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The CA1 Region of the Human Hippocampus Is a Hot Spot in Alzheimer's Disease

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ABSTRACT: Data from an ongoing study of differences in the total number of neurons in the five major subdivisions of the hippocampal regions of the brains of patients with Alzheimer's disease (AD) and normal age-matched controls confirm an earlier finding from our laboratories of a pronounced loss of CA1 neurons associated with AD. In view of an earlier finding that the CA1 region does not suffer normal age-related neuronal loss, these data support the earlier conclusion that the neuropathologic mechanisms involved in the AD-related losses in CA1 are not related to normal aging and that the study of the cellular and molecular events involved in the AD-related loss of CA1 cells can aid in the identification of the unique pathologic processes associated with AD.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease of the central nervous system characterized by disturbances in memory and higher cognitive functions.^{1,2} Pathologically, it is characterized by abnormal numbers of senile plaques and neurofibrillary tangles and the abnormal loss of neurons in specific parts of the brain.³ The hippocampal region is one of the first and most profoundly affected parts of the brain in AD patients.^{4,5} The data presented here are from an ongoing series of studies designed to determine whether or not AD-related changes in neuron number are exaggerations of normal age-related changes, that is, whether AD is accelerated aging. The strategy used to make this determination is based on comparisons of the patterns of neuron loss in the hippocampal subdivisions. We have focused on neuronal loss because it is the pathologic feature that best expresses the cumulative affects of age and AD. Qualitative changes, defined in terms of differences in the subdivisions that show significant changes with normal aging and AD, are deemed evidence that the changes are not the same and that the neurodegenerative processes are not the same in normal aging and AD. Quantitative differences, expressed as differences in the degree of neuronal loss but not the subregions affected, are construed as evidence that AD is accelerated aging.

In earlier stereologic studies, we demonstrated that neurons in the various subdivisions of the hippocampal formation are lost to varying degrees during normal aging⁶ and AD.⁷ In those studies, we found slight though significant normal age-related losses in the hilus of the fascia dentata and the subiculum and no evidence of age-related losses in the dentate granule cell layer, the CA3 region, and the CA1 region. We also found evidence of significant additional AD-related losses in the hilus and subiculum and a massive (68%) AD-related loss in the CA1 region, which did not show normal age-related loss. In the earlier study, we concluded that the regional patterns of

hippocampal neuronal loss associated with normal aging and AD were different and therefore constituted evidence that the neurodegenerative processes associated with these two phenomena were different. The extent and uniqueness of the AD losses in CA1 led to the conclusion that this region would be the most appropriate place in the human hippocampal region in which to examine the cellular and molecular aspects of AD-related neurodegeneration.

MATERIALS AND METHODS

Brain Material

All brain material used in the ongoing study was obtained from the Alzheimer's Disease Research Center (ADRC) at Johns Hopkins University, Baltimore. Only the left hippocampal region of males was used. All individuals in the AD group (n = 9) had both clinical⁸ and pathologic³ diagnoses of AD. None of the subjects in the age-matched control group (n = 6) had a history of long-term illness, dementia, or neurologic disease.

Histology

All brains were fixed in formalin for a minimum of 3 months prior to being sliced in the frontal plane into 1-cm thick slabs. The cut surfaces of the slabs were photocopied for documentation, and the regions of the slabs containing the hippocampal formation were dissected free. The resulting blocks were embedded in paraffin and exhaustively sectioned at 70 μ m, mounted on glass slides (thickness of section now 50 μ m), and stained with cresylviolet.

Stereology

The optical fractionator⁹ was used to estimate the total number of neurons in five of the major subdivisions of the hippocampus¹⁰: (1) granule cells of the dentate gyrus, (2) dentate hilar cells, (3) CA3-2 pyramidal cells, (4) CA1 pyramidal cells, and (5) principal neurons in the subiculum. A systematic random sample of 10–14 sections was taken at 30–40 section intervals from the entire set of sections obtained from the blocks. In accordance with fractionator sampling, these included partial sections from the edges of the blocks. The distance between optical disectors, on both x and y axes, was: (1) 475, (2) 823, (3) 770, (4) 2,000, and (5) 1,164 microns in the five respective subdivisions. The disectors were composed of counting frames with areas of (1) 414, (2) 10,208, (3) 3,710, (4) 3,710, and (5) 10,208 square microns in the respective subdivisions. All had heights of 20 μ m.

TABLE 1. Estimates of the total number of neurons (N) x 106 in each subregion of each individual in the Alzheimer's disease group (AD, n = 9) and the age-matched control group (control, n = 6)

	AD Gran N	Control Gran N	AD Hilus N	Control Hilus N	AD CA3-2 N	Control CA3-2 N	AD CA1 N	Control CA1 N	AD Sub N	Control Sub N
	17.5	11.2	0.72	1.10	2.10	1.57	3.44	7.65	3.09	3.37
	7.9	14.7	0.52	0.78	0.92	2.09	2.73	6.91	1.68	2.54
	3.7	14.5	0.60	0.97	2.54	1.81	5.12	8.03	3.59	2.87
	17.7	12.2	0.60	0.61	1.22	1.59	2.29	6.01	1.24	2.29
	10.1	17.8	0.83	0.85	1.65	1.49	6.02	7.77	2.73	3.15
	10.1	9.8	0.59	0.64	1.79	1.35	2.91	4.97	1.86	1.82
	6.8		0.12		0.45		0.49		0.48	
	7.7		0.80		1.34		2.05		1.09	
	11.7		0.50		1.02		0.63		0.54	
Mean	11.5	13.4	0.59	0.83	1.45	1.65	2.85	6.89	1.81	2.67
CV	0.36	0.21	0.33	0.24	0.44	0.16	0.64	0.17	0.61	0.21
Difference		-1.9 (14%)		-0.24 (29%)		-20.1 (12%)		-4.03 (58%)		-0.86 (32%)
2p		0.35		0.042*		0.48		0.00039*		0.11

NOTE: Gran = granule cells of the dentate gyrus; Hilus = hilus of the dentate gyrus; CA3-2 = principal neurons of the CA3 and CA2 subregions combined; CA1 = principal neurons of the CA1 subregions; Sub = principal neurons of subiculum (for more detailed definitions of subregions, see West and Gundersen10); CV = coefficient of variation = SD/mean; Difference = difference between group means in absolute numbers and (% of controls).

Statistics

For each subdivision, differences between the mean total number of neurons (N) in the AD and control group were tested with Student's t test for significance. The 2p values of 0.05 or less were considered significant.

RESULTS

Estimates of the total number of neurons in each individual in the AD and control groups are shown in TABLE 1 along with the group means, the coefficient of variation of the group means, the difference in means, and the 2p values for the group comparisons.

The current data shows evidence of regionally specific AD-related neuronal losses similar to those observed in the earlier study. Focusing on the individual subdivisions, there is again no evidence of AD-related losses in the dentate granule cell layer and CA3 in the ongoing study. Although the current data still show a significant AD-related loss in the hilus (29%), there is now only a nonsignificant trend towards AD loss in the subiculum in the new data (29%, 2p = 0.11). Notably, however, evidence still exists of a significant, large, AD-related loss of neurons (58%) in the CA1 subdivision.

DISCUSSION

Data from the ongoing study support the observation previously reported by our laboratory that the CA1 loses more neurons than does any other hippocampal subregion

in AD patients and that immediately adjacent subregions do not have AD-related neuron loss. The evidence indicates no age-related loss of neurons in the CA1 region (see, however, Simic et al.¹¹). The present data support our earlier conclusion that the CA1 subregion is particularly susceptible to whatever it is that is killing neurons in AD patients. Confirmation of this finding further supports the conclusion that the CA1 region is an appropriate part of the brain in which to study the pathology of AD at the cellular and molecular level. It is notable that: (1) the material used to obtain the current data came from one source, the ADRC at Johns Hopkins University, (2) the unbiased stereologic method used to obtain the data is different from that used in the previous study (i.e., the optical fractionator was used rather than the $V_{\text{ref}}^2 N_v$ method¹²), (3) the brain material analyzed in the two studies was embedded in two different media (glycolmethacrylate versus paraffin), and (4) counting in the two studies was performed by two different investigators blinded to the identity of the material.

One other finding of note in the ongoing study is the observation of a highly significant correlation ($r > 0.74$, $2p < 0.02$) between performance on the Mini Mental State Examination (MMSE) and the total number of neurons in CA1. This finding indicates that either the hippocampus is more involved in other cognitive processes than previously thought (the MMSE is not generally considered a hippocampal test) or the regionally specific loss of neurons in CA1, for some unknown reason, rigorously reflects critical AD-related changes in other parts of the brain.

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