1. INTRODUCTION

Stroke and cerebral infarction have long been a major health problem worldwide because they are major causes of disability and intellectual impairment in the elderly. Recently, significant advances have been made in our understanding of the molecular and biochemical mechanisms of ischemia-induced brain damage. During the past decade, a considerable amount of experimental studies have been devoted to elucidating the mechanisms of ischemic neuronal death mediated by excitatory amino acids (EAAs) and calcium (1–3). These studies have shown that cerebral ischemia induces a massive release of EAAs, glutamate and aspartate, which in turn lead to an activation of N-methyl-D-aspartate (NMDA) and non-NMDA subtypes of glutamate receptors and an increase in intracellular calcium concentrations, triggering a chain reaction that leads to ischemia-induced neuronal death. A growing number of promising drugs with powerful cerebroprotective effects have been reported in basic pharmacology using experimental animals in line with this excitotoxic hypothesis (4–7).

In addition, recent experimental studies have shed light on other aspects of pathophysiology of ischemic neuronal injury, one of which is inflammatory reactions induced in postischemic brain, including microglial activation. Microglia, which are normally quiescent, may become rapidly activated under various pathological conditions, including cerebral ischemia (8–14). Activated microglia may develop into brain macrophages or phagocytes when neurons are lethally injured. Earlier studies, especially those in vitro, have shown that microglia, when stimulated, release a variety of cytotoxic agents that may be important mediators of neuronal injury, such as certain kinds of cytokines, reactive oxygen radicals, proteases, and glutamate (15–19). Therefore, fully activated microglia may have a neuron-killing effect. After cerebral ischemia in vivo, there is a rapid activation of microglia within minutes, but such activated microglial cells can be seen next to neurons that do not die. Just the presence of microglia therefore does not mean neuronal death. There are various levels of microglial activation, and this graded activation may explain these conflicting observations. The role of microglia during ischemia-induced neuronal injury is not fully understood, and little is known about the functional characteristics of microglia before undergoing phagocytic
transformation. Moreover, microglia, when activated, express a number of immunologically important surface molecules (immunomolecules) \((8,11,13,20,21)\). Therefore, microglia have been considered as intrinsic immunocompetent cells of the central nervous system (CNS), but the functional significance of the molecules remains enigmatic. Thus, the implication of inflammatory reactions in the pathogenesis of cerebral ischemia raises the possibility that its suppression may offer therapeutic benefit. This chapter will provide an overview of the recent findings on inflammatory reactions, especially microglial activation, in experimental cerebral ischemia, and discuss the potential effectiveness of therapies directed against such targets.

2. **BACKGROUND**

2.1. **Cerebral Ischemia and Glial Response**

The neuronal changes that result from cerebral ischemia are accompanied by glial reactions. The astrocytic reaction has been studied in detail by various investigators. These studies have shown that astrocytic hypertrophy and an enhanced expression of glial fibrillary acidic protein (GFAP) occur in the hippocampus within 1–2 d after transient global cerebral ischemia, which produces selective neuronal damage, sparing glial cells \((14,22,23)\). In contrast, astrocytes may be destroyed in an area of cerebral infarction during early reperfusion periods after focal cerebral ischemia, whereas GFAP-positive astrocytes increase in the periphery of the infarct \((24,25)\). Since astrocytes are involved in maintaining the homeostasis of extracellular water and ion concentrations, uptake and inactivation of EAAs, and the formation of the blood–brain barrier (BBB) \((26–29)\), activation of these cells may enhance the survival of ischemic neurons \((17,30)\). The role of astrocytes in ischemic brain, however, is beyond the scope of this chapter.

Compared with astrocytes, microglia are much more rapidly activated in response to ischemia, even to subtle pathologic stimuli. The activation of microglial cells is apparent through changes in their morphology, immunophenotype, migration, and proliferation \((31,32)\). Although microglial activation precedes that of astrocytes, both types of glial reactions to some extent parallel each other in time-course and distribution at later postischemic periods. Whether the early presence of activated microglia reflects regulation of astrocytic hypertrophy by microglia-released growth factor remains to be shown \((33)\).

2.2. **Microglial Activation**

Microglial cells have been reported as a source of brain macrophages after ischemic neuronal death \((34)\). It has been well documented that fully activated microglia are phagocytes \((35)\), but little is known about the functional characteristics of microglia before undergoing phagocytic transformation. Although microglial cytotoxicity has been emphasized, there is little evidence to support the view that microglial activation per se is always pathogenic. Microglial effects of tissue damaging are under strict control \((31)\). The classification of microglial activation into three stages, which has been proposed by Streit et al. \((31)\), is very useful in describing the activational state of microglial cells. This author made a minor modification of this classification for the use in cerebral ischemia (Table 1):