Administration of methionine sulfoximine (MSO) to rats and mice significantly decreased cerebral levels of S-adenosyl-L-homocysteine (AdoHcy). Concurrent administration of methionine prevented this decrease and, when methionine was given alone, significantly elevated AdoHcy levels resulted in both species. Regionally, AdoHcy levels varied from 20 nmol/g in rat cerebellum and spinal cord to about 60 nmol/g in hypothalamus and midbrain. MSO decreased AdoHcy in all regions tested except striatum, midbrain, and spinal cord. AdoMet/AdoHcy ratios (methylation index) varied from 0.48 in hypothalamus to 2.4 in cerebellum, and MSO administration decreased these ratios in all regions except hypothalamus. AdoHcy hydrolase activity was lowest in hypothalamus, highest in brainstem and, generally, varied inversely with regional AdoHcy levels. MSO decreased AdoHcy hydrolase activity in all regions except hypothalamus and spinal cord. Cycloleucine administration resulted in significantly decreased levels of mouse brain AdoHcy, whereas the administration of dihydroxyphenylalanine (DOPA) failed to affect AdoHcy levels. It is concluded that (a) cerebral AdoHcy levels are more tightly regulated than are those of AdoMet after MSO administration, (b) slight fluctuations of AdoHcy levels may be important in regulating AdoHcy hydrolase activity and hence AdoHcy catabolism in vivo, (c) the AdoMet/AdoHcy ratio reflects the absolute AdoMet concentration rather than the transmethylation flux, (d) the decreased AdoMet

1 Supported by USPHS, NINCDS grant NS-06294.
levels in midbrain, cortex, and striatum after MSO with no corresponding
decrease in AdoHcy suggest an enhanced AdoMet utilization, hence an in-
creased transmethylation in the MSO preconvulsant state.

INTRODUCTION

Attempts to elucidate the mechanism(s) responsible for the seizure-
producing properties of methionine sulfoximine (MSO) have demon-
strated that this agent alters methylation processes in brain. Administra-
tion of MSO resulted in (a) decreased levels of cerebral S-adenosylme-
thionine (AdoMet) in the rat (1), (b) increased activity of histamine-N-
methyltransferase (HMT) in rat and mouse brain (2), and (c) increased
activity of catechol-O-methyltransferase (COMT) in rat brain (2,3). The
lack of effect of MSO (in vivo or in vitro) on the activity of the enzyme
responsible for AdoMet synthesis (ATP:L-methionine-S-adenosyltrans-
ferase) (4,5), paired with the finding of the elevated cerebral HMT and
COMT activity (in vivo) (2), has led to the suggestion that MSO acts by
increasing the flux through methylation pathways (2). The product of
these methylations, S-adenosylhomocysteine (AdoHcy), has been pro-
posed as a regulator of the activities of HMT (6,7), COMT (8),
indolethylamine-N-methyltransferase (9), tRNA methyltransferases
(10,11), and phenylethanolamine-N-methyltransferase (12).

This investigation is concerned with the effect of MSO on AdoHcy
levels and on the activity (in vivo) of the enzyme that hydrolyzes
AdoHcy to adenosine and homocysteine (AdoHcy hydrolase, E.C.
3.3.1.1.). The effect of methionine on the above parameters was also
studied since methionine antagonizes MSO seizures (13,14) as well as
the biochemical alterations in AdoMet (1), HMT, and COMT (2).
AdoHcy levels after the administration of dihydroxyphenylalanine
(DOPA) and cycloleucine were also determined since both agents
decrease brain AdoMet, the former by increasing the utilization of
methyl groups (15,16), and the latter by inhibiting AdoMet synthesis
(16,17). Further, these two drugs, although they markedly decrease
AdoMet levels, do not produce seizures. In fact, in the doses we have
used, DOPA and cycloleucine injected concurrently with MSO confer
some degree of protection against MSO seizures (Schatz and Sellinger,
unpublished work).

We have also investigated the validity of using the AdoMet/AdoHcy
ratio as an index of transmethylation activity of brain tissue, as has been
previously suggested (2,7).