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European Journal of Pharmacology 346 (1998) 35–41

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Cardiovascular effects of centrally injected tetrahydroaminoacridine in conscious normotensive rats

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Received 18 November 1997; revised 31 December 1997; accepted 1 January 1998

Abstract

In freely moving rats, intracerebroventricular (i.c.v.) injected tetrahydroaminoacridine (10, 25, 50 μg) increased blood pressure and decreased heart rate in a dose- and time-dependent manner. Intravenous (i.v.) tetrahydroaminoacridine (1 and 3 mg/kg) also increased blood pressure. Atropine sulphate (10 μg; i.c.v.) pretreatment greatly attenuated the blood pressure response to i.c.v. tetrahydroaminoacridine while mecamylamine (50 μg; i.c.v.) failed to change the pressor effect. Neither atropine sulphate nor mecamylamine pretreatment affected the bradycardia induced by tetrahydroaminoacridine. However, the bradycardic response was completely blocked by atropine methylnitrate (2 mg/kg; i.p.) pretreatment. The pressor response to i.c.v. tetrahydroaminoacridine was associated with a several-fold increase in plasma levels of vasopressin, adrenaline and noradrenaline, but not of plasma renin. Pretreatment with prazosin (0.5 mg/kg; i.v.) attenuated the pressor effect without changing the bradycardia. Vasopressin V_1 receptor antagonist [β-mercapto-β,β-cyclopentamethylenepropionyl[1],*O*-Me-Tyr[2]-Arg[8]]vasopressin (10 μg/ kg; i.v.) pretreatment also partially inhibited the pressor response to i.c.v. tetrahydroaminoacridine and abolished the bradycardia. Tetrahydroaminoacridine's cardiovascular effects were completely blocked when rats were pretreated with prazosin plus vasopressin antagonist. The data show that tetrahydroaminoacridine increases blood pressure in normotensive freely moving rats by activating central muscarinic cholinergic transmission. Increases in plasma catecholamines and vasopressin are both involved in this response. The tetrahydroaminoacridine-induced reduction in heart rate appears to be due to the increase in vagal tone and plasma vasopressin. © 1998 Elsevier Science B.V.

Keywords: Tetrahydroaminoacridine; Blood pressure; Muscarinic receptor; Vasopressin; Adrenaline; Noradrenaline

1. Introduction

Tetrahydroaminoacridine is a potent, centrally active acetylcholinesterase inhibitor. It also has some central cholinomimetic properties (Sunaga et al., 1993; Szilagyi and Lau, 1993; Xiao et al., 1993). More importantly, tetrahydroaminoacridine has an ability to improve memory and cognitive functions in patients with Alzheimer's disease and has been used for the treatment of this disease. It has recently been marketed in the USA and several European countries for this purpose.

It has been clearly demonstrated that central cholinergic transmission has an important role in the regulation of blood pressure (Brezenoff and Guiliano, 1982; Kristic, 1982; Brezenoff, 1984; Philippu, 1981, 1988). Centrally injected directly acting agonists, e.g., acetylcholine itself, carbachol, oxotremorine, or indirectly acting cholinergic agents, including the acetylcholine precursor, choline, and the acetylcholinesterase inhibitors, physostigmine and neostigmine, increase blood pressure in conscious and anaesthetised animals of a number of species (see for review the works of Brezenoff and Guiliano (1982) and Arslan et al. (1991)). Although the mechanisms responsible for the pressor response to central cholinergic stimulation are controversial, it has been suggested that, in conscious rats, it is mediated both by an increased impulse flow to the sympathoadrenal system (Brezenoff, 1984; Willete et al., 1984; Arslan et al., 1991; Ulus et al., 1995; Savci and Ulus, 1996) and by increased circulating vasopressin levels (Hoffman and Phillips, 1976; Iitake et al., 1986; Imai et al., 1989; Arslan et al., 1991; Ulus et al., 1995; Savci and Ulus, 1996). The hypertensive response to indirectly acting cholinergic agents requires brain acetylcholine and functional cholinesterase (Brezenoff and Guiliano, 1982). Unlike those of other cholinesterase inhibitors such as physostigmine or neostigmine, the cardiovascular effects of tetrahydroaminoacridine have not been investi-

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gated very well. There is, however, one experimental study reporting the pressor effect of peripherally administered tetrahydroaminoacridine on the cardiovascular system in anaesthetised animals (Kayaalp, 1965). But no data are available for conscious, freely moving animals.

Considering the importance of tetrahydroaminoacridine in the treatment of Alzheimer's disease and the lack of data about its cardiovascular effects, there is a need for more comprehensive experimental studies characterising the effects of tetrahydroaminoacridine on cardiovascular regulation in conscious normotensive rats.

The aims of the present study were (1) to investigate the cardiovascular changes induced by the intracerebroventricular (i.c.v.) injection of tetrahydroaminoacridine in normotensive conscious rats, (2) to determine the type of the central acetylcholine receptors (muscarinic or nicotinic) involved in these responses and (3) to characterise the peripheral mechanisms responsible for the cardiovascular responses to i.c.v. tetrahydroaminoacridine.

2. Materials and methods

2.1. Animals

Male Wistar rats (Experimental Animals Breeding and Research Center, Uludag University Medical Faculty, Bursa, Turkey) weighing 300–350 g were used throughout the experiments. Four to six rats were housed in hanging cages, given ad libitum access to water and food, and were maintained on a regular 12-h light–dark cycle. The surgical and experimental protocols were approved by the Animal Care and Use Committee of Uludag University.

2.2. Surgical procedures

Under light ether anaesthesia, the left jugular vein and left carotid artery of rats were cannulated with PE 50 tubing filled with heparinised saline (250 U/ml). During the arterial cannulation procedure, the vagus nerve and the cervical sympathetic trunk were separated very carefully. The catheters were exteriorised at the nape of the neck and sealed until use. For i.c.v. injection of drugs, a burr hole was drilled through the skull 1.5 mm lateral to the midline and 1.0 mm posterior to bregma, and a 10-mm length of 21-gauge stainless steel hypodermic tubing was directed through the hole toward the lateral ventricle. The cannula was lowered 4.2–4.5 mm below the surface of the skull and was fixed to the skull with acrylic cement.

At the end of the surgical procedures, rats were placed in individual plastic cages and allowed to recover from anaesthesia for 3–4 h. During this period rats were left undisturbed and did not show any evidence of pain.

2.3. Blood pressure recording

After the recovery period the arterial catheter was attached to a volumetric pressure transducer (Statham P23) and blood pressure was recorded on a polygraph recorder (Grass model 7D, Boston, MA, USA). The heart rate was counted from the phasic pressure tracing recorded on the polygraph. The blood pressure is reported as mean arterial pressure and heart rate is expressed as beats/min. Before testing any of the i.c.v. injected drugs, a control baseline recording was obtained for 15–20 min.

2.4. Intracerebroventricular injection of drugs

For i.c.v. injection, the injection cannula (25-gauge, 11.5-mm stainless steel tubing) was inserted through the guide cannula. The injection cannula was connected by polyethylene tubing, which was filled with saline or saline containing the desired dose of the drug of interest, to a 10 to 50-μl microsyringe. Drugs were then infused slowly within 10 s. In one set of experiments, rats received two i.c.v. injections at a 15-min interval.

2.5. Determination of plasma renin, vasopressin and catecholamines

In order to determine plasma renin activity, plasma vasopressin, plasma adrenaline and noradrenaline levels, 2-ml blood samples were removed from the arterial catheter and the volume was replaced with same amount of saline. Samples were placed on ice immediately. After centrifugation at $+4$°C, 1800 rpm, for 20 min, plasma was separated. Plasma renin activity was assayed by measurement of angiotensin I production at 37°C for 60 min. Angiotensin I was measured by radioimmunoassay, using a commercially available kit (Clinical Assay, Cambridge, MA, USA). Plasma renin levels were measured on the same day that the blood samples were obtained. Plasma renin activity is expressed as nanogram of angiotensin I produced by renin per milliliter of plasma during 60 min of incubation.

Plasma noradrenaline and adrenaline were determined by radioenzymatic assay, using a commercially available kit (CAT-A-KIT, Amersham, Buckinghamshire, England). Briefly, an aliquot (50 μl) of fresh plasma was incubated with catechol-*O*-methyltransferase and tritiated *S*-adenosyl methionine. The reaction was stopped by the addition of borate buffer (pH = 8.0) containing authentic metanephrine and normetanephrine. The amines were extracted into toluene-isoamyl-alcohol and then into 0.1 M acetic acid. The radioactive products were separated by thin-layer chromatography, and the appropriate areas were scraped separately into counting vials. After periodate oxidation to vanillin, phosphor-containing toluene was added, and tritium was assayed by liquid scintillation spectrometry.

Aliquots of plasma were also frozen at -20°C for about 10 days. They were then thawed for vasopressin extraction and radioimmunoassay. Vasopressin was ex-

tracted with ethanol and extracts were dried in a vacuum concentrator (Jouan NT, Saint-Herblain, France). During the extraction procedure, the recovery of vasopressin added to rat plasma was 89 ± 2 (mean ± S.E.M. (standard error of the mean)). (n = 16). The dried residues of the extracts were resuspended with 1 ml of assay buffer, and 400-μl aliquots were assayed in duplicate, using a commercially available radioimmunoassay kit (Buhlmann, Basel, Switzerland). The values are expressed as picogram per milliliter and are not corrected for extraction loses.

2.6. Drugs

The following drugs were used: tetrahydroaminoacridine (Aldrich, Milwaukee, WI, USA), atropine sulphate, atropine methylnitrate, mecamylamine, [β-mercapto-β,β-cyclopenta-methylenepropionyl^1,*O*-Me-Tyr^2-Arg^8]vasopressin and prazosin (Sigma, St. Louis, MO, USA). The drugs were dissolved in saline (0.9% NaCl). All doses of drugs refer to the free base. The volume of solution injected into the cerebral ventricle was 10 μl.

2.7. Data and statistical analysis

Data are presented as means ± S.E.M. Student's *t*-test was used to compare the effect of tetrahydroaminoacridine on plasma hormone levels. Statistical analysis of all other data was performed by using (analysis of variance) ANOVA with post hoc Newman–Keuls test. A *P*-value of less than 0.05 was considered significant.

3. Results

3.1. Cardiovascular effects of i.c.v.injection of tetrahydroaminoacridine

The resting blood pressure and heart rate of conscious rats before the injection of any drug used in this study were 117 ± 2 mmHg and 394 ± 9 beats/min (n = 40), respectively. The i.c.v. injection of tetrahydroaminoacridine (10, 25 and 50 μg) increased blood pressure in a dose-dependant manner (Fig. 1, top). The pressor response began 40–60 s after tetrahydroaminoacridine injection and reached its maximum within 5 to 10 min. A small elevation of blood pressure was observed with 10 μg tetrahydroaminoacridine (118 ± 2 vs. 126 ± 2 mmHg, control vs. tetrahydroaminoacridine) and blood pressure returned to basal levels within 20 min (Fig. 1, top). The increase in blood pressure after higher doses of tetrahydroaminoacridine (25 and 50 μg) was much higher and longer lasting (Fig. 1, top).

The i.c.v administration of tetrahydroaminoacridine (10, 25 and 50 μg) decreased heart rate significantly at all doses studied (Fig. 1, bottom). The bradycardic effect of tetrahydroaminoacridine reached maximum values at 10 min and returned to normal levels within 15–40 min, depending on the dose injected (Fig. 1, bottom).

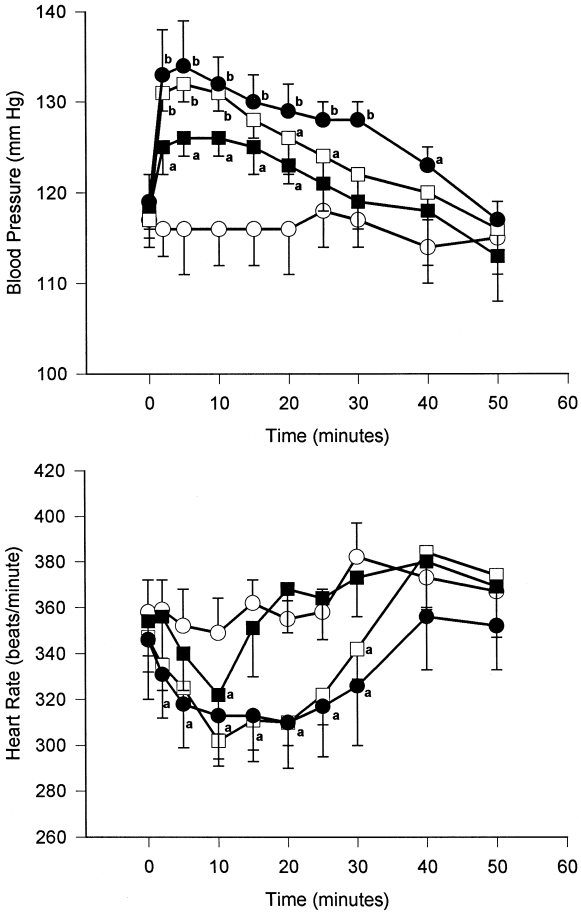

Fig. 1. Effects of i.c.v. injection of tetrahydroaminoacridine on blood pressure (top) and heart rate (bottom): dose and time relationships. Rats were injected with saline (○) or tetrahydroaminoacridine 10 μg (■), 25 μg (□), 50 μg (●) i.c.v. and their blood pressure and heart rates were monitored continuously for 60 min. Values represent the means ± S.E.M. (vertical bar) for 6–8 rats. Statistics were performed by using an ANOVA with post hoc Newman–Keuls test. (a) $P < 0.05$; (b) $P < 0.01$, significantly higher (top) or lower (bottom) than the corresponding preinjection values.

3.2. Cardiovascular response to intravenously injected tetrahydroaminoacridine

In order to determine if the cardiovascular responses elicited by i.c.v. administered tetrahydroaminoacridine were due to the leakage of the drug from its central injection site into the periphery, drug was given i.v. in several doses, starting with 25 μg. The i.v. administration of 25 μg of tetrahydroaminoacridine did not significantly alter blood pressure and heart rate (data not shown). However, i.v. injection of much higher doses of tetrahydroaminoacridine (1 and 3 mg/kg) increased blood pressure and decreased heart rate according to the dose in-

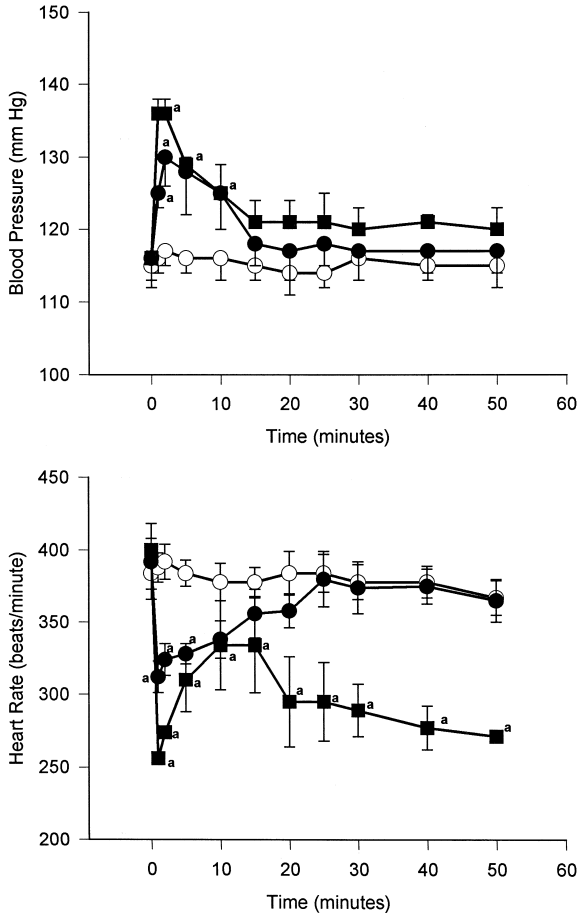

Fig. 2. Cardiovascular effects of tetrahydroaminoacridine given i.v. to rats. Rats received i.v. saline (○) or tetrahydroaminoacridine (●: 1 mg/kg, ■: 3 mg/kg) and their blood pressure (top) and heart rates (bottom) were then monitored for 120 min. The first 50 min of this period is shown. Values represent the means ± S.E.M. for 6–8 rats. Statistics were performed by using an ANOVA with post hoc Newman–Keuls test. (a) Significantly higher (top) or lower (bottom) than the corresponding value obtained in the saline-treated rats ($P < 0.05$).

jected (Fig. 2). Pressor responses were transient and disappeared within 15 min (Fig. 2, top). However, the bradycardia induced by 3 mg/kg tetrahydroaminoacridine was biphasic and longer lasting than that observed with the injection of 1 mg/kg tetrahydroaminoacridine (Fig. 2, bottom). It disappeared within 120 min (data not shown).

3.3. The effect of mecamylamine and atropine pretreatment on the blood pressure response to i.c.v. injection of tetrahydroaminoacridine

In order to determine whether central muscarinic and/or nicotinic receptors were involved in the blood pressure response elicited by tetrahydroaminoacridine (25 μg), rats were pretreated with atropine sulphate (10 μg; i.c.v.), a muscarinic receptor antagonist, or mecamylamine (50 μg; i.c.v.), a nicotinic receptor antagonist. Atropine pretreatment greatly attenuated the pressor response to i.c.v. tetrahydroaminoacridine while mecamylamine did not change the increase in blood pressure (Fig. 3, top).

3.4. The effect of mecamylamine, atropine sulphate and atropine methylnitrate pretreatment on the heart rate response to i.c.v. injection of tetrahydroaminoacridine

In order to examine whether central cholinergic (muscarinic and/or nicotinic) or peripheral muscarinic receptors were involved in the bradycardic effect of i.c.v. injected tetrahydroaminoacridine, rats were injected with mecamylamine (50 μg; i.c.v.), atropine sulphate (10 μg; i.c.v) or atropine methylnitrate (2 mg/kg; i.v.) 15 min before the i.c.v. administration of tetrahydroaminoacridine (25 μg). Both atropine sulphate and atropine methylnitrate

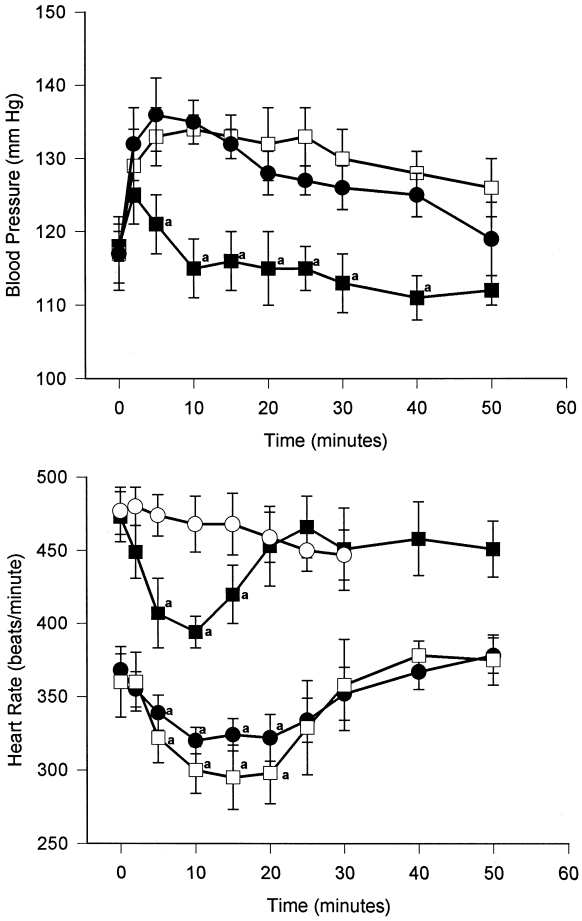

Fig. 3. Top: The effect of mecamylamine and atropine sulphate pretreatment on the pressor response to tetrahydroaminoacridine. Bottom: The effect of mecamylamine, atropine sulphate and atropine methylnitrate pretreatments on the heart rate response elicited by tetrahydroaminoacridine. Rats were pretreated with saline (●: 10 μl, i.c.v.), atropine sulphate (■: 10 μg, i.c.v.), mecamylamine (□: 50 μg, i.c.v.) or atropine methylnitrate (○: 2 mg/kg, i.v.) 15 min prior to i.c.v. injection of tetrahydroaminoacridine (25 μg). Values represent the means ± S.E.M. for 6–8 rats. Statistics were performed by using an ANOVA with post hoc Newman–Keuls test. (a) Significantly lower than the corresponding value obtained in the saline-pretreated rats ($P < 0.05$).

Table 1
Effects of i.c.v. tetrahydroaminoacridine on plasma hormone levels

Parameters	Treatment	
	Saline	Tetrahydroaminoacridine (25 μg)
Plasma renin activity (ng angiotensin-1/h per ml)	14 ± 2	19 ± 4
Vasopressin (pg/ml)	3 ± 0.2	17 ± 4[a]
Noradrenaline (pg/ml)	204 ± 28	321 ± 37[a]
Adrenaline (pg/ml)	249 ± 41	700 ± 164[a]

Rats were given saline (10 μl) or tetrahydroaminoacridine (25 μg) i.c.v. and 2 ml arterial blood samples were obtained from the cannula inserted into the left common carotid artery 10 min after the i.c.v. injection. Plasma vasopressin levels and plasma renin activity were determined by radioimmunoassay. Data are given as the means ± S.E.M. of 6–11 determinations. Statistics were performed by using unpaired Student's *t*-test.
[a]Significantly higher than the corresponding value obtained in the saline-treated rats ($P < 0.05$).

pretreatments increased heart rate while mecamylamine did not change the basal rate. Neither atropine sulphate nor mecamylamine pretreatment influenced the bradycardia produced by i.c.v. tetrahydroaminoacridine (Fig. 3, bottom). However, the tetrahydroaminoacridine-induced reduction in heart rate was totally blocked by atropine methylnitrate pretreatment (Fig. 3, bottom).

3.5. Effects of i.c.v. tetrahydroaminoacridine on plasma renin activity, adrenaline, noradrenaline and vasopressin levels

In order to determine the possible role of three well-known pressor systems in the pressor effect of tetrahydroaminoacridine, plasma adrenaline, noradrenaline, vasopressin and renin activity were determined 10 min after the i.c.v. injection of tetrahydroaminoacridine. As shown in Table 1, i.c.v. administration of tetrahydroaminoacridine (25 μg) increased plasma levels of vasopressin, adrenaline and noradrenaline, but not plasma levels of renin activity (Table 1).

3.6. Effect of prazosin or vasopressin antagonist pretreatments on blood pressure response to i.c.v. tetrahydroaminoacridine

To evaluate further the involvement of plasma catecholamines in the pressor effect of i.c.v. tetrahydroaminoacridine, rats were pretreated with prazosin, an α_1-adrenergic receptor antagonist. After administration of prazosin (0.5

Table 2
Effect of i.c.v. tetrahydroaminoacridine on blood pressure and heart rate in prazosin-, vasopressin antagonist- or prazosin plus vasopressin antagonist-pretreated rats

Groups/pretreatment	Before pretreatment	Time after i.c.v. THA (min)				
		0	2	5	10	20
Saline						
BP	116 ± 2	115 ± 4	129 ± 2[a]	132 ± 3[a]	132 ± 2[a]	124 ± 4
HR	347 ± 15	353 ± 11	335 ± 11	325 ± 9[a]	302 ± 8[a]	322 ± 13
Prazosin						
BP	116 ± 3	84 ± 4	80 ± 5	92 ± 4	97 ± 5[a]	97 ± 6
HR	326 ± 21	415 ± 24	438 ± 23	399 ± 38	354 ± 22[a]	364 ± 27
Vasopressin antagonist						
BP	119 ± 3	117 ± 3	125 ± 5	126 ± 4[a]	125 ± 4[a]	124 ± 6
HR	330 ± 18	334 ± 20	368 ± 17	348 ± 18	338 ± 17	364 ± 27
Prazosin + vasopressin antagonist						
BP	118 ± 3	90 ± 4	96 ± 3	87 ± 3	84 ± 4	88 ± 3
HR	408 ± 22	490 ± 10	487 ± 16	480 ± 16	475 ± 21	478 ± 10

Rats were pretreated with prazosin (0.5 μg/kg; i.v.), vasopressin V_1 receptor antagonist (10 μg/kg; i.v.), or prazosin and vasopressin receptor antagonist simultaneously 5 min before i.c.v. injection of tetrahydroaminoacridine (25 μg). The 'before pretreatment' values represent basal levels obtained immediately before the pretreatments. Data are given as means ± S.E.M. for 5–7 rats. Statistics were performed by using an ANOVA with post hoc Newman–Keuls test.
[a]Values significantly different from the pretetrahydroaminoacridine ($t = 0$) value ($P < 0.05$).
Abbreviations: THA, tetrahydroaminoacridine; BP, blood pressure; HR, heart rate.

mg; i.v.), an approximately 32-mmHg decrease in blood pressure was observed. The i.c.v. injection of tetrahydroaminoacridine (25 μg) 5 min after prazosin caused a small elevation in blood pressure, but blood pressure did not reach control levels (Table 2). Prazosin pretreatment increased heart rate, but did not affect the bradycardia induced by tetrahydroaminoacridine (Table 2).

In order to determine the involvement of vasopressin in the pressor response to tetrahydroaminoacridine, rats were pretreated with the vasopressin receptor antagonist [β-mercapto-β,β-cyclopenta-methylenepropionyl^1,*O*-Me-Tyr^2-Arg^8]vasopressin (10 μg/kg; i.v.) 5 min prior toi.c.v.injection of tetrahydroaminoacridine (25 μg). In these rats, tetrahydroaminoacridine increased blood pressure by 9 ± 4 mmHg. This was significantly lower ($P < 0.05$) than the pressor response of 17 ± 2 mmHg observed in control rats pretreated with i.v. saline (Table 2). Vasopressin receptor antagonist alone did not change blood pressure and heart rate under normotensive conditions. In addition, pretreatment with vasopressin antagonist abolished the bradycardic response to i.c.v. tetrahydroaminoacridine (Table 2).

When rats were pretreated with prazosin (0.5 mg/kg; i.v.) and vasopressin receptor antagonist (10 μg; i.v.) together 5 min prior to i.c.v. administration of tetrahydroaminoacridine, complete blockade was observed of the pressor and bradycardic response to tetrahydroaminoacridine (Table 2).

4. Discussion

These results show that i.c.v. injected tetrahydroaminoacridine increases blood pressure and decreases heart rate in conscious freely moving normotensive rats. Since i.v. administration of 25 μg tetrahydroaminoacridine did not alter cardiovascular function and much higher doses of tetrahydroaminoacridine were required to increase blood pressure, we suggest that the present effects are centrally mediated.

The pressor response to i.c.v. tetrahydroaminoacridine was dose- and time-dependent under normotensive conditions. The pressor effect was observed within a minute. It reached a maximum within 5 to 10 min and lasted for 15 to 40 min, depending on the dose injected (Fig. 1, top). Since pretreatment with the muscarinic receptor antagonist, atropine, but not with mecamylamine, greatly attenuated the pressor response to i.c.v. tetrahydroaminoacridine, central muscarinic receptors appear to be involved in this effect. These results are in good agreement with the previous studies reporting the central muscarinic receptor involvement in the pressor effects of several cholinergic drugs including acetylcholinesterase inhibitors (Buccafusco and Brezenoff, 1979; Caputi et al., 1980; Kristic, 1982; Arslan et al., 1991; Peres-Polon and Correa, 1994; Ally et al., 1995). Besides, depression of the pressor effect of peripherally administered tetrahydroaminoacridine in anaesthetised rats pretreated with atropine has been reported previously (Kayaalp, 1965).

The pressor response to i.c.v. tetrahydroaminoacridine was associated with a several-fold increase in plasma levels of adrenaline, noradrenaline and vasopressin (Table 1). It has been previously reported that central cholinergic stimulation primarily activates the adrenomedullary pathway of the sympathoadrenal system (Ulus and Wurtman, 1979; Arslan et al., 1991). Our observation that the effect of tetrahydroaminoacridine on plasma adrenaline levels was more pronounced than that on noradrenaline levels agrees with these results. The failure of i.c.v. injected tetrahydroaminoacridine to increase plasma renin activity (Table 1) rules out the possibility that the peripheral renin–angiotensin system plays a role in the response to tetrahydroaminoacridine in normotensive conscious rats. The increases in plasma levels of vasopressin and catecholamines strongly suggest that these hormones may mediate the pressor effect of i.c.v. tetrahydroaminoacridine in normotensive freely moving rats. In fact, both prazosin and vasopressin antagonist pretreatment partially inhibited the pressor response to tetrahydroaminoacridine, and complete inhibition of the pressor effect of tetrahydroaminoacridine was observed after the pretreatment with both antagonists simultaneously. These observations support the conclusion that the increased levels of plasma vasopressin and catecholamines both contribute to the pressor action of i.c.v. tetrahydroaminoacridine in conscious rats.

The reduction in heart rate observed after the i.c.v. injection of tetrahydroaminoacridine is not simply mediated via a baroreceptor reflex in response to the increase in blood pressure, since i.c.v. atropine pretreatment greatly attenuated the pressor response to tetrahydroaminoacridine without influencing the change in heart rate. Central administration of the nicotinic antagonist, mecamylamine, did not affect the bradycardic response to tetrahydroaminoacridine, but the response was completely abolished by peripheral administration of atropine methylnitrate, which does not enter the brain and which blocks peripheral muscarinic receptors, and by the vasopressin antagonist. These findings suggested that the reduction of heart rate in response to tetrahydroaminoacridine is mainly mediated via an increase in vagal tone and an increase in plasma vasopressin levels. The later point agrees with previous reports demonstrating the involvement of circulating vasopressin in the bradycardia induced by central cholinergic stimulation (Hoffman and Phillips, 1976; Iitake et al., 1986; Imai et al., 1989).

In conclusion, the present results show that i.c.v. injection of tetrahydroaminoacridine increases blood pressure, decreases heart rate and increases plasma adrenaline, noradrenaline, vasopressin levels in normotensive freely moving rats. The pressor effect appears to result from the activation of central muscarinic cholinergic receptors and the increases in plasma catecholamines and vasopressin levels are involved in this effect. This is the first report

presenting the complete cardiovascular effects of centrally injected tetrahydroaminoacridine in normotensive freely moving rats. Since the drug is widely used in the treatment of Alzheimer's disease, it must be remembered that there might be cardiovascular side effects in patients treated with tetrahydroaminoacridine.

Acknowledgements

This study was supported in part by a grant from The Research Fund of Uludag University (1985/1).

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