A. Introduction

The existence of methylation as a metabolic conjugation reaction was first established over a century ago when \textit{N}-methylpyridinium metabolite was detected by HIS (1887) in dog urine after administration of pyridine. Since then, methyl transfer has been shown as one of the most widely utilized conjugation reactions in nature. A wide variety of endogenous molecules as well as xenobiotics are metabolically transformed by methyl transfer reactions; these molecules include proteins, nucleic acids, phospholipids, catecholamines, steroids, alkyl- and arylamines, and thiols. The transfer of a methyl group to a variety of heteroatoms, such as oxygen, nitrogen, and sulfur, is catalyzed by many methyltransferase enzymes with varying degree of substrate selectivity. It is interesting to note that despite a diversity of enzymes catalyzing the methyl transfer reaction, a common methyl donor is shared by all these enzymes, i.e., \textit{S}-adenosyl-L-methionine (AdoMet). The \textit{O}-methylation (THAKKER and CREVELING 1990; BOUDIKOVA et al. 1990; CREVELING 1993; KLEIN et al. 1992), \textit{N}-methylation (ANSHER and JAKOBY 1990), and \textit{S}-methylation (STEVENS and BAKKE 1990; HOFFMAN 1993) reactions have been discussed in recent comprehensive reviews. In this chapter, we will discuss recent developments in the molecular and structural biology of a few representative methyltransferases, i.e., catechol \textit{O}-methyltransferase (COMT, EC 2.1.1.6), hydroxyindole \textit{O}-methyltransferase (HIOMT, EC 2.1.1.4), phenethanolamine \textit{N}-methyltransferase (PNMT, EC 2.1.1.28), histamine \textit{N}-methyltransferase (HMT, EC 2.3.3.8), and \textit{S}-methyltransferases. The reactions catalyzed by these enzymes are shown in Fig. 1. Important new information regarding the amino acid sequences, existence of isoymes, and tissue distribution of these enzymes has been developed by many investigators in the past 3 years. We have reviewed these studies in context of the metabolic, pharmacological, and toxicological importance of the \textit{O}-, \textit{N}-, and \textit{S}-methylation reactions catalyzed by these enzymes.

B. The Methyl Transfer Reaction

While the catalytic mechanisms of various methyltransferases may differ, they all catalyze the reaction by bringing the methyl acceptor substrate,
Fig. 1. Reactions catalyzed by S-adenosyl-L-methionine (AdoMet)-dependent methyltransferases. The methyltransferases shown are only representative members of this class of enzymes and do not constitute an exhaustive list of methyltransferases. AdoHcy, S-adenosylhomocysteine

specifically the heteroatom being methylated, in proximity of the electrophilic methyl group of AdoMet. This is exemplified in Fig. 2 by the methylation of a catechol substrate at the active site of COMT. In the case of the reaction catalyzed by COMT, the transfer of the methyl group to the phenolic oxygen occurs by a SN$_2$ mechanism. This was originally proposed by Higazi et al. (1976), based on an inverse $\alpha$-deuterium secondary isotope...