Novel selective inhibitor of NLRP3 inflammasome as a suitable strategy for the pharmacological treatment of intestinal inflammation

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Introduction. NLRP3 inflammasome, a protein complex responsible for the proteolytic maturation and secretion of the pro-inflammatory cytokines IL-1β and IL-18 (1), has been shown to regulate the integrity of intestinal mucosal barrier and play a pivotal role in shaping the immune response against commensal microbiota during bowel inflammation (2,3). However, there are currently few selective drug candidates suitable for treatment of intestinal inflammation through the modulation of inflammasomes. This study examined the effects of a novel selective NLRP3 inflammasome inhibitor in an experimental model of colitis.

Methods. The effects of INF39E (novel selective NLRP3 inflammasome inhibitor) and dexamethasone (DEX, used as a standard comparator) were tested in male rats (n=6 for each group) with colitis induced by intrarectal administration of 2,4-dinitrobenzenesulfonic acid (DNBS, 15 mg/rat), to assess systemic [body and spleen weight, and colon length] and tissue inflammatory parameters [macroscopic, tumor necrosis factor (TNF), interleukin-1 β (IL-1β), and myeloperoxidase (MPO) levels]. Animals received INF39E (12.5, 25, 50 mg/kg/day), DEX (1 mg/kg/day) or vehicle orally for 6 days, starting the same day of DNBS administration.

Results. Colitis was associated with a decrease in body weight and an increase in spleen weight. The macroscopic damage score, as well as tissue TNF, IL-1β and MPO levels were increased. Treatment with INF39E, but not DEX, improved body weight. Both drugs counteracted the increase in spleen weight and ameliorated the macroscopic damage score. A significant reduction of IL-β tissue levels was recorded in rats treated with INF39E 25 and 50 mg/kg/day or DEX. Moreover, INF39E 25 and 50 mg/kg/day or DEX ameliorated colonic MPO levels and decreased tissue TNF levels. The overall results concerning the effects of INF39E and DEX on the inflammatory parameters are displayed in the table.

Conclusions. The novel NLRP3 inflammasome inhibitor exerts beneficial effects on bowel inflammation, through a reduction of pro-inflammatory cytokine levels, mainly IL-1β. These findings substantiate the concept that the pharmacological modulation of the NLRP3 inflammasome complex represents a promising strategy to develop novel classes of drugs effective against intestinal inflammation.

References

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