PPAR agonists as new therapeutic agents for the treatment of Alzheimer’s disease

Lynn Welter-Stahl, Janine Diwo, Sander Kersten*, Paul Heuschling and Carsten Carlberg
Life Sciences Research Unit, University of Luxembourg, Gr. D. of Luxembourg
*Department of Agrotechnology and Food Sciences, University of Wageningen, The Netherlands

1 - Background

Alzheimer’s disease (AD) is the primary cause of dementia in the elderly and its increasing prevalence presents a number of social, medical and economic challenges. To date, there are no treatments that halt or reverse AD. Thus, the development of new therapeutic approaches to the disease is of critical importance and urgency.

In recent years an increasing body of evidence suggested that neuroinflammation is critical for driving the Alzheimer’s disease process. Support for this hypothesis came from epidemiological studies showing that long-term intake of non-steroidal anti-inflammatory drugs (NSAIDs) decrease the risk for developing AD and delay the onset of the disease. However, the mechanism behind these NSAIDs is still controversial.

A subset of NSAIDs binds and activates the peroxisome proliferator-activated receptor-γ (PPARγ). PPARγ is a ligand-activated transcription factor that belongs to the superfamily of nuclear receptors. The activation of PPARγ has been associated with potent anti-inflammatory as well as anti-amyloidogenic effects in cell culture and AD animal models. Unfortunately, very little is known about the molecular mechanisms that subserve these effects.

2 - Working hypothesis

Alzheimer disease is a complex disease which progression is accelerated by an inflammatory driven self-sustaining cycle. This cycle is characterised by amyloid peptides that cause microglial activation (M1-type microglia) and astrocytosis, and therefore increased secretion of pro-inflammatory cytokines. These cytokines will suppress PPARγ expression and subsequently increase BACE1 transcription and Aβ generation, initiating the whole process again.

Our key hypothesis is that PPAR agonists may provide an escape from the vicious cycle by helping microglia cells to adopt an anti-inflammatory phenotype (M2-type microglia).

3 - Preliminary results

PPARγ expression is up-regulated during the monocyte / microglia differentiation process

In monocytes: PPARγ activation has mild or no effects on pro- and anti-inflammatory mediator genes expression

In differentiating microglia: PPARγ activation downregulates pro-inflammatory and upregulates anti-inflammatory mediator genes expression

4 - Perspectives and therapeutic impact

Unravelling the cellular and molecular mechanism, through which PPARs achieve neuroprotective actions will provide novel insights into the pathogenesis of AD and will help guide the development of new therapeutic strategies. The following specific aims will be investigated:

4.1. Identification of PPAR responding genes (by microarray screening) in human microglia-like cells (differentiated THP-1, primary monocytes/macrophages) and a human neuron-like cell line (SH-SYSY). Validation of the putative PPAR target genes (by real-time PCR) in response to receptor agonists and antagonists in the context of native receptor expression as well as siRNA receptor inhibition.

4.2. Performing an in silico screening of the whole human genome for PPAR binding sites (PPRE) and comparison with a whole genome localisation of PPARs in living cells (by chromatin immunoprecipitation (ChIP)-on-chip assays). Validation of selected candidate PPREs in vitro (by gelshift and reporter gene assays) and in living cells (by ChIP assays).

4.3. Applying systems biology approaches to unify data derived from our own experiments and others reported in the literature and in databases with clinical data, to generate an in silico predictive model of nutrient-directed PPAR signalling on metabolic, amyloidogenic and inflammatory pathways.

PPARγ agonists of the thiazolidinedione class are currently prescribed for the treatment of type 2 diabetes, while PPARα agonists including fibrates are commonly prescribed for hypertriglyceridemia. If our concept of the central importance of PPAR target genes in AD is true, the availability and approval of PPAR ligands provide new therapeutic strategies and targets for the treatment of AD.