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Blood-Based Biomarkers

MCP-1 and eotaxin-1 selectively and negatively associate with memory in MCI and Alzheimer's disease dementia phenotypes

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Abstract

Introduction: MCP-1 and eotaxin-1 are encoded on chromosome 17 and have been shown to reduce hippocampal neurogenesis in mice. We investigated whether these chemokines selectively associate with memory in individuals with mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia.

Methods: MCP-1 and eotaxin-1 were assayed in controls, MCI, and AD dementia patients with varying phenotypes (n = 171). A subset of 55 individuals had magnetic resonance imaging (MRI) scans available. Composite scores for cognitive variables were created, and medial temporal lobe volumes were obtained.

Results: An interaction was noted between MCP-1 and eotaxin-1, such that deleterious associations with memory were seen when both chemokines were elevated. These associations remained significant after adding *APOE* genotype and comparison (non-chromosome 17) chemokines into the model. These chemokines predicted left medial temporal lobe volume and were not related to other cognitive domains.

Discussion: These results suggest a potentially selective role for MCP-1 and eotaxin-1 in memory dysfunction in the context of varied MCI and AD dementia phenotypes.

Keywords: Inflammation; Neuropsychology; Chemokines; Neuroimaging; Episodic memory

1. Introduction

The role of peripheral inflammation in the pathogenesis of neurodegenerative diseases is complex and controversial, but accumulating evidence suggests that immune-mediated processes may underlie and promote Alzheimer's disease (AD) phenotypes [1,2]. Clarifying how and which specific inflammatory processes impact memory performance is of particular importance, as animal models have consistently linked chronic elevations in pro-inflammatory cascades with untoward cognitive outcomes and hippocampal dysfunction [3].

Within the context of pro-inflammatory process, specific chemokines have recently garnered research attention as potential modulators of memory function both in aging and AD. Monocyte chemotactic protein-1 (MCP-1; CCL2) and eotaxin-1 (CCL11) are both members of the C–C chemokine family clustered closely on the long arm of chromosome 17 and have been linked with memory impairment (eotaxin-1) [4], age at onset in familial AD (eotaxin-1) [5], senescence

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[6], and increased abeta pathology (MCP-1) [7] in animal models of aging and AD. In a seminal study using a parabiosis model, Villeda et al. [8] identified systemic chemokines in plasma, including MCP-1 and eotaxin-1, that correlated with reduced neurogenesis in both aged mice and heterochronic parabionts (i.e., an older mouse surgically connected to a younger mouse). Moreover, when plasma eotaxin-1 levels were increased *in vivo* in young mice, impaired spatial learning, and memory was observed on behavioral tasks. Although these important studies point to a possible role of MCP-1 and eotaxin-1 in aging and AD, few studies have addressed this question in humans [9], and no study has examined these markers with respect to episodic memory functions in older adults. As such, it remains unclear whether peripheral MCP-1 and eotaxin-1 levels are sensitive to verbal or visual memory difficulties in older adults, and whether this association with cognition generalizes to nonmemory domains.

The goal of this study was to assess whether MCP-1 and eotaxin-1 levels predicted memory functions in older adults with mild cognitive impairment (MCI) and Alzheimer's disease dementia. We hypothesized that higher eotaxin-1 and MCP-1 levels would be associated with poorer memory performance on both verbal and visual memory tasks. We further examined whether: (1) the association of eotaxin-1 and MCP-1 levels with cognitive functions were specific to memory and (2) chemokines outside of the chromosome 17 cluster would similarly predict memory functions. This allowed us to determine both the sensitivity and specificity of our findings. Finally, in an exploratory analysis, we further examined the association of these chemokines with medial temporal lobe structures.

2. Methods

2.1. Participants

A sample of 151 carefully phenotyped older adults meeting the National Institute on Aging—Alzheimer's Association (NIA-AA) criteria for either mild cognitive impairment [10] or probable dementia due to AD [11] were included in our AD group. All participants were selected from the University of California, San Francisco Memory and Aging Center database based on the availability of plasma markers of MCP-1 and eotaxin-1 as well as measures of verbal and visual recall. Both evaluations occurred within a 90-day period. MCI participants whose phenotypes suggested the presence of other primary etiologies (i.e., vascular disease; Lewy bodies) were excluded. In addition, 22 healthy controls were included as a comparison group and were selected based on availability of chemokine markers and the same memory evaluation as the MCI and AD dementia participants (see below). MCI and AD dementia participants were recruited from our Alzheimer's Disease Research Center and healthy controls were recruited from our NIH Aging and Cognition study. All patients underwent a history and physical examination, a structured caregiver interview, and neuropsychological tests (see Table 1), and diagnoses were adjudicated in a consensus conference. To confirm the robustness of our findings, we elected to include a range of validated AD phenotypes (e.g., posterior cortical atrophy, logopenic primary progressive aphasia, memory-predominant AD), severity levels (Clinical Dementia Rating Scale of 0–2), and ages (early and late onset). Amyloid imaging biomarkers, obtained via positron emission tomography imaging with Pittsburgh compound B (^{11}C-PiB) [12] or Florbetapir F 18 (^{18}F-AV-45) [13], were available for 57 individuals, and 55 of 57 were positive. We elected to exclude the two individuals who were amyloid negative, resulting in a final n of 149 MCI and AD dementia participants and 22 controls. Of the MCI and AD dementia phenotypes, 102 individuals had a classic memory-predominant phenotype, 28 were diagnosed with a logopenic variant of primary progressive aphasia phenotype, and 19 evidenced a posterior cortical atrophy phenotype. The study was approved by the UCSF institutional review board for human research. Informed consent for the study was provided by the participants or their assigned surrogate decision makers.

2.2. Measures

2.2.1. Global measures

The Clinical Dementia Rating Scale (CDR) was administered to all participants to capture overall severity, and the overall score (0–2) was used as a primary covariate.

2.2.2. Verbal and visual memory

Our primary outcome variable was episodic memory and was selected due to its consistent and robust associations with early stages of Alzheimer's disease [14–17]. Episodic

Table 1
Participant characteristics and neuropsychological assessment

		MCI and AD dementia phenotypes
	Healthy controls	Overall group
Demographic and Cognitive Variables	Mean (SD)	Mean (SD)
Age (y)	75.6 (7.1)	67.8 (10.4)
Gender (% female)	50%	55%
Education (y)	17.9	16.5
CDR (%)	0:100%	0.5:53.6% 1.0:37.6% 2.0:8.7%
Eotaxin levels (pg/mL)	156.7 (48.9)	172.3 (66.1)
MCP-1 levels (pg/mL)	115.1 (19.6)	102.3 (36.7)
IP-10 levels (pg/mL)	495.4 (301.0)	542.5 (526.9)
MDC levels (pg/mL)	954.1 (319.6)	1085.3 (502.0)
TARC levels (pg/mL)	152.3 (155.0)	190.9 (136.4)
MMSE	29.2 (1.1)	22.4 (5.4)
CVLT-short form 10′ Recall	7.4 (1.9)	2.3 (2.6)
CVLT-short form D-prime	3.3 (0.4)	1.7 (1.0)
Benson figure recall	12.5 (2.1)	3.8 (3.8)

Abbreviations: MMSE, mini mental status examination; CVLT, California Verbal Learning Test-II.