Glial and neuronal transport proteins regulate the extracellular glutamate concentration in brain. Glutamate transporters regulate extracellular glutamate concentrations so as to maintain dynamic and high fidelity cell signaling processes in the brain tissue. Some glutamate transporters depend on an electrochemical gradient of sodium ions, whereas other glutamate transporters are Na\(^+\)-gradient independent (Danbolt, 2001). Na\(^+\)-independent glutamate transporters have a low affinity for glutamate. This poorly characterized uptake system supplies brain tissue with amino acids for metabolic purposes (Erecinska and Silver, 1990). Na\(^+\)-dependent glutamate transporters have a high affinity for glutamate and are distributed throughout the brain tissue (Danbolt, 2001).

Five glutamate transporters were identified, characterized, and cloned from brain tissue (Saier, Jr., 1999; Slotboom et al., 1999; Sims and Robinson, 1999) (Fig. 4.1). They include EAAT1 (GLAST), EAAT2 (GLT1), EAAC1 (EAAT3), EAAT4, and EAAT5. EAAT1 and EAAT2 are primarily astrocytic, whereas EAAT3, EAAT4, and EAAT5 are neuronal. EAAT3 is localized to the presynaptic cleft and non-synaptic area of glutamatergic and GABAergic neurons (Rothstein et al., 1994; Conti et al., 1998). EAAT4 is expressed primarily in the cerebellum and EAAT5 is present in retina. EAAT2 predominates quantitatively and is responsible for most of the glutamate uptake activity in juvenile and adult brain tissue. These transporters are homotrimeric complexes. Trimerization of monomers occurs efficiently after synthesis of the individual subunits resulting in stable trimers (Gendreau et al., 2004).

Glutamate transporters possess six to ten transmembrane domains, which may form an aqueous transmembrane pore (Seal and Amara, 1998). Among the five known mammalian EAAT subtypes, the glial carriers, EAAT1 and EAAT2, have the greatest impact on clearance of glutamate released during neurotransmission. These transporters are essential for terminating synaptic transmission as well as for maintaining extracellular glutamate concentration below neurotoxic levels. In addition, brain tissue also contains a cystine-glutamate antiporter (Erecinska and Silver, 1990). This antiporter acts as a cystine transporter that uses the transmembrane gradient of glutamate as a driving force. This transporter may protect neurons against oxidative stress by providing a suitable amount of cysteine to produce glutathione. Glutamate does not cross the blood-brain barrier. Most of the glutamate present...
in the brain is synthesized de novo by astrocytes that have lower levels of cytosolic glutamate than neurons. Astrocytes contain glutamine synthase, an enzyme that converts glutamate into glutamine (Hertz et al., 1999).

These glutamate transport mechanisms provide glutamate to brain tissue for many metabolic activities including synthesis of GABA, glutathione, proteins, and energy production. Glutamate transport mechanisms are modulated by cytokines and growth factors (Danbolt, 2001). Collective evidence suggests that glutamate transporters represent a major mechanism for removal of glutamate from the extracellular fluid (Fig. 4.2). Their activities are important for the long-term maintenance of low and non-toxic concentration of glutamate at the synapse. Although the interactions of glutamate with its transporters decrease the levels of free glutamate in the synaptic cleft, these interactions also slow down the diffusion of glutamate away from the release site. A high density of glutamate transporters on glial cells may provide an opportunity for glutamate to re-enter the synaptic cleft upon dissociation from the glutamate transporter (Danbolt, 2001).

4.1 Astrocytic Glutamate Transporters

EAAT1 and EAAT2 are selective markers for astrocytic plasma membranes. The density of EAAT2 is much higher in hippocampal astrocytes than in cerebellar