

A decorative vertical bar on the left side of the slide. It features a large orange circle at the top, followed by a smaller orange circle, a medium-sized orange circle, a very small orange circle, and another medium-sized orange circle at the bottom. The background of the bar is a light orange color with a fine grid pattern.

THE ROLE OF INFLAMMATORY MARKERS IN BRAIN AGING

Independent Learning Project: Literature review

Biomarker	Description	Production	Peripheral Effects	Effects specific to central nervous system (CNS)
Interleukin-1 (IL-1)	Cytokine	CNS: Astrocytes and microglia Periphery: Macrophages, monocytes, dendritic cells	Immune activation, B and T cell proliferation, increased natural killer cell activity and macrophage cytokine production, haematopoiesis	Microglial proliferation, induce microglia IL-6 expression, autocrine IL-1 induction, neuronal apoptosis, pyrogen
Interleukin-6 (IL-6)	Cytokine (adipokine)	CNS: Astrocytes and microglia Periphery: T & B cells, macrophages, fibroblasts, epithelial cells, adipose tissue	B cell stimulation and differentiation, antibody synthesis, acute phase protein induction, haematopoiesis	Astrogliosis, decrease microglial VCAM-1 and ICAM-1 expression, induce IL-6 production, both neurotoxic and neuronal growth factor
Interleukin-8 (IL-8)	Cytokine	CNS: Astrocytes and microglia Periphery: Monocytes, fibroblasts, epithelial cells	Neutrophil activation and chemotaxis, basophil and T cell attractant, angiogenesis	
Interleukin-10 (IL-10)	Cytokine	CNS: Astrocytes and microglia Periphery: T cells, monocytes, macrophages	Inhibits interferon- γ and IL-12	
Interleukin-12 (IL-12p70)	Cytokine	CNS: Astrocytes and microglia Periphery: Dendritic cells, macrophages, B cells	Induces production of interferon- γ , TNF- α and IL-2 via T cells and natural killer cells and lysosomal discharge	
Tumour Necrosis Factor- α (TNF- α)	Cytokine (adipokine)	CNS: Astrocytes and microglia Periphery: Macrophages, lymphocytes and adipose tissue	IL-1 and IL-6 release, macrophage activation, T cell activation, acute phase protein induction	Microglial ICAM-1 and VCAM-1 production, nitric oxide production, astrogliosis, MHC class I and II expression, pyrogen
Plasminogen Activator Inhibitor 1 (PAI 1)	Serine protease inhibitor (adipokine)	Vascular endothelium and adipose tissue	Inhibits tissue plasminogen activator (tPA) and urokinase, preventing fibrinolysis (breakdown of blood clots)	
Adiponectin	Protein hormone (adipokine)	Adipose tissue	Increases insulin sensitivity, alters lipid catabolism, improves glucose metabolism, reduces expression of endothelial adhesion proteins	
C-Reactive Protein (CRP)	Acute phase protein	Liver	Pro-atherosclerotic; monocyte chemotaxis, promotes vascular smooth muscle activation and proliferation, adhesion molecule expression (including VCAM-1) and classic complement system	Direct neurotoxicity
Serum Amyloid A (SAA)	Acute phase protein Apolipoprotein	Liver	Facilitate cholesterol transport to liver, inflammatory cell chemoattractant, induction of extracellular matrix degrading enzymes	
Vascular Cell Adhesion Molecule (VCAM)	Adhesion molecule	Vascular endothelium	Facilitate leukocyte adhesion, activation and migration through vascular endothelium; implicated in atherosclerosis pathogenesis	

METHOD

- Medline search

- MESH term 'inflammation' OR keywords 'inflammatory markers' AND
- MESH terms 'cognition' OR 'cognition disorders'
- Limit to English language
- Reference lists cross-checked for additional articles



RESULTS

- 1997-2009
- Focus on studies investigating circulating inflammatory markers and cognitive function
 - 14 cross-sectional studies
 - 18 longitudinal studies
 - 8 reported cross-sectional findings



CROSS-SECTIONAL FINDINGS

- IL-6 and CRP most consistently linked to poor performance in individual cognitive domains (particularly memory and executive function)

(Alley et al, 2008; Gimeno, Marmot and Singh-Manoux, 2008; Komulainen et al, 2007; Marshland et al, 2006; Schram et al, 2007; Teunissen et al, 2003; Weaver et al, 2002)

- TNF- α , IL-1 β and IL-6 associated with dementia

(Alvarez et al, 2007; Bruunsgaard et al, 1999; Licastro et al, 2000; Singh & Guthikonda, 1997; Zuliani et al, 2007)

- CRP associated with vascular dementia but not Alzheimer's disease (Licastro et al, 2000; Nilsson, Gustafson & Hultberg, 2008)



LONGITUDINAL FINDINGS

○ Middle aged cohorts

- Inconsistent results for CRP and IL-6
- Only one dementia study
 - Honolulu-Asia Aging Study (n=1050, 25yrs follow up), raised CRP predictive of all cause dementia, weaker for AD alone (Schmidt et al, 2002)

○ Elderly cohorts

- Elevated IL-6 related to cognitive decline (Weaver et al, 2002; Schram et al, 2007, Alley et al, 2008)
- Only CRP correlation with decline linked to metabolic syndrome (Yaffe et al, 2004)
- Studies investigating predictive value of inflammatory markers in dementia inconsistent (Engelhart et al, 2004; Ravalgia et al, 2007; Tan et al, 2007)



MILD COGNITIVE IMPAIRMENT

- Three cross-sectional studies investigated MCI
 - Bermejo et al (2008):
 - IFN- α higher in MCI than AD & controls
 - TNF- α elevated in MCI compared to controls (not statistically sig.)
 - IL-6 higher in AD than MCI
 - Platelet COX-2 elevated in MCI & AD
 - Nilsson, Gustafson & Hultberg (2008)
 - CRP higher in MCI than AD
 - Alvarez et al (2007)
 - Elevated TNF- α in MCI compared to controls
- Inflammatory process begins before clinical dementia??
Changes with progression??
- No longitudinal studies



METHODOLOGICAL ISSUES

- Measure of cognitive function
 - Global measure of cognition (e.g. MMSE) VS individual cognitive domains
- Inflammatory markers studied
 - Exploratory studies
 - Need strong guiding hypothesis, perhaps derived from knowledge of cytokine mechanisms?
- Covariates
 - Is adjustment required for all factors associated with cognitive decline or inflammation?
 - Will adjustment negate associations?



Unknown role of potential confounding factors

