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# The Protective Effect of Moclobemide Against Hypoxia-Induced Lethality in Mice Is Not Due to a Decrease in Body Temperature

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ULUGOL, A., C. H. KARADAG, D. DOKMECI, I. AL-KHATIB AND I. DOKMECI. *The protective effect of moclobemide against hypoxia-induced lethality in mice is not due to a decrease in body temperature.* PHARMACOL BIOCHEM BEHAV **51**(2/3), 245-247, 1995.—The protective effect of moclobemide, a reversible and highly selective inhibitor of monoamine oxidase-A, against hypoxia-induced lethality was investigated in the present experiment. Moclobemide showed an apparent protective potency against hypoxia and significantly prolonged the latencies for convulsions and death in a dose-dependent manner. Hypothermia is known to protect animals from hypoxia. Moclobemide also decreased body temperature in mice; however, the hypothermic effect was unrelated to the antihypoxic effect. These results suggest that the protective effect of moclobemide in hypoxia is not due to a decrease in body temperature.

Moclobemide Hypoxia Body temperature

THE NOVEL antidepressant moclobemide [Ro 11-1163, 4-chloro-*N*-(2-[4-morpholinyl]ethyl)benzamide] is a reversible inhibitor of monoamine oxidase (MAO), preferentially of type A (11,16). The drug improves not only the symptoms of depression, but also the cognitive deficit in dementia (2,14). Moreover, moclobemide has definitive advantages (better tolerability, fewer side-effects, full biochemical effect after the first dose, etc.) over other drugs used in depression (1,6).

Recently, an antihypoxic effect of moclobemide has been observed (22,27). Hypothermia is known to protect animals from hypoxia and cerebral ischemia (19,20,25,26). Minard and Grant reported that protection from hypoxia by drugs can be completely accounted for by drug-induced hypothermia (23). Contrary to this interpretation, some other investigators suggest that some drugs have protective effects against hypoxia that are independent of drug-induced hypothermia (19,20).

In the present study, we observed the effect of moclobemide on hypoxia in relation to hypothermia.

## METHOD

### *Animal*

Male albino mice (Eczacıbaşı-Turkey) weighing 25-30 g were used. The animals were housed at constant room temperature (22 ± 1°C), with food and water ad lib.

### *Measurement of Rectal Temperature*

The temperature was measured to the nearest 0.1°C by an Ellab thermometer. This was done by inserting the probe (2 mm in diameter) 2.5 cm into the rectum of mice. The probe was left in place until steady readings were obtained (20-25 s).

### *Experimental Procedure*

The animals were weighed and injected intraperitoneally, and rectal temperatures were taken in groups of 10. Twenty minutes after the first measurement and 10 min before hypoxia, rectal temperatures were taken for the second time. The animals were subjected to hypoxia by putting them individually in a tightly closed 300-ml glass container. The animals convulsed and died from hypoxia. The latencies for death were noted as described by Bharvaga (4) and Kunchandy and Kulkarni (21). The animals died approximately 2 min after they showed convulsions, and great care was taken to determine the exact time of death. Control studies were run in parallel.

A limitation of the experimental method used here is that body temperatures were measured before hypoxic exposure for practical reasons. However, all treatments, including hypothermia, were affected in a similar manner.

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The experiments had been approved by the Center of the Laboratory Animals—Animal Care Ethics Committee of our faculty.

### *Drugs*

Moclobemide was suspended in 0.3% v/v Tween 80 in distilled water and administered by oral gavage in a volume of 0.1 ml/10 g body weight. The control group received 0.1 ml/10 g vehicle only by oral gavage.

### *Statistical Analysis*

Results were evaluated by ANOVA followed by Duncan's multiple-range test. To observe the relationship of the latencies for death to the decrease in body temperature, correlation analysis were performed. Values are expressed as means ± SEM.

## RESULTS

### *Effect of Hypoxia*

Mice showed increased respiratory rates, tremors, and convulsions followed by death with the induction of hypoxia. An increase in urination and defecation was also observed. Control animals developed convulsions within 24.32 ± 0.65 min and died within 25.68 ± 0.68 min.

### *Effect of Moclobemide on Hypoxia-Induced Convulsions and Death*

Pretreatment with moclobemide (12.5–100 mg/kg, orally) 30 min before exposure to hypoxia dose dependently increased the latencies for convulsions (30.13 ± 0.78 to 44.56 ± 1.04) and for death (31.06 ± 0.76 to 46.00 ± 1.04) (Fig. 1). Moclobemide produced no detectable behavioral change in the tested animals.

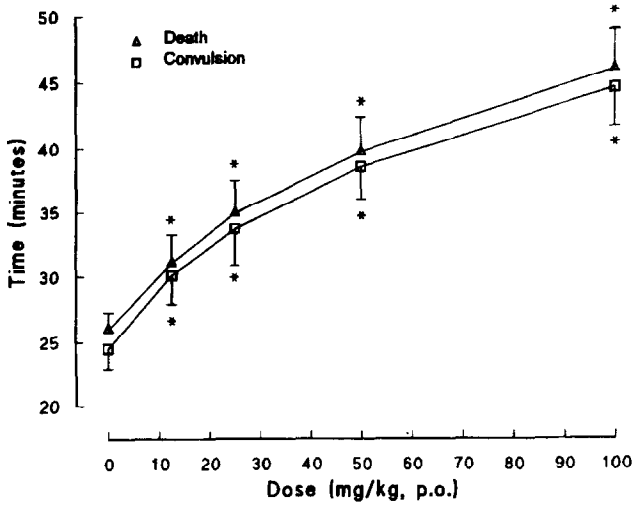


FIG. 1. Effects of various doses of moclobemide on hypoxia-induced convulsions and death in mice. *$p < 0.05$ when comparing groups 1 and 2, 1 and 3, 1 and 4, 1 and 5, 2 and 3, 2 and 4, 2 and 5, 3 and 4, 3 and 5, and 4 and 5 using ANOVA followed by Duncan's multiple-range test. Group 1: vehicle. Groups 2–5 correspond to the doses used, going from lowest to highest (12.5, 25, 50, and 100 mg/kg, orally). Each point is the mean value with SEM (bars).

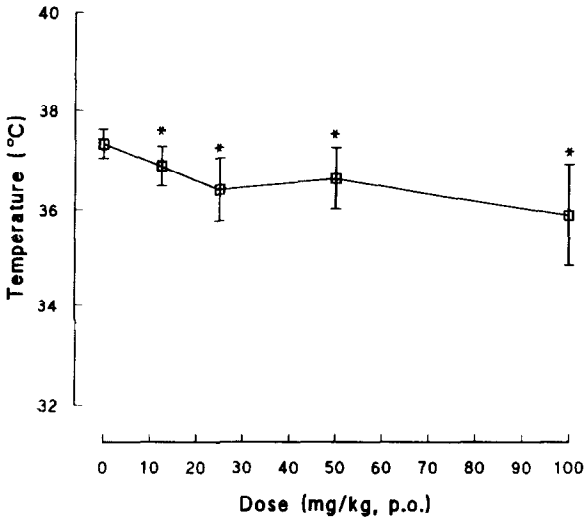


FIG. 2. Effects of various doses of moclobemide on body temperature in mice. *$p < 0.05$ when comparing groups 1 and 2, 1 and 3, 1 and 4, 1 and 5, and 2 and 5 using ANOVA followed by Duncan's multiple-range test. Group 1: vehicle. Groups 2–5 correspond to the doses used, going from lowest to highest (12.5, 25, 50, and 100 mg/kg, orally). Each point is the mean value with SEM (bars).

### *Relationship Between Latencies in Death and Body Temperature*

All doses of moclobemide decreased body temperature significantly ($p < 0.05$), but not dose dependently (Fig. 2). There was no correlation between the decrease in body temperature and latencies in convulsions ($r = -0.27$, $p > 0.05$) and death ($r = -0.29$, $p > 0.05$). Therefore, the antihypoxic effect of moclobemide is unrelated to its ability to induce hypothermia.

## DISCUSSION

Moclobemide, a reversible and highly selective inhibitor of MAO-A, is a very promising drug. Moclobemide is extensively distributed in the body and rapidly eliminated from plasma (9,13,15). The drug has been shown to have a weak potentiating action on the pressor effect of tyramine (cheese effect) (7,12,16). Compared with the other antidepressants, moclobemide produces fewer side-effects and has better tolerability (1,6). Moclobemide is being used successfully in all types of depression and in cognitive impairment in dementia (2,14). Recent studies showed that moclobemide has a protective effect on anoxia-induced lethality (22,27). However, neither study demonstrated that these effects were independent of drug-induced hypothermia.

Hypothermia is known to have protective effects on hypoxia-induced lethality (19,20,25,26). A decrease in the cerebral metabolic rate (17) and an increase in the affinity of hemoglobin for oxygen (8) are the two mechanisms playing a role in the protective effects of hypothermia. Minard and Grant indicated that drug-induced hypothermia is fully responsible for protection from the lethal effects of hypoxia (23). On the other hand, some investigators reported that protection from hypoxia cannot be accounted for by drug-induced hypothermia (19,20).

Several drugs belonging to different pharmacologic classes were found to have protective effects against hypoxia that are independent of drug-induced hypothermia. Physostigmine and oxotremorine, cholinergic drugs, protect mice from the

lethal effects of anoxia; this effect is mediated by stimulation of muscarinic receptors in the CNS (19,20). Anoxia provokes convulsive seizures and increases the rate of oxygen use (24). It has been postulated that the antihypoxic activity of phenobarbital is due to either prevention of hypoxia-induced seizures and/or to reduction of cerebral metabolic rate (18). However, this mechanism cannot explain the antihypoxic effect of diazepam and phenytoin, because these drugs do not alter the cerebral metabolic rate (3,8). Moreover, the antihypoxic effect of phenytoin does not correlate with its activity in standard anticonvulsant tests (3,19). Therefore, the anticonvulsant activity and depression of the cerebral metabolic rate cannot adequately explain the antihypoxic effects of anticonvulsant drugs. The antihypoxic effect of vinpocetine is also not the result of induced hypothermia. King reported that although reduction of the cerebral metabolic rate could be a possible mechanism of action, this mechanism cannot entirely explain the antihypoxic effect of vinpocetine (20).

In the present study, moclobemide prolonged the latencies for convulsions and death significantly and dose dependently. At the same time, moclobemide decreased the body temperature, but not dose dependently. Although moclobemide caused hypothermia, the latencies for convulsions and death were prolonged to a greater extent than could be accounted for by hypothermia alone.

Lorez et al. reported that moclobemide causes a significant reduction in the glucose use of the cerebral cortex and neostriatum, which may point to a decrease in cerebral metabolism (22). However, hypothermia also decreases the cerebral metabolic rate, and this mechanism cannot explain the antihypoxic effect of moclobemide completely. MAO-A inhibition leads to neuroprotection by a reduction in free radical formation or by an increase in neuroprotective synaptic concentrations of monoamines, or both (5,10). Moclobemide might also act by reducing the formation of hydrogen peroxide, which is one of the products of the oxidative deamination of monoamines by MAO.

Our findings are in line with recent reports of the neuroprotective activity of moclobemide (22,27). We also showed that this protection is not due to a decrease in body temperature. However, further experiments are required to delineate the mechanism of the antihypoxic property of moclobemide.

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