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The Actions of Majarine on the Central Nervous System (II)
—The Effects of Dopaminergic and Serotonergic Antagonists on Majarine-induced Hypothermia in the Mouse[1]

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ABSTRACT

Majarine that was isolated from *Berberis Koreana* Palibin (Berberidaceae) is the isoquinoline alkaloid. The effects of dopaminergic and serotonergic antagonists on majarine induced changes in body temperature were studied in the mouse. Intraperitoneal administration of majarine produced dose-dependent hypothermia. At a dose of 0.1 mg/kg, majarine caused a slight increase in body temperature. Majarine-induced hyperthermia was attenuated by the 5-HT antagonist, cyproheptadine. However, it caused hyothermia in mice pretreated with the DA antagonist, haloperidol, and hyperthermia in mice pretreated with haloperidol and cyproheptadine in comparision with haloperidol pretreatment. At a dose of 2.0 mg/kg, majarine-induced hypothermia was attenuated by haloperidol and cyproheptadine, respectively. In reserpine pretreated mice, majarine produced dose-dependent hypothermia. At a dose of 0.1 mg/kg, majarine pretreated with haloperidol caused no significant effect in body temperature. At a dose of 2.0 mg/kg, majarine-induced hypothermia was attenuated by haloperidol pretreatment in mice treated with reserpine and α-methyl-*p*-tyrosine. These data suppose that both dopaminergic and serotonergic mechanisms in the brain mediate the effects of majarine on body temperature. We propose that majarine directly stimulate DA receptor, which secondarilly activate 5-HT neurons to cause changes in body temperature.

Key Words: majarine, temperature regulation, haloperidol, cyproheptadine, reserpine.
Abbreviations: DA; dopamine, 5-HT; serotonin, α-MPT; α-methyl-*p*-tyrosine, LSD; lysergic acid diethylamide

INTRODUCTION

Dopaminergic systems in the brain have been the subject of speculation about their possible role in thermoregulation. Centrally mediated temperature effects of DA and either direct or indirect DA agonists have been demonstrated in various animal species. For instance, apomorphine, which is regarded as a direct DA agonist, induces hyperthermia in rabbits (Hill & Horita, 1972; Quock & Horita, 1974), whereas it displays a hypothermic action in mice (Fuxe & Sjoqvist, 1971) and in rats (Colboc & Costentin, 1980). In most species, DA agonists cause a fall in core temperature which is specifically antagonized by DA antagonists. Ample evidence has indicated a role by DA in regulation of body temperature in animals (for a review, see Cox, 1979).

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The central neural mechanisms in the rat involved in the thermal effect of apomorphine have been elucidated to some extent. Microinjection of apomorphine into the preoptic anterior hypothalamus has been shown to cause hypothermia, an effect blocked by pretreatment with the DA antagonist, pimozide (Cox & Lee, 1977). Similarly, Colboc and Costentin (1980) found that the central locus of DA-induced hypothermia is the medial preoptic area of the hypothalamus.

An involvement of 5-HT in DA receptor-mediated hypothermia has also been suggested. DA agonist-induced hypothermia has been reported to be prevented by either 5,6-hydroxytryptamine or electrolytic lesions of the dorsal raphe nuclei (Maj & Przewlocka, 1975; Przewlocka, 1977). Grabowska *et al.* (1973a, b) have shown that the hypothermia induced by apomorphine in rats and mice could be antagonized by LSD and butyrophenones. Cox and Lee (1979) also suggested a 5-HT link in DA-mediated hypothermia in the rat. Menon and Vivonia (1981) reported that apomorphine-induced hypothermia in the mice was attenuated by 5-HT agonist and potentiated by 5-HT antagonist pretreatments. Recently, Yamawaki *et al.* (1983) reported that apomorphine could simultaneously activate two opposing thermoregulatory DA-related systems: one causes hypothermia; the other, hyperthermia. The DA-hypothermic mechanism is blockable by the DA-receptor antagonist haloperidol, whereas the DA-hyperthermic mechanism is nonsensitive to haloperidol and is activated by apomorphine, but at a lower dose. The latter system is mediated by a secondary activation of a serotonergic mechanism. Thus, the effect of apomorphine on body temperature depends on the difference in response between these two mechanisms.

In our previous studies, we had clarified many pharmacological actions of majarine: the bacteriostatic effect *in vitro* (Cho *et al.*, 1963); the potentiation of hypnotic action of alcohol and the reduction of rectal temperature in mice (Cho *et al.*, 1974); the hypotensive effect in rats (Cho *et al.*, 1984); the depressor response on blood pressure after intracerebroventricular injection of several drugs and locomotor activity in rats (Park *et al.*, 1984). In this paper, we report the results of a series of experiments to investigate the role played by the DA antasgonist, haloperidol, the 5-HT antagonist, cyproheptadine, the catecholamine depletor, reserpine and the catecholamine synthesis inhibitor, α-MPT, further to clarify the central action of majarine on body temperature in the mouse.

MATERIALS AND METHODS

Animals

Mice (ICI strain) of either sex, weighing 20-30 g were used. The animals were provided with a standard diet and water. One h before testing, animals were placed individually into acrylic cages ($12 \times 23 \times 14$ cm) in diffusely illuminated room maintained at a temperature of $21 \pm 1°C$ and at constant humidity.

Drugs and solutions

The following drugs were used: haloperidol (Peridol, Whan-Il Pharma. Co.), cyproheptadine hydrochloride (Shin-Kwang Pharma. Co.), reserpine hydrochloride and α-methyl-*p*-tyrosine (Sigma Co.). Majarine (5,6-Dihydro-9,10-dimethoxybenzo [g]-1,3-benzodioxolo [5,6-a] quinolizinium) used in this study was obtained from *Berberis koreana* Palibin. All drugs were delivered as 0.9% saline solutions in a dose volume of 10 ml/kg.

Treatments of various dosages of majarine on body temperature

Animals were injected intraperitoneally (i.p.) with 0.1, 1.0 or 2.0 mg/kg of majarine. Controls were injected with saline solution. Rectal temperature was measured with the animals unrestained immediately before and at 15, 30, 45, 60, 90 and 120 min after majarine injection with a digital thermometer.

Drug pretreatments on the thermal effects of majarine

The effects of 0.1 mg/kg or 2.0 mg/kg of majarine on body temperature were studied in mice at 1) 60 min after pretreatment with the DA antagonist, haloperidol (0.5 mg/kg i.p.); 2) 15 min after pretreatment with the 5-HT antagonist, cyproheptadine (0.2 mg/kg i.p.)

Drug pretreatments on the thermal effects of majarine in reserpinized mice

The effects of 0.1 mg/kg or 2.0 mg/kg of majarine on body temperature were studied in mice at 1) 2.5 h after pretreatment with α-methyl-*p*-tyrosine (200 mg/kg i.p.), 2) 60 min after pretreatment with haloperidol (0.5 mg/kg i.p.) in reserpinized mice. Animals were treated with reserpine (5 mg/kg i.p.) on the day prior to the experiment.

Rectal temperature measurements

Rectal temperatures were measured electronically with a small thermocouple probe (San-Ei Instrument Co.) inserted to a depth 2.5 cm. Temperatures were read thirty seconds after probe insertion. Temperatures were recorded as changes in temperature (mean ± SEM) immediately before drug injection.

Statistics

The results were analyzed statistically using the two-tailed Mann-Whitney U-test. Difference with $p<0.05$ was considered statistically significant.

RESULTS

Dose-response effect of majarine on body temperature

The thermal effect of majarine investigated is drawn in Fig. 1 Majarine at 1.0 and 2.0 mg/kg significantly lowered the rectal temperature ($p<0.05$ and $p<0.001$, respectively, compared with responses of controls). Responses to 2.0 mg/kg of majarine were significantly different from those of 1.0 mg/kg ($p<0.05$). At 0.1 mg/kg, it produced a slight hyperthermia ($p<0.05$). This response was greatest approximately 90 min after injection of majarine and gradually returned to base-line level after 12 h.

In our experiments, we showed that i.p. injection of 0.1 mg/kg of majarine, which normally caused hyperthermia in mice, produced hypothermia in haloperidol-pretreated animals. However, Majarine-induced hyperthermia was attenuated by the 5-HT antagonist, cyproheptadine. Majarine at 1.0 and 2.0 mg/kg significantly lowered the rectal temperature. At 2.0 mg/kg, majarine-induced hypothermia in animals was attenuated by haloperidol or cyproheptadine, respectively. However, pretreatment haloperidol and cyproheptadine showed no significant effect in comparision with responses to haloperidol pretreatment. Thus, it is apparent from these results that both dopaminergic and serotonergic mechanisms mediate the effect majarine on the body temperature. Our data may be suggested that majarine exerts a biphasic action on the body temperature in the mouse. As suggested by Yamawaki *et al.* (1983), a low dose of apomorphine can simultaneously activate a DA-related mechanism, which tends to decrease body temperature (either by increasing heat loss or decreasing heat production), and a 5-HT-related mechanism, which tends to increase body temperature. High doses of apomorphine (1.0 and 2.0 mg/kg) caused hypothermia (it may be that the DA—hypothermia mechanism overrides the effect of the DA/5-HT hyperthermia mechanism at these doses). The present study shows that a low dose of majarine, which can activate a DA/5-HT-related mechanism, tends to increase body temperature and decrease body temperature in cyprohetadine-pretreated animals. However, majarine caused hypothermia

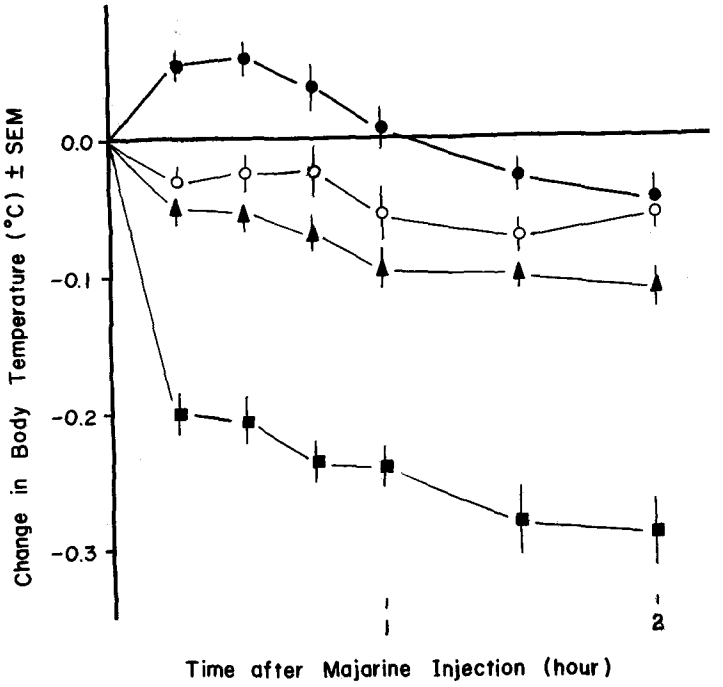

Fig. 1. Body temperature response curves to different dose of majarine in mice. o, control (injected with saline) (n = 10); ●, majarine, 0.1 mg/kg i.p. (n = 12); ▲, majarine, 1.0 mg/kg i.p. (n = 12); ■, majarine, 2.0 mg/kg i.p. (n = 13). Responses to 0.1, 1.0 and 2.0 mg/kg of majarine are significantly different from those of control at $p<0.05$, $p<0.05$ and $p<0.001$, respectively.

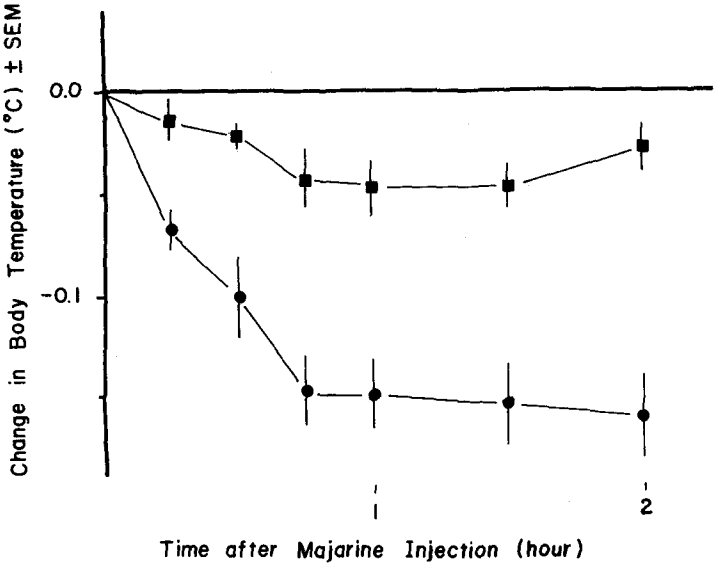

Fig. 2. Effects of the haloperidol (0.5 mg/kg i.p.) pretreatment on majarine-induced change in body temperature. ●, haloperidol + majarine, 0.1 mg/kg i.p. (n = 16); ■, haloperidol + majarine, 2.0 mg/kg (n = 15). Levels of significance: haloperidol + majarine (0.1 mg/kg) vs. majarine (0.1 mg/kg) (from data Fig. 1), $p<0.001$; haloperidol + majarine (2.0 mg/kg) vs. majarine (2.0 mg/kg) (from data Fig. 1), $p<0.001$.

Effects of haloperidol and cyproheptadine on the effects of majarine on body temperature

The effect of pretreatment with haloperidol on majarine-induced hypothermia is shown in Fig. 2. Haloperidol by itself did not significantly change the baseline body temperature. Pretreatment with haloperidol (0.5 mg/kg i.p.) completely blocked the hypothermia normally induced by 2.0 mg/kg of majarine ($p<0.001$, compared with responses to 2.0 mg/kg of majarine with no haloperidol pretreatment). At 0.1 mg/kg of majarine, pretreatment with haloperidol caused a pronounced hypothermia ($p<0.001$, compared with responses to 0.1 mg/kg of majarine with no haloperidol pretreatment). The effect of pretreatment with cyproheptadine on majarine-induced hypothermia is shown in Fig. 3 Cyproheptadine by itself did not significantly change the base-line body temperature. Pretreatment with cyproheptadine (0.2 mg/kg i.p.) completely blocked the hypothermia normally induced by 2.0 mg/kg of majarine ($p<0.001$, compared with responses to 2.0 mg/kg of majarine with no cyproheptadine pretreatment). At 0.1 mg/kg of majarine, pretreatment with cyproheptadine caused a hypothermia ($p<0.05$, compared with responses to 0.1 mg/kg of majarine with no cyproheptadine pretreatment). The effect of pretreatment with haloperidol and cyproheptadine on majarine-induced hypothermia is shown in Fig. 4. Pretreatment with haloperidol and cyproheptadine did not significantly change the baseline body temperature. Pretreatment with haloperidol (0.5 mg/kg) and cyproheptadine (0.2 mg/kg) completely blocked the hypothermia normally induced by 2.0 mg/kg of majarine ($p<0.001$, compared with responses to 2.0 mg/kg of majarine with no pretreatment of haloperidol and cyporheptadine. At 0.1 mg/kg, pretreatment with haloperidol and cyproheptadine did not significantly change the body temperature (no significant difference, compared with responses of majarine alone). On the other hand, pretreatment with cyproheptadine significantly blocked the hypothermia in mice pretreated with haloperidol (see Fig. 2). At 2.0 mg/kg of majarine, pretreatment with haloperidol and cyproheptadine showed no significant effect in comparision with responses to haloperidol pretreatment (see Fig. 2). Thus, haloperidol and cyproheptadine, respectively, could cancel the biphasic effects of majarine on body temperature.

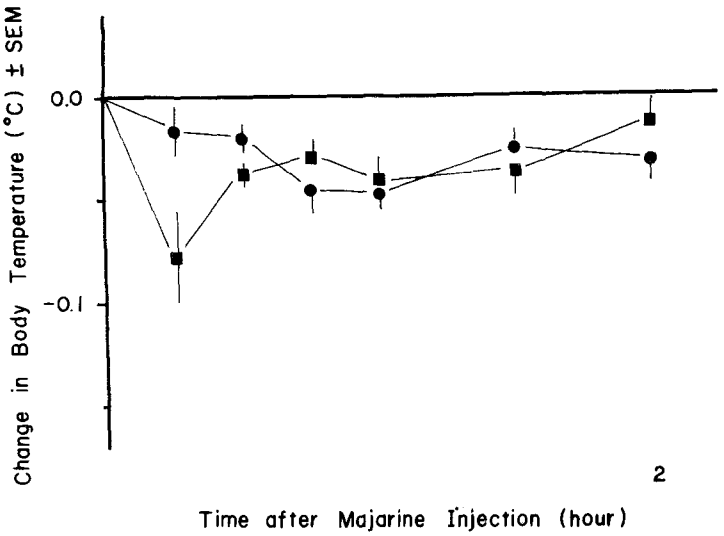

Fig. 3. Effects of cyproheptadine (0.2 mg/kg i.p.) pretreatment on majarine-induced change in body temperature. ●, cyproheptadine + majarine-induced change in body temperature. ●, cyproheptadine + majarine, 0.1 mg/kg i.p. (n = 14); ■, cyproheptadine + majarine, 2.0 mg/kg i.p. (n = 14). Levels of significance: cyproheptadine + majarine (0.1 mg/kg) vs. majarine (0.1 mg/kg) (From data Fig. 1), $p<0.05$; cyproheptadine + majarine (2.0 mg/kg) vs. majarine (2.0 mg/kg (from data Fig. 1), $p<0.001$.

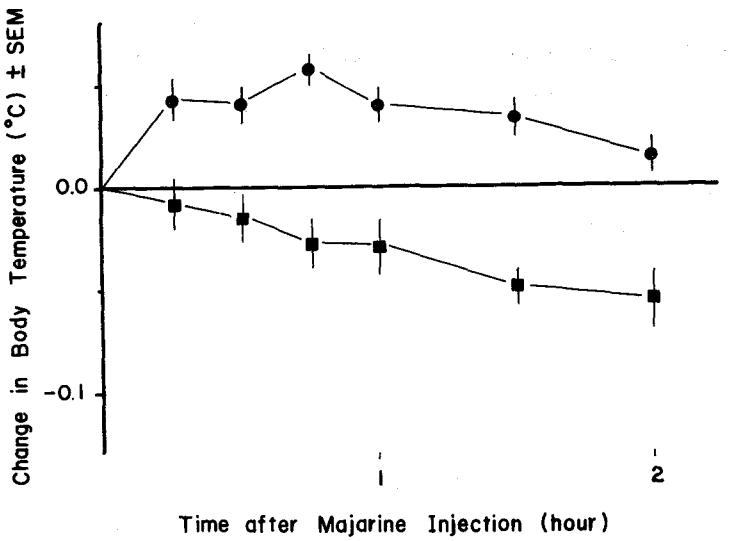

Fig. 4. Effects of haloperidol and cyproheptadine pretreatment on majarine-induced change in body temperature. ●, haloperidol + cypropeptadine + majarine, 0.1 mg/kg i.p. (n = 14); ■, haloperidol + cyproheptadine + majarine, 2.0 mg/kg i.p. (n = 14). Levels of significance: haloperidol + cypropeptadine + majarine (0.1 mg/kg) vs. majarine (0.1 mg/kg) (from data Fig. 1), no significant difference; haloperidol + cyproheptadine + majarine (2.0 mg/kg) vs. majarine (2.0 mg/kg) (from data Fig. 1), $p<0.001$; haloperidol + cyproheptadine + majarine (0.1 mg/kg) vs. haloperidol + majarine (0.1 mg/kg) (from oata Fig. 2), $p<0.001$; haloperidol + cyproheptadine + majarine (2.0 mg/kg) vs. haloperidol + majarine (2.0 mg/kg) (from data Fig. 2), no significant difference.

Effect of α-methyl-*p*-tyrosine and haloperidol on the effect of majarine on body temperature in reserpinized mice

Treatments with reserpine caused the body temperature of mice to drop from a pretreatment value of 37.6 ± 0.4°C (n = 81) to 25.2 ± 0.3°C (n = 81) degrees one day after injection. Temperature of reserpinized mice gradually increased during the subsequent experimental period. This gradual increase was less apparent in reserpinized micr treated with majarine (see Fig. 5). Majarine at 0.1 and 2.0 mg/kg significantly lowered the rectal temperature in reserpinized mice ($p<0.001$ and $p<0.001$, respectively, compared with responses of controls). The effect of additional pretreatment with the catecholamine synthesis inhibitor, α-methyl-*p*-tyrosine (α-MPT), was investigated in further experiment, in which reserpinized mice were treated with 0.1 and 2.0 mg/kg of majarine (see Fig. 6). α-methyl-*p*-tyrosine by itself did not significantly change the base-line body temperature in reserpinized mice. At 0.1 mg/kg of majarine, pretreatment with α-MPT caused a pronounced hypothermia ($p<0.001$, compared with responses to 0.1 mg/kg of majarine in reserpinized mice). At 2.0 mg/kg of majarine, it produced a slight hypothermia ($p<0.05$, compared with responses to 2.0 mg/kg of majarine in reserpinized mice). The effect of pretreatment with α-MPT and haloperidol on majarine-induced hypothermia is shown in Fig. 7. Haloperidol by itself did not significantly change the base-line body temperature in reserpinized mice. At 0.1 mg/kg of majarine, pretreatment with haloperidol showed no significant effect in comparison with responses to α-MPT pretreatment in reserpinized mice. Pretreatment with haloperidol completely blodked the hypothermia induced by 2.0 mg/kg of majarine in mice treated with reserpine and α-MPT ($p<0.001$) (see Fig. 6).

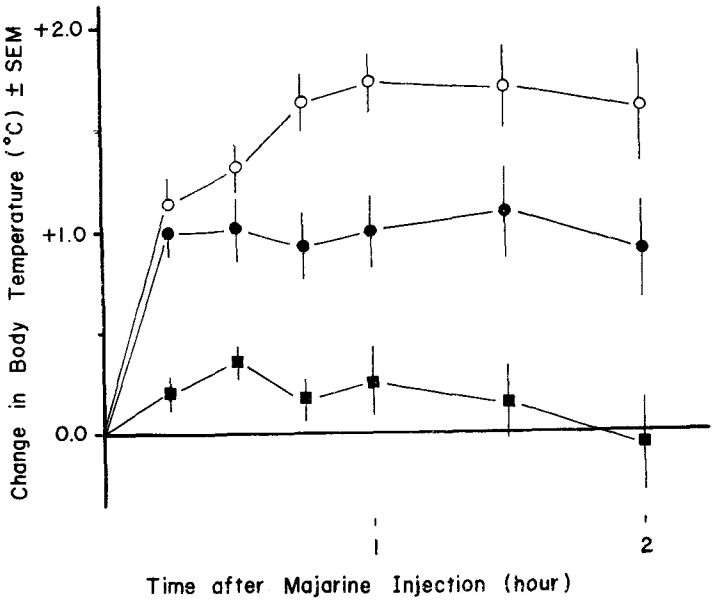

Fig. 5. Effects of reserpine (5 mg/kg i.p.) pretreatment on majarine-induced change in body temperature. o, control (reserpine + saline) (n = 9); ●, reserpine + majarine, 0.1 mg/kg i.p. (n = 9); ■, reserpine + majarine, 2.0 mg/kg i.p. (n = 11). Responses to 0.1 and 2.0 mg/kg of majarine are significantly different from those of controls at $p<0.001$, respectively.

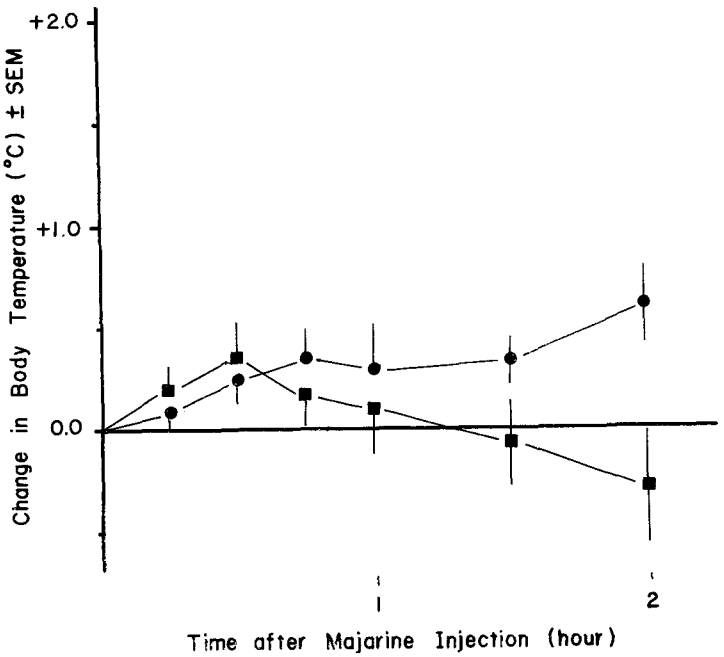

Fig. 6. Effects of reserpine (5 mg/kg i.p.) and α-methyl-*p*-tyrosine (200 mg/kg i.p.) pretreatment of majarine-induced change in body temperature. ●, reserpine + α-MPT + majarine, 0.1 mg/kg i.p. (n = 10); ■, reserpine + α-MPT + majarine, 2.0 mg/kg i.p. (n = 10). Levels of significance: reserpine + α-MPT + majarine (0.1 mg/kg) vs. reserpine + majarine (0.1 mg/kg) (from data Fig. 5), $p<0.001$; reserpine + α-MPT + majarine (2.0 mg/kg) vs. reserpine + majarine (2.0 mg/kg) (from data Fig. 5), $p<0.05$.

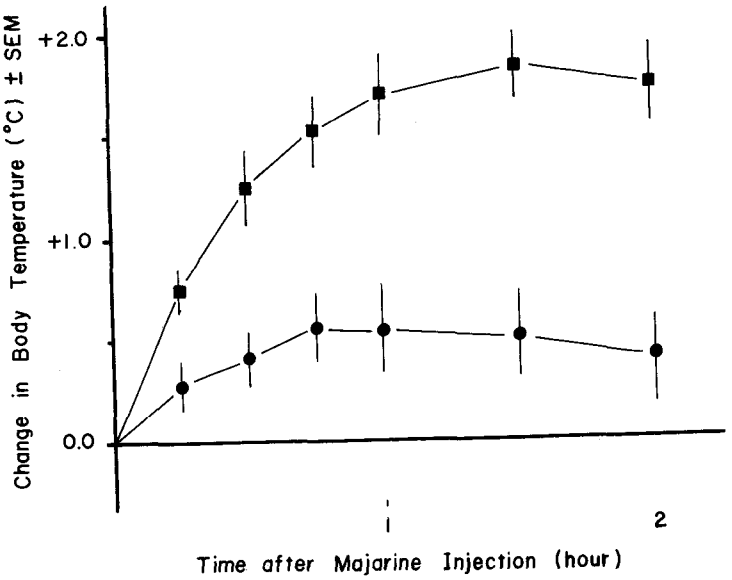

Fig. 7. Effect of reserpine, α-methyl-*p*-tyrosine and haloperidol pretreatment on majarine-induced change in body temperature. ●, reserpine + α-MPT + haloperidol + majarine, 0.1 mg/kg i.p. (n = 10); ■, reserpine + α-MPT + haloperidol + majarine, 2.0 mg/kg i.p. (n = 10). Levels of significance: reserpine + α-MPT + haloperidol + majarine (0.1 mg/kg) vs. reserpine + α-MPT + majarine (0.1 mg/kg) (from data Fig. 6), no significant difference; reserpine + α-MPT + haloperidol + majairne (2.0 mg/kg) vs. reserpine + α-MPT + majarine (2.0 mg/kg) (from data Fig. 6), $p<0.001$.

DISCUSSION

We have previously shown that majarine exerted the potentiation of hypnotic action of alcohol, the reduction of rectal temperature in mice (Cho *et al.*, 1974). Park *et al.* (1984) reported that majarine (5-20 mg/kg) produced dose-dependent decrease in the locomotor activity and the effect of apomorphine (0.1 mg/kg) was not affected by intraperitoneal pretreatment of majarine (20 mg/kg) in comparision with apomorphine alone, but apomorphine (0.5 mg/kg) showed a slightly attenuated effect on the locomotor activity by intraperitoneal pretreatment of majarine (20 mg/kg) in comparision with apomorphine alone in rats. Majarine is isoquinoline alkaloid like apomorphine. Apomorphine, a direct agonist at DA receptor, exerts a biphasic action on the mouse locomotor activity. In low dose levels, apomorphine inhibits locomotor activity, whereas it produces hyperactivity and stereotypy when given in high dose. the excitatory action of apomorphine is thought to be due to the activation of postsynaptic DA receptors (Kelly *et al.*, 1975), whereas the inhibitory effects are thought to be mediated via a DA autoreceptor (Carlsson, 1975; DiChiara *et al.*, 1976; Strömbom, 1975). Indeed, DA autoreceptor in the substantia nigra have been shown to have a lower threshold for inhibition of neuronal fires after intravenously administered apomorphine than do postsynaptic DA receptors (Skirboll *et al.*, 1979). Apomorphine affects body temperature in variety of species. Directed administration of apomorphine into the various areas in the brain in rats has shown that this DA agonist acts on the preoptic anterior hypothalamus to elicit its hypothermic response (Cox & Lee, 1977). The lowering of body temperture caused by centrally injected apomorphine is blocked by centrally or peripherally administered DA antagonist (for review, see Cox, 1979). Hence, it may be inferred that the intraction of peripherally administered drugs, haloperidol and cyproheptadine, with majarine occurs at the central site. Reserpine hypothermia is regarded as a central effect involving catecholamine neurons (Cox & Tha, 1975).

inhaloperidol-pretreated animals. DA agonists caused a fall in core temperature in the rat which is mediated through vasodilation in the tail (Cox *et al.*, 1978; 1980). Apomorphine affected body temperature by increasing heat loss and changing metabolic rate (Lin *et al.*, 1979). Radiation heat loss from the tail can be prevented by a cover of insulating material and aluminum foil. Cox *et al.* (1981) have shown that insulating the tail in rats can attenuate apomorphine-induced hypothermia. Apomorphine at 2.0 mg/kg produced hyperthermia in haloperidol-pretreated tail-covered rats (Yamawaki *et al.*, 1983). In high dose, majarine-induced hypothermia was attenuated by the DA antagonist or the 5-HT antagonist, respectively. The 5-HT antagonist, cyproheptadine, was not sufficient to block completely the hypothermic effect of 2.0 mg/kg of majarine in comparision with haloperidol pretreatment. Indeed, Cools (1978) has proposed the existence of two types of DA receptors in the brain, mediating opposing functions: haloperidol-sensitive DA receptors and haloperidol-nonsensitive DA receptors. Interestingly, in the goat, De Roij *et al.* (1978, 1979) have also suggested the existence in addition to a haloperidol-sensitive heat loss DA mechanism, of a haloperidol-nonsensitive DA mechanism that mediates the vasodilation effect of DA. Anatomical locations of two majarine-related thermoregulatory systems are not known. The drugs used in our experiments have both central and peripheral effects. Thus, both central and peripheral neural mechanism may be involved. In order to provide further evidence of the central action of majarine, we would like to observe in animal given microinjection of majarine into the preoptic anterior hypothalamus in brain. Majarine at 0.1 and 2.0 mg/kg significantly lowered the rectal temperature in reserpinized mice. Pretreatment with α-MPT caused a pronounced hypothermia in reserpinized mice. Our data clearly demonstrate that such as majarine lowered the body temperatures of normals through a process subject to attenuation by haloperidol, a dose of 2.0 mg/kg majarine decreased the body temperatures of reserpinized animals through a process which was attenuated by haloperidol. Danielson *et al.* (1985) reported that pretreatment with reserpine appears to alter the balance which normally exists between apomorphine-sensitive hypo-and hyper-thermic mechanism in a direction which favors hyperthermia. The inverted responses to apomorphine and the lack of attenuation by haloperidol suggest that this paradoxical hyperthermia may be due to stimulation of the normally recessive DA-related hyperthermic mechanism previously described by Yamawaki *et al.* (1983). Our data indicate that haloperidol activity at majarine-sensitive sites on still-active hypothermia-mediating neurons served to potentiate the balance further in favor of hyperthermia. Similar potentiating effects have been described previously with the neuroleptic sulpiride (Horowski, 1978). The major neurochemical effect of reserpine is to deplete central and peripheral stores of catecholamines and serotonin (Danielson *et al.*, 1985). Majarine is thought to rely upon these neurotransmitters in order to produce its thermic responses.

Our results demonstrate that pretreatments with reserpine and α-MPT reduce the animal's ability to respond through apomorphine-sensitive hypo-and hyper-thermic mechanisms to majarine. Assuming that drug-induced thermic responses are mediated through activation of neuronal pathways which are associated with thermoregulation, it is clear that this autonomic function must also be crucially depend upon reserpine-sensitive neurotransmitter stores. These data suppose that both dopaminergic and serotonergic mechanisms in the brain mediate the effects of majarine on body temperature. We propose that majarine directly stimulated DA receptors which secondarily activated 5-HT neurons to cause changes in body temperature. Our data also show that a transmitter may involve in neuronal pathways which serve opposite functions in thermoregulation. The transmitter mechanism may be a part of the multisynaptic pathway or it may modulate the activity of the pathway by synapsing on neurons of the pathway. Thus, the effect of systemic injection of a transmitter agonist or antagonist on body temperature will depend on the sum of the actions on the different synapses (Bligh, 1979). Furthermore, receptors in synapses of different thermoregulatory neuronal pathway may have different sensitivities to drugs.

REFERENCES

Bligh J, Sharman DF, Sunegi I and Szekely M: A preliminary analysis of the effects of norfenfluramine on thermoregulation in the sheep. J Physiol 239: 111-112, 1974

Cho BH and Lee HC: Studies on the crystalization of *Berberis koreana* Palibin and its antimicrobial activity. Theses of Catholic and Medical College 7:129-135, 1963

Cho BH, Kim YS and Park YH: Hypotensive effect of majarine in rats. IUPHAR 9th international congress of pharmacology (London) Abstract 1697p

Cho BH and Kim CI: Effects of *Berberis koreana* Palibin on sleep duration and rectal temperature in mouse. Korean J Pharm 10:23-27, 1974

Colboc O and Constentin J: Evidence for thermoregulation dopaminergic receptors located in preoptic medialis nucleus of the rat hypothalamus. J Pharm Pharmacol 32:624-629, 1980

Cools AR: Haloperidol and the significance of α-NE mediated control of a subpopulation of DA receptors for concepts such as supersensitivity and tolerence: A behavioral study on cats. Life Sci 23:2475-2484, 1978

Cox B: In Body Temperature-Regulation, Drug Effects, and Therapeutic Implications, (ed. P Lomany and E Schonbaun) pp. 231-255, Marcel Dekker New York, 1979

Cox B, Ennis C and Lee TF: The function of dopamine receptor in the central thermoregulatory pathways of the rat. Neuropharmacology 20:1047-1051, 1981

Cox B, Kerwin RW, Lee TF: Dopamine receptors in the central thermoregulatory pathways of the rat. J Physiol 282:471-483, 1978

Cox B, Kerwin RW, Lee TF and Pycock CJ: A dopamine 5-hydroxytryptamine link in the hypothalamic pathways which mediate heat loss in the rat. J Physiol 303:9-21, 1980

Cox B and Lee TF: Do central dopamine receptors have a physiological role in thermoregulation? Br J Pharmacol 61:83-86, 1977

Cox B and Lee TF: Possible involvement of 5-hydroxytryptamine in dopamine receptormediated hypothermia in the rat. J Pharm Pharmacol 31:325-354, 1979

Cox B and Tha SJ: The role of dopamine and noradrenaline in temperature control of normal and reserpine-pretreated mice. J Pharm pharmacol 27:242-354, 1975

Danielson TJ, Coutts RT, Coutts KA, Keashly R and Tang A: Reserpine-induced hypothermia and its reversal by dopamine agonists. Life Sci 37:31-38, 1985

De Roij TAJM, Frens J, Woutersen-Van Nijnanten F and Vianen Mejerink M: Comparison of the thermoregulatory responses to intracerebroventricularly injection dopamine, noradrenaline and 5-hydroxytryptamine in the goat. Eur J Pharmacol 48:395-405, 1978

De Roij TAJM, Frens J, Woutersen-Van Nijnanten F and Vianen Mejerink M:Relation between the thermoregulatory effects of intracerebroventricular injection dopamine and 5-hydroxytryptamine in the rabbit. Naunyn-Schmiedebergs Arch Exp Path Pharmk 306:61-66, 1979

Dichiara G, Porceddu ML, Vargiu L, Argiolas A And Gessa GL: Evidence for dopamine receptors mediating sedation in the mouse brain. Nature (London) 264:564-566, 1976

Fuxe K and Siogrist F: Hypothermic effect of apomorphine in the mouse. J Pharm Pharmacol 24:702-705, 1972

Grabwska M, Antkiewicz L, Maj J and Michaluk J: Apomorphine and central serotonin neuron. Pol J Pharmacol Pharm 25:29-39, 1973a

Grabowska M, Michaluk J and Antkiewicz L: Possible involvement of brain serotonin in apomorphine-induced hypothermia. Eur J Pharmacol 23:82-89, 1973b

Hill HF and Horita A: A pimozide-sensitive effect of apomorphine on body temperature of the rabbit. J Pharm Pharmacol 24:490-491, 1972

Horowski R: Differences in the dopaminergic effects of the ergot derivatives bromocriptine, lisuride and d-LSD as compared with apomorphine. Eur J Pharm 51:157-166, 1978

Kerry PH, Sevour PW and Iversen SD: Apomorphine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Res 94:507-522, 1975

Lin MT, Chern YF, Yang Z and Wang HS: Effects of apomorphine on the thermoregulatory response of rats to different ambient temperatures. Can J physiol Pharmacol 57:469-475, 1979

Maj J and Przewlocka B: The action of l-dopa in rats with the raphe nuclei lesions. Pol J Pharmacol Pharm 27:151-154, 1975

Menon MF and Vivonia CA: Modification of apomorphine hypothermia by drugs affecting brain 5-hydroxytryptamine function. Eur J Pharmacol 76:223-227, 1981

Park YH, Kim YS and Cho BH: The effects of majarine on blood pressure after intracerebroventricular injection and locomotor activity in rats. The Congress of the Society of Pharmacology Republic of Korea 37th (Seoul) Abstract BP-10, 1985

Przewlocki R: The effect of lesions of dopaminergic and serotonergic systems on apomorphine-induced hypothermia in the rats. Pol J Pharmacol Pharm 29:263-270, 1977

Quock RM and Horrita A: Apomorphine: Modification of its hyperthermic effect in rabbits by *p*-chlorophenylalanine. Science (Wash. DC) 183:539-540, 1974

Skirbol LR, Grace AA and Bunney BS: Dopamine auto- and postsynaptic receptor: Electrophysiological evidence for differential sensitivity to dopamine agonist. Science (Wash. DC) 206:80-82, 1979

Strömbom U: Effects of low doses of catecholamine receptor agonists on exploration in mice. J Neural Transm 37:229-235, 1975

Yamawaki S, Lai H and Horita A: Dopaminergic and serotonergic mechanisms of thermoregulation: mediation of thermal effects of apomorphine and dopamine. J Pharm Exp Therp 227:383-388, 1983

=국문초록=

Majarine의 중추신경계에 대한 작용(II)

—마우스에 있어서 Majarine의 체온감소에 미치는 dopamine, serotonin 길항제의 작용에 관한 연구—

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한국특산 매자나무(*Berberis Koreana* Palibin)의 뿌리에서 분리한 majarine은 isoquinoline 알카로이드로서 본 교실에서는 중추신경계에 대한 약리작용을 검토하고 있다.

Majarine을 마우스 복강내로 투여하여 직장온도 변화와 haloperidol, cyproheptadine과 reserpine 등에 대한 약물 상호작용을 관찰하여 다음과 같은 성적을 얻었다.

Majarine은 마우스에 있어서 용량의존적으로 현저한 체온감소를 나타내었으나, 0.1 ㎎/㎏투여시 체온증가의 유의성을 보였다. 체온감소는 haloperidol과 cyproheptadine으로 억제되었다. Reserpine처치 마우스에 있어서 α-methyl-*p*-tyrosine으로 전처치한 다음 majarine 2.0㎎/㎏ 투여시 체온감소를 나타내었다.

이러한 결과로 보아 majarine의 체온변화는 dopamine과 serotonin수용체에 관련성이 있다고 사려되고, 체온감소는 dopamine수용체에 직접적으로 작용한다고 생각되는 바이다.