Session I- Neurochemistry Associated with Pediatric Neurotransmitter Diseases
Darryl C. De Vivo, MD- Chair

Session I included three presentations focusing on basic neurochemical features of GABA, catecholamines and gamma-hydroxybutyric acid (GHB). The objective was to provide the neurochemical fundamentals applicable to the diseases discussed in future sessions. Dr. O. C. Snead presented first on functional aspects of GABA neurotransmission.

Brain function is dependent upon the capacity for neurons within interconnecting neuronal circuitry to excite or inhibit one another. Excitation and inhibition are achieved through synaptic transmission which in turn is mediated by chemical messengers called neurotransmitters. Neurotransmission may be thought of as translation of an electrical signal to a chemical signal (mediated by the neurotransmitter), back to an electrical signal. For a neurochemical in the brain to be considered a neurotransmitter, several criteria must be met: 1) there must be neuronal synthesis; 2) the neurochemical must be found in the presynaptic terminal with release in amounts sufficient to exert a defined action on the postsynaptic neuron; 3) when administered exogenously, it must mimic the actions of the endogenously released transmitter; and 4) there must be a defined biochemical sequence for removal of the neurochemical from the synaptic cleft. In mammalian brain, the primary excitatory neurotransmitter meeting these criteria is glutamic acid, while GABA (gamma-aminobutyric acid) fulfills these criteria as the primary inhibitory neurotransmitter

Once released into the synaptic cleft, GABA may interact at the postsynaptic membrane to induce both fast and slow inhibitory neurotransmission, or it may act on the presynaptic neuron from where it was released to inhibit further release of GABA, so-called pre-synaptic inhibition. GABA may be removed from the synaptic cleft by reuptake both into the presynaptic neuron and into surrounding glia by GABA transporter proteins. Fast postsynaptic inhibition is mediated by the GABAA receptor (GABAAR), a ligand-gated chloride ion channel composed of five different subunits. Slow inhibitory neurotransmission is mediated by the GABAB receptor (GABABR), a metabotropic receptor coupled to various effector systems (G proteins, inwardly-rectifying potassium channels, etc).

The term metabotropic refers to the fact that activation of the GABABR does not induce an electrical change in the postsynaptic membrane directly, but rather leads to a biochemical cascade which then results in postsynaptic membrane hyperpolarization. Depending upon synaptic localization, activation of GABAB receptors can produce either inhibition or disinhibition of synaptic transmission. Presynaptically, GABAB autoreceptors (located on GABAergic neurons) and heteroreceptors (located on other neurotransmitter releasing neurons) may inhibit neurotransmitter release via inhibition of calcium channels. Postsynaptically, GABAB receptor activation produces increased potassium conductance, leading to slow, long-lasting GABAergic inhibition. Any alteration in GABA metabolism has the potential to result in seizures, and therefore the most common disorder in which GABA is targetted as treatment is epilepsy. However, other disorders, including psychiatric disease, spasticity, stiff man syndrome, and succinic semialdehyde dehydrogenase deficiency, may also be related to disordered GABAergic function in brain.

Dr. Teodoro Bottiglieri next presented a concise overview on metabolism and regulation of biogenic amines. Biogenic amines include the catecholamines dopamine (DA), norepinephrine (NE) and epinephrine (EP), in addition to the indoleamines serotonin (5-HT) and melatonin. Alterations in 5-HT, NE and DA levels have been implicated in diverse neurologic disorders

including depression, dementia, schizophrenia, Parkinson's disease, epilepsy, Huntington's disease, Segawa's disease and autism. Serotonin is derived from the physiologic amino acid tryptophan via the combined actions of tryptophan hydroxylase and aromatic amino acid decarboxylase. The major metabolite used to track serotonin turnover, 5-hydroxyindole acetic acid (5-HIAA), is derived from serotonin by the combined actions of monamine oxidase and aldehyde dehydrogenase. In the pineal gland, serotonin is metabolized to melatonin with S-adenosylmethionine as cofactor.

Production of DA begins with the conversion of tyrosine to L-DOPA, catalyzed by tetrahydrobiopterin-dependent tyrosine hydroxylase. L-DOPA is then metabolized to DA by DOPA decarboxylase, a pyridoxine-dependent enzyme. Further metabolism of DA results in production of NE and EP, also requiring S-adenosylmethionine as methyl donor. Drugs which inhibit DA and 5-HT reuptake or breakdown (pargyline, selegeline, imipramine, amphetamine, etc) have demonstrated utility in a variety of neurologic disorders, most likely achieving their therapeutic effect by increasing DA and 5-HT levels within the synaptic cleft.

The final presentation focused on gamma-hydroxybutyric acid, once again presented by Dr. Snead. GHB is an ubiquitous short chain fatty acid whose primary precursor is GABA. The concentration of GHB in brain is < 1% of its parent compound, GABA. GHB may be a neurotransmitter, but this has been contested in the literature. GHB synthetic enzymes correlate in location with GHB high-affinity binding sites, and GHB is released by neuronal depolarization in a calcium-dependent fashion. Further, mammalian brain possesses a sodium-dependent GHB uptake system, and GHB is capable of stimulating second messenger systems (cyclic GMP). These observations suggest that GHB is a neurotransmitter.

The pharmacologic action of GHB is mediated via low- and high-affinity GHB receptors (G protein coupled) as well as through the GABABR, for which GHB is a weak agonist. Pharmacologically, GHB inhibits DA release from the presynaptic receptor. GHB has been the subject of a voluminous literature in the last 30 years, and today research is further expanding. GHB is an emerging drug of abuse (most likely linked to its dopaminergic effects), leading the Department of Justice to categorize it as a Class I controlled substance in 1999. Simultaneously, GHB is utilized clinically to treat cataplexy, alcohol- and opiate-withdrawal syndromes, and to induce anasthesia. Its ability to induce profound EEG abnormalities and behavioral changes has led to its use in the induction of absence seizures in rodent models, and there is speculation that GHB is involved in the pathogenesis of pediatric absence epilepsy. GHB is markedly increased in the inborn error of human metabolism succinic semialdehyde dehydrogenase deficiency, and likely contributes to the neurologic abnormalities seen in patients with this disease.