European Science Foundation
Standing Committee for the European Medical Research Councils (EMRC)

SCIENTIFIC REPORT

ESF EMRC EXPLORATORY WORKSHOP

Links between visceral dysfunction and affective disorders

Graz, Austria, 31 August - 3 September 2006

Convened by:
Peter Holzer

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Co-sponsored by

Medical University of Graz

CONVENOR

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MAIN OBJECTIVES OF THE WORKSHOP

Functional bowel disorders such as functional dyspepsia and irritable bowel syndrome are defined by symptom complexes (e.g., altered bowel habits, abdominal discomfort and pain) in the absence of any organic cause identifiable by conventional diagnosis. From epidemiological studies it is emerging that there is a significant comorbidity of functional bowel disorders with anxiety, depression and other psychiatric disorders. Both functional bowel disorders and mood disorders affect 10 - 20 % of the adult population. However, the underlying links between bowel dysfunction and mood disturbances are not understood, which may be related to the lack of interaction between gastroenterologists and neuroscientists. For this reason, the workshop brought together experts in gastroenterology, neuropharmacology, neuroimmunology, neuroendocrinology, psychology and psychiatry to explore the multidimensional relationships between affective and functional bowel disorders and to conceive new strategies to advance their understanding and treatment.

The workshop on “Links between visceral dysfunction and affective disorders” addressed a novel field of biomedical science and opened up a new direction of interdisciplinary research (“neuro-psycho-gastroenterology”) into an European health issue of high socio-economic impact. The ultimate intention of the workshop was to discuss future plans for follow-up research activities and collaborative actions on a European level.

EXECUTIVE SUMMARY

Session 1: The gut-brain axis from a gastroenterological and psychiatric perspective

The first session of the workshop presented the clinical problem of functional bowel disorders (FBDs), the multifactorial origin of FBDs at the gastrointestinal (GI) and brain level, and the association of GI symptoms with emotional-affective and cognitive processes. Preceding infection, inflammation and disturbances of the immune, nervous and/or effector systems in the gut have been found to be risk factors for the development of irritable bowel syndrome (IBS). Low-grade inflammation in the GI mucosa is a relevant factor in IBS, given that there is evidence for hypermastocytosis as well as infiltration and activation of immune cells within the gut. These processes lead to the release of a host of mediators that influence GI motor function and amplify sensory perception of gut events.

Although visceral hypersensitivity is very commonly associated with FBDs, a majority of FBD patients also presents with psychological disorders such as anxiety, depression, somatization and panic disorder. It is thought, therefore, that visceral hypersensitivity involves abnormal brain processing of sensory signals as well as “top-down” and “bottom-up” psychophysiological processes. Functional brain imaging is emerging as an invaluable asset in elucidating this complex network of neural processes. Visceral pain may be considered as a “homeostatic emotion” in which the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis likewise play an important role. Although the evidence for FBDs being caused by stress remains conflicting, inclusion of psychosocial factors in the analysis enables more clinically meaningful groups of FBD patients to be identified than by bowel symptoms alone. According to the biopsychosocial model, psychological factors interact with biological alterations in the pathogenesis of FBDs.

Session 2: Experimental models to study the geno- and phenotype of gastrointestinal, pain and mood disorders

The second session addressed the experimental models with which FBDs and mood disturbances are currently explored in the laboratory. Almost all current experimental approaches are modelled to reflect GI hyperalgesia and rely on manipulations that induce inflammatory hyperalgesia, noninflammatory hyperalgesia or delayed hyperalgesia. A special problem in animal studies of visceral pain is posed by the choice of pain-related end points. As “animals are not speaking”, indirect indices of pain such as pseudoaffective responses have to be used. In view of several failures to introduce new drugs for the treatment of FBDs, the drug development process needs to be critically analyzed. It was pointed out that pitfalls can occur at every stage of the process, not only in the validity of animal models.

Because FBDs have a wider phenomenology than just visceral hypersensitivity and altered GI motility, relevant animal models need to reflect this complexity and adopt an integrative approach. Specifically, animal models should measure changes in multiple physiological domains, have a behavioural dimension and investigate relevant brain mechanisms. The housing, testing and measurement methods need to be optimized for maximal detectability of effects, and the selection of animals should account for individual differences in behavioural coping style and vulnerability. Intrastrain variabilities in anxiety-related behaviour have been elucidated by a combined neurobiological-genetic approach. Rats and mice can be selectively bred to obtain animals displaying low anxiety-related behaviour (LAB) and high anxiety-related behaviour (HAB). These two animal models represent inborn extremes of trait anxiety that is related to a single nucleotide polymorphism in the arginine-vasopressin (AVP) gene. The HAB phenotype in rats is related to AVP overexpression and overrelease, whereas the LAB phenotype in mice involves a deficit in bioavailable AVP.

Session 3: Genetic, molecular and neurochemical basis of mood disturbances and their impact on brain-gut interactions

The third session continued to address the obviously related aetiology of mood disturbances and FBDs. There are several approaches to drug target validation for neuropsychiatric disorders through pharmacological, immunological and genetic (mutant animal models) techniques as well as somatic gene manipulation including RNA interference. Current research into depression is directed at the identification of endophenotypes that model non-clinical but mechanism-relevant depression symptoms in the mouse. These endophenotypes relate to HPA axis dysfunction, disturbances of several transmitter and neuropeptide systems, immune system alterations, and dysfunction of cell survival pathways. Post-traumatic stress disorder (PTSD) is the only psychiatric condition where the causal factor (trauma) is defined in the diagnosis. PTSD has been associated with depression, anxiety

and various non-psychiatric disorders including functional dyspepsia and IBS. Elucidation of a causal connection between trauma experience and GI disorders requires controlled animal studies. Experimental trauma (usually electric footshocks) proactively increases vulnerability to later stress-induced or chemically evoked GI injury. Increased vulnerability seems to be related to low levels of circulating corticosterone prior to the shock experience, which raises the issue of whether low glucocorticoid levels represent a predisposing factor rather than a consequence of trauma/PTSD.

There is considerable evidence that adverse environmental factors in early life such as parental loss, emotional and physical neglect or abuse are associated with increased long-term vulnerability to develop mood disorders such as depression. Analysis of the impact of the postnatal environment on behaviour and psychiatric disease in adulthood likewise depends on the availability of appropriate animal models. Early maternal deprivation of rodents and primates has been found to lead to long-term depression-like behavioural traits of reduced motivation for reward and impaired coping with adversity. Ongoing studies address the epigenetic mechanisms that underlie these findings and explore opportunities to reverse the adverse effects of parental loss, neglect or abuse. Other factors with relevance to mood disorders are proinflammatory cytokines such as interferon-α (IFN-α) which can induce neurobehavioral symptoms collectively referred to as “sickness behavior”. While the affective disturbances caused by IFN-α (depression, anxiety, cognitive impairment) can be ameliorated by treatment with antidepressant drugs, the neurovegetative (fatigue, anorexia) and somatic (GI symptoms, pain) symptoms evoked by IFN-α are resistant to antidepressant therapy. A mechanistic model proposes that the initial sickness behaviour progresses to delayed depression, if certain vulnerability factors are present and/or activated.

Although the best studied neuroendocrine disturbance in major depression is a dysfunction of the HPA axis, other endocrine systems may also play some part in affective and anxiety disorders. The depression-related disturbance of the HPA axis is characterized by a hyperactivity of the hypothalamic corticotrophin-releasing factor (CRF) and AVP system and elevated cortisol levels. Apart from AVP, hormones involved in the control of body fluid and cardiovascular function such as oxytocin and aldosterone may also contribute to the pathophysiology of depression. Contrary to traditional views, the effect of stress to release cortisol, adrenaline and noradrenaline in subjects with high trait anxiety is decreased, which points to a beneficial influence of cortisol under conditions of high trait anxiety. CRF turns out to regulate many components of the stress response system and to influence activity, arousal, aggression, feeding, fear, anxiety, reproductive behaviour, metabolism, circulation, immune and GI function. The locus coeruleus is a structure that receives CRF-expressing projections not only from the hypothalamus but also from the amygdala, central grey and raphe system. CRF potently activates noradrenaline-containing neurons in the locus coeruleus and in this way regulates arousal and attention in a gender-related manner. In the gut, CRF and the related urocortin system participate in neuroimmunological responses to stress as well as in immune and inflammatory reactions.

The tachykinin substance P is a classical brain-gut neuropeptide. Apart from its peripheral actions in the GI and vascular system, substance P has many central actions related, e.g., to emesis, nociception, cardiovascular regulation and mood. Within the brain, substance P acts mainly through tachykinin NK_1 receptors, and antagonism of central NK_1 receptors has in some, but not all trials been found to exert antidepressant activity with a very favourable adverse effect profile. Experimental studies in rodents show that emotional stressors cause substance P release in specific brain areas (e.g., amygdala, lateral septum, locus coeruleus) and that the neuropeptide is associated with exacerbation of anxiety- and depression-like behaviour in a site-specific manner. It is proposed that blockade of NK_1 receptors is particularly beneficial in individuals with a high degree of anxiety, a pronounced stress history and/or a disturbed stress regulation.

Session 4: General structured discussion

Co-moderated by the chairmen of the individual sessions, the discussion focussed on the identification of important open questions and the outline of an action plan towards a collaborative solution of these issues in the future. There was general agreement that FBDs and mood disorders have many features in common and, based on this, several objectives for cooperation were identified. These objectives relate, among others, to the diagnosis of FBDs, the identification of biomarkers and vulnerability factors, the analysis of neurochemical features, the elucidation of genetic and epigenetic mechanisms, and the establishment of validated animal models. It was agreed to generate a position paper and pursue plans for a follow-up *scientific forward-looking meeting* in order to substantiate specific plans for collaboration within and outside the ESF EMRC frame.

SCIENTIFIC CONTENT OF THE EVENT

Introduction

Functional bowel disorders (FBDs) such as functional dyspepsia and irritable bowel syndrome (IBS) are defined by symptom complexes (e.g., altered bowel habits, abdominal discomfort and pain) in the absence of any organic cause identifiable by conventional diagnosis. However, FBDs also exhibit a high degree of comorbidity with emotional disturbances such as anxiety and depression. In addition, the symptoms of FBDs are often triggered or exacerbated by stress. However, the precise relationships between the gut and brain in FBDs and their therapeutic management remain unknown. One reason for this gap of knowledge is that investigators with an expertise in gastroenterology are not familiar with the central nervous system and investigators specialized in brain research know little of the input that the brain receives from the gut. Therefore, the current workshop was designed to promote the exchange of information between gastroenterology- and neuroscience-oriented investigators and thereby cross-fertilize the study of FBDs in a new dimension.

Progress in the understanding and treatment of both FBDs and mood disorders is badly needed because the current treatment options are limited and because both disease entities are of a major socioeconomic impact. FBDs are very common, and the prevalence of IBS alone may be as high as 22 % of the adult population in certain European countries and is more common in women than in men. Stress-related disorders of mood are likewise very common, and estimates by the World Health Organization predict that unipolar depression will be the second most prevalent cause of illness-induced disability by 2020, only surpassed by cardiovascular diseases.

Session 1: The gut-brain axis from a gastroenterological and psychiatric perspective

The first session of the workshop presented the clinical problem of FBDs, the multifactorial origin of FBDs at the gastrointestinal (GI) and brain level, and the association of GI symptoms with emotional-affective and cognitive processes. Information was presented as to how preceding infection, inflammation and disturbances of the immune, nervous and/or effector systems in the gut may lead to the development of IBS. Recent studies have revealed that low-grade inflammation in the GI mucosa is a relevant factor in IBS, given that there is evidence for hypermastocytosis as well as infiltration and activation of immune cells within the gut. T-lymphocytes and mast cells release a host of mediators that influence GI motor function and amplify sensory perception of gut events. The causes of GI immune activation include infectious, genetic, brain (i.e. stress) and neuroendocrine mechanisms.

A second focus of the session was on the visceral hypersensitivity and hyperalgesia that is typically associated with FBDs. A widely held hypothesis holds that sensitization occurs in response to injury or inflammation. Since, however, 50-80% of FBD patients present with psychological disorders such as anxiety, depression, somatization and panic disorder, the concept of visceral hypersensitivity needs to be extended to include abnormal brain processing of sensory signals as well as “top-down” and “bottom-up” psychophysiological processes. In this context, pain should be considered as a “homeostatic emotion” in which the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis play an important role. In elucidating this complex network of neural processes, functional brain imaging is emerging as an invaluable asset. This approach offers the opportunity to visualize the neural correlates of pain pathways and pain-processing areas in the brain of healthy controls and FBD patients. In addition, distinct differences between somatic and GI pain, gender-based differences in the pain processing of FBD patients, and a significant influence of negative emotions, attention, distraction and anticipation on central pain circuits have been revealed.

The third issue of the session addressed the psychological dimension of FBDs. Although often viewed as psychological disorders that are caused or exacerbated by stress, the evidence supporting the “stress hypothesis” remains conflicting. Despite this uncertainty, there is unequivocal evidence that psychiatric comorbidity and other psychological factors affect patients’ quality-of-life, health-care seeking behaviour, and the reporting and interpretation of symptoms. Inclusion of psychosocial factors in the analysis enables more clinically meaningful groups to be identified than by bowel symptoms alone. According to the biopsychosocial model, psychological factors interact with biological alterations in the pathogenesis of FBDs, and patient subgroups with more prominent psychological disturbances versus biological alterations need to be identified and more accurately characterized. The emerging information may lead to different treatment approaches for patient subgroups.

Session 2: Experimental models to study the geno- and phenotype of gastrointestinal, pain and mood disorders

The second session addressed the experimental models with which FBDs and mood disturbances are currently explored in the laboratory. Initially, the experimental techniques with which FBDs are modelled in the laboratory were presented and subjected to a critical appraisal. Almost all current experimental approaches are modelled to reflect GI hyperalgesia. This pathological state of visceral sensitization is induced by manipulations that induce either inflammatory hyperalgesia, noninflammatory hyperalgesia or delayed hyperalgesia. A special problem in animal studies of visceral pain is posed by the choice of pain-related end points. As “animals are not speaking”, indirect indices of pain such as pseudoaffective responses in the definition of Sherrington are used. A major focus of recent experimental work has been the identification of the mediators that are responsible for GI hyperalgesia, because advances in this respect would reveal new targets for therapy. The factors under study include nerve growth factors, mast cell mediators such as serine proteases, CRF and stress.

In view of the prevalence of FBDs and the limited therapeutic opportunities to treat FBD patients, it has been very disappointing to see that in the past decade several drug candidates that appeared very promising in preclinical research did not make it into the clinic. The critical question therefore is: What went wrong in these endeavours? Drug development proceeds in stages such as (1) clinical observations in the patient, (2) identification of a biological marker, (3) formulation of a disease-specific hypothesis, (4) establishment and validation of an animal model, (5) identification of a specific target, and (6) development and preclinical as well as clinical testing of a promising drug. It needs to be realized that there can be pitfalls at every level of the process, not only in the validity of animal models. As any disease model, relevant animal models of FBDs should meet the criteria of face, construct and predictive validity, i.e., they should resemble one or several clinical or pathophysiological characteristics of FBDs, be consistent with a theoretical rationale (e.g., enhanced stress responsiveness, postinfective visceral hypersensitity) and predict a treatment response. While face and construct validity have been establised to variable degrees for a number of experimental FBD models, their predictive validity has remained questionable due to both animal model-related and patient-related pitfalls.

In response to the apparent shortcomings in the current preclinical development of FBD drugs it was pointed out that experimental FBD models need to account for a multiplicity of factors relevant to the gut-brain axis, because FBDs have a wider phenomenology than just visceral hypersensitivity and altered GI motility. Accordingly, relevant animal models need to reflect this complexity and adopt an integrative approach. Specifically, animal models should account for relevant and multiple aetiologies, measure changes in multiple physiological domains including visceral and somatic pain, have a behavioural dimension and investigate brain mechanisms by various approaches including functional neuroanatomy. In addition, the housing, testing and measurement methods need to be optimized for maximal detectability of effects and minimal interference between measurement domains. Particular attention need to be paid to the selection of animals relative to their behavioural coping style and individual differences in vulnerability.

Intrastrain variabilities in anxiety-related behaviour have been elucidated by a combined neurobiological-genetic approach. Rats and mice can be individually differentiated with regard to trait anxiety and selectively bred to obtain animals displaying low anxiety-related behaviour (LAB) and high anxiety-related behaviour (HAB). These two animal models represent inborn extremes of trait anxiety. Genetic analysis has revealed that single nucleotide polymorphisms (SNPs) in regulatory structures of the arginine-vasopressin (AVP) gene underlie the AVP-mediated HAB phenotype, causing AVP overexpression and overrelease. Conversely, in LAB mice, a SNP in the AVP gene gives rise to a deficit in bioavailable AVP. These data indicate that AVP released within distinct brain areas contributes to behavioural regulation including emotionality, stress-coping and learning/memory.

Session 3: Genetic, molecular and neurochemical basis of mood disturbances and their impact on brain-gut interactions

The third session continued to address the common aetiology that seems to underlie mood disturbances and FBDs and that may hint at common underlying mechanisms. It is particularly worth noting that traumatic events in early life, catastrophic life events leading to post-traumatic stress disorder (PTSD) and chronic stress have been implicated in the pathogenesis of FBDs. It is, therefore, of particular relevance to elucidate which genetic factors predispose individuals to emotional vulnerability by, e.g., stress, trauma or immune activation.

Unipolar depression is predicted to become the second most prevalent cause of illness-induced disability by 2020, its current lifetime prevalence being already 16.2%. There is an urgent need for new antidepressants, given that the current therapies are of limited efficacy in about 35% of the patients and depressed patients are at risk for a variety of somatic conditions including FBDs and for suicide. There are several approaches to drug target validation for neuropsychiatric disorders through pharmacological, immunological and genetic (mutant animal models) techniques as well as somatic gene manipulation including RNA interference. Current research into depression is directed at the identification of endophenotypes that model non-clinical but mechanism-relevant depression symptoms in the mouse. These endophenotypes relate to HPA axis dysfunction, disturbances of monoamine transmitter systems (5-HT, noradrenaline, dopamine), the glutamatergic system, the GABAergic system, neurosteroids and neuropeptides (substance P, CRF), alterations in cell-mediated immunity and in the inflammatory response system, dysfunction of cell survival pathways, and other abnormalities including gut dysfunction.

PTSD is the only psychiatric disorder where the causal factor (trauma) is defined in the diagnosis. Per definition, PTSD sufferers have been exposed to a situation which is perceived as traumatic and involves intense fear, helplessness or horror. Although some trauma types have greater potential than others to lead to PTSD, none produces PTSD in all victims. Comorbid states associated with PTSD comprise depression, anxiety and various non-psychiatric disorders including functional dyspepsia and IBS. Since studies in humans are hampered by subjectivity in reporting traumatic experiences and subject selection, controlled animal studies are necessary to elucidate whether there is a causal connection between trauma experience and GI disorders. In most animal studies electric footshocks are used as traumatic event, and avoidance, arousal and startle enhancement are taken as behavioural indices of a PTSD-like condition. Experimental trauma proactively increases vulnerability to later stress-induced or chemically evoked GI injury. In addition, early childhood abuse seems to be a particular risk factor for dysfunction of the GI system as well as for PTSD. Importantly, the increased vulnerability seems to be related to low levels of circulating corticosterone prior to the shock experience. This raises the issue of whether low cortisol observed in some PTSD patients may represent a predisposing factor rather than a consequence of trauma/PTSD.

There is considerable evidence that adverse environmental factors in early life have a negative influence on emotionality in adulthood. Parenting is the major component of the postnatal environment, and human parental loss, emotional and physical neglect or abuse are associated with increased long-term vulnerability to develop mood disorders such as depression. In order to better understand the impact of the postnatal environment on human behaviour and psychiatric disease in adulthood it is essential to establish appropriate animal models and characterize them with regard to depression-like phenotypes expressed in behavioural, physiological and neurobiological traits and states. Early maternal deprivation of rat pups and marmoset infants has been found to lead to long-term depression-like behavioural traits of reduced motivation for reward and impaired coping with adversity. Neurobiological and pharmacological studies are necessary to establish the relevance of these findings to human disease. Further studies need to address the epigenetic mechanisms that underlie the long-term neurobehavioural impact of the postnatal environment and, most importantly, to explore opportunities to reverse the adverse effects of parental loss, neglect or abuse.

Studies in animals and humans have shown that proinflammatory cytokines released during infection, inflammation and tissue damage are responsible for the development of neurobehavioral symptoms collectively referred to as “sickness behavior”. These symptoms have many features overlapping with those of major depression, and consequently it has been proposed that proinflammatory cytokines participate in the pathophysiology of depression. The behavioural effects of chronic IFN-α administration can be viewed as a model system to study the central effects of cytokines. While the affective disturbances caused by IFN-α including depression, anxiety and cognitive impairment can be ameliorated by treatment with antidepressant drugs, the neurovegetative (fatigue, anorexia) and somatic (GI symptoms, pain) symptoms evoked by IFN-α are resistant to antidepressant therapy. A mechanistic model proposes that the initial sickness behaviour progresses to delayed depression, if certain vulnerability factors are present and/or activated. One such vulnerability marker for cytokine-induced depression may be CRF and HPA axis hyperresponsiveness as well as changes in 5-HT metabolism.

The implication of the HPA axis in GI and affective brain disturbances was a reverberating theme of many presentations, but it must not be neglected that many more endocrine systems have some influence on mood and could be related to affective and anxiety disorders. The best studied neuroendocrine disturbance in major depression is a dysfunction of the HPA axis. Typical of this psychiatric condition is a hyperactivity of the hypothalamic CRF system, resulting in elevated levels of circulating cortisol, which are maintained because the negative feedback of cortisol on the HPA axis is

impaired due to downregulation of glucocorticoid receptors (GRs) in the hypothalamus and pituitary. AVP is likewise involved in the communication between hypothalamus and pituitary and in the manifestation of trait anxiety and depression. Patients with depression have an increased number of AVP neurons in the hypothalamus and elevated levels of circulating AVP, and modulation of the AVP system results in normalization of the overactive HPA axis in depressed patients. Whether other hormones involved in the control of body fluid and cardiovascular function such as oxytocin and aldosterone contribute to the pathophysiology of depression awaits to be investigated. Contrary to traditional views, the effect of stress to release cortisol, adrenaline and noradrenaline in subjects with high trait anxiety is decreased rather than enhanced. It thus appears that potentiation rather than inhibition of neuroendocrine responses during acute stress may be of benefit to individuals with high trait anxiety. Taken together, high trait anxiety is not connected with a global neuroendocrine hyper- or hyporesponsiveness, but rather with alterations in the complex coordination of neuroendocrine responses during stress.

Along with the diverse roles of the neuroendocrine system in the regulation of emotionality and stress coping, CRF is turning out to be not only an important mediator of the HPA axis but also relevant to other components of the stress response system. While the HPA axis takes a central place in the coordination of stress reactions, and CRF and AVP carried to the anterior pituitary via hypothalamic-hypophyseal portal veins act synergistically to stimulate the secretion of ACTH, the actions of CRF concern many more targets than just the pituitary and comprise effects related to activity, arousal, aggression, feeding, fear, anxiety, reproductive behaviour, metabolism, circulation and immune function. In the GI tract, CRF inhibits gastric secretion as well as gastric and small intestinal motility but accelerates large bowel transit. In addition, it causes mucin depletion, mast cell degranulation, oxidative injury and ulceration and reduces mucosal blood flow. Within the brain, the locus coeruleus is a structure that receives CRF-expressing projections not only from the paraventricular nucleus of the hypothalamus but also from the amygdala, central grey and raphe system. CRF potently activates locus coeruleus neurons which represent the largest group of noradrenaline-containing neurons in the brain and are particularly relevant to the regulation of arousal and attention in a gender-related manner. In the periphery, CRF and the related urocortin system seem to participate in neuroimmunological responses to stress as well as in immune and inflammatory reactions, given that mast cells and polymorphonuclear granulocytes express CRF receptors.

The tachykinin substance P is a classical brain-gut neuropeptide that is expressed in enteric neurons within the GI tract, in primary afferent neurons and in distinct central neurons. Apart from its peripheral actions in the GI and vascular system, substance P has many central actions related, e.g., to emesis, nociception, cardiovascular regulation and mood. Clinical studies addressing a possible role of substance P in anxiety and depression have come up with inconsistent results. Within the brain, substance P acts mainly through tachykinin NK_1 receptors, and antagonism of central NK_1 receptors has in some trials been found to exert antidepressant activity with a very favourable adverse effect profile, while other trials have failed to confirm any therapeutic activity. This failure has called for a detailed investigation of the role of tachykinins in stress reactions and in the modulation of anxiety/depression-like behaviour in appropriate animal models. Experimental studies in rodents show that emotional stressors cause substance P release in specific brain areas (e.g., amygdala, lateral septum, locus coeruleus) and that this release of the neuropeptide is associated with exacerbation of anxiety- and depression-like behaviour in a site-specific manner. By local administration of a NK_1 receptor antagonist it has been shown that endogenous substance P acting via central NK_1 receptors also plays a site-specific role in the modulation of anxiety- and depression-like behaviour. Further observations indicate that the substance P/NK_1 receptor system is altered in animal models of high anxiety and comorbid depression. From these findings it would appear that blockade of NK_1 receptors is particularly beneficial in individuals with a high degree of anxiety, a pronounced stress history and/or a disturbed stress regulation.

Session 4: General structured discussion

Co-moderated by the chairmen of the individual sessions, the discussion focussed on the identification of important open questions and the outline of an action plan towards a collaborative solution of these issues in the future. There was general agreement that FBDs and mood disorders have many features in common and, based on this, the major recommendations of the workshop for future efforts were as follows:

1. collaborative interactions between gastroenterology- and behavioural neuroscience-oriented investigators as the basis of a neuro-psycho-gastroenterological approach to the study of FBDs;
2. development of “measures” (gastroenterological and psychological) with which a large number of patients can be screened in a non-invasive, easy and quick manner;
3. analysis of the factors accounting for individual differences of FBD subgroups;

4. analysis of the vulnerability factors relevant to the manifestation of FBDs;
5. analysis of the common features shared by the gut and brain in terms of neurotransmitters and neuropeptides and the interaction between the gut- and brain-based systems;
6. establishment of validated animal models for FBDs that involve a multidimensional approach in a standardized and replicable manner;
7. identification and establishment of valid biomarkers for FBDs;
8. analysis of genetic and epigenetic mechanisms underlying FBDs
9. publication of the workshop proceedings and generation of a position paper;
10. setup of a forum that moves towards specific plans for collaboration within and outside the ESF EMRC frame, based on a follow-up *scientific forward-looking meeting*.

ASSESSMENT OF THE RESULTS, CONTRIBUTION TO THE FUTURE DIRECTION OF THE FIELD, AND OUTCOME

Assessment of the results

The workshop was meant to be an experiment to explore whether interaction between two different groups of scientists, gut-oriented and brain-oriented researchers, could reveal new aspects in the understanding and further analysis of functional bowel disorders (FBDs) which represent disorders that have both a gastrointestinal and brain domain whose interrelationship is epidemiologically obvious but mechanistically little understood. In the convenor's opinion, the workshop was a success beyond expectation, as judged by the in-depth presentation of current knowledge in the domains of FBDs and stress-related mood disorders, by the intensive discussion and interaction of the two groups of scientists who had little, if any, interrelation with each other before, and by the cross-fertilization of ideas and concepts as to how research at the interface between the gut and brain could be significantly advanced. By the end of the meeting all participants felt reassured that *neuro-psycho-gastroenterology*, as Miklós Tóth put it in his report, is a new emerging field of research.

There was general agreement that FBDs and mood disorders have many features in common and, based on this, a number of major recommendations was formulated as to how the field could be significantly advanced. These recommendations are listed in the description of the scientific content of the event. The successful achievement of these goals will critically depend on a collaborative interaction between gastroenterology- and behavioural neuroscience-oriented investigators.

Contribution to the future direction of the field

In order to keep the momentum of the workshop and its encouraging results, the participants expressed the need to summarize the workshop proceedings in a *position statement* and thereafter to organize a *scientific forward-looking meeting*. Support for these action plans within the ESF EMRC frame would be very welcome. The position statement should describe the current status of knowledge and its shortcomings and provide a solid ground wherefrom future discussion and research could depart. Apart from publishing the major outcome of the workshop it appears essential to create a forum that meets again before long to formulate specific research questions, build them into coherent research projects and define the most appropriate experimental approaches. This forum should primarily involve the participants of the workshop but also be open to new members and issues that have come up recently or could not be adequately considered in the current workshop.

Outcome and relevance to European research

The programme of the workshop addressed FBDs and their association with psychiatric disorders as a health care issue of high socio-economic impact. Despite strong international research efforts in this field over the past decade, little, if any progress has been achieved in the therapeutic understanding and management of FBDs. While Europe has a strong scientific expertise in neurogastroenterology, neuroscience and psychiatric research, these disciplines do not significantly interact with each other. One of the major aims and community-added values of the proposed workshop, therefore, was to bring together experts from these disparate fields to seek and discuss novel interdisciplinary approaches to understand the relationship between gastrointestinal disorders and mood disturbances. There was general agreement among the participants that this goal was fully met by the workshop and its proceedings opened up new perspectives in the understanding of the links between gut dysfunction and affective disorders. If the momentum of this novel neuro-psycho-gastroenterological approach to the field can be maintained and advanced, it is likely that significant progress in the management of FBDs can be achieved before long.

ACKNOWLEDGEMENTS

This explorative workshop would not have been possible without the sponsorship of ESF. The convenor is also particularly grateful to Dr. Bengt von Mentzer and Dr. Håkan Larsson of AstraZeneca (Mölndal, Sweden) who generously supported the official workshop dinner and to the Medical University of Graz represented by its Rector, Professor Gerhard Franz Walter, for encouragement as well as administrative and clerical assistance. The support by the Governor of Styria, Mag. Franz Voves, and by the Mayor of the City of Graz, Mag. Siegfried Nagl, in giving receptions for the workshop is also highly appreciated. Dr. Martin Schmiedbauer, Director of the Castle of St. Martin, and his team need to be acknowledged for providing their professional services in running the workshop in a highly agreeable atmosphere.

The idea of the workshop was developed in discussions with Mag. Evelin Painsipp, a psychologist member of the convenor's research unit, who deserves special credit for this initiative. The perfect operation of the workshop was in the hands of further members of the research unit including Mag. Martina Mitrovic, Dr. Anaid Shahbazian and Dr. Martin Edelsbrunner as well as of Professor Ulrike Holzer-Petsche.

FINAL PROGRAMME

Thursday 31 August 2006

15.00 – 18.30	*Arrival at Schloss St. Martin and Registration*
18.30 – 19.00	*Transfer to the City of Graz*
19.00 – 20.00	*Guided tour through the Old City Centre of Graz*
20.00 – 22.00	*Reception by the Mayor of Graz, Mag. Siegfried Nagl, in the Town Hall*

Friday 1 September 2006

Welcome and Introduction

08.45 – 08.50	**Gerhard F. Walter**, Rector of the Medical University of Graz, Austria
08.50 – 09.00	**Peter Holzer**, Medical University of Graz, Austria Convenor of the Workshop
09.00 - 09.15	**Miklós Tóth**, ESF Standing Committee for the European Medical Research Councils *Presentation of the European Science Foundation (ESF)*

Session 1: The gut-brain axis from a gastroenterological and psychiatric perspective

Chair:
Robin Spiller, University of Nottingham, UK

09.15 – 10.00	**Robin Spiller**, University of Nottingham, UK *Functional bowel disorders in a gastroenterological perspective*
	Questions and discussion
10.00 – 10.45	**Peter Paine**, University of Manchester, UK *Psychophysiological variables in central sensitization to oesophageal pain*
	Questions and discussion
10.45 – 11.00	*Coffee break*
11.00 – 11.45	**Bruno Bonaz**, University of Grenoble, France *Functional brain imaging of abdominal pain*
	Questions and discussion
11.45 – 12.30	**Sigrid Elsenbruch**, University of Essen, Germany *Functional bowel disorders in a psychological/psychiatric perspective*
	Questions and discussion

12.30 – 13.15	**Giovanni Barbara**, University of Bologna, Italy *Role of immune system and inflammation in functional bowel disorders* *Questions and discussion*
13.15 – 14.30	*Lunch break*

Session 2: Experimental models to study the geno- and phenotype of gastrointestinal, pain and mood disorders

Chair :
Lionel Buéno, Institut National de la Recherche Agronomique, Toulouse, France

14.30 – 15.15	**Lionel Buéno**, Institut National de la Recherche Agronomique, Toulouse, France *Experimental approaches to model functional bowel disorders* *Questions and discussion*
15.15 – 16.00	**Guy E. Boeckxstaens**, University of Amsterdam, The Netherlands *Validity of animals models for functional bowel disorders* *Questions and discussion*
16.00 – 16.15	*Coffee break*
16.15 – 17.00	**Rianne Stam**, University of Utrecht, The Netherlands *Integrative behavioural, physiological and neuroanatomical approaches to altered brain-gut interactions* *Questions and discussion*
17.00 – 17.45	**Rainer Landgraf**, Max Planck Institute of Psychiatry, München, Germany *Genetics of anxiety and behavioural anxiety models* *Questions and discussion*
19.00	*Reception and dinner on invitation by the Governor of Styria, Mag. Franz Voves*

Saturday 2 September 2006

Session 3: Genetic, molecular and neurochemical basis of mood disturbances and their impact on brain-gut interactions

Chair:
Rainer Landgraf, Max Planck Institute of Psychiatry, München, Germany

09.00 – 09.45	**John F. Cryan**, University College Cork, Ireland *Genetic and behavioural approaches to understand the pathophysiology of depression* *Questions and discussion*

09.45 – 10.30	**Robert Murison**, University of Bergen, Norway *Post-traumatic stress disorder and gut dysfunction*
	Questions and discussion
10.30 – 10.45	*Coffee break*
10.45 – 11.30	**Christopher R. Pryce**, Novartis, Basel, Switzerland *Long-term neurobehavioural impact of the postnatal environment*
	Questions and discussion
11.30 - 12.15	**Lucile Capuron**, University of Bordeaux II, France *Central effects of cytokines: from sickness to depression*
	Questions and discussion
12.15 – 13.00	**Daniela Jezova**, Slovak Academy of Sciences, Bratislava, Slovakia *Neuroendocrinology of affective and anxiety disorders*
	Questions and discussion
13.00 – 14.15	*Lunch break*
	Chair: **Robert Murison**, University of Bergen, Norway
14.15 – 15.00	**Adelheid Kresse**, Karl-Franzens-University, Graz, Austria *The role of corticotropin-releasing factor in the translation of stress into mood and gut disorders: pathways beyond the HPA axis*
	Questions and discussion
15.00 – 15.45	**Nicolas Singewald**, University of Innsbruck, Austria *Substance P in stress, anxiety and depression*
	Questions and discussion
15.45 – 16. 00	*Coffee break*

Session 4: General structured discussion

Moderators:
Robin Spiller, University of Nottingham, UK
Rainer Landgraf, Max Planck Institute of Psychiatry, München, Germany

16.00 – 18.00	*Chairpersons' summary of the workshop*
	Discussion of future plans for follow-up research activities and collaborative actions
	ESF instruments to support follow-up activities
18.30	*Departure for Official Workshop Dinner at "Kirchenwirt" in Kitzeck*

Sunday 3 September 2006

Breakfast and Departure

End of the workshop

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STATISTICAL INFORMATION ON PARTICIPANTS

The participants of the workshop included scientists from a total of 12 European countries including Austria, France, Germany, Hungary, Ireland, Italy, Netherlands, Norway, Slovakia, Sweden, Switzerland and UK, while the active speakers represented 10 European countries. Of the 16 active speakers, 11 were of the male and 5 of the female gender. In terms of their stage of academic career, 7 of the active speakers were full professors or in an equivalent position, whereas 9 investigators belonged to the ranks of Assistant or Associate Professor or equivalent positions.

In selecting the speakers attention was paid to the involvement of representatives from as many member countries of ESF as possible so that the participation across Europe in terms of geographical balance, age and gender was very broad. Apart from these considerations, the active participants were selected on the basis of their scientific excellence, their expert contribution to the interdisciplinary topic of the workshop and their potential participation in a collaborative research project of an European dimension. There were no more than 3 participants from any ESF member country.