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Getting a handle on cholera and the circuits controlling intestinal motility

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A commentary on

Luminal cholera toxin alters motility in isolated guinea-pig jejunum via a pathway independent of 5-HT$_3$ receptors.
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Diarrheal diseases, which are typically bacterial in nature, are a major global health problem (Zuckerman et al., 2007). The majority of diarrheal episodes are associated with *Escherichia coli,* or *Shigella, Campylobacter* or *Samonella* spp., however, infection with the bacterium *Vibrio cholerae* is perhaps the most renowned because it produces diarrhea that can lead to severe dehydration and death, sometimes within hours of the first symptoms, and outbreaks reach epidemic proportions prior to the discovery of the contaminated source. Forced rehydration is the current treatment modality for cholera and while prevention is typically sought by bolstering infrastructure to provide clean water, vaccine development is the most active and controversial front in therapeutic advancement (Chaignat, 2008). Cholera has traditionally been considered to act by increasing cAMP levels in epithelial cells to evoke secretion (Vanden Broeck et al., 2007), but newer lines of evidence point to enteroendocrine-mediated initiation of secretory reflexes within the enteric nervous system (ENS) as a primary cause (Farthing, 2002), the most compelling data of which is that tetrodotoxin, and 5-hydroxytryptamine (5-HT)$_3$ receptor antagonists block cholera toxin-induced secretory diarrhea (Beubler et al., 1989; Jodal, 1990).

The ENS, a network of neurons present within the wall of the alimentary canal, coordinates the complex and varied functions of the gastrointestinal (GI) tract (Furness, 2006). One class of enteric neuron are the secretomotor neurons which, when paired with dilation of intestinal blood vessels, can cause the secretion of vast amounts of fluid. Cholera toxin, perhaps by direct activation, or perhaps indirectly through the release of 5-HT and activation of intrinsic afferent neurons, increases the firing rate of these secretomotor neurons (Jiang et al., 1993; Gwynne et al., 2009). Intrinsic afferent neurons and secretomotor neurons form a recurrent network which is likely to explain the uncontrolled firing of secretory motorneurons following cholera toxin exposure (Chambers et al., 2005).

While the mechanisms by which cholera toxin enhances secretion are becoming clear, it's effects on GI motor function remain murky. On one hand, an early study found an increase in transit in suckling rabbits infected with whole *V. cholerae* (Finkelstein et al., 1964) while on the other hand, a marker perfusion study failed to identify changes in GI transit in patients with cholera (Banwell et al., 1970; Brigham et al., 1970). Similarly, Banwell and Sherr (1973) observed that a small intestinal loop exposed to *V. cholerae* became flaccid but a later myoelectrical analysis of infected open loops of rabbit intestine revealed increases in migrating action potential complexes 4 h post-inoculation with cholera toxin (Mathias et al., 1976; Mathias et al., 1977). Reduced motility has also been seen using strain gages in awake, fed dogs (Cowles and Sarna, 1990a,b) while Kordasti et al. (2006), saw little effect of cholera toxin on the frequency or amplitude of contractions in rats *in vivo*. Interestingly, when the 5-HT$_3$ receptor antagonist, granisetron, was administered to these rats to reduce the secretory effect of cholera toxin, there was a significant increase in contractions (Kordasti et al., 2006). It is into this arena that Fung et al. (2010) have entered, using a relatively new approach for studying GI motility.

High resolution spatio-temporal mapping of intestinal diameter allows the position and magnitude of contractions or dilations to be mapped down to an accuracy of less than a millimeter with data sampled 30 times a second. This allows the experimenter a much greater objectivity when distinguishing between propagating and segmenting contractions. Using this technique, Fung et al. have demonstrated a modest but significant increase in the frequency of propulsive contractions following cholera toxin administration into the lumen of the small intestine, with no change in the occurrence of segmenting contractions. In contrast, in preparations pre-treated with granisetron, cholera toxin caused a dramatic increase in propulsive contractions with a later switch to segmenting contractions. When the lumen of the intestine was perfused with the nutrient decanoic acid, cholera toxin switched segmenting contractions normally associated with decanoic acid, to propulsive contractions. The authors concluded that cholera toxin stimulates several distinct, and in some cases opposing, neural circuits which overall cause an increase in the propulsive contractions at the expense of nutrient induced segmentation.

This study shows convincingly that cholera toxin can induce motility changes in the intestine and begins to explain why evidence to date has been mixed. Nonetheless, some mysteries remain. For example, previous studies have found that changes in motility generally occur later during cholera toxin-induced secretion while in the present study motility was induced much earlier. One drawback of the present study is that it used intestinal segments removed from the animal. This could increase mucosal permeability which may allow cholera toxin more direct access to enteric neurons. In another study using *in vitro* guinea pig ileum, increases in electrogenic secretion were seen within 30–40 min (Carey and Cooke, 1986) as opposed to hours when studied *in vivo* (e.g., Mathias et al., 1976). Perhaps a study utilizing exteriorized small intestine combined with spatio-temporal

mapping (Ferens et al., 2005) would be the best way to clarify the time course of action for cholera toxin.

It is unclear whether the results of this study will directly improve treatments for cholera infection, though they could explain the variable results of 5-HT_3 receptor antagonists in treating cholera toxin-induced hypersecretion in humans (Hunt et al., 1992, Turvill and Farthing, 1997) as 5-HT_3 receptor inhibition in this study markedly enhanced the pro-propulsive effects of cholera toxin. What is clear from the present study is that spatio-temporal mapping provides previously unavailable insights in to the multiple enteric neural reflexes activated by cholera toxin. The results of this study provide an excellent working model to further dissect the complex neural circuitry that contributes to GI motor activity.

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