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Neurotoxic Injury and Astrocytes

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1. INTRODUCTION

The unique functions of the nervous system are largely attributable to the properties of its electrically excitable cells, the neurons. However, there is a more abundant class of nonexcitable cells, collectively referred to as the neuroglia. Within the central nervous system (CNS) they comprise the astrocytes, oligodendrocytes, and microglia. Progress in the understanding of neuroglial function was originally based upon the pioneering histological staining developed by Golgi and Ramon y Cajal, around 1870 and 1890, respectively. The term neuroglia was derived from the essentially erroneous concept of the German pathologist Virchow (1), who postulated that neurons were embedded in a connective tissue to which he coined the name neuroglia, or nerve glue. Although erroneous, it has persisted as the preferred and generic term for these cells, or in its shortened form—"Glia."

Originally, astrocytes were viewed as mere passive support cells for neurons. However, modern experimental techniques have provided ample evidence that astrocytes serve in numerous additional capacities to maintain an optimal environment for neuronal function. Direct contact between astrocytes and neurons determines the morphological and functional differentiation of the latter. It is now well established that the role of astrocytes extends well beyond passive structural support and sensitivity to axon commands. In fact, astrocytes and neurons establish a highly dynamic reciprocal relationship that influences growth, morphology, behavior, and repair within the CNS. Astrocyte interactions with neuronal and nonneuronal cells (oligodendrocytes, microglia, and endothelial cells), and between themselves and the complexity of these interactions provide numerous strategic sites for neurotoxic action. This chapter will provide examples of astrocytic modulation of neurotoxicity. Examples include selective astrocytic toxicants, parent compounds that are metabolized within astrocytes to reactive intermediates with subsequent propensity to selectively damage neurons, as well as toxicants and pathophysiological conditions that affect astrocytic function and lead to altered extracellular fluid composition and secondary neuronal dysfunction.
2. EXCITATORY AMINO ACIDS: THE ASTROCYTIC POOL

Astrocytes occupy about 25% of the brain volume (1A), and their processes are found around synapses and in close association with nodes of Ranvier, axon tracts, and blood vessels. In addition to their structural support for neurons, a partial list of astrocyte functions includes secretion of neurotrophic factors, K+ buffering, control of extracellular fluid pH, inactivation of extracellular glutamate, glycogen storage, synaptic remodeling, and uptake and metabolism of neurotransmitters. During development, astrocytes prominently function in guiding neurons to their final target. The physiological functions of astrocytes in the developing and mature CNS extend beyond the scope of this review. Hence, they will not be discussed herein, but the reader is referred to a number of recent publications that provide extensive reviews of astrocytic functions (2–7).

CNS damage in a number of pathological states (e.g., hypoxia, seizures, hypoglycemia, and hepatic encephalopathy), neurodegenerative disorders (Parkinson’s disease and Huntington’s disease), and aging is thought to be partly due to excessive stimulation of neuronal glutamate-gated ion channels (reviewed in 8). The origin of glutamate (and its analog, aspartate) has been tacitly assumed to be presynaptic nerve endings. However, it is known that astrocytes remove extracellular glutamate by a Na+-dependent mechanism (9). This transport has a likely stoichiometry of 1 glutamate and 3 Na+ transported inwardly, and 1 K+ transported outwardly to offset the negative charge of glutamate. In the presence of ammonia, glutamate is metabolized to glutamine by the astrocyte-specific enzyme glutamine synthetase (GS); (10,11), maintaining [glutamate]_{o} at 0.3 μM (12,13). This represents a 10,000-fold gradient vs [glutamate]_{i} (3 mM). This glutamate-glutamine pathway constitutes the pool of brain glutamate originally described by Berl (14). Astrocytes also efficiently remove extracellular taurine by a Na+-dependent mechanism (15). This transport system generates and maintains a [taurine]/[taurine]_{o} of about 10,000, and has a likely stoichiometry of 1 taurine and 2 Na++ ions transported inwardly, to generate and maintain the observed taurine gradient (15,16). Release from both the glutamate and taurine pools occurs as a result of astrocytic swelling (2,17). Astrocytic swelling is seen as an early event (within an hour of injury), followed by regulatory volume decrease (RVD). RVD is characterized by astrocyte reestablishment of preswelling volume, a process involving the extrusion of ions such as K+ and Cl−, and compensatory organic osmolytes (e.g., taurine, myoinositol). To a lesser extent, glutamate and aspartate (17,18) are also released by swollen astrocytes. The prominence of astrocytic swelling in various diseases, the rapidity of the astrogial response and its evolutionary conservation indicate that astrocytic swelling may fulfill a number of important functions. Unlike gliosis it occurs rapidly (19), and may reverse slowly with time. The consequences and the mechanisms of astrocytic swelling are as yet not fully defined, but are beginning to yield to experimental analysis in vitro. Astrocytic swelling in situ is routinely found to be associated with early pathological states affecting the CNS. Ultrastructural features of head injury suggest that astrocytic swelling precedes neuronal damage (20). A combined magnetic resonance and histochemical study suggests that brain injury after acute cerebral hypoxia is also secondary to astrocytic swelling (21). In situ, astrocytes are also known to swell more readily than neurons in response to lactic acidosis and elevated extracellular K+, glutamate, and other monoamine transmitters (22,23). Similar findings of