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Poster presentation

NO-induced motility effects in distal colon of sGCα_1 knockout mice

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In distal colon, NO plays a less predominant role as relaxant neurotransmitter compared to the upper gastrointestinal tract. As the $\alpha_1\beta_1$ isoform of soluble guanylate cyclase (sGC) is the most important one in the gastrointestinal tract, the aim of this study was to investigate the role of sGC in smooth muscle effects of endogenous and exogenous NO in distal colon using wild type (WT) and sGCα_1 knock-out (KO) mice of both sexes (9–37 weeks old). Results were the same in both sexes except when indicated. Mucosa-free circular muscle strips of distal colon were precontracted with prostaglandin F2α (PGF2α) in the presence of atropine and guanethidine and exposed to electrical field stimulation (EFS) and exogenous NO, before and in the presence of the sGC inhibitor ODQ or the NO synthase inhibitor L-NAME. The contractile response to PGF2α was not different between WT and KO strips. In WT strips, only the relaxation induced by EFS at 1 Hz was significantly reduced by L-NAME and ODQ indicating that only at this stimulation frequency NO, acting at sGC, is released. The EFS-induced response at 1 Hz is decreased in KO strips when compared to WT strips but only in the set where ODQ was tested, while there was no difference in the set where L-NAME was tested. ODQ and L-NAME did not reduce the EFS-evoked responses in KO strips. In WT strips, NO-induced relaxations were not influenced by L-NAME but reduced by ODQ. The NO-induced responses were significantly lower in KO strips when compared to WT strips although this did not reach significance in the strips of male mice where L-NAME was tested. In KO strips, NO-evoked responses were not influenced by L-NAME, but reduced by ODQ. In WT strips, cyclic guanosine monophosphate (cGMP) levels measured at maximal relaxation by NO were increased 4 (male) to 11 (female) fold versus basal, but this increase did not reach significance in strips of male mice; cGMP levels were not changed by EFS at 1 Hz. Basal cGMP levels were lower in KO strips but NO still induced an increase in cGMP levels (5 – 3 fold versus basal in male respectively female). The relaxant response to endogenous NO, released by EFS at 1 Hz, is reduced in KO strips and no longer affected by ODQ, indicating that endogenous NO mainly acts through sGCα_1; the non-ODQ sensitive effect of NO might be related to direct activation of small conductance Ca^{2+}-dependent K^+-channels. The relaxant response to exogenous NO is reduced in KO strips but still sensitive to ODQ, indicating that exogenous NO is able to act through sGCα_2 as well as sGCα_1.