INTRODUCTION

Historically, the brain has been considered an “immunologically privileged site.” An absence of lymphocytes within the parenchyma of the brain and a highly specialized blood-brain barrier that restricts entry of immunocytes and immune mediators are key determinants of this privileged status. In recent years, however, this concept of the brain has been evolving. It is now known that activated lymphocytes gain ready access to the brain parenchyma and that the central nervous system (CNS) itself is populated by resident macrophages, i.e., microglia, which function as the brain’s immune system. Nevertheless, when one considers the extraordinary number of pathogens that have neurotropic properties (Table 1), the brain might be more properly considered an “immunologically underprivileged site.”

From a clinical perspective, infections of the CNS are of major importance, not only because of the large number of microorganisms that have a predilection for this organ system but also based upon the seriousness of many of these infections. Rabies virus infection, for example, remains uniformly fatal, a distinction held by few if any other pathogens. Even for CNS infections for which antimicrobial therapy is available, mortality remains high. For example, the case fatality of antibiotic-treated pneumococcal meningitis is 20-30%, and herpes simplex virus (HSV) encephalitis is fatal in over 30% of adult patients, despite treatment with acyclovir.

Certain pathogens that cause CNS infection target microglial cells, most notably HIV. In addition to providing harbor for such organisms, microglia appear to contribute to brain damage. Because of these properties, our laboratory has been interested in the role of microglia in the pathogenesis of CNS infections. Upon discovery that certain psychoactive drugs alter the function of microglia, our attention has recently turned to studies of the potential benefit of psychoactive drugs in treatment of CNS infections.
MICROGLIA: A DOUBLE-EDGED SWORD

Many of the biological features of microglia were elucidated in the early decades of the twentieth century. In a treatise on microglia published in 1932, Pio del Rio-Hortega argued persuasively for the mesodermal origin of these cells, i.e., arising from bone marrow-derived blood monocytes. He also described the remarkable capacity of microglia to differentiate from a ramified to an amoeboid (motile) form in response to brain injury and infection.

After an eclipse which lasted almost half a century, the recognition in the 1980’s that microglia are the principal brain cell type which supports productive infection of HIV reignited scientific interest in brain macrophages. Additionally, the observations that reactive glial cells and cytokine expression are histopathologic features of Alzheimer’s disease spurred interest in the potential involvement of activated microglia in this neurodegenerative disorder. Presently, a large body of evidence supports the notion that microglia participate not only in defense and repair of the CNS but also in brain damage.

Work in our laboratory, as well as in many others, has focused on the key mediators of these beneficial and deleterious processes, i.e., cytokines and free radicals.

OPIOIDS AND MICROGLIA

It has been known for over a century that exogenous opioids have immunomodulatory properties. Research in the past several decades has shown that drugs of this class, i.e., μ-opioid receptor agonists, can manifest their immunomodulatory activities directly on immune cells or indirectly via CNS-endocrine pathways. Using primary human microglial cell cultures, we have demonstrated that treatment with morphine suppresses microglial cell migration toward the activated complement component C5a. This “anti-inflammatory” property of morphine involves activation of μ-opioid receptors expressed by microglia cells.