Short report

Reduction of arginine-vasopressin in the cerebral cortex in Alzheimer type senile dementia

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SUMMARY Arginine-vasopressin (AVP) concentrations in five cortical areas were measured post mortem in nine patients with senile dementia of Alzheimer's type (SDAT), and compared with the control group of comparable ages. In SDAT patients, AVP was significantly reduced in Brodmann areas 4, 7 and 10 (p < 0.05). In areas 17 and 22, the detectability and the mean concentrations of AVP were also lower than those of control patients, although not significantly.

It has been suggested that the posterior pituitary hormone, arginine-vasopressin (AVP) has an influence on learning or memory processes. AVP is found not only in the hypothalamus, mainly in the paraventricular and supraoptic nuclei, but also in many other areas of the central nervous system, including the locus coeruleus, lateral septum, substantia nigra and hippocampus in rats. Rossor et al demonstrated the widespread distribution of AVP in the human central nervous system. They also reported that the AVP concentration is reduced in the lateral segment of the globus pallidus in senile dementia of Alzheimer’s type (SDAT), and slightly reduced in other areas where AVP was normally present. Rossor’s group did not examine the cerebral cortex, which is affected most severely in SDAT. We investigated the regional distribution of AVP in patients without neurological or psychiatric disorders and found that AVP was detectable in more than half of the cases in some areas of the cerebral cortex, such as the cingulate gyrus, the superior temporal gyrus, and the precentral gyrus.

In the present study, AVP concentrations in the five cortical areas of necropsy brains with SDAT were measured and compared with those of control patients of similar ages.

Materials and methods

Tissue samples
Nineteen brains from patients dying without dementia (10 males and nine females, mean age 77.0 SD = 8.8 years) and nine from patients with SDAT (four males and five females, mean age 80.4 SD = 5.3 years) were obtained at necropsy. The patients without dementia consisted of six patients with motor neuron disease, four with cerebrovascular disease, two with Parkinson’s disease, and seven without neurological or psychiatric disorders. Patients with SDAT were diagnosed clinically and pathologically. Every necropsy was performed within 8 hours after death. After mid sagittal dissection of the brain, one half was studied neuropathologically, and the other half was stored at −70°C until the cortex was dissected. Brodmann’s areas 4, 7, 10, 17 and 22 were dissected in the cryostat at −20°C, and the white matter was separated on a piece of glass.

Radioimmunoassays
The radioimmunoassay for AVP was performed using synthetic AVP (Protein Foundation, Osaka, Japan) coupled with bovine serum albumin by the glutaraldehyde method. The coupled AVP was injected into rabbits subcutaneously several times. The antiserum which was obtained showed no cross reactivity with other peptides such as somatostatin-14 and oxytocin. The method could detect synthetic AVP of less than 2 pg/tube (fig a). The labeling of AVP with iodine-125 was carried out using chloramin-T by the method of Hunter and Greenwood. The Dextran coated charcoal was used to separate the bound form from the free peptides. The buffer solution for the radioimmunoassays contained 0.01 M phosphate, 0.025 M EDTA and 0.5% bovine serum albumin. The tissue samples of the cerebral cortex were weighed and homogenised in 1 M acetic acid. After boiling at 100°C for 10 minutes, boiled
The assay was validated by the close immunological parallelism between the material from tissue extracts of hypothalamus and authentic AVP. High performance liquid chromatography (Waters Assoc. Milford, MA, USA) was used for the identification of AVP in the tissue extract according to the method of Lindeberg. The retention volume of authentic AVP and that of the tissue extract from the hypothalamus and the cerebral cortex were the same as shown in fig (b).

Results

(1) Control patients AVP was detectable in 63% of the samples from areas 4, 10 or 22, 59% of the samples in area 7 and 41% of the samples in area 17 of the examined cases (table). In cases in which AVP could not be detected by the radioimmunoassays, the amounts of AVP were generally less than 0.02 ng/g wet weight, although the value varied with the weight of the sample. The table also shows the median values and the range. The highest mean concentration of AVP in these five areas was found in area 22 (superior temporal gyrus). There were no significant differences between motor neuron disease and others, nor between cerebrovascular disease and others.

(2) SDAT patients AVP in the cerebral cortex of SDAT patients was detectable in 22% of samples from area 4, 7 and 10, 33% in area 22, and 11% in area 17. The rate of detectability was lower than that of the control patients in all cortical areas examined. In addition, the mean AVP content in detectable cases was lower in SDAT patients than in patients without dementia. Significant decreases in AVP concentration were observed in areas 4, 7 and 10 (p < 0.05, according to the Wilcoxon’s Rank Sum Test). Comparison between the seven non-neurological cases and SDAT patients was also performed. AVP was significantly reduced in SDAT patients in areas 7 and 10 (p < 0.05).

Discussion

Various neuropeptides are reported to be present in the cerebral cortex and designated as possible neurotransmitters or neuropeptides. The present study demonstrated the presence of AVP in the cerebral cortex of the human brain. Immunohistochemical studies have revealed fibres containing AVP in the entorhinal cortex of the rat. Studies using radioimmunoassays indicated the presence of AVP in the neocortex of the rat. Substantial amounts of AVP were found in the locus coeruleus in the rat and human brain. Van Leeuwen et al demonstrated many AVP cell bodies in the locus coeruleus in rats treated with colchicine. Kovacs et al reported that AVP accelerates the turnover of norepinephrine in the locus coeruleus. These observations suggest that AVP is...
present in fibres projecting from the locus coeruleus to the neocortex. Some neuropeptides were detected in the cerebral cortex. In SDAT, somatostatin was reported to be reduced in some areas of the cerebral cortex. On the other hand, cholecystokinin and vasoactive intestinal polypeptides abundant in the cerebral cortex have been reported to be unchanged in SDAT patients. Classical neurotransmitter systems, especially cholinergic neurons, were reported to be affected in SDAT. Noradrenergic neurons are also involved in SDAT. The concentration of cortical noradrenaline is reduced in SDAT patients, and the cell loss of the locus coeruleus has also been reported. Rosser et al demonstrated that the amount of AVP in the locus coeruleus is lower in SDAT than in control subjects, although not significantly.

The present study showed a decreased amount of AVP in the cerebral cortex of SDAT patients. The decrease in AVP concentration in SDAT was also examined with another analysis using the Fisher Probability Test. The results were similar, but less conspicuous than those according to the Wilcoxon’s Rank Sum Test; p = 0.09 in areas 4 and 10, and 0.11 in area 7, respectively. The reduction of cortical AVP in SDAT may be attributable to the loss of noradrenergic neurons in the locus coeruleus, though Rosser et al reported that no decrease in AVP concentration was found in the locus coeruleus in Parkinson’s disease in which the pigmented cells of the locus coeruleus were reduced. The finding that AVP is less detectable in area 17 agrees with the report indicating that the content of noradrenaline in area 17 was the most sparse of all cortical areas.

Sørensen et al reported the reduction of AVP in the cerebrospinal fluid of demented patients. Although the origin of AVP in the cerebrospinal fluid is not clear, it is presumed to be of central origin. Our results support this assumption.

AVP appears to influence memory processes through the locus coeruleus or limbic structures such as the hippocampus. Laczi et al reported the reduction of AVP in the hippocampus during the learning tasks in rats. Cortical AVP, however, may participate in other cortical functions as well as memory or learning processes.

AVP appears to be useful in demented patients. The evaluation of the clinical use of AVP is now under investigation. The blood brain barrier for AVP seems to interfere with the entrance into the central nervous system, and the intraventricular administration of AVP to rats causes the barrel rotations which resemble convulsive movements. Peripheral effects of AVP must be considered if a large dose of AVP is administered. However, further investigations of clinical trials would help to clarify the role of AVP in the human central nervous system.

References


Fujiyoshi, Suga, Okamoto, Nakamura, Kameyama