Biochemistry IN PERSPECTIVE

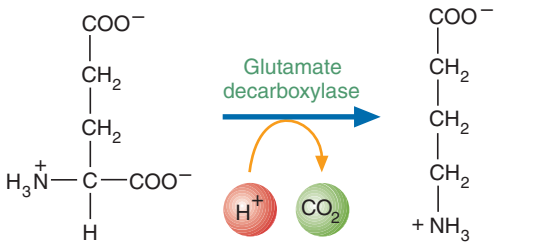
The Amine Neurotransmitters

How are the biogenic amine neurotransmitters GABA and serotonin synthesized and degraded? Neurotransmitters are synthesized in presynaptic neurons and degraded either in the synaptic cleft or within presynaptic cells after an reuptake process. The biosynthesis and degradation of the biogenic amines γ-aminobutyric acid and serotonin are described.

Amine Neurotransmitter Biosynthesis

Biosynthesis of γ-Aminobutyric Acid *γ-Aminobutyric acid* (GABA) is the major inhibitory neurotransmitter in the brain. The binding of GABA to its receptor opens certain channels, which results in the inward flow of Cl^- or the outward flow of K^+. (The benzodiazepines, a class of tranquilizers that alleviate anxiety and aggressive behavior, have been shown to enhance GABA's ability to increase membrane conductance of chloride.)

GABA is produced by the decarboxylation of glutamate. The reaction is catalyzed by glutamate decarboxylase, which is a pyridoxal phosphate–requiring enzyme:



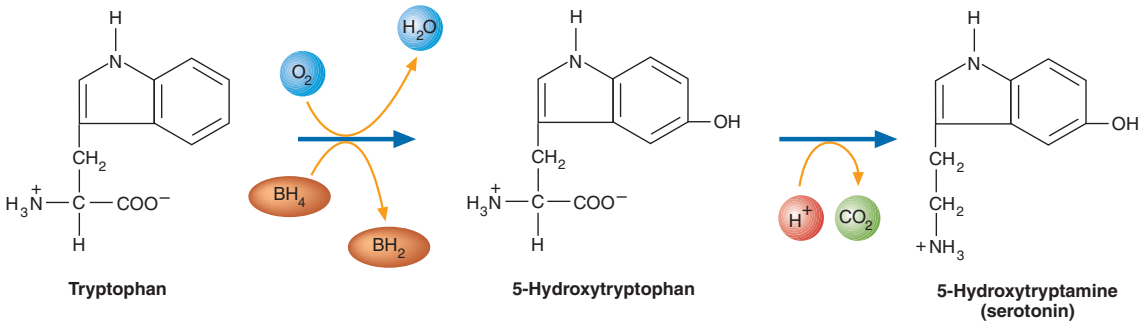
Biosynthesis of Serotonin

Serotonin is produced in the central nervous system and the enteric nervous system. In the brain serotonin regulates mood, sleep, pain perception, memory, body temperature, and feeding behavior. This biogenic amine has been implicated in human eating disorders such as anorexia nervosa, bulimia, and the carbohydrate craving associated with seasonal affective disorder (SAD). SAD is a clinical depression triggered by the decreased daylight in autumn and winter. The hallucinogenic drug LSD (lysergic acid diethylamide) apparently competes with serotonin for specific brain cell receptors. Serotonin (5-hydroxytryptamine or 5-HT) is the major neurotransmitter in the *enteric nervous system*, a nearly autonomous set of a hundred million nerve cells that regulate all aspects of the gastrointestinal tract. Serotonin has been linked to several digestive disorders, such as irritable bowel syndrome.

Serotonin is synthesized from tryptophan in two reactions. Tryptophan hydroxylase uses O_2 and the electron donor BH_4 to hydroxylate C-5 of tryptophan. The product, called 5-hydroxytryptophan, then undergoes a decarboxylation catalyzed by 5-hydroxytryptophan decarboxylase, a pyridoxal phosphate–requiring enzyme. Serotonin, often referred to as 5-hydroxytryptamine, is the product of this reaction.

Amine Neurotransmitter Degradation

Degradation of γ-Aminobutyric Acid GABA is removed from the synaptic cleft by reuptake by Na^+ gradient–driven GABA transporters into the presynaptic neuron or into a nearby astrocyte. (Astrocytes are non-neuronal cells that provide support, nutrients, and protection to neurons.) Within the GABAergic neuron, newly imported GABA molecules may be repackaged into a synaptic vesicle or converted into succinate within a mitochondrion. The reaction catalyzed by GABA transaminase, using the α-keto acid α-ketoglutarate, yields succinate semialdehyde ($^-OOC\text{-}CH_2\text{-}CH_2\text{-}CHO$) and glutamate, the precursor of GABA. Succinate semialdehyde is then rapidly converted to succinate by NAD^+-requiring succinate semialdehyde dehydrogenase. The conversion of GABA to succinate, which yields glutamate, is referred to as the *GABA shunt* of the citric acid cycle. When GABA is transported into astrocytes, the glutamate product of GABA transaminase is converted into glutamine by glutamine synthetase. Glutamine is then transferred to the GABAergic



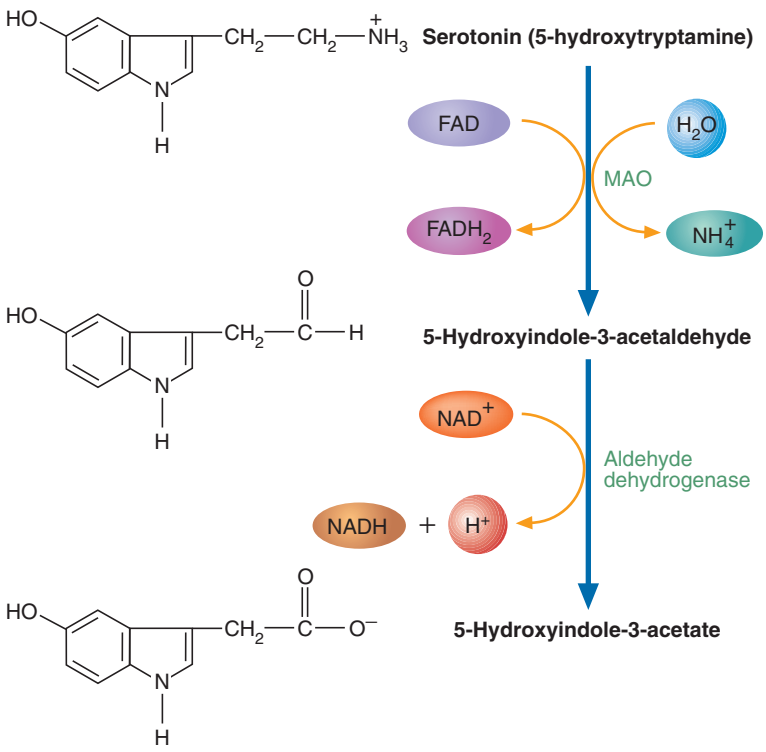


FIGURE 15A

Degradation of Serotonin

In the major catabolic pathway, serotonin is deaminated and oxidized to form 5-hydroxyindole-3-acetaldehyde. The latter molecule is then further oxidized to form 5-hydroxyindole-3-acetate.

neuron where it is reconverted to glutamate, the substrate for GABA synthesis. Astrocytes cannot convert glutamate into GABA because they lack glutamate decarboxylase.

To maintain precise information transfer, neurotransmitters are usually quickly degraded or removed from the synaptic cleft. An extreme example of enzyme inhibition illustrates the importance of neurotransmitter degradation. Recall that acetylcholine is the neurotransmitter that initiates muscle contraction. Shortly afterward, the action of acetylcholine is terminated by the enzyme acetylcholinesterase. (Acetylcholine must be destroyed rapidly so that muscle can relax before the next contraction.) Acetylcholinesterase is a serine esterase that hydrolyzes acetylcholine to acetate and choline. Serine esterases have catalytic mechanisms similar to those of the serine proteases (Section 6.4). Both types of enzyme are irreversibly inhibited by DFP (diisopropylfluorophosphate). Exposure to DFP causes muscle paralysis because acetylcholinesterase is irreversibly inhibited. With each nerve impulse, more acetylcholine molecules enter the neuromuscular synaptic cleft. The accumulating acetylcholine molecules repetitively bind to acetylcholine receptors. The overstimulated muscle cells soon become paralyzed (nonfunctional). Affected individuals suffocate because of paralyzed respiratory muscles.

Degradation of Serotonin Serotonin released by serotonergic neurons into a synaptic cleft is degraded after uptake into the presynaptic cell by a 5-HT transporter, referred to as SERT. After its reuptake, serotonin is degraded in a two-step pathway (Figure 15A). In the first reaction, serotonin is oxidized by the outer mitochondrial membrane enzyme MAO (monoamine oxidase). The product, 5-hydroxyindole-3-acetaldehyde, is then further oxidized by aldehyde dehydrogenase to form 5-hydroxyindole-3-acetate.

SUMMARY: Biogenic amine neurotransmitters are transported into presynaptic cells where they are repackaged into synaptic vesicles or they are degraded by cell-specific enzymes.