Olmesartan attenuates type 2 diabetes-associated liver injury: Cross-talk of AGE/RAGE/JNK, STAT3/SCOS3 and RAS signaling pathways

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Abstract

Olmesartan (OLM), an angiotensin receptor blocker, was tested against diabetes/insulin resistance (IR) models associated with renal/cardiovascular complications. Methods: we tested its potential role against diabetes-induced hepatic hitches using an IR/type2 diabetic (IR/D) model induced by high fat/high fructose diet for 7 weeks + a single sub-diabetogenic dose of streptozotocin (35mg/kg; i.p). IR/D rats were orally treated with OLM (10 mg/kg), pioglitazone (PIO; 5 or 10 mg/kg) or their combinations for 4 consecutive weeks. OLM alone opposed the detrimental effects of IR/D; it significantly improved metabolic parameters, liver function, and abated hepatic oxidative stress, and inflammatory cytokine interleukin-6 (IL-6) and its upstream mediator nuclear factor kappa B. Consequently, OLM turned off the downstream cue p-Jak2/STAT3/SOCS3. Moreover, it suppressed the elevated AGE/RAGE/p-JNK pathway and increased the PPARɔ/adiponectin cue to signify its anti-inflammatory and anti-oxidant capacity (GSH, MDA). Nevertheless, co-administration of OLM to PIO showed a synergistic improvement in all the aforementioned parameters in a dose dependent manner. Additionally, OLM with PIO10 provoked a surge in hepatic PPARɔ and adiponectin (5 and 6 folds) with a sharp decrease of about 85% in the NF-əB/IL-6/p-STAT3/SCOS3 pathway. These effects were confirmed by the histopathological study. In conclusion, OLM and its combination with PIO enhanced insulin sensitivity and guarded against hepatic complications associated with type 2 diabetes probably via modulating various inter-related pathways; namely, metabolic alteration, renin-angiotensin system, inflammatory trajectories, as well as oxidative stress. This study manifests the potential synergistic effects of OLM as an adjuvant therapy to the conventional antidiabetic therapies.

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