94 ± 0.78</td>
<td>2.72 ± 0.55</td>
<td>4.36 ± 0.78</td>
</tr>
<tr>
<td>04.00 h</td>
<td>2.83 ± 0.56</td>
<td>3.59 ± 0.67</td>
<td>4.98 ± 1.10</td>
</tr>
<tr>
<td>08.00 h</td>
<td>2.13 ± 0.33</td>
<td>2.19 ± 0.41</td>
<td>3.58 ± 1.05</td>
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</tbody>
</table>

Table 2. Cerebrospinal fluid vasopressin (ng/l) levels (mean ± sem) in healthy young (group 1), healthy elderly (group 2) and in patients with dementia (group 3).

<table>
<thead>
<tr>
<th>Time</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>08.00 h</td>
<td>1.01 ± 0.03</td>
<td>1.13 ± 0.06</td>
<td>1.16 ± 0.07</td>
</tr>
<tr>
<td>12.00 h</td>
<td>1.09 ± 0.06</td>
<td>1.21 ± 0.12</td>
<td>1.21 ± 0.08</td>
</tr>
<tr>
<td>16.00 h</td>
<td>1.09 ± 0.09</td>
<td>1.27 ± 0.07</td>
<td>1.23 ± 0.07</td>
</tr>
<tr>
<td>20.00 h</td>
<td>1.16 ± 0.07</td>
<td>1.07 ± 0.06</td>
<td>1.28 ± 0.08</td>
</tr>
<tr>
<td>24.00 h</td>
<td>1.14 ± 0.06</td>
<td>1.15 ± 0.05</td>
<td>1.17 ± 0.06</td>
</tr>
<tr>
<td>04.00 h</td>
<td>0.89 ± 0.06</td>
<td>1.08 ± 0.08</td>
<td>1.07 ± 0.07</td>
</tr>
<tr>
<td>08.00 h</td>
<td>1.29 ± 0.11</td>
<td>1.17 ± 0.12</td>
<td>1.14 ± 0.08</td>
</tr>
</tbody>
</table>
Also, the levels at 04.00 h were higher than the previous levels and the differences between them and those measured at 20.00 h also were statistically significant (p = 0.002). The patients with dementia also had significantly higher levels than the age-matched healthy group (p < 0.003).

The secretion of AVP was higher during the night and although the difference between the night and day peaks was not significant, the total nocturnal secretion (from 20.00 h until 08.00 h) was significantly higher than the diurnal secretion (p = 0.002).

Liquor (CSF)

The pattern of secretion here also was similar in all groups, increasing slowly from 08.00 h until 20.00 h in groups 1 and 3 (group 2 showed a decrement at 20.00 h) and then decreasing progressively until 04.00 h, with a new increase afterwards. No significant difference was found in the AVP levels between the three groups at any moment of the test and the characteristic biphasic pattern found in the plasma was absent. Also, in contrast with plasma levels, the CSF concentration of AVP was higher during the day and lower during the night.

The correlation between plasma and CSF levels was significant in samples taken at 16.00 h (p = 0.043), 24.00 h (p = 0.019) and 04.00 h (p = 0.047) in the young healthy group and at 04.00 h (p = 0.022) in patients with dementia. No significant correlation was found in the healthy elderly group at any time.

Plasma osmolality

Although plasma osmolality was within the normal range in all cases, it was higher in the patients with dementia than in the healthy young group (p = 0.003) and also higher than in the healthy elderly group (p = 0.02). Even the differences in the osmolality/AVP ratio were statistically significant (p = 0.036) when these two groups were compared, but not when the patients with dementia were compared with the healthy young group (p = 0.14).

Serum electrolytes

These parameters also were within the normal range and similar in all groups (p = NS). Nevertheless, when the Na/AVP ratio was considered, a statistical difference was found between the group of patients with dementia and the healthy elderly group (p = 0.006), as well as between the two healthy control groups (p = 0.04).

Correlation between osmolality, electrolytes and AVP

Plasma osmolality and AVP had a poor correlation, never reaching statistical significance. A better correlation was found between Na levels and AVP concentration, but solely in the healthy elderly group and only in the samples at 24.00 h (p = 0.04) and at 08.00 h (p = 0.03).

Discussion

Although the secretion of AVP is mediated by a number of individual factors (serum osmolality, plasma volume, stress, etc.), we have found a pattern of secretion in plasma that was similar and constant in all the studied groups, with two secretory peaks during the 24-h test, and was not related to any of the above factors. The levels measured at these peaks were statistically higher than the previous levels, giving a biphasic shape to the secretory pattern. As far as we know, this biphasic model has not been described before, but the fact that the same pattern is reproduced in all cases and in all groups gives a special strength to this finding.

The patients with dementia have higher circulating plasma levels than the other groups and differ significantly from the healthy elderly group (p = 0.003). This
difference is not age-related because both groups were in the same age range.

It is well known that even mild increases of osmolality result in increases in AVP and, certainly, our demented patients had higher osmolality than the healthy groups. Although in absolute terms all three groups had osmolality values within the normal range levels, we cannot ignore the possible role of these minor increases upon the secretion of AVP. Another hypothetical explanation to the higher AVP levels found in the patients with dementia could be the possible existence of an impaired receptor sensitivity in such patients, but our study was not designed with that purpose. This insensitivity might be important enough to require higher concentrations of circulating hormone but not great enough to disturb the physiological rhythm. This difference has not been found in the CSF.

The plasma levels were higher during the night in all three groups. This possibly expresses the physiological function of the hormone at peripheral levels, namely to achieve a more powerful antidiuretic effect during those hours. We think that the peak appearing at 16.00 h also fills the same physiological function during the middle part of the day. The fact that even our patients with dementia, all of them with urinary incontinence, had higher plasma levels at night does not support a possible hormonal aetiology to their incontinence. This pattern is, nevertheless, inverted in the CSF, where the levels are higher during the day. In all animal species in which a rhythm is present, the AVP levels seem to follow the light–dark period pattern: this may also be so in humans. It seems reasonable to think that the different physiological role of AVP at these two levels (as a neurotransmitter only in the CSF and as an antidiuretic hormone at the peripheral level) might be responsible for this distinct pattern between plasma and CSF.

Considered as a whole, the correlation between plasma and CSF levels is rather poor because only on very few occasions (and mainly in the healthy young group) was it significant. We do not have any definite explanation for these results at the moment.

Much has been speculated about the possible influence of AVP on the memory processes. We can neither confirm nor rule out this possibility with our study, but it seems evident in view of our results that if such an effect upon memory exists, this cannot be due to insufficient hormonal liquor levels in patients with dementia because their values during the test period did not differ from those of the healthy participants. Further studies, including the viability and the response of the central receptors to CSF AVP, are needed to clarify this question.

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References

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