The osmotic thresholds for thirst and vasopressin release are similar in healthy man

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(Received 28 February/6 May 1986; accepted 1 July 1986)

Summary

1. The relationship between thirst perception and plasma osmolality was studied during hypertonic and physiological saline infusion in ten healthy volunteers.

2. Thirst perception was quantified using a linear visual analogue scale which volunteers marked at intervals during the infusion periods.

3. Infusion of hypertonic saline caused a steady rise in plasma osmolality together with a progressive linear increase in thirst perception and also plasma arginine vasopressin. No significant changes in thirst, plasma osmolality or plasma arginine vasopressin occurred during infusion of physiological saline.

4. Linear regression analysis of the results defined the functions. Thirst (cm) = 0.3 (plasma osmolality - 281) (r = + 0.92, P < 0.001) and plasma arginine vasopressin (pmol/l) = 0.4 (plasma osmolality - 285) (r = + 0.96, P < 0.001). The osmolar threshold for thirst onset thus defined (281 mosmol/kg) was much lower than in previous studies and similar to the theoretical osmolar threshold for vasopressin release (285 mosmol/kg).

5. We conclude that thirst perception rises in a progressive fashion throughout a wide range of plasma osmolality and that the osmolar threshold for thirst onset is similar to the theoretical osmolar threshold for vasopressin release.

6. The results are compatible with the concept of either a single osmoreceptor subserving both thirst and vasopressin release, or two osmoreceptors sharing similar functional characteristics.

Key words: drinking, osmoregulation, thirst, vasopressin.

Abbreviations: MAP, mean arterial blood pressure; pAVP, plasma arginine vasopressin; PCV, packed cell volume; pOsm, plasma osmolality.

Introduction

Body fluid homoeostasis in healthy man is maintained by regulation of renal water loss, principally by the hormone arginine vasopressin, and an adequate fluid intake dependent on an intact thirst mechanism. Verney first demonstrated that anti-diuresis followed the intercarotid injection of various solutes in dogs [1], and the characteristics of osmoregulated vasopressin release in man have since been well defined [2-5]. In these latter studies, however, thirst was described as an absolute sensation occurring at plasma osmolalities of approximately 299 mosmol/kg. More recently, however, studies utilizing a visual analogue scale have suggested a graded increase in thirst appreciation during progressive elevation of plasma osmolality with a hypertonic sodium chloride infusion in healthy volunteers [6]. As the mean peak plasma osmolality in this study [6] did not exceed 293 mosmol/kg, thirst was obviously experienced at lower plasma osmolalities than previously recorded [2-5]. In this study we have employed a new visual analogue scale to explore the characteristics of osmotically induced thirst throughout a wider range of plasma osmolalities than previously examined, and analysed the data to identify the osmolar threshold for thirst onset and its relationship to the theoretical osmolar threshold for vasopressin release.
Methods

Subjects

Ten healthy male volunteers on no regular medication were studied. Mean age was 24.3 years (range 20–30 years) and all were within ±20% of ideal body weight (range 60–90 kg, mean 75.2 kg). All subjects underwent infusion of hypertonic saline (855 mmol/l NaCl) on one occasion and six received physiological saline (150 mmol/l NaCl) on a separate occasion at an interval of not less than 2 months; in these subjects the order of infusion was randomized and the study performed single-blind. Subjects were told when recruited that they would receive an infusion of salt solution which would be either the same concentration as blood or of a higher concentration than blood. All patients gave oral consent to the studies which were approved by the local Ethical Committee.

Protocol

Before the studies, volunteers fasted, and abstained from tobacco, caffeine and alcohol for 12 h overnight, but were allowed free access to tap water. Studies commenced at 08.00 hours. Subjects voided urine, were weighed and had indwelling intravenous cannulae inserted into veins of both antecubital fossae: a Braunula 0.5 G-18 (Braun Melsunger AG) in the left for withdrawal of blood, and a Venflon 18G (Viggo Products Ltd) in the right for infusion of saline. After 30 min resting recumbent, two basal aliquots of blood separated by a 15 min interval were withdrawn into chilled syringes and transferred to chilled heparinized tubes. Infusion of either hypertonic or physiological saline was then commenced at 0.06 ml min⁻¹ kg⁻¹ for 2 h using an Infusomat II rotary pump (Braun Melsunger AG). Aliquots of blood were withdrawn at 30 min intervals during the infusion period and a further sample taken 15 min after the infusion had stopped. Thirst was recorded on a visual analogue scale at the times of blood sampling. Blood pressure was measured at 5 min intervals during the study by a Bosomat II automatic sphygmomanometer (Bosch & Sohn). Fluid was withheld during the infusion period though subjects were free to terminate the study at any time. At the end of the infusion, subjects again voided urine and after 15 min were allowed to drink tap water at room temperature. The volume of fluid imbibed in the first 2 h of drinking was noted.

Hypertonic saline infusion was repeated in four individuals in order to assess intra-individual variations in thirst response to osmotic stimulation.

Thirst ratings

Thirst was measured on an uncalibrated linear visual analogue scale [7] which was a modification of that of Rolls et al. [8] in that subjects defined their own thirst rating before infusion of saline rather than be assigned to zero thirst rating. Subjects were presented with an unmarked 10 cm line on a sheet of paper and asked to mark a point on the line which answered the question ‘How thirsty do you feel?’ between the extremes of ‘Not at all thirsty’ (0 cm) and ‘Very thirsty indeed’ (10 cm). The distance from the end representing ‘Not at all thirsty’ represented the thirst rating at that time.

Assay methods

Aliquots of blood were transferred into heparinized capillary tubes for measurement of packed cell volume (PCV) (Hawksley microhaematocrit centrifuge) and the remainder centrifuged at 4°C for 20 min, within 15 min of sampling, and the plasma separated. Plasma arginine vasopressin (pAVP) was measured by a sensitive and specific radioimmunoassay [9] after Florisil extraction of plasma (lower limit of detection 0.3 pmol/l, intra- and inter-assay coefficients of variation 9.7% and 15.3% respectively). Osmolality of plasma (pOsm) and urine was measured by the depression of freezing point method (Advanced Instruments Osmometer, model AD 3R).

Statistics

Mean arterial blood pressure (MAP) was calculated by adding one-third of pulse pressure to the diastolic blood pressure. Changes in blood volume were estimated from changes in PCV using standard formulae (Documenta Geigy Scientific Tables) and corrected for experimental blood loss. Values of pAVP, pOsm, thirst, MAP and PCV were compared at respective times during the infusion of physiological and hypertonic saline using unpaired Student’s t-tests. The relationship between pOsm and pAVP, and between thirst and pOsm, was calculated using linear regression analysis.

Results

The infusion of hypertonic saline caused a progressive linear increase in pOsm from 287±1 (mean ± SEM) to 306±1 mosmol/kg (P<0.001), of pAVP from 0.7±0.2 to 8.9±1.3 pmol/l (P<0.001), and of thirst from 2.2±0.3 to 7.7±0.3 cm (P<0.001). MAP rose from 92±2 to 98±2 mmHg (P<0.01) and PCV fell from 42±1 to
Vasopressin, thirst and osmoreceptors

Fig. 1. Mean responses of plasma osmolality, plasma vasopressin, thirst, mean arterial blood pressure, and packed cell volume to hypertonic saline infusion (–––) and physiological saline infusion (○–○). SEM for each point is marked. A single asterisk above points on the lines of responses to hypertonic saline infusion represent significant differences from corresponding points on lines of responses to physiological saline infusion where \( P < 0.01 \). Double asterisk represents differences where \( P < 0.001 \). LD on the graph for plasma vasopressin responses represents the lower limit of detection for vasopressin (0.3 pmol/l) on our radioimmunoassay.

The results demonstrate that in healthy humans, elevation of plasma osmolality by the infusion of hypertonic sodium chloride produces a graded increase in thirst appreciation throughout a wide range of plasma osmolality. Changes in thirst appreciation were evident when plasma osmolality was within the normal physiological range, and continued in a progressive fashion while subjects were clearly hyperosmolar. Plasma vasopressin rose in the linear fashion during hypertonic saline infusion but there were no changes in thirst or plasma vasopressin during infusion of physiological saline.

Our work confirms the findings of previous workers who have studied thirst during changes in plasma osmolality within the normal physiological range [6], and provides additional information on the perception of thirst when normal subjects are rendered hyperosmolar. In addition, our modification of the visual analogue scale used in previous studies [6, 8] has allowed us to examine the osmotic threshold for thirst. In previous studies a zero thirst rating was ascribed to each subject before the start of the experiment, thus prejudging thirst appreciation at that time. Our subjects were invited to define the raw data for changes in thirst and plasma vasopressin with elevation in plasma osmolality are shown in Fig. 2.

Subjects drank significantly larger volumes of water in the 2 h after hypertonic saline (1900 ± 240 ml) than in the 2 h after physiological saline (290 ± 30 ml) \( (P < 0.001) \). There was a close relationship between thirst ratings and volume of water drunk in the 2 h after hypertonic saline infusion \( (r = +0.92 ± 0.04, P < 0.01) \).

Simple linear regression analysis of plasma vasopressin and plasma osmolality was applied to the results of hypertonic saline infusion for each individual (Table 1). The mean regression line had the equation \( pAVP = 0.4(pOsm - 285) \) \( (r = +0.96, P < 0.001) \). Linear regression applied to thirst and plasma osmolality defined the mean function \( Thirst = 0.3(pOsm - 281) \) \( (r = +0.92, P < 0.001) \) (Table 2). Extrapolation of the two linear regression lines showed similar threshold osmolalities at the abscissal intercepts for vasopressin release (285 mosmol/kg) and thirst onset (281 mosmol/kg). The mean plasma osmolality for onset of severe thirst was 299 ± 1 mosmol/kg.

The results of repeat hypertonic saline infusion in four subjects demonstrated a high degree of repeatability in the individual thirst responses to osmotic stimulation, when linear regression analysis was applied to the relationship between thirst and plasma osmolality on each occasion (Table 3).

Discussion

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Results of regression analysis of changes in plasma vasopressin (pAVP) and plasma osmolality (pOsm) during hypertonic saline infusion in individual subjects expressed in the form

\[ pAVP = m(pOsm - c) \]

<table>
<thead>
<tr>
<th>Subject</th>
<th>Slope (m)</th>
<th>Abscissa intercept (c)</th>
<th>Correlation coefficient</th>
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</thead>
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<tr>
<td>1</td>
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<td>0.94</td>
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<tr>
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</tr>
<tr>
<td>10</td>
<td>0.69</td>
<td>287</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>0.41 ± 0.05</td>
<td>285 ± 1</td>
<td>0.96 ± 0.03</td>
</tr>
</tbody>
</table>

Table 1. Results of regression analysis of changes in plasma vasopressin (pAVP) and plasma osmolality (pOsm) during hypertonic saline infusion in individual subjects expressed in the form

The osmotic threshold for thirst which we have calculated from our data (281 mosmol/kg) is at the lower end of the physiological range of plasma osmolality and much lower than that quoted in many previous studies [2–4, 10]. Previous workers have referred to absolute thirst onsets occurring at plasma osmolalities as high as 299 mosmol/kg; as thirst is one of the homoeostatic mechanisms which maintains plasma osmolality within normal limits (280–295 mosmol/kg), it seems unlikely to be only experienced at plasma osmolalities well above the upper limit of normal. Recent work has suggested that in healthy man thirst and drinking occur before any significant changes in plasma osmolality or body fluid deficits occur [11], and we therefore feel that the lower figure which our data suggest is a more accurate estimation of the osmolar thirst threshold than that previously quoted.

The fall in PCV and rise in MAP noted at the end of hypertonic saline infusion are well recognized [4]. Although blood volume expansion can theoretically inhibit vasopressin release [12], the effect on thirst is uncertain, and the influence of increased blood volume on thirst in our studies is not clear.

The theoretical osmolar thresholds for vasopressin release (285 mosmol/kg) and thirst onset (281 mosmol/kg) which we have calculated from our data were in close approximation. Previous literature suggests that the hypothalamic osmoreceptors governing thirst and antidiuresis in man are in close anatomical proximity [13]; work in the dog has in fact demonstrated these structures to be on the blood side of the blood–brain barrier, in the circumventricular organs [14–16], with the putative central receptor sites in the organum vasculosum lamina terminalis [17, 18]. Since our data show close similarity of the osmotic threshold for thirst and the theoretical osmolar threshold for vasopressin release, it is conceivable that both vasopressin release and thirst perception are governed by a single osmoreceptor or set of osmoreceptors. Alternatively, these two complementary homoeostatic
mechanisms are subserved by two similar osmoreceptors responding in a similar fashion to a common stimulus. This concept may help explain the lesion in patients who suffer from the combination of adipsia and lack of osmoregulated vasopressin release [3]. Further work is necessary to explore this hypothesis.

Acknowledgments

This work was supported by a grant from the Scientific and Research Committee, Newcastle Area Health Authority. We thank Miss Wendy Pearson for much appreciated secretarial work, and Professor D. J. Newell, Department of Medical Statistics, University of Newcastle upon Tyne, for statistical advice.

References


