Moringin activates Wnt canonical pathway by inhibiting GSK3-β in a mouse model of experimental autoimmune encephalomyelitis

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INTRODUCTION

Aberrant canonical Wnt/β-catenin signaling has been reported in multiple sclerosis (MS), although still with controversial results (1). The present study was aimed to examine the role of the Wnt/β-catenin pathway in experimental MS and also to test the moringin (4-(α-L-rhamnopyranosyloxy) benzyl isothiocyanate (GMG-ITC) resulting from exogenous myrosinase-hydrolysis of the natural phytochemical glucomoringin 4(α-l-rhamnosyloxy)-benzyl glucosinolate (GMG) as a modulator of neuroinflammation via β-catenin/PPARγ axis.

MATERIALS AND METHODS

Experimental autoimmune encephalomyelitis (EAE), the most common model of MS, was induced in C57BL/6 mice by immunization with myelin oligodendroglial glycoprotein peptide $(MOG)_{35–55}$ (2). Released moringin (10mg/kg of GMG + 5μl myrosinase/mouse) was daily administered 1 week before EAE induction and continued until mice were sacrificed on day 28 after EAE induction.

RESULTS

Our results have clearly shown that Wnt/β-catenin pathway is turned off in EAE model, whereas moringin treatment is able to turn it on. Moringin treatment normalizes the aberrant Wnt/β-catenin pathway, resulting in GSK3-β inhibition and β-catenin upregulation, which downregulates the main inflammatory mediators, such as IL-1β, IL-6 and COX-2, through activation of PPARγ. In addition, moringin attenuates apoptosis by reducing the expression of Fas-ligand and cleaved caspase-9 and in parallel increases antioxidant Nrf2 expression in EAE mice.

CONCLUSION

In EAE mice, moringin normalizes the aberrant Wnt/β-catenin pathway, resulting in GSK3-β inhibition and β-catenin upregulation, which downregulates the main inflammatory mediators through activation of PPARγ and thus attenuates apoptosis. Therefore, moringin could be a potential PPARγ agonist in the treatment of MS.

Taken together, our results provide an interesting discovery at identifying moringin as a modulator of the Wnt/β-catenin signaling cascade and as a new potential therapeutic target for MS treatment.

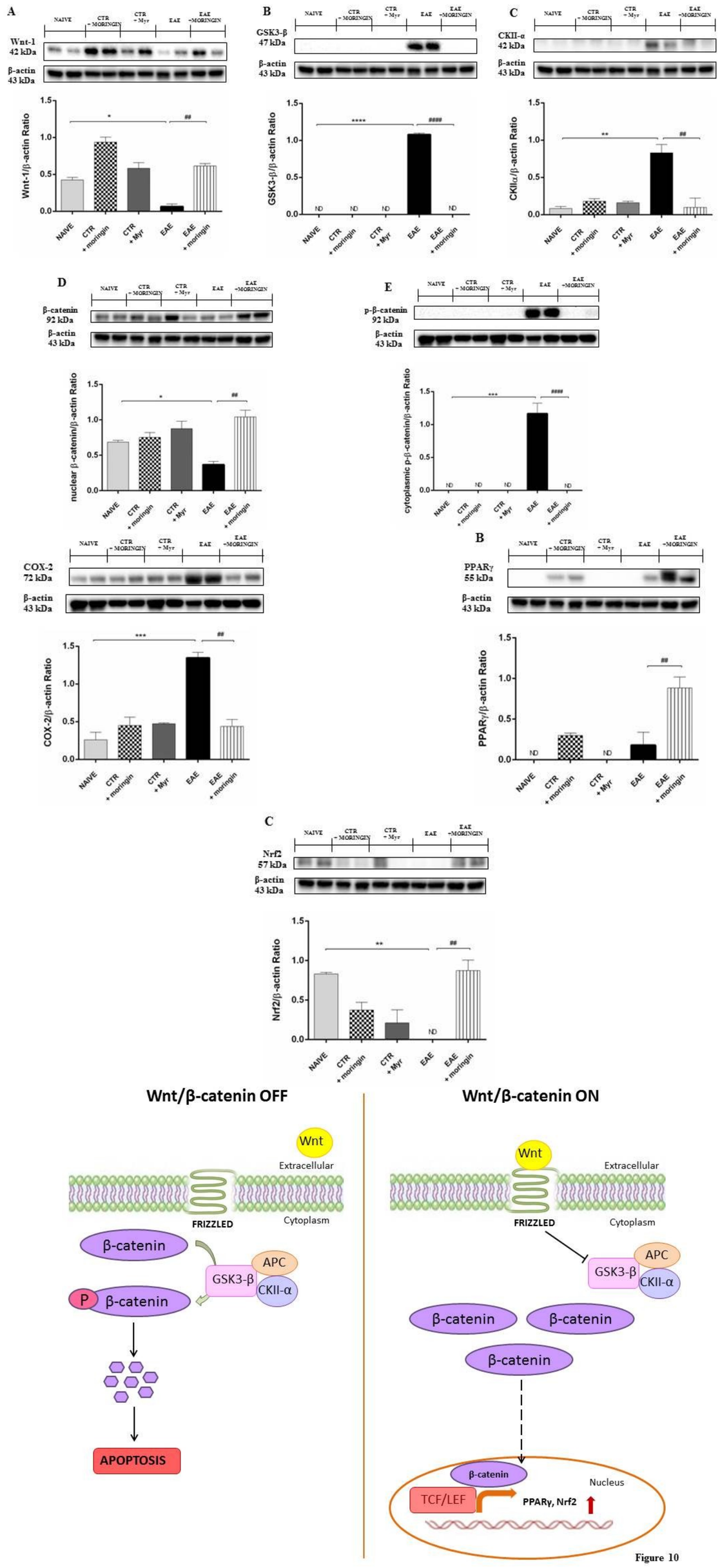

Figure 10

Wnt/β-catenin canonical pathway. In the absence of the Wnt ligand (OFF), β-catenin is phosphorylated by the destruction complex formed by Axin, APC, CKII-α, and GSK3-β, leading to β-catenin degradation and subsequent induction of neuronal cell death. In the presence of the Wnt ligand, the Wnt canonical pathway is activated (ON), β-catenin is not phosphorylated by the destruction complex and is free to translocate into the nucleus where it binds with the Tcf/Lef transcription factors and promotes the transcription of Wnt target genes.

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2. Paschalidis N, Iqbal AJ, Maione F, et al. Modulation of experimental autoimmune encephalomyelitis by endogenous annexin A1. *J Neuroinflammation.* 2009;6:33.

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