

2012

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Recommended Citation

Mani, Venkatesh; Hollis, James; and Gabler, Nicholas K. (2012) "Bitter Compounds Decrease Gastric Emptying and Influence Intestinal Nutrient Transport," *Animal Industry Report*: AS 658, ASL R2725.

DOI: https://doi.org/10.31274/ans_air-180814-941

Available at: https://lib.dr.iastate.edu/ans_air/vol658/iss1/57

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Bitter Compounds Decrease Gastric Emptying and Influence Intestinal Nutrient Transport

A.S. Leaflet R2725

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Summary and Implications

The effect of bitter tasting compounds on gastric emptying and nutrient transport from the intestine was studied using *in vivo* and *ex vivo* models. Sixteen pigs were fed a diet containing the bitter compound phenylthiocarbamide (PTC). The animals were euthanized 45 minutes postprandially and gastric contents were measured to quantify the gastric retention. Additionally, freshly isolated small intestines were mounted into modified Ussing chambers to study the effects of PTC on *ex vivo* nutrient transport. In summary, bitter compounds decreased the gastric emptying *in vivo* and increased the nutrient transport *ex vivo*. Further, cell culture studies identified that bitter compounds might exert their action through stimulating the secretion of the intestinal hormone cholecystokinin (CCK) from the enteroendocrine cells by increasing the intracellular calcium concentrations. Altogether, these data suggest that bitter compounds regulate feed intake and nutrient transport.

Introduction

Taste contributes to food perception and may influence body weight regulation. The sensing of bitter compounds in the oral cavity is important because it protects against the consumption of potentially harmful substances and toxins. Bitter taste receptor (BTR) expression has been demonstrated in the tongue, stomach, intestine, and lung. The activation of BTR has been shown to increase the intracellular calcium in the enteroendocrine cells. Increased intracellular calcium leads to activation of different signaling cascades and cellular processes leading to augmented secretion of intestinal peptides such as glucagon like peptide-1, peptide YY, gastric inhibitory peptide and cholecystokinin (CCK). Increased secretion of these peptides is associated with decreased gastric emptying, intestinal motility and appetite. Cholecystokinin, in particular is secreted mainly from the duodenum by stimulation of presence of food in the intestine. It induces the secretion of pancreatic enzymes and bile to the intestine to digest the food and controls the rate of gastric emptying

there by indirectly acting as an appetite regulator. Therefore, the first objective of this study was to assess the effect of bitter compounds on gastric emptying (GE) and nutrient transport (NT) in pigs. The second objective is to test the hypothesis that decreased gastric emptying is a result of bitter compound signaling in enteroendocrine cells via BTR leading to increased CCK secretion.

Materials and Methods

Sixteen pigs (35±3 kg body weight) were fasted overnight and fed one of two 600 g pudding meals: 1) Control meal containing milk, guar gum, sugar and chocolate powder or 2) as control plus 1 mM phenylthiocarbamide (PTC) bitter compound. Exactly 45 min after offering and completing the meal, pigs were euthanized and gastric contents were measured to assess the effect of PTC on gastric emptying. Jejunum segments from these pigs were immediately excised, mounted into modified Ussing chambers, voltage clamped and nutrient transport measured in the presence or absence of 5 mM PTC. After a 30 min period of stabilization, tissues were challenged sequentially with 10 mM glucose, lysine and glutamine on the mucosal side with equimolar concentration of mannitol added to the serosal side for measuring the transport.

Mouse enteroendocrine cell line STC-1 (a gift from Dr. Steven Young, University of California at San Francisco) was cultured in DMEM supplemented with 10% fetal bovine serum and 1% antibiotics in a humidified atmosphere with 5% CO₂. Passages 3 to 7 of cells were used for the experiment. The cells were plated into 12 well plates and when confluent, they were treated either with 5 mM PTC or 10 μM calcium ionophore A23187. The media was collected after 15, 30, 45 and 60 minutes and cholecystokinin concentrations were determined using a commercially available EIA kit. All data were analysed using PROC Mixed procedure of SAS (SAS Inst. Inc., Cary, NC).

Results and Discussion

Pigs were fed a meal (approximately 600g) with or without 1 mM PTC (Bitter). There was no difference between the two groups in feed consumption, indicating that the PTC meal still was palatable (P=0.88, Table 1). The stomach contents in the bitter fed group was significantly higher (P=0.037, Table 1). When the gastric retention was calculated, the Bitter group had a significantly higher meal retention than the control group (P=0.017, Table 1). Compared to the Control meal, the Bitter meal pigs had a 30% increase in stomach contents 45 minutes after completing the meal (P < 0.01). This data suggests that PTC

bitter compound slows gastric emptying. Ex-vivo jejunum nutrient transport in the pigs was measured using modified Ussing chambers. Glucose, lysine and glutamine transport was increased by 250% in the Bitter meal fed pigs, compared to the control pigs ($P < 0.05$, Table 2). However, when these jejunum tissues were treated ex-vivo with 5 mM PTC, no effect on nutrient transport was observed irrespective of the pig treatment (Table 2).

Sensing of nutrients in the intestine can occur via enteroendocrine cells. Using the murine STC-1 enteroendocrine cell line, we investigated the effect of bitter compound (PTC) on CCK secretion (Figure 1). Further, we used the calcium ionophore A23187 to increase the intracellular calcium concentration and subsequent CCK secretion. The media concentrations of CCK increased over time ($P = 0.030$). Compared to the vehicle, PTC and A23187

treatments also had increased media CCK concentrations ($P < 0.0001$, Figure 1). However, we observed no treatment by time interaction with regard to STC-1 CCK secretion ($P = 0.42$, Figure 1). In conclusion, these data indicate that adding PTC to food results in increased amount of gastric contents 45 minutes after consuming a meal suggesting reduced gastric emptying rate. Interestingly, feeding bitter compounds increase active nutrient transport in vivo, but not ex vivo. Our accompanying enteroendocrine cell culture data indicates that PTC increases the secretion of CCK. Furthermore, treatment with the calcium ionophore, A23187, increased media CCK concentrations. This suggests that intracellular calcium signaling may be critical in the regulation of appetite and gastric emptying by bitter compounds.

Table 1. The effects of bitter compound, phenylthiocarbamide (PTC, 1 mM) on meal intake and gastric emptying in pigs' 45 min post meal offering.

	Control	Bitter	SEM	P-value
Food Offered (g)	653.0	625.0	14.21	0.34
Meal Eaten (g)	507.5	533.8	49.25	0.88
Stomach contents (g)	298.9	443.0	47.47	0.037
Meal Retained (%)	55.4	81.2	6.11	0.017

Table 2. Jejunum nutrient transport in pigs fed either a control meal (Con) or a meal containing 1 mM phenylthiocarbamide (PTC) bitter compound. These tissues were then treated without (Veh) or again with 5 mM PTC for 30 min. Nutrient transport was then assessed using modified Ussing chambers.

	Con-Veh	Con-PTC	Bitter-Veh	Bitter-PTC	SEM	P-value		
						Pig	Trt	Pig x Trt
Glucose	100.0	100.1	216.9	273.9	71.11	0.02	0.63	0.63
Lysine	100.0	97.5	188.4	262.5	75.33	0.051	0.56	0.54
Glutamine	100.0	101.4	205.8	279.4	85.60	0.052	0.59	0.61

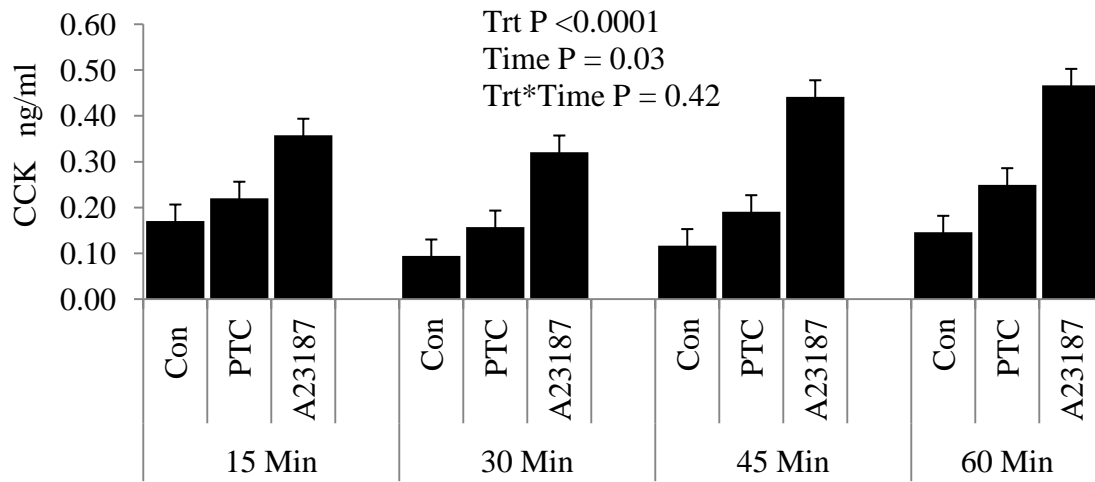


Figure 1. Mouse enteroendocrine STC-1 cells were treated either with no treatment (Con), 5mM (PTC) or 10 μ m calcium ionophore (A23187) and the media was collected at 15, 30, 45 and 60 minutes and CCK concentration was estimated using an EIA kit.