Baicalein regulates FGF21 expression through RORα-mediated transcriptional activity

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Obesity is an emerging global medical issue and has been considered one of the most prominent risk factors of metabolic syndrome. Several studies have demonstrated that fibroblast growth factor 21 (FGF21), a member of the FGF family, plays important roles in regulation of peripheral glucose tolerance and hepatic lipid metabolism, and is expressed in multiple tissues including liver, pancreas, white and brown adipose tissues, and skeletal muscle. The ability of FGF21 to improve and protect against metabolic disorders such as obesity makes it an attractive drug candidate for the treatment of metabolic diseases.

Nuclear receptors (NRs) are eukaryotic transcription factors that activate or repress gene expression in response to binding small signaling molecules such as steroid hormones, lipophilic vitamins, and fatty acids. The retinoic acid receptor-related orphan receptors (ROR) α is NR that activate the transcription of clock genes, brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1 (BMAL1), CLOCK, and REV-ERBα, involved in regulating metabolism, inflammation, and the circadian clock. Additionally, Recent studies indicated that circadian disruption (altered gene expression of clock and clock-controlled genes) is associated with metabolic disorders. In this study, we found that overexpression of RORα up-regulated FGF21 expression in pluripotent C3H10T1/2 cells. In addition, synthetic ROR α/γ agonist SR1078 stimulated FGF21 expression in C3H10T1/2 brown adipocytes. Therefore, we attempted to identify novel naturally occurring ROR α agonists and to determine its contribution to FGF21 production. A total of 86 crude herbal drugs frequently used in Kampo prescriptions (traditional Japanese medicine) were selected and screened for ROR α agonist activity using a BMAL1-luciferase reporter assay. Among them, the methanol extract of Scutellaria root enhanced ROR α -mediated transcriptional activity in this assay. Furthermore, we also found that a natural product baicalein can activate ROR α -mediated transcriptional activity. Importantly, baicalein stimulated FGF21 production in brown adipocytes. These results suggest that baicalein stimulates FGF21 expression through the enhancement of ROR α -mediated transcriptional activity.