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REVIEW ARTICLE

Could fibrates (PPAR-alpha ligands) have a therapeutic potential in glioblastoma multiforme?

Carlos Rodrigo Cámara-Lemarroy, René Rodríguez-Gutiérrez, Miguel A. Villarreal-Alarcón

Department of Internal Medicine, Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Monterrey, N.L., México

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Abstract

Gliomas are the most common type of primary brain tumors. They are divided in four grades, grade 4 being the highest grade, where glioblastoma multiforme (GBM) is the main representative. It is one of the most malignant primary brain tumors, and despite of decades of research and surgical developments, therapy has notably failed to alter prognosis significantly. There is an increasing need for novel therapies in the treatment of GBM. Peroxisome proliferator-activated receptor-alpha (PPAR-alpha) is known to modulate multiple inflammatory, metabolic and cell growth pathways, and there is experimental evidence that it has some antineoplastic properties. Recent experimental evidence suggests that GBM cell lines use PPAR-alpha signaling in controlling their growth. Additionally, it is known that GBM cells use cell adhesion factors, pro-inflammatory cytokines and oxidative stress as pathophysiological mechanisms of differentiation and invasion. PPAR-alpha has been shown to inhibit these mediators in multiple *in vivo* and *in vitro* experimental models. This suggests a potential use for PPAR-alpha ligands in the treatment of GBM, a possibility not yet fully explored. Fibrates, such as fenofibrate, are drugs commonly prescribed in the management of dyslipidemia, and they are known to act as ligands for PPAR-alpha. In this paper we propose the use of fibrates in the adjuvant management of GBM in human clinical trials.

Correspondence: Carlos Rodrigo Cámara Lemarroy, MD. Department of Internal Medicine, Hospital Universitario "Dr. José Eleuterio González". Av. Francisco I. Madero y Dr. Eduardo Aguirre Pequeño s/n, colonia Mitras Centro, Z.P. 64460, Monterrey, N.L., México. Telephone/Fax: (+52 81) 8329 4203. E-mail: crcamara83@hotmail.com

PALABRAS CLAVE

Receptor activado por proliferador de peroxisomas alfa (PPAR-alfa), glioblastoma multiforme, tumor cerebral, fibratos, México.

¿Pueden los fibratos (ligandos de PPAR-alfa) tener un potencial terapéutico en el glioblastoma multiforme?

Resumen

Los gliomas son los tumores cerebrales primarios más frecuentes. Son divididos en cuatro grados, siendo el cuarto grado el más agresivo, en donde el glioblastoma multiforme (GBM) es el representante principal. Es uno de los tumores primarios malignos de cerebro más agresivos; a pesar de décadas de estudios de investigación y de avances en técnicas quirúrgicas, el tratamiento actual ha fallado en mejorar el pronóstico de manera significativa. Por lo tanto, existe una necesidad de nuevos tratamientos para el GBM. Los receptores de los peroxisomas-proliferador-activado alfa (PPAR-alfa), han demostrado modular múltiples vías inflamatorias, metabólicas y de crecimiento celular, existiendo la evidencia experimental, que indica que pudiera tener también propiedades antineoplásicas. Evidencia experimental reciente sugiere que las líneas celulares del GBM, utilizan PPAR-alfa para controlar su crecimiento. Adicionalmente, es ya bien reconocido que las células del GBM utilizan factores de adhesión, citocinas proinflamatorias y estrés oxidativo como mecanismos patofisiológicos de diferenciación e invasión. Los ligandos de PPAR-alfa, han demostrado ya en múltiples estudios experimentales in vivo e in vitro, que pueden inhibir estos mediadores. Esto sugiere un potencial uso de los ligandos de PPAR-alfa en el tratamiento del GBM. Los fibratos, tal como el fenofibrato, son medicamentos comúnmente utilizados para el tratamiento de dislipidemias y su mecanismo de acción es precisamente como ligandos de PPAR-alfa. En este trabajo proponemos el uso en estudios clínicos, de los fibratos como terapia adyuvante en el tratamiento de GBM.

Introduction

Gliomas are the most common type of primary brain tumors, deriving from astrocytes, oligodendrocytes and ependymal cells. They are divided in four grades, grade 4 being the highest grade, where glioblastoma multiforme (GBM), the most common type of glioma, is the main representative. It is one of the most malignant primary brain tumors, with dismal survival rates in the short term, and despite of decades of research and surgical developments, therapy has notably failed to alter prognosis significantly.^{1,2}

Peroxisome proliferator-activated receptors (PPARs), discovered in rodents in 1990, are proteins that belong to the superfamily of the nuclear hormone factor receptor. They are similar in structure to thyroid, estrogen, retinoic acid and glucocorticoid receptors. This structure include the amino-terminal activation function-1 trans activation domain, a DNA-binding domain, and a ligand-binding domain in the carboxy-terminal region.³ PPARs exist in three subtypes; alpha, beta/delta and gamma. PPAR-alpha is highly expressed in hepatocytes, cardiomyocytes, enterocytes, and the proximal tubule cells of kidney. PPAR-beta is expressed ubiquitously and often at higher levels than PPAR-alpha and -gamma. On the other hand, PPAR-gamma is expressed predominantly in adipose tissue and also in the immune system. They all mediate the physiological actions of fatty acids and fatty acid derived molecules, and their natural activating ligands are themselves lipid-derived substrates. Their activation

regulates gene transcription, modulation of additional transcription factors and DNA responses that aim at maintaining lipid and glucose homeostasis.^{3,4} They mediate lipid metabolism, cell growth, and have demonstrated pleiotropic effects over the immune system and other pathways.^{4,5}

The modulation of PPARs using various drugs has proven clinically useful in the treatment of diabetes (PPAR-gamma agonists, such as pioglitazone) and dyslipidemia (PPAR-alpha agonists, such as fibrates). PPAR-alpha in particular is known to modulate the activities of fatty acid oxidation systems, to modulate the transcription of cytokine genes, to alter the cell growth cycle, change the expression profiles of lymphocytes, among many other pleiotropic effects.⁶ The presence of PPAR-alpha receptors in glioblastoma cell lines has been demonstrated, and these are implicated in brain development, neural cell differentiation and lipid metabolism in the brain. The hypothesis here advanced is that PPAR-alpha activators, such as fibrates, have anti-tumor activity against GBM.

PPAR-gamma

PPARs are ubiquitous in GBM cell lines, and there is plenty of evidence, experimental and even clinical, that PPAR-gamma agonists (thiazolidinediones), have anti-tumor effects over GBM.⁷ Indeed, a recent phase II study showed that low dose combination of pioglitazone, rofecoxib and chemotherapy, is moderately active and well tolerated regimen in patients with high-grade gliomas.⁸

However, comparatively few information exists on PPAR-alpha agonists.

PPAR-alpha

Traditionally, PPAR-alpha activation has been linked to the carcinogenesis, and specifically, development of liver tumors.⁹ However, anti-tumor effects of PPAR-alpha have also been described. Selective ligands for PPAR-alpha exert protective role against mouse skin tumor promotion.¹⁰ It has also been shown that PPAR-alpha is up-regulated in endometrial cancer, and a PPAR-alpha-activating ligand reduces the proliferation of endometrial cancer cells.¹¹ Similar results have been obtained in ovarian cancer cells.¹² Recent evidence points towards general anti-tumor effects of PPAR-alpha, and indeed, recent research has studied these effects over glioma cell lines.

GBM cell anti-tumor activity of PPAR-alpha and PPAR-alpha agonists

In an *in vitro* study, Pineau et al. showed that phenylacetate, an aromatic fatty acid anti-tumor agent, could enhance PPAR-alpha in glioblastoma cell lines in a direct proportion to its cell stasis activity, suggesting a role for PPAR-alpha in tumor cell growth.¹³ The induction of PPAR-alpha by linoleic acid has been shown to lead to the induction of apoptosis in tumor cell lines, suggesting a possible mechanism of action for this effect.¹⁴ The presence of PPAR-alpha in human GB cell lines has not only been confirmed, but the incubation of these cells in fenofibrate, a PPAR-alpha agonist, leads to the inhibition of cell proliferation and elevated apoptosis, through the attenuation of insulin-like growth factor-I (IGF-I) dependent phosphorylation of kinases involved in cell growth.¹⁵ Further studies showed that PPAR-alpha induction indeed inhibited IGF-I, a contributing factor in supporting malignant growth and invasion of glioma cells, and led to accumulation of reactive oxygen species inside tumor cells, which in turn caused mitochondrial dysfunction and apoptosis.¹⁶ These alterations impaired GB cell motility. Also, a recent study performed on human glioblastoma cell lines U-87 MG, T98G, A172 and U-118 MG showed that ligands of PPAR alpha (bezafibrate, gemfibrozil) negatively affected the viability, proliferation, differentiation and expression of cell cycle related proteins, and led to increased apoptosis.¹⁷ Finally, a recent *in vitro* study showed that TZD18 a novel PPAR alpha/gamma dual agonist inhibited cell grow and induced apoptosis in human glioblastoma T98G cells reinforcing the possibility that in an *in vivo* study this could be replicated.¹⁸

Other possible mechanisms

Cyclooxygenase (COX)-2 and vascular endothelial growth factor (VEGF) are crucial agents in inflammatory and angiogenic processes. Both have been implicated in tumor progression and both are modulated by PPAR-alpha.¹⁹

PPAR-alpha agonists can inhibit VEGF and suppress endothelial cell proliferation, resulting in potent antiangiogenic effects.²⁰ VEGF not only is known to be crucial in GBM angiogenesis and progression, but currently, anti-VEGF therapy is the standard of care in GBM chemotherapy.²¹ PPAR-alpha activators have also been shown to inhibit the tumor necrosis factor-alpha/Nuclear factor KappaB (TNF-alpha/Nf-KappaB) axis in mantle cell lymphoma, a transcription pathway of various cytokine and inflammation genes.²² The TNF-alpha/Nf-KappaB signaling pathways is thought to drive the tumor phenotype and participate in GBM pathogenesis as well,²³ and there is direct evidence of Nf-KappaB modulation in cultured microglia by fenofibrate.²⁴ These pleiotropic effects could be relevant for the anti-tumor effects of fibrates.

Conclusion

Fibrates (fenofibrate, clofibrate, bezafibrate, ciprofibrate) are commonly used, safe and well tolerated drugs. Their current approved indication lies mainly in the realm of management of dyslipidemia, and they are effective in reducing triglyceride and cholesterol levels. In combination with a HMG-CoA inhibitor (statins), they constitute the most effective lipid lowering pharmacological strategy. Fibrates and statins act synergistically. Interestingly, statins have also shown potential in the treatment of GBM. The combination of lovastatin and troglitazone was shown to synergistically inhibit GB cell line growth.²⁵ Considering the information reviewed in this article, the use of fibrates, in combination with currently approved chemotherapy regimens, in human clinical trials, holds great promise.

Conflict of interest

The authors declare no conflict of interest.

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