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Immunology and Psychiatry

From Basic Research to Therapeutic Interventions

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Preface

Although Emil Kraepelin, the founder of modern psychiatric classification, described the influence of infections on psychiatric disorders as early as 1890 in his manuscript "Ueber Psychosen nach Influenza" ("On psychoses after influenza"), he was by far not the first one to perform research in the field of psychoneuroimmunology. In 1887, the later Nobel Laureate Julius Ritter Wagner von Jauregg published a sort of ancient meta-analysis on the therapeutic influence of typhus infections on patients with psychiatric disorders. He merged data from observations in Austrian, German and Swiss asylums during typhus epidemics, showing that psychiatric symptoms improved in about half of the patients and that about one-third of them were cured after the infection had subsided. These observations served as the basis for Wagner von Jauregg's fever therapy, which was adopted in some European countries during the 1920s and 1930s. One extremely intriguing example of the effect of "immunological" research is the identification of *Treponema pallidum* as the causative agent of neurosyphilis and the discovery of Salvarsan, the first chemotherapeutic drug against *Treponema*. These findings resulted in the causative treatment of about one-third (!) of all psychiatric patients at that time. He won the Nobel Prize in 1927 for his treatment of paralysis using malaria inoculation.

After World War II and the triumphal procession of the neuroleptics in the 1950s and 1960s, research in biological psychiatry focused on neurotransmitter disturbances and their influence on psychiatric disorders. Without doubt, those neurotransmitter disturbances play a key role in disorders such as schizophrenia, major depression, autism and anxiety, but—despite huge amounts of research—the causes of the neurotransmitter changes are widely unknown. Unfortunately, the spectacular progress in psychopharmacotherapy had a negative impact on immunological research in psychiatry. In the 1980s, investigations of autoantibody titres in patients with schizophrenia were a kind of revival of immunological research in psychiatry. Only in recent years was it proven, for example, that autoantibodies directed against the NMDA receptor can cause schizophrenia (or rather a schizophrenia-like syndrome). This example highlights the extremely difficult path from a hypothesis to a proven finding in the field of immunological research in psychiatry.

The growing, fascinating and future-oriented field of psychoneuroimmunology claims to close the gap between the neurotransmitter disturbances and the underlying processes such as infections or other body/environmental processes. The immune system, consisting of an innate and adaptive part, shows an extremely high multiplicity and variability of cellular and humoral components and in addition underlies multiple influences that hinder especially clinical research with patients.

Thanks to encouraging scientific results, interest in the field of psychoneuroimmunology has grown over the last few years with regard to basic and clinical research, including therapeutic studies. The growing number of scientific groups in the field reflects this growing interest.

Therefore, the editors decided to prepare a more or less representative overview of the current activities in the field by asking internationally established scientists and junior researchers from experienced groups to contribute a chapter reflecting their current research. Practically, all scientists we addressed agreed to write a chapter.

One of the scientific platforms of psychoneuroimmunological research in the field of psychiatry is the section "Immunology in Psychiatry" of the World Psychiatric Association (WPA), which was founded in the early 1990s by Manfred Ackenheil from Germany, Oakley Rey from the USA and Costas Stefanis from Greece. Many of the contributors to this book are active members in the section, which regularly organizes workshops, symposia and lectures at WPA congresses and co-organizes many additional meetings and research activities. The editors of this book, Aye-Mu Myint (secretary of the section), Markus J. Schwarz (past secretary) and Norbert Müller (chair), therefore dedicate their contributions to the WPA section "Immunology in Psychiatry."

The editors cordially thank all authors of this book for the tremendous work they have invested and the publisher Springer for their help and support. Furthermore, we thank Richard Kostrzewa, the editor of the series, for the inspiration for this book and Karin Koelbert for her help with handling the manuscripts. We think we have succeeded in assembling a representative overview of the current state of psychoneuroimmunological research in the field of psychiatry and related topics.

Munich, Germany

Norbert Müller
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About the Editors

Norbert Müller After studies of psychology and medicine, Dr. Müller was trained in psychiatry, psychotherapy and neurology at the University Hospital of the Ludwig-Maximilians-University in Munich. He did research in the field of psychoneuroimmunology since 1983, primarily in schizophrenia, affective disorders and Tourette's syndrome. The research focused on pathophysiological aspects and on therapy with anti-inflammatory compounds. Since 2000, he is Professor of Psychiatry, at the department of Psychiatry and Psychotherapy, LMU Munich. He was president of the German Society of Biological Psychiatry and member of the executive committee and treasurer World Federation of Societies of Biological Psychiatry (WFSBP), since 2006 he was chair of the section "Immunology in Psychiatry" of the World Psychiatric Association (WPA). He won several honours and scientific awards including the Emil-Kraepelin Research Award.

Dr. Aye-Mu Myint is a Medical Doctor and obtained her Ph.D. in Neuroscience from the University of Maastricht, The Netherlands and has done Habilitation in Experimental Psychiatry at Magdeburg University, Germany. She is working as visiting scientist at Ludwig-Maximilian University Munich, Germany since 2007 as well as senior research scientist at Advanced Practical Diagnostics bvba (apDia), Belgium since 2006. She is also an honorary assistant professor at the School for Mental Health and Neuroscience from Maastricht University. In 2003, she proposed the "neurodegeneration" hypothesis explaining the neurotoxic changes induced through the involvement of immune system imbalance and imbalance of the kynurenine metabolites beyond the activity of tryptophan pathway. She is one of the leading scientists in the field of neuroscience and psychiatry, and is working on major psychiatric disorders, depression-dementia link, psychoneuroimmunology, kynurenine pathway, and related neuroendocrinology in clinical settings as well as animal and in vitro models of depression, schizophrenia, and neurodegenerative disease. She is also involved in antibodies and immunoassay developments through EU consortia. Outside the EU consortium, she has collaborations with several universities including the University of New South Wales, Australia, and the Universities of Chicago, Illinois, and John Hopkins of the United States.

Markus J. Schwarz studied Medicine in Munich from 1990 to 1996. After finishing his dissertation on autoimmune mechanisms in schizophrenia, he started his research career and received his habilitation (venia legendi) in Experimental Psychiatry in 2005. From 2004 to 2012, he was head of the laboratory section "PsychoNeuroImmunology and Therapeutic Drug Monitoring" at the Psychiatric Hospital of Munich University. Since 2012, he is head of the research group on Neurobiochemistry at the Institute for Laboratory Medicine of Munich University. His main research interests are the impact of the two main metabolism pathways of tryptophan (serotonin and kynurenine) in psychiatric disorders, immunological investigations to identify a distinct subgroup of schizophrenia with immune-related pathogenesis, basic psychoneuroimmunologic research on the crosstalk between neurotransmitter and cytokine system and role of therapeutic drug monitoring for enhancing efficacy and safety in psychopharmacotherapy. He published more than 130 research articles in international peer-reviewed journals.

Part I
Basic Science

Chapter 1
Animal Models Based on Immune Challenge: The Link to Brain Changes and Schizophrenia

Georg Juckel

Abstract Within the pathophysiology of schizophrenia, microglial cells seem to play the most important role. Early changes within the embryonal phase and neurodegenerative processes lead to activation of microglia cells, which—via the neurotoxic activities of these cells—induces a rarification of synaptic connections in frontal and temporal brain regions, i.e. reduction of the neuropil. Promising inflammational models in rodents for schizophrenia with high validity can be today used to mimic behavioral as well as neurobiological findings in patients, e.g. the well-known neurochemical alterations within the dopaminergic, glutamatergic, serotonergic, and other neurotransmitter systems. The microglial activation can also be well modelled within one of these models, i.e. the inflammational PolyI:C animal model of schizophrenia, having a time peak in late adolescence/early adulthood. The exact mechanism, by which activated microglia cells then trigger neurodegeneration, must be now investigated further on in broad detail. Thus, these animal models can be used to understand the pathophysiology of schizophrenia especially concerning the interaction of immune activation, inflammation, and neurodegeneration. Furthermore, this should lead to the development of better treatment options and of preventive interventions.

Keywords Inflammational animal models • Schizophrenia • Dopamin • Glutamate • Microglia • Neurodegeneration

Introduction

A leading hypothesis today about the pathophysiology of schizophrenia is the so-called neurodevelopmental hypothesis. Impairment of important brain developmental genes in the 2. trimenon of pregnancy leads to disturbances of the normal brain maturation with the result of neurotransmitter imbalance and dysfunction of

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the limbic system, accompanied by structural changes in the areas of hippocampus, regio entorhinalis, and the ventricular system (Juckel et al. 1994, 1996, 2003a, b; Weinberger 1995; Heinz et al. 1999; Falkai et al. 2003). This neural dysgenesis becomes clinically relevant with considerable postnatal delay. It is supposed that further brain development processes or additional pathogenic factors are likely to elicit the illness finally (Heinz and Weinberger 2000; Heinz et al. 2003). In many patients, progressive cortical volume reduction is found mainly in frontotemporal regions (gyrus cinguli, prefrontal cortex) (Mathalon et al. 2001; Cahn et al. 2002; Pantelis et al. 2003). These findings may be caused by a reduction of neuropil with relatively increased number of cells (Scherk et al. 2003).

Inflammatoric and immunological reactions are discussed as being main reasons for the impairment of brain development in the 2. trimenon. Big cohort studies have shown the result that children of mothers who suffered from, e.g., influenza in the 2. trimenon developed schizophrenic disorders more often than others (Mednick et al. 1988; Takei et al. 1996; Munk-Jørgensen and Ewald 2001; Limosin et al. 2003). Serologic evidence also points to multiple prenatal exposures to various viruses as causative factors in rise of schizophrenic births with a sevenfold increase of risk (Brown et al. 2004). This could be the reason for the activation of the immune system and immune competent cells in schizophrenia, which was often found in patients with schizophrenic disorders since years. Thus, the unspecific immune system shows clear signs of overactivation in unmedicated patients with schizophrenic disorders with an increased number of gamma/delta cells and monocytes/macrophages, and, as consequence of the activation of these cells, to an increase of interleukin 6 (Müller et al. 1997, 1998; Gaughran 2002). The specific immune system shows an imbalance of cytokines in favor to an increased activity of T-helper cells; in addition, there were changes concerning the immunglobulines, antibodies, and the complement system (Müller and Ackenheil 1998; Rothermundt et al. 2001). Interestingly, a 5-week add-on therapy with the antiinflammatory substance celecoxib, a COX-2 inhibitor, showed better clinical improvement in acute patients with schizophrenic disorders than the treatment with the atypical neuroleptic risperidone alone (Müller et al. 2002).

Activation of microglia/macrophages is a key event in the reaction of the central neuro-immune system as answer to any pathological changes (Kreutzberg 1996; Monji et al. 2009). Two post-mortem studies found activated microglia (stained by HLA-DR) in older patients with chronic schizophrenic disorders in particular in the dorsolateral prefrontal cortex (DLPFC), in the gyrus temporalis superior (GTS) and in the anterior gyrus cinguli (ACC), which are known as the main areas of schizophrenic pathophysiology (Bayer et al. 1999; Radewicz et al. 2000). Concerning astroglia, no differences were found in these two first studies. Activated microglia could be either a reaction of the brain immune system to a constant disturbance of neuroplasticity due to, e.g., the degenerative changes that are found in patient suffering from schizophrenia (increasing number of microglia cells with age) or could be stored as an early answer to any inflammatory or non-inflammatory events during pregnancy staying up to the adult age (relatively stable cell number) (Radewicz et al. 2000; Munn 2000; Rothermundt et al. 2001). Thus, activated microglia could lead to neuropil reduction with rarification of synapses, dendrites, and spines in

patients with schizophrenic disorders due to their neurotoxic properties (e.g., release of cytokines or free radicals), either in the early stage of brain development or progressively with the course of illness (Radewicz et al. 2000). Many questions concerning the role of activated microglia for schizophrenia are still unexplained. Furthermore, there is still no proof of activated microglia in vivo in patients suffering from schizophrenia. Using PK11195, a PET ligand for the peripheral benzodiazepine receptor, which is expressed in activated microglia, the Dutch working group around R. Kahn was able to find first hints that there seem to be more activated microglial cells in living patients with schizophrenia (van Berckel et al. 2008), which was replicated by Doorduin et al. (2009).

A promising animal model of the inflammatory genesis of schizophrenia is the model of the motherly influenza infection in mice (BALB/c) developed by H. Fatemi in Minneapolis (Fatemi et al. 1998a, b, 1999, 2000; Shi et al. 2003). Descendants of female mice, who were exposed to a mouse-adapted influenza virus in the middle of pregnancy and had gone through a respiratory infection, show several changes in brain morphology, physiology, and behavior after puberty (fertility) comparably to those of schizophrenic patients. Influenza infection at E9 of pregnancy in mice leads to abnormal corticogenesis, pyramidal cell atrophy, and alterations in levels of several neuroregulatory proteins, such as Reelin, and GFAP, in the exposed mouse progeny: volume reduction of neocortex and hippocampus with relatively raised cell number, pyramid cell dystrophy, wide ventricles, reduced Reelin and immune reactivity, changes from nNOS and SNAP-25, deficits in prepulse inhibition (PPI) within the acoustic startle response, in the open field test, in the novel object test and in social interactions (Fatemi et al. 1999; Shi et al. 2003; see Table 1.1).

A further promising animal model is the administration of viral mimetic polyriboinosinic–polyribocytidilic acid (PolyI:C) in vulnerable periods during pregnancy: Descendants of female mice, who were exposed to PolyI:C at day 9, show changes in brain morphology, physiology, and chemistry as well as in behavior after puberty that are partly reminiscent to changes observed in human schizophrenia (e.g., Meyer and Feldon 2010; Winter et al. 2009). Especially, the following findings were described (Meyer 2014):

– Impairments in several behavioral measurements incl. PPI, LI, startle response, sensory gating etc.
– Changes of interleukin-10 and -1 beta, and other immune reactions

Table 1.1 Similar chances of behavioral and neurobiological markers in influenza mouse model and in patients with schizophrenia (H. Fatemi)

	Brain markers			Brain structure		Brain genes				Behavior
Group	nNOS	Reelin	GFAP	Pyramidal cell atrophy	Brain atrophy	MBP	PLP	Net-nd P	HSCP70	Prepulse inhibition
Influenza mouse model										
Adulthood	↓	↓	↑	+	+	↓	↓	↑	↑	Abnormal
Schizophrenia										
Adulthood	↓	↓	↓/–	+	+	↓	↓	↑	↑	Abnormal

– Changes of GABA-A receptors in limbic areas
– Dopamine- and glutamate related pharmacological and neuroanatomical
– Disturbances
– Reduced D1 receptors in PFC and reduced hippocampal NMDA receptor
– Increased number of mesencephalic dopamine neurons in the fetal brain
– (middle/late gestation) (accompanied by specific gene changes)
– Reduction of Reelin- and parvalbumin expressing PFC neurons

Evidence has shown that the time of prenatal insult may provide distinct changes in the exposed offspring. In a recent series of experiments by Meyer et al. (2006) using the viral mimic polyribocytidilic acid (PolyI:C) at E9 (which corresponds to midpregnancy) and E17 (which corresponds to late pregnancy) there were distinct behavioral deficits, neuropathological differences, and acute cytokine responses (Meyer et al. 2006). Adult mice that were exposed on E9 displayed reduced exploratory behavior while those exposed on E17 displayed perseverative behavior (Meyer et al. 2006). At P24, mice that were exposed on E9 displayed a more pronounced reduction of Reelin immunoreactivity in hippocampus than mice exposed at E17 (Meyer et al. 2006). In contrast, mice exposed at E17 displayed an increase in apoptosis as visualized by immunoreactivity of caspase-3, a key enzyme involved in apoptosis (Rami 2003), in the dorsal dentate gyrus (Meyer et al. 2006). Finally, Meyer et al. (2006) found that late gestational immune challenge uniquely stimulated increased IL-10 and TNF-α in fetal brain (Meyer et al. 2006). Taken together, these results provide evidence that the time of prenatal insult results in important differences that are persistent through adulthood.

Neurochemical Findings in the Influenza and PolyI:C Models

Since neurochemical alterations such as in the dopaminergic, glutamatergic, or serotonergic system are highly characteristic for the neurobiology of schizophrenia, some of such findings in the animal models should be reported here in greater detail. The efficacy of dopamine D2 receptor blocking drugs in the treatment of schizophrenia, as well as SPECT studies on neuroleptic naïve patients, suggests that dopamine hyperfunction in the ventral striatum and dopamine hypofunction in the prefrontal cortex may be responsible for the positive symptomology of schizophrenia (Abi-Dargham et al. 2000; Abi-Dargham 2002). Additionally, electrophysiological studies have suggested increased serotonergic function in schizophrenia (Juckel et al. 2003a, b, 2008).

As mentioned above, viral infection causes deleterious effects on brain structure and function in mouse offspring following late first trimester (E9) and late second trimester (E18) administration of influenza virus. Neurochemical analysis following infection on E18 using this model has revealed significantly altered levels of serotonin, 5-hydroxyindoleacetic acid, taurine, but not dopamine. In order to monitor these different patterns of monoamine expression in exposed offspring in more detail and to see if there are changes in the dopamine system at another time point,