2.2.1 Introduction

Homocysteine (Hcy) metabolism is closely linked to that of the essential amino acid methionine and thus plays a central role in several vital biological processes. Methionine itself is needed for protein synthesis and donates methyl groups for the synthesis of a broad range of vital methylated compounds. It is also a main source of sulphur and acts as the precursor for several other sulphur-containing amino acids such as cystathionine, cysteine and taurine. In addition, it donates the carbon skeleton for polyamine synthesis [1, 2]. Hcy is also important in the metabolism of folate and in the breakdown of choline. Hcy levels are determined by its synthesis from methionine, which involves several enzymes, its remethylation to methionine and its breakdown by trans-sulphuration.

The metabolism of Hcy-related pathways in man are shown in Fig. 2.2.1. Methionine is converted to its active form S-adenosylmethionine (AdoMet) by methionine adenosyltransferase (MAT). AdoMet is the compound donates a methyl group as co-substrate for at least 39 methyltransferases involved in the formation of important methylated compounds, for example creatine, epinephrine, dopamine, phosphatidylcholine, methylated proteins and methylated DNA [3]. The highly abundant glycine methyltransferase, which transfers a methyl group to glycine, forming sarcosine (N-methylglycine) [4], is a particularly important methyltransferase that fulfils the need for a high-capacity utilisation of AdoMet and is considered to be an integral enzyme in the trans-sulphuration sequence.

The loss of a methyl group from AdoMet in each of the reactions yields S-adenosylhomocysteine (AdoHcy) and this is subsequently hydrolysed to adenosine and Hcy by AdoHcy-hydrolase. Hcy sits at a metabolic branch point and can be remethylated to methionine by way of two reactions. One is the 5-methyltetrahydrofolate dependent reaction catalysed by methionine synthase, which itself is reductively methylated by cobalamin (vitamin B12) and AdoMet, requiring methionine synthase reductase. 5-Methyltetrahydrofolate is generated from 5,10-methylenetetrahydrofolate (MTHF) by MTHF reductase. The second remethylation reaction is catalysed by betaine methyltransferase, which is restricted to the liver, kidney and brain, while methionine synthase is widely distributed.

As well as remethylation, Hcy can be degraded in the trans-sulphuration pathway, which first involves condensation of Hcy with serine forming cystathionine, then breakdown of this compound to cysteine and α-oxo-butyrate. These reactions
are catalysed by cystathionine β-synthase and γ-cystathionase, respectively, both requiring pyridoxal 5’phosphate (vitamin B\textsubscript{6}) as a coenzyme. Cysteine is needed for both protein synthesis and as the precursor of the important antioxidant glutathione. Several enzymatic reactions [5] lead to oxidation of the sulphur atom and further breakdown of cysteine, ultimately forming inorganic sulphate.

The metabolic control of methionine metabolism is complex and involves, for example, changes of enzyme levels in particular tissues, mechanisms linked to the kinetic properties of the various enzymes and their interaction with metabolic effectors [6, 7]. A particularly important metabolic effector is AdoMet. This inhibits the low K\textsubscript{m} isoenzymes of MAT, and MTHF reductase, inactivates betaine methyltransferase, but activates MAT III (the high-K\textsubscript{m} isoenzyme) and cystathionine β-synthase. Therefore, high methionine intake and thus higher AdoMet levels favour trans-sulphuration, and when levels are low methionine is conserved. AdoHcy potently inhibits AdoMet-dependent methyltransferases and both Hcy remethylating enzymes. Another important control mechanism is the export of Hcy from cells into the extracellular space and plasma, which occurs as soon as intracellular levels increase [8].