STUDIES ON RECTAL TEMPERATURE OF RATS IN RELATION TO SEASONAL AIR TEMPERATURE AND MORPHINE ADMINISTRATION

UDAI PRAKASH AND P.K. DEY

Department of Physiology,
*Institute of Medical Sciences, Banaras Hindu University, Varanasi-*221 005

(Received on May 5, 1980)

Summary: The present findings demonstrate that seasonal air temperature does not only influence the basal core temperature of rats, but also modifies the physiological/pharmacological actions of drugs. Thus, at low ambient temperature, intracerebroventricular on intraperitoneal administration of morphine produces mainly hypothermia followed by a secondary rise in rectal temperature. On the other hand, at high ambient temperature, the drug produces hyperthermia only. The hypothermic response at low ambient temperature is abolished by pretreatment of rats with 6-hydroxydopamine but not with phenoxybenzamine administration. This suggest that catecholamine pathway in the central nervous system is involved in morphine induced hypothermic response. Further, the role of cholinergic neurons in such response is also indicated.

Key words: body temperature phenoxybenzamine 6-hydroxydopamine seasonal temperature hemicholinium morphine hypothermia intracerebroventricular infusion

INTRODUCTION

The role of biogenic amines like noradrenaline (NA), serotonin (5-HT) and acetylcholine (Ach) in the central mechanism of regulation of body temperature has been well recognised following their demonstration in the hypothalamus, their profound ability to influence body temperature following intracerebroventricular (i.c.v.) or microinjection into the hypothalamic region, and the evidence for their release in response to change in ambient temperature and excellent reviews on these works have appeared (6, 7, 8, 20, 21). Based on this biochemical basis of central thermoregulation, the alteration of body temperature produced by several centrally acting drugs has been explained through perturbation of metabolism of these amines (6, 13, 14, 24). But such drug-induced alteration of body temperature has been shown to be different when the experiments were carried out at different controlled ambient temperature at which the animals were exposed for a definite period (3, 11, 23, 26). But such short term studies at experimentally controlled ambient temperature are not akin to the exposure of the animals and consequent adaptation occuring during natural seasonal changes in ambient temperature. In order to throw some light on the participation of biogenic amines like NA and Ach in the interrelationship between different seasonal air temperatures (at which the animals were reared) and drug-induced alteration of body temperature in animals, the effect of centrally administered morphine was carried out in rats with the following advantages: that the site of action of morphine is mainly at the preoptic/anterior hypothalmic (PO/AH) region (13, 15, 16) which is the anatomical substrate for controlling system of heat production and heat loss mechanism, as well as this hypothalamic region is normally rich in biogenic amines (10). Secondly,

the principal action of morphine is hypothermia at low ambient temperature in rats (2
therefore the modification of this response following pharmacological manipulation
the metabolism of biogenic amines can be evaluated.

MATERIALS AND METHODS

The experiments were carried out on different groups of inbred male albino rats (C
strain, 150–250 g) reared up at ambient temperatures existing at different seasons of th
year. Drugs (morphine hydrochloride, U.P. Govt. Opium Factory; 6-hydroxydopamin
hydrobromide, Sigma Chemical Co., U.S.A.; phenoxybenzamine hydrochloride and hem
cholinium-3 bromide, obtained from the Department of Pharmacology, Institute of Medic
Sciences, Banaras Hindu University) were prepared in sterile 0.9% (W/V) normal saline, an
ascorbic acid (*1 mg/ml*) was added in the solution of 6-hydroxydopamine for preventi
oxidation of the compound. All the drugs were administered through intracerebro-ventri
cular route (i.c.v.). In addition, morphine was also injected through intraperitonea
route (i.p.) in some experiments.

Administration of drug through intraventricular route :

Under nembutal anaesthesia (35 *mg/kg* i.p.) the animal was placed in the rat stereo
taxic apparatus (INCO, Ambala) and a stainless steel guide cannula (21 gauge) having
shaft length of 4 mm was chronically implanted into the anterior horn of the right later
ventricle (9). Acrylic dental cement was used to secure the cannula with a cheese-hea
screw driven into the skull.

After 7 days of postoperative period, the drug solutions were infused into th
lumen of the lateral ventricle of the animal. For that, a 26 gauge stainless steel infusio
needle connected to a 50 µl Hamilton syringe by thin polythene tubing, was passed throug
the guide cannula so that its tip lied a little (0.5 mm) beyond the guide cannula. A
constant volume of 20 µl of all the drugs solutions were infused into the lateral cerebra
ventricle by a slow injector apparatus (INCO, Ambala), which delivered the solution a
the rate of 2 µl/min.

Measurement of rectal temperature :

The animal was kept in a rectangular perspex box (18 x 5 x 6 cm) having severa
round holes on its wall for free ventilation of air.

Rectal temperature was recorded from Aplab 6 channel Telethermometer through
a thermistor probe (Yellow Spring Co., U.S.A.). The probe was inserted 6 cm deep
inside the rectum and was held in place by wrapping adhesive leucoplast around the base
of the tail of the animal. Temperature was noted at every 5-10 min intervals.

Drug solutions were administered once the basal rectal temperature of rats were
stabilized, which generally occured within 30 min.

Post mortem examination :

Placement of cannula in lateral cerebral ventricle and distribution of drug solutions in the brain tissue were confirmed at the end of the experiment. Bromophenol blue dye (0.8%) in a volume of 20 μ/ was infused into the lateral cerebral ventricle of rat adopting exactly the similar method as for infusion of other drug solutions. The extent of blue staining on the wall of cerebral ventricles and brain tissue was ascertained by naked eye observation. The results obtained from those rats which failed to show such blue stainings of the cerebral ventricles have not been included in the present investigations.

RESULTS

Rectal temperature at different ambient temperature :

The results are shown in Table I. It appears that the basal rectal temperature of rats shifts to a new low level when the air temperature falls from the thermoneutral zone

TABLE I : Rectal temperature of rats at ambient temperatures existing at different seasons of the year. (Rectal temperature values are mean±SD. Range is given in parenthesis)

No. of obs.	*Seasonal air temp. range*	*Rectal temperature*
34	15.5° — 21.5°C	*35.98°±0.95°C (33.75°—37.8°C)
13	23.0° — 24.0°C	*36.75°±0.50°C (36.0°—37.5°C)
10	27.5° — 28.5°C	37.92°±0.43°C (37.25°—38.5°C)
42	29.0° — 32.5°C	37.96°±0.33°C (37.35°—38.65°C)

*P <0.001 as compared to rectal temperature at thermoneutral ambient temperature (27.5° – 28.5°C)

Thus, the mean rectal temperature in 10 rats was 37.92°C (37.25° to 38.5°C) at thermoneutral zone (27.5° to 28.5°C). But when they were maintained at an air temperature of 23° to 24°C. the mean temperature in 13 rats was stabilized at 36.75°C (36.0° to 37.5°C); and such decline in rectal temperature became more pronounced with the further fall in the air temperature (15.5° to 21.5°C)

On the other hand, at higher ambient temperature of 29.0° to 32.5°C, the mean rectal temperature (37.96°C) of 42 rats did not significantly differ as compared to that at thermoneutral zone.

Effect of morphine on rectal temperature :

(a) *Morphine administered through intra-cerebroventricular route (i.c.v.) :*

In a pilot study, the different doses of morphine in 20 μl volume were administe to observe their effect on rectal temperature. 200 μg of morphine was found to pro a consistent effect on rectal temperature, and therefore, this dose was used throug the investigation. The results are shown in Table II.

At an ambient temperature of 23° to 24°C, morphine produced a biphasic ef on rectal temperature. Thus there was an initial hypothermia varying between 0.4 1.1°C (mean 0.75°C) within 10 min, and the time period for attaining maximum hy thermia varied between 17 and 70 min (mean 39.25 min). This initial hypothermia w subsequently followed by hyperthermia. The rise in temperature varied between 2. and 3.5°C (mean 3.2°C) and the time period for maximum rise varied between 70 120 min (mean 87.5 min).

This hypothermic effect of morphine became further accentuated with more in the ambient temperature. Thus, at an ambient temperature between 17.5° to 21.5 morphine produced a maximum fall in rectal temperature varying between 1.3° and 2.8 (mean 2.07°C). The subsequent rise in rectal temperature in this group was found vary between 1.8° to 4.6°C (mean 2.54°C).

There were no significant difference observed regarding the latency of fall in rec temperature, the initial rate of fall in temperature, and the initial rate of rise in temperature.

On the other hand, the hypothermic response of morphine was absent at the moneutral ambient temperature or at warm ambient temperature; the only response w hyperthermia. The maximum rise in rectal temperature at thermoneutral zone (27.5° 28.5°C) was between 2.3° to 3.35°C (mean 2.74°C) and this rise was attenuated a small degree at warm ambient temperature (29.5° to 30.5°C) as shown in Table The initial rate of rise in rectal temperature was not different in these two groups. Th became apparent from time taken for 50% of maximum rise in rectal temperature.

The latency for rise in rectal temperature showed that the hyperthermic respons commenced immediately after morphine infusion in several rats, and in other cases showed a mean value of 9.6 min i.c.v. or i.p. administration of 0.9% sterile norm saline did not influence the normal rectal temperature.

(b) *Morphine administered through intraperitoneal route (i.p.) :*

The results are shown in Table II. It was observed that morphine administrat in rats exposed at low ambient temperature (18° to 21°C) produced a pronounced h

TABLE II : Effect of morphine on rectal temperature of rats at different seasonal air temperatures.
(Values are mean ± SD. Range is given in parenthesis)

No. of expts.	Seasonal air temp. range (°C)	Morphine dose & route	Rectal temperature: Latency of fall (min)	Maximum fall (°C)	Time period for maxm. fall (min)	Time period for 50% of maxm. fall (min)	Maximum rise (°C)	Time period for maxm. rise (min)	Time period for 50% of maxm. rise (min)
7	17.5 – 21.5	200 µg, icv	4±5.03 (0—10)	*2.07±0.67 (1.3—2.8)	59.3±42.9 (20—120)	20.9±16.3 (5—55)	2.54±1.03 (1.8—4.6)	82.9±32.5 (40—126)	34.3±23.9 (15—35)
4	23.0 – 24.0	200 µg, icv	2.5±5 (0—10)	0.75±0.31 (0.4—1.1)	39.25±22.2 (17—70)	21.5±13.4 (8—40)	3.2±0.31 (2.8—3.5)	87.5±22.1 (70—120)	41.75±11 (27—50)
4	18.0 – 21.0	40 mg/kg, ip	0	3.47±1.74 (1.0—5.0)	92.5±21.0 (70—120)	28.7±12.5 (15—45)	0.55±0.63 (0—1.1)	25±33.1 (0—70)	8.75±11.8 (0—25)
						Latency of rise (min)			
5	27.5 – 28.5	200 µg, icv				9.6±6.8 (0—16)	2.74±0.44 (2.3—3.35)	82±37.01 (40—130)	29±13.82 (16—50)
4	29.5 – 30.5	200 µg, icv				0	2.0±0.76 (1.0—2.6)	87.5±21.01 (65—110)	23±11.66 (7—35)
4	28.5 – 30.5	40 mg/kg, ip				0	1.77±0.97 (1.4—2.15)	75±44.3 (40—140)	25±8.16 (15—35)

*P $<$ 0·01 as compared to maximum fall in rectal temperature at 23.0° – 24.0°C ambient temperature.

in temperature varying between 1° to 5°C (mean 3.47°C) which reached within 70
120 min (mean 92.5 min).

The commencement of fall in rectal temperature following morphine was fou
to be almost immediate, and the initial slope of fall was similar to that observed with i.c.
morphine administration. But subsequent rise in rectal temperature was very much le
(0° to 1.1°C) as compared to that of i.c.v. administration of morphine

At warm ambient temperature of 28.5° to 38.5°C, morphine produced o
hyperthermia of about 1.4° to 2.15°C (mean 1.77°C), which reached within 40 to 1
min (mean 75 min).

Thus, the general pattern of response following either i.c.v. or i.p. injection
morphine at cold ambient temperature were found to be similar except that the hyperther
effect of morphine given i.p. at cold ambient temperature was very much less in comparis
to that of i.c.v. morphine.

It has been observed that salivation occured when the rise in rectal temperatu
reached to a certain magnitude following administration of morphine either through i.c.
or i.p. route.

Modification of hypothermic effect of morphine :

(i) *Pretreatment with 6-hydroxydopamine (6-OHDA) :*

The results are shown in Table III. In 5 rats remained exposed to low ambie
temperature of 17.5° to 22.0°C, 250 μg of 6-OHDA was administered through the cer
broventricular route once daily for 2 days. At the end of 5 days from the last injection
200 μg morphine (i.c.v.) was administered. The usual hypothermic response of morphin
was abolished in this 6-OHDA pretreated rats. But the hyperthermic effect was no
influenced in such pretreated animals.

(ii) *Pretreatment of rats with phenoxybenzamine (PBZ) :*

The results are shown in Table III. In 3 rats, 20 μg phenoxybenzamine wa
administered through i.c.v. route. In 2 rats, morphine 200 μg (i.c.v.) was administere
between 80 to 90 min, and in 1 rat after 40 min, following PBZ administration. Th
animals were maintained at low ambient temperature of 19.0° to 20.5°C. The hypotherm
and hyperthermic response of morphine in such PBZ-pretreated rats were not significant
altered as is apparent from Table III.

TABLE III : Hypothermic effect of morphine after treatment with 6-hydroxydopamine (6-OHDA), phenoxybenzamine (PBZ) and hemicholinium-3 (HC-3).
(Values are mean ± SD. Range is given in parenthesis)

No. of expts.	Seasonal air temp. range (°C)	Drugs, dose & route	Time interval between drug & morphine	Rectal temperature: Latency of fall (min)	Maximum fall (°C)	Time period for maxm. fall (min)	Time period for 50% of maxm. fall (min)	Maximum rise (°C)	Time period for maxm. rise (min)	Time period for 50% of maxm. rise (min)
5	17.5 – 21.5	6-OHDA, 250 µg, icv + Morphine 200 µg, icv	5 days	Nil	Nil	Nil	Nil	3.31±0.67 (2.2–4.0)	132±58 (45–190)	47.6±29.4 (15–90)
2	19.0 – 24.0	6-OHDA, 250 µg, icv + Morphine 40mg/kg, ip	5 days	Nil	Nil	Nil	Nil	2.95 (2.6–3.3)	170 (130–210)	120 (100–140)
3	19.0 – 20.5	PBZ, 20 µg, icv + Morphine 200 µg, icv	70 min (40–90 min)	3.33 (0–10)	1.45 (0.85–2.1)	24 (15–30)	7.33 (2–10)	2.07 (1.65–2.7)	121 (100–150)	47 (32–72)
2	23.0 – 24.0	HC-3, 80 µg, icv + Morphine 200 µg, icv	40 min	0	*6.0	125	35	Nil	Nil	Nil
		HC-3, 90 µg, icv + Morphine 200 µg, icv	45 min	0	*6.0	120	35	Nil	Nil	Nil

*HC-3 alone produced 3.0°C fall in rectal temperature prior to morphine administration.

(b) *Pretreatment with hemicholinium-3 (HC-3)* :

The experiments were carried out at ambient temperature range of 23.0° to 24.0°. The results are shown in Table III. In 2 rats, when HC-3, 80 μg and 90 μg respectively were given i.c.v. 40 to 45 min prior to the administration of 200 μg, i.c.v. morphine, the drug HC-3 itself produced fall of 3°C in rectal temperature of both rats, and following morphine infusion, there was further fall of 3°C in both rats. The tendancy of return of temperature to normal was not observed in any case even after 5 hours following morphine infusion.

In one rat HC-3, 90 μg (i.c.v.) was infused alone and a fall of 4.5°C rectal temperature occured. The temperature returned to normal after 4 hours of HC-3 infusion of this case.

DISCUSSION

The present investigation shows that at thermoneutral zone of seasonal ambient temperature (27.5° to 28.5°C) the basal rectal temperature of rat is generally around 37.5°C; but it undergoes considerable diminution (35.98°C) *pari passu* with low seasonal air temperature (15.5° -21.5°C). Generally, this variation of normal rectal temperature in relation to seasonal ambient temperature may not usually be revealed, when the rearing of the animals and the experiments are carried out at a controlled ambient temperature which is generally set around 22° to 25°C.

That the air temperature can become an important determinant in modifying the physiological functions or altering the pharmacological actions of a drug, has been apparent from the present investigations. Thus, the cerebroventricular (i.c.v.) infusion of 200 μg morphine in rats maintained at low ambient temperature between 17.5° to 21.5°C produces biphasic response (hypothermia followed by hyperthermia). But the same i.c.v. infusion of morphine produces only hyp rthermia when the rats were maintained at thermoneutral zone (27.5° to 28.5°C) or at high ambient temperature between 29.5° to 30.5°C. The similar changes on rectal temperature were also obtained with intraperitoneal (i.p.) administration of morphine at low and high air temperature. These results corroborated well with the earlier findings of Paolino and Bernard (23) following morphine injection into anterior hypothalamus of rat. This dependence of drug induced alteration in rectal temperature on the air temperature has also been reported by other workers (11,18,26). Thus, the peripheral thermal drive is an important determinant in influencing the body temperature responses to the drug.

It thus appears that the conflicting results often reported in literature on thermoregulatory responses to i.c.v., i.p. or intrahypothalamic injections of drugs may have been due to the experiments carried out at different ambient temperatures as already pointed

out by Bligh *et al.* (3), and not because of whether the rats were restrained or unrestrained as suggested by Avery (1).

It has been well established that the hypothermic action of morphine administered through central or systemic routes is mediated mainly from the PO/AH region of hypothalamus (13, 15, 16), and Lotti *et al.* (17) have shown that this morphine induced hypothermia in rats mainly results from reduction of metabolic heat production, and not through activation of heat loss mechanism.

That this hypothermic effect of morphine is very much dependent on the noradrenergic pathways has been apparent from the present investigation. The morphine induced hypothermia observed at low ambient temperature was abolished following i.c.v. infusion of 6-hydroxydopamine (6-OHDA), a drug which almost specifically causes degeneration of the axonal fibres and nerve terminals of catecholamine neurons (12) without damaging the postsynaptic neuronal noradrenergic receptors. In other words, it follows from this observation that morphine most probably brings its hypothermic action by acting on these noradrenergic nerve terminals and not on the noradrenergic receptors of post synaptic neurons. An idea about the type of NA receptor located in the catecholamine pathway was provided from the present observation that phenoxybenzamine (PBZ), an alpha-adrenergic receptor blocker, did not inhibit or annal morphine induced hypothermia significantly, which indicated that postsynaptic NA receptor located in the heat production pathways did not belong to alpha-adrenergic type. From these observations, it may be postulated that in rats, at cold ambient temperature, the signals from the cold thermosensitive sensors of the skin and those from hypothalamic sensors normally activate the catecholamine pathway in PO/AH region and the release of NA from these pathways stimulate the neurons operating the heat production control system in order to maintain the body temperature in cold environment. This possibility gains support from the observation of hyperthermia following injection of small amount of NA through i.c.v. route (9), into anterior hypothalamus (2) or counteraction of pilocarpine induced hypothermia with injection of NA at PO/AH region (13) in rats. In the light of the above facts, the fall in rectal temperature following morphine administration (i.c.v. or i.p.) at low ambient temperature, can be explained through the inhibition or prevention of release of NA from noradrenergic nerve terminals resulting in withdrawal of the "tonic drive" of these NA neurons from those responsible for heat production system. The evidence that morphine can inhibit the release of NA catecholamine nerve terminals was recently shown by Montel *et al.* (19). Bruinvels and Sourkes (4) and Bruinvels and Kemper (5) also showed that harmaline and tetrahydronaphthlylamine induced hypothermia in rats was prevented after combined inhibition of biosynthesis and depletion of NA.

On the other hand, the promotion of hypothermic effect of morphine at cold ambient temperature following pretreatment of rats with hemicholinium-3 (HC-3), an Ach synthesis blocking drug, supports the involvement of cholinergic neurons in the heat production pathways. This has been further strenthened from the observation that HC-3 itself produces a marked fall in rectal temperature of rats at low ambient temperature. The involvement of cholinergic neurons in the heat production system has also been implicated by other workers (20-22). Recently Yaksh and Yamamura (25) reported that morphine inhibits resting and evoked release of Ach from neurons.

All these observations taken together likely to indicate in rats that a noradrenergic-cholinergic link operates for control of heat production at PO/AH region of hypothalamus particularly at cold air temperature, and morphine probably produces hypothermia through impairment of this mechanism.

ACKNOWLEDGEMENTS

The authors are grateful to Prof. J. Nagchaudhuri for extending laboratory facilities in the department, and to University Grants Commission, New Delhi for partial financial assistance to this project.

REFERENCES

1. Avery, D.D. Thermoregulatory effect of intrahypothalamic injection of adrenergic and cholinergic substances at different environmental temperatures. *J. Physiol. (Lond.)*, **220** : 257-266, 1972.
2. Beckman, A.L. Effect of intrahypothalamic norepinephrine on thermoregulatory responses in the rat. *Amer. J. Physiol.*, **218** : 1596-1604, 1970.
3. Bligh, J., W.H. Cottle and M. Maskrey. Influence of ambient temperature on thermoregulatory responses to 5-hydroxytryptamine, noradrenaline and acetylcholine injected into the lateral cerebral ventricles of sheep, goats and rabbits. *J. Physiol. (Lond.)*, **212** : 377-392, 1971.
4. Bruinvels, J. and T.L. Sourkes. Influence of drugs on the temperature lowering effect of harmaline. *Eur. J. Pharmacol.*, **4** : 31-39, 1968.
5. Bruinvels, J. and G.C.M. Kemper. Role of noradrenaline and 5-hydroxytryptamine in tetrahydronaphthylamine-induced temperature changes in the rat. *Br. J. Pharmacol.*, **43** : 1-9, 1971.
6. Cooper, K.E., P. Lomax and E. Schonbaum. Eds. *Drugs, Biogenic Amines and Body Temperature*. Basel, S. Karger, 1977.
7. Cox, B. and P. Lomax. Pharmacologic control of temperature regulation. *Ann. Rev. Pharmacol.*, **17** : 341-353, 1977.
8. Feldberg, W. The Ferrier Lecture 1974, Body Temperature and fever; changes in our view during the last decade. *Proc. R. Soc. Lond. B.*, **191** : 199-229, 1975.
9. Feldberg, W. and V.J. Lotti. Temperature responses to monoamines and an inhibitor of MAO injected into the cerebral ventricles of rats. *Br. J. Pharmacol.*, **31** : 152-161, 1967.
10. Fuxe, F. Evidence for the existence of monoamine-containing neurons in the central nervous system. VI. The distribution of monoamine terminals in the central nervous system. *Acta Physiol. Scand.*, Suppl. 247, **64** : 37-85, 1965.
11. Haavik, C.O. and H.F. Hardman. The effect of tetrahydrocannabinols on body temperature. In *"The Pharmacology of Thermoregulation"*, eds. Schonbaum, E. and P. Lomax, Basel, S. Karger, p. 410-416 and 483, 1973.
12. Kostrzewa, R.M. and D.M. Jacobowitz. Pharmacological action of 6-hydroxydopamine. *Pharmacol. Rev.*, **26** : 199-288, 1974.

13. Lomax, P. Drug and body temperature. *Int. Rev. Neurobiol.*, **12** : 1-43, 1970.

14. Lomax, P., E. Schonbaum and J. Jacob. Eds. *Temperature Regulation and Drug Action.* Basel, S. Karger, 1975.

15. Lotti, V.J. Body temperature responses to morphine. In *"The Pharmacology of Thermoregulation"*, eds. Schonbaum, E. and P. Lomax. Basel, S. Karger, p. 382-384, 1973.

16. Lotti, V.J., P. Lomax and R. George. Temperature responses in the rat following intracerebral microinjection of morphine. *J. Pharmacol. Exp. Ther.*, **150** : 135-139, 1965.

17. Lotti, V.J., P. Lomax and R. George. Heat production and heat loss in the rat following intracerebral and systemic administration of morphine. *Int. J. Neuropharmacol.*, **5** : 75-83, 1966.

18. Milton, A.S. Thermoregulatory effects of prostaglandin E_1 (PGE_1). In *"The Pharmacology of Thermoregulation"*, eds. Schonbaum, E. and P. Lomax. Basel, S. Karger, p. 498-499, 1973.

19. Montel, H., K. Starke and H.D. Taube. Influence of morphine and naloxone on the release of noradrenaline from rat cerebellar cortex slices. *Naunyn–Schmiedebergs Arch. Pharmacol.*, **288** : 427-433, 1975.

20. Myers, R.D. Temperature regulation. In *"Handbook of Drug and Chemical Stimulation of the Brain"* by R.D. Myers. New York, Van Nostrand Reinhold Co., p. 237-301, 1974.

21. Myers, R.D. Neurochemical mechanisms of two hypothalamic temperature control systems. In *"Benchmark Papers in Human Physiology"*, ed. T.H. Benzinger. Stroudsburg, Dowden, Hutchinson and Rose Inc., p. 377-391, 1977.

22. Myers, R.D. and T.L. Yaksh. Control of body temperature in the unanaesthetized monkey by cholinergic and aminergic systems in the hypothalamus. *J. Physiol (Lond.)*, **202** : 483-500, 1969.

23. Paolino, R.M. and B.K. Bernard. Environmental temperature effects on the thermoregulatory response to systemic and hypothalamic administration of morphine. *Life Sci.*, **7** : 857-863, 1968.

24. Schonbaum, E. and P. Lomax. Eds. *The Pharmacology of Thermoregulation.* Basel, S. Karger, 1973.

25. Yaksh, T.L. and E.J. Yamamura. Depression by morphine of the resting and evoked release of (^{3}H) acetylcholine from the cat caudate nucleus *in vivo*. *Neuropharmacol.*, **16** : 227-233, 1977.

26. Yehuda, S. and R.J. Wurtman. Hypothermic effects of d-amphetamine at low ambient temperature: possible mediation by dopaminergic neurons. In *"The Pharmacology of Thermoregulation"*, eds. Schombaum, E. and P. Lomax, Basel, S. Karger, p. 500-501, 1973.