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Enteric glial

Glial regulation of neuronal plasticity in the gut: implications for clinicians

A Rühl

Enteric glia regulate gastrointestinal physiology by controlling neurochemical phenotypes in the enteric nervous system

The enteric nervous system (ENS) is a complex network in the gut wall, extending throughout the gastrointestinal tract and coordinating vital gastrointestinal functions, such as motility, perception, mucosal permeability and secretion, blood flow, as well as immune and inflammatory processes.[1] The ENS is connected to the central nervous system (CNS) by sympathetic and parasympathetic nerves which relay information to and from the brain via pre- and paravertebral ganglia, spinal cord, and medulla; yet, it can perfectly function independently of the CNS.

The ENS contains as many neurones as the spinal cord.[1] Enteric neurones have been neurochemically and immunohistochemically classified based on characteristic combinations of neurotransmitters, their synthesising enzymes, and neuronal markers, which ultimately constitute a ''neurochemical code'' (for review see Kunze and Furness[2]). Neurochemical coding has provided an important tool to identify functionally distinct neuronal subpopulations, and it is generally assumed that the neurochemical phenotype of differentiated postmitotic neurones is finally determined.[3 4]

The most abundant cells in the ENS are glia.[5] Enteric glia lie adjacent to neuronal cell bodies in the enteric ganglia, but probably as many of them accompany the extraganglionic nerve strands throughout all layers of the intestinal wall, from serosa to mucosa.[5–7] Enteric glia envelop neuronal cell bodies and axon bundles without producing myelin. Historically, enteric glia used to be seen as little more than packing material, holding the ENS together (''glia'' derives from the Greek word for ''glue''). Presently, however, evidence is accumulating to support a much more active role for glia in enteric neurotransmission and information processing (for review see Rühl[8]).

In this issue of *Gut*, Aubé and colleagues[9] report exciting findings which further extend the potential roles of enteric glia in gastrointestinal physiology ***(see page 630)***. Employing a mouse model which has been previously used to ablate enteric glia in newborns—resulting in rapidly fatal intestinal inflammation[10]—the authors targeted enteric glia in the mature ENS. They injected activated influenza virus haemagglutinin (HA) specific CD8+ T cells into adult mice specifically expressing HA on enteric glia as well as on astrocytes and spinal glia.[10–12] Surprisingly, this treatment did not induce any overt loss of enteric glia, nor was there any neuronal cell loss in the ENS of treated animals. However, when the authors analysed the neurochemical coding in the jejunum of treated animals, they found a marked reduction in the vasoactive intestinal peptide (VIP) and substance P (SP) immunoreactive neuronal populations in the submucosal plexus (SMP), whereas in the myenteric plexus (MP) the proportions of choline acetyltransferase (ChAT) and nitric oxide synthase (NOS) immunoreactive neurones were significantly increased and decreased, respectively.

The neurochemistry of the murine ENS is not yet well characterised, and the authors did not try to further decipher the neurochemical code in this species. However, there is some evidence that nitric oxide (NO) and VIP contribute to nerve mediated relaxation in the mouse.[13] While currently there is no evidence that VIP neurones are secretomotor neurones in the murine SMP, the primary transmitter of excitatory motor neurones in the mouse is acetylcholine.[14] In addition, it has been postulated that SP containing nerves in the mouse gut may also be excitatory (table 1).[13]

The strength of this paper clearly lies in the detected correlation between the numerical changes in myenteric neuronal phenotypes and the functional alterations revealed in in vitro and in vivo analyses of gastrointestinal motor functions. An example of how neural regulation of gastrointestinal functions depends on the presence of specific neuronal phenotypes is provided by the fact that neurally mediated jejunal relaxation in vitro was dramatically impaired in the relatively NOS deficient transgenic mice, which in addition convincingly endorses the contention that in mouse—like in guinea pig—NOS immunoreactive neurones are inhibitory. Because the role of nitric oxide (NO) in normal gastric emptying and gastrointestinal transit is well established, loss of NOS immunoreactive neurones would also explain the observed delay in gastrointestinal transit.[15 16] While it is currently impossible to account for the seemingly contradictory alterations observed in the SMP, together the reported data strongly indicate that enteric glia regulate gastrointestinal physiology by controlling neurochemical phenotypes in the ENS.

In spite of these exciting implications, some words of caution are necessary: On close examination, this study does not provide convincing evidence that enteric glia are indeed functionally impaired in transgenic mice. On the other hand, quite extensive inflammatory alterations have been previously described in the brain and spinal cord of these animals.[11] Thus gastrointestinal motility changes observed by the authors could directly result from CNS dysfunction via extrinsic neuronal modulation. Alternatively, the motility

Table 1 Neurochemistry of myenteric neurones and their suggested functions in mice (adapted from Sang and Young[13 14])

Major class of neurones in murine small intestine	Proportion (% of total)	Suggested functions
CalR/CalB	26	Interneurones and/or sensory neurones
NOS/VIP ± NPY	25	Inhibitory motor neurones (circular and longitudinal muscle); may be some interneurones
SP/−	15	Excitatory interneurones and/or sensory neurones and circular muscle motor neurones
ACh/CalR/SP	14	Excitatory cholinergic motor neurones to circular and longitudinal muscle
VIP/−	9	Inhibitory circular muscle motor neurones; interneurones and/or sensory neurones
NOS/−	1	Inhibitory interneurones and/or sensory neurones
5-HT ± SP	1	Interneurones and/or sensory neurones
NPY/−	?	Inhibitory longitudinal muscle motor neurones and interneurones and/or sensory neurones

5-HT, 5-hydroxytryptamine; ACh, acetylcholine; CalB, calbindin; CalR, calretinin; NOS, nitric oxide synthase; NPY, neuropeptide Y; SP, substance P; VIP, vasoactive intestinal peptide

changes could be secondary to ganglionic T cell infiltrates in the ENS of these mice because it is well recognised that intestinal inflammation affects gastrointestinal motility.[17]

However, the most striking findings in the current report are not the motility changes but the neurochemical changes in the ENS which are unlikely to be CNS mediated or secondary to inflammation. Until now, changes in the enteric neurochemical coding have been mainly observed in inflammatory conditions, and mostly *increased* expression of VIP was found in the SMP which is in contrast with the current report.[18 19]

Mechanistically, inflammation induced changes in enteric neurophenotypes have been generally attributed to degenerative and regenerative processes as they may occur subsequent to chronic inflammatory insults.[18 19] However, the changes revealed by Aube and colleagues[9] became detectable within seven days, there were no signs of enteric neuronal degeneration, and neuronal numbers were unaltered, which strongly argues against *structural* changes of the ENS. Recently, the same group reported marked phenotypic and functional changes in the ENS after 16 hours of exposure to serum of achalasia patients, again without evidence of neuronal loss.[20] Thus the findings of both reports cannot be accounted for by apoptotic or other neurodegenerative mechanisms, but strongly indicate that—in contrast with earlier beliefs—terminally differentiated postmitotic neurones have the capacity to change their chemical phenotype and, subsequently, their function.[21]

Cells of a multicellular organism are genetically homogeneous, but structurally and functionally heterogeneous, owing to differential gene expression controlled by transcriptional repressors and activators. Neurochemical ''transcoding'' in the mature ENS, therefore, most likely reflects transcriptional changes of gene expression, but we do not currently know the repressors and activators involved in controlling enteric neurophenotypes. What then do we currently know to explain glial modulation of the neurochemical composition of the adult ENS?

One explanation may be derived from indirect evidence that enteric glia regulate substrate supply for neurotransmitter synthesis: for example, enteric immunoreactivity for L-arginine is exclusively found in glia,[22] and as L-arginine is an essential precursor for neuronal NO synthesis, nitrergic neurones may depend on glial L-arginine delivery for proper function. Consequently, loss of glia could seriously diminish neuronal L-arginine availability and thus NO synthesis, which in turn may induce a phenotypic shift in nitrergic neurones. Recent data further indicate that enteric glia may be involved in the inactivation and removal of neuropeptide transmitters from the extracellular space. In the gut wall, the high affinity oligopeptide transporter PEPT2 is predominantly expressed on enteric glial cells which are thus in a position to rapidly take up di- or tripeptide neuropeptide degradation products.[23] Overall, it is conceivable that an intricate balance between neurotransmitter synthesis and removal has a key role in transcriptional regulation and post-transcriptional modulation of neurotransmitter and/or synthesising enzyme expression, which may happen within a few hours and could determine enteric neuronal phenotypes.

On the other hand, we do not know if the actual presence of enteric glia is required, or if enteric glia secrete factors which stabilise the neurochemical composition of the ENS. In the CNS, glia are well recognised as sources of neurotrophins and neurotrophic factors which in turn are master regulators not only of ontogenetic differentiation but also of adult function.[24–29] The neurotrophin family in particular—including nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), neurotrophin 4/5, and neurotrophin-6—have been implicated in the translational control of gene expression and, in turn, maintenance of neuronal phenotypes.[28 29] In the adult ENS, expression of neurotrophins as well as their tyrosine receptor kinases *trk* A, B, and C has been reported,[30–34] and some evidence supports glial secretion of these factors.[31] Moreover, the current study indicates expression of BDNF and NT-3 in the intestinal wall, and using isolated enteric glial cells, we have found evidence of glial expression of NGF, BDNF, and NT-3 (unpublished observations). Together, these data strongly suggest that neurotrophins may indeed be produced by enteric glia to modulate neuronal gene expression and eventually enteric neurophenotypes.

While Aube and colleagues[9] argue that significant changes in jejunal expression of NT-3 and BDNF did not occur in transgenic mice, their data suggest that, in fact, there were differences which may have passed unnoticed because the number of tissues studied in each group may have been too small to yield sufficient statistical power. Hence the possibility that neurotrophins may be the major mediator underlying their novel observations has not been convincingly refuted. If indeed there was a decrease in intestinal NT-3 and BDNF expression, this may have further contributed to the altered motility observed in their model because NT-3 and BDNF accelerate gastrointestinal transit directly.[35]

Thus it seems worthwhile to reassess and confirm the observations reported in this paper, ideally in a different model of glial disruption. A recent preliminary report appears to confirm that disruption of enteric glial function alters jejunal motor functions.[36] These findings were obtained in a model in which enteric glia were chemically targeted and inflammatory side effects were ruled out.

So, what are the clinical implications? Overall, the importance of enteric glia for normal gastrointestinal function is becoming increasingly clear,[8] and the concept that abnormalities in glial structure and/or function may underlie certain, still to be defined, disturbances in gastrointestinal physiology opens an extremely exciting area of research

which may ultimately lead to novel approaches in the treatment of both functional and inflammatory bowel diseases. To gain further insight into glial roles in human gastrointestinal disorders, any histopathological investigation of intestinal full thickness biopsies should not only assess enteric neurones but start searching for abnormalities in the glial network. There are promising indications that the interest in this field of research is growing rapidly, as a number of histopathological studies on glial changes in functional or structural bowel disorders have been published recently.[37 38]

We should now make every possible effort to further elucidate glia-neurone interactions in the adult ENS and use the most sophisticated approaches—including gene and protein expression profiling—to identify genes and mediators whose expression is induced or suppressed after glial ablation. This may provide molecular targets for future therapeutic interventions to restore or replace glial functions and in turn restore appropriate neurochemical phenotypes in order to ultimately restore proper ENS function.

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IBS

Self-help interventions in irritable bowel syndrome

A P S Hungin

Self-management approach in irritable bowel syndrome was effective in reducing primary care consultations and perceived symptom severity

What if someone offered you a simple, accessible, and low cost management for irritable bowel syndrome (IBS) which offered results? And moreover, all that was needed was an initial clinical diagnosis without going through the strictures of research led definitions? This is what is proposed by Robinson and colleagues[1] in this issue of *Gut*—an outwardly simple study backed by complex prior work with IBS sufferers ***(see page 643)***.

In a randomised study, IBS sufferers were enrolled in one of three interventions: a guidebook on IBS, the booklet plus a self-help group session, or management as usual. Set in primary care, the study was pragmatic, relying on the clinicians' own diagnosis and not stipulating any specific diagnostic criteria. The results indicated that the guidebook group did as well as the guidebook plus self-help group and both were better than care as usual. A substantial reduction in primary care consultations was achieved. Although there were no changes in symptom scores in any of the groups, both groups using the guidebook reported a reduction in perceived symptom severity.

This study poses a number of intriguing questions. Of course the guidebook was no mere handy booklet prepared by a keen clinician—it was the result of prior qualitative research with IBS patients who described the information they required to help them cope with their symptoms better.[2] It can thus be seen as rooted in patients' own perceptions and beliefs and dealing with their likely concerns. None the less, both the apparent lack of adjunctive effect from the group therapy (although it might well be that the effect in those who attended was more pronounced) and the fact that only a minority (40%) attended their session are worth considering. And what does it mean when patients say they are better but their specific symptoms are not?

Explaining peoples' response to non-pharmacological interventions probably has to do with their personal concepts of health and their health seeking behaviour.[3 4] Some people, highly aware and informed about things that can go wrong (the so- called ''high monitors'') are prone to seek advice early and often. Equally, those who have a lower general concern about health and lower perceptions of worrying pathology (the ''low monitors'') are less likely to consult. Within these groups, people sometimes comprise the ''low blunters'' (those whose perceptions and anxiety cause them to have a low threshold for consultation) and their opposites, the ''high blunters'' (classically, doctors themselves who, while aware of the potential consequences of their own symptoms, will avoid consultation as far as possible). (Blunting is defined as the tendency to under react to symptoms.)

A possible reason why patients might be able to modify or in pragmatic terms reduce their consultation behaviour for conditions that do not have dangerous consequences is through increased knowledge and understanding of their symptoms. This is likely to go some way towards allowing them to live with their symptoms. Much psychological intervention is geared to this and it would seem that a well researched tool, such as a guidebook, can serve that function.

Non-pharmacological interventions in IBS have not become as common practice as some might have hoped. In a critique of psychological treatments, Talley and colleagues[5] indicated that although the majority of studies reported psychological treatments to be superior to control therapy, the overall efficacy of such treatments could not be established because of methodological inadequacies. On the other hand, Svedlund,[6] in a review of 22 studies that used a controlled design comparing psychological treatment with conventional medical treatment and/or supportive therapy, concluded that psychological treatment appeared superior and that psychotherapy was an efficient complement to drugs. Recently, in a trial of cognitive behavioural therapy delivered by primary care nurses, Kennedy *et al* showed additional benefit over mebeverine alone for up to six months.[7] The methodological problems referred to often centre on the control or ''placebo'' comparison used. Even in drug intervention trials for IBS the role and indeed the definition of placebo continues to cause confusion. Against a backdrop of placebo effects ranging from 16% to 70%,[8] identifying the exact role of the pharmaceutical intervention is challenging.

Where then do the psychological interventions come in against this backdrop? Some extremists might go so far as to say that the psychological intervention itself might be a placebo and that such interventions will naturally produce a measurable effect. However, harnessing this effect represents an important therapeutic tool. As Enck and Klosterhalfen[9] point out, high placebo responses in functional bowel disorders are similar to those in non gastrointestinal diseases and even ''not too dissimilar'' to those in organic gastrointestinal disorders, such as duodenal ulcer and inflammatory bowel disease. Furthermore, psychobiological mechanisms of the placebo response can be identified in brain function studies such as imaging. Clinicians frequently use therapeutic approaches which seem to work even if they do not understand how they work and even if they know that their approach is probably no different from what might be regarded as placebo.

However, not everyone will want to avail themselves of certain types of psychological intervention. A low level of participation in groups is known to happen when sensitive or embarrassing topics are being explored. Researchers collecting information are familiar with the dilemma of having to decide whether alternative techniques, such as individual interviews, might be more successful under these circumstances. Those participating in self-help groups for such conditions (and IBS is a sensitive issue for many sufferers)[10] are likely to be self-selected having overcome their apprehensions or are more desperate.

The guidebook concept, as described by Robinson and colleagues,[1] is an attractive one. An instrument derived from patients' own perceptions and experiences elevates it beyond an information tool alone and probably constitutes a psychological intervention in its own right. This team has also demonstrated that a self-management approach in inflammatory bowel disease was effective in reducing hospital visits and increased sufferers' confidence.[11] Similar interventions, perhaps utilising other media such as video or interactive information technology, may offer more promise than might be anticipated if