

CYTOKINES, STRESS, AND DEPRESSION

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PREFACE

Cytokines had been characterized in the early eighties as communication molecules between immune cells, and between immunocytes and other peripheral cells, such as fibroblasts and endothelial cells. They play a key role in the regulation of the immune response and the coordination of the host response to infection. Based on these biological properties, nobody would have predicted that one decade later cytokines would burst upon neurosciences and permeate into several avenues of current research.

In neurology, the connection between cytokines and inflammation, and the demonstration of a pivotal role of some of these molecules in cell death by apoptosis, prompted the investigation of their involvement in several neurological diseases involving an inflammatory component, including multiple sclerosis, brain trauma, stroke, and Alzheimer's disease. This movement started in the late eighties, and the corresponding field of research, known as neuroimmunology, is presently booming. In psychiatry, however, the relationship between cytokines and mental disorders was much less evident and took longer to materialize. The first indication that cytokines might be involved in psychopathology came from cancerology and internal medicine. Clinicians who were injecting purified or recombinant cytokines to patients afflicted with cancer and hepatitis B observed a rapid induction of flu-like symptoms, followed in a vast majority of the patients by psychiatric disorders, in the form of acute psychosis or major depressive episodes. These side effects of cytokine therapy obliged clinicians to reduce doses and find safer routes of administration than the intracerebral and intravenous routes used initially. However, they left the world of psychiatry relatively indifferent, especially since, with the possible exception of schizophrenia, the relationship between immunity and mental disorders was seen more as a coincidence than a causal chain of events. Even if depression, because of its commonality, was sometimes viewed as a form of brain flu, and antidepressant drugs as centrally acting inhibitors of prostaglandins synthesis (Leonard, 1987), there was not much evidence to go beyond metaphor. In 1991, Smith proposed for the first time what he called the "macrophage theory of depression". Based on the potent brain effects of proinflammatory cytokines such as interleukin-1, and the anecdotally reported association between pathological states of immune activation and depression, he claimed that excessive secretion of interleukin-1 and other macrophage products causes depression.

Since the discovery of proinflammatory cytokines, many reports had repeatedly demonstrated that administration of these molecules to experimental animals and

volunteers induces most of the symptoms of depression, including activation of the hypothalamic pituitary-adrenal axis, depressed mood, lack of interest in daily activities, suppression of food intake, psychomotor retardation, sleep disorders, fatigue, confusion, and alterations in cognition. The problem was, however, that there was no evidence that depression was associated with immune activation. On the contrary, the predominant view was that depressed patients were immunodepressed, as evidenced, for example, by reduced natural killer cell activity and lymphocyte proliferation in response to mitogens. It took several years after publication of Smith's provocative hypothesis to collect sufficient data for accepting the possibility that mental depression is not merely associated with immunodepression but also with an imbalance in the functioning of the immune system, with an activation of the monocyte/macrophage arm of the immune response, and a relative depression of lymphocyte functions. Evidence for immune activation in depressed patients was first collected by Maes, and was mainly based on the measurement of acute phase proteins and cytokines in the plasma of patients suffering from major depressive disorders and treatment resistant depression (Maes, 1995).

If cytokines are involved in the pathogenesis of depressive symptoms, antidepressant drugs should attenuate cytokine production and action, and conversely, cytokine antagonists should alleviate symptoms of depression in animal models and in patients. Studies testing these predictions have been initiated during the recent years, and the first demonstration that chronic, but not acute, antidepressant treatment alleviated the anhedonic effects of cytokines in laboratory rodents was provided by Yirmiya in 1996. In addition, a few reports indicated that cytokine expression could be experimentally induced not only by immune stimuli, but also by psychological stressors, which have long been regarded as contributors to the development and maintenance of depression.

The converging evidence between the brain effects of cytokines and the immunological correlates of depression prompted the editors of the present volume to bring together for a discussion meeting most, if not all, of the scientists working in this field from either a clinical or an experimental perspective. This meeting was carried out as part of the activities of the European Community Programs on Neurobiology of Interleukin-1 Receptors (TMR, CT97-0149) and the Expression and Action of Anti-Inflammatory Cytokines in the Brain (Biomed2, CT97-2492). It took place in Roscoff, France, on May 14–17, 1998, and was made possible thanks to the generosity of the Association pour la Neuropsychopharmacologie and the Institut de Recherches Internationales Servier.

The present volume contains the information presented at this meeting. It aims at providing a review of the current knowledge on the role of cytokines in depression by discussing the brain actions of cytokines, their role in the stress response, their relationship to depression, and their sensitivity to antidepressant treatment. Although there is some overlap between the contents of the different chapters, nothing has been done to reduce or even to hide it. It is the editors' opinion that its mere existence, despite the heterogeneity of disciplines that are represented, reflects very well the converging clinical and experimental evidence in favor of an intersection between cytokines and depression. Whether this intersection will prove to be of practical and theoretical importance in the pathophysiology of depression is still difficult to determine, but hopefully its delineation will encourage further work aiming at elucidating the role of cytokines in psychopathology.

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