Pharmacology Biochemistry & Behavior, Vol. 31, pp. 797–802. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Study of the Hypothermia Induced by Methionine Sulfoximine in the Rat

MADELEINE GINEFRI-GAYET AND JACQUES GAYET

Laboratoire de Physiologie Générale, Faculté des Sciences, Université de Nancy I
B.P.239, 54506 Vandoeuvre-lès-Nancy Cedex, France

Received 10 February 1988

GINEFRI-GAYET, M. AND J. GAYET. *Study of the hypothermia induced by methionine sulfoximine in the rat.* PHARMACOL BIOCHEM BEHAV 31(4) 797–802, 1988.—L-Methionine sulfoximine (MSO) intraperitoneally injected at subconvulsive and convulsive doses induced a rectal hypothermia in the restrained rat maintained at an ambient temperature of 23°C; this hypothermia developed during the preconvulsive period, and it was not suppressed by simultaneous injection of L-methionine which antagonized the behavioral effects of ammonia elevated contents in the central nervous sytem. The development of rectal hypothermia was faster when the injection of MSO was made into the lateral cerebral ventricle and particularly into the third ventricle. MSO-induced hypothermia seemed to be a poikilothermia-like state in the cold environment with retention of a normal regulation in the heat environment. Infusion of MSO into the anterior hypothalamic/preoptic (AH/PO) area induced a rapid rectal hyperthermia, but infused into the mammillary region MSO had no effect on rectal temperature. It is suggested that rectal hypothermia induced by MSO may be directly related to a depressive effect on glucose oxidative metabolism in cell structures, maybe astroglial cells, located in the vicinity of the ventricle or the capillary walls.

Methionine sulfoximine Rectal hypothermia Preconvulsive period Intracellular ammonia Glucose metabolism Astrocytes

THE molecule of L-methionine-d,l-sulfoximine (MSO) induces seizures which are of particular interest to the neurochemist and the neurophysiologist because of their resemblance to human epilepsy and their ready reproducibility in various species of experimental animals (37). Since these seizures occur only after a long latency, and seem to involve generalized changes in transmitter levels or metabolism (4, 8, 25–27, 29), it appears that no single brain region or pathway is uniquely involved (32). In rat and mouse, tonic and clonic convulsions appeared only after a 3- to 6-hour period, depending on the dose of MSO intraperitoneally injected; during this preconvulsive latency period the animals exhibited an increasing syndrome of ataxia, associated with an inability to respond to external nociceptive stimuli (12, 14, 31, 35). In the freely moving rat at a room temperature of 20°C the rectal temperature first dropped about 2°C below control levels and reached the low between the 5th and 7th hour following administration of MSO, 100 mg/kg IP, and between the 3rd and 4th hour following 200 mg/kg. Subsequently, there was a gradual rise to a rectal normothermia or a mild hyperthermia, and it was during this rise that the rats developed episodic behavioral manifestations: an episodic running behavior and/or generalized convulsions (35). The transient hypothermia occurring immediately before the onset of episodic running behavior was considered to be a poikilothermia-like condition rather than true hypothermia. The temperature of MSO-treated rats submitted to a severe cold challenge progressively lowered, while it progressively rose when the rats were kept in a heat environment. These data indicated an unstable state, but not a complete loss, of the regulating mechanism for the maintenance of body temperature (35). Studies involving genetically nonsensitive rats treated by MSO revealed that this molecule is an "audiogenic agent" in that it produced reversible audiogenic susceptibility which closely followed the initial transient rectal hypothermia of animals (34). Moreover, the treatment of genetically audiogenic sensitive rats with MSO made them temporarily insensitive to audiogenic stimulation, corresponding with the period of transient hypothermia (36). Chronologically, the reduction of audiogenic susceptibility is coincident with the hypothermia induced by MSO and its development occurs during the recovery stage of the transient hypothermia.

It is tempting to investigate the possible relationship between MSO-induced hypothermia and reduced seizure susceptibility. Does this early transient drop in body temperature create, in particular, structures of the central nervous system neurochemical and neurophysiological conditions suited for induction of spontaneous or physically- or chemically-induced seizures? For this purpose, it is necessary to study the possibility that the induction of hypothermia by MSO may be mediated at least in part by an action on the central nervous system. In the present report, we confirm that MSO intraperitoneally injected to the restrained rat in-

duced a deep rectal hypothermia for several hours; its rate was accelerated after an intracerebroventricular injection of the molecule, particularly into the third ventricle; it appeared to be a poikilothermia-like state against cold with retention of a normal regulation against heat. We suggest that this drop in body temperature probably originated from an impairment of energy metabolism at the level of cerebral structures, maybe astroglia, in the vicinity of ventricle and capillary walls.

METHOD

Animals

Male Wistar and Sprague-Dawley rats weighing between 225 and 300 g were used throughout the experiments; they were housed individually in Plexiglas cages in a temperature-controlled environment of 23±1.0°C, with a 12-hr dark/light cycle and with free access to granular feed and water. All experiments began between 09:00 and 11:00 hr.

Measurement of Rectal and Skin Temperatures

The rat was placed in a well-ventilated Harvard universal acrylic restrainer. Rectal temperature was monitored with a lubricated temperature probe (Yellow Springs Instrument Co., Yellow Springs, OH, model 402) inserted 6 cm into the rectum, with a tele-thermometer (Yellow Springs Instrument Co., model 43) connected to a potentiometric recorder (Servotrace, model PE-10). The probe was secured in place by taping it lightly to the base of the tail. For measurement of skin temperature the probe (Yellow Springs Instrument Co., model 421) was placed at the surface of the shaved skin at the base of the tail and was secured in place by taping it.

Environmental Temperature

Experimental environmental temperature was controlled throughout the testing period. Heated environment (36±0.5°C) was maintained in a thermostated, ventilated, and lighted incubator. Cold environment (11±1.0°C) was achieved in a thermostated, ventilated, and lighted cold box.

Intraperitoneal Injection

L-Methionine-d,l-sulfoximine (MSO) (Sigma, St. Louis, MO) (50–150 mg/kg body weight) dissolved in 1.0 ml per 200 g body weight of sterile 0.9% NaCl was injected intraperitoneally; control animals received the same volume of sterile 0.9% NaCl. In some experiments, MSO (150 mg/kg) was administered jointly with L-methionine (Sigma) (700 mg/kg) in a total volume of 1.0 ml per 200 g body weight of sterile 0.9% NaCl.

Intracerebroventricular Injections

One week prior to the experiment, the rat was placed in a David Kopf model 900 stereotaxic apparatus, under Equithesin (3 ml/kg IP) anesthesia. A unilateral 26-gauge guide cannula cut to a length of 11.0 or 13.0 mm from stainless steel tubing (Hamilton) was implanted, perpendicularly to the surface of the skull, with the tip resting 1.0 mm above one lateral ventricle or the third ventricle, respectively. The coordinates (1) for the lateral ventricle were (in mm): A=7.0, L=1.4, H=8.5 and for the third ventricle were (in mm): A=6.1, L=0.0, H=3.5; the cannula was held in place by dental cement and stainless steel anchor screws inserted into the calvarium (18). A stainless steel stylet cut to a length of 11.0 or 13 mm was placed into the guide cannula and left until the experiment began. MSO (50–75 μg per rat), dissolved in sterile 0.9% NaCl or sterile artificial cerebrospinal fluid (20), was injected in a volume of 10 μl over a period of 2 min, through a 33-gauge injector needle cut to a length of 12 or 14 mm from stainless steel tubing (Hamilton), connected with a length of polyethylene tubing (internal diameter 0.30 mm) to a 50 μl-capacity Hamilton microsyringe driven by a Braun variable speed infusion pump. The injector needle extended 1.0 mm beyond the tip of the guide cannula. The injector needle was kept in place for 1 min on completion of the injection, before being slowly withdrawn. Immediately following removal of the needle the stylet was inserted into the guide cannula. After each experiment, 10 μl of a 1% bromophenol blue solution in bidistilled water were injected into the lateral or the third ventrical under Equithesin (4 ml/kg IP) anesthesia, then the rat was perfused intracardially with buffered formalin and the brain was cut longitudinally in order to verify the coloration of all the ventricle cavities (18).

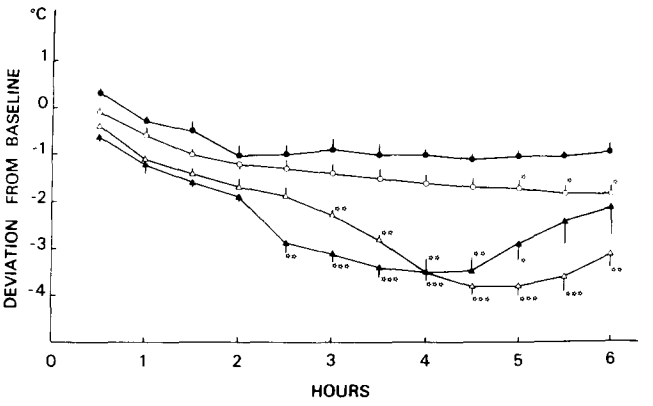

FIG. 1. Changes in rectal temperature by an intraperitoneal injection of varying doses of MSO to restrained rats, at an ambient temperature of 23°C. ●: saline controls (n=5); ○: 50 mg/kg of MSO (n=9); △: 100 mg/kg of MSO (n=10); ▲: 150 mg/kg of MSO (n=10). Time in hours. *$p<0.05$, **$p<0.01$ and ***$p<0.001$, for significant differences compared with saline controls.

Intracerebral Infusions

Surgical procedure was the same as for intracerebroventricular injection. An indwelling 26-gauge guide cannula was implanted unilaterally 1.0 mm above a site in the anterior hypothalamic/preoptic area (AH/PO area) using the following coordinates (1) (in mm): A=7.3, L=0.4, H=3.0, and in the mammillary region using the following coordinates (22) (in mm): A=5.2, L=0.5, H=16, the interaural line being the reference point. MSO (25 μg per rat) dissolved in sterile 0.9% NaCl solution was infused in a volume of 0.5 μl over a period of 3 min through a 33-gauge injector needle using a 5 μl-capacity Hamilton microsyringe, as described for intracerebroventricular injection. The injection needle extended 1.0 mm beyond the tip of the guide cannula, and it was kept in place for further 10 min, before being slowly withdrawn. After each experiment, 0.5 μl of a 1% bromophenol blue solution in bidistilled water was infused in the AH/PO area and the mammillary region of the rats under Equithesin

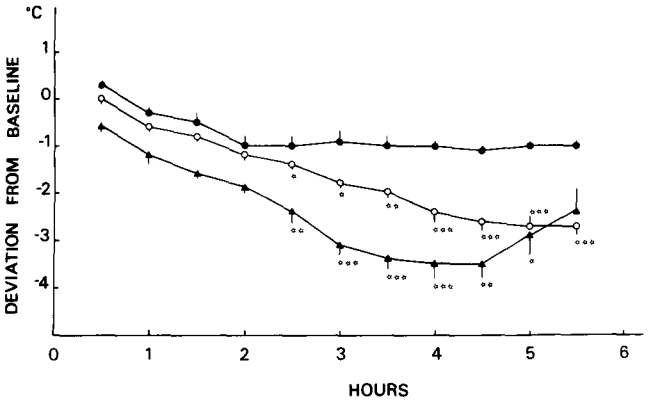

FIG. 2. Changes in rectal temperature produced by an intraperitoneal injection to restrained rats of either MSO (▲: 150 mg/kg of MSO) (n=4) or MSO together with L-methionine (○: 150 mg/kg of MSO plus 700 mg/kg of L-methionine) (N=4), at an ambient temperature of 23°C. ●: saline controls (n=5). Time in hours. ⋆$p<0.05$, ⋆⋆$p<0.01$ and ⋆⋆⋆$p<0.001$, for significant differences compared with saline controls.

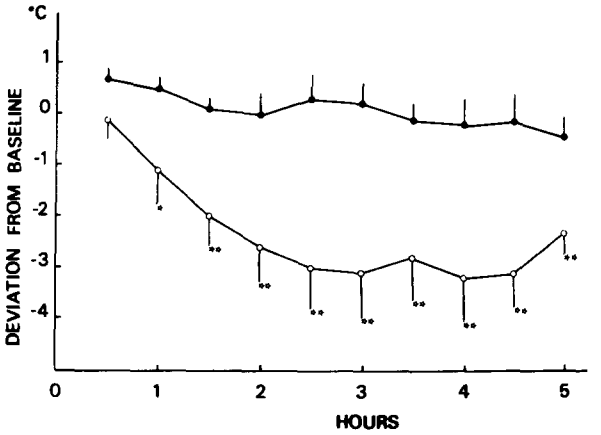

FIG. 3. Changes in rectal temperature produced by an injection of MSO into a lateral cerebral ventricle of restrained rats, at an ambient temperature of 23°C. ●: saline controls (n=5); ○: 50 μg of MSO per rat (n=4). Time in hours. ⋆$p<0.05$ and ⋆⋆$p<0.01$, for significant differences compared with saline controls.

anesthesia (4 ml/kg IP), then they were perfused intracardially with buffered formalin, and the brain was sliced in cryostat in order to verify the stereotaxic placement of the microinfusion site (18).

Statistical Analysis

In the statistical treatment of the values obtained the level of significance was set to 0.05 and calculated by Student's *t*-test.

RESULTS

Mean rectal temperature of normal restrained rats was 38.4±0.4°C at an ambient temperature of 23±1.0°C, and it was considered as a baseline in our experiments.

Hypothermia Induced by an Intraperitoneal Injection of MSO

MSO (50–150 mg/kg) was intraperitoneally injected to restrained rats kept at an ambient temperature of 23±1.0°C (Fig. 1). At a subconvulsive dose of 50 mg/kg, a moderate rectal hypothermia developed with a minimum of 1.75±0.2°C ($p<0.05$) between the 4th and 6th hour following injection of MSO. At a dose of 100 mg/kg, MSO induced a deep and transient hypothermia with a nadir of 3.80±0.2°C ($p<0.001$) at about 4.30 hours; this hypothermia was associated with the development of a syndrome of ataxia which extended up to the period of rectal normothermia. At a dose of 150 mg/kg, rectal temperature dropped more rapidly since it reached a decrease of 2.9±0.2°C ($p<0.01$) at 2.30 hours and a minimum of 3.5±0.2°C ($p<0.001$) at 4 hours; the subsequent rise of rectal temperature coincided with the beginning of episodic tonic and clonic seizures. A series of experiments performed in the same experimental conditions showed that skin temperature of the MSO-treated rats did not vary significantly relative to saline controls. The administration of MSO (150 mg/kg IP) together with L-methionine (700 mg/kg IP) was followed by a progressive rectal hypothermia reaching a minimum of 2.7±0.2°C ($p<0.01$) at 5 hours; this drop in the rectal temperature was never followed by any syndrome of ataxia or episodic behavioral manifestation (Fig. 2).

Hypothermia Induced by an Intracerebroventricular Injection of MSO

MSO was injected unilaterally into the cerebral lateral ventricle using doses ranging from 50 to 75 μg per restrained rat. Figure 3 illustrates a series of experiments performed at a dose of 50 μg of MSO at an ambient temperature of 23±1.0°C. The rectal hypothermia developed rapidly reaching 2.0±0.6°C ($p<0.01$) at 1.30 hours and a minimum of about 3.0±0.8°C ($p<0.01$) between 2.30 and 4.30 hours. The rat exhibited a syndrome of ataxia and tonic and clonic seizures appeared as soon as the 5th hour following MSO injection. As for its systemic injection, intraventricular administration of MSO was followed by a rectal hypothermia which was not dose-dependent within the range of 50 to 75 μg MSO per rat.

In the same experimental conditions, MSO (50 to 75 μg per rat) was injected in the third ventricle. Figure 4 illustrates a series of experiments performed at a dose of 60 μg of MSO at an ambient temperature of 23±1.0°C. Rectal temperature decreased rapidly the minimum of 2.6±0.3°C ($p<0.01$) being reached 2 hours after the injection, followed by very rapid return to rectal normothermia 4 hours later. The rats showed a rapid development of the syndrome of ataxia appearing approximately at 30 minutes, with episodic seizures appearing as soon as 4 hours. About 8 hours later a righting reflex was restored without episodic tonic and clonic seizures. Injected at a dose of 75 μg per rat, MSO appeared to be lethal for a high percentage of animals.

Influence of a Warm or Cold Ambient Temperature

Two sets of experiments were performed with restrained rats submitted to an unilateral intracerebroventricular injection of MSO (75 μg per rat into a lateral ventricle). The

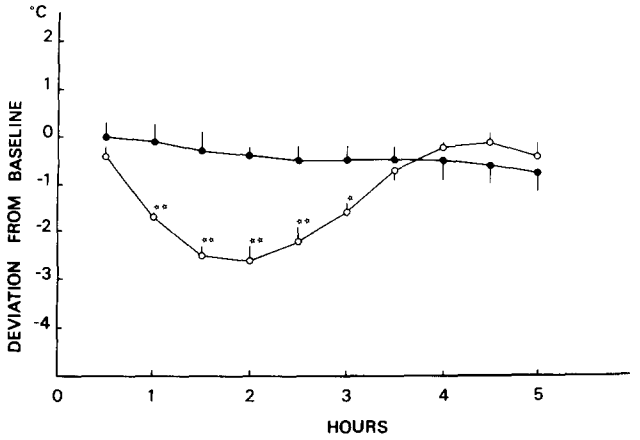

FIG. 4. Changes in rectal temperature produced by an injection of MSO into the third ventricle of restrained rats, at an ambient temperature of 23°C. ●: saline controls (n=4); ○: 60 μg of MSO per rat (n=5). Time in hours. ⋆$p<0.01$ and ⋆⋆$p<0.001$, for significant differences compared with saline controls.

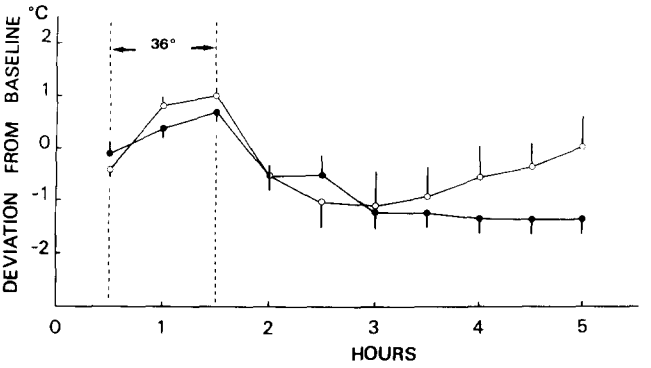

FIG. 5. Changes in rectal temperature produced by an injection of MSO into a lateral cerebral ventricle of restrained rats, at an ambient temperature of 23°C. Ambient temperature was raised to 36°C, 30 min after the injection, for an interval of 60 min denoted by vertical dash lines. ●: saline controls (n=5); ○: 75 μg of MSO per rat (n=5). Time in hours. No statistically significant differences were observed compared to saline controls.

animals were exposed for one hour to either a warm (36±0.5°C) or cold (11±1.0°C) ambient temperature half an hour after the injection of MSO. The exposure to warm air had no significant influence on the rectal temperature in the MSO-submitted rats comparatively to the saline controls since at 1.30 hours the rise of temperature reached 1.0±0.15°C (NS) for the former and 0.7±0.2°C for the latter (Fig. 5). When ambient temperature was reinstated to 23°C a rapid return to normothermia occurred in MSO-treated rats, and all the animals exhibited a severe syndrome of ataxia with episodic seizures (Fig. 5). On the other hand, the exposure to cold air had dramatically enhanced the development of rectal hypothermia in the MSO-treated rats comparatively to the saline controls: at 1.30 hours the drop of temperature reached 6.1±0.6°C ($p<0.01$) for the former and 3.25±0.3°C for the latter (Fig. 6). When ambient temperature was reinstated to 23°C a significant but progressively less severe rectal hypothermia was recorded in MSO-treated rats, with loss of righting reflex but without manifestation of episodic convulsions (Fig. 6).

Infusion of MSO Into AH/PO Area and Mammillary Region

MSO (25 μg in 0.5 μl per restrained rat) was unilaterally infused at a rate of 0.5 μl/3 min into seven sites in the AH/PO area at an ambient temperature of 23±1.0°C. About 1.30 hours after the infusion a rectal hyperthermia developed rapidly reaching a plateau of 2.0±0.2°C ($p<0.001$) at 4 hours, without any syndrome of ataxia or episodic seizure (Fig. 7). The same experiments were made with MSO (25 μg in 0.5 μl per restrained rat) unilaterally infused into ten sites in the mammillary region with no significant changes in rectal temperature (data not shown).

DISCUSSION

In the rat, when intraperitoneally administered (at a dose of 150–170 mg/kg), the molecule of MSO is rapidly taken up by liver and kidney and crosses the blood-brain barrier: in the central nervous system the peak uptake of [^{3}H] MSO was

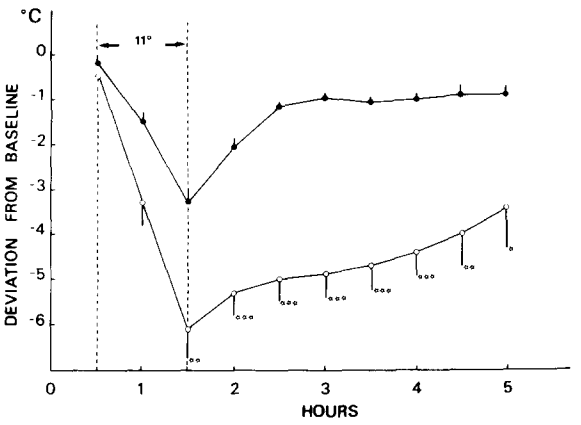

FIG. 6. Changes in rectal temperature produced by an injection of MSO into a lateral cerebral ventricle of restrained rats, at an ambient temperature of 23°C. Ambient temperature was lowered to 11°C, 30 min after the injection, for an interval of 60 min denoted by vertical dash lines. ●: saline controls (n=6); ○: 75 μg of MSO per rat (n=6). Time in hours. ⋆$p<0.05$, ⋆⋆$p<0.01$ and ⋆⋆⋆$p<0.001$, for significant differences compared with saline controls.

at 2 hours and amounted to about 1% of the administered dose (10); then, at 6 hours the molecule was rapidly and uniformly distributed without any preferential accumulation (28) and it bound to protein, especially to the active site of glutamine synthetase (16), particularly in gray matter astrocytes in all areas of the brain (21). The irreversible inhibition of the activity of glutamine synthetase (16) leads to a rise of ammonia contents in extra- and intracellular compartments of the brain: in the arterial blood and the cerebrospinal fluid the values approached 0.3 mmol/kg wet weight and in the brain it was close to 0.9 mmol/kg wet weight, at 1.30 hours (7,13). In the same experimental conditions, in the restrained rat, MSO induced a deep rectal hypothermia at the ambient temperature of 23°C, thus confirming the results previously

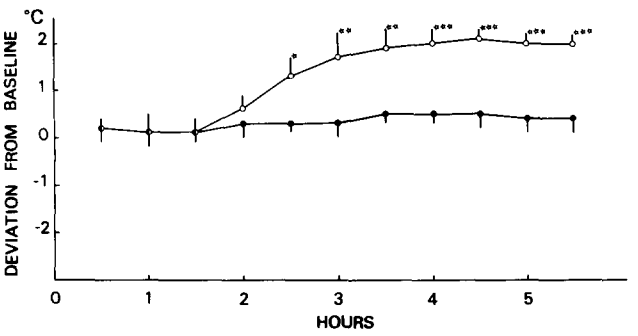

FIG. 7. Changes in rectal temperature produced by an unilateral infusion of MSO into the anterior hypothalamic/preoptic (AH/PO) area of restrained rats, at an ambient temperature of 23°C. ●: saline controls (n=7); ○: 25 μg of MSO per rat (n=5). Time in hours. $*p<0.05$, $**p<0.01$ and $***p<0.001$, for significant differences compared with saline controls.

obtained in the freely-moving rat (35). The thermolytic action of MSO did not seem to be strictly dose-dependent, though the minimum of rectal temperature reached 1.75°C at a dose of 50 mg/kg and 3.80°C at a dose of 100 mg/kg, but at a dose of 150 mg/kg the level of hypothermia did not lower, only its rate of development accelerated (Fig. 1). It was always during the decrease of rectal temperature that the rat progressively lost its capacity to carry out a righting reflex and for respond to external nociceptive stimuli leading to settlement of ataxia; episodic tonic and clonic seizures did not begin before rectal temperature reached a value close to normothermia. The MSO-induced hypothermia did not involve a peripheral mechanism since, in the same experimental conditions, skin temperature recorded at the surface of the base of the tail did not change significantly (data not shown). Unilateral injection of MSO into the lateral ventricle, at a dose of 50–75 μg per animal, induced a decrease of rectal temperature reaching the same value as that induced by systemic administration of the molecule (Fig. 3).

We have shown that MSO (150 mg/kg, IP), administered jointly with L-methionine (700 mg/kg), suppressed the development of the syndrome of ataxia together with the subsequent episodic seizures observed following administration of MSO alone, but it had only little influence on the rate of development of rectal hypothermia (Fig. 2). It had been previously found that glutamine synthetase activity was uniformly decreased in all brain regions (approximately 10% of control value) when MSO was given intraperitoneally, but when MSO was administered IP together with IP L-methionine, glutamine synthetase activity was below 20% of control values (30); on the other hand, it appeared that a high percentage of the total [^{3}H] MSO was found in the hippocampus, the cerebellum and the hypothalamus of animals receiving [^{3}H] MSO + methionine than in those receiving [^{3}H] MSO only. Conversely, a lower percentage was found in the cortex of rats receiving [^{3}H] MSO + methionine than was present in those receiving [^{3}H] MSO only (28). In conclusion, it would seem that MSO-induced rectal hypothermia is dependent on the stage of inhibition of glutamine synthetase activity in gray matter astrocytes, in particular, areas of the brain leading to a rise of ammonia content confined to these areas. Previous results had revealed an apparent absence of a direct causal relationship between the MSO-elicited glutamine synthetase inhibitor and the MSO-elicited seizures (30).

Our present results prove that MSO-induced rectal hypothermia was a poikilothermia-like state in the cold environment without impairment of thermoregulation in the heat environment. At a laboratory room temperature of 23°C the restrained rat faced a cold challenge (19,23) resulting in a decline in rectal temperature. Therefore, MSO can be considered as a hypothermic molecule, but a direct causal relationship cannot be stated between the MSO-induced hypothermia and the MSO-elicited progressive syndrome of ataxia associated with the impediment to respond to external nociceptive stimuli, since the rats submitted to a warm ambient temperature exhibited this behavior. The MSO-induced hypothermia was a state resembling the development of poikilothermia following lesion of the posterior hypothalamic area (11). We have shown that injection of MSO into the third ventricle induced a drop in rectal hypothermia with a minimum at 2 hours followed by a return to normothermia, associated with a rapid development of ataxia with episodic seizures at about 4 hours (Fig. 4). Thus, it would seem that cells in the hypothalamus in the vicinity of the ventricle walls may be metabolically affected by MSO. Previous studies in mice had shown that after a systemic administration of MSO, cerebral levels of phosphocreatine and ATP did not change, but those of glucose and glycogen rose [2, 3, 9] correlatively with a 55% increase of glycemia (Nehlig and Gayet, unpublished results). On the other hand, MSO depressed glucose oxidation, the oxidation of other compounds (acetate, phenylalanine and proline) considered as precursors of the small glutamate compartment (astrocytes, nerve endings) might be increased (6, 7, 33). Since MSO slowly and irreversibly inhibited glutamate-aspartate transaminase (5) with subsequent blockade of the malate-aspartate shuttle in brain mitochondria (17), the transfer of energy from the oxidative metabolism of these substrates would be severely affected. It was proven that a defect experimentally-induced in glucose utilization in the brain led to a hyperglycemia, inducing a "functional" hypoglycemia to which intracellular milieu was exposed (15), followed by a drop in the body temperature (24). Our experiments have shown that a unilateral infusion of MSO into seven sites in the AH/PO area induced a rapid rectal hyperthermia, whereas the same infusion into ten sites in the mammillary region was not followed by any effect in the rectal temperature. Furthermore, in the two series of experiments, the behavior of the rats was not affected.

We may conclude that the hypothermic effect of MSO may be directly related to the depression of glucose oxidative metabolism associated with the inhibition of glutamine synthetase and glutamate-aspartate transaminase activities in cell structures belonging to the small glutamate compartment of the brain, maybe astroglial cells, and probably located at sites of blood-brain and cerebrospinal fluid-brain junctions.

ACKNOWLEDGEMENT

The study was supported by grants from the Foundation pour la Recherche Médicale.

REFERENCES

1. Albe-Fessard, D.; Stutinsky, F.; Libouban, S. Atlas stéréotaxique du diencéphale du rat blanc. Paris: C.N.R.S.; 1971.
2. Bérel, A.; Lehr, P. R.; Gayet, J. Inhibition by metyrapone of convulsions and storage of brain glycogen in mice induced by methionine sulfoximine (MSO). Brain Res. 128:193–196; 1977.
3. Bérel, A.; Lehr, P. R.; Gayet, J. Inhibition by metyrapone of convulsions and of accumulation of brain glucose and glycogen in mice induced by methionine sulfoximine (MSO). 6th Int. Meeting of the I.S.N. Copenhagen, 1977, Abstract No. 211.
4. Blizard, D. A.; Balkoski, V. Tryptophan availability, central serotonergic function and methionine sulphoximine-induced convulsions. Neuropharmacology 21:27–30; 1982.
5. Cooper, A. J. L.; Stephani, R. A.; Meister, A. Enzymatic reactions of methionine sulfoximine. Conversion to the corresponding α-imino and α-ketoacids and to α-ketobutyrate and methane sulfinimide. J. Biol. Chem. 251:6674–6682; 1976.
6. Cooper, A. J. L.; Vergara, F.; Duffy, T. E. Cerebral glutamine synthetase. In: Hertz, L.; Kvamme, E.; McGeer, E. G.; Schousboe, A., eds. Glutamine, glutamate, and GABA in the central nervous system. New York: Alan Liss; 1983:77–93.
7. Cooper, A. J. L.; McDonald, J. M.; Gelbard, A. S.; Gledhill, R. F.; Duffy, T. E. The metabolic fate of ^{13}N-labeled ammonia in rat brain. J. Biol. Chem. 254:4982–4992; 1979.
8. Engelsen, B.; Fonnum, F. The effect of methionine sulfoximine, an inhibitor of glutamine synthetase, on the levels of amino acids in the intact and decorticated rat neostriatum. Brain Res. 338:165–168; 1985.
9. Folbergrova, J.; Passonneau, J. V.; Lowry, O. H.; Schulz, D. W. Glycogen, ammonia and related metabolites in the brain during seizures evoked by methionine sulphoximine. J. Neurochem. 16:191–203; 1969.
10. Ghittoni, N. E.; Ohlsson, W. G.; Sellinger, O. Z. The effect of methionine and the regional and intracellular disposition of [^{3}H] methionine sulphoximine in rat brain. J. Neurochem. 17:1057–1068; 1970.
11. Hardy, J. D. Posterior hypothalamus and the regulation of body temperature. Fed. Proc. 32:1564–1571; 1973.
12. Hevor, T. K.; Gayet, J. Cyclic nucleotides in the brain of mice and rats submitted to the convulsant, methionine sulfoximine. Biochem. Pharmacol. 28:3507–3512; 1979.
13. Hindfelt, B. L-Methionine DL-sulphoximine (MSO) and ammonia distribution between extra and intracellular compartments of the rat brain. J. Neurol. Sci. 25:499–506; 1975.
14. Lamar, C.; Sellinger, O. Z. The inhibition in vivo of cerebral glutamine synthetase and glutamine transferase by the convulsant methionine sulfoximine. Biochem. Pharmacol. 14:489–506; 1965.
15. McCandless, D. W.; Abel, M. S. Hypoglycemia and cerebral energy metabolism. In: McCandless, D. W., ed. Cerebral energy metabolism and metabolic encephalopathy. New York: Plenum Press; 1985:27–41.
16. Meister, A. Inhibition of glutamine synthetase and γ-glutamylcysteine synthetase by methionine sulfoximine and related compounds. In: Seiler, N.; Jung, M. J.; Koch-Weser, J., eds. Enzyme-activated irreversible inhibitors. Amsterdam: Elsevier/North-Holland; 1978:187–210.
17. Minn, A.; Gayet, J. Kinetic study of glutamate transport in rat brain mitochondria. J. Neurochem. 29:873–881; 1977.
18. Myers, R. D. Chronic methods: intraventricular infusion, cerebrospinal fluid sampling, and push-pull perfusion. In: Myers, R. D., ed. Methods in psychobiology. vol. 3. New York: Academic Press; 1977:281–315.
19. Myers, R. D. Alcohol's effect on body temperature: Hypothermia, hyperthermia or poikilothermia? Brain Res. Bull. 7:209–220; 1981.
20. Myers, R. D.; Ruwe, W. D. Is alcohol induced poikilothermia mediated by 5-HT and catecholamine receptors or by ionic setpoint mechanisms in the brain? Pharmacol. Biochem. Behav. 16:321–327; 1982.
21. Norenberg, M. D. Immunochemistry of glutamine synthetase. In: Hertz, L.; Kvamme, E.; McGeer, E. G.; Schousboe, A., eds. Glutamine, glutamate, and GABA in the central nervous system. New York: Alan Liss; 1983:95–111.
22. Paxinos, G.; Watson, C. The rat brain in stereotaxic coordinates. New York: Academic Press; 1982.
23. Poole, S.; Stephenson, J. D. Body temperature regulation and thermoneutrality in rats. Q. J. Exp. Physiol. 62:143–149; 1977.
24. Robinson, S. M.; Mager, M.; Freinkel, N. Interrelationship between nervous system glucopenia and heat production in mice. In: Schoenbaum, E.; Lomax, P., eds. The pharmacology of thermoregulation. Basel: Karger; 1972:112–123.
25. Rothstein, J. D.; Tabakoff, B. Effects on the convulsant methionine sulfoximine on striatal dopamine metabolism. J. Neurochem. 39:452–457; 1982.
26. Rothstein, J. D.; Tabakoff, B. Alteration of striatal glutamate release after glutamine synthesis inhibition. J. Neurochem. 43:1438–1446; 1984.
27. Rothstein, J. D.; Tabakoff, B. Glial and neuronal glutamate transport following glutamine synthetase inhibition. Biochem. Pharmacol. 34:73–79; 1985.
28. Schatz, R. A.; Harris, R.; Sellinger, O. Z. The effect of methionine on the uptake, distribution and binding of the convulsant methionine sulfoximine in the rat. Neurochem. Res. 1:53–63; 1976.
29. Sellinger, O. Z.; Dietz, D. D. The metabolism of 5-hydroxytryptamine in the methionine sulfoximine epileptogenic rat brain. J. Pharmacol. Exp. Ther. 216:77–82; 1981.
30. Sellinger, O. Z.; Azcurra, J. M.; Ohlsson, W. G. Methionine sulfoximine seizures. VIII. The dissociation of the convulsant and glutamine synthetase inhibitory effects. J. Pharmacol. Exp. Ther. 164:212–222; 1968.
31. Stone, W. E. Systemic chemical convulsants and metabolic derangements. In: Purpura, D. P.; Penry, J. K.; Tower, D.; Woodbury, D. M.; Walter, R., eds. Experimental models of epilepsy. New York: Raven Press; 1972:407–432.
32. Toussi, H. R.; Schatz, R. A.; Waszczak, B. L. Suppression of methionine sulfoximine seizures by intranigral γ-vinyl GABA injection. Eur. J. Pharmacol. 137:261–264; 1987.
33. Van den Berg, C. J.; Van den Velden, J. The effect of methionine sulphoximine on the incorporation of labelled glucose, acetate, phenylalanine and proline into glutamate and related amino acids in the brain of mice. J. Neurochem. 17:985–991; 1970.
34. Wada, J. A.; Ikeda, H. The susceptibility to auditory stimuli of animals treated with methionine sulfoximine. Exp. Neurol. 15:157–165; 1966.
35. Wada, J. A.; Ikeda, H.; Berry, K. Reversible behavioral electrographic manifestations induced by methionine sulfoximine. Neurology 17:854–868; 1967.
36. Wada, J. A.; Asakura, T.; Ikeda, H. Transient reduction of audiogenic susceptibility by methionine sulfoximine in genetically sensitive rats. Exp. Neurol. 19:346–349; 1967.
37. Wolfe, L. S.; Elliott, K. A. C. Chemical studies in relation to convulsive conditions. In: Elliott, K. A. C.; Page, I. H.; Quastel, J. H., eds. Neurochemistry. Springfield: CC Thomas; 1962:694–727.