

Neuroscience Center of Excellence

Chancellor's Award Lecture

in Neuroscience



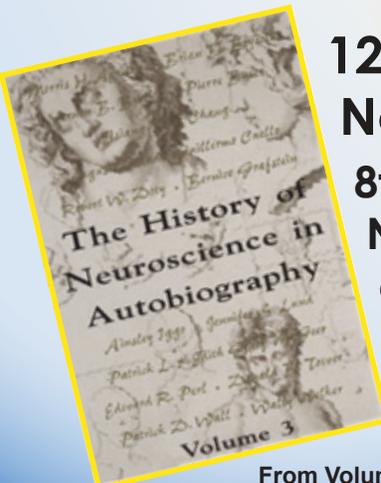
Alzheimer's Pathology: a Pre-Plaque Inflammatory Process and NGF Metabolic Deregulation

Our lab is interested in the early events of the Alzheimer's disease (AD) pathology. For these investigations we use (and developed) transgenic animal models and human brain material. Thus, we have observed in transgenic models that in pre-plaque stages, and coincidental with the intracellular accumulation of A-beta amyloid peptides, there is a "pro-inflammatory" process which differs from the classical, amyloid plaque-related overt inflammation. We postulate, that this process is driven by soluble A-beta oligomers and that should occur in the earliest, pre-diagnostic, stages of the disease.

The application of A-beta oligomers in the CNS of naïve rats is sufficient to unleash a similar "pro-inflammatory" profile. Along with it, the up-regulation of the NGF precursor molecule: proNGF. A similar increase in brain proNGF has been reported in AD. The apparent abundant trophic support in AD conflicts with the known atrophy of forebrain cholinergic neurons and synapses; a system highly dependent on NGF offer. Our lab has demonstrated that proNGF and not the mature NGF (mNGF) is released in the CNS in an activity-dependent manner, and that it is matured and eventually degraded in the extracellular space by a cascade of zymogens, convertases and inhibitors. We have found this pathway to be importantly compromised in AD and in Down Syndrome (DS) such that the conversion of proNGF to mNGF is diminished and the degradation of mNGF likely to be increased. This metabolic compromise would explain the "trophic disconnect" in both AD and DS.

A. Claudio Cuello, MD, DSc, FRSC, OC
Chair, Brain at McGill
Professor and Charles E Frosst/Merck
Chair in Pharmacology
Department of Pharmacology
McGill University
Montreal, PQ, Canada

**12 p.m., Monday
November 3, 2014
8th Floor
Neuroscience Center
of Excellence
Conference Room**



The History of Neuroscience
in Autobiography

From Volume 3: Autobiographical
Essay on Dr. Cuello (pdf)