Author's response to reviews

Title: Oxytocin and cholecystokinin secretion in women with colectomy.

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Version: 2  Date: 9 August 2004

Author's response to reviews: see over
No. 1 PS Wang. Thankyou for valuable criticism. We have made the following corrections according to Your questions, and think that the manuscript has been improved after this revision. Now we hope it will be accepted for publication in BMC Gastroenterology.

1. We have now mentioned the physiological significance of oxytocin in the GI function in the discussion page 10, line 9. Relatively few studies have been performed in man, but we are currently investigating additional functions. We have found it irrelevant to discuss the physiological role of oxytocin in animals. Even in animal few studies have been performed, and then with pharmacological doses rather than physiological.

2. The aim of this study was to study if there was any difference in oxytocin secretion between women with intact GI tract and those with colectomy. Our hypothesis that oxytocin concentrations decrease after colectomy developed from the finding after earlier studies when we examined oxytocin release in women and included one woman with colectomy (14), and also the fact that oxytocin has been demonstrated in the GI tract (18). The finding of higher CCK levels in colectomized women after injection was a surprise and not predicted. This raised the question that colectomy affects the clearance of CCK. The aim of this study therefore was not to examine the clearance. However, we have suggested in our manuscript that the hyperCCKemia depends on decreased clearance. In subsequent studies this has to be further evaluated. We believe it is beyond the aim of this study to investigate metabolic clearance rate (MCR). We have changed our conclusions in the abstract and discussion, page 11, last para, to be more circumspect, suggesting a possible decreased clearance. You are correct that the postulate has not yet been proved. Rather, another hypothesis has been raised.

3. It would be difficult to design such a study. As CCK acts on CCK receptors on afferent vagal nerves to stimulate oxytocin release from the pituitary gland (ref 12), a CCK receptor blocker would lead to inhibition both on centrally and locally secreted oxytocin. We do not know what mechanisms stimulate the release of oxytocin in the bowel wall, but one may speculate that CCK receptors are also involved in the regulation of autocrine/paracrine oxytocin release from the bowel as they are present throughout the GI tract (ref 4 and 5), page 9, line 17. We have no patients who have had their stomach or small intestine deleted.

4. We have revised the figures with a scale on X-axis, included the number of patients in the figure and explained the symbols for patients and controls in legends to figures. The other reviewer prefere a Table to figs 1 and 3, and these have been replaced with Table 1.
1. CCK was infused as a bolus instead of an infusion as this was the method we used in our previous study (ref 14). The CCK we used in the former study was produced for injection and not infusion. We felt it appropriate to mimic that study as much as possible, as both studies were performed to examine oxytocin release. Furthermore, also CCK infusion leads to high unphysiological plasma levels of CCK. The actual bolus dose chosen was the only dose in an earlier study that induced a small but not significant oxytocin release (ref 19), page 6 last line.

2. As we knew from our earlier study (ref 14) that the elevated oxytocin level persisted for some time, we wanted to take blood samples for up to 2 h to be sure not missing a difference late in the course. Ethical reasons limited the sampling. We also knew from the other study that the oxytocin release did not occur immediately. The aim of this investigation was to study the effect on oxytocin release. Our finding of hyperCCKemia after an injection was not predicted, but raised another hypothesis that CCK clearance decreased after colectomy. Although this finding was interesting, we cannot abandon our first hypothesis. Our unsuspected findings may however lead to further studies in the future to determine what causes the hyperCCKemia. We have changed our conclusions in the abstract and discussion to be more circumspect, suggesting a decreased clearance instead of saying it is like that. Both You and the other reviewer are right that we have too strong conclusions without proving it involves decreased degradation. However, we think it lies outside the aims of this investigation to perform clearance studies and have indicated this under "in summary", page 11, last para in the discussion.

3. The stimulus of CCK was standardised to a dose of 0.2 microgram / kg bw. Your question is relevant and interesting. However, there was no correlation between CCK concentrations and oxytocin concentrations, as described last line under Results. Thus, it seems unlikely that the same CCK level in plasma would give exactly the same oxytocin level. Further, there was no difference between basal levels of oxytocin Table 1.

4. We have replaced Fig 1 and 3 with Table 1.