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Long-term exposures to higher environmental temperature and body temperature
Effect of chlorpromazine in relation to hypothalamic GABA

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Abstract

Treatment with a single dose of chlorpromazine (CPZ; 1 mg/kg, ip) at room temperature (28°±0.5°C) significantly reduced body temperature by its anticholinergic action. Long-term exposures to higher environmental temperature (40°±0.5°C, 2 h/day, for 30 consecutive days) increased body temperature significantly by reduction of hypothalamic GABAergic activity, but this increase in body temperature was attenuated from that observed with a single exposure to higher environmental temperature (40°C for 2 h). Treatment with a single dose of CPZ on the last day of 30 consecutive days of exposures to higher environmental temperature increased body temperature of rats more than that observed with long-term exposures to higher environmental temperature possibly due to (i) reduction of hypothalamic GABAergic activity, (ii) heat dissipation and (iii) reverse-anticholinergic action of CPZ at higher environmental temperature.

Keywords: Higher environmental temperature; Chlorpromazine; Long-term exposures; Body temperature; GABA; Hypothalamus

1. Introduction

Chlorpromazine (CPZ), a well-known phenothiazine has been used as a psychotropic drug since early fifties. It has poikilothermic (Chai and Lin, 1977; Sato et al., 1986b), anticholinergic and antidopaminergic (Anden et al., 1966) activities. Single dose of CPZ has been found to reduce body temperature under normal room temperature via its anticholinergic action (Sato et al., 1986a,b). It does not affect central γ-aminobutyric acid (GABA). Single dose of CPZ is known to be unable to reduce higher environmental temperature-induced hyperthermia under single exposure (Sato et al., 1986a). Higher environmental temperature has specific effects on mammalian central nervous system (Berry et al., 1984; Siesjo, 1978), and these effects are interregulated by GABAergic, dopaminergic and cholinergic systems (Biswas and Poddar, 1988; Lin et al., 1979; Poddar et al., 1986). A single exposure to higher environmental temperature causes reduction in central GABAergic activity (Biswas and Poddar, 1989), while long-term (repeated) exposures to higher environmental temperature cause adaptation leading to a lesser reduction in GABAergic activity (Lishmanov et al., 1987). Brown and Taylor (1996) have reported that a single exposure to higher environmental temperature and CPZ increases body temperature of rats by reverse-anticholinergic action. This is a phenomenon exhibited by many phenothiazines, which behave as a procholinergic drug under higher environmental temperature, i.e. it cannot produce its anticholinergic action but, in turn, reverses it (Brown and Taylor, 1996). Recently, Mukherjee and Poddar (1999) have shown that a single dose of CPZ under higher environmental temperature does not affect higher environmental temperature–induced reduction of central GABA. Long-term exposures to both higher environmental temperature and CPZ potentiated the increase of body temperature observed with a single exposure to higher environmental temperature. The neurotransmitters that are involved in thermoregulation generally have been known to maintain a body balance under both normal and higher ambient temperature (Biswas and Poddar, 1990; Brown et al., 1982; Cabanac and Massonet, 1977) by heat-sensitive neuronal connections through the hypothalamus (Brownstein et al., 1976). The authors have already studied the effect of a single dose of CPZ under single exposure to higher environmental temperature, as well as the effect of long-term CPZ treatment under higher environmental tem-

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perature on body temperature in relation to the involvement of central GABA (Mukherjee and Poddar, 2000a, b). In the present investigation, the authors are interested to study the effect of a single treatment of CPZ in rats exposed to higher environmental temperature under long-term condition on changes, if any, of body temperature in relation to the involvement of central GABA along with interaction(s) of other neurotransmitters.

2. Methods

2.1. Animals

Adult male albino rats (125–140 g body weight) of Charles Foster strain, kept in a 12-h dark–12-h light cycle at room temperature (28 ± 0.5°C) having constant relative humidity (80 ± 5%), were maintained with standard laboratory diet and water ad libitum.

2.2. Chemicals and drugs

Sodium glutamate, pyridoxal phosphate (PALPO), GABA, ninhydrine, methyl-benzothiozolinone hydrazine (MBTH) and ethanolamine-*O*-sulphate (EOS) were purchased from Sigma Chemical Co., St. Louis, MO, USA. Muscimol, bicuculline, physostigmine and atropine were also purchased from Sigma Chemical Co. CPZ–HCl was purchased from Rhone-Poülenc, Bombay, India. All other reagents used in the present study were of analytical grade.

2.3. Exposure of animals to higher environmental temperature

The animals maintained at room temperature (28° ± 0.5°C) were exposed to higher environmental temperature (40° ± 0.5°C) in a chamber having constant relative humidity under a long-term period (2 h/day for 30 consecutive days).

2.4. Administration of drug(s) with or without exposure to HET

The animals were divided into several groups. Each group contained four to six animals, and they were treated according to the following schedules:
At the end of the exposure to higher environmental temperature (2 h) and/or treatment with CPZ (1 h), both experimental and control groups were sacrificed by cervical dislocation between 10 and 11 AM to avoid the effects of circadian variation.

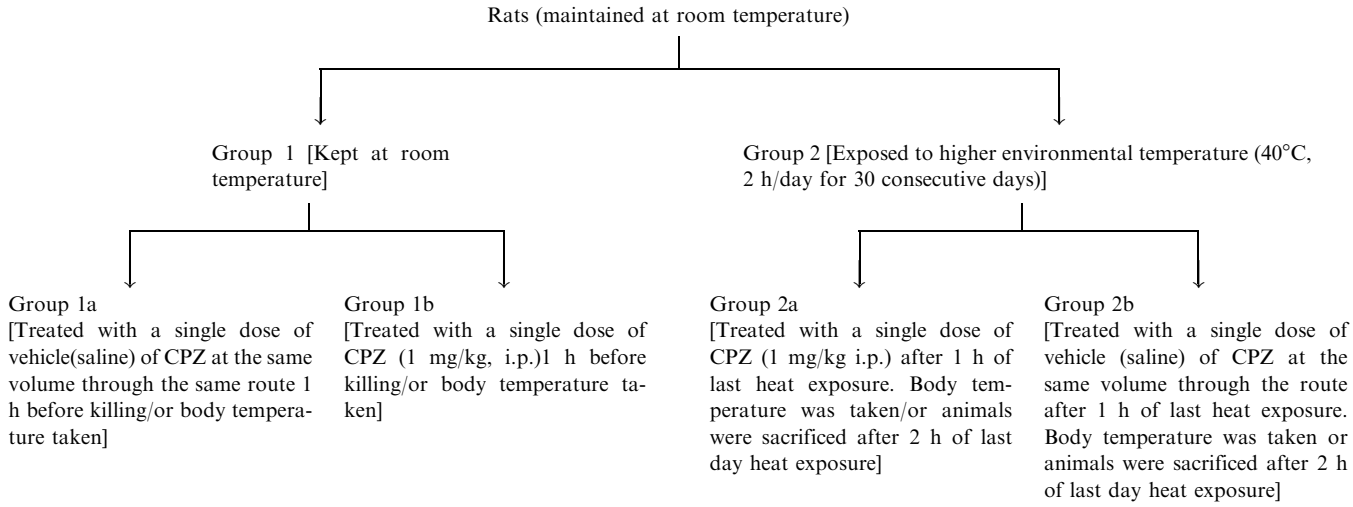
2.5. Treatment with agonists and/or antagonists of cholinergic and GABAergic systems to rats kept at room (normal) temperature or exposed to higher environmental temperature (heat)

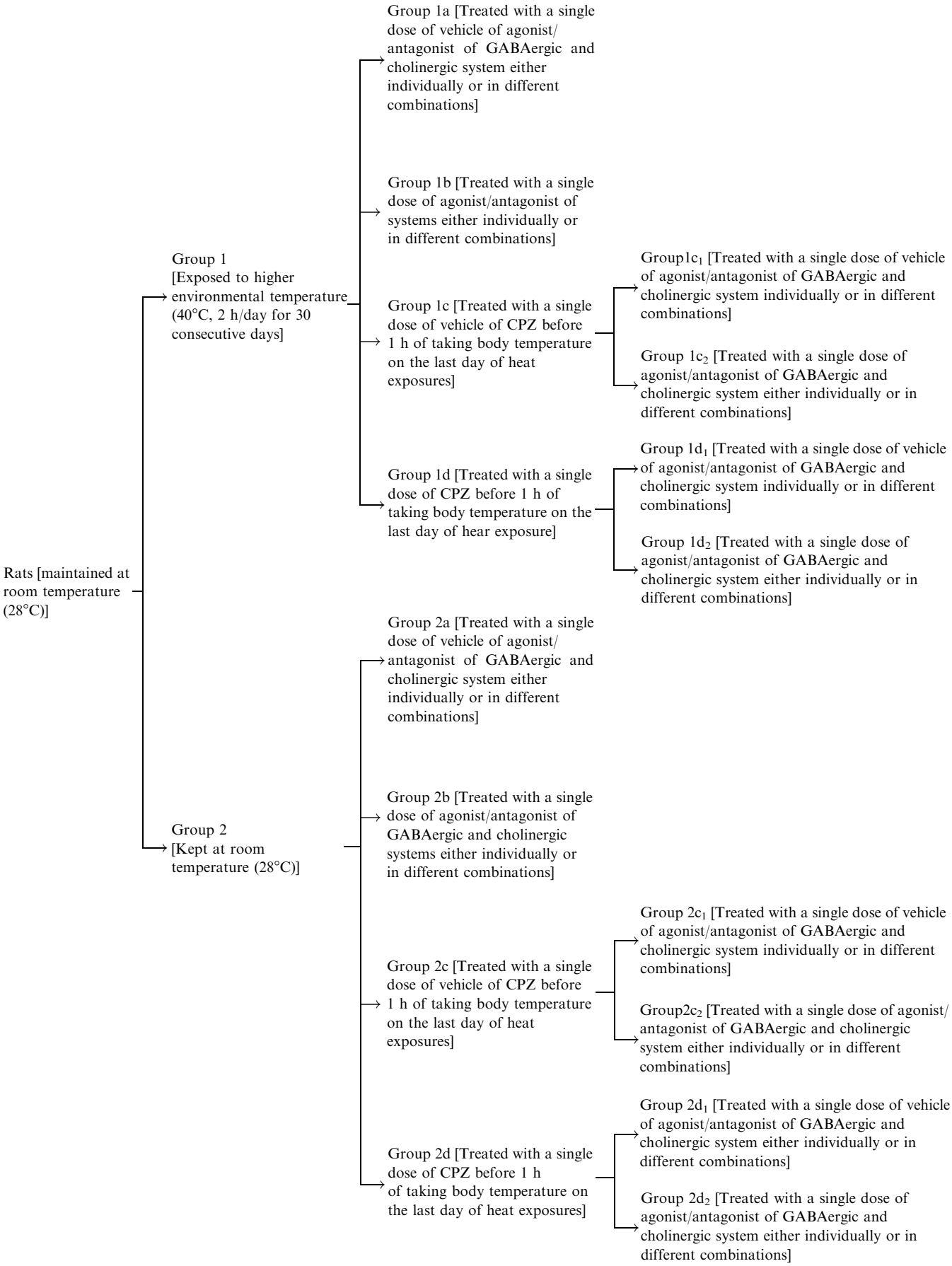
In this pharmacological study, animals were divided into several groups (as described below).

Muscimol (GABA agonist, 1 mg/kg, ip), atropine (cholinergic antagonist, 5 mg/kg, ip) or bicuculline (GABA antagonist, 1 mg/kg, ip) was given 30 min and physostigmine (acetylcholine esterase inhibitor, 0.2 mg/kg, ip) was applied 15 min before measurement of rectal temperature under 28°C or 40°C. Rectal temperature was measured after 2 h of the last exposures to higher environmental temperature (40°C, 2 h/day, for 30 consecutive days). Dosages of the drug in combination were the same as mentioned above in the parenthesis of the individual drug.

2.6. Collection of brain tissue

Brains of both control and experimental rats were taken immediately after sacrifice by cervical dislocation and were immersed in liquid nitrogen for the estimation of GABA and glutamate levels. Brains were also kept in an ice-cold (0–4°C) condition for enzymes assay and for the




Rats [maintained at room temperature (28°C)]
Group 1 [Exposed to higher environmental temperature (40°C, 2 h/day for 30 consecutive days]
Group 1a [Treated with a single dose of vehicle of agonist/ antagonist of GABAergic and cholinergic system either individually or in different combinations]
Group 1b [Treated with a single dose of agonist/antagonist of systems either individually or in different combinations]
Group 1c [Treated with a single dose of vehicle of CPZ before 1 h of taking body temperature on the last day of heat exposures]
Group1c1 [Treated with a single dose of vehicle of agonist/antagonist of GABAergic and cholinergic system individually or in different combinations]
Group 1c2 [Treated with a single dose of agonist/antagonist of GABAergic and cholinergic system either individually or in different combinations]
Group 1d [Treated with a single dose of CPZ before 1 h of taking body temperature on the last day of hear exposure]
Group 1d1 [Treated with a single dose of vehicle of agonist/antagonist of GABAergic and cholinergic system individually or in different combinations]
Group 1d2 [Treated with a single dose of agonist/antagonist of GABAergic and cholinergic system either individually or in different combinations]
Group 2 [Kept at room temperature (28°C)]
Group 2a [Treated with a single dose of vehicle of agonist/ antagonist of GABAergic and cholinergic system either individually or in different combinations]
Group 2b [Treated with a single dose of agonist/antagonist of GABAergic and cholinergic systems either individually or in different combinations]
Group 2c [Treated with a single dose of vehicle of CPZ before 1 h of taking body temperature on the last day of heat exposures]
Group 2c1 [Treated with a single dose of vehicle of agonist/antagonist of GABAergic and cholinergic system individually or in different combinations]
Group2c2 [Treated with a single dose of agonist/ antagonist of GABAergic and cholinergic system either individually or in different combinations]
Group 2d [Treated with a single dose of CPZ before 1 h of taking body temperature on the last day of heat exposures]
Group 2d1 [Treated with a single dose of vehicle of agonist/antagonist of GABAergic and cholinergic system either individually or in different combinations]
Group 2d2 [Treated with a single dose of agonist/antagonist of GABAergic and cholinergic system either individually or in different combinations]

[^{3}H]-GABA receptor binding study. The hypothalamus was dissected out following the method as described by Poddar and Dewey (1980).

2.7. Estimation of biochemical parameters

GABA and glutamate were estimated according to the method of Lowe et al. (1958). The activities of glutamic acid decarboxylase (GAD) and GABA-transaminase (GABA-T) were estimated by the method of MacDonnel and Greengard (1975) and Sytinsky et al. (1975), respectively. The accumulation of GABA was measured with EOS (GABA-T inhibitor), according to the method of Leech and Walker (1977) and in vitro [^{3}H]-GABA binding to different regions of rat brain was assayed according to method as described by Ticku (1980). Protein was estimated following the method of Lowry et al. (1951) using BSA as standard.

2.8. Measurement of rectal temperature

Rectal temperature, considered as an index of body temperature, was recorded using a thermistor probe inserted 2 cm into the rectum of both control and experimental rats according to the method of Cox et al. (1981). The rectal temperature of rat exposed to higher environmental temperature was measured immediately at the end of 2 h of heat exposure without allowing the animal to cool off.

2.9. Statistical analysis

The statistical significance between the mean values were assessed by two-way analysis of variance (ANOVA), unless otherwise stated.

3. Results

Table 1 represents that treatment with a single dose of CPZ (1 mg/kg, ip) at normal temperature (28°C) did not show any significant change in the steady state levels of GABA and glutamate, activities of GAD and GABA-T, EOS-induced GABA accumulation and [^{3}H]-GABA binding in the hypothalamus of rats. Long-term heat (40°C) exposure (40°C) significantly increased hypothalamic steady state levels of GABA (34%; $P<.025$), glutamate (27%; $P<.025$), activity of GAD (36%; $P<.025$) and EOS-induced GABA accumulation (35%; $P<.025$) without any appreciable change of its GABA-T activity. The [^{3}H]-GABA binding in this region, on the other hand, significantly reduced (28%; $P<.025$) under similar conditions of heat exposure to rats. The administration of a single dose of CPZ on the last day of the long-term heat exposures significantly increased the steady state levels of hypothalamic GABA (34%; $P<.025$), glutamate (28%; $P<.025$), its activity of GAD (21%; $P<.025$), EOS-induced GABA accumulation (35%; $P<.025$), with a significant reduction in the [^{3}H]-GABA binding (30%; $P<.025$) to its receptor with respect to their corresponding control but not with respect to long-term heat exposure alone. No appreciable change in the hypothalamic GABA-T activity was observed with CPZ under similar condition of heat exposure with respect to either of the above comparisons.

Table 2 appears to show that long-term exposures to higher environmental temperature or heat significantly increased ($P<.05$) body temperature of normal rats. A single dose of CPZ significantly reduced ($P<.05$) body temperature of normal rats but was unable to reduce higher environmental temperature (heat)-induced hyperthermia when applied on the last day of the long-term heat exposure, rather, the body temperature was potentiated under this condition.

Table 1
Effect of single administration of CPZ with or without long-term exposure to higher environmental temperature on hypothalamic steady-state levels of GABA and glutamate, activities of GAD and GABA-T, EOS-induced GABA accumulation and [^{3}H]-GABA binding

	Conditions			
	Kept at room temperature (28°C)		Exposed to higher environmental temperature[a]	
Parameters measured	Control (saline)[b]	CPZ[b]	Saline[b]	CPZ[b]
Steady state level of GABA (nmol/mg protein)	29.48 ± 1.26	28.25 ± 0.96	39.54 ± 2.01 *	39.48 ± 1.69 *, **
Steady-state level of glutamate (nmol/mg protein)	50.41 ± 3.10	44.75 ± 2.18	63.00 ± 3.80 *	64.40 ± 4.02 *, **
Activity of GAD (nmol GABA/mg protein/h)	384.07 ± 12.80	407.90 ± 13.26	520.76 ± 15.21 *	463.47 ± 18.78 *
Activity of GABA-T (ΔO.D.$_{660}$/mg protein/h)	2.89 ± 0.26	2.84 ± 0.20	2.68 ± 0.21	2.54 ± 0.23
EOS-induced GABA accumulated (nmol GABA/mg protein/h)	2.48 ± 0.19	2.26 ± 0.08	3.30 ± 0.10 *	3.36 ± 0.26 *, **
[^{3}H]-GABA binding (fmol/mg protein)	549.80 ± 26.10	436.93 ± 48.83	398.72 ± 16.20 *	387.19 ± 18.38 *

Results are expressed as means ± S.E.M. of four separate observations.
GABA indicates γ-aminobutyric acid; GAD indicates glutamic acid decarboxylase; GABA-T indicates GABA-transaminase; EOS indicates ethanolamine-*O*-sulphate.

[a] 40°C; 2 h/day, for 30 consecutive days.

[b] CPZ at a dose of 1 mg/kg (ip) or saline was administered to rats either kept at room temperature (28°C) or after 1 h of the last day of long-term exposure to higher environmental temperature (40°C; 2 h/day, for 30 consecutive days). Rats were sacrificed after 1 h of CPZ or saline administration.There was no significant changes between any of the control sets of rats (as depicted in the Methods section) and so results of only one control is depicted here.

* Significantly different from control at 28°C, $P<.025$, using Tukey test for ANOVA.

** Significantly different from CPZ for 1 day at 28°C, $P<.025$, using Tukey test for ANOVA.

Table 2
Measurement of rectal temperature of rats with a single dose of CPZ with or without agonists and/or antagonist of GABAergic and cholinergic systems under normal and long-term exposure to higher environmental temperature

	Rectal temperature (°C) at			
	Room temperature (28°C)		Higher environmental temperature[a]	
Treatment	Control (saline)[b]	CPZ[b]	Saline[b]	CPZ[b]
Saline (control)	36.2 ± 0.14	35.5 ± 0.10 *	37.8 ± 0.19 *	39.4 ± 0.22 *
Muscimol (1 mg/kg, ip)	35.2 ± 0.10 *	35.0 ± 0.15 *	37.2 ± 0.19 *	38.4 ± 0.20 *
Bicuculline (1 mg/kg, ip)	37.0 ± 0.30 *	36.3 ± 0.14 *	38.7 ± 0.20 *	39.2 ± 0.20 *
Physostigmine (0.2 mg/kg, ip)	37.1 ± 0.20 *	36.6 ± 0.20	38.8 ± 0.18 *	39.4 ± 0.22 *
Atrophine (5 mg/kg, ip)	35.5 ± 0.15 *	35.5 ± 0.26	38.9 ± 0.18 *	39.6 ± 0.20 *
Muscimol + atropine	35.1 ± 0.18	35.0 ± 0.08 *	37.1 ± 0.18 *	38.2 ± 0.19 *
Bicuculline + atropine	36.5 ± 0.25 *	36.1 ± 0.20 *	37.8 ± 0.19 *	39.2 ± 0.20 *
Bicuculline + physostigmine	38.9 ± 0.20 *	36.8 ± 0.26 *	38.4 ± 0.19 *	39.5 ± 0.20 *

Results are expressed as mean ± S.E.M. of four to six separate observations. There were no significant changes between any of the control sets of rats treated with vehicle of drug(s) (agonists and/or antagonists).
Other details are the same as described in Table 1.
Significance was calculated by two-way analysis of variance (ANOVA), and it was found that the interaction effect was not significant ($P < .05$).

[a] Exposure to higher environmental temperature was given at 40°C (2 h/day for 30 consecutive days).

[b] CPZ was administered (ip) at a dose of 1 mg/kg.

* Significance was calculated by two-way analysis of variance (ANOVA), and it was found that between the groups, the effect was significant, $P < .05$.

GABA-agonist muscimol, reduced body temperature of normal rats, but did not significantly change the long-term higher environmental temperature-induced hyperthermia. Treatment with CPZ to long-term heat-exposed rats potentiated ($P < .05$) the long-term heat-induced hyperthermia in presence of muscimol. Bicuculline (the GABA antagonist)-induced hyperthermia at 28°C was reduced ($P < .05$) with a single dose of CPZ to that of normal rats. Increase of long-term higher environmental temperature-induced hyperthermia by bicuculline was potentiated to the same extent as that produced by an application of a single dose of CPZ on the last day of the long-term heat exposure. Physostigmine (the cholinergic agonist)-induced increase in body temperature of rats at 28°C was attenuated with a single dose of CPZ, but application of a single dose of CPZ on the last day of the long-term heat exposure elevated ($P < .05$) the potentiating effect of physostigmine on long-term heat-induced hyperthermia ($P < .05$). Atropine, the cholinergic antagonist, which was hypothermic at 28°C, potentiated the long-term heat-induced hyperthermia. Treatment of rats with a single dose of CPZ on the last day of long-term exposure to higher environmental temperature increased ($P < .05$) the atropine-induced potentiation of long-term heat-induced hyperthermia. A single dose of CPZ at 28°C did not affect the hypothermic effect of coadministration of muscimol and atropine at that environmental temperature. Though atropine in presence of muscimol, attenuated the long-term heat-induced hyperthermia, the application of CPZ on the last day of the long-term heat exposure did not withdraw this attenuating effect, and, rather, the body temperature was potentiated to the same temperature as observed with long-term heat alone. Body temperature observed with coadministration of muscimol + atropine with CPZ on the last day of long-term heat exposure was attenuated from that observed (in absence of muscimol + atropine) with CPZ on the last day of the long-term heat exposure. The potentiating effect of atropine on the long-term higher environmental temperature-induced hyperthermia was attenuated in presence of bicuculline, but treatment with a single dose of CPZ on the last day of heat exposure greatly potentiated the body temperature, which was greater than that observed with long-term heat exposure alone. The hyperthermic effect of bicuculline in the presence of physostigmine at 28°C (which was more than that produced by bicuculline or physostigmine alone) was attenuated by a single dose of CPZ at 28°C. Long-term heat-induced hyperthermia in presence of bicuculline + physostigmine was potentiated with a single dose of CPZ on the last day of the long-term heat exposure.

4. Discussion

Like previous studies (Chai and Lin, 1977; Sato et al., 1986a,b), present findings also suggest that CPZ is a potent hypothermic agent (Table 2) under normal room temperature. Further, it has been found that a single dose of CPZ under the same ambient temperature produced no effect on hypothalamic GABAergic system, because CPZ, under this condition, showed no change in any of the parameters of the hypothalamic GABA system (Table 1). The results of the present study (Table 2), using agonists and antagonists of cholinergic and GABAergic systems, suggested that CPZ produces hypothermia possibly by its anticholinergic action (Anden et al., 1966) and not through the involvement of GABAergic system. The anticholinergic action of CPZ being the cause of its hypothermic effect under room temperature has been suggested by others (Chai and Lin, 1977; Sato et al., 1986a). Previous results of our laboratory (Biswas and Poddar, 1989; Mukherjee and Poddar, 2000a) and the results of the present study (Tables 1 and 2) suggest that long-term exposures to higher environmental temperature attenuates single heat-induced decrease of hypothalamic GABAergic activity, as well as increase of body temperature under similar condition (Biswas and Poddar, 1989; Mukherjee and Poddar, 2000a; Otero Losada, 1988) possibly by stimulating the β-endorphin release (Nicoll et al., 1980; Robins et al., 1987) and activating cholinergic system via the inhibition of central GABAergic activity and ultimately produced hyperthermia. This long-

term heat-induced hyperthermia has been found to be less than that produced following a single exposure to heat (Mukherjee and Poddar, 2000a).

Treatment with a single dose of CPZ on the 30th day of the long-term heat exposures increased the steady-state level of hypothalamic GABA (34%), its GAD activity (36%) and also EOS-induced GABA accumulation (35%) (Table 1). However, its [^{3}H]-GABA binding to its receptor was significantly reduced with CPZ under similar conditions of CPZ treatment. It has also been noticed that this CPZ-induced reduction in hypothalamic [^{3}H]-GABA binding has been found to be identical to that produced by long-term exposures to higher environmental temperature (Table 1). These indicate that there may be an increase in hypothalamic GABA synthesis with a decrease of its release under long-term heat exposures and also with the application of a single dose of CPZ on the 30th day of the long-term heat exposures. However, no significant change in hypothalamic GABAergic activity in comparison to that observed in long-term heat exposures alone (Table 1) indicates that CPZ on the last day of the long-term heat exposures do not produce any effect on the long-term higher environmental temperature-induced inhibition in hypothalamic GABA.

The measurement of body temperature with agonists and antagonists of GABAergic and cholinergic systems under normal room temperature and higher environmental temperature predicts that a single dose of CPZ reduces body temperature by its anticholinergic action under 28°C and not by the involvement of the GABA system or by its interregulation with other neurotransmitters (Table 2). Long-term higher environmental temperature-induced hyperthermia may be a result of an inhibition of central GABAergic activity and stimulation of central cholinergic system because long-term heat-induced hyperthermia has been found to be potentiated by (a) bicuculline, a GABA antagonist, which has been found to be attenuated by muscimol, a potent GABA agonist and also by atropine, a cholinergic antagonist and (b) physostigmine (acetyl cholinesterase inhibitor), a cholino-mimicking drug, which has been found to be further potentiated with bicuculline (Table 2). Further, an apparent enhancement of body temperature with a single dose of CPZ on the last day of the long-term heat exposures (Table 2) from the observed with a single exposure to heat and CPZ (Mukherjee and Poddar, 2000b) may be explained by the reverse effect on atropine-like or anticholinergic activity of CPZ (which may be called as reverse-anticholinergic action of CPZ) under heat-exposed condition and suppression of heat dissipation (Brown and Taylor, 1996). The possibility of reduction in sweat secretion by development of adaptation (Lishmanov et al., 1987) due to long-term heat exposures cannot be ignored.

Body temperature is known to depend largely on ambient temperature and may or may not indicate much about thermoregulatory status. Further study is needed in evaluating thermoregulatory response thresholds (i.e. triggering core temperatures) for cold response (i.e. nonshivering thermogensis) and warm response (i.e. panting) to quantify thermoregulatory status in relation to ambient temperature: From this study, one could distinguish between changes in the thermal set point and reductions in the precision of thermoregulatory control. Considering this view, the results of the present study may suggest that atropine may change the set point without impairing thermoregulatory precision. Chloropromazine, on the other hand, may impair the accuracy over thermoregulatory control. No change in intrathreshold range (temperatures between a warm and cold response) with atropine and increase in intrathreshold range with CPZ further suggest that CPZ may produce a nonspecific impairment of thermoregulatory control.

Finally, it can be concluded that CPZ under normal room temperature reduces body temperature by its anticholinergic action. Long-term exposure to higher environmental temperature reduces hypothalamic GABAergic activity to increase its cholinergic activity and may increase body temperature. A single dose of CPZ on the last day (30th day) of the long-term heat exposure shows no change in hypothalamic GABAergic activity from that observed with long-term heat exposure alone, but it potentiates long-term heat-induced hyperthermia possibly by (i) reverse anticholinergic action of CPZ on heat-induced mechanism and/or also by (ii) suppression of heat dissipation by reducing the activity of sweat glands. Since muscimol and bicuculline, the agonist and antagonist, respectively, of $GABA_A$ receptors (Matsumoto, 1989) have been used in the present study, it is reasonable to assume that the hypothalamic $GABA_A$ receptors may be involved in the regulation of body temperature under the present experimental condition.

In addition to the dominant thermoregulatory controlling role of hypothalamus, there may be the involvement of other nuclei and spinal cord where the lateral spinothalamic pathway goes through. The spinothalamic pathway is composed of three orders of sensory neurons. The first-order neuron conveys the impulse for temperature of the body from the appropriate receptor to the posterior gray horn on the same side of the spinal cord. In the horn, the first-order neuron synapses with a second-order neuron. The axon of the second-order neuron crosses to the opposite side of the cord, where it becomes a component of the lateral spinothalamic tract in the lateral white column. The second-order neuron passes upward in the tract through the brainstem to a nucleus in the thalamus known as ventral posterolateral nucleus. Thus, in the thalamus, temperature recognition occurs. The sensory impulse is then conveyed from thalamus to the somesthelic area of the cerebral cortex by a third-order neuron. Therefore, it is quite reasonable like hypothalamic GABA, the cerebro-cortical, thalamic, brainstem and spinal cord GABA with other neurotransmitters may play a role in the regulation of body temperature under higher environmental temperature.

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