Brain Methylation and Epileptogenesis: The Case of Methionine Sulfoximine

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A brief review of the neurochemical effects of the convulsant agent L-methionine-dl-sulfoximine (MSO) on cerebral methylation reactions is presented. Our findings point to the involvement of a number of endogenous methyl acceptor molecules, including histamine, membrane phospholipids, and membrane proteins, in the mediation of the convulsant effect. Our findings also associate the inhibition of methylations by high levels of S-adenosyl-L-homocysteine in brain with protection against MSO-induced seizures. We propose that MSO acts by eliciting the acceleration of a regulatory methylation–demethylation sequence at key molecular sites, including the benzodiazepine receptor complex, which creates an imbalance in this sequence's normal mediation of convulsant–anticonvulsant mechanisms.

In our epilepsy-related research, we have been investigating the mechanism of action of the long-latency chemical convulsant agent L-methionine-dl-sulfoximine (MSO), which is the neurotoxic factor in nitrogen trichloride–treated wheat gluten and in the resulting canine hysteria [1, 23, 24]. Because of the similarity of MSO-induced convulsions in animals to those of human epilepsy [17, 21, 22], this agent has been the object of numerous physiological and biochemical investigations (see [45] for review).

Biochemical studies have explored the effects of MSO on cerebral glutamate, glutamine, and γ-aminobutyric acid metabolism [8, 9, 20, 25, 29, 36, 38, 41, 42], biogenic amines [2, 6, 28, 37], cyclic nucleotides [12, 13], ammonia [10, 14, 18, 27, 44], and polyamines [26].

In addition, in 1975 we reported that the intraperitoneal administration of MSO to rats resulted in a significant decrease in the level of cerebral S-adenosyl-L-methionine (AdoMet), the universal methyl donor molecule [31]. We subsequently showed that this decrease is not the result of a reduced biosynthesis of AdoMet [35], but rather, it is a consequence of an overall increase in the utilization of AdoMet that sets in about halfway through the 5- to 6-hour MSO preconvulsant period [30, 32]. Obversely, we also showed that higher than normal levels of brain S-adenosyl-L-homocysteine (AdoHcy), the demethylated product of AdoMet and a potent inhibitor of cellular transmethylations, are associated with significant antagonism to the action of MSO.

In the present report, the effects in the mouse of a convulsant dose of MSO, which results in an increase in cerebral methylations, are contrasted with the effects of a joint administration of adenosine and DL-homocysteine thiolactone (Ado + HcyT), a treatment that results in extremely high AdoHcy levels in brain [34], significant inhibition of cerebral methylations [33, 34], and protection against MSO seizures.

Methods

Mice were injected intraperitoneally with MSO and with Ado + HcyT at the doses indicated in Figures 1 to 4 and Tables 1 to 4. In experiments in which the specific radioactivities of brain methionine, AdoMet, and AdoHcy were to be determined, carbon 14–labeled methionine ([1-^{14}C] methionine) was used, while in experiments in which the in vivo phospholipid and carboxyl methylation of proteins was to be determined, tritium-labeled methyl methionine ([methyl-^{3}H]methionine) was used. [3,4-^{14}C]Methionine was used as the precursor of polyamines. The radioactively labeled methionine and [2,5-^{3}H]histamine were injected intraventricularly while the animals were under light ether anesthesia.

The specific radioactivity values of methionine, AdoMet, and AdoHcy were determined by the procedure of Schatz and colleagues [34], those of methyl histamine were determined by the procedure of Schatz and colleagues [30], and those of the polyamines were determined by the procedure of Porta and colleagues [26]. In vivo phospholipid methylation was determined by the procedure of Hirata and colleagues [16], as modified by Schatz and colleagues [33], while in vivo protein carboxyl methylation was quantitated by
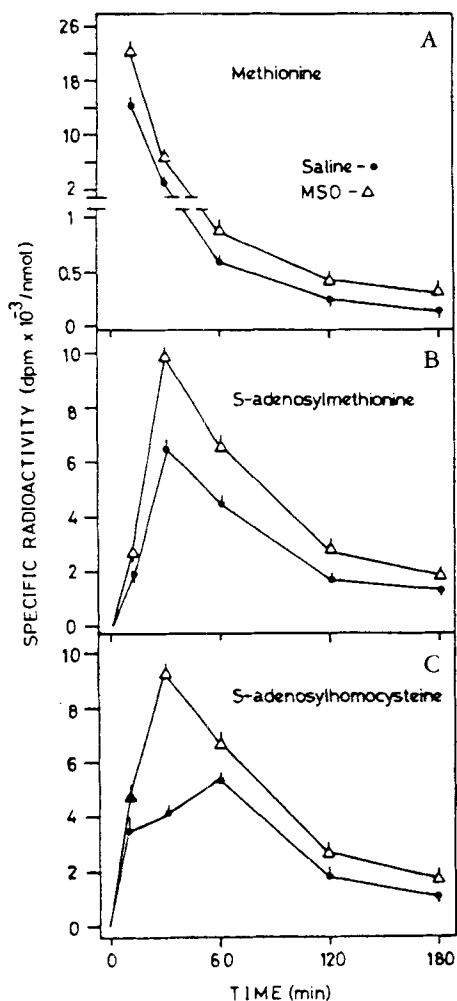
Fig 1. Effect of L-methionine-dl-sulfoximine (MSO) on the specific radioactivity of (A) methionine, (B) S-adenosyl-L-methionine, and (C) S-adenosyl-L-homocysteine in mouse brain. Mice were injected intraperitoneally with saline (10 ml/kg) or MSO (150 mg/kg) 180 minutes prior to killings. Carbon 14–labeled methionine (2 μCi/10 μl of artificial cerebrospinal fluid) was injected into the lateral cerebral ventricle 10, 30, 60, 120, and 180 minutes prior to killing. Specific radioactivity values are expressed in disintegrations per minute (dpm) × 10⁻³ per nanomole as means ± SEM in from 5 to 7 mice. Open symbols denote values significantly different from corresponding controls at the 0.05 level using Student's t test (two-tailed).

the procedure of Kim [19], as modified by Schatz and colleagues [33].

Results

The specific radioactivity of [¹⁴C]methionine was increased 52 to 120% in MSO-treated mice (Fig 1A). This increase could not be offset by the 25% decrease in endogenous methionine levels noted after MSO administration (data not shown). Conversely, the administration of Ado + HcyT resulted in increases in endogenous methionine (data not shown) and in [¹⁴C]methionine specific radioactivity values that were of similar magnitude (28 to 34%). The [¹⁴C]AdoMet specific radioactivity values after MSO administration (Fig 1B) were significantly elevated, whereas they remained unchanged after Ado + HcyT administration (Table 1). The MSO and Ado + HcyT treatments had opposite effects on the specific radioactivity values of cerebral AdoHcy, as illustrated by the relevant data in Figure 1C and Table 1, respectively. Table 2 shows that MSO administration increased the rate of conversion of cerebral histamine to its single metabolite, methyl histamine, while Ado + HcyT administration decreased this conversion rate.

Similarly, Table 3 illustrates the opposite effects of MSO and Ado + HcyT on the conversion of methionine (through AdoMet and decarboxylated AdoMet) to the cerebral polyamines spermidine and spermine. Cerebral phospholipid methylation was selectively and differentially affected by the MSO and Ado + HcyT treatments, as illustrated in Figure 2.

Protein carboxyl methylation was also significantly increased (90%) after MSO administration and was significantly decreased after Ado + HcyT administration (Fig 3). Most recently, we also found that in rat brain, the MSO treatment increases the carboxyl methylation of proteins contained in a detergent-solubilized membrane fraction that also contains benzodiazepine receptor proteins (Sellinger OZ, Gregor P: unpublished observations, 1983) (Table 4).

Finally, we established that treatment of mice with Ado + HcyT increases the MSO seizure latency period. The maximal (80%) increase occurred in mice with markedly elevated AdoHcy levels in brain (Fig 4).

Table 1. Effect of Ado + HcyT on the Specific Radioactivity of Methionine, AdoMet, and AdoHcy in Mouse Brain[a]

Experimental Group	Methionine	AdoMet	AdoHcy
Control	5.94 ± 0.59	5.53 ± 0.27	2.18 ± 0.31
Ado + HcyT (200 mg/kg, 40 min prior to killing)	7.94 ± 0.82[b]	5.88 ± 0.39	0.72 ± 0.05[c]

[a]The values are in disintegrations per minute × 10⁻³ per nanomole (mean ± SEM). There were 7 animals per group. Two microcuries of carbon 14–labeled methionine was given to each animal intraventricularly 1 hour prior to killing.
[b]$p < 0.05$.
[c]$p < 0.001$.

Ado + HcyT = adenosine + DL-homocysteine thiolactone; AdoMet = S-adenosyl-L-methionine; AdoHcy = S-adenosyl-L-homocysteine.

Table 2. *Effects of MSO and Ado + HcyT*
on the Methyl Histamine Conversion Index in Mouse Brain

Experiment[a]	Conversion Index (nmol/gm)[b]	% Change
EXPERIMENT 1		
Control	2.2	
MSO (170 mg/kg, 3 hr prior to killing)	4.5	+105
EXPERIMENT 2		
Control	7.3	
Ado + HcyT (200 mg/kg, 40 min prior to killing)	2.5	−66

[a]Two microcuries of [2,5-^{3}H]histamine (specific activity, 7.7 Ci/mmol) was injected intraventricularly in each animal, 15 and 5 minutes before killing, in Experiments 1 and 2, respectively.
[b]Disintegrations per minute per gram of tritium-labeled methyl histamine ([methyl-^{3}H]histamine) divided by disintegrations per minute per nanomole of [^{3}H]histamine.

MSO = L-methionine-*dl*-sulfoximine; Ado + HcyT = adenosine + DL-homocysteine thiolactone.

Fig 2. *Effects of* L-methionine-dl-sulfoximine *(MSO) and adenosine +* DL-homocysteine thiolactone *(Ado + HcyT) on brain phospholipid methylation. Mice were injected intraperitoneally with saline (10 ml/kg) or MSO (150 mg/kg) 180 minutes prior to killing, while Ado + HcyT (200 mg/kg) or saline and polysorbate 80 (20 ml/kg) was injected intraperitoneally 40 minutes prior to killing. Tritium-labeled methyl methionine (5 μCi/10 μl of artificial cerebrospinal fluid) was injected into the lateral cerebral ventricle 60 minutes prior to killing. Values are expressed as means ± standard error of the mean (indicated by the height of the single vertical lines on the bars) in 6 or 7 mice. Asterisks denote values significantly different from values in control mice at the 0.05 level using Student's t test (two-tailed).* DPM = disintegrations per minute; PME = {^{3}H} phosphatidylmonomethylethanolamine; PMME = {^{3}H}phosphatidyldimethylethanolamine; PC = {^{3}H}phosphatidylcholine.

Discussion

One assumption guiding the interpretation of the results depicted in Figure 1 is that intraventricularly administered [^{14}C]methionine mixed with endogenous methionine. The higher-than-control specific radioactivity values of methionine (see Fig 1A) suggest that this increase occurred despite a partial decrease in endogenous methionine levels (data not shown). A likely explanation of the increased specific radioactivity values of AdoMet and AdoHcy in brains of the MSO-treated mice (see Fig 1B, C) is that the methionine was derived from a "hotter" pool than the control
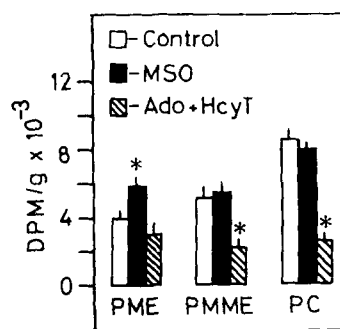
pool. The finding that the specific radioactivity of AdoMet peaked at 30 minutes in both control and MSO-treated brains (see Fig 1B), while that of AdoHcy peaked at 30 minutes in the MSO-treated brains but at 60 minutes in the control brains, is consistent with the premise that the overall flux of methionine through the transmethylation and polyamine-formation pathways of brain accelerates in the brains of MSO-treated mice.

Table 3. *Effects of MSO and Ado + HcyT on the Conversion of {3,4-^{14}C}Methionine to {^{14}C}Spermidine and {^{14}C}Spermine in Mouse Brain*

Experiment	[^{14}C]Spermidine (dpm/nmol)	[^{14}C]Spermine (dpm/nmol)
EXPERIMENT 1[a]		
Control	28.4 ± 1.0 (7)	40.1 ± 1.2 (7)
MSO (150 mg/kg, 3 hr prior to killing)	42.7 ± 3.9 (11)[c]	60.6 ± 4.3 (11)[d]
EXPERIMENT 2[b]		
Control	12.3 ± 0.7 (6)	16.8 ± 0.9 (6)
Ado + HcyT (500 mg/kg, 40 min prior to killing)	8.84 ± 0.67 (6)[c]	13.0 ± 1.19 (6)[c]

[a]Two microcuries of carbon 14–labeled methionine ([^{14}C]methionine) was injected intraventricularly.
[b]One microcurie of [^{14}C]methionine was injected intraventricularly.
[c]$p < 0.005$.
[d]$p < 0.001$.
[e]$p < 0.05$.

N.B.: The pulse time was 1 hour in both experiments. Values are mean ± SEM.

MSO = L-methionine-*dl*-sulfoximine; Ado + HcyT = adenosine + DL-homocysteine thiolactone; dpm = disintegrations per minute.
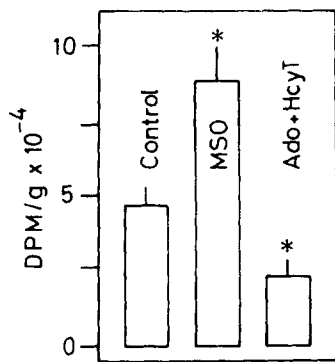
Fig 3. Effects of L-methionine-dl-sulfoximine (MSO) and adenosine + DL-homocysteine thiolactone (Ado + HcyT) on in vivo brain protein carboxyl methylation. (For details of drug treatment, expression of results, statistical analysis, and definition of terms see Figure 2.)

Table 4. Effect of MSO on the In Vivo
Carboxyl Methylation of Rat Brain Proteins

Experimental Group	Homogenate		Soluble		
	dpm	dpm/mg	dpm	% H	dpm/mg
Control	30,400	294	980	3.2	260
MSO	33,300	445	1,430	4.3	591
MSO/control	1.10	1.52	1.46	. . .	2.27

N.B.: MSO (150 mg/kg) was injected intraperitoneally, and tritium-labeled methyl methionine ([methyl-^{3}H] methionine) (specific activity, 8 Ci/mmol) containing 18.7 μCi of radioactivity per gram of brain was injected intraventricularly 2 hours later. One hour after the intraventricular injection, the brains of the 26-day-old rats containing 18.7 μCi of radioactivity per gram of brain were homogenized individually (4 controls and 4 MSO-treated) by means of the Polytron homogenizer (Brinkmann Instruments) in 10 mM sodium phosphate buffer containing 0.2 M sodium chloride, at pH 6.8. The crude membrane fraction was prepared according to Burch and Ticku [3]. The membrane pellet was suspended in buffer containing 1% Lubrol-Px (Sigma products; L = 3753), and after 30 minutes at 4°C, the suspension was centrifuged for 45 minutes at 100,000 g. The clear supernatant was dialyzed against buffer for approximately 12 hours at 4°C, yielding the soluble fraction, which contained the solubilized benzodiazepine receptor complex.

H = homogenate; MSO = L-methionine-dl-sulfoximine; dpm = disintegrations per minute.
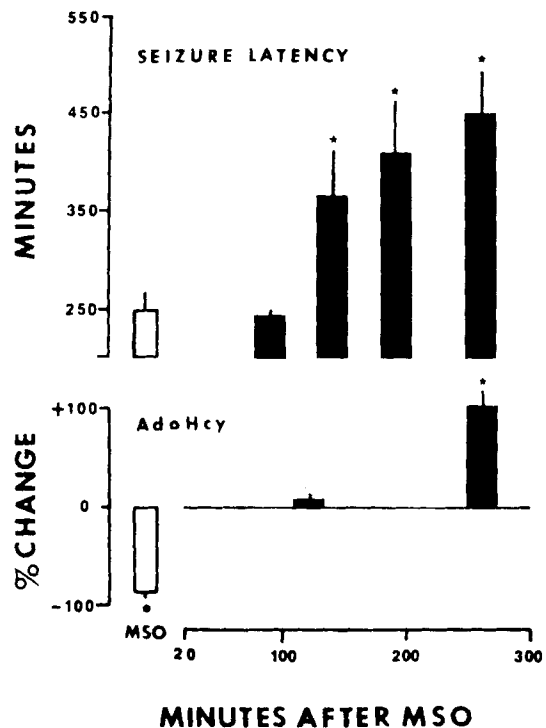

Fig 4. Effect of adenosine + DL-homocysteine thiolactone (Ado + HcyT) on S-adenosyl-L-homocysteine (AdoHcy) levels and L-methionine-dl-sulfoximine (MSO) seizure latency. Mice were injected intraperitoneally with MSO (125 mg/kg), after which seizure latency was determined (top panel, open bar). Animals not convulsing within 8 hours were arbitrarily assigned a seizure latency of 480 minutes. Another group of mice received MSO 180 minutes prior to killing, after which the AdoHcy levels in brain were determined (bottom panel, open bar). Mice were also injected with MSO followed by Ado + HcyT, at the times indicated following MSO administration, after which either seizure latency values (top panel, closed bars) or AdoHcy levels (bottom panel, closed bars) were determined. Values are expressed in minutes (top panel) or in percentage changes (bottom panel) as means ± SEM in 8 mice. Stars denote values significantly different from values in mice treated with MSO only (open bars) using Student's t test (two-tailed) at the 0.05 level.

It should be noted that these interpretations are still not conclusive, given the metabolic and dynamic complexities of the biochemical pathways involving methionine in cerebral tissue. Our failure to measure the extent of the recycling of cerebral homocysteine back to methionine under the prevailing experimental conditions further biases the purely quantitative aspects of the findings. In our estimation, however, the diametrically opposite qualitative effects of MSO and Ado + HcyT are sufficiently documented so as to be of physiological validity in the convulsant context within which they were obtained.

Since the ability of MSO to elicit seizures presum-

ably involves neural membranes, it was of interest to examine the effects of MSO and Ado + HcyT on the methylation of some membrane components. The increase in [^{3}H]phosphatidylmonomethylethanolamine ([^{3}H]PME) levels after MSO administration (see Fig 2) reflects increased phospholipid methyltransferase I (PMT I) activity and increased synthesis of PME, a normal constituent of brain [39]. It has been proposed that the methylation of phosphatidylethanolamine (PE) to PME is the initiating event in decreasing membrane microviscosity [15]; hence the increase in [^{3}H]PME after MSO administration may reflect increased membrane fluidity. This may further indicate that cerebral membranes become labile, or more apt to promote impulse firing in the MSO-treated brain than in the normal brain. Conversely, treatment with Ado +

HcyT inhibited the formation of [³H]phosphatidyl-dimethylethanolamine ([³H]PMME) and [³H]phosphatidylcholine ([³H]PC) without altering [³H]PME levels [33] (see Fig 2). The lack of an effect on [³H]-PME may be related to the fact that membranes are relatively impermeable to AdoHcy [7, 34, 43] and thus prevent access to the PMT I located on the cytoplasmic side of the cell membrane [4, 5, 15, 35]. Conversely, the Ado + HcyT–induced decrease in [³H]PMME and [³H]PC reflects inhibition of the enzyme PMT II located on the outside of the synaptosomal membrane [4, 5] and therefore readily accessible to external Ado-Hcy, which is known to bind to brain membranes [11].

The stimulation of particulate protein carboxyl methylation after MSO administration (see Fig 3) further supports the hypothesis that membrane function may be altered during MSO-induced epileptogenesis. The marked inhibition of this process after Ado + HcyT administration (see Fig 3) agrees with this premise. Additional evidence that MSO may alter membrane function is provided by the recent finding that (Na⁺ + K⁺)-adenosinetriphosphatase activity in brain is increased after MSO administration [40] and by our preliminary results on the enhancing effects of MSO on the carboxyl methylation of synaptic membrane proteins (Sellinger OZ, Gregor P: unpublished observations, 1983).

The administration of Ado + HcyT also greatly increased the latency period to MSO-induced seizures and decreased their incidence (see Fig 4). The finding that this protective effect was greatest when AdoHcy levels in brain were markedly elevated further supports the concept that it is the ensuing inhibition of brain transmethylations that mediates this effect.

The bulk of the findings presented in this paper thus tend to be in support of the principal premise that motivated our research, namely, that the convulsant action of MSO is mediated by the hypermethylation of a variety of cerebral methyl acceptor molecules. Work is in progress to determine whether benzodiazepine receptor proteins are the molecular mediators of this convulsant–anticonvulsant process, via a mechanism of on-and-off carboxyl methylation and demethylation involving their glutamate and aspartate residues.

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