

## The NO/ONOO- cycle as the cause of CFS/ME and related diseases and also the three classic neurodegenerative diseases, Alzheimer's, Parkinson's and ALS

**Martin L Pall**

Washington State University, USA

The nine types of stressors reported to initiate cases of CFS/ME can all raise levels of nitric oxide (NO), acting through other cycle elements. The stressors, in turn, are thought to initiate CFS/ME cases by turning on the NO/ONOO- cycle mechanism, a complex biochemical vicious cycle made up of a series of interacting cycles. There are 35 proposed cycle mechanisms, 31 of which are well accepted biochemistry and physiology. The cycle is based on five principles, each of which is well supported in CFS/ME and such related diseases as fibromyalgia and multiple chemical sensitivity (MCS), explaining the similarities of these diseases. This mechanism is extensively supported by published studies of case initiation, by a large number of studies of correlates found in the chronic phase of the disease, by evidence of the primarily local nature of the disease, by genetics of susceptibility studies, by animal model studies, by gene expression studies and most importantly by a published studies showing that a series of agents that are reported in clinical trials to produce improvements in CFS/ME patients, can act to lower aspects of the NO/ONOO- cycle. Plausible mechanisms link the cycle elements to the generation of the symptoms of CFS/ME and related diseases, including post-exertional malaise, the most characteristic symptom of CFS/ME. The NO/ONOO- cycle as a paradigm of human disease can be confirmed

from studies of Alzheimer's (AD), Parkinson's disease (PD) and ALS, which each show an excellent fit to the first four principles of the cycle and where we have much more extensive evidence for this fit than we do with CFS/ME and related diseases. The most important consideration supporting a NO/ONOO- cycle etiology comes from AD, where there is compelling evidence that the amyloid beta ( $A\beta$ ) protein has a causal role. The only way that  $A\beta$  can be causal, if the NO/ONOO- cycle is causal is if  $A\beta$  is part of the cycle. Strong evidence will be presented that  $A\beta$  is produced as a consequence of three cycle elements and that it, in turn, stimulates much of the cycle, acting through two known pathways of action. The role of  $A\beta$  as part of the cycle provides an explanation for the widespread impact of AD on much of the brain. It provides, for the first time, a smoking gun type of evidence supporting the NO/ONOO- cycle mechanism and confirms, therefore, the NO/ONOO- cycle as a major paradigm of human disease. This, in turn, strengthens the case for the cycle as the central cause of CFS/ME and other diseases.

It is high time, in my view, that patients with CFS/ME benefit from these various studies by focusing therapy on agents lowering the cycle instead of unnecessarily suffering from this serious disease.