

The authors in the manuscript "The anti-inflammatory effect and mechanism of WIN55-212-2 on mice with experimental colitis", Manuscript NO: 27964 are studying in an animal model DSS induced colitis and the anti-inflammatory effects of WIN55-212-2 on inflammation. The manuscript is well written and the experiments thoughtfully designed. However since it is known that endocannabinoids alleviate inflammation through a wide range of pathways including through JAK-STAT and COX, the title needs to pinpoint results on p38.

Answer: The authors thank you very much for the positive evaluation and the good suggestions for our paper. Accordingly, the title has been changed to "*The anti-inflammatory effect of cannabinoid agonist WIN55,212 on mouse experimental colitis is related to inhibition of p38MAPK.*" And your questions are answered below, one by one, in red.

Minor points

Interplay between ECS and p38-MAPK when showing only CB1 and CB2 is an overstatement. I suggest that the authors rewrite such statements to be more precise.

Answer: Thank you for the suggestion. This part you mentioned has been rewritten, and the statement is modified. Please find it in line 7-15 of page 15 in the revised version. We will continue to investigate the interplay between p38MAPK and ECS in depth in the future study.

Why was TNF-alpha and IL-6 not measured in colitis tissue? This would have validated the MPO activity data and could have been compared with those in plasma.

Answer: When we designed the topic, the main purpose was to explore the anti-inflammatory effect of WIN55 on mice with experimental colitis. Besides, aiming at p38-MAPK pathway, we designed to explore the possible mechanism of the effect of WIN55. Therefore, parts of the typical indexes were chosen, such as the intestinal pathological indexes and MPO activity in the local tissue (a direct sign of gut neutrophil infiltration), and some proinflammatory cytokines as TNF- α , IL-6 in plasma to reflect systemic involvement. Your suggestion is very helpful. We plan to detect these indicators in local and compare them with the systemic ones in the following study, which may be represented in another story. Thank you again for the kind suggestion.

Figure 2 A-D please include insets with higher magnification.

Answer: The Figure 2 A-D have been changed in the revision accordingly. Thanks a lot for your suggestions.