Unchanged Vasopressin Innervation of the Locus Coeruleus in Alzheimer’s Disease

E. J. VAN ZWIETEN, R. RAVID AND D. F. SWAAB

INTRODUCTION

The locus coeruleus (LC) is located bilaterally in the dorsal pontine brainstem at the ventrolateral edge of the fourth ventricle. It consists of a distinct cluster of noradrenaline (NA)-containing neurons and is, in primates, because of the presence of neuromelanin, clearly visible without staining. Records of interest in the LC extend back to the description by Reil in 1809 (1) of a streak of blue-black substance in the floor of the fourth ventricle of man. In 1955, Russel reviewed and extended the study of the comparative anatomy of this nucleus and showed that the LC has a similar location in several species (2).

The LC provides an extensive noradrenergic innervation to almost every brain region. Recently, Aston-Jones and co-workers (3) showed that the major inputs to the LC are found in two distinct structures, i.e. the nucleus paragigantocellularis and the perifascicular area of the nucleus prepositus hypoglossi, both located in the rostral medulla. Minor inputs to the LC are found in the paraventricular nucleus of the hypothalamus, the periaqueductal grey and the ventromedial pericoerulear region, which is probably of importance in local circuitry.

Because of its extensive efferents through the entire brain (4), the LC may be involved in general processes like emotion, level of vigilance and sleep–wake cycle (5). These processes are compromised in neurodegenerative diseases like Alzheimer’s disease (AD). In this condition the main symptoms are attributed to impaired function of frontal and temporal cortex and hippocampus (6). In addition, several subcortical afferent projection systems are affected in AD, one of them being the LC. Changes in the LC in Alzheimer’s disease were showed by measuring NA in projection regions of the LC, which showed a decrease in the course of the disease (7). Furthermore, recent studies show an extensive neuronal loss in the LC, using different markers for the NA neurons, i.e. neuromelanin (8), tyrosine-hydroxylase (TH) (9) and dopamine-β-hydroxylase (DBH) (10). This neuronal loss appeared to be topographically
distributed, the rostral part of the LC being most affected, the medial part less and the caudal part least affected (9). In rat it is reported that the efferent pathways of the LC have a spatial distribution within the nucleus, i.e. the anterodorsal neurons of the LC project mainly to the cortex, while ventrally located neurons project to the caudal parts of the brain (11). In AD the loss of rostral neurons in the LC may thus reflect cortical impairment.

In addition to the spatial distribution of its efferents, parts of the LC exhibit distinct neurochemical properties with respect to the coexistence of neuropeptides and NA (12). In our laboratory, Caffé and co-workers (13) showed that the neuropeptide vasopressin was co-localized within NA-neurons in rat LC.

Vasopressin (VP) is synthesized in the brain as part of the precursor protein propropressophysin. This precursor consists, besides VP, of C-terminal glycopeptide (CPP) and neurophysin (NP) (14). Vasopressin is present in the classical neurosecretory hypothalamo-hypophyseal system, which comprises cells of the paraventricular and supraoptic nucleus (15). In addition, several other VP-containing cell groups and their projections have been described in rat, monkey and human brain (16,17). In human LC, VP-containing neurons have not been observed. However, the VP-innervation is more dense in the human LC than in rat.

Pilot experiments in our laboratory showed a stable VP-innervation in the region of the LC in which the highest density of neuromelanin-containing neurons was present (Fliers, personal communication). However, since a preferential loss of neurons in the rostral part of the LC was subsequently reported (9), the present study aimed to investigate whether the VP-innervation indeed remained intact during AD, especially in the rostral part.

MATERIAL AND METHODS

The complete LC of five control and five clinically and neuropathologically diagnosed Alzheimer’s patients were collected at rapid autopsy. The patients were matched for age, sex and post-mortem interval. The material was immersion fixed for 1 week and subsequently frozen and stored at −80°C. Subsequently, the complete LCs were serially cut into 40 μm cryostat sections. Every 25th section was stained with thionin and used for orientation. Based on these thionin-stained sections the LC was divided into a rostral, medial and caudal part, using morphological landmarks described by Chan-Palay & Asan (18). Of each part, five evenly distributed sections were chosen, which were processed for immunocytochemistry (ICC) and stained using a purified antibody against VP.

This resulted in 15 levels (five rostral, five medial and five caudal sections) per patient. Within each level the sections of all patients were ranked according to their VP density in the LC region, using a procedure in which the investigator was not aware of the patient number.
RESULTS

In Alzheimer’s patients a clear reduction in neuromelanin-containing neurons was present in the rostral part of the LC compared to controls. In addition, many extracellular deposits of neuromelanin could be observed.

The ICC stainings revealed a very dense VP innervation of the entire LC. In rostral regions of the LC of AD patients, even when no neuromelanin-containing neurons were no longer present, dense VP innervations were found. Analysis of the two patient groups per level, using the Mann–Whitney U test, showed no significant difference in any of the levels.

CONCLUSIONS

In accordance with the literature a decrease in the number of neuromelanin-containing neurons was observed in the rostral part of the LC. The VP innervation in the rostral part of the LC was, however, not affected. This observation suggests that there may be no major direct functional contacts between neuromelanin-containing noradrenergic neurons and VP fibres.

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