ODOMENE JUSTICE

17/SCI03/006

BCH 308 ASSIGNMENT

Describe in details the synthesis of two named neurotransmitters.

Serotonin synthesis

Serotonin is a neurotransmitter that has been linked to a wide variety of behaviors including feeding and body-weight regulation, social hierarchies, aggression and suicidality, obsessive compulsive disorder, alcoholism, anxiety, and affective disorders.

The biochemical pathway for serotonin synthesis initially involves the conversion of L-tryptophan to 5-hydroxytryptophan by the enzyme L-tryptophan hydroxylase (TPH), which has been found both in cytosolic and particulate brain cell fractions. This enzyme provides the rate-limiting step for serotonin synthesis, in the same manner that norepinephrine and dopamine synthesis in adrenergic and dopaminergic neurons is controlled by the ability of the related enzyme, L-tyrosine hydroxylase, to convert L-tyrosine to L-dihydroxyphenylalanine (L-DOPA). Some inhibitors of TPH (e.g. α-propyldopacetamide) are also active against tyrosine hydroxylase, whereas others such as p-chlorophenylalanine are more selective for TPH. Although p-chloroamphetamine and fenfluramine can also inhibit TPH, they have important actions (including neurotoxic effects) upon various other regulatory processes of serotonergic neuronal function. The identification of two enzyme isoforms, called TPH1 and TPH2, which are apparently associated selectively with peripheral tissues and the brain, respectively, suggests the possibility that drug inhibitors with specificity for targeting individual isoforms may be found in the future.

The subsequent metabolic step in the synthesis of serotonin (and also norepinephrine or dopamine) involves the decarboxylation of 5-hydroxytryptophan (and L-DOPA) by the action of the cytosolic enzyme L-aromatic amino acid decarboxylase. Inhibitors of this enzyme include the drugs benserazide and carbidopa, which do not cross the blood brain barrier, and are used clinically to prevent peripheral decarboxylation of the L-DOPA administered as a precursor for central dopamine formation in Parkinsonian patients.

Glutamate synthesis

Glutamate (Glu) is a key substance in the brain, being involved in metabolism, pathology, and neurotransmission and is an essential source of energy. It is involved in the synthesis of proteins and peptides, as well as other compounds and in the detoxication of ammonia in the brain.

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 below). 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.