# 48 Phenylalanine and tyrosine metabolism in health and disease

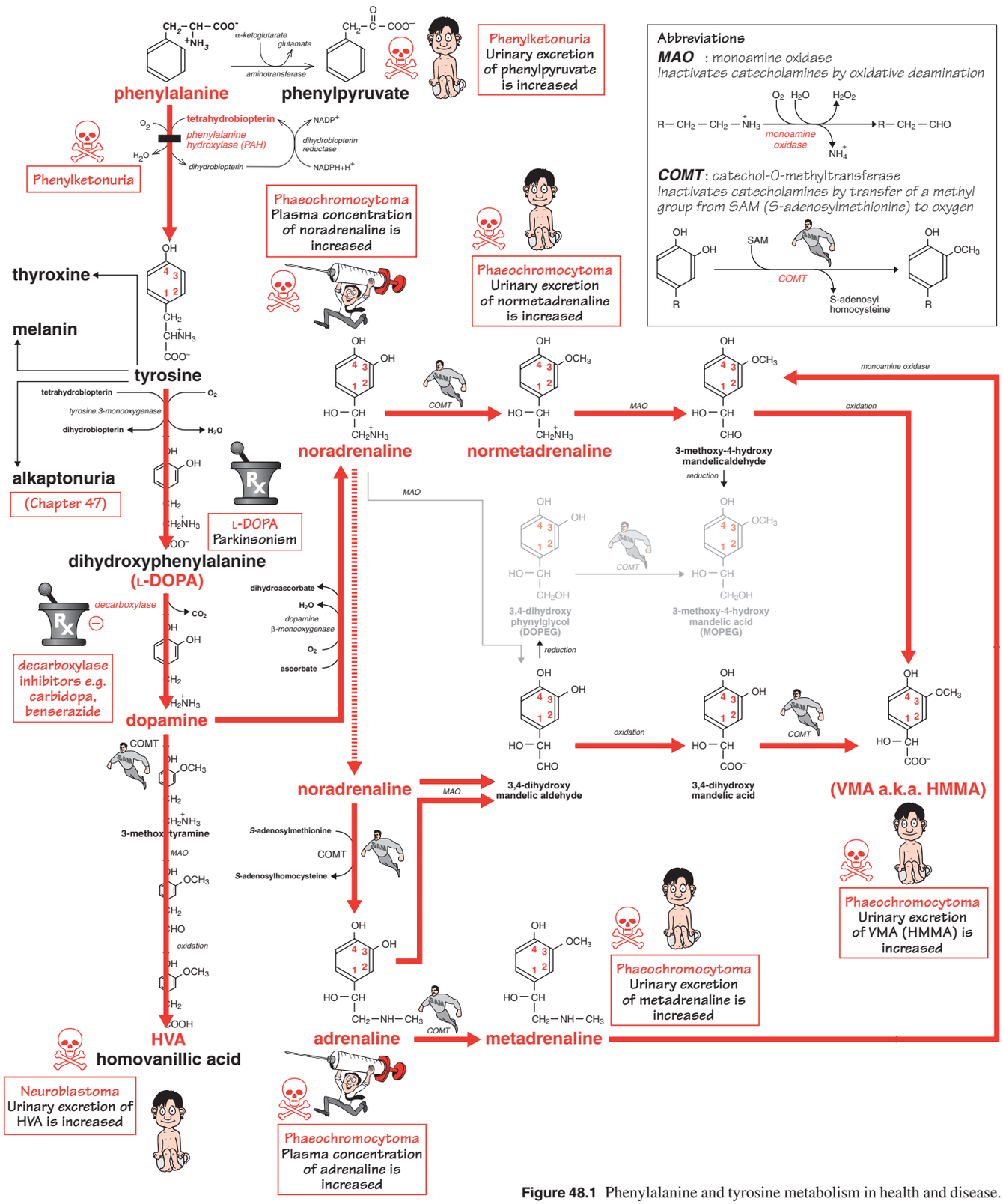


**Figure 48.1** Phenylalanine and tyrosine metabolism in health and disease.

## Metabolism of phenylalanine and tyrosine in health

**Phenylalanine** is an essential amino acid which can be oxidised at position 4 of the aromatic ring by **phenylalanine hydroxylase (PAH)** to form **tyrosine**. PAH (also known as phenylalanine 4-mono-oxygenase), needs **tetrahydrobiopterin ($BH_4$)** as a co-factor. Tyrosine is a precursor of the catecholamine hormones: **dopamine**, **noradrenaline** and **adrenaline**; and also the thyroid hormone **thyroxine**. **Adrenalin**e (the English name from the Latin roots which describes its anatomical relationship to the "*kidney*") has been named in their spirit of independence by our American cousins as **epinephrine** from the Greek roots meaning "*above the kidney*". The name derives from its secretion by the medulla of the adrenal gland (which is situated above the kidney) and awaits renaming by the New World as the "epinephral" gland!

## Metabolism of phenylalanine in disease: Phenylketonuria (PKU)

PKU is a genetic disorder characterised by deficient metabolism of phenylalanine, which results in the accumulation of phenylalanine and of the ketone, phenylpyruvate. Neonatal screening (recently improved by the introduction of tandem mass spectrometry) for PKU assists diagnosis and treatment, which minimises the mental retardation associated with this disorder. Classic PKU is an autosomal recessive disease due to deficient activity of PAH and needs treatment with a low phenylalanine diet. However, some patients lower their blood phenylalanine in response to a tetrahydrobiopterin (**$BH_4$**) loading test, particularly if the pure 6R-**$BH_4$** diastereoisomer is used.

## Metabolism of tyrosine in disease: Alkaptonuria and albinism

These disorders of tyrosine metabolism are described in Chapter 47.

## Metabolism of dopamine, noradrenaline and adrenaline

### Biosynthesis

Tyrosine is the precursor of the **catecholamines** dopamine, noradrenaline and adrenaline. **Adrenaline** is stored in the chromaffin cells of the adrenal medulla and is secreted in the "fight or flight" response to danger. **Noradrenaline** (the "nor" prefix means it is adrenaline without the methyl group) is a neurotransmitter which is secreted into the synaptic cleft at nerve endings. **Dopamine**, which is an intermediate in the biosynthesis of noradrenaline and adrenaline, is localised in dopaminergic neurones, notably in the substantia nigra region of the brain.

### Catabolism

The major enzymes in catecholamine catabolism are **catechol-*O*-methyltransferase (COMT)** and **monoamine oxidase (MAO)**. COMT transfers a **methyl** group from ***S*-a**denosyl**m**ethionine (**SAM**) (Chapter 47) to the **o**xygen at position 3 of the aromatic ring (Fig. 48.1). The pathway taken is a lottery depending whether the noradrenaline and adrenaline are first of all **methylated** (by **COMT**) or alternatively **oxidatively deaminated** (by **MAO**). If chance determines methylation has priority, then the "methylated amines" **normetadrenaline** and **metadrenaline** are formed prior to the MAO reaction and subsequent oxidation to **HMMA** (also known as **vanillylmandelic acid (VMA)** or **3-methoxy-4-hydroxymandelic acid (MHMA)).** On the other hand, if fate determines that the MAO reaction occurs first, then oxidation followed by methylation by COMT is the route taken to HMMA.

## Catecholamine metabolism in disease

### Dopamine deficiency in Parkinson's disease

In this "shaking palsy" as it was first described in 1817, the dopamine-containing neurones in the substantia nigra region of the brain degenerate. Dosing with **L-DOPA**, which crosses the **blood–brain barrier (BBB)** and is a precursor of **dopamine** (which cannot cross the BBB), provided a dramatic breakthrough in treatment. This was refined by combination with drugs such as **carbidopa** and **benserazide** (which cannot cross the BBB) as they inhibit the wasteful catabolism of L-DOPA by peripheral **decarboxylase** activity enabling much smaller doses of L-DOPA to be used as a precursor for dopamine in the brain.

### Excessive production of adrenaline in phaeochromocytoma

A phaeochromocytoma is a rare tumour of the adrenal medulla that produces large amounts of adrenaline and/or noradrenaline. Until the 1990s they were frequently overlooked and most cases were diagnosed *post mortem*. Nowadays, abdominal MRI scans reveal the tumours which can be removed by surgery. Patients suffer episodes of severe hypertension, sweating and headaches. The episodic nature of this condition means that blood and urine samples for laboratory analysis should be collected immediately after an attack as the results of tests collected between episodes are frequently normal. Laboratory investigations are urine collections for **metadrenaline**, **normetadrenaline** and **HMMA**. Sometimes, it is useful to measure blood levels of **adrenaline** and **noradrenaline**.

### Excessive production of dopamine

Neuroblastomas produce large amounts of dopamine anywhere in the body. They usually occur in children under 5 years old and are of neural crest cell origin. Biochemical markers are **HMMA** and the dopamine catabolic product **homovanillic acid (HVA)**.