Development and Validation of MSU-Induced Acute Gouty Arthritis Mouse Model for Therapeutic Evaluation

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Abstract

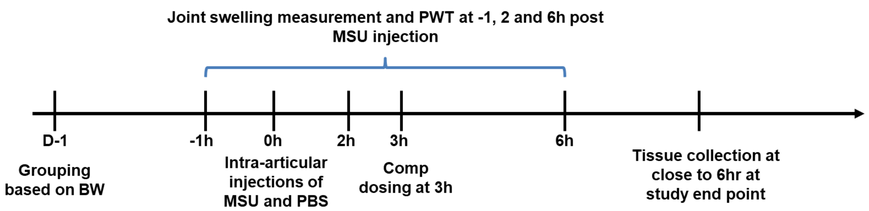
Gouty arthritis is a common and painful inflammatory condition caused by the deposition of monosodium urate (MSU) crystals in the joints. This condition is often associated with metabolic complications such as hyperuricemia, obesity, insulin resistance, and dyslipidemia, which can exacerbate the severity and progression of the disease.

To better understand the pathophysiology and potential treatments for this condition, we developed an acute gouty arthritis model by in mice induced by intra-articular injection of MSU crystals. We also tested a reference agent MCC950 to evaluate therapeutic potential.

Intra-articular injection of MSU crystals successfully established a model of acute gouty arthritis, demonstrating joint edema, mechanical allodynia and a drastic increase of joint IL-1β, IL6 levels and synovial fluid granulocytes and monocytes infiltration. Our data suggested MCC950, NLRP3 inflammasome inhibitor, effectively alleviated these complications, highlighting its potential therapeutic benefits.

Experimental Design

Acute gouty arthritis was induced by intra-articular injection of MSU (10 µL of 15 mg/mL, Invivogen) in male C57BL/6J mice (7–8 wk). MCC950 (100 mg/kg, i.p.) was given 3 h later. Joint edema was assessed as the increase in joint diameter measured with a digital caliper; mechanical hyperalgesia by von Frey; IL-6 and IL-1β by ELISA of joint homogenates; and synovial immune cells by FACS (CD45+/CD11b+ granulocytes and CD45+/CD11b+/Ly6C+ monocytes).



Experimental Procedure of MSU Induced Acute Gouty Arthritis Mouse Model.

Results

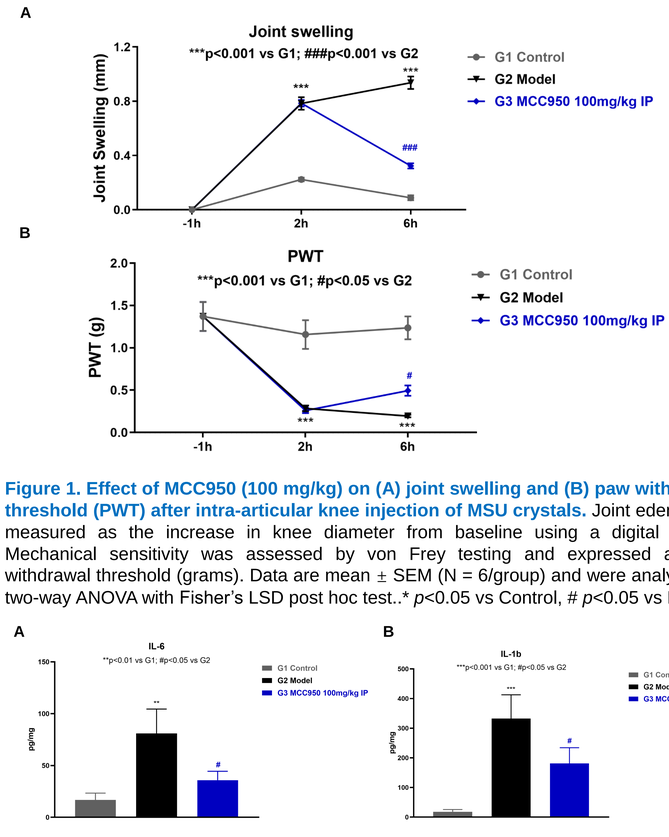


Figure 1. Effect of MCC950 (100 mg/kg) on (A) joint swelling and (B) paw withdrawal threshold (PWT) after intra-articular knee injection of MSU crystals. Joint edema was measured as the increase in knee diameter from baseline using a digital caliper. Mechanical sensitivity was assessed by von Frey testing and expressed as paw withdrawal threshold (grams). Data are mean ± SEM (N = 6/group) and were analyzed by two-way ANOVA with Fisher's LSD post hoc test..* p<0.05 vs Control, # p<0.05 vs Model

Figure 2. Effect of MCC950 (100 mg/kg) on cytokine levels in knee joint tissue after intra-articular MSU injection. Levels of (A) IL-6 and (B) IL-1β were measured by ELISA in knee joint homogenates. Data are mean ± SEM (N = 8/group) and were analyzed by one-way ANOVA with Fisher's LSD post hoc test. * p<0.05 vs Control, # p<0.05 vs Model

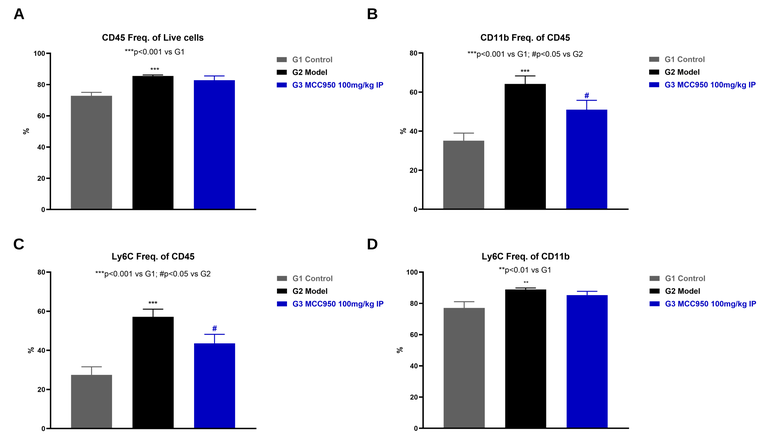


Figure 3. Effect of MCC950 (100 mg/kg) on synovial immune cells after intra-articular MSU injection. Flow cytometry quantification of (A) CD45+ leukocytes, (B) CD45+/CD11b+ granulocytes, (C) CD45+/Ly6C+ cells, and (D) CD45+/CD11b+/Ly6C+ monocytes in synovial fluid. Data are mean ± SEM (N = 6/group) and were analyzed by one-way ANOVA with Fisher's LSD post hoc test. * p<0.05 vs Control, # p<0.05 vs Model

Conclusions

MCC950, a selective NLRP3 inflammasome inhibitor, significantly attenuated MSU-induced joint pathology. At 6 h MCC950 reduced joint swelling and mechanical hypersensitivity, suppressed MSU-induced increases in IL-1β and IL-6 in knee tissue, and decreased synovial recruitment of CD45+/CD11b+ granulocytes and, to a lesser extent, CD45+/CD11b+/Ly6C+ monocytes. These data indicate that pharmacologic inhibition of NLRP3 blunts the early proinflammatory cascade initiated by MSU crystals and support further evaluation of MCC950 as a therapeutic candidate for gouty arthritis.

References

1. Dalbeth N, Merriman TR, Stamp LK. Gout. *Lancet*. 2016 Oct 22;388(10055):2039-2052

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