

Optimization of a small intestinal segment perfusion model for heat-stable enterotoxin A induced secretion in pigs

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Enterotoxigenic *Escherichia coli* (ETEC) are a major cause of dehydrating diarrhoea in children and weaned piglets living under subhygienic conditions. After colonization of the small intestine, ETEC produce heat-labile (LT) and/or heat-stable (ST) enterotoxins. Individual human ETEC strains generally produce only one type of enterotoxin, and in symptomatic patients from developing countries the heat-stable enterotoxin A (STa) producing strains seem by far the most prevalent. STa binds to and activates guanylyl cyclase C (GC-C) in the brush border of intestinal epithelium. An increase in cGMP in turn activates cGMP-dependent protein kinase II (cGKII) leading to phosphorylation of the cystic fibrosis transmembrane regulator (CFTR) driving Cl⁻ secretion and inhibition of NaCl absorption followed by net loss of water through osmotic diarrhoea.

We used a small-intestinal segment perfusion model of ETEC diarrhea in pigs [1] in which we investigated the possibility of eliciting STa induced secretion. Five consecutive mid-jejunal segments of anaesthetized piglets were perfused for 6 hours with different concentrations of STa (150-0.62 nM) in a physiologic salt solution. Changes in intestinal net fluid absorption were measured. We concluded that the STa response was dose-dependent and that continuous perfusion with 50 nM of STa or more was required to reduce net absorption. In all piglets the control segments showed net absorption. Fifty nanomolar of STa was sufficient to reduce net absorption compared to control segments in 10 out of 12 piglets; in 8 of them net absorption was reversed to net secretion. STa-induced responses showed relative high variation between different jejunal segments similar to the inter-segment variation seen in control animals where segments were perfused with physiologic salt solution. Results indicate that more optimization is required before this model could be used to test compounds that could interfere with the STa induced fluid secretion.

1. Nabuurs, M.J., et al., *A long-term perfusion test to measure net absorption in the small intestine of weaned pigs*. Res Vet Sci, 1993. **55**(1): p. 108-14.