Immunology and multimodal system interactions in health and disease

Rainer H. Straub, Manfred Schedlowski and the Steering Committee of GEBIN

The 7th Conference of the Volkswagen Foundation and 2nd Conference of the German Brain Immune Network (GEBIN) on Psycho–Neuro–Endocrino Immunology was held in Regensburg, Germany from 15–17 November 2001.

This symposium provided an update of the research achievements in the field of psycho–neuro–endocrine immune interactions that have been made during the past decade in Germany.

Neuroimmunology in the central nervous system

In experimental autoimmune encephalomyelitis (EAE), different disease stages are characterized by the altered production of cytokines by splenocytes and peritoneal macrophages, but the adrenergic modulation of peripheral cytokine production is not different in rats with EAE compared with control rats (K. Haerter, Essen, Germany). Patients with multiple sclerosis with fatigue have a hyperreactive hypothalamus–pituitary–adrenal axis compared with those without fatigue (M. Gottschalk, Munich, Germany). In stiff-man syndrome, patients have defective GABAergic intrinsic inhibition in the motor cortex, which is correlated with elevated levels of antibodies specific for glutamic acid decarboxylase (GAD), suggesting that autoimmunity against GAD plays a causative role in the disease (C. Körner, Heidelberg, Germany). E. Weihe (Marburg, Germany) presented a hypothesis that AIDS dementia might be caused by neurochemical alterations that are reversible initially but become imprinted and resistant to antiretroviral treatments at some point during the course of the disease.

Neuroimmune–endocrine network in psychiatric disease

Patterns of immunity in patients with major depression and schizophrenia vary greatly because patients are psychiatrically heterogeneous. For example, melancholic and nonmelancholic patients have different immune patterns (V. Arolt, Münster, Germany). In families at risk of schizophrenia, polymorphism analyses of the genes encoding transporter for antigen processing (TAP) and low molecular-weight protein (LMP), which are involved in the processing of MHC-class-I-restricted peptides, demonstrated alterations in the gene encoding TAP1 compared with normal individuals. This might lead to the selective transport and presentation of antigens. Individuals with the *TAP1*A1–TAP1*B1* genotype have a tenfold greater risk of developing schizophrenia than the general population, whereas individuals with the *TAP1*A1–TAP1*B4* genotype are 9.8 times less likely to develop schizophrenia (B. Fellerhoff, Munich, Germany). Other MHC loci were typed and excluded, indicating that there is a primary association between schizophrenia and TAP1.

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A neuroinflammatory model of Alzheimer's disease was presented in which the microglial synthesis of interleukin-1β (IL-1β) is followed by the neuronal activation of p38 mitogen-activated protein kinase and NF-κB, and overexpression of cyclooxygenase-2 (M. Hüll, Freiburg, Germany). The expression of IL-6, a neuropoietin, is thought to play an important role in this disease. The level of IL-6 is increased in the rat hippocampus during long-term potentiation (LTP) of synaptic transmission, a process considered to underlie learning and memory. Blockade of the action of IL-6 caused a remarkable prolongation of LTP, which might alter learning and memory (H.O. Besedovsky, Marburg, Germany).

Anorexia nervosa is characterized by extreme weight loss and alterations in the neuroendocrine–immune system. In anorexic patients at the time of hospital admission, an increased expression of tumor necrosis factor (TNF) and IL-6 mRNA was found in peripheral-blood mononuclear cells (PBMCs) (K.G. Kahl, Würzburg, Germany).

In a subgroup of schizophrenic patients, a switch from T helper 1 (Th1) to Th2 predominance has been observed. The cyclooxygenase-2 inhibitor celecoxib, which induces a Th2 to Th1 switch, plus an antipsychotic (risperidone) gave a faster reduction of psychotic symptoms than risperidone alone (M.J. Schwarz, Munich, Germany). In psychiatric patients, treatment with the antipsychotic clozapine increased serum levels of TNF. In rats, clozapine reduced wakefulness, increased the proportion of non-rapid eye movement (NREM) sleep, prolonged NREM episodes and elevated levels of TNF in the frontal cortex (S. Sorge, Munich, Germany).

Peripheral neuroimmune interactions

Efferent nerve fibers reach almost every site in our body to communicate with cells distant from the central nervous system (CNS) by the transmission of neurotransmitters. These transmitters include small molecules, such as catecholamines, as well as neuropeptides.

Neurotransmitters affect immune cells

Norepinephrine (NE) affects naive T cells by promoting their differentiation to Th1 cells, which secrete interferon γ. The signaling pathways of NE and IL-12 are linked; thus, NE enhances the IL-12-mediated differentiation of naive $CD4^+$ T cells into Th1 cells (V.M. Sanders, Chicago, IL, USA). Strong induction of transcription of the gene encoding μ opioid receptor was observed in B cells, monocytes and endothelial cells after stimulation with either IL-4 (through STAT6) or TNF (through NF-κB) (J. Kraus, Magdeburg, Germany).

G-protein-coupled receptor kinases (GRKs) regulate the desensitization of G-protein-coupled receptors. During inflammatory disease, the expression of GRK-2, GRK-3 and GRK-6 in splenocytes

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and mesenteric lymph nodes is decreased, which is an important mechanism for the local regulation of neurotransmitter–immune-cell interactions (C.J. Heijnen, Utrecht, The Netherlands).

Catecholamines induce apoptosis
NE induces apoptosis of the lymphocytes of lpr/lpr mice, in which a profound decrease in the splenic level of NE, reduction in the number of sympathetic nerves and inverse correlation between the levels of serum IgM and splenic NE were observed (A. Del Rey, Marburg, Germany). In normal rats, α-adrenergic treatment with implantable tablets leads to enhanced lymphocyte apoptosis in lymphoid organs (R. Stevenson, Graz, Austria). Catecholamine-induced B-cell apoptosis is reduced in rheumatoid arthritis (RA) patients (M. Wahle, Leipzig, Germany).

Role of neuropeptides in disease
Bone-marrow-derived dendritic cells (BMDCs) were treated with α melanocyte-stimulating hormone (α-MSH) and/or hapten [dinitrobenzene sulphonic acid (DNBS)], then injected intravenously into naive mice. Five days later, mice were challenged with hapten and the extent of ear swelling was measured. After rechallenge, mice treated with DNBS-pulsed BMDCs developed more ear swelling than mice injected with BMDCs exposed to α-MSH plus DNBS, indicating that tolerance had developed in these mice (T. Brzoska, Münster, Germany).

'Blockade of the action of IL-6 caused a remarkable prolongation of LTP, which might alter learning and memory.'

Chronic asthma is accompanied by allergic inflammation; it is suggested that nerve growth factor (NGF) produced by invading immune cells might be responsible for this response. Blocking the NGF receptor p75 decreased allergic inflammation and the influx of eosinophils into the airways (S. Kerzel, Marburg, Germany).

Neuroendocrinology and immune function
The activation of the CNS by peripheral immune stimuli is a matter of debate, because of the presence of the dense blood–brain barrier (BBB). Several newly discovered mechanisms allow signal transduction from the periphery to the CNS.

Immunological activation of the central neuroendocrine system
S.M. McCann (Baton Rouge, LA, USA) gave an overview of the modulation of secretion of hypothalamic releasing hormone by cytokines, with particular emphasis on nitric oxide (NO). NO activates guanylate-cyclase-liberating cyclic guanosine monophosphate, cyclooxygenase and lipoxygenase, resulting in the liberation of prostaglandin E_2 and leukotrienes.

Activated microglia are an endogenous source of oncostatin M (OSM) in the CNS, and OSM interacts with the endothelium of the BBB, signaling through gp130 and the OSM receptor β. Similarly, OSM produced by PBMCs can influence the BBB from the extracerebral side to activate the central neuroendocrine system (K. Ruprecht, Würzburg, Germany). Cutaneous nerves participate in the transfer of proinflammatory immune signals to the brain (E. Zeisberger, Giessen, Germany). The direct stimulation of pituitary folliculostellate (FS) cells appears to be mediated by functionally active Toll-like receptor 4 (TLR4), TLR9 and CD14; lipopolysaccharide stimulates the secretion of IL-6 by FS pituitary cells (U. Renner, Munich, Germany).

Stress, behavior and immune function
It has become obvious that stress can influence the immune system. The pathways between the CNS and peripheral immune cells that are involved in this regulation are under intense investigation.

Stress influences immune function
Many stressful events during fetal life and early infancy affect the development of immune responses in animals. The proliferation of lymphocytes is extremely sensitive to prenatal stress. Animals that were stressed in prenatal life are more susceptible to opportunistic bacterial infection and allergic airway disease than nonstressed controls (C.L. Coe, Madison, WI, USA).

'Chronic asthma is accompanied by allergic inflammation;…nerve growth factor…might be responsible for this response.'

In a natural killer (NK)-cell-dependent tumor model of metastasis, confrontation-stressed animals had a tenfold increase in lung tumor load compared with undisturbed controls (L. Dawils, Bayreuth, Germany). Stress with ultrasonic sound increased murine allergen-induced airway inflammation and bronchoalveolar eosinophil efflux, which could be inhibited by blocking the substance P receptor (NK1) (R. Joachim, Berlin, Germany).

Dysregulation of the adrenergic stress system is suggested to affect disease activity in RA. Infusion of adrenaline increased NK-cell cytotoxic activity and the number of IL-8- and IL-10-producing

Key outcomes of the meeting

- In AIDS patients, neurochemical alterations become imprinted and resistant to antiretroviral treatments at some point during the course of the disease.
- The *TAP1*A1–TAP1*B1* genotype is associated with a tenfold elevated risk of schizophrenia.
- The selective cyclooxygenase-2 inhibitor celecoxib supports classical antipsychotic therapy for schizophrenia.
- IL-4 induces transcription of the gene encoding μ opioid receptor in immune cells.
- Inflammation alters neurotransmitter signaling through the decreased expression of G-protein-coupled receptor kinases.
- The role of norepinephrine as a stimulator of immune-cell apoptosis has become clearer, and this effect might be altered in inflammatory disease.
- Functional toll-like receptors are present not only on immune cells but also, cells of the endocrine system.
- In clinical disease models, stress induces an increase in opportunistic bacterial infections, tumor metastasis and allergic airway disease.
- There has been some suggestion that Pavlovian conditioning of immune functions is possible in human subjects.

monocytes (J. Kittner, Hannover, Germany) and decreased the level of serum cortisol in patients with RA, but not in healthy subjects (R.H. Straub, Regensburg, Germany).

In a vaccination study using inactivated hepatitis A virus (HAV), subjects who had regular sleep following vaccination had a nearly twofold higher anti-HAV antibody titer after four weeks than subjects who stayed awake on the first night after vaccination (T. Lange, Lübeck, Germany).

Conditioned immunomodulation

Pavlovian conditioning of immune functions provided early impetus to the idea of bidirectional communication between the immune, endocrine and central nervous systems. Using cyclosporin A as an unconditioned stimulus and a novel beverage as the conditioned stimulus, it was demonstrated that re-exposure to the novel beverage alone induced the suppression of lymphocyte proliferation, and IL-2 production and mRNA expression by PBMCs, which was similar to cyclosporin-A-induced immunosuppression (M. Goebel, Essen, Germany).

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Dichotomy of glucocorticoid action in the immune system

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The 40th International Workshop of the Ernst Schering Research Foundation, focusing on Recent Advances in Glucocorticoid Action, was held in Berlin, Germany from 31 October to 2 November 2001.

It has been known since 1948 that hydrocortisone (cortisol), the principal glucocorticoid (GC) produced by the human adrenal cortex, has potent anti-inflammatory and immunosuppressive effects when administered pharmacologically. Today, GCs are standard therapy for disorders such as rheumatoid arthritis, asthma, connective tissue diseases, vasculitis, allergic reactions, inflammatory bowel disease, psoriasis and eczema. However, when administered over a prolonged period of time, their beneficial effects are overshadowed by a number of side-effects, including osteoporosis, skin atrophy and diabetes. Therefore, attempts are being made to separate their beneficial effects from the undesired effects.

From a clinical point of view, one way of reducing side-effects is the use of better devices to avoid over-treatment. Immunomonitoring to determine optimal dose regimes in individual patients is of prime importance. H-D. Volk (Berlin, Germany) reported that the flow-cytometric determination of HLA-DR expression and capacity for tumor necrosis factor α (TNF-α) secretion in monocytes by whole-blood *ex vivo* assays is an easy to handle, highly predictive method. With such assays, it is possible to detect over-suppression of the immune system, which is associated with a high risk of infection. If these assays prove successful, it is conceivable that therapy might be tailored to suit individual patients. Another possibility is the use of GCs with more-selective anti-inflammatory profiles and reduced side-effects (dissociated GCs). H. Schäcke (Berlin, Germany) and G. Haegeman (Gent, Belgium) reported initial successes in generating such GCs, termed selective GC receptor agonists (SEGRAs). It is hoped that a better understanding of the molecular action of GCs, particularly in the immune system, will provide additional information that will help in the search for more effective dissociated GCs.

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Molecular action of glucocorticoids

At the molecular level, GCs act by binding to the GC receptor (GR), which upon ligand binding is transported from the cytoplasm into the nucleus to modulate the expression of specific genes. J. Cidlowski (Research Triangle Park, NC, USA) reported that a GR isoform termed GR-β, which was thought to be nonfunctional, antagonizes GR activity and might contribute to GC resistance in ulcerative colitis and leukemia. He showed that the expression of GR-β could be increased from very low levels to two–fourfold the level of the classical GR by TNF-α [1]. The GR modulates gene expression both positively (transactivation) and negatively (transrepression). In contrast to transactivation, in which the GR binds to DNA as a homodimer to induce gene expression, during transrepression, the receptor interacts directly or indirectly with transcription factors, such as AP-1 and NF-κB. These actions of GCs were

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