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Introduction

Proliferator-activated receptor γ coactivator 1α (PGC-1α) is a transcriptional co-activator involved in the regulation of energy production and utilization in metabolic tissues. Target genes are induced through both PGC-1α co-activators and their interactions with nuclear receptors and additional transcription factors at specific regulatory sites. Estrogen related receptor (ERRα) is an orphan nuclear receptor that controls metabolism. Studies have established that the activation of ERRα by PGC-1α induces genes with roles in lipid transport, fatty acid oxidation, TCA cycle, oxidative phosphorylation, mitochondrial biogenesis, mitochondrial dynamics, and oxidative stress defense. ERRα is a potential intermediate in PGC-1α action. PGC-1α co-activator properties allow it to control gene expression through specific DNA binding transcription factors at the promoters of target genes.

PGC-1α is a potent co-activator of ERRα, and it is likely that ERRα is an important transcriptional regulator of PGC-1α induced genes. Lower basal levels of PGC-1α expression are detected in the brain, suggesting a low preference for fatty oxidation under normal conditions. The brain has efficient OXPHOS machinery to support impulse transmission and expresses a significant level of PGC-1α.

Potential Therapeutics for Drug Discoveries

Kaempferol ($C_{15}H_{10}O_6$), a polyphenolic non-steroidal plant compound commonly found in dietary flavonoids, has been isolated in many plant sources including, tea, broccoli, and grapefruit. Studies have been able to determine that Kaempferol functions as an inverse agonist for estrogen related receptors alpha and gamma (ERRα and ERRγ). Kaempferol binds to ERRα and ERRγ and blocks their interaction with co-activator peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α).

Inhibition of ERRα activity by its inverse agonist impairs the ability of PGC-1α to induce expression of energy metabolism genes and enhances mitochondrial biogenesis and oxidative capacity. XCT 790 is one inverse agonist for ERRα that disrupts the interaction between ERRα and PGC-1α. Bioinformatics analysis confirmed that the TCAAGGTCA motif serves as the main ERR binding site (in vivo). XCT 790($C_{23}H_{13}F_9N_4O_3S$) acts as a selective inverse agonist of ERRα that demonstrates ≈90-100% inhibition of ERRα constitutive activity in previous studies. Past experiments indicate XCT790 most likely binds in the ligand-binding pocket of ERRα.

There have been many proposed mechanisms that explain what possible effects of the interactions of PGC-1α and ERRα in different environments. One scenario could be the interaction of PGC-1α and ERRα expressing their target genes. These target genes could be hindered from carrying out a specific function in the presence of an inverse agonist, such as XCT 790. ERRα could be activated through other coactivators, which could express both PGC-1α and ERRα target genes. Further investigation of the transcriptional pathway could help determine what types of drugs could assist with neurological diseases.

Medical Significance in Neurological Diseases

ERRα and PGC-1α can regulate the target gene expression cooperatively. PGC-1α also plays a crucial role in metabolic regulation and reduced amounts have been hypothesized to cause neuronal vulnerability and mitochondrial defects in Huntington's Disease (HD). The abundant evidence of disruptions in neuronal metabolism and mitochondrial respiration in HD reinforces this hypothesis. Consequently, PGC-1α has been suggested as a potential therapeutic target in HD. PGC-1α also plays a crucial role in metabolic regulation, and reduced amounts may cause neuronal vulnerability and mitochondrial defects in HD.

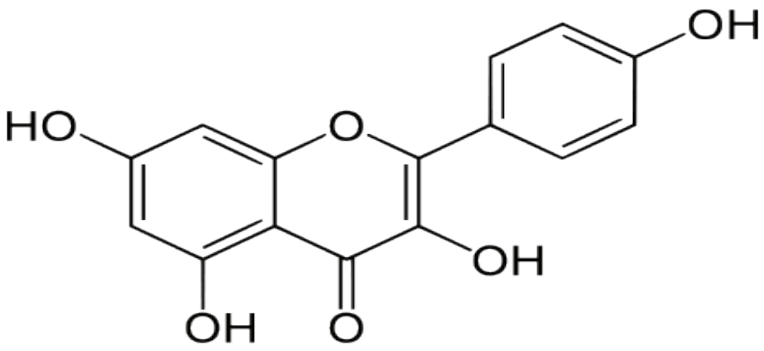

Figure 1: Kaempferol ($C_{15}H_{10}O_6$) structure

Various metabolic diseases might be treated with ERRα ligands. For example, an ERRα agonist might be able to prevent the loss of PGC-1α expression by increasing ERRα activity and other target genes, which can potentially lead to an increase in energy production and insulin sensitivity. Thus, targeting PGC-1α and ERRα in HD could increase metabolism and improve mitochondrial function.

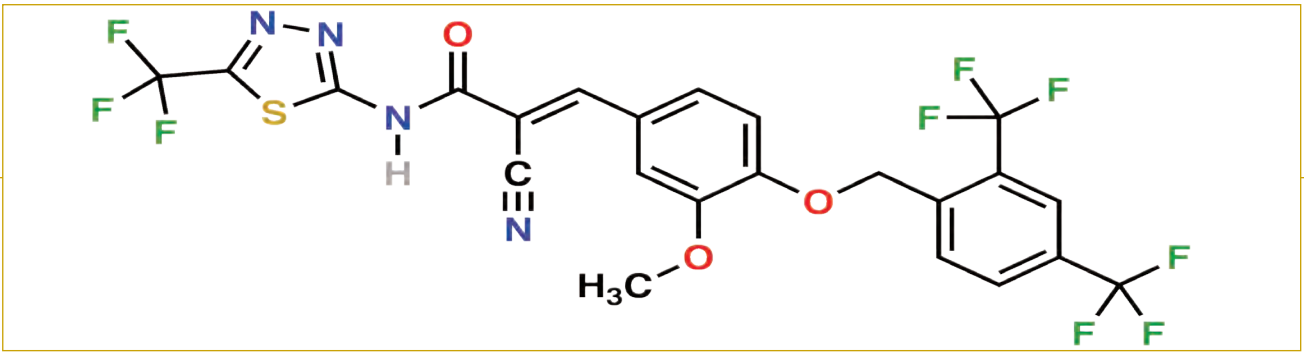

Figure 2 - XCT 790($C_{23}H_{13}F_9N_4O_3S$) structure

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