Potassium channel regulation of murine gut motility and contractility

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INTRODUCTION

Investigating the mechanisms regulating gastrointestinal (GI) motility and contractility are essential if we are to understand GI dysfunction associated with GI disorders and developmental issues such as ageing.

Studies have demonstrated a role for ion channel regulation of GI smooth muscle function[1], whereas studies focussing upon ion channel regulation of enteric nervous system function are lacking especially regarding the ageing process.

One important ion channel family demonstrated to regulate GI contractility are the potassium (K^+) channels (Kv7 and TREK)[2,4]. This study investigates the role of Kv7 and TREK channels in modulating gastrointestinal motility and smooth muscle contractility and forms the beginning of a project to elucidate age-related changes in ion channel function and the effect of this upon GI motor function.

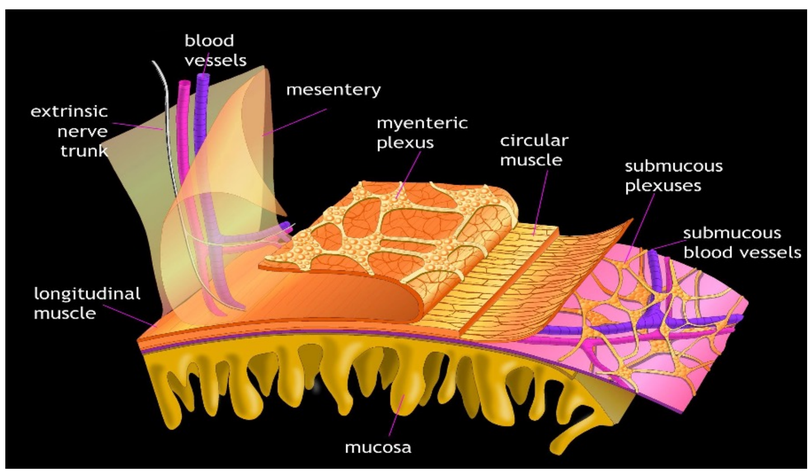

Figure 1 - Anatomical structure of the gastrointestinal tract wall

MATERIALS AND METHODS

- Electric field stimulation and motility experiments were performed on female C57BL/6 animals.
- **Electrical Field Stimulation (EFS):** Standard protocols were used to stimulate the intestinal segments and test the effect of the different drugs on the EFS response.
- **In-vitro motility model:** Colonic peristaltic motor complexes (CPMCs) were initiated in colonic segments using a modified motility bioassay[3].
- **Statistical Analysis:** The data was analysed using repeat measures one-way ANOVA with Tukey's/Dunnett's post hoc tests. $P<0.05$ was considered significant. The statistical analyses were done using GraphPad Prism 10 software.

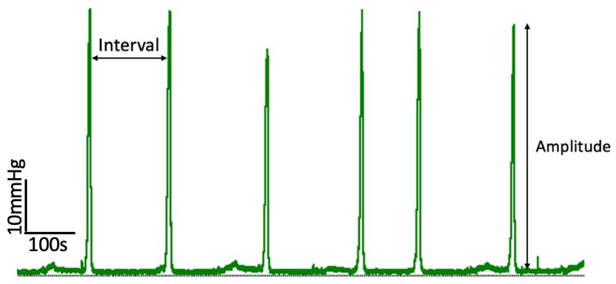

Figure 2 – Representative trace of basal murine colonic peristaltic motor complexes (CPMCs).

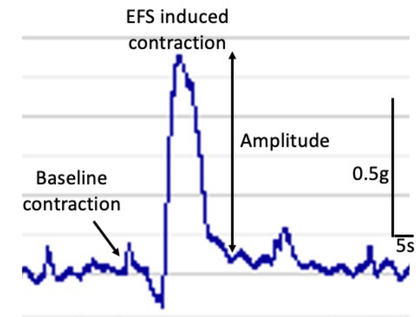

Figure 3 – Representative trace of an EFS response.

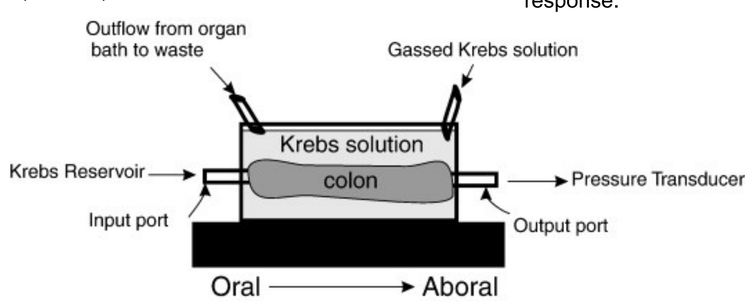

Figure 4 -Schematic diagram of the in vitro organ bath apparatus used for the motility experiments[3].

RESULTS

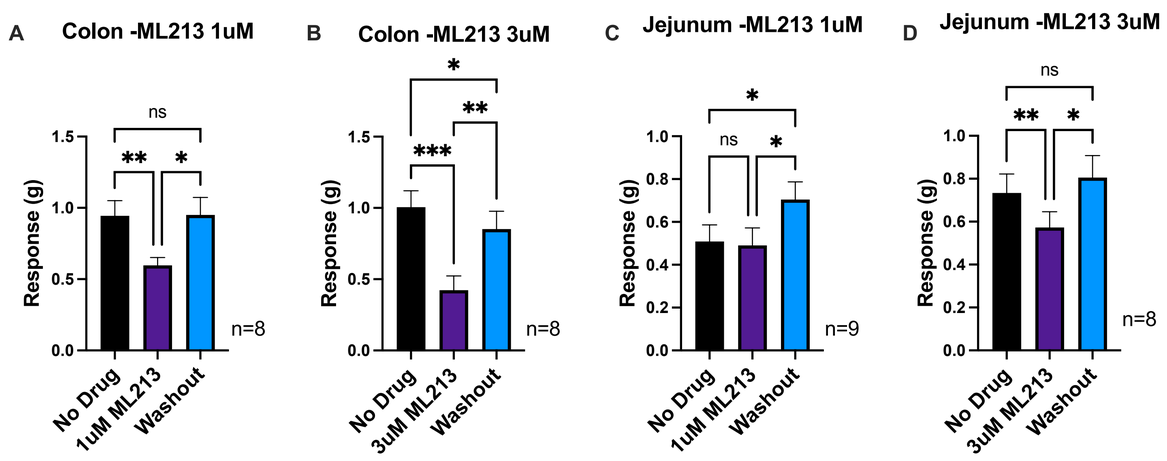

Figure 5: A - D show the dose-dependent effect of ML213 on EFS responses in the jejunum and colon. Data is mean +/- sem. *p<0.05, **p<0.01, ***p<0.001

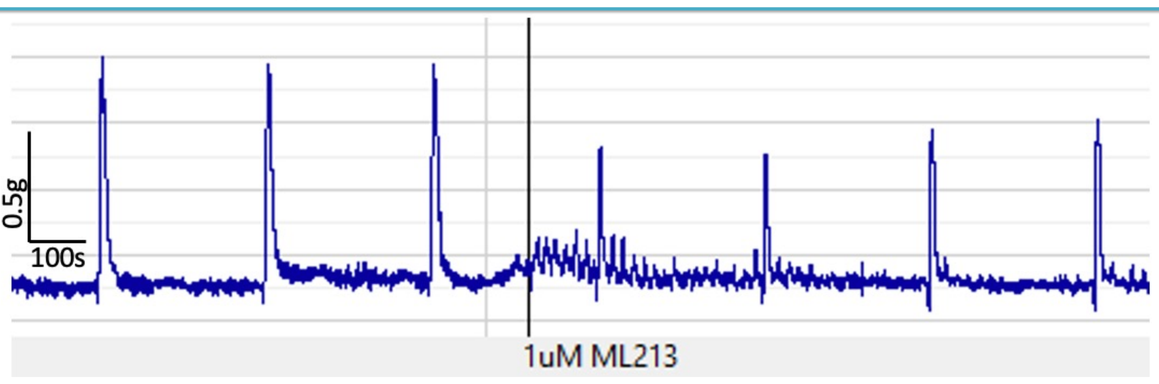

Figure 6: Example trace showing the effects of 1uM ML213 on EFS-induced responses in the colon.

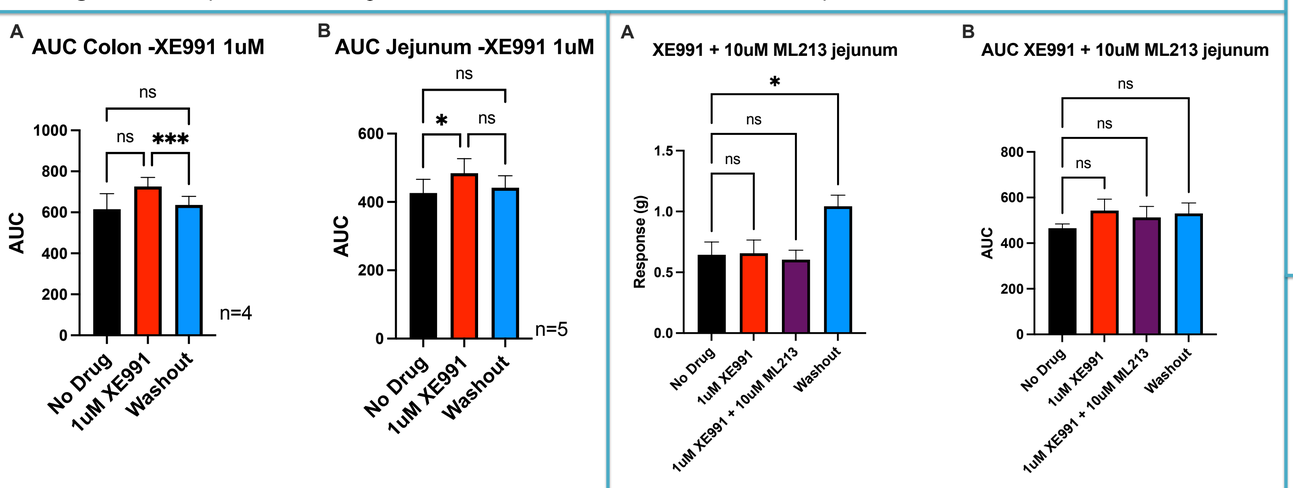

Figure 7: A and B also show the effect of 1uM XE991 on the EFS responses in the colon and jejunum but the area under the curve (AUC) was measured instead of the amplitude. Data is mean +/- sem

Figure 8: A shows the effect of 1uM XE991 on EFS response in the jejunum and it also shows the effect of the addition of 10uM ML213 on XE991 response. B shows the same data as graph A but the area under the curve (AUC) of the traces was measured instead of the peaks. Data is mean +/- sem

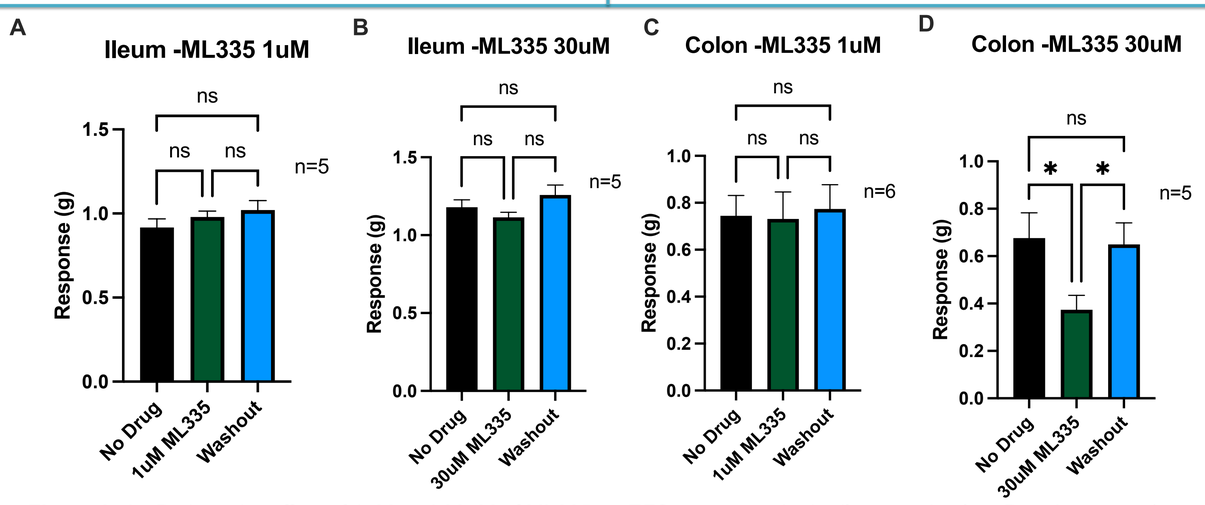

Figure 9: A - D show the effect of 1uM and 30uM of ML335 on EFS responses in the ileum and colon. Data is mean +/- sem

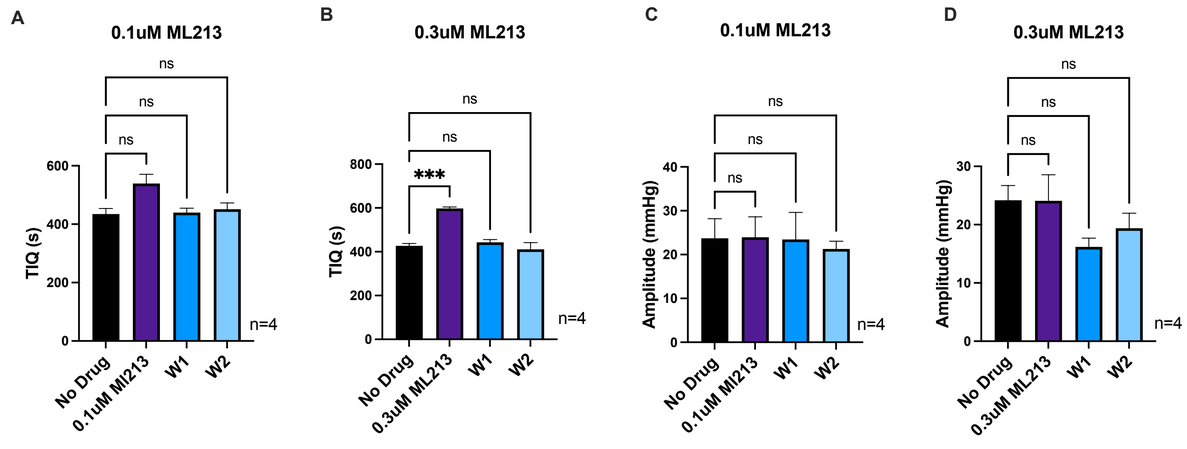

Figure 10: Graphs illustrating the concentration-dependent effects of ML213 on TIQ (A-B) and amplitude (C-D) of peristaltic motor complexes in mouse colonic segments. Data is mean +/- sem

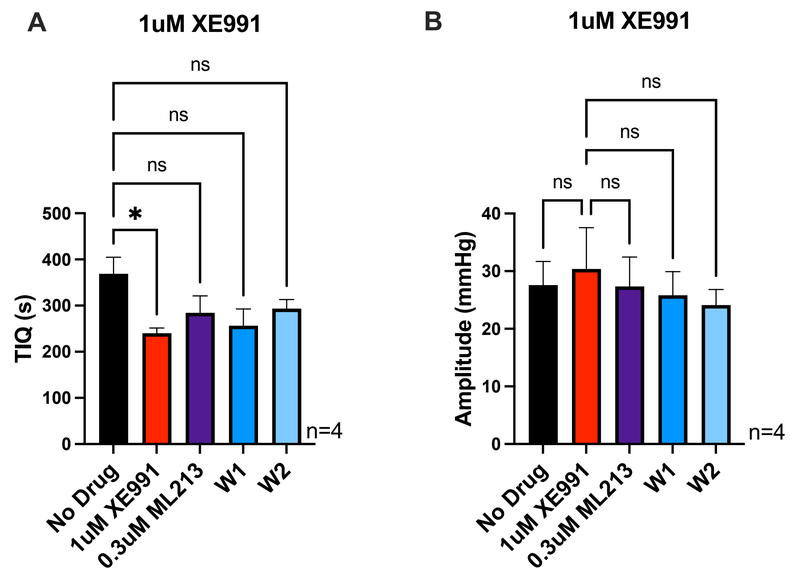

Figure 11: Graphs illustrating the effects of 1uM XE991 on TIQ (A) and amplitude (B) of peristaltic motor complexes in mouse colonic segments. These graphs also show the effect of ML213 in the presence of XE991. Data is mean +/- sem.

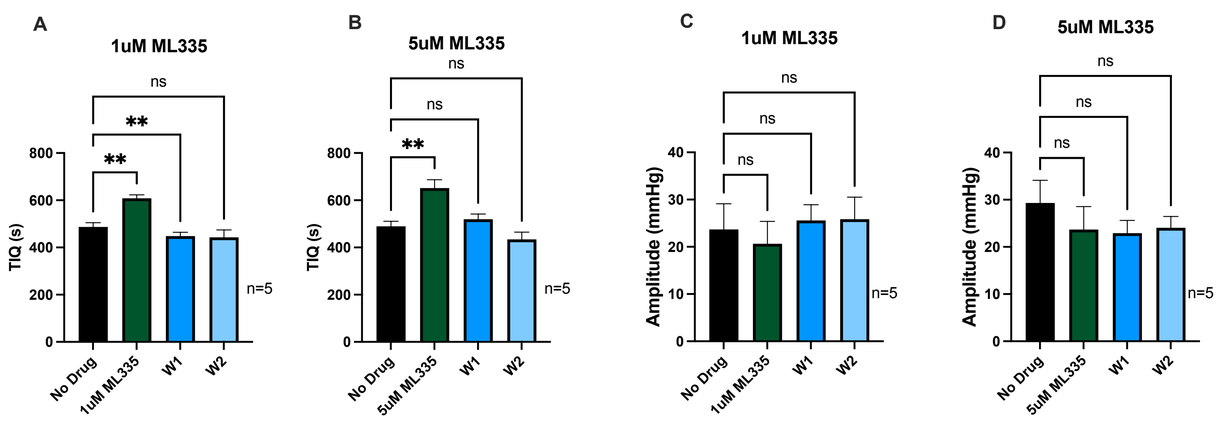

Figure 12: Graphs illustrating the effects of ML335 on TIQ (A-B) and amplitude (C-D) of peristaltic motor complexes in mouse colonic segments. Data is mean +/- sem.

CONCLUSION/DISCUSSION

- Kv7 and TREK channels play a significant inhibitory role in the contractility and motility of the gut and their actions appear to be mediated via neuronal effects.
- Future work aims to investigate the effects of ageing upon Kv7 and TREK channel function within the GI tract with a specific focus on these channels' responses to inflammatory stimulation.

References

[1]Beyder, A. and Farrugia, G. (2011) 'Targeting ion channels for the treatment of gastrointestinal motility disorders', *Therapeutic Advances in Gastroenterology*, 5(1), pp. 5–21. doi:10.1177/1756283x11415892.
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[3]Keating, C. *et al.* (2010) 'The validation of an in vitro colonic motility assay as a biomarker for gastrointestinal adverse drug reactions', *Toxicology and Applied Pharmacology*, 245(3), pp. 299–309. doi:10.1016/j.taap.2010.03.014.
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