autonomic and pain signals.[262] Formation of both serotonin and 5-HTP within the spinal cord have been shown to be stimulated by administration of 5-HTP, and the increase is enhanced in experimentally induced encephalomyelitis (EAE), an experimental model system for human multiple sclerosis.[263] Spinal cord generation of 5-HIAA increases in the initial inflammatory phase of the disease and decreases after destruction of nerve fibers.[264] Decreased serotonin reuptake by damaged neurons and disruption of the blood-brain barrier have been suggested as mechanistic explanations. Such rationale allows understanding of how serotonin may enter the CNS from 5-HTP produced in the periphery.[263] The inflammatory phase in the more caudal regions of the spinal cord also results in marked elevation of quinolinate in rats with induced EAE.[265] Quinolinate is discussed further in the next section. Tryptophan supplementation increases survival in EAE.[266]

Carcinoid tumors composed of chromaffin tissue can release large amounts of serotonin.[268, 269] Urinary 5-HIAA has been recommended for diagnosis of some types of carcinoid tumor cases.[270] Investigations of the pathogenesis of serotonin secretion and high 5-HIAA excretion in carcinoid heart disease showed no association with transforming growth factor beta or fibroblast growth factor.[271] Among patients with carcinoid tumors, only those who show high variability in 5-HIAA excretion in overnight urine experience watery diarrhea.[272]

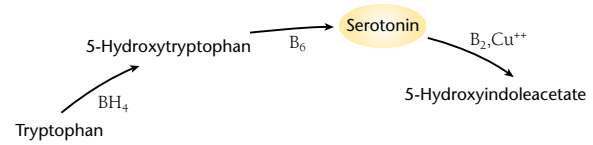

FIGURE 6.13 — **Formation and Clearance of Serotonin**

The availability of tryptophan in serotonergic neurons determines their ability to sustain serotonin levels. Anything that increases serotonin turnover, such as increased neuronal activity or drugs that block synaptic re-uptake cause increased rates of 5-hydroxyindoleacetate formation and higher concentrations of the catabolic product in urine.

Cerebrospinal fluid 5-HIAA and HVA showed highly significant positive correlations with Alzheimer's disease.[273] These monoamine disturbances may be in response to the pathophysiology of this disease. Experimental allergic neuritis also exhibits elevated serotonin precursors, indicating that they may play a role in the clinical course of this disorder.[274] 5-HIAA is also greatly increased in the first attack of chronic relapsing allergic encephalomyelitis, indicating a potential explanation of neurological signs.[264]

TABLE 6.8 — **RELATIVE SELECTIVITY OF NEW ANTIDEPRESSANTS FOR SEROTONIN OVER NORADRENALINE AND DOPAMINE UPTAKE**[230]

Antidepressive Drug	5HT vs. Norepinephrine Selectivity	Likelihood for elevation of 5-HIAA AND VMA
Citalopram	1500	Low
Paroxetine	320	
Sertraline	190	
Fluvoxamine	180	
Fluoxetine	20	
Venlafaxine	3.1	
Nefazodone	1.1	
Clomipramine	13	
Imipramine	0.65	
Amitriptyline	0.91	High

Antidepressive Drug	5HT vs. Dopamine Selectivity	Likelihood for elevation of 5-HIAA AND HVA
Citalopram	3900	Low
Paroxetine	1800	
Fluvoxamine	1600	
Clomipramine	1200	
Fluoxetine	170	
Imipramine	85	
Amitriptyline	54	
Sertraline	32	
Venlafaxine	13	
Nefazodone	-	High

The values show the relative selectivity for serotonin reuptake versus either noradrenaline or dopamine. Citalopram, with a ratio of 1500:1, is highly selective for serotonin receptors, so it produces increased turnover of serotonin with corresponding tendency to deplete tryptophan pools with little effect on tyrosine demand for noradrenaline production. Amitriptyline, on the other hand, has a ratio near 1:1, so it tends to cause increases in both neurotransmitters, thus increasing the urinary concentrations of their catabolic products, 5-HIAA and VMA. For most of the drugs, the effects on dopamine relative to serotonin parallel those for noradrenaline. A notable exception is that a patient using clomipramine is unlikely to show elevated HVA along with the elevating effect on 5-HIAA. The data do not indicate the potencies for serotonin uptake. Thus, while citalopram is more selective than sertraline, it is a less potent serotonin reuptake inhibitor.