

Glutamate/GABA Synthesis and Metabolism

Key References

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Overview

Glutamine is a common precursor for the biosynthesis of both glutamate and GABA. Glutamine can be transported in and out of neurons and astrocytes utilizing different glutamine carriers. Three such carriers have been cloned and characterized, referred to as ASCT2, GlnT and SN1. They are differentially expressed in brain cells; ASCT2 and SN1 being astrocytic and GlnT being neuronal. They play different roles in glutamine influx and efflux and hence control the availability of glutamine in glutamatergic and GABAergic neurons.

The neurotransmitter glutamate can be synthesized from glutamine by the action of phosphate-activated glutaminase. It appears, however, that glutamate derived from glutamine via this route is produced intramitochondrially and may subsequently undergo a transamination catalyzed by the mitochondrial isoform of aspartate aminotransferase. The α -ketoglutarate thus formed is translocated out of the mitochondria by the dicarboxylate carrier and transaminated in the cytoplasm by the cytoplasmic isoform of aspartate aminotransferase. Alternatively, glutamate may be formed from α -ketoglutarate and alanine catalyzed by alanine aminotransferase. This cytoplasmic glutamate is transported into vesicles by vesicular glutamate transporters. Three vesicular glutamate transporters have been cloned and they exhibit differential expression in glutamatergic neurons in various brain regions. This has important implications with regard to characterization of subpopulations of glutamatergic neurons. Glutamate metabolism, which to a large extent takes place in astroglial cells, is catalyzed either by glutamine synthetase or glutamate dehydrogenase.

The inhibitors for the enzymes involved in glutamate biosynthesis are not absolutely specific. This is particularly serious for aminooxyacetic acid which at high concentrations will inhibit all pyridoxal phosphate-dependent enzymes. Another problem with amino-oxyacetic acid is that it potently inhibits both glutamate decarboxylase and GABA-transaminase (see table). Even methionine sulfoximine, which is proven to be an extremely useful tool to study the functional importance of glutamine synthetase, is not strictly specific for this enzyme, but also inhibits, for example, α glutamylcysteine synthetase, a key enzyme in the biosynthesis of glutathione. Therefore, these inhibitors must be used with caution.

The neurotransmitter GABA is formed from glutamate by the action of glutamate decarboxylase. It appears that glutamine serves as the precursor for glutamate, making phosphate-activated glutaminase, an important enzyme for GABA synthesis as well. Recent studies of these processes, using [13 C]-labeled substrates and [13 C] NMR spectroscopy to follow the metabolic fate of individual C-atoms, have suggested that this biosynthetic route is somewhat more complex than previously thought. It appears that glutamate formed from glutamine may be metabolized in the tricarboxylic acid (TCA) cycle prior to its conversion to GABA, which may allow new alternative regulatory mechanisms. Moreover, it appears that this pathway involving TCA cycle activity is differentially involved in the biosynthesis of GABA destined for the cytoplasmic and vesicular pools, respectively. GABA is metabolized by the action of GABA-transaminase, which is a ubiquitous enzyme being present in GABAergic neurons as well as other

types of neurons and astrocytes. Inhibitors of this enzyme generally exhibit anticonvulsant actions.

Inhibitors of glutamate decarboxylase generally also inhibit GABA-transaminase due to the fact that both enzymes require pyridoxal phosphate for activity. However, in the case of the carbonyl-trapping agent aminooxyacetic acid its K_i value for inhibition of GABA-transaminase is 10-fold lower than that for glutamate decarboxylase. The two catalytic site directed suicide inhibitors of GABA-transaminase, γ -vinyl GABA and GABAculine, are excellent inhibitors of this enzyme in terms of specificity and potency.

Glutamate/GABA Synthesis and Metabolism

COMPOUND	ENZYME	Co-FACTORS/SUBSTRATE	INHIBITORS
GLUTAMATE			
L-Glutamine (G3126)	→ Glutaminase (G5894)	Phosphate (S0751, S0876)/glutamine (G3126)	L-Glutamate (G1626, G1251) Ammonia (A6899) 6-Diazo-5-oxo-L-nor-leucine
L-Glutamate (m) (G1626, G1251)	→ Aspartate aminotransferase (m) (G2751)	Pyridoxal phosphate (P9255)/ oxaloacetate (O4126)/aspartate (A9256)	Aminooxyacetic acid (C13408)
α-Ketoglutarate (m) (K1750)	→ Dicarboxylate carrier	Malate (M0750)	Phenylsuccinate (P35200)
α-Ketoglutarate (c) (K1750)	→ Aspartate aminotransferase (c) (G2751)	Pyridoxal phosphate (P9255)/ oxaloacetate (O4126)/aspartate (A9256)	Aminooxyacetic acid (C13408)
L-Glutamate (c-ves) (G1626, G1251)	→ Vesicular glutamate carrier		
(A) α-Ketoglutarate (K1750) + NH ₄ ⁺ (A6899)	→ L-Glutamate dehydrogenase (G2626)	NAD ⁺ (N7004)/glutamate (G1626, G1251)	
(B) L-Glutamine (G3126)	→ Glutamine synthetase (G1270)	ATP (A2383)/NH ₄ ⁺ (22128)/glutamate (G1626, G1251)	Methionine sulfoximine (M5379)
GABA			
L-Glutamate (G1626, G1251)	→ L-Glutamate decarboxylase	Pyridoxal phosphate (P9255)/ glutamate (G1251)	Aminooxyacetic acid (C13408), 3-Mercaptopropionic acid (M5801), γ-Acetylenic GABA (A230)
GABA (A2129)	→ GABA-transaminase	Pyridoxal phosphate (P9255)/ α-ketoglutarate (K1750)	Aminooxyacetic acid (C13408), 3-Mercaptopropionic acid (M5801), γ-Vinyl GABA (V8261)
Succinate semialdehyde (S1505)			GABAculine (A3539)
Succinate (S7501)	→ Succinate semialdehyde dehydrogenase		NADH (N8129)/succinate semialdehyde (S1505)

Abbreviations

c: Cytoplasmic
c-ves: Vesicles in cytoplasm
m: Mitochondrial

Enzyme

Glutaminase
Aspartate aminotransferase
L-Glutamate dehydrogenase
Glutamine synthetase
L-Glutamate decarboxylase
GABA-transaminase
Succinate semialdehyde
dehydrogenase

Tissue expression

Kidney, brain and other tissues
Liver, brain and other tissues
Brain, liver, muscle and other tissues
Brain, liver and other tissues
Brain, pancreas and intestine
Brain, liver and other tissues
Brain, liver and other tissues

Function

Generation of Ammonia and Glutamate
Malate-aspartate shuttle
Amonia-fixation and -generation
Amonia-fixation
GABA synthesis
GABA metabolism
GABA metabolism (GABA-shunt)

Disease

Not known
Not known
Olivoponto-cerebellar atrophy
Not known
Epilepsy, schizophrenia
Epilepsy
Not known