Adenosine regulating agents as novel strategies for the pharmacological treatment of inflammatory bowel diseases

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Adenosine-regulating agents comprise a special class of ligands, that are pharmacologically inactive under physiological conditions, but are able to increase adenosine levels in an event-specific and site-specific manner under adverse conditions (i.e. ischemia and/or inflammation), thus harnessing the beneficial effects of this protective autacoid while avoiding its limiting adverse effects (Antonioli et al., 2014). The prototypic compound of this novel pharmacological class is the nucleoside analog acadesine, which is able to increase extracellular adenosine levels by inhibiting adenosine deaminase and adenosine kinase with a consequent local accumulation of endogenous adenosine. Acadesine activates also AMP-activated protein kinase (AMPK), a pivotal intracellular enzyme involved in the regulation of cellular energy supply and ATP production (Newman et al., 2012). The effects of acadesine on intestinal inflammation have been scarcely investigated.

The aims of the present study were: A) to evaluate the effects of acadesine in an experimental model of colitis, characterizing the underlying anti-inflammatory mechanisms; B) to design novel AMPK activators, endowed with improved pharmacokinetic/pharmacodynamic features.

The effects of acadesine and dexamethasone (standard comparator) were tested in male Sprague-Dawley rats with colitis induced via intrarectal administration of 2,4-dinitrobenzenesulfonic acid (DNBS, 15 mg in 0.25 ml of 50% ethanol), to assess systemic [body and spleen weight] and tissue inflammatory parameters [macroscopic and microscopic damage, tumor necrosis factor (TNF), interleukin-10 (IL-10), *in situ* superoxide anion production (dihydroethidium fluorescence) and malondialdehyde (MDA) levels]. Animals received acadesine (10 mg/kg/day), dexamethasone (0.1 mg/kg/day) or vehicle intraperitoneally for 6 days, starting 1 day before DNBS administration. In addition, groups of animals were treated with Compound C (AMPK inhibitor; 20 mg mg/kg/day) or CGS 15943 (non selective adenosine receptor antagonist; 10 mg mg/kg/day) alone or in combination with acadesine or dexamethasone. Systolic blood pressure was measured by the tail-cuff method at baseline and after injection of experimental drugs or vehicle.

The induction of colitis was associated with a decrease in body weight (-12±3 g versus vehicle; $P<0.05$) and an increase in spleen weight (+28±4.5% vs vehicle; $P<0.05$). Microscopic damage score, tissue TNF and oxidative stress were markedly increased, while tissue IL-10 levels were significantly reduced. Acadesine, but not dexamethasone, improved body weight. Both drugs counteracted the increase in spleen weight and ameliorated the histological damage (DNBS: 5.8±0.7; acadesine 10 mg/kg/day: 2.6±0.5; dexamethasone: 1.4±0.3; $P<0.05$ versus DNBS; ANOVA). A decrease in TNF and an increase in IL-10 tissue levels were also recorded in rats treated with test drugs. Moreover, acadesine or dexamethasone ameliorated colonic oxidative injury.

The ameliorative effects of acadesine were completely prevented by treatment with Compound C and significantly counteracted by CGS 15943 administration. By contrast, the effects of dexamethasone were not affected. Based on these findings, we were prompted to design a novel series of aminopyrazole derivatives, to develop lead compounds less responsive to xanthine oxidase degradation and able to directly activate the target enzyme *in vitro* and *in vivo*.

The present results suggest that adenosine regulating agents can exert beneficial effects on bowel inflammation, without displaying relevant cardiovascular adverse events. In conclusion, adenosine regulating agents represent a novel strategy for developing innovative drugs able to manage bowel inflammation.

References

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