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Identification and Treatment of Symptoms Associated with Inflammation in Medically Ill Patients

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Abstract

Medically ill patients present with a high prevalence of non-specific comorbid symptoms including pain, sleep disorders, fatigue and cognitive and mood alterations that is a leading cause of disability. However, despite major advances in the understanding of the immune-to-brain communication pathways that underlie the pathophysiology of these symptoms in inflammatory conditions, little has been done to translate this newly acquired knowledge to the clinics and to identify appropriate therapies. In a multidisciplinary effort to address this problem, clinicians and basic scientists with expertise in areas of inflammation, psychiatry, neurosciences and psychoneuroimmunology were brought together in a specialized meeting organized in Bordeaux, France, on May 28–29, 2007. These experts considered key questions in the field, in particular those related to identification and quantification of the predominant symptoms associated with inflammation, definition of systemic and central markers of inflammation, possible domains of intervention for controlling inflammation associated symptoms, and relevance of animal models of inflammation associated symptoms. This

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Conflict of Interest
None

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resulted in a number of recommendations that should improve the recognition and management of inflammation-associated symptoms in medically ill patients.

Keywords

Inflammation; Depression; Fatigue; Proinflammatory cytokines; Brain; Acute phase protein; Symptom burden; Biologic marker; Therapy; Animal models; Neuroimaging

The most harmful and costly health problems in the Western World are originating from a few diseases that include coronary heart disease, cancer, obesity, type II diabetes, physical disability and neurodegenerative disorders associated with ageing. In addition to the specific symptoms that are characteristic of each of these conditions, most patients experience non-specific symptoms that are similar in all these conditions and include depressed mood, altered cognition, fatigue, and sleep disorders.

The possible mechanisms for this commonality of symptoms are gradually emerging from the results of two convergent lines of research. Research carried out on sickness behavior induced in laboratory rodents by activation of the innate immune system has demonstrated that the brain forms a cellular and molecular image of the peripheral inflammatory response of the host to pathogens (Dantzer, 2006; Dantzer et al., 2007; Dantzer, in preparation 2007). The proinflammatory cytokines that are produced by activated macrophages and monocytes induce the expression of the same cytokines in the brain. These brain cytokines are responsible for development and duration of the non-specific behavioral signs that are associated with disease and are known as sickness behavior.

Results of experiments carried out in patients afflicted with hepatitis C or with cancer and treated with recombinant cytokines accord with the data from laboratory animals. Activation of the immune system results not only in the development of sickness behavior but also in the occurrence of neurovegetative (i.e., fatigue, decreased appetite, sleep disorders) and psychological (depressed mood, altered cognition, anhedonia) signs of depression (Raison et al., 2006). These alterations of mental health are likely to have an impact on the immune system, resulting in a shift toward TH1 immunity that further increases inflammation.[i]

The possibility that immune-to-brain communication pathways represent the main biological mechanism for symptom burden experienced by medically ill patients has now gained credibility in the medical community. This hypothesis is currently being tested in the context of various clinical disorders that have a chronic inflammatory component. However, this type of investigation represents an enormous task due to the diversity of these clinical conditions for a given symptom. Moreover, for a given clinical condition, the number of different stages of the disease adds to the complexity. This heterogeneity at the clinical level is made even greater because of the diversity of psychological scales that can be used for assessing subjective health complaints and the lack of consensus on the best biological markers of inflammation and the intermediate mechanisms that are involved. Because these clinical studies require substantial amounts of time and money, the temptation is often to limit the investigation to only one time point. This makes longitudinal studies an exception, despite the advantage of assessing in the same subjects the relationship between the temporal dimension of activation of the immune system and onset and evolution of symptoms. In addition, the usually low number of subjects under consideration does not permit a critical analysis of the issue of vulnerability (e.g., genetic variation in the expression of inflammatory cytokines). Last but not least, proposed interventions tend to reflect the investigators' scientific and commercial

[i]TH1 refers to a specific profile of cytokine production by T helper immune cells.

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interests rather than a concerted effort aimed at pinpointing the basic processes that mediate relationships between inflammation and subjective health complaints.

For all the previously delineated reasons, it is clear that the success of translational research and advance of knowledge on the relationship between inflammation and symptoms in medically ill patients are critically dependent on the ability to achieve some consensus on methods of investigation and on the proposed targets for intervention. As a first step in this direction a discussion meeting entitled “Cytokines and Depression III: Identification and Treatment of Symptoms Associated with Inflammation in Diseases with Inflammation in Medically Ill Patients,” was held in Bordeaux, France on May 28 and 29, 2007 thanks to the sponsorship of the “Association pour la Neuropsychopharmacologie” (Paris, France). This meeting brought together clinicians and basic scientists with a common interest in understanding inflammation and associated symptoms in medically ill patients, along with related expertise in immunology, psychiatry, neurosciences, and psychoneuroimmunology. The meeting was divided into five sessions that focused on (a) predominant symptoms associated with inflammation, (b) markers of inflammation at the periphery, (c) possible markers of brain inflammation associated with low grade peripheral inflammation in humans, (d) animal models of inflammation associated symptoms, and (e) domains of intervention for controlling inflammation associated symptoms. In this report, opinions of participants on these questions are presented, and recommendations for future studies aimed at identifying and treating symptoms in medically ill patients are put forward.

Characterization of symptoms associated with inflammation

Among the myriad of clinical questionnaires that are available to categorize or quantitatively assess depression, fatigue, sleep disorders, altered cognition and pain, none specifically refers to inflammation-associated neurobehavioral alterations. Rather than developing new diagnostic or psychometric tools more suited to assessment of symptoms associated with inflammation, all scientists working in this field have made use of the instruments with which they were familiar, even if this was in a different context.

The diagnostic tools that are favored by psychiatrists are clearly not the best ones. As pointed out by Joel Dimsdale (San Diego, California), the concept of somatization that is used for characterizing symptoms in the absence of any detectable disease is of little operational value if not misleading. For instance, the enduring fatigue experienced by the vast majority of breast cancer survivors could be easily labeled as a somatization disorder according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders. This would appear useful a priori because such a categorization acknowledges the fact that fatigue can cause distress and impair a person’s ability to function normally. However, making fatigue a somatization disorder overlooks the fact that fatigue has both mental and physical components, thereby denying a possible organic etiology to explain such fatigue (Dimsdale et al., 2007). Furthermore, this emphasis on the lack of an organic basis favors unrecognized or missed diagnoses (e.g., fatigue and thyroid abnormalities or fatigue and inflammation).

A diagnosis of major depression is not necessarily more helpful. Over several years of clinical studies of depression induced by recombinant cytokine immunotherapy in cancer and hepatitis C patients, Lucile Capuron (Bordeaux, France) was able to demonstrate the usefulness of deconstructing this form of depression into two main dimensions, the neurovegetative (fatigue, decreased appetite, sleep disorders) and the psychological (depressed mood, anxiety, altered cognition) dimensions (Capuron et al., 2002; Raison et al., 2006). While the neurovegetative syndrome develops rapidly in most individuals exposed to systemic cytokines, the mood and cognitive symptoms only develop in vulnerable patients with chronic immune system activation and/or chronic exposure to proinflammatory cytokines (Capuron et al., 2002; Raison

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et al., 2006). Whereas the mood and cognitive syndrome is highly responsive to pharmacotherapy with antidepressants, this is not the case for the neurovegetative syndrome, most likely because these two syndromes have different pathophysiological mechanisms. It remains unclear whether this operational categorization can be applied to symptoms that are reported by patients suffering from pathologies with an inflammatory component.

An important factor in the consideration of relationships between inflammation and depression is time. Inflammation is not a stable condition. In a given individual it can fluctuate rapidly according to a number of environmental factors (e.g., microbiological burden, stressors) and internal variables (e.g., diurnal variation of cortisol). As emphasized by Joel Swendsen (Bordeaux, France), ambulatory monitoring techniques, known alternatively as the Experience Sampling Method (ESM) or Ecological Momentary Assessment (EMA), are suited for studying the relationship between short-term fluctuations in inflammation, daily activities, and mood states, without the recall bias of psychological questionnaires (Tournier et al., 2003). Ambulatory data collection methods permit examination of a representative sample of mental and physical states in real time through the use of electronic devices that indicate to subjects the exact point in time to provide specific information. An additional advantage of these methods is that they allow scientists to gain insights into temporal relationships between the different symptoms under consideration (e.g., does pain precede sleep disorders which ultimately lead to fatigue and depressed mood, or does depressed mood amplify pain that becomes then unbearable to the point of impacting on sleep?). Recent development of computerized approaches to data collection and the use of multi-level statistical techniques for processing these time series data have eliminated most of the problems that plagued prior use of these methods.

During the general discussion, it was re-emphasized that the major challenge for research aimed at linking inflammation to behavioral symptoms and/or syndromes is that basic aspects of diagnosis of behavioral disorders remain controversial and lack solid scientific foundations. Specifically, many behavioral disorders and psychiatric diagnoses relevant to inflammation suffer from: (a) a lack of biological markers; (b) a lack of specific treatments (i.e., treatment specificity is the exception rather than the rule); (c) high “comorbidity” (i.e., individuals are difficult to classify); (d) a lack of longitudinal stability; and (e) an extreme diversity in the diagnostic or psychometric instruments that are commonly used to assess them. Hence, to understand whether inflammation might contribute to behavioral disorders, emphasis should be first focused on generating improved phenotypic definitions that clarify and quantify specific behavioral disturbance.

The further challenge to understand inflammatory-behavioral phenotypes will be advanced by research that: (a) spans conventional diagnostic boundaries; and (b) examines phenotypic behavioral variations across species. By studying multiple syndromes that share behavioral features and symptoms (e.g., fatigue, anhedonia, sleep disturbance), shared pathology that might possibly share etiologies should be easier to assess. Even if syndromes share a feature that reflects different pathological bases, studying the syndromes together will better isolate the unique inflammatory mechanisms leading to a final common path between specific cytokines and symptoms. Second, while some syndromes involve “uniquely human” features (e.g., depressed mood), many behaviors (e.g., sleep disturbance) overlap substantially with non-human measures. Hence, understanding the role of inflammatory mechanisms on behavioral symptoms in humans depends on the ability to examine this overlap between humans and animals using translational models.

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Selection of appropriate biomarkers of peripheral inflammation

Peter Ward (Ann Arbor, Michigan) reviewed how the acute inflammatory response involves three stages: (a) increased vascular permeability leading to leakage of fluids and proteins into the extravascular space, (b) adhesion of leukocytes to endothelial cells followed by their transmigration into the extravascular space, and (c) activation of residential tissue macrophages, which produce and release proinflammatory cytokines and chemokines by a nuclear factor kappa B (NFκÂ)-dependent mechanism (Ward and Lentsch, 2002). The inflammatory response can be blocked, suppressed, or modulated by at least four mechanisms: (a) neutralizing or destroying the proinflammatory mediators by enzymes in plasma and tissues, (b) producing anti-inflammatory mediators (e.g., IL-4, IL-10) by tissue macrophages and T cells that interfere with NFκÂ activation, (c) activating the adrenergic and cholinergic pathways, and (d) engaging intracellular signaling pathways that negatively regulate via receptor cross-talk the signaling pathways involved in the inflammatory response. The balance between proinflammatory and anti-inflammatory cytokines is an essential determinant of containment of the inflammatory reaction and its consequences on the integrity of the injured tissue.

Biomarkers of inflammation can be selected among the effector components of the inflammatory response (e.g., cytokines and their soluble receptors) or their target molecules (e.g., acute phase proteins such as C-reactive protein – CRP). Because of the role of inflammation in atherothrombogenesis, the field of cardiovascular disease is certainly the most advanced one in the search for biomarkers of inflammation. As reported by Wolfgang Koenig (Ulm, Germany), the largest epidemiological database is for CRP and fibrinogen, although their contribution to treatment strategies and risk prediction is still under test (Koenig, 2007). Other emerging biomarkers include more proximal factors involved in pathogenesis of the disease process. This is the case for cellular adhesion molecules and IL-18 that both appear to be associated with plaque progression and disease activity, and lipoprotein-associated phospholipase A2 that generates inflammatory mediators from oxidized low density lipoproteins. According to Lucy Browning (Cambridge, United Kingdom), the circulating cytokine IL-6 and the acute phase marker sialic acid have the greatest ability to discriminate between subjects in overweight women, as revealed by the discrimination ratio analysis of several biomarkers of inflammation (Browning et al., 2004). Such a discrimination ratio can only be calculated with repeated sampling of the population under study, because it corresponds to the ratio of the between- to the within-subject variance. All these approaches rely on factors that are already known either for their potential as biomarkers or their role in pathogenesis. The recourse to techniques derived from genomic biology does not require such a priori hypothesis. Differential gene expression can help identifying genes of interest by comparing genes expressed in probands with genes expressed in controls. The limit for this and other approaches is the enormous amount of data these techniques can generate. According to Costas Mitsoupoulos (London, United Kingdom), bioinformatics is the appropriate tool to convert information into knowledge, and this was illustrated by studies on cross-talk between intra-cellular signaling pathways (Ng et al., 2006). Signaling network analysis involves building models of pathways of interest, annotating protein/gene information, identifying mutually exclusive interactions, and mapping mutations onto binding interfaces. It provides a platform for system-wide modeling of pathways and networks.

Julie Bower (Los Angeles, California) provided a practical example of relating symptoms to peripheral inflammation. In a study of fatigue in breast cancer survivors, she showed that fatigued survivors had elevated plasma levels of IL-1ra and the soluble IL-6 receptor (sIL-6R) (Bower, 2007). Increases in plasma sIL-6R result from shedding of the receptor and were accompanied by significant reductions in cell surface expression of IL-6R on CD14+ monocytes among fatigued participants. Analysis of the cellular immune system revealed

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decreases in the frequency of circulating dendritic cells and activated T cells among fatigued survivors, as well as a selective increase in CD4+ T lymphocytes. More traditional markers of inflammation such as CRP were not included in this study whereas IL-6 was discriminative only when analyzed using flow cytometry to measure stimulated intracellular production of this cytokine in monocyte populations.

If a consensus is to be established regarding the optimal strategies to identify peripheral inflammatory biomarkers as they relate to development and expression of behavioral disorders, a more systematic approach is required. Unfortunately, a “shotgun” or haphazard approach to biomarker characterization has been used so far. Hence, four strategies were identified in the general discussion to address this limitation, ranging from (a) standardized assessments that allow comparisons across studies, (b) mechanism-based assessments that focus on specific pathways of interest, (c) exploratory assessments that are designed for hypothesis generation and the identification of novel biomarkers and (d) novel approaches that are designed to provide new means for assessing inflammatory biomarkers in select populations.

Standardized assessments

In order to provide consistency across studies of diverse clinical samples and allow for sharing of data, all studies examining the potential impact of inflammatory pathways on behavioral changes should include a standard set of inflammatory biomarkers. Recommendations were made to include the acute phase proteins, C-Reactive Protein (CRP), sialic acid and haptoglobin; the inflammatory mediators, prostaglandins E2 and C3A and the innate immune cytokine, IL-6 as measured by high sensitivity (hs)-Enzyme-Linked ImmunoSorbent Assay (ELISA) in plasma. These biomarkers, especially hs-CRP and IL-6 have been found to reproducibly identify the presence of an activated innate immune response in a number of disorders including behavioral disorders such as depression (Browning et al., 2004; Raison et al., 2006; Ridker, 2003; Ridker et al., 2000; Schmidt et al., 1999; Zorrilla et al., 2001). Moreover, most of these assessments (e.g., acute phase proteins) can be run in certified commercial or hospital laboratories, further reducing variability across research sites. In addition, in the case of hs-CRP, cut-off values have been established that have been shown to have both predictive validity and categorization of risk in relation to disease outcome in cardiovascular disorders (Ridker, 2003).

Given well-known fluctuations in behavior as well as immunologic status, it was suggested that whenever possible, standardized assessments of inflammatory biomarkers should be measured longitudinally in conjunction with longitudinal behavioral assessments. This aspect is important since it bears on the reliability of a single measurement of what is supposed to be an inflammatory biomarker when it is carried out at a random point of time. There are only a few longitudinal studies in which repeated samples have been taken from the same subjects over a period supposedly free of inflammatory clinical events. Variable results have been obtained for IL-6 with reliability coefficients ranging from .87 to .37 (Cava et al., 2000; Rao et al., 1994; Tsirpanlis et al., 2004). The intrinsic biologic variability of inflammatory biomarkers can represent a serious caveat in cross-sectional studies if it is not controlled for by appropriate validation procedures. Conversely, this variability can certainly benefit longitudinal studies.

Standardized inflammatory biomarkers were also considered an essential component for defining patient populations in clinical trials and should be used for stratification purposes or as inclusion/exclusion criteria. Such markers would also provide benchmarks for measuring immunologic responses in clinical trials targeting inflammatory pathways for the treatment of behavioral disorders. Finally, the routine use of multiplex bead assays to measure inflammatory molecules was discouraged until higher sensitivity assays with greater specificity become available. Results with multiplex assays should be confirmed with standard ELISA assays.

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However, multiplex assays were considered to be ideal for assessing relevant inflammatory molecules in supernatants of stimulated cells in the context of hypothesis generation (see below).

Mechanism Based Assessment

The second level of assessment includes analysis of specific molecules that reflect relevant pathways of interest. Such assessments would capitalize on a wide array of immunologic techniques (including ELISA (with selective, phosphospecific antibodies), flow cytometry, pathway arrays, DNA binding ELISA, electromobility gel shift assays, and the assessment of specific polymorphisms or epigenetic changes in candidate genes) to track a relatively targeted set of molecules that lie along relevant inflammatory pathways. For example, studies examining the role of TNFα and/or IL-1 in behavioral changes would track not only these cytokines, but also their soluble receptors, the activation status of their intermediate signaling pathways (e.g. NFκB or MAPK), their downstream products and polymorphisms in associated genes. A similar approach would be relevant for studies examining the predictive capacity of polymorphisms in relevant inflammatory genes, where both the gene and gene products would be measured together in conjunction with behavior. Such a strategy would also be recommended for treatment trials where, for example, levels of prostaglandins E2 would be measured before and after treatment with a COX-2 inhibitor, to establish proximal endpoints of subsequent behavioral outcomes. Such pathway assessments would add considerable validity to the results of clinical trials; it can be established whether a given inflammatory biomarker was present prior to therapy, whether the inflammatory biomarker was successfully altered by treatment, or whether the change in the biomarker was associated with clinical improvement. These data can be used for standardizing clinical algorithms for using immune-based therapies in subsequent research studies and in the clinic.

Hypothesis Generation

Given the need to generate new knowledge regarding pathways and molecules involved in the effects of the immune system on the brain and behavior, it was considered essential to explore approaches that would be classified as hypothesis generating. There has been an explosion in techniques that fall into this category including proteomics, metabolomics, microarray assessments, genomics (especially genome-wide scans), and cytokine multiplex assays. Although potentially an exciting opportunity to generate new knowledge, in many instances, the amount of data generated is massive and belies integration into more focused hypotheses. In addition, requisite analytic strategies are highly complex, and often require additional expertise in bioinformatics. These limitations warrant an approach that includes large samples of well-characterized patients. Indeed, hypothesis generation may be most successful if combined with the recommendations noted above for standardized assessments such that patients with known activation of inflammatory responses can be evaluated in relation to the behavioral disorder of interest.

Development of Novel Measurement Strategies

Novel approaches to the measurement of inflammatory biomarkers are needed to improve the efficiency and ease of testing of relevant clinical populations as well as to improve the scope of information that can be gained from clinical samples. Such techniques would include development of blood spotting approaches, measurement of inflammatory markers in sweat or saliva, and the use of in vitro challenge strategies to reveal altered inflammatory pathway function that might otherwise appear within normal limits without perturbation. In addition, sampling and biomarker characterization of other bodily compartments including cerebrospinal fluid (CSF), joint spaces and amniotic fluid would be of relevance. Given that inflammatory processes are transmitted to the CNS, further development of strategies to

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measure inflammatory biomarkers in the CSF is of primary importance and should include the strategies noted above.

Biomarkers of brain inflammation

Our understanding of the role of systemic inflammation and its impact on brain function in health and disease would be considerably advanced if we could monitor or view the signaling pathways within the living brain. There have been significant advances in imaging techniques during the past ten years and there were presentations and discussion as to how these techniques might be used to address this problem. A variety of imaging techniques have enabled inflammation in the brain, which is associated with various pathologies, to be viewed in real time. However, whether these approaches can be used to view signaling pathways in the brain associated with peripheral inflammation is not known.

Magnetic resonance imaging (MRI) has played a major part in the diagnosis, monitoring and research into multiple sclerosis (MS), the most common inflammatory disease of the central nervous system. In this disease, inflammation in the brain is viewed as a consequence of either tissue damage per se or damage to the blood brain barrier (BBB) revealed as gadolinium enhancing lesions (McFarland et al., 2002). Brain biochemistry in inflammatory disease can also be studied using magnetic resonance spectroscopy (MRS), but this is only applicable to the study of molecules that are present at a sufficiently high concentration in the parenchyma. For example, the reduction in N-acetyl aspartate levels in white matter was one of the first indicators that inflammation in the MS brain leads to axon degeneration rather than just demyelination. However, except in conditions of severe systemic inflammation, signaling of systemic inflammation to the healthy brain does not involve breakdown of the BBB, does not involve structural damage, and furthermore does not likely involve molecular signaling pathways that can be detected by MRS.

It is important to highlight the distinction between signaling by molecules typically associated with inflammation and an inflammatory response per se. In other words, it is inappropriate to describe the activation of these signaling pathways as “inflammation.” During systemic inflammation there is induction of IL-1β and other proinflammatory cytokines, with synthesis of these markers in the brain including cells of the mononuclear phagocyte lineage, perivascular macrophages and microglia. But, there is no inflammatory response in the brain (Galea et al., 2007). These cytokines are a component of the communication pathway within the brain. It is of interest that microinjection of IL-1β into the brain at concentrations that would typically give rise to inflammation in peripheral tissues, or even at supraphysiological concentrations, does not lead to typical inflammation within the brain parenchyma (Anthony et al., 1997). This simple observation indicates that the biological significance of IL-1β in the brain parenchyma is different from that in other tissues and, hence, its presence should not necessarily be interpreted as evidence of an inflammatory response. If cytokines are expressed in the brain as signaling molecules we can consider whether there are secondary changes in the brain that might be indicative of the presence of these molecules and/or whether these changes be detected by imaging techniques *in vivo*. One possible candidate would be a change in the phenotype of the microglia.

High resolution autoradiography studies have shown that activated but not resting microglia and macrophages will bind PK11195, a ligand for the peripheral benzodiazapine receptor (PBR) (Banati, 2002; Banati et al., 1997). Activated microglia are typically distinguished from resting microglia by a change in morphology relative to the resting state and the upregulation or de novo synthesis of various cytoplasmic or cell surface antigens such as CD68 and MHC Class II. Using carbon-11 labelled PK11195, microglia can be imaged by positron emission tomography (PET) in patients with diverse brain pathologies including stroke, multiple

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sclerosis and Alzheimer's disease (Banati, 2002). David Brooks (Hammersmith, UK) described how microglial activation in multiple sclerosis, as detected by upregulation of the PBR, is more widespread than might have been presumed from structural MRI studies of gadolinium enhancing lesions. Brooks pointed out that beyond the presence of activated microglia, it is not altogether clear what is indicated by increased expression of PBR. It is known that microglia in MS plaques have a phenotype typical of a proinflammatory macrophage whereas those in white mater tracts have the phenotype of alternatively activated macrophages. (Boven et al., 2006) Yet, both are revealed by PK11195 imaging. It is not known how PBR expression relates to the many potential phenotypes that microglia can express and it is not known if PBR expression changes when the cells switch their phenotype (Perry et al., 2007). PET imaging with PK11195 has not been used to study the impact of systemic inflammation on the brain or in disease states associated with a change in functional state such as in psychiatric disorders. Limitations in sensitivity and potential lack of phenotypic specificity indicate that there is a need for new ligands that might reveal phenotypic changes in microglia.

If changes in the phenotype of microglia are likely limited in sensitivity, there was discussion as to whether there are other populations of cells in the brain that would be sensitive to systemic inflammation and offer a target for differential labeling in imaging modalities; endothelial cells of the cerebral vasculature are an obvious potential target. It is known that the cerebral endothelium expresses molecules that are necessary for leukocyte adhesion and migration into the brain, and that expression of these molecules is upregulated by systemic inflammation such as that following systemic endotoxin challenge (Bell and Perry, 1995). One approach that has been used to image adhesion molecule expression such as E-selectin on the cerebral endothelium is to conjugate the ligand for E-selectin sLeX to a contrast agent such as gadolinium so that the conjugated and bound ligand (Gd-DTPA-B(sLeX)A) can be detected by MRI (Sibson et al., 2004). There have been a number of MR studies using different ligands and contrast agents, which have provided an imaging assessment of activation of the endothelium during systemic inflammation (Boutry et al., 2006; Reynolds et al., 2006). At the present time we have little idea of the sensitivity of this approach but this will depend on the affinity and avidity of the ligand-receptor interaction, the nature of the contrast agent coupled to the ligand, and the extent to which unbound ligand-contrast agent constructs are removed from the circulation. It is of note that murine cerebral endothelial expression of these adhesion molecules is induced by very low doses of endotoxin (Teeling et al., 2007).

One weakness of imaging the cerebral endothelium during systemic inflammation is that it does not inform as to whether the signal has been transduced at the BBB to generate a signal within the brain parenchyma. An interesting approach was described by Daniel Anthony (Oxford, UK) who has been investigating how neurochemically induced blood-oxygenation-level-dependent (BOLD) contrast functional magnetic resonance imaging (fMRI) signals are acutely modified by systemic inflammation. At present however, we have little idea as to how sensitive this approach will be for monitoring signaling in the brain induced by different types or severity of systemic inflammation. Although we have the necessary tools to image inflammation in the brain it seems that we do not have sufficiently sensitive tools to image signaling in the brain consequent to a systemic inflammatory response. Increases in sensitivity will require new ligands for both PET and MRI modes.

One possible route to studying the impact of systemic inflammation on signaling processes in the brain is to take note of observations indicating that systemic infections alter the speed of processing as indicated by changes in reaction times but not task accuracy (Smith et al., 1998). A battery of different cognitive tasks has demonstrated that reaction times are significantly slowed in persons with naturally occurring upper respiratory infections. Electrical activity in the brain can be readily monitored by electroencephalograhy (EEG) and

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developments in magnetoencephalography (MEG) also offer opportunities for monitoring spatial and temporal electrical activity in brain. These techniques have yet to be applied to investigations into communication between systemic inflammation and the brain. They could make use of the progress in knowledge of the way bodily sensations are perceived and represented in the brain. According to Bud Craig (Phoenix, Arizona), there is a specific neuroanatomical basis for awareness of interoceptive feelings of the body. Humans have a distinct cortical image of homeostatic afferent activity that reflects the physiological condition of the body (Craig, 2003). Cognitive representations of interoceptive sensations takes place in the right anterior insular cortex and form the basis for emotional awareness (Craig, 2004; Critchley et al., 2004). In a typical experiment, brain activity was measured using fMRI and voxel-based morphometry during a heartbeat perception task. The activity and size of right anterior insular cortex activation were related to the subject's accuracy in sensing heartbeat timing (Critchley et al., 2004). This is consistent with the James-Lange theory of emotion and Damasio's somatic marker hypothesis (Damasio, 1993; Domasio, 1993; James, 1884). The processing of interoceptive sensation would be lateralized, with a predominance of the left forebrain when the parasympathetic nervous system is activated (e.g., positive affect) and the right forebrain when the sympathetic nervous system is activated (e.g., negative affect) (Craig, 2005). According to this view, awareness of sickness behavior should be associated with an activation of the right anterior insular cortex.

Relevance of animal models of inflammation-induced depression

Preclinical studies represent a necessary step for identification of new drug targets in the chain of events that link inflammation to symptoms. In the case of depression, however, this can only be done if inflammation is first shown to be able to induce depressive-like behavior. Such an approach is based on the assumption that animal models of depression are relevant to our understanding of the pathophysiology of depression. Michel Hamon (Paris, France) addressed this issue. He pointed out from the start that it is hard to envision an animal model that duplicates all the human symptoms of depression. Part of the problem is that depression is a heterogeneous condition with quite variable symptoms, such as reduced or increased food intake; psychomotor retardation or agitation; hyposomnia or hypersomnia. It is therefore obvious that a single animal model cannot mimic all these opposing symptoms. Secondly, depression is a comorbid disease and frequently occurs in combination with other conditions such as pain, anxiety and abuse of alcohol and drugs. Despite these limitations, several acute animal models of depression have been developed, which have proven empirically useful for preclinical screening of potentially active antidepressant drugs. For example, this is the case with the forced swim test (FST) and tail suspension test (TST). However, in order for animal models to be made more relevant to depression, the following conditions should be advanced: (a) behavioral alterations in the animal model must closely resemble the human disorder, (b) the causative factors must be closely related in the human disorder and the animal model, and (c) treatments that reduce symptoms in the human disorder must also relieve behavioral changes in the animal model. Exposure of rodents to chronic mild stressors, repeated inescapable electric shocks or social defeat are currently the most heuristic animal models of depression. Their relevance to clinical depression can be further improved by making use of genetically modified animals so as to mimic possible vulnerability factors (e.g., serotonin transporter-deficient mice). It is also important to note that the ability of collecting and sectioning tissues from animal models is indispensable for developing and testing new compounds for human use. Indeed, it was the development of animal models of sickness behavior that led to the idea that depression and inflammation might be related in a causal way.

Raz Yirmiya (Jerusalem, Israel) used the chronic mild stress (CMS) depression model to investigate the role of IL-1 in chronic stress-induced depression. Depressive symptoms such as reduced social exploration and sucrose consumption were observed in mice subjected to 5

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weeks of CMS, as well as increased IL-1β levels in the hippocampus concurrently with pituitary-adrenal axis activation and reduced hippocampal neurogenesis. In contrast, IL-1 receptor type 1 knockout (IL-1rKO) mice or mice with transgenic over-expression of brain IL-1ra did not exhibit any depressive-like effects of CMS (Goshen et al., 2007). In addition, these behavioral and neuroendocrine effects of CMS could be mimicked in naïve mice by administering IL-1β via osmotic minipumps for 4 weeks. These results demonstrate that elevated levels of IL-1 in the brain, present in many inflammatory conditions, can produce depression associated with these conditions. Therefore, therapeutic procedures aimed at reducing IL-1 levels in the brain may have potent antidepressive activity.

Nathalie Castanon (Bordeaux, France) presented evidence in favor of a role of activation of the tryptophan degrading enzyme indoleamine 2,3 dioxygenase (IDO) in the pathophysiology of depressive-like behavior in mice using two mouse models of acute (lipopolysaccharide, LPS) and chronic (Bacillus Calmette-Guerin: BCG, an attenuated form of *Mycobacterium bovis* and a potent inducer of IFNγ) immune stimulation. Both models resulted in elevated brain proinflammatory cytokines and increased activity of IDO (Lestage et al., 2002; Moreau et al., 2005) coincident with development of depressive-like behavior, as revealed by enhanced duration of immobility in the FST and TST and reduced sucrose consumption. Preliminary evidence indicates that blockade of IDO activity abrogates cytokine-induced depressive-like behavior. Jonathan Godbout (Columbus, Ohio) showed that the inflammatory component of aging that propagates the brain makes aged mice more sensitive to LPS-induced depressive-like behavior, probably as a consequence of the prolonged activation of IDO in response to inflammation.

Based on this accumulating body of evidence, there is little doubt that preclinical investigation using animal models of depression will increase our understanding of how activation of immune-to-brain communication pathways modulates behavior and mood. In accordance with the already cited clinical literature, administration of a single dose of the TNFα antagonist etanercept was sufficient to restore responding for rewarding electrical brain self stimulation that was attenuated in a rat model of congestive heart failure (Grippo et al., 2003).

Identification of possible targets for intervention

In the last two decades, the resurgence of interest in the molecular basis of inflammation, and its points of control, has fueled an intense research effort for the development of new anti-inflammatory drugs. Although this movement has not yet penetrated the field of inflammation-associated subjective health complaints, the potential of research and development is certainly worthwhile. Abandoning this opportunity to the many unfulfilled promises of over-the-counter drugs and the vagaries of alternative and complementary medicine would be unfortunate.

Andrew Miller (Atlanta, Georgia) reviewed the possible targets for intervention in the chain of events linking inflammation and depression. The production and action of proinflammatory cytokines represent the most obvious target since they are at the beginning of the chain. Modulation of cytokine production and action can be achieved by administration of cytokine synthesis inhibitors, anti-inflammatory cytokines and soluble receptors. Proinflammatory cytokines often act in synergy, via activation of common intracellular signaling pathways involving either MAP kinases, MyD88 or NFκB. MAP kinases and NFκB represent interesting targets since their activation mediates not only the induction of effector genes in the action of proinflammatory cytokines on their cell targets but also the synthesis of proinflammatory cytokines by themselves. In particular, binding of pathogen-associated molecular patterns to Toll-like receptors activates the synthesis of proinflammatory cytokines such as IL-1 and TNFα in a NFκB dependent manner. Binding of IL-1 and TNFα to their cogent receptors activates the NFκB signaling pathway, which mediates for instance the anti-apoptotic effect

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of TNFα and the transcription of IL-1 inducible genes such as cyclo-oxygenase 2 that is responsible for the synthesis of prostaglandins E2. Michael May (Philadelphia, Pennsylvania) reported on the ability to specifically block the activation of this pathway upstream of NFκB activation, at the level of the IκB-kinase complex, using an inhibitor of the regulatory protein NEMO (NFκB essential modifier) coupled to a cell permeable peptide (May et al., 2000). Such blockade abrogates inflammation in various in vivo animal models, including cytokine-induced sickness behavior (Nadjar et al., 2005). Activation of stress-activated protein/mitogen-activated protein kinase (SAPK/MAPK) pathways also plays an important role in inflammation. As pointed out by Charles Malemud (Cleveland, Ohio), inhibitors of MAP kinases have potent anti-inflammatory activity and several of them are under Phase I clinical trials (Malemud, 2007). A target of choice could be the c-Jun N-terminal kinase (JNK) since inhibition of JNK by a cell penetrating peptide that blocks TNFα-induced IGF-I resistance (Strle et al., 2006) protects against excitotoxicity and cerebral ischemia (Borsello et al., 2003) and abrogates TNFα-induced sickness behavior (Palin et al., 2007). However, even if blockade of SAPK/MAPK signaling pathway helps to ameliorate inflammation, this does not necessarily imply that it will abrogate inflammation-associated depression. Indeed, there is evidence that acute inhibition of an upstream kinase in this pathway, MAPK kinase (MEK), actually produces depressive-like behavior and blocks the effects of several conventional antidepressants (Duman et al., 2007).

Several cytokine antagonists are already in clinical use or under advanced development stages, including the IL-1 receptor antagonist (Anakinra), several TNF-α blockers (including etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira)), and the anti-inflammatory cytokine IL-10. Indeed, during the last few years, preliminary clinical studies pointed to the potential of this approach. For example, 618 patients with moderate to severe psoriasis who were treated with etanercept for 12 weeks displayed a marked improvement in depression scores independently of any ameliorating effect of the treatment on skin condition and joint pain (Tyring et al., 2006). In a study of the tolerability of high dose chemotherapy in cancer patients, etanercept was found to significantly decrease the incidence of asthenia and fatigue while at the same time preserving the maintenance of dose intensive chemotherapy (Monk et al., 2006). However, increased sensitivity to infections could represent a serious side effect of any treatment targeting the antagonism of proinflammatory cytokines.

Proinflammatory cytokines induce the production of several downstream inflammatory mediators, such as prostaglandins and nitric oxide, which could constitute appropriate targets for antidepressant medication. Indeed, a recent prospective, double-blind study demonstrated that administration of the non-steroidal anti-inflammatory drug celecoxib, a specific inhibitor of Cox-2, significantly improved the therapeutic efficacy of the conventional antidepressant drug reboxetine in patients with major depression (Muller et al., 2006). Another secondary process that has been implicated in inflammation-associated depression is tryptophan depletion, as a consequence of activation of IDO (Capuron and Dantzer, 2003). It is still unknown whether activation of IDO leads to depression because of the reduction in serotonergic neurotransmission that results from tryptophan depletion or because of an increased production of kynurenine, which in microglia can be converted to the neurotoxic compound quinolinic acid (Schwarcz, 2004). The possibilities of modulating kynurenine actions in the brain were discussed by Robert Schwarcz (Baltimore, Maryland). Specific inhibitors of IDO, as well as some recently discovered modulators of kynurinergic pathways (Schwarcz, 2004), may represent interesting strategies for treating inflammation-associated depression.

Proinflammatory cytokines and other inflammatory mediators are produced by accessory immune cells, such as macrophages and monocytes in the periphery and microglia within the central nervous system. As pointed out in the previous section, targeting cell trafficking into

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the central nervous system is unlikely to be a very useful approach since symptoms of sickness and depression are dependent on the activation of brain cytokine signaling independently of any blood cell recruitment. However, it is possible to decrease the production of brain proinflammatory cytokines by down-regulating brain macrophage-like cells and microglia. This can be achieved by using the tetracycline derivative minocycline (e.g., (Fan et al., 2007)) or by blockers of NADPH oxidase activation, although this last mechanism is predominantly implicated in the damaging effects of microglia on neurons, as demonstrated by Michelle Block (Research Triangle Park, North Carolina) (Block et al., 2007). Microglial activation that takes place during inflammation induced-neuronal death is a two-edge sword. Its inhibition is beneficial early in the process but deleterious later. Whether the same balance between injury and repair applies to functional rather than structural alterations in neurons as a consequence of microglial activation is still unknown. Another strategy that applies to inflammatory processes both at the periphery and in the brain is to dampen cytokine production by enhancing cholinergic neurotransmission (Pollak et al., 2005; Tracey, 2007).

Instead of simply applying to the field of inflammation and depression therapeutic strategies already developed for more traditional inflammatory disorders, it might be useful to define specific steps for the rational design of new therapies. These steps are as follows:

1. Identify possible candidates in the form of inflammatory-related processes or molecules that are altered in the brains (post-mortem), CSF or blood of depressed patients (begin by examining patients with clear indication of inflammation-induced depression, and then assess other populations of clinically-depressed patients).
2. Find similar inflammatory-related processes or molecules in animal models of depression.
3. Assess the effects of conventional antidepressants (e.g., tricyclic antidepressants or selective serotonin reuptake inhibitors) on these process or molecules.
4. Study the effects of specific inhibitors of these processes or molecules in animal models of depression.
5. Examine the effects of these inhibitors in clinical trials – first in populations of depressed patients in which inflammation is likely to play an important role, such as IFN-α treated patients and patients with autoimmune disorders, and then with other depressed patient populations, such as treatment-resistant depression.

In the intervention studies defined in steps 4 and 5, it is important to measure markers of the inflammatory processes that are supposed to be modulated, that is, confirm that there are basal changes in this processes in the treated population (either in an animal model or in depressed patients) and verify that the treatment is indeed having the expected effect on these processes.

Most current anti-inflammatory compounds target peripheral immune processes, whereas depressive symptoms are obviously generated within the brain. Nevertheless, novel anti-inflammatory antidepressants may work even if their effects are restricted to the periphery, for the following reasons. If the source of the depressive condition is peripheral (e.g., following acute or chronic peripheral infection, surgery, trauma, myocardial infarction), the rationale for using a peripherally active drug is obvious. This is particularly important since peripheral infections can also sensitize or exaggerate existing brain inflammatory processes (Perry et al., 2007). Furthermore, there is evidence that even subclinical daily fluctuations in immune activation can elicit depressive symptoms (Reichenberg et al., 2001). Finally, although in most depressive conditions there is no obvious source of peripheral (or central) immune stimulation, the levels of peripheral inflammatory markers can be elevated in many patients (Raison et al., 2006). Whatever their cause, elevated cytokine levels in blood have the potential to reverberate and activate central inflammatory systems. Therefore, while future studies should focus on

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development of centrally active anti-inflammatory drugs, the more widely available peripheral anti-inflammatory treatments could still be beneficial for alleviating inflammation-associated depression.

In conclusion, mounting evidence for the involvement of inflammatory processes in depression indicates that various anti-inflammatory approaches could be beneficial for patients with several forms of depression. Thus, in parallel to basic research aimed at elucidating the mechanisms of inflammation-associated depression, clinical studies should be carried out to examine novel approaches for treatment of symptoms of depression.

Conclusions

The intense discussion that accompanied experts' presentations at the meeting resulted in the generation of a series of recommendations for improving our understanding of the relationship between inflammation and subjective health complaints and the development of appropriate treatments. These recommendations are as follows:

1. Because inflammation-associated sickness symptoms and depression are a major impediment to human health that encompasses various medical conditions, research on the mechanisms and treatment of such symptom burden in physically ill patients should be strongly encouraged.
2. Clinical tools for assessing inflammation-associated symptoms should be standardized and made available to the clinical research community in the form of a tool box. Appropriate monitoring techniques should be developed for assessing short-term fluctuations in symptoms.
3. Markers of peripheral inflammation should be assessed in a standardized manner so as to allow comparison between studies. The minimum set of inflammatory biomarkers should include acute phase proteins (C-reactive protein, sialic acid and haptoglobin), IL-6, and inflammatory mediators (prostaglandins E2 and C3A). When necessary, this basic set can be accrued by markers for pathways of interest and implementation of novel approaches to measurement of inflammatory biomarkers. Recourse to techniques derived from genomic biology is encouraged.
4. Markers of brain inflammation are not sufficiently sensitive for being incorporated into clinical studies of the relationship between inflammation and symptoms, due to the fact that this relationship is mediated by activation of brain cytokine signaling pathways in the absence of any immune cellular invasion of the brain. However, exploration of cytokines and other markers in the cerebrospinal fluid is encouraged.
5. Brain neuroimaging techniques should be used for revealing the brain structures that are influenced by peripheral inflammatory processes and whose ability to process information is impaired by excessive amounts of interoceptive stimuli.
6. The sensitivity of animal models of depression to inflammatory mediators makes possible the investigation of pathophysiological mechanisms and treatment efficacy at the preclinical level. Such research should be highly encouraged.
7. The high prevalence of inflammation-associated symptoms in physically ill patients provides a sufficient background against which it is possible to test the possible alleviating effects of therapies targeting immune-to-brain communication pathways based on positive studies in animal models. Well-organized small clinical trials in a well-defined population of subjects with a well characterized chronic inflammatory condition should be sufficient to test the efficacy of the drug(s) of interest, providing that the actions of such drugs are investigated not only at the level of clinical endpoint

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of interest (the neurobehavioral symptoms) but also the inflammatory condition. Such small clinical Phase I trials represent the prelude to Phase III clinical trials.

8. Although not discussed at the meeting, industry-university-government partnerships are necessary to advance these endeavors.

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