Rosiglitazone

Early experiments confirmed that rosiglitazone (RSG), a peroxisome proliferator-activated receptor γ (PPARγ) agonist, had therapeutic potential for the treatment of diffuse axonal injury (DAI) by inhibiting the expression of amyloid-beta precursor protein and reducing the loss and abnormal phosphorylation of tau, but the underlying mechanisms were not fully defined. In this study, we aimed to investigate a possible role for PPARγ in the protection of blood-brain barrier (BBB) integrity in a rat model of DAI, and the underlying mechanisms. PPAR agonists and antagonists were intraperitoneally injected after DAI. Treatment with RSG ameliorated axonal injury, cell apoptosis, glia activation, and the release of inflammatory factors such as TNF-α, IL-1β, and IL-6. It also increased the expression of tight junction-associated proteins like ZO-1, claudin-5, and occludin-1, whereas the PPARγ antagonist GW9662 had the opposite effects. These effects were also studied in a BBB in vitro model, consisting of a monolayer of human microvascular endothelial cells (HBMECs) subjected to oxygen and glucose deprivation (OGD). Treatment with RSG ameliorated the loss of BBB integrity and the increased permeability induced by OGD by reducing the release of inflammatory factors and maintaining the expression of tight junction-associated proteins. Interestingly, caveolin-1 was found located mainly in endothelial cells, and RSG increased the expression of caveolin-1, which decreased following OGD. In contrast, caveolin-1 siRNA abrogated the protective effects of RSG in the in vitro BBB model.

In conclusion, they provide evidence that PPARγ plays an important role in a series of processes associated with DAI, and that the PPARγ agonist RSG can protect BBB integrity by decreasing the levels of inflammatory mediators through a caveolin-1-dependent pathway.

Increasing evidence indicates that activated microglia play an important role in the inflammatory response following traumatic brain injury (TBI). Inhibiting M1 and stimulating M2 activated microglia have demonstrated protective effects in several animal models of central nervous system diseases. However, it is not clear whether the polarization of microglia to M2 attenuates axonal injury following TBI. In this study, we used a lateral fluid percussion injury device to induce axonal injury in mice. Mice were randomly assigned to the sham, TBI, TBI + rosiglitazone (peroxisome proliferator-activated receptor gamma [PPAR-γ] agonist), and TBI + GW9662 (PPAR-γ antagonist) groups. Axonal injury was assessed using immunohistochemical staining for beta amyloid precursor protein. The inflammatory response was assessed by enzyme-linked immunosorbent assay, microglia polarization was assessed using specific markers of M1 and M2 microglia, and neurological function was assessed using the neurological severity score. Following TBI, microglia of the M1 phenotype increased significantly, while those of the M2 phenotype decreased. Rosiglitazone-induced PPAR-γ activation promoted microglia polarization to the M2 phenotype, which reduced the inflammatory response, attenuated axonal injury in the cerebral cortex, and improved neurological function. Conversely, GW9662 inhibited the polarization of microglia to M2 and aggravated inflammation and axonal injury. Our in vitro findings in lipopolysaccharide-induced microglia were consistent with those of our in vivo experiments. In conclusion, the polarization of microglia to the M2 phenotype via PPAR-γ activation attenuated axonal injury following TBI in mice, which may be a potential therapeutic approach for TBI-induced axonal injury [1)].

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3. Biosci Rep. 2018 Jan 10;38(1). pii: BSR20171109. doi: 10.1042/BSR20171109. Print 2018 Feb 28.

miR-27b promotes type II collagen expression by targetting peroxisome proliferator-activated receptor-γ2 during rat articular chondrocyte differentiation.

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MicroRNAs (miRNAs) play an essential role in articular cartilage development and growth. However, the exact mechanisms involved in this process remain unknown. In the present study, we investigated the biological functions of miR-27b during hypertrophic differentiation of rat articular chondrocytes. Based on in situ hybridization and immunohistochemistry, we report that miR-27b expression is reduced in the hypertrophic zone of articular cartilage, but expression of peroxisome proliferator-activated receptor γ (Pparγ) is increased. Dual-luciferase reporter gene assay and Western blot analysis demonstrated that Pparγ2 is a target of miR-27b Overexpression of miR-27b inhibited expression of Pparγ2, as well as type X collagen (Col10a1) and matrix metalloproteinase 13 (Mmp13), while significantly promoting the expression of Sex-determining Region-box 9 (Sox9) and type II collagen (Col2a1) at both the mRNA and protein levels. Rosiglitazone, a Pparγ agonist, suppressed Col2a1 expression, while promoting expression of runt-related transcription factor 2 (Runx2) and Col10a1 in a concentration-dependent manner. siRNA-mediated knockdown of Pparγ2 caused an increase in protein levels of Col2a1. The present study demonstrates that miR-27b regulates chondrocyte hypertrophy in part by targetting Pparγ2, and that miR-27b may have important therapeutic implications in cartilage diseases.

DOI: 10.1042/BSR20171109 PMID: 29187585 [Indexed for MEDLINE]

4. Endocr Pract. 2017 Aug;23(8):962-970. doi: 10.4158/EP171787.OR. Epub 2017 Jun 14.

BIOCHEMICAL CONTROL DURING LONG-TERM FOLLOW-UP OF 230 ADULT PATIENTS WITH CUSHING DISEASE: A MULTICENTER RETROSPECTIVE STUDY.

Geer EB, Shafiq I, Gordon MB, Bonert V, Ayala A, Swerdloff RS, Katznelson L, Lalazar Y, Manuylova E, Pulaski-Liebert KJ, Carmichael JD, Hannoush Z, Surampudi V, Broder MS, Cherepanov D, Eagan M, Lee J, Said Q, Neary MP, Biller BMK.

OBJECTIVE: Cushing disease (CD) results from excessive exposure to glucocorticoids caused by an adrenocorticotropic hormone-secreting pituitary tumor. Inadequately treated CD is associated with significant morbidity and elevated mortality. Multicenter data on CD patients treated in routine clinical practice are needed to assess treatment outcomes in this rare disorder. The study purpose was to describe the burden of illness and treatment outcomes for CD patients. METHODS: Eight pituitary centers in four U.S. regions participated in this multicenter retrospective chart review study. Subjects were CD patients diagnosed at ≥18 years of age within the past 20 years. Descriptive statistical analyses were conducted to examine presenting signs, symptoms, comorbidities, and treatment

outcomes. RESULTS: Of 230 patients, 79% were female (median age at diagnosis, 39 years; range, 18 to 78 years). Length of follow-up was 0 to 27.5 years (median, 1.9 years). pituitary neuroendocrine tumors were 0 to 51 mm. The most common presenting comorbidities included hypertension (67.3%), polycystic ovary syndrome (43.5%), and hyperlipidemia (41.5%). Biochemical control was achieved with initial pituitary surgery in 41.4% patients (91 of 220), not achieved in 50.0% of patients (110 of 220), and undetermined in 8.6% of patients (19 of 220). At the end of follow-up, control had been achieved with a variety of treatment methods in 49.1% of patients (110 of 224), not achieved in 29.9% of patients (67 of 224), and undetermined in 21.0% of patients (47 of 224). CONCLUSION: Despite multiple treatments, at the end of follow-up, biochemical control was still not achieved in up to 30% of patients. These multicenter data demonstrate that in routine clinical practice, initial and long-term control is not achieved in a substantial number of patients with CD. ABBREVIATIONS: BLA = bilateral adrenalectomy CD = Cushing disease CS = Cushing syndrome eCRF = electronic case report form MRI = magnetic resonance imaging PCOS = polycystic ovary syndrome.

DOI: 10.4158/EP171787.OR PMID: 28614003 [Indexed for MEDLINE]

5. Toxicol Sci. 2017 Oct 1;159(2):290-306. doi: 10.1093/toxsci/kfx093.

Insulin Resistance Disrupts the Interaction Between AKT and the NMDA Receptor and the Inactivation of the CaMKIV/CREB Pathway in Minimal Hepatic Encephalopathy.

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Erratum in

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Toxicol Sci. 2018 Jan 1;161(1):208.
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Hepatic cirrhosis-induced Minimal hepatic encephalopathy (MHE) has been characterized for cognitive dysfunction and central nervous system (CNS) insulin resistance (IR) has been acknowledged to be closely correlated with cognitive impairment while hepatic cirrhosis has been recognized to induce IR. Thus, this study aimed to investigate whether CNS IR occurred in MHE and induced MHE, as well as the underlying mechanism. We found IR in the MHE rats, an especially decreased level of the insulin receptor (InsR), and an increased serine phosphorylation of IRS1 in CNS. PI3K/AKT pathway signaling to the phosphorylation of N-Methyl-d-Aspartate receptors (NMDA receptors, NRs, NR1/NR2B) and downstream activation of the CaMKIV/CREB pathway and final production of neurotrophic factors were triggered by insulin, but impaired in the MHE rats. Additionally, CNS IR, memory impairment, the desensitization of the PI3K/AKT/NMDA receptor (NR)/CaMKIV/CREB pathway and decreased production of BDNF/NT3 in MHE rats were improved by rosiglitazone (RSG). These results suggested that IR, which induces the deficits in the insulin-mediated PI3K/AKT/NR/CaMKIV/CREB/neurotrophin pathway and subsequent memory decline, contributes to the pathogenesis of MHE.

DOI: 10.1093/toxsci/kfx093 PMID: 28505381 [Indexed for MEDLINE]

6. Neural Regen Res. 2016 Jun;11(6):944-50. doi: 10.4103/1673-5374.184493.

Rosiglitazone ameliorates diffuse axonal injury by reducing loss of tau and up-regulating caveolin-1 expression.

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Rosiglitazone up-regulates caveolin-1 levels and has neuroprotective effects in both chronic and acute brain injury. Therefore, we postulated that rosiglitazone may ameliorate diffuse axonal injury via its ability to up-regulate caveolin-1, inhibit expression of amyloid-beta precursor protein, and reduce the loss and abnormal phosphorylation of tau. In the present study, intraperitoneal injection of rosiglitazone significantly reduced the levels of amyloid-beta precursor protein and hyperphosphorylated tau (phosphorylated at Ser(404)(p-tau (S(404))), and it increased the expression of total tau and caveolin-1 in the rat cortex. Our results show that rosiglitazone inhibits the expression of amyloid-beta precursor protein and lowers p-tau (S(404)) levels, and it reduces the loss of total tau, possibly by up-regulating caveolin-1. These actions of rosiglitazone may underlie its neuroprotective effects in the treatment of diffuse axonal injury.

DOI: 10.4103/1673-5374.184493 PMCID: PMC4962592 PMID: 27482223

7. Biochem Biophys Res Commun. 2016 Sep 9;478(1):439-445. doi: 10.1016/j.bbrc.2016.06.154. Epub 2016 Jul 1.

Sirtuin1 promotes osteogenic differentiation through downregulation of peroxisome proliferator-activated receptor γ in MC3T3-E1 cells.

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Osteoporosis is a skeletal disorder characterized by bone loss, resulting in architectural deterioration of the skeleton, decreased bone strength and an increased risk of fragility fractures. Strengthening osteogenesis is an effective way to relieve osteoporosis. Sirtuin1 (Sirt1) is a nicotinamide adenine dinucleotide (NAD(+))-dependent deacetylase, which is reported to be involved in improving osteogenesis. Sirt1 targets peroxisome proliferator-activated receptor γ (PPARγ) in the regulation of adipose tissues; however, the molecular mechanism of Sirt1 in osteogenic differentiation is still unknown. PPARγ tends to induce more adipogenic differentiation rather than osteogenic differentiation. Hence, we hypothesized that Sirt1 facilitates osteogenic differentiation through downregulation of PPARγ signaling. Mouse pre-osteoblastic MC3T3-E1 cells were cultured under osteogenic medium. Sirt1 was overexpressed through plasmid transfection. The results showed that high expression of Sirt1 was associated with increased osteogenic differentiation, as indicated by quantitative PCR and Western blot analysis of osteogenic markers, and Von Kossa staining. Sirt1 overexpression also directly and negatively regulated the expression of PPARγ and its downstream molecules. Use of the PPARγ agonist Rosiglitazone, reversed the effects of Sirt1 on osteogenic differentiation. Using constructed luciferase plasmids, we demonstrated a role of Sirt1 in inhibiting PPARγ-induced activity and expression of adipocyte-specific genes, including acetyl-coenzyme A

carboxylase (Acc) and fatty acid binding protein 4 (Fabp4). The interaction between Sirt1 and PPARγ was further confirmed using co-immunoprecipitation analysis. Together, these results reveal a novel mechanism for Sirt1 in osteogenic differentiation through downregulation of PPARγ activity. These findings suggest that the Sirt1-PPARγ pathway may represent a potential target for enhancement of osteogenesis and treatment of osteoporosis.

DOI: 10.1016/j.bbrc.2016.06.154 PMID: 27378422 [Indexed for MEDLINE]

8. Biochem Biophys Res Commun. 2016 Apr 15;472(4):648-55. doi: 10.1016/j.bbrc.2016.03.003. Epub 2016 Mar 3.

Rosiglitazone attenuates inflammation and CA3 neuronal loss following traumatic brain injury in rats.

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Rosiglitazone, a potent peroxisome proliferator-activated receptor (PPAR)-γ agonist, has been shown to confer neuroprotective effects in stroke and spinal cord injury, but its role in the traumatic brain injury (TBI) is still controversial. Using a controlled cortical impact model in rats, the current study was designed to determine the effects of rosiglitazone treatment (6 mg/kg at 5 min, 6 h and 24 h post injury) upon inflammation and histological outcome at 21 d after TBI. In addition, the effects of rosiglitazone upon inflammatory cytokine transcription, vestibulomotor behavior and spatial memory function were determined at earlier time points (24 h, 1-5 d, 14-20 d post injury, respectively). Compared with the vehicle-treated group, rosiglitazone treatment suppressed production of TNFα at 24 h after TBI, attenuated activation of microglia/macrophages and increased survival of CA3 neurons but had no effect on lesion volume at 21 d after TBI. Rosiglitazone-treated animals had improved performance on beam balance testing, but there was no difference in spatial memory function as determined by Morris water maze. In summary, this study indicates that rosiglitazone treatment in the first 24 h after TBI has limited anti-inflammatory and neuroprotective effects in rat traumatic injury. Further study using an alternative dosage paradigm and more sensitive behavioral testing may be warranted.

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9. Mol Med Rep. 2015 Nov;12(5):6591-7. doi: 10.3892/mmr.2015.4292. Epub 2015 Sep 7.

Rosiglitazone exerts neuroprotective effects via the suppression of neuronal autophagy and apoptosis in the cortex following traumatic brain injury.

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Traumatic brain injury (TBI) is one of the leading causes of mortality and morbidity in adults and children worldwide. Recent studies have demonstrated that both apoptosis and autophagy participate in TBI-induced neuronal cell death and functional loss. The peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist rosiglitazone (RSG) is a well-known anti-inflammatory, which carries out its effects via the activation of PPAR-γ. Previous studies have suggested that RSG may exert neuroprotective effects in animal models of both chronic and acute brain injury; however, whether RSG is involved in autophagic neuronal death following TBI remains to be elucidated. The present study aimed to determine whether RSG carries out its neuroprotective properties via the attenuation of neuronal apoptosis and autophagy, following TBI in a rat model. Furthermore, the role of RSG was investigated with regards to the modulation of inflammation and glutamate excitotoxicity, and the impact of RSG on functional recovery following TBI was determined. The rats were subjected to controlled cortical impact injury, prior to being randomly divided into three groups: A sham-operated group, a TBI group, and an RSG treatment group. The RSG treatment group was intraperitoneally treated with 2 mg/kg RSG immediately after TBI. The results of the present study demonstrated that RSG treatment following TBI significantly reduced neuronal apoptosis and autophagy, and increased functional recovery. These effects were correlated with a decrease in the protein expression levels of tumor necrosis factor α and interleukin-6. However, no significant changes were observed in the protein expression levels of glutamate transporter-1 in the brain cortex. The results of the present study provide in vivo evidence that RSG may exert neuroprotective effects via the inhibition of neuronal apoptosis and autophagy following experimental TBI in rats, and the mechanism underlying these effects may be associated with the anti-inflammatory action of RSG. The present study offers a novel insight into the potential use of RSG as a neuroprotective agent for the treatment of cerebral injuries.

DOI: 10.3892/mmr.2015.4292 PMCID: PMC4626137 PMID: 26351751 [Indexed for MEDLINE]

10. Brain Res. 2015 Oct 22;1624:199-207. doi: 10.1016/j.brainres.2015.07.025. Epub 2015 Jul 26.

Rosiglitazone attenuates early brain injury after experimental subarachnoid hemorrhage in rats.

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Early brain injury (EBI) plays a crucial role in the pathological progress of subarachnoid hemorrhage (SAH). This study was designed to determine whether rosiglitazone protects the brain against EBI in rats, and discuss the role of the anti-apoptotic mechanism mediated by Bcl-2 family proteins in this neuroprotection. 86 male Sprague-Dawley rats were divided into the sham group, the SAH+ vehicle group and the SAH+ rosiglitazone group. SAH was induced via an endovascular perforation technique and rosiglitazone (3mg/kg) or vehicle was administered. Mortality, neurological scores, brain water content, Evans blue dye assay, TUNEL stain assay, Gelatin zymography, and western blot analysis were performed. Rosiglitazone significantly improved mortality, neurological scores, brain water content, blood brain barrier (BBB) and apoptosis compared with the vehicle group within 24h after SAH. The TUNEL staining assay demonstrated that apoptosis was ameliorated. Cleaved Caspase-3 and MMP-9 expression was reduced, whereas Bcl-2 and p-Bad was markedly preserved by rosiglitazone. A significant elevation of p-Akt was detected after rosiglitazone treatment. Our study demonstrated that

rosiglitazone plays a neuroprotective role in EBI after SAH via attenuation of BBB disruption, brain edema and apoptosis.

DOI: 10.1016/j.brainres.2015.07.025 PMID: 26220473 [Indexed for MEDLINE]

11. Acta Neurochir (Wien). 2014 Nov;156(11):2103-9. doi: 10.1007/s00701-014-2196-4. Epub 2014 Aug 20.

The role of rosiglitazone in the proliferation of vascular smooth muscle cells after experimental subarachnoid hemorrhage.

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BACKGROUND: Recent evidence has demonstrated that rosiglitazone can attenuate cerebral vasospasm following subarachnoid hemorrhage (SAH). Some studies have shown that rosiglitazone can suppress inflammation and immune responses after SAH. However, the precise molecular mechanisms by which cerebral vasospasm is attenuated is not clear. METHODS: In this study, SAH was created using a “double hemorrhage” injection rat model. Rats were randomly divided into three groups and treated with saline (control group), untreated (SAH group), or treated with rosiglitazone. Using immunocytochemistry, hematoxylin and eosin (HE) staining, and measurement of the basilar artery, we investigated the formation of pathologic changes in the basilar artery, measured the expression of caveolin-1 and proliferating cell nuclear antigen (PCNA), and investigated the role of rosiglitazone in vascular smooth muscle cell (VSMC) proliferation in the basilar artery after SAH. RESULTS: In this study, we observed significant pathologic changes in the basilar artery after experimental SAH. The level of vasospasm gradually increased with time during the 1st week, peaked on day 7, and almost recovered on day 14. After rosiglitazone treatment, the level of vasospasm was significantly attenuated in comparison with the SAH group. Immunocytochemistry staining showed that caveolin-1 expression was significantly increased in the rosiglitazone group, compared with the SAH group. Inversely, the expression of PCNA showed a notable decrease after rosiglitazone treatment. CONCLUSIONS: The results indicate that rosiglitazone can attenuate cerebral vasospasm following SAH. Up-regulation of caveolin-1 by rosiglitazone may be a new molecular mechanism for this response, which is to inhibit proliferation of VSMCs after SAH, and this study may provide a novel insight to prevent delayed cerebral vasospasm (DCVS).

DOI: 10.1007/s00701-014-2196-4 PMID: 25139403 [Indexed for MEDLINE]

12. Biomed Res Int. 2014;2014:309151. doi: 10.1155/2014/309151. Epub 2014 Feb 13.

Rosiglitazone increases cerebral klotho expression to reverse baroreflex in type 1-like diabetic rats.

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Reduced baroreflex sensitivity (BRS) is widely observed in diabetic human and animals. Rosiglitazone is one of the clinically used thiazolidinediones (TZD) known as PPAR γ agonist. Additionally, the klotho protein produced from choroid plexus in the central nervous system is regulated by PPAR γ . In an attempt to develop the new therapeutic strategy, we treated streptozotocin-induced diabetic rats (STZ) with rosiglitazone (STZ + TZD) orally at 10 mg/kg for 7 days. Also, STZ rats were subjected to intracerebroventricular (ICV) infusion of recombinant klotho at a dose of 3 μ g/2.5 μ L via syringe pump (8 μ g/hr) daily for 7 days. The BRS and heart rate variability were then estimated under challenge with a depressor dose of sodium nitroprusside (50 μ g/kg) or a pressor dose of phenylephrine (8 μ g/kg) through an intravenous injection. Lower expression of klotho in medulla oblongata of diabetic rats was identified. Cerebral infusion of recombinant klotho or oral administration of rosiglitazone reversed BRS in diabetic rats. In conclusion, recovery of the decreased klotho in brain induced by rosiglitazone may restore the impaired BRS in diabetic rats. Thus, rosiglitazone is useful to reverse the reduced BRS through increasing cerebral klotho in diabetic disorders.

DOI: 10.1155/2014/309151 PMCID: PMC3943406 PMID: 24683546 [Indexed for MEDLINE]

13. J Cereb Blood Flow Metab. 2013 Jan;33(1):106-14. doi: 10.1038/jcbfm.2012.138. Epub 2012 Oct 3.

Prevention of JNK phosphorylation as a mechanism for rosiglitazone in neuroprotection after transient cerebral ischemia: activation of dual specificity phosphatase.

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Rosiglitazone, a synthetic peroxisome proliferator-activated receptor-γ (PPARγ) agonist, prevents cell death after cerebral ischemia in animal models, but the underlying mechanism has not been clarified. In this study, we examined how rosiglitazone protects neurons against ischemia. Mice treated with rosiglitazone were subjected to 60 minutes of focal ischemia followed by reperfusion. Rosiglitazone reduced infarct volume after ischemia and reperfusion. We show that this neuroprotective effect was reversed with a PPARγ antagonist. Western blot analysis showed a significant increase in expression of phosphorylated stress-activated protein kinases (c-Jun N-terminal kinase (JNK) and p38) in ischemic brain tissue. Rosiglitazone blocked this increase. Furthermore, we observed that rosiglitazone increased expression of the dual-specificity phosphatase 8 (DUSP8) protein and messenger RNA in ischemic brain tissue. Dual-specificity phosphatase 8 is a mitogen-activated protein kinase phosphatase that can dephosphorylate JNK and p38. Another key finding of the present study was that knockdown of DUSP8 in primary cultured cortical neurons that were subjected to oxygen-glucose deprivation diminished rosiglitazone's effect on downregulation of JNK phosphorylation. Thus, rosiglitazone's neuroprotective effect after ischemia is mediated by blocking JNK phosphorylation induced by ischemia via DUSP8 upregulation.

DOI: 10.1038/jcbfm.2012.138 PMCID: PMC3597369 PMID: 23032483 [Indexed for MEDLINE]

14. Neurochem Res. 2012 Oct;37(10):2076-84. doi: 10.1007/s11064-012-0828-8. Epub 2012 Jun 16.

Rosiglitazone suppresses glioma cell growth and cell cycle by blocking the transforming growth factor-beta mediated pathway.

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Glioma is one of the most malignant tumors in the central nervous system. As a peroxisome proliferator-activated receptor γ (PPAR-γ) activator, the thiazolidinediones (TZDs) induce growth arrest and cell death in a broad spectrum of tumor cells. In this study, we investigated the role of rosiglitazone in glioma cells. We found that rosiglitazone, a member of TZDs, suppresses growth of human glioma cell lines U87 and U251. Rosiglitazone also induces cell cycle arrest and apoptosis, which may be the mechanism of its anti-proliferation effect. Next, we found that rosiglitazone suppresses the expression of TGF-beta and its receptor TGF-betaR2, and suppresses phosphorylation of Smad3. Rosiglitazone also inhibits formation of the Smad3/Smad4 complex. Furthermore, Rosiglitazone affects the expression of Smad3/Smad4 associated regulators of gene expression, including p21 and c-Myc. These results suggest that rosiglitazone suppresses growth and cell cycle of human glioma cells by blocking the TGF-beta mediated pathway.

DOI: 10.1007/s11064-012-0828-8 PMID: 22707243 [Indexed for MEDLINE]

15. Folia Neuropathol. 2011;49(2):142-51.

Rosiglitazone protects the dorsal root ganglion cells and sciatic nerve after crush in rat.

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The aim of this study was to investigate the histological changes in the dorsal root ganglion (DRG) and the sciatic nerve in rats after sciatic nerve crush (SNC) and treatment with rosiglitazone. The rats were divided into four groups, each including seven animals, and underwent the following intervention. Group I: control animals which received carboxy methyl cellulose (0.5 w/v, p.o.). Group II: sham operated animals whose skin of the posterior thigh was opened, closed and the animals received the vehicle (carboxy methyl cellulose). Group III: SNC animals; the animals received the vehicle. Group IV: SNC with rosiglitazone (5 mg/kg body weight/day) dissolved in the vehicle. On the 28th day the fifth lumbar DRG and sciatic nerve were removed. Volume of the dorsal root ganglion, total volume and number of cells (A and B cells) of DRG, total surface area of the cells, and total number, diameter and cross-sectional area of the myelinated nerve fibres were estimated using stereological techniques. No change was observed in volume of the DRG, but all of the other parameters were decreased after nerve crush. In SNC+ rosiglitazone treated rats, the parameters decreased but to a lesser extent in comparison with the non-treated SNC group. It can be concluded that rosiglitazone has a protective effect on the DRG cells and sciatic nerve after crush in rats.

PMID: 21845544 [Indexed for MEDLINE]

16. J Int Med Res. 2011;39(3):805-14.

Effects of a single dose of methylprednisolone versus three doses of rosiglitazone on nerve growth factor levels after spinal cord injury.

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Acute spinal cord lesions result in dramatic changes in neuronal function. Studies have shown that the

peroxisome proliferator-activated receptor-γ agonist, rosiglitazone, has neuroprotective properties. The effect of rosiglitazone after acute spinal cord injury was examined in the present study. Rats were subjected to laminectomy only; laminectomy with spinal cord contusion injury; laminectomy with contusion injury plus 30 mg/kg body weight methylprednisolone administered 5 min after surgery; or laminectomy with contusion injury plus 2 mg/kg body weight rosiglitazone administered intraperitoneally 5 min, 6 h and 24 h after surgery. Both drugs increased neurotrophin gene and protein expression 24 h after injury compared with injured rats without drug treatment. Rosiglitazone increased neurotrophin expression at 7 days to a greater extent than methylprednisolone. Early functional recovery was observed in rats treated with rosiglitazone. The greater increase in rosiglitazone-induced nerve growth factor expression soon after injury could explain, at least in part, the improved recovery of motor function compared with methylprednisolone or saline.

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17. PLoS One. 2011 Mar 30;6(3):e14787. doi: 10.1371/journal.pone.0014787.

MHC mismatch inhibits neurogenesis and neuron maturation in stem cell allografts.

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BACKGROUND: The role of histocompatibility and immune recognition in stem cell transplant therapy has been controversial, with many reports arguing that undifferentiated stem cells are protected from immune recognition due to the absence of major histocompatibility complex (MHC) markers. This argument is even more persuasive in transplantation into the central nervous system (CNS) where the graft rejection response is minimal. METHODOLOGY/PRINCIPAL FINDINGS: In this study, we evaluate graft survival and neuron production in perfectly matched vs. strongly mismatched neural stem cells transplanted into the hippocampus in mice. Although allogeneic cells survive, we observe that MHC-mismatch decreases surviving cell numbers and strongly inhibits the differentiation and retention of graft-derived as well as endogenously produced new neurons. Immune suppression with cyclosporine-A did not improve outcome but non-steroidal anti-inflammatory drugs, indomethacin or rosiglitazone, were able to restore allogeneic neuron production, integration and retention to the level of syngeneic grafts. CONCLUSIONS/SIGNIFICANCE: These results suggest an important but unsuspected role for innate, rather than adaptive, immunity in the survival and function of MHC-mismatched cellular grafts in the CNS.

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Therapeutic potential of peroxisome proliferator-activated receptor γ agonist rosiglitazone in cerebral vasospasm after a rat experimental subarachnoid hemorrhage model.

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The pathogenesis of cerebral vasospasm is closely associated with inflammation and immune response in arterial walls. Recently, the authors proved the key role of Toll-like receptor (TLR)4 in the

development of vasospasm in experimental subarachnoid hemorrhage (SAH) model. Because peroxisome proliferator-activated receptor (PPAR) gamma agonists are identified as effective inhibitors of TLR4 activation, we investigated the anti-inflammation properties of PPAR-gamma agonist rosiglitazone in basilar arteries in a rat experimental SAH model and evaluated the effects of rosiglitazone on vasospasm. Inflammatory responses in basilar arteries were assessed by immunohistochemical staining for intercellular molecule (ICAM)-1 and myeloperoxidase (MPO). Expression of TLR4 was determined by western blot analysis. The degree of cerebral vasospasm was evaluated by measuring the mean diameter and cross-sectional area of basilar arteries. Rosiglitazone suppressed the SAH-induced inflammatory responses in basilar arteries by inhibiting the TLR4 signalling. Furthermore, rosiglitazone could attenuate cerebral vasospasm following SAH. Therefore, we suggested that PPAR-gamma agonists may be potential therapeutic agents for cerebral vasospasm.

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Cytotoxic effect of different statins and thiazolidinediones on malignant glioma cells.

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PURPOSE: Glioblastoma multiforme is still a tumor with very poor prognosis. Statins are actually used for the treatment of dyslipidemias and thiazolidinediones for improving insulin sensitivity in diabetes. Statins are inhibitors of the cholesterol pathway, while thiazolidinediones are peroxisomal proliferator activator receptor γ (PPAR) agonists. For both, a potent pro-apoptotic activity has been suggested. METHODS: We compared the antiglioma effect of simvastatin, atorvastatin, lovastatin, pravastatin, rosuvastatin, rosiglitazone, pioglitazone and their combinations at several concentrations on human glioblastoma cell lines U87, U 138, LN 405 and rat RG II. The cytotoxic effect was assessed using a cell proliferation assay after 48 and 144 h. Caspase 3 activity and the addition of isoprenoids and PPAR-γ inhibitor GW9662 were assessed. Experiments were as well conducted under hypoxia for 24 h. RESULTS: We demonstrated a significant cytotoxic effect with a combination of statins plus pioglitazone. The effect was observed after 48 h and dramatically increased after 144 h. The combination of 2 types of statins (synthetic and natural) allowed a fivefold dose reduction. Statin effect was reversed with isoprenoids and partially with PPAR-γ antagonists, while thiazolidinediones effect was slightly affected by PPAR-γ antagonists. A marked increase in caspase 3 activity was achieved by combining atorvastatin with lovastatin. Cytotoxicity of the combination of statins and thiazolidinediones did not decrease under hypoxia. CONCLUSION: The assessed combination of statins with thiazolidinediones shows a synergistic cytotoxic effect against glioblastoma cells in vitro, which could represent a feasible therapeutic schema.

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20. Front Aging Neurosci. 2010 May 21;2. pii: 21. doi: 10.3389/fnagi.2010.00021. eCollection 2010.

The Nuclear Receptor PPARgamma as a Therapeutic Target for Cerebrovascular and Brain Dysfunction in Alzheimer's Disease.

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Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear transcription factors that regulate peripheral lipid and glucose metabolism. Three subtypes make up the PPAR family (alpha, gamma, beta/delta), and synthetic ligands for PPARalpha (fibrates) and PPARgamma (Thiazolidinediones, TZDs) are currently prescribed for the respective management of dyslipidemia and type 2 diabetes. In contrast to the well characterized action of PPARs in the periphery, little was known about the presence or function of these receptors in the brain and cerebral vasculature until fairly recently. Indeed, research in the last decade has uncovered these receptors in most brain cell types, and has shown that their activation, particularly that of PPARgamma, is implicated in normal brain and cerebrovascular physiology, and confers protection under pathological conditions. Notably, accumulating evidence has highlighted the therapeutic potential of PPARgamma ligands in the treatment of brain disorders such as Alzheimer's disease (AD), leading to the testing of the TZDs pioglitazone and rosiglitazone in AD clinical trials. This review will focus on the benefits of PPARgamma agonists for vascular, neuronal and glial networks, and assess the value of these compounds as future AD therapeutics in light of evidence from transgenic mouse models and recent clinical trials.

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21. Brain Res. 2010 Mar 31;1322:102-8. doi: 10.1016/j.brainres.2010.01.073. Epub 2010 Feb 2.

Peroxisome proliferator-activated receptor gamma agonist rosiglitazone attenuates oxyhemoglobin-induced Toll-like receptor 4 expression in vascular smooth muscle cells.

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Inflammation and immune response have been implicated in the pathogenesis of cerebral vasospasm after subarachnoid hemorrhage (SAH). Recently, increased TLR4 expression has been associated with the development of cerebral vasospasm in a rabbit model of SAH. Peroxisome proliferator-activated receptor gamma (PPARgamma) agonists, effective inhibitors of TLR4 activation, may modulate the vasospasm progression via their anti-inflammation effects. We investigate whether the blood component oxyhemoglobin (OxyHb) can induce the expression of Toll-like receptor (TLR) 4 in vascular smooth muscle cells (VSMCs), and evaluate the modulatory effects of PPARgamma agonist rosiglitazone on OxyHb-induced inflammation in VSMCs. Cultured VSMCs incubated with or without rosiglitazone were exposed to OxyHb at 10muM for up to 48h. Expression of TLR4 was assessed by immunocytochemistry and Western blot analysis. Production of tumor necrosis factor alpha (TNF-alpha) in conditioned medium were quantified by ELISA. A marked increase of TLR4 production and TNF-alpha release was observed at 48h after cells were treated with OxyHb. Rosiglitazone reduced TLR4 immunocytochemistry staining and protein production significantly in VSMCs. A specific antagonist for PPARgamma, GW9662, could reverse the anti-inflammatory effects of rosiglitazone. The results demonstrated that OxyHb exposure could induce TLR4 activation in cultured VSMCs. Rosiglitazone suppressed TLR4 expression and cytokine release via the activation of PPARgamma and may have a therapeutic potential for the treatment of vasospasm following SAH.

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No effect of the PPAR-gamma agonist rosiglitazone on ACTH or cortisol secretion in Nelson's syndrome and Cushing's disease in vitro and in vivo.

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OBJECTIVE: Surgical tumor resection remains the primary treatment strategy in ACTH-secreting pituitary neuroendocrine tumors, i.e. Cushing's disease (CD) and Nelson's syndrome (NS). However, an effective long-term pharmacological regime is not available in patients with persistent ACTH-hypersecretion. The nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-gamma) is abundantly expressed in most pituitary neuroendocrine tumors. First encouraging data reported that the PPAR-gamma ligand rosiglitazone antagonizes ACTH hypersecretion and exerts also antiproliferative effects in pituitary cell lines. Herein, we studied the potential therapeutical effects of rosiglitazone in patients with ACTH-secreting pituitary neuroendocrine tumors in vitro and in vivo. MATERIALS AND METHODS: Seven patients with persistent ACTH-hypersecretion (3 with NS, 4 with persistent CD) were treated 5 months with rosiglitazone (4 - 16 mg/day). In vitro assays were performed in primary cell cultures obtained from eight additional patients with ACTH-secreting pituitary neuroendocrine tumors applying 80 microM rosiglitazone repeatedly over a time period of 14 days. RESULTS: Our long-term clinical trial with the PPAR-gamma activator rosiglitazone showed no amelioration of clinical symptoms nor an inhibiting effect on ACTH-secretion in vivo. In vitro, rosiglitazone treatment led to a statistically significant decrease of ACTH levels in 2 out of 8 primary cell cultures after 14 days compared to untreated controls. CONCLUSION: In contrast to the initially promising laboratory data gathered in pituitary cell line experiments and nude mice models, our experimental data obtained in primary human ACTH-expressing pituitary neuroendocrine tumor cell cultures as well as our clinical experience with a long-term rosiglitazone trial in approved antidiabetic doses support the recently reported disappointing reports on acute or short-term medical treatment of ACTH-hypersecretion with PPAR-gamma activators.

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[The medical management of Cushing's syndrome].

[Article in Spanish]

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Cushing's syndrome results from prolonged exposure to excessive circulating glucocorticosteroids and is associated with significant morbidity and mortality. While the treatment of choice in most patients is surgical, the metabolic consequences of this syndrome, including hypertension and diabetes mellitus, increase the risks of such surgery. Hypercortisolemia and its sequelae can be efficiently reversed or controlled using medical therapy, either as a temporary measure prior to definitive

treatment or as a longer-term treatment in some particularly difficult cases. Drug treatment has been targeted at the hypothalamic/pituitary level, the adrenal glands and at glucocorticoid receptors. The present review discusses the pharmacotherapeutic agents that have been used in Cushing's syndrome and the criteria for their use, as well as recent drugs that may improve the medical treatment of this complex endocrinological disorder in the future. Finally, the short-and long-term follow-up of patients with Cushing's syndrome after surgery is also discussed.

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PPARalpha and PPARgamma effectively protect against HIV-induced inflammatory responses in brain endothelial cells.

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Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors which down-regulate inflammatory signaling pathways. Therefore, we hypothesized that alterations of PPAR functions can contribute to human immunodeficiency virus-1 (HIV-1)-induced dysfunction of brain endothelial cells. Indeed, treatment with HIV-1 transactivator of transcription (Tat) protein decreased PPAR transactivation in brain endothelial cells. We next stably over-expressed PPARalpha and PPARgamma in a newly developed cell line of human brain endothelial cells (hCMEC/D3 cells). Tat-induced up-regulation of inflammatory mediators, such as interleukin (IL)-1beta, tumor necrosis factor-alpha, CCL2, and E-selectin were markedly attenuated in hCMEC/D3 over-expressing PPARalpha or PPARgamma. These results were confirmed in CCL2 and E-selectin promoter activity studies. Similar protective effects were observed in hCMEC/D3 after activation of PPARgamma by exogenous PPAR agonists (dPGJ(2) and rosiglitazone). PPAR over-expression also prevented Tat-induced binding activity and transactivation of nuclear factor-kappaB. Importantly, increased PPAR activity attenuated induction of IL-1beta, tumor necrosis factor-alpha, CCL2, and E-selectin in hCMEC/D3 cells co-cultured with HIV-1-infected Jurkat cells. The protective effects of PPAR over-expression were reversed by the antagonists of PPARalpha (MK886) or PPARgamma (GW9662). The present data suggest that targeting PPAR signaling may provide a novel therapeutic approach to attenuate HIV-1-induced local inflammatory responses in brain endothelial cells.

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25. Brain Res. 2008 Jun 18;1215:218-24. doi: 10.1016/j.brainres.2008.04.025. Epub 2008 Apr 22.

Rosiglitazone, a PPAR gamma agonist, attenuates inflammation after surgical brain injury in rodents.

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INTRODUCTION: Surgical brain injury (SBI) is unavoidable during many neurosurgical procedures. This inevitable brain injury can result in post-operative complications including brain edema, blood-brain barrier disruption (BBB) and cell death in susceptible areas. Rosiglitazone (RSG), a PPAR-gamma agonist, has been shown to reduce inflammation and provide neuroprotection in experimental models

of ischemia and intracerebral hemorrhage. This study was designed to evaluate the neuroprotective effects of RSG in a rodent model of SBI. METHODS: 65 adult male Sprague-Dawley rats were randomly divided into sham, vehicle and treatment groups. RSG was administered intraperitoneally in two dosages (1 mg/kg/dose, 6 mg/kg/dose) 30 min before surgery, and 30 min and 4 h after surgery. Animals were euthanized 24 h following neurological evaluation to assess brain edema and BBB permeability by IgG staining. Inflammation was examined using myeloperoxidase (MPO) assay and double-labeling fluorescent immunohistochemical analysis of IL-1beta and TNF-alpha. RESULTS: Localized brain edema was observed in tissue surrounding the surgical injury. This brain edema was significantly higher in rats subjected to SBI than sham animals. Increased IgG staining was present in affected brain tissue; however, RSG reduced neither IgG staining nor brain edema. RSG also did not improve neurological status observed after SBI. RSG, however, significantly attenuated MPO activity and qualitatively decreased IL-1beta and TNF-alpha expression compared to vehicle-treated group. CONCLUSION: SBI causes increased brain edema, BBB disruption and inflammation localized along the periphery of the site of surgical resection. RSG attenuated inflammatory changes, however, did not improve brain edema, BBB disruption and neurological outcomes after SBI.

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26. J Huazhong Univ Sci Technolog Med Sci. 2007 Jun;27(3):295-8.

Effect of Rosiglitazone Maleate on inflammation following cerebral ischemia/reperfusion in rats.

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In order to evaluate the neuroprotective effect of Rosiglitazone Maleate (RSG) against brain ischemic injury, the effects of Rosiglitazone Maleate on the inflammation following cerebral ischemia/reperfusion were investigated. Focal cerebral ischemia was induced by the intraluminal thread for cerebral middle artery (MCA) occlusion. Rosiglitazone Maleate at concentrations of 0.5, 2 and 5 mg/kg was infused by intragastric gavage twice immediately and 2 h after MCA occlusion, respectively. The effects of Rosiglitazone Maleate on brain swelling, myeloperoxidase and interleukin-6 mRNA level in brain tissue after MCA occlusion and reperfusion were evaluated. The results showed that as compared with the model control group, RSG (0.5 mg/kg) had no significant influence on brain swelling ($P>0.05$), but 2 mg/kg and 5 mg/kg RSG could significantly alleviate brain swelling ($P<0.05$). All different doses of RSG could obviously reduce MPO activity in brain tissue after MCA occlusion and reperfusion in a dose-dependent manner. RSG (0.5 and 2 mg/kg) could decrease the expression levels of IL-6 mRNA in brain tissue after MCA occlusion and reperfusion to varying degrees ($P<0.05$) with the difference being significant between them. It was concluded that RSG could effectively ameliorate brain ischemic injury after 24 h MCA occlusion and inhibit the inflammatory response after ischemia-reperfusion in this model.

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Wen L, You W, Wang H, Meng Y, Feng J, Yang X. Polarization of Microglia to the M2 Phenotype in a Peroxisome Proliferator-Activated Receptor Gamma-Dependent Manner Attenuates Axonal Injury Induced by Traumatic Brain Injury in Mice. J Neurotrauma. 2018 Oct 1;35(19):2330-2340. doi: 10.1089/neu.2017.5540. Epub 2018 Jun 7. PubMed PMID: 29649924.