THE BIOSYNTHESIS OF METHIONINE*

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Summary

The methylation of the thiol group of homocysteine leading to methionine is a biochemical reaction of particular interest since it represents a crossroad of the action of two vitamins, folic acid and cobalamin, both in bacteria and in animals. This enzymic reaction, its mechanism and its regulation which has been studied in detail in several laboratories is discussed. Another route which does not require cobalamin occurs in bacteria and plants. Bacteria possessing both pathways of methionine synthesis show regulatory interconnections between them. Plants which generally are devoid of cobalamin synthesize methionine solely by the cobalamin-independent pathway the mechanism of which is as yet not fully understood.

Introduction

Methionine biosynthesis, i.e. the methylation of the homocysteine sulphydryl group by folic acid derivatives, has attracted considerable attention during the past decade. This pathway is not only important for the production of methionine as a protein building block, but is the very source of metabolically available tetrahydrofolic acid, the one-carbon transfer cofactor required to form N-formyl-methionine, the starter of protein biosynthesis. Moreover, methionine is the precursor of S-adenosyl methionine, the most important and probably universal methyl donor and modifier of macromolecules. Up to now only one methylation reaction bypassing S-adenosyl methionine has been described.

The biosynthesis of methionine from 5-methyl tetrahydrofolates is known to be catalyzed by two types of methyl transferases differing in donor and catalysts. The first type occurs in numerous microorganisms and in animals; it is characterized by the participation of vitamin B\textsubscript{12} (cobalamin) as a cofactor in the reaction. Recent reviews concerning the biochemistry of this vitamin dealt repeatedly with methionine biosynthesis, but because of the limited scope of these articles, this topic could only be touched lightly. The second type which has been comparatively neglected does not require vitamin B\textsubscript{12} and is operative in microorganisms and in higher plants. There are microorganisms which can be caused to synthesize either type of methyl transferase as a consequence of the nutritional environment as in the case of Escherichia coli and Aerobacter aerogenes, or constitutively as in the case of Salmonella typhimurium. Communications on methionine biosynthesis are scattered throughout the literature and often are conflicting; therefore, it seems to be worthwhile to collect the present state of knowledge.

The Vitamin B\textsubscript{12}-Dependent Methyltransferase

As mentioned above, this enzyme type occurs in various organisms. However, the mammalian enzyme appears not to function in de novo methionine synthesis since most mammals are not able to form homocysteine. Instead, it recycles this four-carbon compound into the transmethylation cycles of S-adenosyl methionine.

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This limited function is indicated by the low specific activity of about 20 nmoles/h • mg of the mammalian enzyme in crude extracts as compared to bacterial extracts which possess a tenfold higher activity.

In microorganisms, B12-dependent methyl transfers not only occur in B12-producing species but also in those requiring this vitamin or its precursors. The E. coli cobalamin-dependent enzyme has been studied most thoroughly. It uses 5-methyl tetrahydropteroylmonoglutamate as methyl group donor; the transmethylating activity with the corresponding triglutamate is considerably smaller.

The enzyme is specific for one of the diastereomers of L-5-methyt tetrahydrofolate. Its racemic mixture is produced by boranate reduction of folic acid in presence of excess formaldehyde and may be resolved by ion exchange. However, it is more practical to separate the isomers of 5,10-methylene tetrahydrofolate (the structure of which has been questioned by VISCONTI) and to reduce them separately.

The rotational values of the methylene derivatives which had been reported to differ not only in direction but also considerably in absolute amount were later shown to be nearly identical apart from sign. The dextrarotatory, more acidic methylene compound is the mother substance of the 5-methyl tetrahydrofolate active in methionine biosynthesis.

The methyl transferase may be used analytically to determine the amount of biologically active 5-methyl tetrahydrofolate. Though equilibrium favors the formation of methionine and tetrahydrofolate, it was known that at least the first part of the transmethylation, namely the interaction between folic acid derivative and enzyme, is reversible.

However, the methyl transfer between enzyme and homocysteine is also reversible, since the whole reaction may be forced into the "wrong" direction by incubating the enzyme with its cofactors and the products of the "normal" reaction, L-methionine and tetrahydrofolate. The small amount of 5-methyl tetrahydrofolate thus formed was separated from excess tetrahydrofolate by ion exchange chromatography and determined enzymatically. The equilibrium constant of the formation of methionine from 5-methyl