NOVEL NONSTEROIDAL ANTI-INFLAMMATORY DRUG AND CARBONIC ANHYDRASE INHIBITOR HYBRIDS FOR THE TREATMENT OF INFLAMMATION

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Carbonic anhydrases (CA), the enzymes catalyzing the hydration of $CO_2$to bicarbonate and protons, have been identified as potential therapeutic targets for the treatment of several inflammatory diseases. Hybrid molecules composed of nonsteroidal anti-inflammatory molecules and carbonic anhydrase inhibitor (NSAID–CAI) exhibit anti-inflammatory effects in terms of potency and activity when compared to the reference NSAID.

The aim of this study was to investigate the pharmacological profile of novel NSAID-CAI in the modulation of inflammation, through COX-1and COX-2inhibition, and in the inhibition of histamine release.

Macrophage cell line (RAW 264.7) was incubated for 18hrs with LPS (1μg/mL) and pre-treated or not with different concentrations of the studied drugs. The production levels of prostaglandin E_2(PgE_2), interleukin 6(IL-6) and interleukin 10 (IL-10) were quantified on macrophages culture medium. The inhibition of platelet aggregation was measured on human platelet-rich plasma (PRP).

Guinea pigs were sensitized with ovalbumin and serosal mast cells were collected 15days after sensitization. The cells were pre-incubated with the studied compounds for 30 minutes at 37°C and then stimulated for further 30 min with the antigen, to evaluate the immunological role of these hybrid molecules in inhibiting the histamine release.

Our results show that PgE_2production is lowered in LPS-stimulated RAW 264.7cells treated with NSAID-CAI compounds with a dose-response effect, while these drugs do not modify the inhibition of platelet aggregation in comparison with the reference molecules. Moreover, these hybrid molecules are able to induce the production of the anti-inflammatory cytokine IL-10, and to reduce the production of IL-6, a pro-inflammatory cytokine. Finally, the SB2-120B compound, one of the most active drug derived from ibuprofen, is able to decrease the immunological release of histamine from guinea pig serosal mast cells.

In conclusion, our findings provided evidence that these NSAID-CAI hybrid compounds are valuable molecules for the management of inflammation, suggesting a novel therapeutical approach to treat inflammatory diseases.