

Effects of Methamphetamine and Methyl dopa on Ethanol Induced Hypothermia in Mice

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Abstract—The effects of D-methamphetamineHCl (1, 2 and 4 mg/kg. p.) and a-methyl dopa (1, 2 and 4 mg/kg. i.p.) on rectal temperature and on ethanol (3 g/kg, i.p.)-induced hypothermia have been investigated in mice. Methamphetamine caused a dose-dependent hyperthermia, but methyl dopa induced hypothermia, which decreased with increases in dose. Methamphetamine antagonized the hyperthermic effect of ethanol, but methyl dopa (1 and 2 mg/kg) did not affect it. Methyl dopa (4 mg/kg), however, reversed ethanol hypothermia. Ethanol pretreatment significantly potentiated the hypothermic effect of methyl dopa (4 mg/kg). and it prevented methamphetamine-induced hyperthermia. A possible central action for the tested drugs on biogenic monoamines and a peripheral component in their thermoregulatory effects are discussed in this report.

The acute administration of ethanol induces hypothermia in a dose-dependent manner in both animals and man (1—3). The hypothermic action of ethanol is probably through its effect on the neurotransmitters noradrenaline and 5-hydroxytryptamine in the thermoregulatory center of the hypothalamus (4, 5). A peripheral mechanism of ethanol-induced hypothermia is probably the result of enhancement of heat loss by it, causing cutaneous vasodilatation (6).

In this study, we have investigated the effects of drugs that may influence central noradrenaline and 5-hydroxytryptamine on ethanol-induced hypothermia. For this purpose, D-methamphetamine and a-methyl dopa were used. These drugs affect biogenic monoamines in opposite directions. The former is an indirectly acting sympathomimetic drug and thus causes increased monoamines concentration, particularly that of catecholamines in the brain (7—9), via mechanisms involving their increased release, inhibition of their uptake and monoamine oxidase inhibition. The latter drug inhibits biogenic monoamines synthesis (10). It has been demonstrated that a-methyl dopa is metabolized in the brains and hearts of mice to form a-methyl dopamine and a-methylnoradrenaline (11). The metabolites of a-methyl dopa act as “false transmitters”. and hence transmission within central catecholaminergic systems is impaired. In the periphery, methamphetamine causes vasoconstriction via its release of noradrenaline. The metabolite a-methylnoradrenaline proved to be almost equipotent with noradrenaline as a pressor agent (12).

Materials and Methods

Male albino mice weighing 30—40 g obtained from King Saud University, College of Pharmacy, colony were used. Animals were housed at a temperature of 23 ± 1 °C. Food and water were made available freely, and each mouse was used on only one occasion. Groups of eight mice were used.

Ethanol (3 g/kg) in the form of a 20% solution (v/v) in saline was used to induce hypothermia (13). Drugs tested were D-Nmethamphetamine hydrochloride (E. Merck) and a-methyl dopa hydrochloride (methyl dopate hydrochloride injection, MSD). Drugs were dissolved in 0.9% NaCl and given p. Doses were expressed as mg/kg of the salt.

Two experiments were performed. In the first experiment, animals were injected with saline or the drug under investigation. Animals received another injection of saline or ethanol 30 mm later. In the

second experiment, the order of injection was reversed, i.e. animals received saline or ethanol injection and 30 mm later, they were injected with saline or the drug under investigation.

Rectal temperature was recorded 15 mm before any treatment; thus each animal was its own control. Temperature records were then obtained 15 mm after the first injection and at 30 mm intervals after the second injection. Rectal temperature was measured by inserting a lubricated temperature probe 3 cm into the rectum of a mouse. The temperature probe was connected to a digital thermometer (Apelex, France) which gave the temperature to the nearest 1/10 of a degree Celsius.

In order to reduce variability between animals, the difference in the rectal temperatures before and after drug administration was used as an index.

Statistical significance was assessed using Student's t-test, significance being accepted where $P < 0.05$.

Results

Effect of D-methamphetamine HCl on ethanol-induced hypothermia:

The effects of various doses of D-methamphetamine HCl pretreatment on ethanol-induced hypothermia are shown in Fig. 1. Methamphetamine caused a significant hyperthermic effect in a dose-dependent manner. The peak hyperthermic effect was seen one hour after the drug administration, and it started to be non significant two hours after the drug administration. Ethanol caused a significant reduction in rectal temperature which lasted from the time interval starting at 60 mm to the end of the experiment. Methamphetamine pretreatment significantly reversed the hypothermic effect of ethanol at time intervals of 60–120 mm (except for methamphetamine, 2 mg/kg; at the time interval of 120 mm). However, the hyperthermic effect of methamphetamine in the methamphetamine/ethanol groups was only observed with the high dose of 4 mg/kg (at time intervals of 60 and 90 mm).

Effect of methyl dopa HCl on ethanol-induced hypothermia:

In contrast to methamphetamine, methyl dopa caused hypothermia as shown in Fig. 2. The hypothermic effect of methyl dopa, while significant, decreased when the dose was increased. It is clear that methyl dopa (1 and 2 mg/kg) did not affect ethanol-induced hypothermia; but with methyl dopa (4 mg/kg), there was almost total reversal of ethanol hypothermia. It must be emphasized that groups which received methyl dopa (2 mg/kg)/ethanol and methyl dopa (4 mg/kg)/ethanol showed less hypothermic effects than their respective groups receiving methyl dopa / saline.

Effects of ethanol pretreatment:

The effects of ethanol pretreatment on methamphetamine hyperthermia and on methyl dopa hypothermia are respectively shown in Figs. 3 and 4. It is clear that ethanol caused significant reduction in the hyperthermic effects of all doses of methamphetamine tested, but there were no significant differences

from the mean rectal temperature recorded for the saline/saline group at time intervals of 90 and 120 mm. Thus, methamphetamine was not capable of inducing hyperthermia after ethanol pretreatment.

As shown in Fig. 4, ethanol blocked the hypothermic effect of methyl dopa (1 mg/kg) at the time interval of 60 mm; ethanol did not affect methyl dopa hypothermia at the interval of 90 mm, but markedly potentiated it at the interval of 120 mm. Ethanol was without any significant effect on methyl dopa (2 mg/kg) hypothermia at all time intervals. The most striking effect of ethanol was on methyl dopa (4 mg/kg), where it caused significant potentiation of methyl dopa induced hypothermia.

Discussion

Brain monoamines among other brain neurotransmitters play a role in thermoregulation (14). D-methamphetamine and methyl dopa differ in their effects on brain monoamines. The former causes increased brain monoamines levels, while the converse is true for the latter. In the present study, methamphetamine caused hyperthermia in agreement with previous findings (15), (16). Methyl dopa, on the other hand, produced pronounced hypothermia. The hypothermic effect of methyl dopa has been demonstrated in man (17). Thus it appears that increased brain monoamines lead to hyperthermia, while decreased brain monoamines lead to hypothermia, although the relative roles of noradrenaline, dopamine and 5-hydroxytryptamine remain unclear. It must also be recalled that these drugs exert contrasting effects on locomotor activity which may contribute to their different effects on thermoregulation.

It has been demonstrated that inhibition of catecholamines synthesis and peripheral sympathectomy abolish the hyperthermic response to amphetamine (18); thus it appears that peripheral heat production is

involved in the hyperthermia caused by amphetamine. Both methamphetamine and methyl dopa cause peripheral vasoconstriction via release of noradrenaline by methamphetamine and of methyl noradrenaline by methyl dopa. Peripheral vasoconstriction may contribute to methamphetamine hyperthermia and may well explain the reduced hypothermic effect observed with

high doses of methyl dopa.

Like methyl dopa, ethanol caused hypothermia, although its biochemical effects on brain monoamines appear to be different from those of methyl dopa. There is no general agreement about the effects of ethanol administration on brain levels of monoamines (19). It may increase the turnover rate of noradrenaline in the brain. High concentrations of ethanol reduce the rate of nor-adrenaline release from electrically stimulated rat brain slices (20), and in vivo ethanol treatment accelerates the decline of nor-adrenaline levels after tyrosine hydroxylase inhibitors (21). Ethanol does not affect brain levels of dopamine or 5-hydroxytryptamine (19). Soliman et al. (22), however, reported an increase in brain 5-hydroxytryptamine after ethanol administration. With that uncertain picture of the effects of ethanol on biogenic amines, it seems that other mechanisms may be involved in ethanol hypothermia. Mice receiving ethanol became sedated and ataxic; sedation and cutaneous vasodilatation caused by ethanol may contribute to its hypothermic effect.

The results obtained in this study indicates that methamphetamine was able to antagonize ethanol hypothermia. Apart from their physiologically antagonistic effects on cutaneous blood vessels and their opposite effects on locomotor activity, these drugs may have opposite influences on brain monoamines if a central action is to be sought.

The situation with methyl dopa/ ethanol or ethanol /methyl dopa combinations on thermoregulation seemed to be rather difficult to explain. Both drugs cause sedation, and they may have opposite effects on peripheral blood vessels as mentioned earlier. These combinations were expected to cause drastic reductions in brain catecholamines, hence a greater hypothermic effect than that caused by either drug alone. That was true at least in the ethanol/methyl dopa (4 mg/kg) group, but it was rather paradoxical that methyl dopa (4 mg/kg) was able to antagonize ethanol hypothermia when it was administered before ethanol.

It can be concluded from the present study that methamphetamine antagonizes ethanol hypothermia, and the converse is true. Methyl dopa, on the other hand, may potentiate the hypothermic effect of ethanol only when administered in large doses after ethanol. It may antagonize ethanol hypothermia when administered before ethanol.

References

- 1 **Freund, G.:** Hypothermia after acute ethanol and benzyl alcohol administration. *Life Sci.* 13, 345—349 (1973)
- 2 **Ritzman, R.F. and Tabakoff, B.:** Body temperature in mice: A quantitative measure of alcohol tolerance and physical dependence. *J. Pharmacol. Exp. Ther.* 199, 158—170 (1976)
- 3 Fox, G., Hayward, J. and Hobson, G.: Effect of alcohol on thermal balance of man in cold water. *Can. J. Physiol. Pharmacol.* 57, 860—865 (1979)
- 4 Carrodi, H., Fuxe, K. and Hokfelt, T.: Effect of ethanol on activity of central catecholamine neurons in rat brain. *J. Pharm. Pharmacol.* 18, 821—822 (1966)
- 5 Cox, B. and Lomax, P.: Pharmacological studies on the central regulation of body temperature. *Annu. Rev. Pharmacol. Toxicol.* 17, 341—353 (1977)
- 6 **Hirvonen, J.:** Accidental hypothermia. *In* Body Temperature, Edited by Lomax, P. and Schonbaum, E., p. 561—585. Marcel Dekker, Inc., New York and Basel (1979)
- 7 Glowinski, J., Axelrod, J. and Iverson, L.L.: Regional studies of catecholamines in the rat brain. IV. Effects of drugs on the disposition and metabolism of H³-norepinephrine and H³-dopamine. *J. Pharmacol. Exp. Ther.* 153, 30—41 (1966)
- 8 **Glowinski, J.:** Effects of amphetamines on various aspects of catecholamine metabolism in the central nervous system of the rat. *In* Amphetamines and Related Compounds, Edited by Costa, E. and Garattini, S., p.301—318. Raven Press, New York (1970)
- 9 Garattini, S., Bizzi, A., DeGaetano, G., Jori, A. and Samanin, R.: Recent advances in the pharmacology of anorectic agents. *In* Recent Advances in Obesity Research, Edited by Howard, A., p. 354—367, Newman Publ., London (1975)
- 10 Baum, T., Shropshire, AT. and Varner, L.L.: Contribution of the central nervous system to the action of several antihypertensive agents (methyl dopa, hydralazine and guanethidine). *J. Pharmacol. Exp. Ther.* 182, 135—141 (1972)
- 11 Carlsson, A. and Lindqvist, M.: In vivo decarboxylation of *a*-methyl dopa and *a*-methyl metatyrosine. *Acta Physiol. Scand.* 54, 87—94 (1962)
- 12 Henning, M.: Central action of alpha-methyl dopa. *In* Central Action of Drugs in Blood Pressure Regulation, Edited by Davies, O. and Reid, J.L., p. 157—165, Pitman Medical, Kent (1975)
- 13 Soliman, **K.F.A. and Gabriel, N.N.:** Effect of biogenic amines reuptake inhibition on ethanol induced hypothermia. *Ceol. Pharmacol.* 14, 461—463 (1983)
- 14 Lomax, P. and Schonbaum, E.: Body Temperature. Marcel Dekker, Inc. New York and Basel (1979)
- 15 Britain, R.T.: The intracerebral effects of nor-adrenaline and its modification by drugs in the mouse. *Br. J. Pharmacol.* 18, 621—623 (1966)
- 16 Feldberg, W. and Lang, W.J.: Effects of monoamine oxidase inhibitors and amphetamine on hypothermia produced by halothane. *Br. J. Pharmacol.* 38, 181—191 (1970)

- 17 Oollery, C.T. and **Bulpitt, C.J.:** Alpha-methyl dopa. *In* Central Action of Drugs in Blood Pressure Regulation. Edited by Davies, D. and Reid, J.L., p. 256—266. Pitman Medical, Kent (1975)
- 18 Caldweil, J., Server, P.S. and Treliniski, M.: On the mechanism of the hyperthermia induced by amphetamine in the rat. *Br. J. Pharmacol.* **26**, 821—823 (1974)
- 19 Goldstein, D.B.: Interaction of ethanol with neurotransmitter systems. *In* Pharmacology of Alcohol, p. 141—155. Oxford University Press, Oxford (1983)
- 20 Carmichael, F.J. and Israel, Y.:** Effect of ethanol on neurotransmitter release by rat brain cortical slices. *J. Pharmacol. Exp. Ther.* **193**, 823—834 (1975)
- 21 Hunt, W.A. and Majchrowicz, E.:** Alterations in the turnover of brain noradrenaline and dopamine in alcohol dependent rats. *J. Neurochem.* **23**, 549—552 (1974)
- 22 Soliman, K.F.A., Walker, C.A. and Ross, F.H.:** Effect of acute ethanol administration on brain biogenic amines. *In* Chronopharmacology and Chronotherapeutics, p. 109—114, Florida A. and M. University Foundation, Tallahassee (1981)