

We thank the Editor and the Reviewers for the helpful comments and suggestions that have been taken into account to revise and improve our paper.

Reviewer #1: I read with great interest the manuscript entitled "Relaxin influences ileal muscular activity through a dual signaling pathway in mice" by Indrizaj et al. The manuscript is interesting and important in its field of investigation.

However, the main criticism regards the translation of their findings in the clinical practice. The Authors should discuss this issue more in depth.

Our results derive from a basic study so that, even if we agree with the Reviewer on the importance of the translation of our findings in the clinical practice, we can only make some speculations. We have indeed underlined in the MS that the observation that the two pathways engaged by RLX to cause myorelaxation may create the basis for identifying new therapeutic targets, offering stimulating translational perspectives in the treatment of those intestinal dysmotilities characterized by hypermotility states.

In addition, the action of Relaxin is well known so the question remains: what's new? Is it to consider the ileal muscle?

The novelty of this study is represented by the observation that in the ileum RLX engaged two signaling pathways to cause myorelaxation, at variance with the others gastrointestinal segments studied (stomach and colon), in which the effects of the hormone occurred only through the NO pathway. The ability of RLX to activate a dual signaling pathway in the ileum may have physiological implications that underlie the importance of the relaxant effects of the hormone: the alternative pathway engaged by RLX could guarantee its depressant effects that may be addressed to increase intestinal transit time, so favoring the absorption phenomena. Furthermore, this is the first study, to our knowledge, that shows the ability of RLX to influence ileal smooth muscle biophysical properties.

In general the manuscript should be shortened and more focusing.

Your suggestions have been taken into account in the revised version of the MS. Thank you.

Reviewer #2: Dr. Idrizaj and Dr. Squecco, et al. investigated 'Relaxin influences ileal muscular activity through a dual signaling pathway in mice'. The article is informative and well-presented. The reviewer has some comments.

Comments 1. The authors treated TTX and nifedipine. The reviewer would like to know the results of TTX and nifedipine on the mechanical activities by RLX. Please show the results in Figures, Tables or text.

The effects of TTX on the mechanical activity as well as those of RLX in the presence of TTX have been better specified in the text. Further experiments have been performed to evaluate the effects of nifedipine on the mechanical activity and those of RLX in the presence of nifedipine. The results obtained have been added in the text.