CHAPTER 1

Control of Plasma Phenylalanine Levels

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Virtually all of the molecules of the essential amino acids that enter the body derive from dietary proteins; high-quality protein sources such as eggs or milk provide around 5 g of phenylalanine (Phe) per 100 g of protein. A large fraction of dietary Phe is hydroxylated to tyrosine in the liver, a process catalyzed by the enzyme Phe-hydroxylase. Plasma Phe levels, like those of the other amino acids, are not regulated, and at any given time they reflect the proportions of protein and carbohydrates in the meal most recently consumed. Since people eat during the day-time, there is an apparent circadian rhythmicity in plasma amino acid concentrations. Protein consumption tends to decrease brain Phe concentrations because although it raises plasma Phe, it increases much more the level of the other neutral amino acids (e.g., valine, leucine, isoleucine, tyrosine, and tryptophan), which compete with Phe for brain uptake. In contrast, consumption of pure Phe or of aspartame increases brain Phe because of the lack of these competing amino acids. In rodents, which have a very active Phe-hydroxylating system, administration of pure Phe or aspartame causes larger increases in plasma and brain tyrosine than in Phe, unless very high doses are given. This does not occur in humans, because Phe hydroxylation is much slower.

The plasma phenylalanine (Phe) pool, like that of other amino acids, is very small compared with the total amount of Phe in the tissues or with the daily Phe turnover. Plasma Phe concentrations are subject to wide variations subsequent to protein intake. However, as discussed below, these variations normally have little or no effect on brain Phe because they are buffered by parallel changes of the other plasma amino acids that compete with Phe for brain uptake (Fernstrom and Faller 1978).

Phe is an essential amino acid, and its requirement, among healthy adults, is estimated at 1 to 2 g per day, equivalent to about 50 g of high-quality protein. When dietary protein is digested and its constituent amino acids absorbed, a large portion of Phe is taken up from the portal blood into the liver; a portion of this Phe is utilized for hepatic protein synthesis.

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and over 95% of the rest is hydroxylated to tyrosine (Tyr). Endogenously released Phe (from tissue proteins, catabolized during periods of fasting) is disposed of by the same biochemical pathway.

Phe is one of the large neutral amino acids (LNAA), a group that also includes the aromatic amino acids tyrosine and tryptophan; the branched-chain amino acids valine, leucine, and isoleucine; and such other amino acids as threonine and methionine. All of the neutral amino acids are transported into the brain by a common facilitated diffusion system present in the capillary endothelial cells comprising the blood-brain barrier, and Phe must compete with these other LNAA to be affected by this transport system. Hence, even when plasma Phe levels remain constant, an increase or decrease in the plasma concentration of the other LNAA will decrease or increase brain Phe levels. Moreover, since the affinity of Phe for the LNAA transport binding sites is somewhat greater than that of the other LNAA, ingestion of pure Phe can have a disproportionately greater effect in reducing brain levels of these other LNAA. The aromatic amino acids relate directly to neurotransmitter synthesis; tyrosine and tryptophan as precursors for the monoamines, and Phe as an inhibitor of the monoamine-synthesizing hydroxylase enzymes. The other LNAA also have an important effect on brain neurotransmitter synthesis by determining the rates at which the aromatic amino acids are allowed to pass from the blood into the brain.

The flux of Phe into and out of peripheral tissues is largely hormone dependent. Insulin secreted in response to food intake facilitates the uptake of phenylalanine into skeletal muscle, with a consequent reduction in plasma Phe levels (Schauder et al. 1983, Felig and Wahren 1971). Hormones that enhance protein breakdown, such as some of the steroid hormones, increase the output of amino acids from peripheral tissues into the plasma. Urinary excretion is a minor route of Phe disposal, accounting for only 120 mg of Phe per day in adults consuming a balanced diet and with average level of physical activity (Tewksbury and Lohrenz 1970).

**Phenylalanine Metabolism**

The liver disposes of most excess Phe by converting it to Tyr. Although products of other pathways of Phe catabolism, such as phenylpyruvic acid and acetyl-phenylalanine, can be detected in the plasma or urine under conditions when the conversion of Phe to Tyr is impaired (e.g., in phenylketonuria), Phe levels rapidly increase to the toxic range, causing tissue damage.

Phe-hydroxylase is a mixed-function oxidase present only in the liver. There are marked species differences in the basal activity of this enzyme, which is highly substrate inducible (Kaufman 1986). Isotopic studies in rats show that the rate of conversion of Phe to Tyr in the fasting state is about 75 μmol/kg per hour; this process contributes about 20% of the tyrosine