Mini Review
Volume 8:7, 2022

Journal of Pharmacognosy & Natural Products

ISSN: 2472-0992 Open Access

Natural PPAR Agonist that Doesn't Cause Corpulence

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Abstract

In clinical settings, PPAR (peroxisome proliferator-activated receptor gamma) agonists are utilized to combat hyperglycemia. The search for new PPAR activators, on the other hand, is fueled by the experience of undesirable side effects like weight gain. We utilized a mix of in silico, in vitro, cell-based and in vivo models to distinguish and approve regular items as promising leads for halfway original PPAR$_{\gamma}$ agonists. It was predicted in silico that the natural product honokiol from the traditional Chinese medicine Magnolia bark would bind as a dimer into the PPAR ligand binding pocket. In fact, in a PPAR-mediated luciferase reporter assay, Honokiol acted as a partial agonist by binding directly to the purified LBD of PPAR. After that, the effects of Honokiol on adipogenic differentiation in 3T3-L1 pre-adipocytes and mouse embryonic fibroblasts and the stimulation of glucose uptake in adipocytes were directly compared to those of the full agonist pioglitazone, which is currently in use in clinical settings. Unlike pioglitazone, which induced adipogenesis, honokiol did not stimulate basal glucose uptake to the same extent as pioglitazone did. The oral administration of honokiol slowed weight gain and prevented hyperglycemia in diabetic KKAy mice. In vivo, we found that honokiol was a partial non-adipogenic PPAR agonist that stopped hyperglycemia and weight gain.

Keywords: Pioglitazone • Hyperglycemia • Adipogenesis

Introduction

This observed activity profile provides a molecular explanation for the utilization of Magnolia in traditional medicine and suggests honokiol as a promising new pharmaceutical lead or dietary supplement to combat metabolic disease. Obesity, metabolic syndrome, and type 2 diabetes are exacerbated by a sedentary lifestyle that leads to a lack of physical activity and high caloric intake. These conditions have a significant impact on a person's quality of life and are a burden on the health care systems of industrialized societies. Clinically, PPAR (peroxisome proliferator activated receptor gamma) agonists are used to treat these pathological conditions hyperglycemia and related comorbidities Most of the time, PPARs are nuclear receptors and ligand-dependent transcription factors that control the metabolism of lipids and glucose PPARs form heterodimers with the nuclear receptor retinoid X receptor (RXR) upon ligand binding and bind to response elements in the promoter region of their target genes. Further chromatin rearrangement transcription is initiated following the recruitment of nuclear receptor coactivators. Among the three PPAR subtypes that are known to, PPAR has received the most research. Adipose tissue, the lung, the large intestine, the kidney, the liver, the heart, and macrophages all express it.PPAR is an appropriate pharmacological target for the treatment of metabolic diseases because of its well-established significance in the regulation of glucose and lipid metabolism. Pioglitazone, a full PPAR agonist represented by thiazolidinediones, is clinically effective; however, it has serious side effects and off-target effects (such as weight gain or edema formation), necessitating the search for new PPAR agonists [1,2].

Discussion

The reason for this isn't completely clear. However, partial agonists may cause a different conformation of the receptor–ligand complex than full agonists, resulting in an altered recruitment of transcriptional co-activators and repressors to a smaller number of expressed target genes. Neolignans are a new class of dimers of partial agonists that occupy the PPAR ligand-binding domain, as determined by computer-aided methods. We were able to identify and further characterize the novel non-adipogenic partial PPAR activator, neolignan honokiol, which is a major bioactive component of the traditional Chinese herbal drug Magnolia bark, using the in silico tools that were generated and improved here. Similar to pioglitazone, the previously discovered neolignans have adipogenic properties that are PPAR-dependent. In contrast, we demonstrate that the newly discovered PPAR partial agonist honokiol maintains its antihyperglycemic activity both in vitro and in vivo while preventing weight gain in the murine KKAy in vivo diabetes model and preventing adipogenesis in two in vitro cell systems. Prior to the addition of filtered OilRed O solution for ten minutes, the cells on the plates were fixed with 10% formaldehyde for at least one hour, washed with 60% isopropanol, and dried. Photos were taken after the excess dye was removed with water. The bound dye was then solubilized in equal volumes of 100 percent isopropanol per well and immediately measured photometrically at 550 nm in a Tecan spectrophotometer. All animal tests were carried out in full compliance with authority regulations and ethical principles at the local, national, and international levels.A high-fat diet consisting of sucrose, pork lard, egg yolk powder, and regular feed in a ratio of 10:10:10:7 was fed to the KKAy mice while they were raised in an SPF experimental room. As well as potable water that is readily available. In this study, we describe how the natural product honokiol was found to be a novel, non-adipogenic partial PPAR agonist. It is interesting to note that honokiol is one of the main bioactive components of the traditional Chinese herbal medicine Magnolia bark, which is used to treat metabolic disease and other conditions. This means that honokiol may play a role in the herb's beneficial properties by partially activating PPAR. We utilized two distinct in vitro adipogenesis models to carefully examine the possibility of honokiol's pro-adipogenic activity. Honokiol did not exhibit adipogenic properties, whereas the full agonist pioglitazone caused a significant PPAR-dependent adipogenic differentiation in both cellular models [3-4].

Conclusion

In addition, honokiol's favorable activity profile was confirmed in vivo in the diabetic KKAy mouse model, where, like pioglitazone, it prevented rising hyperglycemia, but it also slowed down weight gain and clearly had a negative effect on adipogenesis in our tests. However, it is currently impossible to rule out

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Date of Submission: 02 July 2022, Manuscript No. jpnp-22-81733; **Editor assigned:** 04 July 2022, PreQC No. P-81733; **Reviewed:** 16 July 2022, QC No. Q-81733; **Revised:** 21 July 2022, Manuscript No. R-81733; **Published:** 28 July 2022, DOI: 10.37421/2472-0992.2022.8.196

the possibility that proteins other than PPAR contribute to the beneficial effects of honokiol in vivo may provide additional evidence for in vivo PPAR activation by honokiol. who demonstrate that administration of honokiol has a similar modulatory effect to that of rosiglitazone on the activation of hypothalamic neuronal circuits that are involved in controlling body weight. However, the authors did not take into account the possibility that the compound could act as a direct activator of PPAR, and this observation was then interpreted as a result of the ROS scavenging properties of honokiol. Overall, honokiol is an intriguing natural product that has a good chance of being further investigated as a pharmaceutical lead or dietary supplement due to its suppression of hyperglycemia and weight gain, as well as the partial PPAR activation pattern that was found here.

Acknowledgement

None.

Conflict of interest

No potential conflict of interest was reported by the authors.

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How to cite this article: Galán, Javier. "Natural PPAR Agonist that Doesn't Cause Corpulence." J Pharmacogn Nat Prod 08 (2022): 196.