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Commentary

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PPARγ, neuroinflammation, and disease

Robert E Mrak*[1] and Gary E Landreth[2]

Address: [1]Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA and [2]Alzheimer Research Laboratory, Department of Neurosciences, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA

Email: Robert E Mrak* - mrakroberte@uams.edu; Gary E Landreth - gel2@po.cwru.edu

* Corresponding author

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Abstract

Background: Peroxisome proliferator-activated receptors (PPARs) are a class of nuclear transcription factors that are activated by fatty acids and their derivatives. One of these, PPARγ, regulates responsiveness to insulin in adipose cells, and PPARγ-activating drugs such as pioglitazone are used in the treatment of type 2 diabetes. PPARγ acts in myeloid-lineage cells, including T-cells and macrophages, to suppress their activation and their elaboration of inflammatory molecules. PPARγ activation also suppresses the activated phenotype in microglia, suggesting that PPARγ-activating drugs may be of benefit in chronic neuroinflammatory diseases. Some, but not all, nonsteroidal anti-inflammatory agents (indomethacin and ibuprofen in particular) also have activating effects on PPARγ.

Discussion and conclusions: These observations suggest on the one hand a role for PPARγ-activating drugs in the treatment of chronic neuroinflammatory diseases-as shown for a patient with secondary progressive multiple sclerosis by Pershadsingh et al. in this issue of the Journal of Neuroinflammation-and suggest on the other hand a possible explanation for confusing and contradictory results in trials of nonsteroidal anti-inflammatory agents in Alzheimer's disease.

Introduction

There are still times in modern medicine when a single patient can enlighten our understanding of a disease or disease process, and can serve as an impetus for further discovery. In this issue of Journal of Neuroinflammation, Harrihar Pershadsingh and his colleagues [1] describe stabilization and, indeed, clinical improvement in a patient with progressive secondary multiple sclerosis who was treated with pioglitazone over a three-year period. These observations suggest that larger, controlled trials of such treatment may be warranted.

The possible connection between pioglitazone and multiple sclerosis is a fascinating story in itself, and one that not only provides interesting parallels between chronic CNS inflammatory diseases and chronic peripheral diseases, but also illuminates an area of current interest for diseases such as Alzheimer's disease as well.

Discussion

Pioglitazone is currently used in the treatment of type 2 diabetes. The mechanism of action involves activation of a nuclear transcription factor known as the peroxisome proliferator-activated receptor gamma, or PPARγ, that controls lipid metabolism in adipocytes, and sensitizes these cells to insulin. PPARγ agonists also suppress T-cell activation suggesting that they may be useful in treating inflammatory diseases. Moreover, activation of PPARγ in microglia (as well as in macrophages) results in decreased activation of these cells, with decreased expression of pro-inflammatory cytokines and related molecules. This suggests that PPARγ agonists might be useful in a number of

central nervous system diseases with inflammatory components.

Peroxisomes, or microbodies as they were originally known, were discovered by early electron microscopists in the 1950s [2]. Christian de Duve, in Brussels, Belgium, subsequently isolated these structures, demonstrated hydrogen peroxide generation, and renamed them peroxisomes [3]. The discovery of PPARs grew out of the War on Cancer in the 1970s. A class of drugs was identified that promoted cancer-like growths in animals, but that did not cause DNA damage [4]. What these drugs did do was to stimulate proliferation of peroxisomes in target cells. At the time, this suggested a specific genetic trigger for tumorigenesis, and there ensued two decades of attempts to identify the receptor for these peroxisome proliferation-activating drugs.

By the 1990s, when PPARs were identified and shown to be transcription factors [5], interest had waned in cancer circles. PPARs are a class of transcription factors that are activated by fatty acids and their derivatives. They were found to control a number of genes, most of which have little or nothing to do with peroxisomes. PPARγ is important both in fat cell metabolism and in modulating cellular responsiveness to insulin - hence the connection with diabetes [6]. PPARγ-activating drugs were subsequently found to regulate T-cell responsiveness [7,8] and to suppress macrophage and microglia activation [9-11]. Both of these actions are relevant to multiple sclerosis, and may have implications for other chronic neurodegenerative diseases as well. In addition to pioglitazone, some (but not all) nonsteroidal anti-inflammatory drugs (in particular indomethacin and ibuprofen) have activating effects on PPARγ in addition to their effects on cyclooxygenase [12]. NSAID use has been linked with decreased risk of Alzheimer's disease in epidemiological studies [13-15], but prospective trials of NSAIDs in Alzheimer patients have yielded contradictory and inconclusive results [16-18]. The NSAID-PPARγ connection might explain some of these contradictions, as the only one of these clinical trials that reported a benefit was also the only one that used a PPARγ-activating drug [16]. There are currently two clinical trials in progress testing the efficacy of PPARγ agonists in AD patients.

Conclusions

Pioglitazone and related drugs activate PPARγ, and activation of PPARγ suppresses T-cell, macrophage, and microglial immune responses. If suppression of these immune responses is of potential benefit for inflammatory diseases of the brain, then pioglitazone should provide therapeutic benefit in multiple sclerosis. Multiple sclerosis, of course, is notoriously variable in its course, but the secondary progressive variant is an exception to this. Pershadsingh et al. show clinical stabilization in such a patient, treated for three years with the PPARγ-activating drug pioglitazone. This single clinical case thus provides support for a link between PPARγ activation and suppression of neuroinflammation, and suggests avenues of research for the further treatment of multiple sclerosis as well as other chronic neuroinflammatory diseases.

List of abbreviation used

PPAR – peroxisome proliferator-activated receptor

NSAID – nonsteroidal anti-inflammatory drug

Competing interests

None declared.

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