Comparative Gut Physiology and Nonruminant Nutrition Symposium:
The gut–brain axis—Sensing and signaling

43   Nutrient and non-nutrient sensing in the gastrointestinal tract. Soraya P. Shirazi-Beechey*, *University of Liverpool, Institute of Integrative Biology, Liverpool, UK.*

The intestinal epithelium is a major interface with the outside world. This interface is separated from the body's internal milieu by a single layer of epithelial cells consisting of absorptive enterocytes, goblet, enteroendocrine and Paneth cells. These cells are exposed, at the luminal domain, to an external environment that is continuously changing by types and amounts of nutrients, microorganisms, microbial products, gastrointestinal secretions and potentially toxic chemicals. The intestinal epithelium constantly monitors the composition of its contents to optimize nutrient absorption, as well as defending threats to its integrity. In recent years significant advances have been made in the understanding of the molecular recognition events involved in sensing the luminal contents of the gastrointestinal tract. The sensing of various nutrients in the gastrointestinal tract is accomplished by several G-protein coupled receptors, expressed on the luminal membrane of enteroendocrine cells. Sensing of nutrients by these receptors leads to secretion of hormones that control vital physiological functions such as food intake, nutrient digestion and absorption, intestinal barrier function and insulin secretion. The intestine also contains approximately 1000 different species of bacteria and has to discriminate between pathogenic and commensal bacteria to maintain a balance between immune protection and inflammatory over-reactions. A class of proteins known as pattern recognition receptors, in particular toll-like receptors (TLRs 1–10) play a key role in the recognition of microbes via detection of conserved molecular features. The sensory receptors that face the lumen of the intestine and are responsive to luminal contents provide a unique therapeutic opportunity. In my talk I will present data on the role of the gut expressed taste 1 receptor (T1R) family in intestinal nutrient sensing and the contribution of TLR9-recognition of bacteria in control of gut hormone release. The impact of these findings to animal nutrition will be discussed.

Key Words: intestine, taste 1 receptor (T1R), toll-like receptor 9 (TLR9)

44   Effects of supplemental amino acids in low-protein diets on intestinal tight junction and amino acid transporters in growing pigs. S. J. Zhang*[1,2], W. Parnsen[1], and S. W. Kim[1], *[1]Department of Animal Science, North Carolina State University, Raleigh, NC, [2]College of Animal Science and Technology, China Agricultural University, Beijing, China.*

This study was to determine the effects of supplemental AA in low-protein diets on tight junction and AA transporters in the small intestine of growing pigs. 72 pigs (19.7 ± 1.1 kg, 36 barrows and 36 gilts) were allotted to 3 treatments with 8 pens per treatment (3 pigs per pen, 4 barrow pens and 4 gilt pens) using sex and initial BW as blocks: NC (supplemental Lys, Met, and Thr at 18% CP), PC (supplemental Lys, Met, and Thr at 16% CP), and PCT (PC + 0.05% Trp). The NC and PC diets had AA to meet the NRC 2012 requirements (0.98% Lys, 0.55% Met + Cys and 0.59% Thr) whereas PCT diet had additional 0.05% Trp exceeding the requirement. After 4 wk feeding, 24 pigs (1 pig per pen with median BW) were euthanized to obtain duodenum and jejunum to quantify tight junction proteins (claudin-1, occludin-1, and ZO-1) and jejunum to quantify mRNA of AA transporters (CAT-1, $b^{0,+}AT$, rBAT, y^+LAT, 4F2hc, and B^0AT). Tight junction proteins were separated by

Western blot and bands densities were measured. The mRNA of AA transporters was quantified by a real-time PCR. Data were analyzed using the Mixed procedure of SAS. Treatment and sex were the fixed effects and initial BW was a random effect. Pigs in PCT had increased ($P < 0.05$) claudin-1 in duodenum and jejunum compared with pigs in NC and PC. No difference in ZO-1 in duodenum and jejunum was detected among treatments. Pigs in PC had decreased ($P < 0.05$, 39.3%) occludin-1 in duodenum compared with pigs in NC. There was no difference in occludin-1 between PC and PCT. Pigs in PC and PCT had increased ($P < 0.05$) mRNA concentrations of CAT-1 (2.29 and 1.92 fold), 4F2hc (2.76 and 2.45 fold), and B^0AT (2.12 and 2.26 fold, respectively) compared with pigs in NC. Collectively, use of supplemental amino acids (Lys, Met, Thr, and Trp) in low protein diet to meet the NRC 2012 requirements could increase AA transporters in jejunum and additional 0.05% Trp exceeding the NRC 2012 requirements enhanced intestinal tight junction.

Key Words: amino acid transporters, low-protein diet, tight junction

45   The emerging role of bile acids as nutrient-sensing signals. Ignacio R. Ipharraguerre*[1,2], *[1]Institute of Human Nutrition and Food Science, University of Kiel, Kiel, Germany, [2]Lucta S.A., Montornes del Valles, Spain.*

Traditionally, bile acids (BA) have been viewed as detergent molecules involved in the intestinal digestion and absorption of lipids and hepatic maintenance of cholesterol homeostasis. During the last 15 years, however, it has become clear that BA are important regulatory molecules with systemic endocrine functions that signal changes in luminal nutrients and microbial activity during the fed-fast cycle. The regulatory actions of BA are primarily mediated by the nuclear receptor FXR (farnesoid X receptor), the G-protein coupled receptor TGR5 and cellular signaling pathways (AKT and ERK1/2). These proteins are highly expressed in the liver as well as enterocytes, endocrine cells and enteric neurons in the small intestine. Surprisingly, BA receptors are also present in several tissues outside the biliary tree including adipose tissue, pancreas, and immune cells. In mice, via interaction with these sensors and pathways, BA control the expression of genes and concentration of circulating hormones involved in the regulation of lipid and glucose metabolism, energy expenditure, intestinal integrity, motility, and immune homeostasis, gut microbial growth, and inflammation. In pigs, evidence from seminal studies indicates that BA signaling is implicated in the intestinal secretion of glucagon-like peptides, gut mucosal growth and protection, nutrition-related liver disease, and changes in host weight and metabolism resulting from variations in gut microbiota. It is important to note that BA differ in their ability to activate signaling pathways and that the composition of the BA pool varies remarkably among non-ruminant animals. In fact, all non-ruminant species of interest (e.g., pig, chicken, rabbit, horse) have unique BA signatures. In view of these differences and the emerging role of BA as regulatory molecules, the study of their involvement in signaling outside the enterohepatic circulation and in mediating reciprocal communication between the host and its microbiota will become a relevant and expanding field of research in animal nutrition and physiology.

Key Words: bile acid signaling, FXR, TGR5

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46 The role of gut peptides in the gut-brain-axis of livestock.
Andrew P. Foote*, *USDA-ARS, US Meat Animal Research Center, Clay Center, NE.*

Gut peptides are small hormones produced within the gut that are involved in many biological processes including, but not limited to, appetite regulation, mucosal growth, and metabolism regulation. Some peptides, such as cholecystokinin (CCK) and xenin-25 may affect appetite by altering gut motility through cholinergic pathways, but most of the hunger/satiety signals are processed through the brain. Ghrelin is a peptide produced mostly in the gastric stomach or abomasum and increases before a meal. The ghrelin receptor is expressed in neurons in the arcuate nucleus of the hypothalamus and binding leads to the release of neuropeptide Y and agouti-related peptide, thereby stimulating appetite. While ghrelin is thought to serve as a hunger signal in meal fed animals, it may also be involved in the variability of DMI in ad libitum fed animals. Other gut peptides, including peptide YY, oxyntomodulin, and glucagon-like peptide-1 (GLP-1), act as satiety signals and are inhibitory to ghrelin. These peptides stimulate neurons in the arcuate nucleus to release α-melanocyte-stimulating hormone (α-MSH) and cocaine and amphetamine regulated transcript (CART), thereby decreasing appetite. The actions of gut peptides are not limited to appetite regulation. Glucagon-like peptide-2 (GLP-2) is a potent stimulator of intestinal mucosa growth and gut blood flow, and could be important for gut health of livestock. Glucose-dependent insulinotropic polypeptide (GIP) increases insulin secretion and regulates lipid metabolism. Because the complete functions of many gut peptides in livestock species are not known, studying their regulatory roles is critically important in nutritional physiology and animal health.

Key Words: appetite regulation, metabolism regulation, gut function

47 Nutrient sensing by glucagon-like peptide-1 secreting cells.
Frank Reimann*, *Institute of Metabolic Science & MRC Metabolic Diseases Unit, University of Cambridge, Cambridge, UK.*

Glucagon-like peptide-1 (GLP-1) is an enteroendocrine hormone secreted by L-cells found throughout the intestinal epithelium, but with increased frequency in the ileum and colon. GLP-1 acts as an incretin, boosting postprandial insulin secretion, inhibits glucagon secretion and is anorexigenic. Using transgenic mouse models allowing labeling and manipulation of GLP-1 and GLP1R expressing cells we investigated molecular mechanisms underlying hormone secretion and responses in the GLP-1 axis. L-cells are electrically excitable cells, displaying an increased action potential firing rate when nutrients are available. This can be achieved by electrogenic nutrient uptake, for example by the sodium coupled glucose transporter (SGLT-1) or the proton coupled dipeptide transporter (PepT1). L-cells isolated from knockout mice for these transporters have attenuated responses to glucose and dipeptide, respectively. Lipid derived molecules and bile acids, by contrast were shown to be detected by the G-protein coupled receptors FFAR1 and TGR5 (GPBAR), predominantly coupling to increases in cytosolic Ca^{2+} and cAMP, respectively. In the distal intestine, where most nutrients are likely to be processed by the intestinal microbiota, L-cells can be shown to respond to short chain fatty acids (via FFAR2/3) and indole, with the latter inhibiting voltage gated potassium channels and ATP-production, resulting in stimulatory and inhibitory signals respectively. Distal L-cells also differ from small intestinal L-cells in that they co-secrete peptideYY (PYY) and the orexigenic peptide Insulin-like peptide-5 (Insl5), whereas duodenal/jejunal L-cells co-express glucose-dependent insulinotropic polypeptide (GIP, the other incretin) and cholecystokinin (CCK). It is hoped that an improved understanding of the gut hormone signaling will facilitate the development of new therapies that harness endogenous gut hormone reserves for the treatment of metabolic disease.

Key Words: glucagon-like peptide-1 (GLP-1), hormone secretion, nutrient sensing

48 Effect of feeding rate and glucose provision on plasma glucagon-like peptide 2 concentration in dairy calves.
Sarah Y. Morrison*[1], Juan. J. Castro[1], Kristen M. Glosson[1], Jens. J. Holst[2], James K. Drackley[1], and Ignacio R. Ipharraguerre[3,4], *[1]University of Illinois, Urbana, IL, [2]Department of Biomedical Sciences, University of Copenhagen, Denmark, [3]Institute of Human Nutrition and Food Science, University of Kiel, Germany, [4]Lucta SA, Barcelona, Spain.*

Glucagon-like peptide 2 (GLP-2) may have therapeutic potential in young calves encountering stressors, such as weaning and diarrheal disease, because of its pleiotropic actions on intestinal mucosal and barrier function. During diarrhea, feed intake decreases, which is a major negative effector of GLP-2 secretion and increases intestinal atrophy. We determined the effects of feeding rate and supplementation with potential GLP-2 secretagogues in milk replacer (MR) on GLP-2 concentration [GLP-2] in calf plasma. Three days after birth, male Holstein calves (n = 45) were randomly assigned to 1 of 12 treatments arising from factorial combination of feeding rate (FR) and supplement type. Feeding rates were 25, 50, 75, and 100% of standard feeding level on d 5 (1.5% of BW as DM). Supplement treatments were Control: MR, no supplement; GLC: MR plus glucose (220 mg/kg BW per day); and 3OMeGLC, MR plus 3-O-Methyl glucose (6 mg/kg of BW per day). A commercial MR (12.5% solids) was fed twice daily at 10% of BW for d 1–2 and 12% of BW for d 3–5. On d 6–7 calves were fed the FR plus supplement treatments. On d 8, calves were fed 0, 25, 50, and 75% of respective MR allowance on d 5 plus supplement treatments, and plasma was obtained at −15, 15, 30, 60, 90, and 240 min relative to feeding for determination of [GLP-2]. No starter was fed but water was offered ad libitum. Generalized linear models with normal and Poisson distributions were used to analyze [GLP-2] and fecal score data, respectively. As designed, MR intake differed ($P < 0.0001$) among treatments. Occurrence of diarrhea did not differ among treatments. For log [GLP-2], there was a quadratic effect of FR ($P = 0.0003$) and effect of supplement, with 3OMeGLC greater than GLC but not control ($P = 0.002$). Increasing FR increased ($P < 0.0001$) area under the curve for [GLP-2] after feeding; calves fed the 25% rate had the lowest area under the curve and calves fed 100% had the greatest (10,188 vs. 22,023 pg·h/mL). Feeding rate had a significant effect on GLP-2 with calves allotted greater MR intakes having greater plasma [GLP-2].

Key Words: glucagon-like peptide 2, feeding rate, glucose

49 The brain within the gut—Activation of enteric cells and sensory neurons.
John B. Furness*[1], David M. Bravo[2], Jeremy J. Cottrell[1], and Frank R. Dunshea[1], *[1]University of Melbourne, Parkville, Australia, [2]InVivo Animal Nutrition & Health, Talhouët, Saint-Nolff, France.*

For optimal digestive efficiency, the contents of the gastrointestinal tract need to be detected and the information needs to be conveyed to control systems: the gut endocrine system, the nervous system and the immune and tissue defense systems. The contents include nutrients, products of digestion, bacteria, viruses, fungi and potentially injurious substances in foods. Sensory neurons that innervate the gut lining detect hormones released from enteroendocrine cells (EEC) and also detect other signals, for example cytokines and other substances released when

the gut is inflamed, and contractile activity of the gut. There are 4 classes of enteric sensory neurons, intrinsic primary afferent neurons (IPANs), with cell bodies in the gut wall, vagal primary afferent neurons, spinal primary afferent neurons and intestinofugal neurons, and within each class there are subclasses that detect different sensory signals. From a comparative point of view, the functioning of the enteric nervous system (ENS) is similar between species, although there are some differences in its organization, as will be discussed. The ENS works in concert with CNS reflex and command centers to control digestive function, so it cannot be considered in isolation. There is bidirectional information flow between the ENS and CNS. The major type of sensory ENS neuron is the IPAN. These neurons have distinctive shapes and electrophysiological characteristics, similar to primary afferent neurons of dorsal root ganglia. Their axons in the mucosa sense the chemical environment of the lumen and mucosal distortion. They also detect toxins (they are nociceptive neurons). Other processes of the neurons are sensitive to muscle movement. Their outputs are to other enteric neurons (interneurons and motor neurons) and to intestinofugal neurons. The major functions they control are gut movements, water and electrolyte secretion and blood flow.

Key Words: enteric nervous system, sensory neurons

50   Xylanase supplementation in feed reduces incretin and PYY levels in piglets. Katherine May*[1], Saoirse E. O'Sullivan[2], John M. Brameld[1], Helen V. Masey O'Neill[3], Tim Parr[1], and Julian Wiseman[1], *[1]School of Biosciences, University of Nottingham, Loughborough, Leicestershire, UK, [2]School of Medicine, University of Nottingham, Derby, Derbyshire, UK, [3]AB Vista Feed Ingredients, Marlborough, Wiltshire, UK.*

The objective of this study was to investigate the effects of xylanase supplementation on gut hormone production in newly weaned piglets. In experiment 1, 32 female Camb12 weaned piglets (8.8 ± 1.38 kg, mean $\pm$ SD) were randomly assigned to 1 of 2 diet groups in period 1 (0–2 wk postweaning; P1), a control diet (Co) or the same diet supplemented with xylanase (XS). During period 2 (2–6 wk postweaning; P2) half the pigs were kept on their original diet while the rest were swapped onto the other diet, resulting in 4 groups. At the end of P2 the pigs were culled by electrical stun and exsanguination at which point blood samples were collected using EDTA coated tubes. The samples were centrifuged at 3000 g for 10 min at 4°C and the plasma was aliquoted and stored at −80°C for further analysis. A Human Metabolic Hormone Milliplex HMHMAG-34K kit (Merck Millipore) was used to assess the concentrations of PYY, PP, Insulin, C-Peptide and GIP (total) in the plasma. In experiment 2, 16 female Camb12 weaned piglets (9.2 ± 0.95 kg) were assigned to the same 2 diet groups as in experiment 1 (Co and XS). After P1, the pigs were culled and blood samples taken as in experiment 1; however, protease inhibitors were added to the collection tubes so extra gut hormones could be analyzed [amylin (active), ghrelin (active) and GLP-1 (active)]. The data were tested for normality and analyzed with the appropriate parametric or non-parametric test (one/two-way ANOVA or Kruskal-Wallis), significance was accepted at $P < 0.05$. In experiment 1, XS in P2 significantly decreased plasma PYY concentrations ($P = 0.008$). In experiment 2, XS significantly decreased plasma GIP ($P = 0.027$) and GLP-1 ($P = 0.002$) concentrations in P1. GIP and GLP-1 are known as incretin hormones that affect pancreas function. In conclusion, xylanase supplementation to newly weaned piglets affects the production of certain gut hormones. The effect was dependent upon the timing of supplementation as different hormones were affected between P1 and P2.Further trials are needed to investigate

whether there are longer-term effects when the piglets are grown to a commercial slaughter weight.

Key Words: gut hormone, piglet, xylanase

51   Perinatal nutrition and the gut–brain axis. Ryan N. Dilger*, *University of Illinois, Urbana, IL.*

There exists a need to better understand complex interrelationships between dietary intake and cognitive function, and animal models are critically important in this endeavor. The field of nutritional neuroscience has, as a primary goal, the application of findings to the human clinical setting, and therefore, models that closely mimic the human condition are highly valued. Thus, based on similarities in patterns of brain development and structure, the pig has emerged as a biomedical and preclinical model for studying human brain development and cognitive function. Building upon the storied history of using the neonatal pig as a research model for studying pediatric nutrition and metabolism, recent emphasis has been placed on understanding how signaling mechanisms in the gut, being largely synonymous with microbial interactions, influence neurodevelopment and brain function. As a precocial species, the young pig can be artificially reared with relative ease, thus providing strict control over dietary intake. Moreover, validated methods to assess learning and memory using behavioral assays now exist, and these outcomes provide a powerful and integrated view of how nutrition influences brain development. Sensitive neuroimaging sequences are also available, and along with cellular and molecular techniques optimized for the pig, there exists a fruitful area to generate new knowledge of how early-life nutrition influences neurodevelopmental processes. As such, nutritional strategies to alter the delivery of specific components to the brain, or influence the microbial composition or production of bioactive compounds in the gastrointestinal tract, are currently being tested. There are many advantages to extending the field of pediatric nutrition research by integrating outcomes related to the microbiome, routes of information transfer between the gut and brain, and processes associated with cognitive function and brain development, and the young pig will play a pivotal role in these investigations.

Key Words: nutrition, neuroscience, pig

52   Effects of increasing standardized ileal digestible tryptophan:lysine ratio on performance and ileal expression of cytokine mRNA in weaned pigs challenged with *Escherichia coli* K88. B. Jayaraman*[1], A. Regassa[1], W. K. Kim[1], J. K. Htoo[2], and C. M. Nyachoti[1], *[1]University of Manitoba, Winnipeg, Manitoba, Canada, [2]Evonik Industries AG, Nutrition Research, Hanau-Wolfgang, Germany.*

A study was conducted to determine the optimal standardized ileal digestible (SID) tryptophan:lysine (Trp:Lys) ratio in piglets challenged with *Escherichia coli* K88 (*E. coli* K88) and fed antibiotic-free diets. Thirty individually housed mixed-sex pigs (Duroc × [Yorkshire × Landrace]) with an initial BW of 6.41 ± 0.4 kg and weaned at 21 ± 1 d were randomly assigned to 5 dietary treatments with 6 replicates per treatment. Dietary treatments consisted of increasing levels of SID Trp:Lys ratios (16, 18, 20, 22 and 24%). Diets were corn-wheat-soybean meal-based with a constant SID Lys of 1.18% that was set to be the second limiting AA but adequate in other AA. Pigs had ad libitum access to feed and water for 13 d. Piglets were fed the experimental diets for 6 d and on d 7, they were orally challenged with 6 mL of *E. coli* K88 (2×10^9 cfu/mL). Body weights and pen feed disappearance were recorded weekly to determine ADG, ADFI and G:F. On d 13, all pigs were euthanized

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to obtain ileal tissue samples to measure mRNA expression of tumor necrosis factor-α (TNF- α) and interleukin-10 (IL-10) using qRT-PCR. During the pre-challenge period, increasing dietary SID Trp:Lys increased (linear, $P < 0.05$) ADG (157, 162, 173, 179 and 201 g) and G:F (0.71, 0.73, 0.74, 0.81 and 0.84). During the post-challenge period, there was an increasing trend (linear, $P = 0.076$) in ADG (177, 180, 208, 210 and 213 g), whereas there was no effect on G:F ($P > 0.10$). The optimal SID Trp:Lys determined using the broken-line regression analysis for ADG and G:F in piglets subjected to *E. coli* K88 challenge was 21 and 24.2%, respectively. The expression of pro-inflammatory cytokine, TNF-α mRNA, linearly decreased ($P = 0.10$) with increasing SID Trp:Lys ratio. The expression of anti-inflammatory cytokine, IL-10 mRNA, increased (linear and quadratic, $P < 0.01$) with increasing SID Trp:Lys ratio. In conclusion, in antibiotic-free starter diets, an average optimal SID Trp:Lys of 22.6% optimized performance and immune status of piglets under *E. coli* challenge.

Key Words: tryptophan:lysine, *Escherichia coli* K88, piglet

53   Effect of dietary intervention of probiotic *Lactobacillus helveticus* MTCC 5463 on fecal beta-glucuronidase activity in geriatric volunteers. Suja Senan*[1], Jashbhai Prajapati[2], Chaitanya Joshi[2], Sreeja V[2], Manisha Gohel[3], Sunil Trivedi[3], Rupal Patel[3], Himanshu Pandya[3], Ajay Phatak[3], Uday Shankar[3], and Hasmukh Patel[1], *[1]South Dakota State University, Brookings, SD, [2]Anand Agricultural University, Anand, Gujarat, India, [3]H. M. Patel Center for Medical Care & Education, Karamsad, Gujarat, India.*

Probiotics may reduce the risk for the onset of colorectal cancer by modulating the activity of fecal bacterial enzymes that catalyze the liberation of procarcinogenic substances in the intestine. The aim of this study was to investigate the influence of probiotic *Lactobacillus helveticus* MTCC 5463 (5463) on fecal microbial-related functions in geriatric volunteers. The subjects were randomized into 2 groups, fed either fermented drink containing 5463 (test group) or without 5463 (placebo group). The volunteers consumed 200 mL of the product once a day for 4 weeks. Fecal samples were collected in sterile plastic containers at the beginning and end of the intervention period. β-glucuronidase was considered as the marker enzyme for anti-colonic carcinogenesis activity, and measured in terms of unit activity per mg of protein in fecal samples. Total fecal protein was determined by Folin-Lowry method with bovine serum albumin as a standard. The data were analyzed with Student's *t*-test, and the levels of significance were expressed as p values. The mean β-glucuronidase activity was reduced in test group from 1.40 to 0.73 (µg/min/mg of protein) while in case of placebo group, no effect on enzyme activity was observed. Enzyme β-glucuronidase activity in the feces of all subjects in the probiotic group, were highly significant ($P < 0.001$), whereas the placebo group showed nonsignificant differences ($P = 0.40$). We were able to demonstrate consistent reduction in the fecal β-glucuronidase activity in the probiotic group. Results suggested that the metabolic activity of the fecal flora was altered by 5463 therapy, which further decreased procarcinogenic enzyme levels in the large intestine. Probiotic MTCC 5463 interaction with the geriatric host microbiome, affects β-glucuronidase activity, which can be exploited as an alternate therapy against colonic carcinogenesis.

Key Words: probiotics, geriatics, β-glucuronidase

54   Brain–gut interactions in stress. Jackie D. Wood*, *The Ohio State University, Columbus, OH.*

Stress can be viewed as exposure of an animal to a hostile environment that compromises bodily homeostasis. Stress of this nature can occur in many forms, examples of which are extremes in environmental temperature, fear, predator attack and crowding. Elevation of heart rate, blood pressure, respiration rate and emotional agitation are among the many bodily manifestations of stress. In the gut, they can include diarrhea, constipation, incontinence, gastric regurgitation and gastrointestinal mucosal inflammation. Corticotropin-releasing factor (CRF) is a neuropeptide that plays a major role in the body's overall responses to stress, including the gut. The physiology of central CRF signaling pathways in stress-induced changes in gastrointestinal motility and gastric acid secretion has been well characterized. Recent work elucidates how the physiology of peripheral CRF-related mechanisms contribute to stress-induced changes in gut motility and intestinal mucosal function. Acute stress, intramural CRF release and experimental application of selective CRF_1 receptor agonists evoke excitatory responses in neurons in the enteric nervous system (i.e., the brain-in-the-gut). Enteric neurons express CRF and its receptors. Exposure to acute and chronic stresses increases intestinal ion secretion and mucosal permeability to macromolecules and evokes diarrhea. Effects of stress on intestinal mucosal function are mimicked by peripheral injection of CRF and blocked by peripheral injection of non-selective peptide CRF receptor antagonists. CRF mRNA knock down in the enteric nervous system prevents intestinal responses to environmental stress in rodents. These findings constitute strong evidence that activation of peripheral CRF receptors in the enteric nervous system is a key mechanism involved in stress-related alterations of gut motility and mucosal function. In the cotton-top tamarin (*Siquinus oedipus*) model for ulcerative colitis and associated colon cancer, evidence suggests that environmental stress initiates the inflammatory response, which is then sustained by factors in the feces.

Key Words: stress, CRF, enteric nervous system

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