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Cortical and Subcortical Neuropeptides in Alzheimer's Disease

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NUMEROUS peptide molecules are found in the mammalian central nervous system (CNS). The biologic role of these neuropeptides in brain function is not well understood, though many are thought to act as either neurotransmitters or neuromodulators. The potential role of these substances in the pathophysiology of neurologic and psychiatric illnesses has, consequently, been the subject of intense scientific scrutiny, and this is particularly true with regard to Alzheimer's disease (AD).

AD is a degenerative neuropsychiatric disease that produces progressive cognitive, behavioral, and functional decline in older adults. The dementia of AD is characteristically a cortical dementia (31,32) with relatively severe cognitive impairment and relatively little motor dysfunction. The cognitive impairments characteristically seen in AD include impaired memory for newly acquired information (amnesia), language dysfunction (aphasia), impaired recognition of familiar items (agnosia), and loss of the ability to perform learned acts (apraxia). All of these cognitive skills depend heavily on the functional integrity of the cerebral cortex.

In addition to functional abnormalities of cerebral cortex, structural changes in cerebral cortex are a prominent feature of AD. Gross examination of brains from patients with AD reveals severe atrophy of cortical gyri with corresponding widening of cortical sulci (63). Microscopically, neuritic plaques and neurofibrillary tangles are seen throughout the cerebral cortex, particularly in limbic and paralimbic regions (65,80). For these reasons, much of the research on neuropeptides in AD has focused on the cerebral cortex. In this review, we will also focus chiefly on cerebrocortical neuropeptide changes in AD. To a lesser extent, we will review AD-related neuropeptide changes in subcortical brain regions that connect with cerebral cortex, either as primary afferent projections to cerebral cortex, or as targets of cerebrocortical efferent pathways.

Examination of cerebral cortex reveals a multilayer cytoarchitecture (22). Neuropeptide-containing neurons are primarily found in layers II, III, and VI (59). The neuropeptide-containing neurons in these layers are bipolar or multipolar cells whose processes remain within a local region of cortex. Many of these local circuit neurons contain gamma-aminobutyric acid (GABA) as a transmitter (54). In contrast, pyramidal cortical cells generally contain the excitatory amino acid transmitters glutamate or aspartate, and do not contain neuropeptides (41). These pyramidal cells are projection neurons, whose axons innervate distant cortical and subcor-

tical brain regions. Pyramidal neurons are primarily located in cortical layers II, III, V, and VI (60).

The neuropeptides found in high concentrations in cerebral cortex include somatostatin (SS), neuropeptide Y (NPY), cholecystokinin (CCK), vasoactive-intestinal polypeptide (VIP), and galanin. Lower concentrations of corticotropin-releasing factor (CRF), substance P (SP), neurotensin (NT), and other neuropeptides are also present in cerebral cortex. Subcortical regions that project to cortex (e.g., nucleus basalis) contain galanin, SS, NPY, SP, and other neuropeptides. Subcortical brain regions that receive direct projections from cortex (e.g., caudate nucleus and putamen) contain SS, SP, NPY, enkephalins, and other neuropeptides.

CEREBRAL CORTEX

Somatostatin

The most extensively studied neuropeptide in AD cerebral cortex is SS. Davies et al. (34) were the first to document decreased levels of cortical SS in AD brains. They observed low levels of SS in the hippocampus, frontal, parietal, and superior temporal cortices of AD brains. Since then, others have documented decreased levels of SS in hippocampus (3,15,17,35), frontal cortex (3,15,17,35,45,64,73,86,87,97,103), parietal cortex (35,45,64,73,97,117), temporal cortex (15,17,35,38,45,64,70,73,86,87,97,103,105), and occipital cortex (15,17,35,73) from AD patients. A few studies have found no change in SS concentration in hippocampus (86), frontal cortex (38,117), parietal cortex (86), or cingulate cortex (35) in AD. No studies have found increased levels of cerebrocortical SS in AD.

Investigators employing immunocytochemical methods have described abnormalities in SS neurons in AD. Joynt and McNeil (61) described shrunken and irregularly shaped SS-immunoreactive (SS-IR) cells in the frontal cortex of AD patients. Chan-Palay (24) reported loss of SS-IR cells and terminals in temporal cortex and in hippocampus from AD brains. Dysmorphic SS-IR cell profiles and processes have also been described by others (82). Some investigators have found abnormally shaped SS-IR fibers and less extensive SS-IR plexuses, but no changes in the density of SS-IR cell bodies in AD (11,68,84). A recent study employing techniques to correct for tissue atrophy (33) has shown significantly reduced numbers of SS-IR neurons in the temporal cortex of AD patients compared to controls.

There is evidence suggesting that AD in younger patients is

clinically more aggressive, and is associated with more severe reductions of cortical SS concentrations (35,103). Furthermore, the decrease in SS in the temporal cortex has been shown to correlate with the density of both senile plaques (38,105) and neurofibrillary tangles (38).

Decreased density of SS receptors has been reported in hippocampus (16) and in neocortex (16,66,120) from AD patients. The decrease in cortical SS receptor density has been correlated with decreased cortical SS-like immunoreactivity (16). This finding may reflect loss of both SS-containing cortical neurons and cortical neurons innervated by SS-containing cells (16). Alternatively, if some cortical SS receptors are autoreceptors located on SS pre-synaptic nerve terminals, then degeneration of cortical SS neurons could produce both reduced SS-like immunoreactivity and reduced SS receptor density (27).

Corticotropin-Releasing Factor

Low levels of CRF have been found in frontal (19,87), temporal (19,70,87), and occipital (70,121) cortices of AD patients. One study (121) has shown that reduction in neocortical CRF correlated with reductions in choline acetyltransferase activity. Using immunocytochemical staining methods, investigators (92,93) have observed abnormal appearing CRF-immunoreactive fibers in the brains of AD patients. An increase in the number of CRF receptors in the cerebral cortex of AD brains has also been described (120). Some investigators have found both decreases in CRF levels, and reciprocal increases in CRF receptors in corresponding cortical regions, suggesting upregulation of CRF receptors in response to disease-associated CRF cell loss (39,40,52).

Substance P

Beal et al. (13) measured reductions in SP of up to 40% in hippocampus and in inferior temporal gyrus of AD patients. Decreases in the level of SP in frontal, temporal, parietal, and occipital cortices of AD brains have also been demonstrated (30). However, two studies (45,126) reported no change in cerebrocortical levels of SP in AD. This discrepancy may reflect differences in patient age, as younger AD patients generally show more severe neurochemical changes. Using immunocytochemical methods, Armstrong and Terry (7) observed swollen SP immunoreactive processes in the brains of AD patients. The authors suggested that the distorted processes belong to degenerating SP-containing neurons.

Neuropeptide Y

Most studies have found normal levels of NPY in the cerebral cortex of AD patients (1,38,48). One group (14) found widespread reductions in cortical NPY concentration, especially in the temporal lobe, of AD patients. Studies using immunocytochemical techniques have revealed reduced numbers of NPY immunoreactive neurons and abnormal appearing NPY immunoreactive processes in the hippocampus of AD patients (26). In the neocortex, abnormalities affecting NPY immunoreactive cell bodies, dendrites, and axons have also been described (25). Beal et al. (11) reported finding abnormal NPY immunoreactive neuronal processes and axonal plexuses, but no alterations in the density of NPY immunoreactive cell bodies in the cerebral cortex of AD patients. A recent study employing techniques to correct for tissue atrophy (33) reported a reduction in the density of NPY immunoreactive neurons in both frontal and temporal cortices from AD

brains. The density of NPY receptors in temporal cortex and in hippocampus was found to be significantly reduced in AD brains compared to controls in one study (71).

Vasopressin, Vasoactive-Intestinal Polypeptide, and Cholecystokinin

Concentrations of vasopressin in neocortex from AD patients have been found to be normal (70,75,77,102) or decreased (50) by different investigators. In the hippocampi of AD patients, concentrations of vasopressin are reduced (75,77).

Most investigators have found no change in levels of VIP in cerebral cortex from AD patients (45,48,90,101). Arai et al. (3) found decreased levels of this peptide in the insular and angular cortices of AD patients. Mazurek et al. (76) measured 20–30% reductions of VIP immunoreactivity in the temporal lobes of AD patients.

Cholecystokinin levels were not found to be altered in early studies of cerebral cortex from AD patients (21,45,90,104). One recent study (73) has shown significantly reduced levels of CCK in several cortical regions from AD brains.

Other Peptides

Arai et al. (4) reported decreased levels of alpha-melanocyte stimulating hormone in cingulate cortex from AD patients. Mazurek et al. (74) found 33% increases in oxytocin content in the hippocampus and temporal cortex of AD patients. Beal et al. (9) found no change in galanin-like immunoreactivity in the hippocampus and cerebral cortex from AD patients. Cerebrocortical levels of neurotensin (45,86,99,125), thyrotropin-releasing hormone (18,86,126), luteinizing hormone-releasing hormone (126), bombesin (87), and methionine-enkephalin (100), are not altered in AD.

Plaques and Tangles

Senile plaques have been shown to contain immunoreactivity to SS (5,6,67,82,93,112), CRF (93), SP (5,7,93), NPY (25,37,67), NT (111), VIP (112), CCK (112), bombesin (111), and leucine-enkephalin (112). Both SS-like immunoreactivity and NPY-like immunoreactivity have been colocalized in the same senile plaque (67). Colocalization of SS-like immunoreactivity and SP-like immunoreactivity in the same senile plaque has also been observed (5). Neurofibrillary tangles have been found in neurons immunoreactive to SS (98), NPY (98), and VIP (69).

CEREBROSPINAL FLUID

Many studies have examined neuropeptide levels in the cerebrospinal fluid (CSF) from patients with AD. Results from these studies tend to support results from biochemical and immunocytochemical studies on cerebral cortex. This suggests that CSF neuropeptide levels closely reflect cerebrocortical neuropeptide levels in AD. This relationship has important implications for the study of neuropeptides in living patients with AD. The results from studies of CSF from AD patients are summarized below.

Somatostatin

Many investigators have found low levels of SS in the CSF of AD patients (8,10,20,29,36,49,57,79,81,85,89,95,97,106,108,110,118,122,124). The low CSF SS levels have been correlated with poor performance on cognitive tests (97,108,118) and

with low cerebrocortical glucose metabolism (118). In addition, reduced CSF SS levels were found to be most severe in very demented AD patients (29,57,110) and in AD patients less than 70 years old (29,49,57,95,110). Decreased SS levels in CSF have also been described in Parkinson's disease with dementia (106), non-Alzheimer's type dementia with frontotemporal degeneration (79), normal pressure hydrocephalus (122), schizophrenia (20), depression (20,36,51,81), and other neuropsychiatric conditions (85). Similar reductions in CSF SS have not been found in multi-infarct dementia (10,95,122). Thus, although CSF levels of SS are reproducibly decreased in AD, this finding lacks diagnostic specificity in the evaluation of dementing conditions.

Corticotropin-Releasing Factor

Mouradian et al. (83) measured 16% decreases in CSF CRF levels in AD; similarly, May et al. (72) measured 30% decreases. The patients in the May et al. study were more severely demented than those in the study by Mouradian et al. Pomara and colleagues (91) did not find a significant change in CSF CRF levels in AD, but did note a correlation between lower CSF CRF levels and poorer performance on global neuropsychological ratings. Differences in assay methods may underlie these discrepant results (42). Nemeroff et al. (88) found normal levels of CRF in CSF from a mixed group of AD and multi-infarct dementia patients. In a study of 80 drug-free AD patients and matched controls, no alterations in CSF CRF concentrations were found in AD (Sunderland and Nemeroff, in preparation). The reasons for the inconsistent CSF CRF results and for the poor correspondence between CSF CRF and cerebrocortical CRF findings remain unknown.

Neuropeptide Y, Vasopressin, and β -Endorphin

Two groups of investigators (8,114) have found normal NPY levels in the CSF from AD patients, and two groups (2,79) have reported reduced levels. Cerebrospinal fluid NPY levels were not found to correlate with severity of cognitive impairment in AD (2).

Several studies (78,95,96,109,115) have found decreased CSF vasopressin in AD. However, Tsuji et al. (119) found elevated levels of this peptide in CSF from AD patients.

Kaiya et al. (62) reported decreased CSF levels of β -endorphin in AD patients. Other investigators have also found decreased CSF β -endorphin levels, but only in very demented AD patients (56,58). Raskind et al. (95) found no change in CSF levels of β -endorphin in AD patients.

Other Peptides

Reduced CSF levels of SP (28), dynorphin (114), thyrotropin-releasing hormone (89), and alpha-melanocyte stimulating hormone (94) have been reported in AD. CSF levels of galanin (114), oxytocin (95), VIP (107, 114,122,123), and peptide YY (122) are unaltered in AD. One report (122) described normal CSF levels of delta sleep-inducing peptide in AD, while another report (79) found reduced levels.

SUBCORTICAL BRAIN REGIONS PROJECTING TO CORTEX

Subcortical brain regions that send afferent projections to cerebral cortex and which have been studied in AD include substantia innominata (including nucleus basalis), locus coeruleus, the septal nuclei, hypothalamus, and thalamus.

Substantia Innominata/Nucleus Basalis

Most investigators have found normal concentrations of SS in the substantia innominata of AD patients (3,12,15,17), although

one group (45) reported an increased concentration. Levels of NPY in the substantia innominata from AD brains have been found to be normal (12,14), or increased (1). Beal et al. found no change in SP immunoreactivity in the nucleus basalis of AD patients (12). However, these investigators reported a twofold increase in galanin immunoreactivity in the nucleus basalis from AD patients (12). Chan-Palay (23) observed hypertrophic galanin-immunoreactive terminals in the nucleus basalis of AD patients and commented that these terminals appear to hyperinnervate remaining choline acetyltransferase-immunoreactive cells in this nucleus. These authors (12,23) have speculated that increased galanin in nucleus basalis may inhibit the diffuse cholinergic inputs from this nucleus to cerebral cortex, thereby contributing to the cognitive deficits seen in AD.

Locus Coeruleus and Septal Nuclei

One study (14) found reduced concentrations of NPY in the locus coeruleus of AD patients. Concentrations of vasopressin in AD have also been found to be decreased in locus coeruleus (102). Low concentrations of SS and of NT have been measured in the septal nuclei of AD patients (45). There is also a report (125) describing no change in septal NT levels in AD.

Hypothalamus and Thalamus

Both low concentrations (86,87) and normal concentrations (125) of SS have been measured in the hypothalamus of AD patients. No change in SS concentration was found in the thalamus from AD patients (97). Immunocytochemical studies (47,116) have revealed loss of vasopressin immunoreactive neurons in the suprachiasmatic nucleus, but no change in vasopressin immunoreactive neurons in the supraoptic or paraventricular nuclei in AD patients. Similar studies (47,116) have found no changes in oxytocin immunoreactive neurons in the supraoptic or paraventricular nuclei in AD patients.

SUBCORTICAL BRAIN REGIONS RECEIVING PROJECTIONS FROM CORTEX

Subcortical brain regions that receive direct projections from cerebral cortex and which have been studied in AD include caudate nucleus, putamen, nucleus accumbens, and substantia nigra.

Caudate Nucleus and Putamen

In the caudate nucleus of AD patients, normal levels of SS (86) and NT (125) have been measured. Caudate levels of CRF (19,87) and of alpha-melanocyte stimulating hormone (4) are decreased in AD. An increase in binding to the kappa opioid receptor has been observed in the caudate and putamen of AD brains (53). Because dynorphin is the endogenous ligand for the kappa opioid receptor, these authors (53) have speculated that reduced caudate/putamen levels of dynorphin in AD may lead to an upregulation of kappa opioid receptors in these brain regions.

Investigators have reported both diminished (3) and unchanged (97) levels of SS in the putamen of patients with AD. Ferrier et al. (45) reported decreased levels of SP in the putamen of AD patients. The density of NPY receptors in the putamen of AD brains was found to be no different than in control brains (71).

Nucleus Accumbens and Substantia Nigra

SS levels were found to be normal in the nucleus accumbens from AD patients (45,86). Levels of vasopressin are decreased in this nucleus in AD (75,77). Arai et al. (4) found decreased alpha-

melanocyte stimulating hormone levels in the substantia nigra from AD patients.

SUMMARY

Given the clinical features of AD, the severe atrophy of cerebral cortex that accompanies the disease, and the predominant cortical location of plaques and tangles, it is not surprising to find the most consistent changes in neuropeptides in this disease occurring in the cerebral cortex. The neuropeptide changes that have been reproducibly demonstrated in AD are reduced hippocampal and neocortical SS and CRF concentrations and a reduced CSF level of SS. In cerebral cortex, SS and CRF are found in GABAergic local circuit neurons in layers II, III, and VI. The function of these neurons is not well established, although these cells may act to integrate the flow of incoming and outgoing information in cerebral cortex. If this is true, then dysfunction of this integration could produce widespread failure of cerebrocortical function, resulting in the various neurobehavioral deficits seen in AD.

The interpretation of neuropeptide changes in subcortical brain regions, either those that project to cortex, or those that are the efferent targets of cortical projections, is also uncertain. The observed neuropeptide abnormalities in these brain regions in AD are less consistent than are those seen in cerebral cortex. Perhaps the most intriguing result in these regions is the increases in galanin-immunoreactive terminals seen in the nucleus basalis of AD

brains. Galanin has been shown to inhibit acetylcholine release and to impair memory function in rats (46,113). Because the nucleus basalis is the principle source of cholinergic afferents to the cerebral cortex (55), and because acetylcholine has been repeatedly shown to be important in memory function (43,44), the presence of high levels of an inhibitory substance like galanin in this brain region suggests a possible role for galanin in the pathogenesis of AD. It remains unclear whether increased galanin in nucleus basalis is a primary change in AD or whether it represents an epiphenomenon secondary to the loss of cholinergic nucleus basalis neurons. In either case, development of pharmaceutical agents that could interact with the galanin system in the nucleus basalis may be a promising approach to the treatment of AD.

As newer methods of analyzing prohormone mRNA and receptor mRNA expression are applied to AD, a better understanding of the involvement of neuropeptide-containing neurons in this disease will be obtained. This, coupled with the development of radioligands to label peptide receptors in vivo using position-emission tomography, will undoubtedly provide considerably more information concerning the pathophysiology of neuropeptidergic neurons in AD.

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