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Effects of valproic Acid, berberin and resveratrol on human mesenchymal stem cells adipogenic differentiation

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Nowadays obesity and its related diseases represent a major health problem with an increasing worldwide prevalence. Hyperplasia and hypertrophy of adipocytes lead to an excessive fat accumulation that is not efficiently prevented by current pharmacological treatments. So the research on anti-obesity drugs with good efficacy and tolerability able both to prevent and to reduce fat accumulation is of pivotal interest.

In the present study we evaluated in vitro the effects of Valproic Acid, Berberin and Resveratrol on adipogenesis. Our experimental model was represented by human Mesenchymal Stem Cells (hMSCs), physiological precursors of adipocytes that can differentiate into adipocytes also in vitro.

Preliminary cytotoxicity assays were performed in order to choose non-toxic doses of the three drugs. hMSCs were induced to adipogenic differentiation and treated with Valproic Acid, Berberin and Resveratrol at the selected doses. Controls were represented by hMSCs treated for adipogenesis in absence of the drugs.

At different time points intracellular lipid droplets accumulation, a typical feature of adipogenesis, was assessed by Oil Red O staining. Valproic Acid, Berberin and Resveratrol inhibited hMSCs adipogenic differentiation in a dose dependent manner as demonstrated by the reduction of the lipid droplets accumulation.

To understand the molecular mechanisms of the drugs-induced adipogenesis inhibition, we focused our attention on the effects of the drugs treatment on cell cycle progression, known to be altered by many antiadipogenic drugs, and on the MAP Kinases ERK1 and ERK2, involved in the adipogenesis control. We evaluated the expression of cyclins and CDKs by immunoblotting and flow-cytometry analyses, demonstrating that Valproic Acid, Berberin and Resveratrol interfere on cell cycle progression. The expression and the phosphorylation status of the two kinases ERK1 and ERK2 were assessed by immunoblotting demonstrating an increase of ERK1 phosphorylation (i.e. activation) in hMSCs treated with Berberin and a reduction in hMSCs treated with Valproic Acid and Resveratrol compared to control cells. No changes in phosphorylation and expression of ERK2 were observed.

Our study demonstrate that Valproic Acid, Berberin and Resveratrol exert an anti-adipogenic effect in our experimental model. The mechanisms of action of these drugs involve the alteration of cell cycle progression and, at least in part, ERK1/2 modulation. However other molecular pathways are likely implicated and other studies are required to identify them.

Keywords: valproic acid, berberin, resveratrol, human mesenchymal stem cells, adipogenic differentiation, in vitro study

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