Involvement of glial cells in transmitter synthesis and elimination from the extracellular space

Astrocytes can release neurotransmitters. Glutamate is probably the most important transmitter that the brain uses. The pre-synaptic neuron release glutamate, which binds to receptors on the dendrite, signaling the dendrite to fire. Astrocytes can release glutamate too, made by rising calcium levels within the cell. On top of the cell, astrocytes can release ATP, which here acts as a signal between neighboring astrocytes.

Astrocytes can use glutamate to signal, affecting the neuron's calcium levels. Rising calcium levels in astrocytes can induce glutamate release. This glutamate release is associated with a right increase in calcium levels. Increasing the calcium levels can influence the neuron’s signaling pattern.

Astrocytes had a third function, it can affect synaptic transmission. Because it wraps around synapses, they play an active role in influencing the communication between neurons. Neural activity can affect calcium levels in nearby astrocytes and then cycle into the astrocytes signaling back to the neurons through glutamate release. This released glutamate binds to receptors on the axon terminal and inhibits the release of more transmitters.

Suggested pathway for coupled production and metabolism of transmitter glutamate using aspartate transamination for exchange between α-KG and glutamate. Coupled pyruvate carboxylase and pyruvate dehydrogenase activation generate a “new” molecule of citrate. Citrate-derived α-KG exiting, the mitochondrial membrane quits the astrocytic TCA cycle and is transaminated with aspartate to form glutamate, with accompanying oxaloacetate (OAA) formation from aspartate. The mitochondrial exit of α-KG occurs through the α-ketoglutarate/malate exchanger, generally acknowledged to be expressed in astrocytes, and the cytosolic malate with which it is exchanged and generated via NADH-supported reduction of oxaloacetate generated from aspartate. Glutamate is amidated to glutamine, which is transferred to glutamatergic neurons. High extracellular concentrations of glutamate or glutamine will at least in cultured astrocytes make the astrocytic production of glutamate and glutamine unnecessary (and/or prevent the reaction for thermodynamic reasons) and thereby prevent glutamate formation from α-KG and the associated transamination of aspartate. In neurons, glutamine is in a complex pathway transformed to glutamate, accumulated in vesicles and released as transmitter glutamate. Subsequent reuptake of glutamate and oxidative metabolism in astrocytes is normally of similar magnitude as the production of glutamate described above. Cytosolic glutamate is transferred to mitochondria through the aspartate-glutamate exchanger AGC1 in exchange with mitochondrial aspartate generated from OAA formed during the synthesis of glutamate and re-converted to aspartate during transamination of glutamate to α-KG. In turn, the cytosolic aspartate is used during glutamate synthesis in the transamination of α-KG to glutamate after the formation of the last step. However, when glutamate production from α-KG is inhibited by high extracellular concentrations of glutamate or glutamine or by excess ammonia (inhibiting the neuronal glutaminase ), the exit of aspartate to the cytosol in exchange with glutamate during glutamate oxidation will no longer be countervailed by aspartate use during glutamate formation. This cancels glutamate oxidation through AAT, so that formation of α-KG must be catalyzed by glutamate dehydrogenase (GDH). This is unlikely normally to take place in vivo since increased extracellular glutamate only happens during bursts of neuronal activity and glutamate uptake and glutamine synthesis quickly clear extracellular and intracellular glutamate. Metabolism of α-KG is only shown through malate exit and pyruvate formation. Since this is oxidation in the cytosol it must be followed by malate aspartate shuttle (MAS)-mediated transfer of a reducing equivalent to the mitochondria. Synthesis of glutamine and export from the glia is critical since it restores nitrogen balance (otherwise concentrations of glutamate and aspartate would seriatim rise).