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# Vasopressin and Oxytocin Content in Cerebrospinal Fluid and in Various Brain Areas after Administration of Histamine and Pentylenetetrazol

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MENS, W. B. J., F. LACZI, J. A. D. M. TONNAER, E. R. DE KLOET AND TJ. B. VAN WIMERSMA GREIDANUS. *Vasopressin and oxytocin content in cerebrospinal fluid and in various brain areas after administration of histamine and pentylenetetrazol.* PHARMACOL. BIOCHEM BEHAV 19(4) 587–591, 1983.—The content of vasopressin (AVP) and oxytocin (OXT) in the septum, hippocampus, hypothalamus and cortex was determined at 5 min and 24 hr after peripheral (intraperitoneal) administration of histamine (20.0 mg/kg) and pentylenetetrazol (45.0 mg/kg) and in the cerebrospinal fluid at 24 hr after pentylenetetrazol treatment. At 5 min after administration of histamine the AVP content in the septum was increased whereas the OXT level in the various areas was not changed. At 24 hr, neurohypophyseal peptide contents were unaffected in the brain regions analyzed. Pentylenetetrazol did not alter AVP content at 5 min after its administration, however, the OXT level in the septum and the cortex was diminished. At 24 hr after administration of pentylenetetrazol a decreased AVP content in the hippocampus and in the cortex was observed. In contrast, OXT content in the cortex was increased at this time. AVP and OXT levels in CSF were not changed at 24 hr following pentylenetetrazol treatment. The present results suggest that the levels of neurohypophyseal hormones can be differentially altered in particular brain regions at short- (5 min) and long- (24 hr) term intervals after treatment with histamine or pentylenetetrazol. Long-term changes in AVP and OXT levels after pentylenetetrazol may be implicated in the amnesic properties of this convulsive drug. Furthermore, the present findings point to a possible relationship with previously reported pentylenetetrazol-induced changes in peptide levels in the CSF.

Vasopressin Oxytocin Cerebrospinal fluid Brain Histamine Pentylenetetrazol

ARGININ-8-VASOPRESSIN (AVP) and oxytocin (OXT) originating from the supraoptic nucleus (SON) and the paraventricular nucleus (PVN) of the hypothalamus are transported together with their associated neurophysin (NP) via the hypothalamo-neurohypophyseal tract to the posterior lobe of the pituitary [25, 26, 30, 31]. Other AVP, OXT and NP containing pathways have been traced as well, such as projections from the PVN towards the dorsal and ventral hippocampus, the amygdaloid nuclei, substantia nigra and substantia grisea, nucleus tractus solitarius, nucleus ambiguus and to the substantia gelatinosa of the spinal cord [6, 7, 29, 35]. In addition, neurons containing AVP and its specific NP have been found running from the suprachiasmatic nucleus (SCN) towards the lateral septum, the medial dorsal thalamus, the lateral habenular nuclei, the diagonal tract nuclei (of Broca), to the posterior hypothalamus and the interpenduncular nucleus [6, 7, 28, 29].

The effects of various stimuli on neurohypophyseal hormone release into the peripheral circulation are well established. However, only a few studies have investigated the effect of these stimuli on AVP and OXT content in various regions of the brain. AVP levels were found to be mostly decreased in hypothalamic nuclei, the median eminence, and the organum vasculosum lamina terminalis after 3 and 7 days of water-deprivation [13,23]. Hawthorne *et al.* [15] described a decreased AVP content in the hypothalamus and in the pituitary gland after 48 hr of dehydration, whereas in other areas of the brain unchanged or increased AVP levels were found. Furthermore, Russell [27] reported an increased synthesis of AVP and OXT in the PVN and SON after water-deprivation.

Histamine and pentylenetetrazol, a convulsive agent, have been shown to increase the release of AVP and OXT into the peripheral circulation [11, 19, 20]. In addition, al-

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though neither the AVP nor OXT content of the CSF was altered shortly after the administration of histamine, the OXT content of CSF was increased by pentylenetetrazol, whereas levels of AVP were unaltered [19]. It was suggested that histamine preferentially influenced the release of AVP, whereas pentylenetetrazol mainly affected that of OXT. Therefore, it was deemed of interest to investigate the effect of histamine and pentylenetetrazol on brain content of AVP and OXT at different times after their administration. Furthermore, levels of AVP and OXT in the CSF were determined 24 hr after administration of pentylenetetrazol in order to investigate whether or not changes in brain content of these two peptides at this time point were reflected in the CSF.

## METHOD

Male rats of an inbred Wistar strain, weighing 200–220 g, were used. The animals were maintained in a temperature controlled environment (23±1°C) on a 14 hr light and 10 hr dark schedule of illumination, with free access to food and water.

In order to collect CSF a permanent stainless steel cannula was implanted in the cisterna magna. The details of the surgical and the implantation technique are described elsewhere [5,22]. Using this method aliquots of 70 to 100 μl of CSF could be withdrawn repeatedly from freely moving rats.

### *Experimental Design*

Twenty mg/kg histamine (Histamine phosphate, B.H.D. Chemicals Ltd, Poole, England) or 45.0 mg/kg pentylenetetrazol (Amsterdamsche Chininefabriek, The Netherlands) were applied intraperitoneally (IP) to rats and 24 hr later CSF was collected for the determination of AVP and OXT levels.

To investigate the influence of histamine and pentylenetetrazol on AVP and OXT content in certain brain regions the following four experiments were performed. Either histamine (20.0 mg/kg) or pentylenetetrazol (45.0 mg/kg) was administered IP and either at 5 min or 24 hr after injection rats were sacrificed by decapitation between 8.00 and 9.00 a.m. Animals that received saline (0.25 ml or 0.5 ml, respectively) were used as controls in each of the four different experiments. Immediately after decapitation the skull was opened and the brain removed and placed on a polyvinyl chloride plate. The following 5 brain areas were dissected: the septum, hippocampus, hypothalamus, and cortex cerebri (for details of the dissection method see [14]). Tissues were homogenized, using a Plytron PT 10 OD Kinematical GMBH (Lucerne, Switzerland) in 1.0 ml ice-cold 1.0 N HCl and subsequently 1.0 ml of buffer containing 67 mM $Na_2HPO_4$ and 67 mM $KH_2PO_2$ was added. The pH was adjusted to 4.0 with 1.0 N NaOH. A 100 μl aliquot of the homogenate was kept for determination of the protein content [18]. The residual homogenate was then centrifuged (10 min, 9,000 cpm 4°C) and the supernatant was divided into two equal portions for the measurement of AVP and OXT. For the extraction of AVP and OXT activated Vycor glass powder (25 μl/sample) was added to the supernatants. After extraction and subsequent centrifugation (20 min, 3,000 cpm 4°C) the supernatant was aspirated and discarded. The pellets were then washed with 0.5 ml aqua dest. Subsequently, the samples were resuspended and shaken for 30 min with 0.5 ml of aqueous acetone to elute AVP and OXT from the glass powder. After centrifugation (20 min, 3,000 cpm 4°C) the supernatant was evaporated at 55°C under a nitrogen stream. The residues were redissolved in 120 μl of RIA-assay buffer [12] that was adjusted to pH 8.0 for the determination of AVP and to pH 9.0 for OXT. Two samples of 50 μl were taken from these solutions to determine the amount of neurohypophyseal peptides. In the case of hypothalamic tissues, appropriate dilutions were made.

For the determination of AVP and of OXT in the CSF the procedures used have been described previously [12,22].

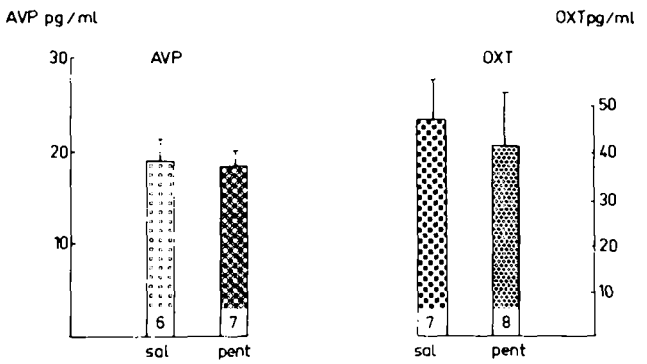


FIG. 1. CSF levels of AVP and OXT at 24 hr after administration of pentylenetetrazol. Levels of AVP and OXT are expressed in pg/ml. Each point represents the mean ± SEM. The number in the bar refers to the number of samples.

### *Radioimmunoassays*

AVP and OXT were determined in duplicate by radioimmunoassay (RIA). The details of the assay procedure have been described elsewhere [12,22]. The antiserum used for the determination of AVP was highly specific. The cross-reactivity with OXT was less than 0.1% and with arginine-vasotocin (AVT) 12.4%. The detection limit of the assay was 0.5 pg/ml.

The OXT antiserum was also highly specific. The cross-reactivity with AVP was less than 0.3% and with AVT approximately 1.5%. The limit of detection was 1.0 pg/ml.

### *Calculations and Data Analysis*

The data are given in pg peptide per mg protein and expressed as mean±SEM. The results from the RIA's were calculated on a Hewlett Packard 104 calculator programmed with a logit curve fitting program. Statistical significance was evaluated by unpaired Student's *t* test. A difference between drug-treated and saline-treated controls within each of the four different experiments of $p < 0.05$ was considered as significant.

## RESULTS

### *CSF Levels of AVP and OXT 24 hr After Pentylenetetrazol Administration*

The onset of the pentylenetetrazol-induced convulsion, with a duration of about 10 sec, was observed between 60 and 80 sec after the administration. Neither AVP nor OXT levels in CSF, as determined 24 hr after treatment, were different from those of saline treated controls (Fig. 1).

TABLE 1

AVP AND OXT CONTENT (pg/mg PROTEIN) IN VARIOUS BRAIN REGIONS AT 5 MIN AFTER ADMINISTRATION OF HISTAMINE (20.0 mg/kg)

| | AVP | | | OXT | | |
|---|---|---|---|---|---|---|
| | saline | histamine | | saline | histamine | |
| Septum | 11.4 ± 0.4 | 14.3 ± 0.5* | +25.2%† | 12.7 ± 3.3 | 15.7 ± 2.3 | +23.6% |
| Hypothalamus | 16694 ± 1248 | 15223 ± 2862 | − 8.8% | 1157 ± 220 | 1464 ± 226 | +26.3% |
| Hippocampus | 7.3 ± 1.6 | 5.2 ± 0.8 | 28.6% | 2.3 ± 0.6 | 2.8 ± 0.7 | +21.7% |
| Cortex | 4.4 ± 0.8 | 4.1 ± 0.7 | − 8.9% | 1.4 ± 0.2 | 1.2 ± 0.3 | −14.3% |

*Different from saline-treated animals $*p < 0.05$.
†Percentage decrease (−) or increase (+) of hisamine-treated animals versus saline-treated animals (100%).
Each value represents the mean ± SEM from 8–14 animals.

TABLE 2

AVP AND OXT CONTENT (pg/mg PROTEIN) IN VARIOUS BRAIN REGIONS AT 24 HR AFTER ADMINISTRATION OF HISTAMINE (20.0 mg/kg)

| | AVP | | | OXT | | |
|---|---|---|---|---|---|---|
| | saline | histamine | | saline | histamine | |
| Septum | 9.0 ± 1.1 | 12.9 ± 2.4 | +43.3%* | 17.1 ± 3.0 | 17.8 ± 2.6 | +4.1%* |
| Hypothalamus | 13797 ± 1021 | 10072 ± 1124 | 27.0% | 1063 ± 102 | 1109 ± 148 | +4.3% |
| Hippocampus | 22.6 ± 4.1 | 24.3 ± 3.1 | + 7.5% | 4.8 ± 1.2 | 5.0 ± 1.5 | +4.0% |
| Cortex | 5.6 ± 0.6 | 5.3 ± 1.0 | − 5.4% | 2.5 ± 0.3 | 2.6 ± 0.4 | +4.0% |

*Percentage decrease (−) or increase (+) of histamine-treated animals versus saline-treated animals (100%).
Each value represents the mean ± SEM from 8–14 animals.

*AVP and OXT Content in Various Brain Areas*

AVP content in the brain areas studied was highest in the hypothalamus followed by the hippocampus, septum and cortex (Tables 1–4). The highest amount of OXT was also found in the hypothalamus, followed by septum, hippocampus and the cortex (Tables 1–4).

*Levels of AVP and OXT in Various Brain Regions After Administration of Histamine*

AVP content in the septum was increased 5 min after administration of histamine (Table 1). In none of the other areas analyzed was the amount of AVP significantly affected. No significant changes in OXT levels in the various brain areas were observed (Table 1).

At 24 hr after administration of histamine, AVP or OXT content in the various brain areas was not changed significantly (Table 2).

*Levels of AVP and OXT in Various Brain Areas After Administration of Pentylenetetrazol*

AVP levels were not significantly changed in any of brain regions 5 min after administration of pentylenetetrazol (Table 3). In contrast OXT levels in the septum and the cortex were markedly decreased at 5 min after the onset of the convulsion (Table 3).

Diminished levels of AVP in the hippocampus and the cortex were measured 24 hr after the administration of pentylenetetrazol (Table 4). A significant rise in the amount of OXT in the cortex was found 24 hr after this treatment, whereas the levels of this peptide in the septum, hypothalamus and hippocampus were not significantly altered.

## DISCUSSION

In the hypothalamus, the hippocampus and the cortex the amount of radioimmunoassayable AVP exceeded that of OXT. Similar ratios of AVP versus OXT in brain regions have been found by others [10], although the authors measured lower amounts of OXT as compared to AVP in the septum. The marked variation found in the individual experiments between the levels of AVP and OXT of the saline-treated animals, especially in the 24 hr group of Table 2, seems to make these data difficult to interpretate. However, in the course of these studies it was discovered that AVP levels in particular brain regions are sensitive to a variety of environmental stimuli, such as the conditions of housing, handling of the animals prior to the experiment and even the time of the year (Laczi, submitted). Similar observations have been made for the levels of neurohypophyseal hormones in plasma and CSF [16, 17, 35] and daily changes in AVP CSF concentrations have been found [21, 24, 25]. In addition, it is known that in these studies generally high variations in hormone levels in brain regions and CSF are found [24,25].

TABLE 3

AVP AND OXT CONTENT (pg/mg PROTEIN) IN VARIOUS BRAIN REGIONS AT 5 MIN AFTER ADMINISTRATION OF PENTYLENETETRAZOL (45.0 mg/kg)

| | AVP | | | OXT | | |
|---|---|---|---|---|---|---|
| | saline | pentylene-tetrazol | | saline | pentylene-tetrazol | |
| Septum | 12.7 ± 2.2 | 19.0 ± 4.4 | +49.6%† | 31.8 ± 6.9 | 17.4 ± 2.1* | -45.3% |
| Hypothalamus | 19366 ± 3360 | 16740 ± 2690 | -13.6% | 1107 ± 189 | 1216 ± 397 | + 9.8% |
| Hippocampus | 14.9 ± 2.0 | 15.8 ± 1.3 | + 6.0% | 5.2 ± 1.7 | 3.9 ± 1.3 | -25.0% |
| Cortex | 8.2 ± 1.7 | 5.9 ± 0.6 | 28.0% | 2.0 ± 0.1 | 1.3 ± 0.2‡ | -35.0% |

*Different from saline-treated animals, *$p<0.05$; ‡$p<0.02$.

†Percentage decrease (-) or increase (+) of pentylenetetrazol-treated animals versus saline-treated animals (100%).

Each value represents the mean ± SEM from 8–14 animals.

TABLE 4

AVP AND OXT CONTENT (pg/mg PROTEIN) IN VARIOUS BRAIN REGIONS AT 24 HR AFTER ADMINISTRATION OF PENTYLENETETRAZOL (45.0 mg/kg)

| | AVP | | | OXT | | |
|---|---|---|---|---|---|---|
| | saline | pentylene-tetrazol | | saline | pentylene-tetrazol | |
| Septum | 4.4 ± 0.6 | 4.9 ± 0.8 | -12.0%† | 14.8 ± 2.8 | 9.4 ± 1.5 | - 36.5%‡ |
| Hypothalamus | 5901 ± 1110 | 7262 ± 1638 | +23.1% | 1237 ± 72.9 | 1260 ± 73.2 | 1.8% |
| Hippocampus | 13.5 ± 2.1 | 7.3 ± 0.9* | -45.9% | 2.4 ± 0.5 | 2.0 ± 0.5 | - 16.7% |
| Cortex | 1.7 ± 0.2 | 1.1 ± 0.1* | -35.3% | 1.8 ± 0.2 | 3.7 ± 0.3‡ | +105.5% |

*Different from saline-treated animals, *$p<0.05$; ‡$p<0.01$.

†Percentage decrease (-) or increase (+) of pentylenetetrazol-treated animals versus saline-treated animals (100%).

Each value represents the mean ± SEM from 8–14 animals.

Administration of pentylenetetrazol results in increased OXT levels in the CSF within 5 min after its peripheral administration [19]. In the present study it was shown that at this timepoint OXT levels in the septum and in the cortex were significantly decreased. Neither the AVP levels in the CSF [19] nor those in the brain were altered by pentylenetetrazol treatment at this time-point. This suggests a relationship between the increased OXT levels in the CSF and the decreased OXT content in the septum and the cortex. This is supported by the finding that 5 min after the administration of histamine the levels of OXT in the various brain areas were not changed and no concomitant change in OXT concentration in the CSF was observed [19].

At 24 hr after administration of pentylenetetrazol CSF levels of AVP and OXT were unchanged. At the same time increased OXT levels in the cortex and decreased AVP levels in the cortex and the hippocampus were observed. Therefore, it seems that under these experimental conditions changes in brain content of neurohypophyseal peptides are not reflected in the CSF.

Histamine and pentylenetetrazol enhance the release of AVP and OXT from the posterior lobe of the pituitary into the peripheral circulation [11, 19, 20]. The present data demonstrate that histamine has little effect on AVP or OXT content of various brain regions at 5 min or 24 hr after its administration. In contrast, pentylenetetrazol induced changes in OXT content in various brain regions which were generally opposite to its effects on AVP. In particular, 24 hr after administration of pentylenetetrazol opposite effects on the AVP and OXT content of the septum and cortex were observed.

These generally opposite changes in AVP and OXT levels in various brain regions are of interest with respect to the pentylenetetrazol-induced deficit in memory function, which is expressed 24 hr after its administration [2,8] and the opposite effects of AVP and OXT on memory function. AVP affects memory processes by facilitation of both storage and retrieval of information [1, 26, 32], whereas OXT has an opposite effect and possesses amnesic properties [3]. Since the effects of AVP and OXT on memory function are mediated by a central action it is conceivable that a change in the ratio in AVP versus OXT, as observed in the brain after pentylenetetrazol administration, may contribute to the distributed memory function of these rats. This assumption is

further supported by the finding that administration of lysine-vasopressin restores the pentylenetetrazol-induced impairment in behavior [4].

In conclusion the present data suggest that the levels of neurohypophyseal hormones can be altered differentially in particular brain regions at short- (5 min) and long- (24 hr) term intervals after administration of histamine or pentylenetetrazol. Long-term changes in AVP and OXT levels after pentylenetetrazol may be implicated in the amnesic properties of this convulsive agent.

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