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Hypothermic effect of GABA in conscious stressed rats: its modification by cholinergic agonists and antagonists

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γ-Aminobutyric acid (GABA) intraperitoneally injected (i.p.) produced a dose-dependent hypothermia in restrained rats. GABA-induced hypothermia (1000 mg kg^{-1}) was antagonized by pretreatment with atropine (2·5 and 10 mg kg^{-1} i.p.), hyoscine butylbromide (2·5 mg kg^{-1} i.p.), hexamethonium (0·75 mg kg^{-1} i.p.) or physostigmine (0·2 mg kg^{-1} s.c.). Hexamethonium (7·5 mg kg^{-1} i.p.) did not influence the hypothermia induced by GABA. The antagonism by physostigmine of GABA-induced hypothermia was attenuated by pretreatment of the rats with either α-methyl-*p*-tyrosine (200 mg kg^{-1} i.p.) or hexamethonium (7·5 mg kg^{-1} i.p.), but it was potentiated by either atropine (5 mg kg^{-1} i.p.) or hexamethonium (0·75 mg kg^{-1} i.p.). The data indicate that GABA-induced hypothermia may be partly mediated by acetylcholine release. Muscarinic receptors may play an important role in the effect of GABA. The results support the hypothesis of nicotinic presynaptic receptors modulating noradrenergic nerve endings that play a part in the hypothermic response of GABA.

Considerable evidence now exists for the involvement of central cholinergic mechanisms in thermoregulation. In the rat, cholinomimetic substances cause a fall in body temperature following their injection into the rostral hypothalamus (Lomax et al 1969). Atropine, injected systemically (Kirkpatrick & Lomax 1970) or directly into the hypothalamus of the rat (Beckman & Carlisle 1969), reduced or abolished the hypothermic response to a subsequent hypothalamic injection of acetylcholine. In contrast to this is the finding that the intraventricular injection of acetylcholine or physostigmine produces a rise in temperature of rats (Myers & Yaksh 1968).

Biochemical studies have indicated the presence of both γ-aminobutyric acid (GABA) and glutamate decarboxylase, the enzyme responsible for the synthesis of GABA, in high amounts in the hypothalamus (Brownstein et al 1976). GABA and GABA-agonists have been reported to alter the concentration or rate of turnover of several neurotransmitters in rats including catecholamines (Andén & Wachtel 1977), 5-hydroxytryptamine (5-HT) (Waldmeier & Fehr 1978) and acetylcholine (Nakahiro et al 1985).

Different types of stress of various durations induce significant alterations in hypothalamic GABA synthesis (Manév & Pericic 1983) and central GABA-receptors of several brain regions of rats (Johnston et al 1982), suggesting the involvement of brain GABA in stress reactions.

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It has been demonstrated that in conscious rats, intraventricular and intracisternal (Sgaragli & Pavan 1972; Dhumal et al 1976) or intraperitoneal (Serrano et al 1985, 1986) injection of high doses of GABA produced hypothermia. GABA may act centrally to induce hypothermia in rats through a 5-HT-acetylcholine pathway (Serrano et al 1986), however the complete mechanisms implied remain to be clarified.

The purpose of the present investigation was to study the role of acetylcholine in GABA-induced hypothermia in restrained rats, at an ambient temperature of 22 ± 1 °C.

MATERIALS AND METHODS

General

The general methods have been previously described (Serrano et al 1985). Unanaesthetized female Wistar rats, 220–250 g at the start of the experiments, were housed in groups of three to five per cage in a room at 22 ± 1 °C with natural light-dark cycles. The animals were given free access to food and water for at least 1–2 weeks before experiments and were then starved for 48 h but had free access to water. All experiments began at 1000h to avoid changes due to circadian rhythms. The animals were immobilized on boards allowing 1 h before drug administration until a stable base-line temperature was reached.

Temperature measurement and statistical analysis

Core temperature (CT) was measured by inserting a precalibrated thermistor probe (Ellab Instruments,

model A-RM 6), 6 cm into the rectum and taping it securely to the base of the tail. The probes were plugged into a 10 channel input box (Ellab A-SE 10) which was connected to a thermometer (Ellab TE 3S).

The average of CT readings at 0, 30 and 60 min before the initial injection was used as the base-line from which changes were measured. After drug or saline administration, deviations of CT from base-line were tabulated at 30 min intervals for 3 h. Temperature responses were assessed as a thermal response index (TRI), calculated so that 1 unit is equivalent to a 1 °C change over a 1 h period (Clark & Cumby 1975). This index is an estimate of the CT change after an injection in relation to the base-line temperature. TRIs after saline or drug injection were determined for the same period of time as for the corresponding GABA test.

All results are expressed as the mean ± s.e.m. Statistical analyses of the TRI were performed between the treatment groups using the Student's *t*-test for unpaired data and the level of significance was set at $P < 0.05$.

The interaction of drug with the effect of GABA (or GABA + physostigmine) on CT might be expressed as percent of antagonism or agonism, calculated according to a general equation where positive or negative values are indicative of antagonism or agonism, respectively,

$$\frac{\text{A} - \text{combination}}{\text{A} - \text{control drug}} \times 100 = \text{Percent antagonism or agonism}$$

A represents GABA (or GABA + physostigmine).

Drugs used

All drugs were injected i.p., except physostigmine which was injected s.c. To look for antagonism, the potential antagonistic agent was injected 30 min before GABA (1000 mg kg^{-1}), except hexamethonium which was injected 5 min before, α-methyl-*p*-tyrosine 19 h before, and *p*-chlorophenylalanine 48 before GABA, respectively. The following drugs were used: γ-aminobutyric acid (GABA), hyoscine butylbromide, hexamethonium bromide, physostigmine salicylate, DL-*p*-chlorophenylalanine (PCPA), DL-α-methyl-*p*-tyrosine methyl ester (α-MPT) (Sigma Chemical Co), atropine sulphate (Miró). All drugs, except PCPA, were dissolved in sterile 0·9% NaCl solution and were administered in a volume of 2 mL kg^{-1}. PCPA was administered as a fine suspension in 1% carboxymethylcellulose. All drugs were prepared immediately before use.

RESULTS

Base-line temperature before drug administration exhibited minor variations, its mean value for all groups was 37·4 ± 0·05 °C (36·7–37·8) (Tables 1–5).

The CT of rats injected with saline showed a small increase within the first 90 min, which was followed by a slow mean decrease over 3 h of restraint.

Effects of GABA on the CT of rats

GABA injected i.p. produced a dose-dependent decrease in CT (Table 1). At the dose of 1000 mg kg^{-1} GABA consistently produced a nearly maximal hypothermic response (Table 1). Since this response is also near the lower limit of thermosensitivity in rodents (Kluger 1979), the dose of GABA 1000 mg kg^{-1} was chosen as the test dose for subsequent experiments.

Table 1. Effect of GABA on core temperature in restrained rats.

Drug	Dose (mg kg^{-1})	Base-line temp. (°C)[a]	TRI_3 (°C h)[a]
Control (saline)	2 mL kg^{-1}	37·3 ± 0·2	−0·73 ± 0·48
GABA	250	36·9 ± 0·1	−1·49 ± 0·45
GABA	500	37·0 ± 0·2	−2·06 ± 0·17*
GABA	1000	36·8 ± 0·1	−4·10 ± 0·45***
GABA	2000	36·7 ± 0·1	−5·44 ± 0·60***

Base-line temperature was calculated from the average of CT at 0, 30 and 60 min before saline or GABA injection (i.p.).

[a] Mean ± s.e.m. Each experimental group consisted of 10 rats. TRI_3 = thermal response index during 3 h after drug administration (see text).

* $P < 0.05$, *** $P < 0.001$. Significantly different from the control.

Although an objective evaluation of locomotor activity was not attempted in this work, it was observed that spontaneous locomotor activity decreased in all rats injected with GABA (1000 mg kg^{-1}) and these animals could be easily distinguished from controls in the same cage. At 3 h, normal locomotor activity was recovered. The animals did not appear drowsy; their eyelids were open. They showed tachypnoea and cutaneous vasodilation. The righting reflex was normal. They reacted to external stimuli (clapping of the hands). Only a slight decrease of spontaneous locomotor activity was observed with 250 and 500 mg kg^{-1} of GABA.

Effects of muscarinic cholinoceptor antagonists on GABA-induced hypothermia

Pretreatment with either hyoscine butylbromide (2·5 mg kg^{-1}) or atropine (2·5 or 10 mg kg^{-1}), significantly inhibited the hypothermia induced by

1000 mg kg^{-1} of GABA (Table 2). The percentage of antagonism was found to be atropine 10 > atropine 2·5 > hyoscine butylbromide (Table 2).

Intraperitoneal injection of atropine caused a slight non-significant decrease in CT over the 3 h of the experimental period, when compared with the saline control group during the time that the effects of GABA were being assessed. Hyoscine butylbromide produced an insignificant change in CT (Table 2).

Table 2. Effect of muscarinic cholinoceptor antagonists on the hypothermia induced by i.p. injection of GABA (1000 mg kg^{-1}) in rats.

Drug	Dose (mg kg^{-1})	Base-line temp. (°C)[a]	TRI_3 (°C h)[a]	% Inhibition
Control	2 mL kg^{-1}	37·8 ± 0·2	−0·80 ± 0·33	
GABA	1000	37·7 ± 0·2	−3·98 ± 0·45†††	
Saline + atropine	2·5	37·5 ± 0·2	−1·36 ± 0·36	
GABA + atropine	2·5	37·6 ± 0·2	−2·04 ± 0·27***	74
Saline + atropine	10	37·5 ± 0·1	−1·20 ± 0·17	
GABA + atropine	10	37·6 ± 0·1	−0·35 ± 0·27***	131
Saline + hyoscine bu Br	2·5	37·5 ± 0·2	−0·60 ± 0·12	
GABA + hyoscine bu Br	2·5	37·8 ± 0·2	−1·57 ± 0·20***	71

See explanations to Table 1. Each experimental group consisted of 7 rats. Drugs were given i.p. 30 min before GABA.
††† $P < 0·001$ vs control
*** $P < 0·001$ vs GABA

Effects of hexamethonium on GABA-induced hypothermia

Pretreatment with hexamethonium (0·75 or 7·5 mg kg^{-1}) produced a dose-dependent antagonism, since an intermediate effect has been found with doses between 0·75 and 7·5 mg kg^{-1} in preliminary experiments, the effect appears to be dose-dependent. Hexamethonium at 0·75 and 7·5 mg kg^{-1} produced 131 and 20% antagonism, respectively. At 0·75 mg kg^{-1} it antagonized the hypothermia induced by GABA, whereas the 7·5 mg kg^{-1} dose did not effectively inhibit GABA-induced hypothermia (Table 3).

Table 3. Effect of hexamethonium on the hypothermia induced by i.p. injection of GABA (1000 mg kg^{-1}) in rats.

Drug	Dose (mg kg^{-1})	Base-line temp. (°C)[a]	TRI_3 (°C h)[a]	% Inhibition
Control	2 mL kg^{-1}	37·1 ± 0·2	−1·03 ± 0·39	
GABA	1000	37·2 ± 0·3	−4·18 ± 0·2†††	
Saline + HEX	0·75	37·5 ± 0·2	−1·67 ± 0·50	
GABA + HEX	0·75	37·4 ± 0·1	−1·49 ± 0·24***	131
Saline + HEX	7·5	37·6 ± 0·2	−0·35 ± 0·15	
GABA + HEX	7·5	37·1 ± 0·1	−3·41 ± 0·46	20

See explanations to Table 1. Each experimental group consisted of 7 rats. HEX, hexamethonium was injected i.p. 5 min before GABA.
‡‡‡ $P < 0·001$ vs saline-control.
*** $P < 0·001$ vs GABA.

At the doses used and over a period of 3 h hexamethonium did not significantly affect CT (Table 3).

Effects of physostigmine on GABA-induced hypothermia

A dose of 0·2 mg kg^{-1} physostigmine produced an increase in CT which was statistically significant ($P <$ 0·001) when compared with the effect of saline alone (Tables 4, 5). Pretreatment with physostigmine produced an inhibition of the hypothermia induced by GABA (48–55% antagonism) (Tables 4, 5, Fig. 1).

Effects of cholinergic antagonist pretreatment on physostigmine-antagonized, GABA-induced hypothermia

After i.p. pretreatment with either atropine (5 mg kg^{-1}) or hexamethonium (0·75 mg kg^{-1}), the

Table 4. Effect of cholinergic antagonists pretreatment on physostigmine antagonized GABA-induced hypothermia (1000 mg kg^{-1}).

Drug	Dose (mg kg^{-1})	Base-line temp. (°C)[a]	TRI_3 (°C h)[a]	% Inhibition
Control	2 mL kg^{-1}	37·5 ± 0·2	−0·93 ± 0·46	
GABA	1000	37·5 ± 0·1	−4·19 ± 0·49†††	
Saline + PHYS	0·2	37·7 ± 0·2	+1·25 ± 0·10†††	
GABA + PHYS	0·2	37·8 ± 0·2	−1·20 ± 0·43***	55
GABA + PHYS + atropine	0·2 5	37·4 ± 0·1	−0·28 ± 0·30***	−31[b]
GABA + PHYS + HEX	0·2 0·75	37·7 ± 0·2	+0·11 ± 0·27***	−44[b]
GABA + PHYS + HEX	0·2 7·5	37·8 ± 0·2	−4·07 ± 0·45	96[b]

See explanations to Table 1. Each experimental group consisted of 7 rats. PHYS, physostigmine, was injected s.c. 30 min before GABA. HEX, hexamethonium, was injected i.p. 5 min before GABA.
††† $P < 0·001$ vs control.
*** $P < 0·001$ vs GABA.
[b] % inhibition vs GABA + PHYS.

Table 5. Effect of amine-depleting drugs on physostigmine antagonized GABA-induced hypothermia (1000 mg kg^{-1}).

Dose	Dose (mg kg^{-1})	Base-line temp. (°C)[a]	TRI_3 (°C h)[a]	% Inhibition
Control	2 mL kg^{-1}	37·7 ± 0·2	−0·85 ± 0·44	
GABA	1000	37·4 ± 0·2	−4·41 ± 0·57†††	
Saline + PHYS	0·2	37·7 ± 0·2	+1·21 ± 0·15†††	
GABA + PHYS	0·2	37·5 ± 0·3	−1·73 ± 0·48**	48
Saline + MPT	200	37·6 ± 0·2	−1·42 ± 0·61	
GABA + MPT + PHYS	200	37·4 ± 0·1	−3·91 ± 0·33	81[b]
Saline + PCPA	300	37·3 ± 0·2	−1·70 ± 0·42	
GABA + PCPA + PHYS	300	37·5 ± 0·2	−0·94 ± 0·66***	−29[b]

See explanations to Table 1. Each group consisted of 7 rats. PHYS, physostigmine, was injected s.c. 30 min before GABA; α-methyl-*p*-tyrosine, α-MPT, was administered i.p. 19 h before GABA, and *p*-chlorophenylalanine, PCPA, 48 h before GABA.
††† $P < 0·001$ vs control.
** $P < 0·01$.
*** $P < 0·001$ vs GABA.
[b] % inhibition vs GABA + PHYS

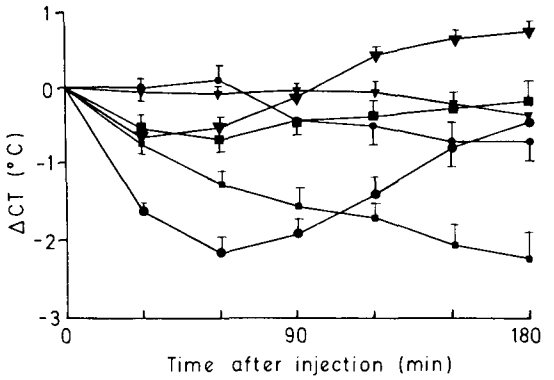

FIG. 1. Effects of cholinergic antagonists upon physostigmine-antagonized GABA-induced hypothermia (1000 mg kg^{-1} i.p.) in restrained rats kept at the ambient temperature of 22 ± 1 °C. Pretreatment with physostigmine 0·2 mg kg^{-1} s.c. (■) was made 30 min before GABA injection. Atropine, 5 mg kg^{-1} i.p. (▼) was injected 30 min before GABA, and hexamethonium, at 0·75 (▼) and 7·5 mg kg^{-1} i.p. (●) was administered 25 min after physostigmine and 5 min before the injection of GABA. Saline, 2 mL kg^{-1} (•); GABA, 1000 mg kg^{-1} (■). Each point represents the mean ± s.e.m. of seven observations. Refer to Table 4 for statistical analysis of thermal response indices.

effect of physostigmine on GABA-induced hypothermia was markedly increased (−31 and −44%, respectively) (Table 4, Fig. 1).

After pretreatment with hexamethonium (7·5 mg kg^{-1}), the effect of physostigmine on GABA-induced hypothermia was markedly reduced (96% antagonism) (Table 4, Fig. 1).

Effects of amine-depleting drugs pretreatment on physostigmine-antagonized, GABA-induced hypothermia

PCPA (300 mg kg^{-1}) did not antagonize the effect of physostigmine but seemed to potentiate it (−29%). However, after α-MPT pretreatment (200 mg kg^{-1}) it was markedly reduced (81% antagonism) (Table 5).

None of these drugs caused a significant change in CT on their own over a 3 h period, when compared with saline-treated animals (Table 5).

DISCUSSION

The present data confirm and extend previous findings that GABA induced hypothermia in rats (Sgaragli & Pavan 1972; Dhumal et al 1976), which is not antagonized by bicuculline or picrotoxin (Serrano et al 1985, 1986). The present studies suggest that this hypothermic effect is mediated, at least in part, by cholinergic mechanisms.

Like several other workers (Thornhill et al 1979; Cox & Lee 1981), we have found that the use of restrained rats showed a slight increase in CT within the first 90 min of the experiment which was probably due to the effort involved in attempts to escape. This transient hyperthermia was followed by a slight fall in CT as the animals calmed down.

It has been demonstrated that systemically administered GABA-agonists increase ACh hypothalamic concentration in the rat (Scatton & Bartholini 1982), and facilitate ACh release in peripheral organs (Giotti et al 1983). Only high doses of GABA i.p. can cross the intact blood-brain barrier and increase brain GABA levels in rats (Löscher & Frey 1982). In addition, at high doses (1000 mg kg^{-1} i.p.), GABA produced behavioural changes as well as anticonvulsant action (Biswas & Carlsson 1978; Löscher & Frey 1982). Since only a small proportion of systemically administered GABA penetrates through the normal blood-brain barrier, a high dose of GABA has been evaluated. This dose of GABA can gain access to the brain via the area postrema or the hypothalmus which have a less restrictive blood-brain barrier.

It must be considered that body temperature is a state illustrating the interdependence between an integrative control centre in the hypothalamus and peripheral components for maintaining thermic equilibrium. The hypothermia induced by GABA could be secondary to other effects that this compound exerts on such functions as respiration, blood circulation and motor co-ordination. An impairment of oxygen supply to the brain could be involved in the effect of thermoregulation produced by GABA, since brain hypoxia is accompanied by hypothermia (Wood et al 1968; Priano et al 1969). In fact, i.c.v. administration of GABA induced hypothermia, arterial hypotension and motor incoordination (Sgaragli & Pavan 1972). However, the hypothermia produced by GABA i.c.v. appears to be dependent on the direct action of GABA on nervous centres, since no consistent biochemical evidence of brain hypoxia has been found after GABA administration (Sgaragli & Pavan 1972).

The involvement of acetylcholine (ACh) in the GABA-induced hypothermia is suggested by the fact that the usual prominent hypothermic response of restrained rats to GABA was inhibited by the pretreatment with both atropine and hyoscine butylbromide. Since hyoscine butylbromide does not penetrate the blood-brain barrier (Visscher et al 1954), the data confirm previous findings and suggest that peripheral muscarinic cholinoceptors may con-

tribute to GABA hypothermia (Serrano et al 1986).

To find whether GABA-induced hypothermia was a central or peripheral effect involving nicotinic receptors, physostigmine and hexamethonium were tested. Hexamethonium blocked GABA-induced hypothermia in the rat but, at high doses the antagonistic effect was less than that reported at low doses. This result suggests a negative correlation between GABA-induced hypothermia and central nicotinic receptors.

Although hexamethonium is not believed to pass readily into the brain, Asghar & Roth (1971) found it in "pharmacologically significant amounts" after i.v. administration. Thus, in spite of blood-brain and blood-cerebrospinal fluid barriers, it seemed possible that hexamethonium might reach the central nervous system, but be so rapidly removed that only a minimal concentration remained. The possibility remains that its nicotinic action is entirely central inasmuch as a portion of hexamethonium could be entering the brain.

Physostigmine, an anticholinesterase agent that readily penetrates the blood-brain barrier (Van Meter & Karczmar 1971) and increases total brain ACh content (Rosecrans et al 1968; Bartolini et al 1973), antagonized GABA-induced hypothermia. This antagonistic action was further characterized by using a variety of other antagonists.

Nicotine injected into the hypothalamus of rats (Knox & Lomax 1972) evokes a dose-dependent hyperthermia, fitting well with the results obtained in the present study and suggesting a central site of action for the hyperthermic effect of physostigmine that could, in part, account for its effect on GABA-induced hypothermia.

The present experiments suggest that a specific neurochemical mechanism may underlie the physostigmine-induced attenuation of GABA-hypothermia. This mechanism seems to be related to central noradrenaline concentration, as indicated by the pharmacological analysis. Thus, pretreatment with α-MPT, an inhibitor of noradrenaline synthesis, which affects central noradrenaline and dopamine (Metcalf & Thompson 1975), prevented the blockade by physostigmine of GABA-hypothermia, while PCPA, which depletes brain 5-HT (Koe & Weissman 1966), did not inhibit this effect. In addition, pretreatment with atropine did not prevent the antagonistic effect on GABA-hypothermia. In a similar context, Varagić & Kristić (1966) suggested that the pressor response to physostigmine in rats is a central cholinergic phenomenon mediated by hypothalamic adrenergic mechanisms. Furthermore, the phenomenon of anticholinesterase block of recruitment seems to be related to central noradrenaline concentrations and may be explained by an interaction between the cholinergic and adrenergic systems (Van Meter & Karczmar 1971).

Thus, physostigmine may antagonize GABA-induced hypothermia in restrained rats by adrenergic mechanisms. Neither 5-HT nor muscarinic cholinoceptors appear to be involved.

If physostigmine's inhibition of GABA-induced hypothermia was mediated by an action of ACh at prejunctional ganglionic-type nicotinic cholinoceptors, it would be expected that hexamethonium, a selective antagonist of ACh in autonomic ganglia, would selectively antagonize the effect. However, we found that only high doses of hexamethonium prevented the effect of physostigmine on GABA-hypothermia. The biphasic effect seen in the interaction of hexamethonium, 0·75 mg kg^{-1}, with GABA + physostigmine (Fig. 1) may reflect the potentiation of central cholinergic hyperthermia by physostigmine when hexamethonium is not centrally acting. When hexamethonium 0·75 mg kg^{-1} is given before GABA + neostigmine, a quaternary cholinesterase inhibitor, the biphasic effect is not seen (Serrano et al 1986). These facts suggest that a central cholinergic mechanism, through nicotinic cholinoceptors, contributes to the antagonistic effect of physostigmine on GABA-hypothermia.

Noradrenaline release through activation of central nicotinic presynaptic receptors by physostigmine might inhibit GABA-induced hypothermia. The blockade by physostigmine of GABA-hypothermia seems to be an example of the interrelation of cholinergic and aminergic processes. A functional interplay between cholinergic and aminergic synapses controlling body temperature has been previously demonstrated (Milanés et al 1983).

In conclusion, the present results demonstrate that GABA-induced hypothermia in restrained rats is mediated, at least in part, by an action on the cholinergic system. Since both central and peripheral muscarinic cholinoceptor blockade, and ganglion blockade, antagonized GABA-hypothermia, while central nicotinic activation had the opposite effect, the GABA-mediated increase in cholinergic activity (muscarinic rêceptors) could well be causally related to the hypothermia induced by GABA.

The results support in part the hypothesis of a central nicotinic modulation of the decrease in CT by GABA, mediated through nicotinic presynaptic facilitatory receptors in noradrenergic nerve endings (Serrano et al 1986).

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