PPARs

PPARs: a new target for neuroprotection

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PPAR agonists are potential neuroprotective drugs

Peroxisome proliferators-activated receptors (PPARs) are ligand activated transcription factors belonging to the nuclear receptor superfamily.[1] Three isoforms of PPARs (α, β/δ, and γ) have been identified and display distinct physiological and pharmacological functions depending on their target genes and their tissue distribution.[2 3] Indeed, the activation of PPARα, both by natural ligands such as fatty acids and eicosanoid derivates or by synthetic ligands (lipid lowering fibrates), regulates lipid and lipoprotein metabolism.[4] Activation of PPARγ by prostaglandins or by synthetic ligands, such as anti-diabetic thiazolidinediones, regulates glucose metabolism by modulating insulin sensitivity.[4] Non-steroidal anti-inflammatory drugs are also weak agonists of PPARγ and PPARα. PPARβ/δ is one of the most widely expressed members of the PPAR family. Until recently, the function of PPARβ/δ remained elusive but recent data have shown that PPARβ/δ also plays a key role in lipid metabolism, as it regulates serum lipid profiles and fatty acid β-oxidation in muscle and adipose tissue. Synthetic ligands of PPARβ/δ are currently in preclinical phases of development.[5]

INFLAMMATORY PATHWAYS

In addition to affecting metabolic pathways, PPARs are also able to regulate inflammatory pathways by transrepression of transcription factors (NFκB) and to regulate oxidative pathways.[1] PPARα activation induces expression and activation of anti-oxidant enzymes such as superoxide dismutase or glutathione peroxidase. As regards inflammatory pathways, PPARα activation prevents the synthesis and release of cytokines (interleukin 6, tumour necrosis factor α) or the induction of some inflammatory mediators such as cyclooxygenase-2 or adhesion proteins. PPARγ activation also reduces the expression of inducible nitric oxide synthase and cyclooxygenase-2 as well as the production of proinflammatory cytokines. These mechanisms explain how activation of PPARs by synthetic ligands reduces inflammation in different tissues and different animal models of inflammatory diseases (vascular inflammation of atherosclerosis, inflammatory bowel disease, arthritis, etc).

More recently, it has been supposed that PPAR activation also helps regulate neuronal death in ischaemic, neurodegenerative, and inflammatory cerebral diseases. Firstly, PPARs have been described in brain and in spinal cord.[6 7] In addition to expression in cerebral and spinal blood vessels, PPARs are also expressed in neurons and astrocytes; oligodendrocytes exclusively show PPARβ/δ expression. The extent of this expression depends on the PPAR isoform. PPARβ/δ has been found in numerous brain regions while PPARα and PPARγ have been localised to more restricted brains areas.[7] Secondly, whatever the aetiology, neuronal death is induced by inflammatory and oxidative processes with a link between the two phenomena.[8] Inflammation and oxidative stress induce both necrotic and apoptotic neuronal death. The transcription factor NFκB plays a key role in regulating inflammation and oxidative stress leading to neuronal death, which explains why PPARs have been suggested as possible targets for neuroprotection.[9] In vitro studies have demonstrated that PPARγ agonists modulate inflammatory responses to bacterial endotoxin in brain and also prevent endotoxin induced neuronal death.[10] PPARα and PPARγ can inhibit macrophage and microglial activation which contributes to many degenerative, ischaemic, or inflammatory processes leading to neuronal death.[11] Troglitazone and ciglitazone inhibit both post-glutamate and low-potassium induced neurotoxicity in cerebellar granule neurons.[12] PPARs are also able to inhibit the entry of inflammatory cells into the CNS from the periphery by inhibition of chemokines, adhesion molecules, and metalloproteinases.[11]

ALZHEIMER'S DISEASE

PPARγ and PPARα agonists have been tested in models of Alzheimer's disease. The classical histopathological hallmarks of Alzheimer's disease include extracellular amyloid peptide (Aβ) deposition in neuritic plaques and intracellular deposits of hyperphosphorylated tau protein. This results in the formation of neurofibrillary tangles and finally neuronal death, causing progressive memory loss and decline in cognitive functions. In vitro, it has been demonstrated that a PPARα agonist inhibited Aβ stimulated expression of tumour necrosis factor α and interleukin-6 reporter genes in a dose dependent manner but failed to inhibit Aβ stimulated elaboration of neurotoxic factors.[13] Moreover, some recent experimental data suggest that fenofibrate could raise Aβ1-42 production,[14] suggesting that PPARα remains a controversial target in Alzheimer's disease. Nevertheless, clinical data suggest that the PPARα agonists used as lipid lowering agents are associated with slower cognitive decline in Alzheimer's disease.[15] PPARγ agonists were also shown to inhibit the β-amyloid stimulated expression of inflammatory cytokines and cyclooxygenase-2.[16] In addition to inhibition of Aβ induced inflammation, PPARγ could also induce clearance for the β-amyloid peptide.[17] Another mechanism of PPARγ induced neuroprotection against β-amyloid peptide neurotoxicity could involve the Wnt/β-catenin signalling pathway which is involved in neuronal development and survival and plays a role during β-amyloid neurotoxicity.[18] A last explanation for the potential effect of PPARγ in Alzheimer's disease involves the relationship between PPARγ regulated insulin resistance and Alzheimer's disease pathophysiology, since insulin may contribute to normal cognitive functioning and may also play a role in regulating the amyloid precursor protein (APP) and its derivate β-amyloid peptide.[19] In addition to in vitro data, recent in vivo data are also in favour of a beneficial effect of PPARγ activation since acute 7 day oral treatment with the PPARγ agonist pioglitazone resulted in a reduction in glial activation as well as a reduction in the number of Aβ-positive plaque areas in the hippocampus and cortex of a murine transgenic model of the amyloid pathology of Alzheimer's disease.[20]

PARKINSON'S DISEASE

PPAR agonists have also been also assessed in a model of Parkinson's disease. Parkinson's disease is characterised by a progressive loss of dopaminergic neurons in the substantia nigra, which is experimentally mimicked by systemic administration of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Oral administration of the PPARγ agonist pioglitazone attenuated MPTP induced

glial activation and prevented dopaminergic cell loss in the substantia nigra pars compacta. Pioglitazone also prevented MPTP induced expression of inducible nitric oxide synthase.[21] This protective effect of pioglitazone is also associated with an increase in inhibitory protein IκBα expression and inhibition of translocation of the NFκB subunit p65 to the nucleus in dopaminergic neurons, glial cells, and astrocytes.[22]

ISCHAEMIC STROKE

Treatment of ischaemic stroke is limited to the prevention of cerebrovascular risk factors and modulation of the coagulation cascade during the acute phase. Because fibrates, used as lipid lowering agents, contribute to secondary prevention of stroke, it has been supposed that these PPARα activators could also preventively protect the brain against noxious biological reactions induced by cerebral ischaemia such as oxidative stress and inflammation. It has been demonstrated that a 14 day preventive treatment with fenofibrate reduced susceptibility to stroke in apolipoprotein E deficient mice and also decreased cerebral infarct volume in wild type mice.[23] Fenofibrate administration is associated with: (i) an improvement in middle cerebral artery sensitivity to endothelium dependent relaxation unrelated to an increase in endothelial nitric oxide synthase expression; (ii) a decrease in cerebral oxidative stress depending on the increase in activity of numerous anti-oxidant enzymes; and (iii) the prevention of ischaemia induced vascular expression of adhesion molecules.[23] Administration of the PPARγ agonists troglitazone or pioglitazone 24 or 72 h before and at the time of cerebral infarction dramatically reduced infarction volume and improved neurological function following transient middle cerebral artery occlusion in rat.[24 25] This neuroprotective effect of PPARγ agonists is related to inhibition of ischaemia induced inflammatory markers (interleukin-1β, cyclooxygenase-2, inducible nitric oxide synthase) and to an antioxidant effect (increase expression of superoxide dismutase 1).[24 25]

MULTIPLE SCLEROSIS

Microglial activation and inflammation are key to the pathophysiology of multiple sclerosis, which is why PPAR agonists have been tested in relation to this disease, in particular in the model of experimental autoimmune encephalomyelitis (EAE), which is characterised by CNS inflammation and demyelination together with remittent paralysis.[11] Oral administration of the PPARγ agonist pioglitazone reduces motor symptom severity in monophasic EAE without delaying disease onset. In a relapsing model of EAE, pioglitazone reduces the severity of relapses and overall mortality without affecting onset and the severity of the initial attack.[26] The mechanisms of action of PPARγ agonists in EAE are complex. PPARγ activation inhibits production of nitric oxide, pro-inflammatory cytokines (tumour necrosis factor α, interleukin-1β, interleukin-6), and the chemokine MCP-1 by microglia and astrocytes.[27] Prevention of phenotypical changes to the progenitor T cells is also probably involved and related to inhibition of interleukin-12 release.[11] Moreover, PPARγ activators also modulate the maturation and differentiation of oligodendrocytes.[11] From a clinical point of view, PPARγ activators suppressed T cell proliferation by 40–50% and secretion of interferon-γ and tumour necrosis factor α by 30–50%, supporting the potential use of PPAR-γ for immunomodulation in multiple sclerosis.[28] Oral administration of gemfibrozil and fenofibrate, two PPARα agonists, also inhibits clinical signs of EAE by mechanisms involving secretion of interferon-γ and interleukin-4.[29] Preferential localisation of PPARβ/δ in oligodendrocytes and its role in oligodendrocyte differentiation suggest that PPARβ/δ could also be a pharmacological target for treatment of multiple sclerosis.[30]

CONCLUSIONS

Many experimental data now support the hypothesis that PPAR agonists could be potential neuroprotective drugs in neurodegenerative diseases, cerebral ischaemia, and multiple sclerosis. These data have been essentially obtained with PPARγ and PPARα activators while the PPARβ/δ pathway remains largely unexplored despite interest in it as a target for the treatment of multiple sclerosis. The development of new and more potent PPAR activators as well as research on the combined effects of the different isoforms of PPAR are future tasks in the area of neuroprotection and neurorepair.

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NEUROLOGICAL PICTURE

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Terson's syndrome in subarachnoid haemorrhage

A 28 year old man complained of thunderclap headache and shortly after became unconscious. Upon arrival to the emergency department he was comatose and exhibited sluggishly reactive pupils and extensor posturing. His CT scan of the brain revealed subarachnoid haemorrhage with global brain oedema (fig 1A). On careful examination, the CT scan also showed right intraocular blood (fig 1B). Fundoscopic examination confirmed the presence of right vitreous haemorrhage (Terson's syndrome). Twelve hours later the patient was declared brain dead.

Intraocular haemorrhages occur in approximately one third of patients with acute aneurysmal subarachnoid haemorrhage. The main types are intraretinal, subhyaloid without vitreous involvement, and vitreous haemorrhage (known as Terson's syndrome). Terson's syndrome, present in 5–8% of cases,[1] is the most serious form and may lead to blindness. It is commonly associated with coma, perhaps because both are caused by a sudden massive rise in intracranial pressure. While radiological findings are typically subtle,[2] more prominent intraocular haemorrhage may be noted on CT scan in very severe cases, as illustrated in this report. The management of this condition in survivors is controversial. Some experts recommend early vitrectomy to hasten visual recovery and prevent complications from proliferative vitroretinopathy.[1–3] Others advocate initial conservative approach in light of data indicating that spontaneous visual recovery often occurs.[4]

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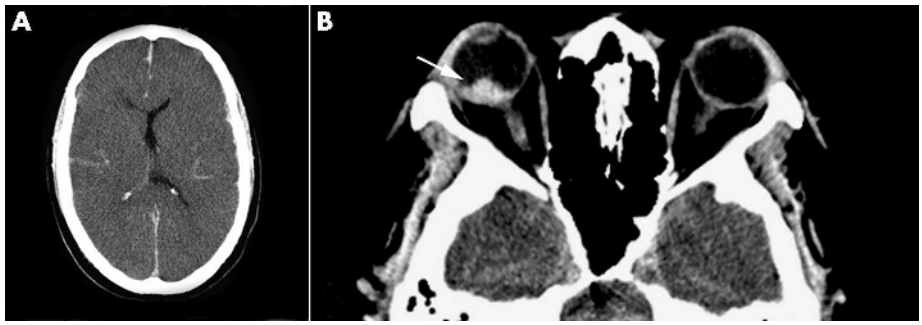

Figure 1 (A) CT scan of the brain showing subarachnoid haemorrhage with severe global brain oedema. (B) Magnified axial cut through the orbits showing a large right vitreous haemorrhage seen as a crescent-shaped hyperdense signal on the temporal retinal surface (arrow) adjacent to the optic nerve.