A natural modulator of the PKA and AMPK signaling regulates lipid metabolism in a steatosis model

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Abstract:
Non-alcoholic fatty liver disease (NAFLD) is a metabolic disorder characterized by excessive lipid accumulation in hepatocytes and impaired lipid degradation[1]. In its early stages, NAFLD is considered reversible, and targeting key metabolic pathways represents a promising therapeutic strategy. Plants are a valuable source of bioactive molecules with beneficial effects in metabolic and chronic diseases[2].

Here, we investigated the metabolic effects of a natural flavonoid (C3) extracted from *Glycyrrhiza glabra* leaves in an *in vitro* model of steatosis. C3 treatment stimulated AMPK activation and in HepG2 cells overloaded with oleic and palmitic acids it significantly reduced intracellular lipid droplet accumulation, in a AMPK and PKA dependent manner. Kinome profiling revealed the activation of kinases associated with metabolic regulation, lipolysis, autophagy, and cellular stress responses. Functional assays confirmed that C3 enhanced lipolytic activity. In addition, autophagy induction was validated through LC3 puncta formation and increased lipid droplet-lysosome colocalization in an AMPK-dependent manner. Mitochondrial function was also improved, as assessed by Seahorse metabolic analysis.

In summary, this natural compound exerts protective metabolic effects in steatotic hepatocytes by activating the PKA-AMPK pathway, stimulating lipolysis and autophagy, and enhancing mitochondrial activity. These findings support its potential as a promising therapeutic agent for early-stage NAFLD.

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