Acetylcholine induces intestinal secretion indirectly, by releasing vasoactive intestinal peptide from enteric neurones in rat jejunum.

Saeed Al-Saadi, Sahar D Mohammed, David E Burleigh. Institute of Cell and Molecular Science, Centre for Digestive Diseases, Wingate Institute for Neurogastroenterology, London, United Kingdom.

Background: Intestinal fluid secretion is controlled by reflexes whose final effecter neurones are believed to release vasoactive intestinal peptide (VIP) and acetylcholine (ACh) as their neurotransmitters (NT) at the neuroepithelial junction (NEJ). PG 97-269, a novel competitive antagonist of VIP type1 receptors effectively inhibits secretory responses of rat jejunum to stimulation of mucosal neurones[1]. The inhibition was in sharp contrast to the weak action of anti-cholinergic muscarinic antagonists (unpublished data). This implies a dominant role for VIP as the NT released at NEJ. Support for such a view came from observations that secretory responses of rat colonic mucosa to ACh were inhibited by the neurotoxin and tetrodotoxin[2].

Aim: to investigate the mechanism of action of ACh in eliciting secretory responses from intestinal mucosa.

Method: The Ussing voltage-clamp technique is used to indirectly measure chloride ion (Cl^-) transport by intestinal epithelial cells. The potential difference (PD) resulting from electrogenic transport of Cl^- is measured as necessary current to nullify the PD i.e. short-circuit current (Isc). Muscle-stripped preparations of rat jejunum were set up in Ussing chambers for recording of transepithelial Isc. Values quoted are mean +/- SEM $\mu A.cm^{-2}$; Mann-Whitney U test used to analyse unpaired data.

Results: Responses to submaximal concentrations of ACh (3µM & 10µM) were obtained before and after administration of antagonist drugs or vehicle (H_2O). In the presence of tetrodotoxin (1µM), PG 97-269 (12.5µM) or hyoscine (0.1µM) responses to ACh were reduced by 89% (59+/-3 to 6+/-1 $\mu A.cm^{-2}$, n=6, $P<0.05$) 88% (94+/-14 to 11+/-3 $\mu A.cm^{-2}$, n=6, $P<0.05$) and 97% (68 to 2 $\mu A.cm^{-2}$, n=1) respectively. Vehicle was without effect (72+/-11 to 72+/-13 $\mu A.cm^{-2}$, n=6, $P>0.05$).

Conclusion: In rat jejunum, ACh elicits a marked secretory response. The response probably results from stimulation of muscarinic receptors located on enteric neurones given the magnitude of inhibition produced individually by, hyoscine and tetrodotoxin. Such neurones are probably peptidergic releasing VIP as the NT, as responses to ACh are greatly reduced in the presence of PG 97-269. Our results indicate that VIP is the dominant NT, acting at the NEJ, to initiate electrolyte and water secretion.

(1) Banks MR et al, Br.J. Pharmacol. 2005, 144:994–001.
(2) Ashraf MF & Burleigh DE, Br.J.Pharmacol. 2005, Vol3; 2; abst099P.

We are grateful to Dr. Francoise Gregoire-Cerf, at The University of Libre de Bruxelles, for providing a gift of the VIP antagonist (PG 97-269).