The brain–gut axis in health and disease

Conference rapporteur: John McLaughlin

This conference, held on 30 November 1999 at the Royal College of Physicians, was organised by Professor D G Thompson of the University of Manchester.

Dating back to Pavlov, the concept and study of the connections between brain and gut, the brain–gut axis, has recently become a rapidly evolving area of collaborative interest. It ranges from the psyche to the hardwired physiology of the enteric and central nervous systems. Clinically, it covers the common functional gut disorders (FGDs) such as irritable bowel syndrome (IBS) and functional dyspepsia, as well as organ-specific visceral pain, the intestinal regulation of appetite, and disorders of neuroenteric control (particularly dysphagia following stroke).

The emerging model will probably resolve one key question by rendering it obsolete: are FGDs primarily psychological or gastrointestinal in origin? As will be seen, this distinction may represent a false dichotomy. In reality, the practical consequences of the hardwiring between psyche and gut are a common and essentially normal experience, and mostly do not present to physicians. Many patients volunteer connections they have noticed for themselves. However, the science has lagged behind. Much effort has been directed to a fruitless pursuit of simple single explanations for FGD, for example of disordered motility or hidden psychiatric illness, and all the best efforts are hampered by imperfect definitions of the different FGDs, relying on expert consensus opinion of the significance of syndromes of common symptoms. Even when rigid criteria are applied, patient A with a once weekly bowel habit is labelled as having IBS, along with patient B with five loose stools daily, and patient C who alternates between the two extremes. Unsurprisingly, consistent objective abnormalities in these patients or satisfactory responses to treatment have not readily emerged.

Gut to brain pathways

Most sensory information arriving from the gut never reaches consciousness, particularly the vegetative information conveyed via the vagus nerves, 90% of which are composed of afferent fibres. Painful stimuli travel along spinal afferents, activating multiple spinal segments. Spinal central sensitisation to somatic sensory input is well documented following peripheral (eg, skin) injury – changes occurring within the dorsal horn leading to secondary alterations (hyperalgesia, allodynia) around the site of injury. These can become permanent. Visceral spinal afferents posses similar properties: brief application of acid to the distal oesophagus causes hyperalgesia in the unacidified proximal part of the organ and in cutaneous segments from the same spinal segment. Could 'trivial' acid reflux or undetected mucosal inflammation contribute to the aetiology of FGD, particularly non-cardiac chest pain? Could brief injury lead to persistent hyperalgesia?

Functional MRI and PET scanning have revealed the cortical representation of visceral sensation in a 'viscerotopic' order, with a degree of lateral dominance. The most sensory regions, proximal oesophagus and anus, are represented close to the primary somatosensory cortex, while painful visceral stimuli activate limbic areas and the prefrontal cortex. These powerful tools should help unravel how much visceral hypersensitivity is due to peripheral sensitisation in the gut or to abnormal central sensory processing. Early data show that psychological manipulations

Conference programme

- **Gut pain in health and disease**
  Dr Q Aziz, University of Manchester and Institute of Psychiatry, London
- **The vagus nerve and gut function**
  Professor D Grundy, University of Sheffield
- **The brain control of gut function and swallowing**
  Professor N E Diamant, University of Toronto, Canada
- **Swallowing and its disorders in stroke. What are the prospects for improving therapy?**
  Dr S Hamdy, University of Manchester
- **Trans-epithelial signalling in the gastrointestinal tract**
  Professor G J Dockray, University of Liverpool
- **Functional dyspepsia: state of mind or a disorder of gut function?**
  Professor J Tack, University of Leuven, Belgium
- **Irritable bowel syndrome: colon, brain or both?**
  Dr R C Spiller, University of Nottingham
- **Irritable bowel syndrome: all in the mind?**
  Professor F Creed, University of Manchester
- **Drug therapies for functional bowel disorders. What is the prospect for a cure?**
  Dr K B Klein, International Drug Development Consulting, Seattle, USA
- **Functional bowel disorders: non-pharmacological approaches**
  Dr E Guthrie, University of Manchester

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do have a significant impact on the cortical responses to oesophageal stimulation, but stimuli more physiological than electric currents and balloons attached to uncomfortable catheters need to be developed for further studies.

The vagus nerve integrates the gastrointestinal response to luminal contents, perhaps by direct neuronal activation but certainly by enteroendocrine cells through paracrine release of cholecystokinin (CCK), 5-HT and other mediators. This sensory traffic is mostly subperceptual, but normal satiation and nausea arising from the gut are also vagally mediated. Intact vagal input to the brain-stem exerts an antinociceptive effect on spinal afferent input. An interesting discussion ensued about whether intrinsic disorders of the vagus (or its peripheral terminals or central connections) could be implicated in FGD, especially functional dyspepsia. Even if not intrinsically faulty, it certainly represents a tractable target to manipulate gut sensation or feeding behaviour. Vagal afferents are also activated by mast cell products, released in response to luminal macromolecules, so providing an organic substrate for brain-immune system interactions within the gut. Descending vagal input may also reciprocally effect mast cell degranulation, with local effects on secretomotor activity.

Professor G J Dockray gave a fascinating account of recent cellular and molecular work toward understanding the key role of enteroendocrine cells as signal transducers across the gastrointestinal epithelium, precisely sensing luminal contents and effecting appropriate integrated responses.

Brain to gut pathways

The work presented in this section dealt entirely with the neurophysiology of swallowing, the best understood aspect of how the brain controls gut function. This is of particular interest since it has both voluntary and involuntary components, and is the most commonly disturbed aspect of gut function seen in structural brain disease, particularly stroke. Here too, the vagus nerves play a key role. Recent functional studies have revealed that the cortical swallowing centre exhibits hemispheric dominance, largely independent of handedness, and that dysphagia follows stroke of the dominant cortex. These studies have made good use of the developing technique of magnetic stimulation. Externally applied magnetic pulses, applied through coils held over the cranium, are focused onto selected cortical regions and cause neuronal activation in the targeted area. The cortical surface area responsive to magnetic stimulation can be mapped and measured by recording responses, such as EMG activity in target muscle groups used in volitional swallowing. Recovery of swallow during sequential mapping appears to be due to compensatory changes in the nondominant hemisphere, rather than recovery in the affected side. This phenomenon is an example of neuronal plasticity, and may offer a therapeutic target to accelerate recovery. Studies using direct electrical stimulation of the pharynx show that its cortical representation in the nondominant hemisphere is increased by 50–60%, with no change in the affected hemisphere. Studies are now underway to see whether peripheral stimulation can be used to drive neuronal plasticity and so accelerate clinical recovery. An interesting discussion ensued, some wondering if the passive 'nil by mouth' strategy currently adopted may delay recovery, albeit while preventing aspiration.

Symptoms and dysfunction of the brain–gut axis

Are functional dyspepsia and IBS disorders of mind or gut or both? To determine whether functional dyspepsia is primarily a disorder of gastric function, patients' usual symptoms were compared with four objective measures. *Helicobacter pylori* status proved irrelevant. *Delayed gastric emptying* was uncommon (19%) but correlated with reported sensations of fullness and nausea. In detailed examination by balloon distension for *visceral hypersensitivity*, low thresholds were noted in 70% of patients and, perhaps unsurprisingly, were linked to epigastric pain as a presenting symptom. The severity of pain reported also correlated with the measured hypersensitivity in terms of inflation volume required to induce pain. Intraluminal balloons can also be used to measure *gastric accommodation*, as the proximal stomach normally relaxes to distend such that increases in volume do not cause a parallel rise in pressure, a reflex largely under vagal direction. Although only 40% of patients exhibited impaired accommodation, this was statistically associated with early satiety as a presenting symptom on normal eating.

These findings appear compelling, but their interpretation poses some problems. First, although ostensibly abnormal aspects of gastric sensorimotor function could be linked to the intuitively predicted symptoms, this required complex multivariate analysis to reveal statistical associations, and these did not apply to many patients. One-third had no demonstrable abnormalities of function, and half had only one abnormality, yet most patients report multiple symptoms. All the symptoms are more common than their linked abnormalities. Second, one must accept that inflating balloons on catheters placed in the stomach of these patients recruited in a tertiary centre, yields helpful information about usual experience. Third, none of the abnormalities uncovered can be assumed to be intrinsically gastric in origin; any could be end-organ consequences of abnormal central control. Hence the data do not shed light on the key question posed, brain or gut? Nonetheless, this symptom-function link may offer a starting point for a rational therapeutic strategy, using prokinetics, novel analgesics or drugs acting on gastric muscle tone (eg, 5-HT receptor agonists or uptake inhibitors, NO donors) according to predominant symptoms.

There appear to be links (again as statistical associations) between traumatic life events and visceral hypersensitivity, and between an antecedent febrile gastroenteritic illness

and disordered gastric motility. Experimental gut inflammation in rats is linked to reduced myenteric neuronal NO synthesis, and administering a 5-HT agonist or a NO synthase substrate has a smaller effect on gastric tone in patients with an antecedent history of upper-gut infective symptoms than in those without. The intriguing possibility that a neurotropic virus may be responsible for some functional dyspepsia was raised in discussion. Perhaps dysmotility will transpire to be a disorder of the enteric nervous system, and visceral pain to be a consequence of abnormal central processing? But as many patients have both problems, this is likely to prove too simplistic.

A similar story is evolving in IBS. Persistent IBS-type symptoms are common following acute infective diarrhoea, possibly after one-quarter of episodes, and a symptomatic state is more likely to develop in women, or after recent adverse life events. This could suggest a psychological cause, but recent studies have shown an increase in gut permeability and rectal enteroendocrine cells following *Campylobacter* infection, which persist in subjects with ongoing symptoms. Does this represent ongoing inflammation or a post-inflammatory change? Is the normal gut flora implicated by a need to reacquire tolerance? Or are emotional factors implicated in modulating intestinal mucosal cellular and immune responses? A trial of corticosteroids in post-infective IBS is now underway in Nottingham.

A key belief, largely driven by those in health care settings most consulted for functional gut diarrhoea, has been that anxiety and depression are highly prevalent in IBS, or even the cause of it. Many patients have been dismissed as having a problem which is 'all in the mind', and in hospital settings psychopathology is readily demonstrable in up to 60% of patients with IBS. But this is also the case in patients with lactose intolerance, which is a disorder with similar symptoms but wholly organic origins. This biased perception thus appears to be an artefact of the study setting, and psychopathology is no more common in community-based IBS 'patients' (ie, people satisfying diagnostic criteria) than in asymptomatic controls. Psychosocial factors thus appear to determine the likelihood to attribute significance (eg, cancer fear) and seek professional consultation. This anxiety-driven consulting pattern is equally true for asthma, migraine, hypertension and other chronic disorders. Health worries are not the same as psychological illness or somatisation, and need to be tackled rather than misattributed. Although true psychological problems may, of course, require intervention on their own merit and may affect symptom severity (trait anxiety certainly predicts poor outcome in IBS and other causes of chronic pain), they should no longer be considered as primarily causative. In discussion, this view was not universally accepted, but perhaps more challenged by those with a long experience of 'difficult' patients with clear psychological illness (who may be missing the bigger picture). The zeitgeist is well ahead of conventional medicine in seeing that the mind and body exist in unison, and we need to move closer – in the clinic and in research – to an integrated understanding of the links and interplay between organic and psychosocial factors. In this respect, the observation that adverse life events increase the risk of post-infective IBS may be particularly pertinent. It was mooted that instead of one-dimensional thinking about individual causes for symptoms, we should consider various aspects of psychological health, neural and epithelial function, luminal environment and gut immunology as additive risk factors for the development of symptoms, in the same way that cardiovascular risk factors are additive for the likelihood of ischaemic heart disease.

Managing patients with FGD

Herein lies the problem. A rather disheartening review of the 50 or so trials of pharmacotherapies revealed overall benefit for none. Several reasons were offered for this, including the application of imperfect diagnostic criteria, which attach concrete labels to groups of symptoms, but perhaps without any equally concrete meaning. A lack of understanding about their true pathophysiology, common comorbidity with other 'functional' symptoms (such as fatigue or fibromyalgia), and inappropriate therapeutic goals are also likely to be important. Explanation, exclusion of alternative diagnoses and emotional support may be more achievable than 'cure'. A discussion of psychotherapeutic approaches suggested that any benefits may be small, require intensive input, and may be least in secondary and tertiary care where serious psychopathology, eg, related to sexual abuse, is more prevalent. Motivation and 'psychological mindedness' are important in predicting those likely to benefit, while the stigma attached to psychiatric care presents a major barrier for many. Psychotherapy is difficult to study by conventional means, as placebo therapy and blinding are rarely achievable. Studies have been further flawed by trying to answer too many questions about too many variables rather than adopting a simpler one study, one question approach.

Overview

The conference covered a wide range of topics, which gave rise to fascinating and free ranging discussion. Perhaps an inappropriately negative mood was inadvertently created just at the end of the day: the final session on management was inevitably a little down-beat since least progress has been made here. Some thoughts about hypnotherapy might have fitted in well here, but this was not addressed in any of the sessions. However, the research tools to map, dissect and unravel physiological processes and abnormalities are rapidly evolving, and those involved in current research have liberated themselves from hunting for single explanations, while moving towards closer collaboration with colleagues in a broad range of other disciplines. This approach is likely to bear much fruit in the next few years.