INTRODUCTION

The concept supporting the existence of functionally important "brain-gut axis" was originally proposed to account for the fact that several peptides including bombesin, neurotensin and calcitonin-gene-related peptide (CGRP) occur both in brain and gut and seem to exert opposite actions on gut function when administered centrally and peripherally. Although this important concept was first developed in the early 1980s, considerable progress has been made since that time. The present symposium was the fourth organized meeting held on this topic. The symposium provided an overview of new basic and practical aspects of the brain-gut axis, particularly its involvement in pain perception, visceral sensitivity, neuromodulation, gastrointestinal protection, motility disorders and mechanism of action of various enterohormones. The meeting was organized into five major categories. In addition, there was a poster session concurrently held with the oral presentations. The presentations provided compelling evidence that the brain-gut concept is constantly evolving with new understanding of various factors affecting it. The presenters are committed investigators and leaders in their respective fields of research. Although it would be most difficult to review all the lectures and posters presented at this meeting to provide justice to the presenter, nevertheless, we are providing summary or take home messages for the salient points of reviews of this symposium. The remaining papers with original
results presented at this symposium will be published in volume 55, No 1 2004 of J. Physiol. Pharmacol.

**I. Peripheral Sensors and Signaling to CNS in Health and Disease:**

Dr. G.J. Dockray reviewed information which indicate that the gut responds to impressive arrays of signals originating in the lumen, including nutrient and non-nutrient chemicals, intestinal hormones such as cholecystokinin (CCK), leptin and ghrelin, mechanical factors and microorganisms. The molecular recognition mechanisms include G-protein coupled receptors (GPCRs). CCK is involved in gut-brain signaling acting as primary integrator through the primary vagal afferents, that appear to express various receptors including those responding to orexin, ghrelin and leptin.

Dr. J.D. Kaunitz and Y. Akiba reviewed, on the basis of their own studies, the mucosal acid-sensing protective mechanism of duodenum. They demonstrated that repeated exposure to luminal acid induces increase of cellular bicarbonate concentration and mucus gel thickness and increase of duodenal mucosal blood flow. Their data demonstrate that the acid-induced duodenal hyperemia involved activation of afferent neurons. They concluded that luminal acid enters the duodenal epithelial cells via sodium hydrogen transporter 3 and exits the epithelial cells via sodium proton transporter 1. Vanilloid-1 receptor acts as submucosal acid sensor that transduces the signal which releases CGRP and generates endothelial nitric oxide in the mucosal and submucosal microcirculatory structures.

Dr. B. Bonaz summarized novel findings concerning visceral sensitivity in patients with functional digestive disorders such as irritable bowel syndrome (IBS) and showed that multiple components are involved in this process including sensory-discriminative components, affective components and cognitive components using brain imaging techniques such as PET scanning. These imaging techniques appear to be useful tools to characterize normal and abnormal brain processing of visceral pain in patients with functional digestive disorders. However, it would be important to study the effect of new IBS drugs on these neuronal circuits.

Dr. P. Holzer investigated the afferent signaling of gastric acid challenge in studies performed in rats. He showed that the blockade of gastric acid secretion reduces the afferent signaling from acid challenged stomach to rat brain stem, whereas the stimulation of gastric acid, the exposure to proinflammatory cytokines or induction of experimental gastritis or ulceration enhance these acid-related signals in vagal afferent pathways. These observations are clearly relevant to the understanding and treatment of dyspeptic pain.

Dr. A. Mulak showed that visceral hypersensitivity is associated with altered reflex activity and central processes. Testing of this visceral sensitivity in humans may be based on distention stimuli using barostat or tensostat as well as the
transmucosal electrical, chemical or thermal stimulation. Visceral sensitivity depends upon various factors such as meal, psychological factors, gender and age. The sensory function of the gut involves various mediators and receptors and could be affected by pharmacological agents, especially acting on serotonin- and CCK-receptors. Testing of visceral sensitivity may be applied in diagnosis of functional GI disorders, especially of functional dyspepsia and IBS but standardization of the testing procedures are required.

II. GI Hormones and Brain-Gut Axis

Dr. J.F. Rehfeld et al. reported that the biosynthesis of CCK requires endoproteolytic cleavage of proCCK at several mono- and dibasic sites by hormone convertases (PC). In PC1 deficient mice the brain processing of proCCK was not affected at all, while in those deficient in PC2 only cerebral processing of proCCK was altered. It was concluded that PC1 plays a decisive role in maturation of proCCK in intestinal endocrine cells, whereas PC2 governs the processing of cerebral proCCK.

Dr. R. Zabielski examined the role of luminal CCK and its neuronal action on exocrine pancreatic secretion. He showed that luminally applied CCK-8 induced pancreatic protein secretion by activation of CCK1-receptors in gastro-duodenal mucosa and vagal afferent nerves to trigger long vago-vagal reflex stimulation of exocrine pancreas. The result indicated a neuronal mediation of CCK and questioned the physiological relevance of a direct mechanism of CCK on the pancreatic acini.

Dr. T.L. Peeters investigated the central and peripheral mechanisms of ghrelin regulation of gut motility. He showed that ghrelin, most abundant in the gastric mucosa, shows structure-function similarity to motilin and like motilin may induce migrating motor complex and acceleration of gastric emptying that can be blocked by vagotomy. Furthermore, the centrally administered ghrelin accelerated gastric emptying and changed the activity of neurons of the central nuclei involved in signaling information from the GI tract. It was concluded that ghrelin may affect gastrointestinal motility via specific ghrelin receptors located on myenteric, vagal and central neurons.

Dr. W.Y. Chey and T-M. Chang reviewed the role of neuronal control of secretin release from the intestinal mucosa and its action on pancreatic secretion. They showed that the release of secretin by acidification of duodenal mucosa is mediated by secretin-releasing peptide (SRP). The release of this SRP is neurally mediated depending on vagal afferent pathway. The stimulation of pancreatic secretion by secretin is also dependent upon the vagal nerves and can be abolished by vagotomy, atropine and anti-gastrin-releasing peptide (GRP) as well as by inhibition of nitric oxide (NO) synthase. They concluded that the release and action of secretin is neurally regulated involving both the vagus nerves and intrapancreatic neurons such as releasing acetylcholine, GRP and NO.
III. Neurotransmitters and growth factors in Brain-Gut Axis:

Dr. R.J. Reiter et al. reviewed the actions of melatonin in the GI tract. Melatonin was initially identified in the pineal gland but was subsequently shown to exist in much larger quantities in the GI tract and pancreas. In the GI tract, melatonin exerts gastroprotective activity against various noxious agents, promotes ulcer healing, has gastric antisecretory, free radical scavenging effects, mucosoprotective activity and prevents oxidative injury to the liver and pancreas and reduces gallstone formation. Its mucosal protective effects may involve prostaglandins, calcitonin-gene related peptide (CGRP) and nitric oxide. In summary, melatonin that has been linked to circadian biology, shows beneficial neurally-mediated and neurally-independent actions on the gastrointestinal system, particularly due to its direct scavenging effect on toxic oxygen-based reactants.

Dr. J. Morisset reviewed the role of GI neuropeptides as trophic agents mediating pancreatic growth and regeneration after pancreatitis or partial pancreatectomy. He showed that among various neuropeptides released by intrapancreatic neurons, only gastrin-releasing peptide (GRP) has growth promoting action on the pancreatic cells through activation of specific GRP receptors and mitogen-activated protein kinases. The inhibitory effects on pancreatic growth of pancreatic polypeptide (PP), PYY or calcitonin gene related peptide (CGRP) originating from afferent neurons are probably indirect and involve somatostatin.

Dr. A.P.N. Majumdar examined the regulation of gastric mucosal growth during aging in rats. They showed that aging is associated with altered mucosal proliferative activity in the GI tract. The age-related rise in the mucosal proliferation in aged rats could not be attributed to the gastrin or somatostatin but probably to some growth factors such as EGF and TGFα and increased activation of EGF receptors common for these two growth factors. However, the functional properties are either decreased or remain unchanged during advancing age.

IV. Brain Gut Axis in Pathogenesis and Healing of gastrointestinal lesions

E. Dajani and associates reviewed the role of prostaglandins in the brain-gut axis. Prostaglandins are widely distributed in nearly all tissues and considered locally acting hormones, synthesized on demand and rapidly metabolized. Although PGs have been shown to modulate CNS effects of several neurotransmitters, there is no meaningful data concerning their direct central effects on GI functions. The evidence for a clear physiological role of central PGs on the GI tract is not convincing and additional studies are needed to clarify their CNS role on the gut functions.

K. Takeuchi and his colleagues reviewed the pathomechanisms of intestinal lesions induced by nonsteroidal anti-inflammatory drugs (NSAID) and emphasized that the development of such lesions requires the inhibition of both
cyclooxygenase-1 (COX-1) and COX-2. Selective inhibition of COX-1 e.g. by SC-560 or COX-2 by coxibs does not cause intestinal lesions but combined COX-1 and COX-2 blockers produce such lesions. Their development is accompanied by the increase in intestinal motility, bacterial invasion and myeloperoxidase and inducible NO synthase and COX-2 expression that are caused by COX-1 inhibition but the PGE2 derived from overexpressed COX-2 counteracts these deleterious events and maintains mucosal integrity.

Dr. D. Hollander reviewed data concerning stress and inflammation in inflammatory bowel disease (IBD), which occurs via neural, hormonal and cytokine signals. Stress appears to play a key role in exacerbating and accentuating the intestinal inflammation in IBD through brain-gut interactions. Stress is perceived by central nervous system, especially by the hypothalamus that may modulate the degree of intestinal inflammation by release of corticotropin releasing factor (CRF) and its effect on adrenal-cortical secretion, the autonomic nervous system and enteric nervous system with numerous neuropeptides and systemic alteration of immune functions. Using techniques such as measurement of the permeability of the gut in animals or in humans it is now possible to investigate the mechanism of the effects of stress on intestinal inflammation and possible evaluation of therapeutic attempts.

Dr. M.V. Singer and associates developed a rat animal model of alcohol dependence in order to investigate the role of alcohol in the brain-gut axis and related GI diseases. They did not present any results, but we will look forward to learn the outcome of this research in future meetings related to brain-gut axis.

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