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PPARγ AGONISTIS A1 AND E1 ON THE IMMUNOMODULATION OF THE INNATE IMMUNE RESPONSE

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INTRODUCTION

The peroxisome proliferator activated receptors-γ (PPARγ) agonists are known to have important anti-inflammatory effects by promoting down-regulation of the NF-κB pathway and consequently the decrease of inflammatory cytokines, allied to genomic effects. Synthetic PPARγ agonists are being extensively investigated, especially partial agonists, due to their reduced toxic effects. This study had the aim of investigating the mechanisms involved in the modulation of the macrophages and neutrophils activation by the A1 and E1 glitazones partial PPARγ agonists.

MATERIAL AND METHODS

To evaluate the neutrophil activity, the Glitazones A1 and E1 (0.1 to 10 μM) were added to neutrophils, obtained from Swiss mice´s peritoneal cavity, together with bacterial membrane lipopolysaccharide (LPS; 150 μg/mL). After 1 h of incubation, the neutrophils were used to evaluate the adhesion molecule (anti-CD62L, anti-CD18b, anti-CD49d) expression by flow cytometry. Similar protocol was performed with neutrophil or Raw 264.7 macrophages and supernatant culture, after 18 h of incubation, was used to quantify the cytokine IL-1β, IL-6, TNF by ELISA and nitric oxide (NO) levels. Neutrophil chemotaxis was evaluated on agarose gel with chemotactic agent fMLP (0.1 μM). The superoxide anion production was investigated in neutrophils and macrophages using nitroblue tetrazolium (NBT) reduction assay. The cells were incubated in the presence or absence of compounds A1 or E1, and stimulated with LPS or PMA. Cytomorphological findings, was conducted by counting the cells containing formazan deposits. The NBT test was also spectrophotometric quantified (630 nm). The glitazone was also *in vivo* evaluated in the carrageenan-induced inflammation in the air-pouch mice model and the neutrophil infiltrate, cytokine and NO levels were evaluated. CEUA #025/18.

RESULTS

A1 and E1 glitazones have different immunomodulatory effects. There was an increase in CD62L, a decrease in CD11b/CD18 and a reduction in chemotaxis by A1 and E1 in neutrophils. There was also an important reduction of all inflammatory cytokines and NO in both neutrophils and macrophages. Both compounds at all doses inhibited of the superoxide anion production and possible affected the NADPH oxidase activity. *In vivo*, the glitazones reduced the neutrophil infiltrate in the air-pouch accompanied by reduction in the cytokine and NO levels. There was no change observed in peripheral blood and bone marrow parameters.

CONCLUSIONS

In summary, the results of the present study are promising and suggest a broad immunomodulatory properties of the A1 and E1 glitazones, including impairment of immune cell migration, inflammatory mediators production and/or release and reduction of oxidative stress.

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