

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 recently 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.

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. This cytoplasmic glutamate is transported into vesicles by the vesicular glutamate transporter. Alternatively, glutamate may be formed from α -ketoglutarate and alanine catalyzed by alanine aminotransferase. 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. 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 [¹³C]-labeled substrates and [¹³C] 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 an ubiquitous enzyme. Inhibitors of this enzyme generally exhibit anticonvulsant actions.

The inhibitors for glutamate decarboxylase also inhibit GABA-transaminase. This is particularly serious for aminooxyacetic acid, which is much more potent with regard to

inhibition of the latter enzyme. 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 (G 3126) | → Glutaminase (G 5894) | Phosphate (S 0751, S 0876)/glutamine (G 3126) | L-Glutamate (G 1626, G 1251) Ammonia (A 6899) 6-Diazo-5-oxo-L-nor-leucine |
| ↓ | | | |
| L-Glutamate (m) (G 1626, G 1251) | → Aspartate aminotransferase (m) (G 2751) | Pyridoxal phosphate (P 9255)/oxaloacetate (O 4126)/aspartate (A 9256) | Aminoxyacetic acid (A 4508) |
| ↓ | | | |
| α-Ketoglutarate (m) (K 1750) | → Dicarboxylate carrier | Malate (M 0750) | Phenylsuccinate (P3,520-0) |
| ↓ | | | |
| α-Ketoglutarate (c) (K 1750) | → Aspartate aminotransferase (c) (G 2751) | Pyridoxal phosphate (P 9255)/oxaloacetate (O 4126)/aspartate (A 9256) | Aminoxyacetic acid (A 4508) |
| ↓ | | | |
| L-Glutamate (c-ves) (G 1626, G 1251) | → Vesicular glutamate carrier | | |
| ↓ | | | |
| (A) α-Ketoglutarate (K 1750) + NH ₄ ⁺ (A 6899) | → L-Glutamate dehydrogenase (G 2626) | NAD ⁺ (N 7004)/glutamate (G 1626, G 1251) | |
| (B) L-Glutamine (G 3126) | → Glutamine synthetase (G 1270) | ATP (A 2383)/NH ₄ ⁺ (A 6899)/glutamate (G 1626, G 1251) | Methionine sulfoximine (M 5379) |
| GABA | | | |
| L-Glutamate (G 1626, G 1251) | → L-Glutamate decarboxylase (G 3757) | Pyridoxal phosphate (P 9255)/glutamate (G 1251) | Aminoxyacetic acid (A 4508) 3-Mercaptopropionic acid (M 6750) γ-Acetylenic GABA (A-230) |
| ↓ | | | |
| GABA (A 2129) | → GABA-transaminase | Pyridoxal phosphate (P 9255)/α-ketoglutarate (K 1750) | Aminoxyacetic acid (A 4508) 3-Mercaptopropionic acid (M 6750) γ-Vinyl GABA (V 8261) GABAculine (A 3539) |
| ↓ | | | |
| Succinate semialdehyde (S 1505) | → Succinate semialdehyde dehydrogenase (S 3907) | NADH (N 8129)/succinate semialdehyde (S 1505) | |
| ↓ | | | |
| Succinate (S 7501) | | | |

ABBREVIATIONS

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