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Central cardiovascular effects of tacrine in the conscious dog: a role for catecholamines and vasopressin release

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Abstract

Centrally acting cholinergic agents are currently reported to increase blood pressure in various species through the stimulation of muscarinic cholinoceptors. Moreover, several cardiovascular adverse effects have been reported from clinical studies. The aim of this study was to investigate the effects of tacrine, an acetylcholinesterase inhibitor which has been reported to have therapeutic potential in Alzheimer's disease, on blood pressure and two vasopressor systems (sympathetic and vasopressinergic) in Beagle dogs. Intravenous (i.v.) tacrine (2 mg kg^{-1}) induced, in conscious and anesthetized dogs, an increase in systolic and diastolic blood pressure, accompanied by bradycardia. This increase was dose-dependent with a peak effect at 1.5 min following administration. Tacrine also induced an increase in noradrenaline, adrenaline and vasopressin plasma levels. Pretreatment with the muscarinic receptor antagonist, atropine (2 mg kg^{-1}, i.v.), abolished the pressor response to i.v. injection of tacrine while pretreatment with the peripheral muscarinic receptor antagonist, methylscopolamine (0.2 mg kg^{-1}, i.v.), did not alter the increase in blood pressure. Similarly, noradrenaline and adrenaline changes in plasma levels were not modified by methylscopolamine but were abolished by atropine pretreatment. A similar tendency although not significant was observed for vasopressin plasma levels. The present results demonstrate that in dogs, tacrine (2 mg kg^{-1}, i.v.) stimulates central muscarinic cholinoceptors to increase blood pressure through activation of the two components of the sympathetic nervous system (i.e., neuroneuronal noradrenergic and the neurohormonal adrenergic pathways) as well as through increasing noradrenaline, adrenaline and vasopressin plasma levels.

Keywords: Tacrine; Blood pressure; Noradrenaline; Muscarinic receptor; Cholinergic system; Central

1. Introduction

Tetrahydroaminoacridine or tacrine is a reversible inhibitor of acetylcholinesterase which has been reported to improve cognitive function and behavioural deficits in laboratory animals (Gheusi et al., 1994) as well as in patients suffering from the most common form of dementia, namely Alzheimer's disease (Summers et al., 1986). Several cardiovascular adverse effects are to be expected with any cholinomimetic agent because acetylcholine plays a crucial role in blood pressure and heart rate regulation, both centrally and peripherally (Brezenoff and Giuliano, 1982; Buccafusco, 1996). The stimulation of central muscarinic cholinoceptors induces a rise in blood pressure (Brezenoff and Giuliano, 1982) mediated at the periphery by an increase in both sympathetic tone (Krstic and Djurkovic, 1978a; Buccafusco and Brezenoff, 1979) and the release of vasopressin (Rascol et al., 1990). Therefore, like other cholinergic agents, tacrine is likely to induce significant cardiovascular effects. Indeed, bradycardia has been reported as a frequent side-effect of tacrine in humans (Wagstaff and McTavish, 1994). Changes in blood pressure have been more rarely reported or investigated but recently, a case report has described a significant and clinically relevant increase in blood pressure induced by treatment with tacrine in a patient suffering from Alzheimer's disease (Allain et al., 1996).

The aims of the present study were thus (1) to describe the cardiovascular changes induced by the intravenous (i.v.) injection of tacrine in conscious and anesthetized dogs and (2) to characterize the central and/or peripheral

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mechanisms implicated in these cardiovascular effects of tacrine.

2. Materials and methods

Experiments were performed with conscious and anesthetized Beagle dogs of either sex weighing 10 to 17 kg and trained to remain quiet on a Pavlov-type stand. The dogs were fasted on the morning of the experiment but had free access to water ad libitum in order to be normally hydrated. All animal procedures were conducted in strict compliance with approved French Agriculture Department's Animal Use for Research and Education protocols.

2.1. Dose–response experiments in anesthetized dogs

In the first part of this study, dose–response experiments were run in anesthetized animals (α-chloralose 80 mg kg^{-1}). The dogs were anesthetized in order to minimize tacrine's side-effects such as restlessness or vomiting induced by the highest doses of the drug (4 mg kg^{-1}), as we had observed in preliminary experiments (data not shown). Nine dogs received increasing doses of tacrine (1, 2 and 4 mg kg^{-1}). Each injection was separated from the previous one by at least 30 min (time necessary to return to the resting blood pressure value). In these experiments, blood pressure and heart rate were only measured at 1.5 min after tacrine administration (at which time the peak effect of tacrine is reached).

2.2. Intravenous injection of tacrine in conscious dogs

In a second series of experiments, the cardiovascular and hormonal effects of tacrine (2 mg kg^{-1}, i.v., $n = 6$) were investigated in conscious dogs, in comparison with those of a saline i.v. injection (3 ml, $n = 6$). Then, the mechanisms implicated in the pressor response to tacrine i.v. were studied by comparing the pressor response following pretreatment with peripheral and/or central muscarinic receptor antagonists. For this purpose, the dogs were injected with methylscopolamine (0.2 mg kg^{-1}, i.v., $n = 7$) or atropine (2 mg kg^{-1}, i.v., $n = 6$) 5 min before tacrine injection. According to previous reports from our laboratory suggesting the participation of catecholamines and arginine–vasopressin in the pressor response to acetylcholine (Rascol et al., 1990), the effects of i.v. tacrine (and saline) were assessed on blood pressure, heart rate and plasma levels of noradrenaline, adrenaline and vasopressin at 4 different times: 0.5 min (T0.5), 1.5 min (T1.5), 5 min (T5) and 15 min (T15) after tacrine administration. Cardiovascular and hormonal parameters were also assessed 1 min before and 4 min after muscarinic receptor antagonist (or saline) administration. Each treatment group was evaluated in at least six separate experiments each performed in a different animal. All i.v. injections were given in a volume of 3 ml.

2.3. Experimental protocol

A catheter was introduced into the left femoral artery at the beginning of the experiment. It was connected to a Statham P23 Db transducer to monitor systolic and diastolic blood pressure and was removed at the end of each experiment. Heart rate was counted on the electrocardiogram (lead II). These parameters were continuously recorded on a Beckman recorder.

Blood samples for catecholamines and vasopressin plasma levels assay were obtained from the femoral artery. The volume of blood removed for plasma assay was immediately replaced by an equivalent volume (10 ml) of isotonic saline.

2.4. Measurement of catecholamines and vasopressin plasma levels

All measurements were done blind. For each catecholamine plasma level determination, blood was collected in lithium-heparin tubes. For noradrenaline and adrenaline, the tubes contained 10 mM of sodium metabisulphite. Blood samples were then centrifuged at $4000 \times g$ for 15 min at 0°C. Plasma was stored at -80°C.

Noradrenaline, adrenaline and vasopressin were measured as previously described by Brefel et al. (1995).

2.5. Drugs

The following drugs were used: α-chloralose (Prolabo, Paris, France), atropine sulfate (a nonselective muscarinic receptor antagonist which crosses the blood–brain barrier), scopolamine methyl bromide (a nonselective muscarinic receptor antagonist which does not cross the blood–brain barrier) (Sigma-Aldrich, St. Quentin Fallavier, France). The drugs were dissolved in physiological saline. All doses of drugs refer to the free base.

2.6. Statistical analysis

All results are expressed as means $\pm$ S.E.M. Data were statistically evaluated by means of one-way analysis of variance (ANOVA) for repeated measures. Significant treatment effects were subsequently delineated by using Dunnett's post-hoc test. According to the homogeneity of variances (Hartley's test), Student's *t*-test or the Mann–Whitney *U*-test was used for the comparison of time–response curves obtained for the saline and tacrine groups. A paired-sample Student's *t*-test was used to compare the individual effects of the muscarinic receptor antagonists. According to the homogeneity of variances, we used a two-way ANOVA followed by a post hoc Scheffe test, or a Kruskal–Wallis test for the comparison of time–response

Table 1
Baseline parameters in conscious Beagle dogs

	Saline	Tacrine	Atropine	Methylscopolamine
n	6	6	6	7
Systolic BP (mmHg)	186 ± 6	175 ± 11	185 ± 4	186 ± 7
Diastolic BP (mmHg)	86 ± 7	81 ± 6	92 ± 5	96 ± 6
Heart rate (beats/min)	93 ± 6	105 ± 5	96 ± 8	98 ± 8
Noradrenaline (pg ml^{-1})	210 ± 52	169 ± 25	137 ± 29	267 ± 74
Adrenaline (pg ml^{-1})	263 ± 52	205 ± 41	207 ± 37	360 ± 67
Vasopressin (pg ml^{-1})	2 ± 1	3 ± 1	2 ± 1	3 ± 1

Values are expressed as means ± S.E.M.

curves obtained for tacrine, atropine and methylscopolamine groups. The level of statistical significance was considered to be $P < 0.05$.

3. Results

The baseline values for cardiovascular parameters were not significantly different before i.v. injections in the four groups of conscious dogs (Table 1). Saline induced no significant change in any parameter after its i.v. injection at any time (data not shown).

3.1. Dose–response experiments

In anesthetized dogs, tacrine ($n = 8$) induced significant changes in diastolic and systolic blood pressure at the three doses studied: 1, 2 and 4 mg kg^{-1} ($P < 0.005$).

Ninety seconds after tacrine administration, diastolic and systolic blood pressure increased by +5 ± 2% and +3 ± 1% mmHg (1 mg kg^{-1}), +10 ± 3% and +7 ± 1% (2 mg kg^{-1}) and +23 ± 3% and 13 ± 2% (4 mg kg^{-1}), respectively. When the effects of the three doses of tacrine (1, 2 and 4 mg kg^{-1}) on systolic and diastolic blood pressure at 1.5 min were compared, there was a clear dose-dependent effect (slope of the linear regression for systolic and diastolic blood pressure: $y = 2.924x + 0.605$ with $r^2 = 0.335$ and $P < 0.005$, $y = 6.018x - 1.664$ with $r^2 = 0.313$ and $P < 0.005$, respectively).

3.2. Cardiovascular and plasma levels changes induced by i.v. tacrine

Fig. 1 shows a typical example of the effects of an i.v. tacrine injection (2 mg kg^{-1}) on blood pressure and heart rate in the conscious dog. At this dose, tacrine i.v. injection induced, within 30 s, a modest, transient and non-significant decrease in systolic and diastolic blood pressure (−11 ± 6 mmHg and −6 ± 7 mmHg, respectively) followed by a significant increase in systolic and diastolic blood pressure. This increase was maximal after 90 s (T1.5 min) (+68 ± 10 mmHg, $P < 0.001$ and +48 ± 10 mmHg,

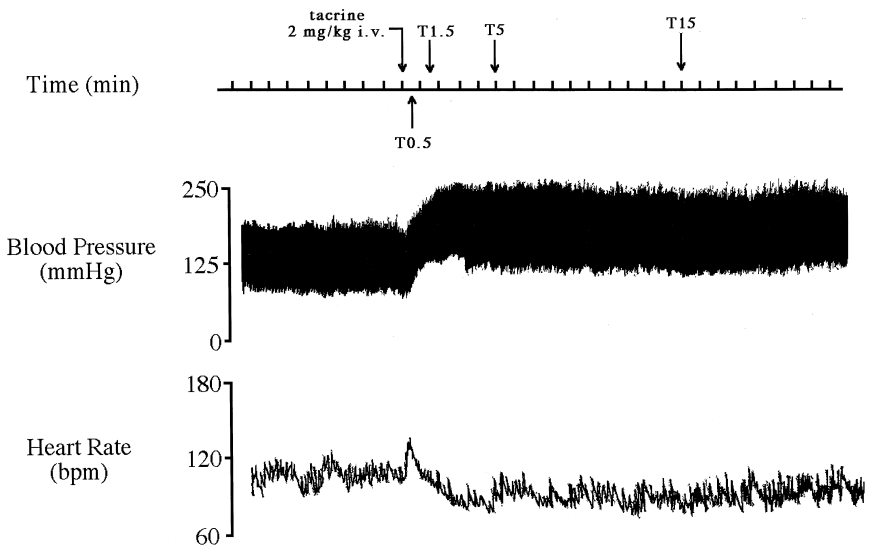

Fig. 1. Typical example of the cardiovascular changes in blood pressure and heart rate after an intravenous injection of tacrine (2 mg kg^{-1}) in a conscious Beagle dog.

$P < 0.01$, respectively). Blood pressure values remained increased up to 10 min after administration, until they returned progressively to their preinjection values within 15 min. Tacrine's effects on blood pressure were significantly greater than those of saline at times T1.5 min and T5 min (Student's *t*-test, $P < 0.05$) (Fig. 2a and b). The i.v. administration of tacrine also induced a significant bradycardia, when compared to preinjection values (-15 ± 4 bpm, ANOVA, $P < 0.01$) (Fig. 2c), lasting more than 15 min.

Catecholamine and vasopressin plasma levels were also modified by tacrine (Fig. 3). Noradrenaline and adrenaline plasma levels showed similar changes: 90 s following tacrine administration, noradrenaline and adrenaline were significantly increased ($+651 \pm 151$ and $+1039 \pm 176$ pg ml^{-1}, respectively, ANOVA $P < 0.05$). These plasma levels remained significantly increased at T5 min ($+671 \pm 242$ and $+730 \pm 129$ pg ml^{-1}, respectively, ANOVA $P < 0.05$) and then returned to their basal values. These effects were significantly different from those of saline at T1.5 min and T5 min (Mann–Whitney *U*-test, $P < 0.01$).

The vasopressin plasma levels were also significantly increased by tacrine: $+13 \pm 6$ at T5 min and $+9 \pm 3$ pg ml^{-1} at T15 min (ANOVA, $P < 0.05$). This effect was different from that of saline (Mann–Whitney *U*-test, $P < 0.01$).

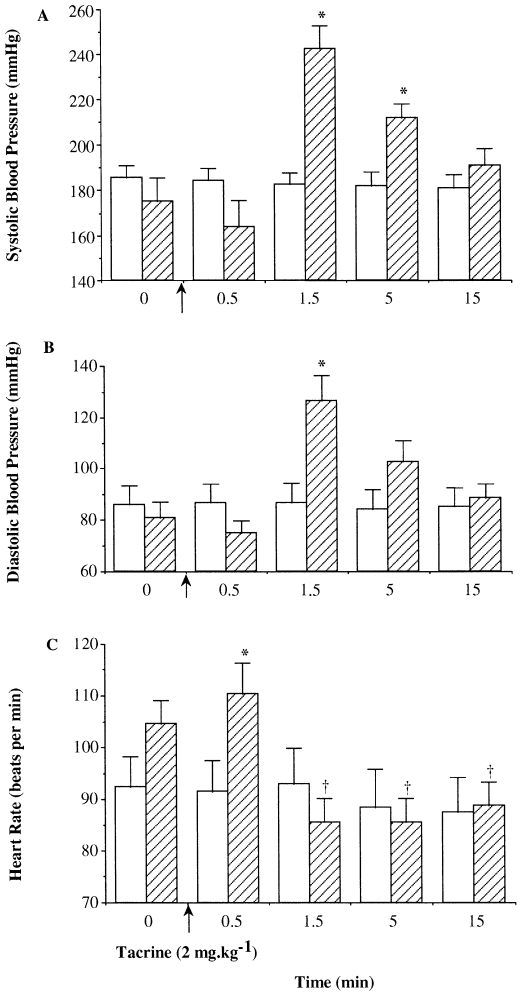

Fig. 2. Changes in systolic (A) and diastolic (B) blood pressure and heart rate (C) elicited by intravenous (i.v.) saline injection (open columns) ($n = 6$) and by i.v. injection of 2 mg kg^{-1} of tacrine (hatched columns) ($n = 6$). Values are expressed as means ± S.E.M. Statistical significance was accepted for $P < 0.05$. Cardiovascular parameters were compared: to saline group, $* P < 0.01$ (Student's *t*-test) and in each group $P < 0.01$ (ANOVA for repeated measures followed by a Dunnett post-hoc test).

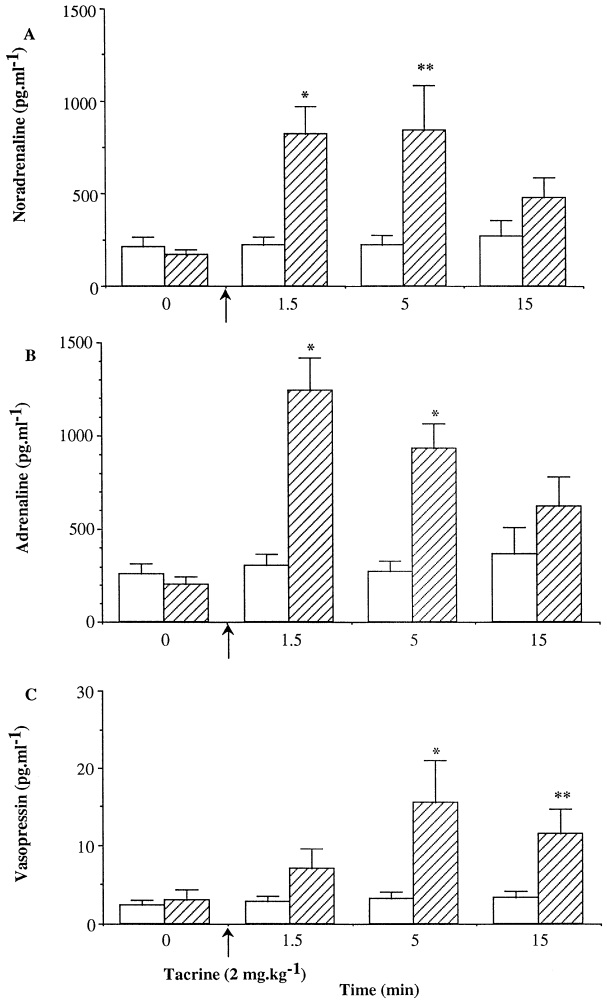

Fig. 3. Changes in plasma levels of noradrenaline (A), adrenaline (B) and vasopressin (C) elicited by i.v. saline injection (open columns) ($n = 6$) and by i.v. injection of 2 mg kg^{-1} of tacrine (hatched columns) ($n = 6$). Values are expressed as means ± S.E.M. Statistical significance was accepted for $P < 0.05$. Catecholamines and vasopressin plasma levels were compared to those of the saline group, $* P < 0.05$ and $** P < 0.01$ (Student's *t*-test).

3.3. Effects of muscarinic receptor antagonists pretreatment

Pretreatment with methylscopolamine and atropine induced a marked and similar tachycardia ($+250 \pm 14$ bpm)

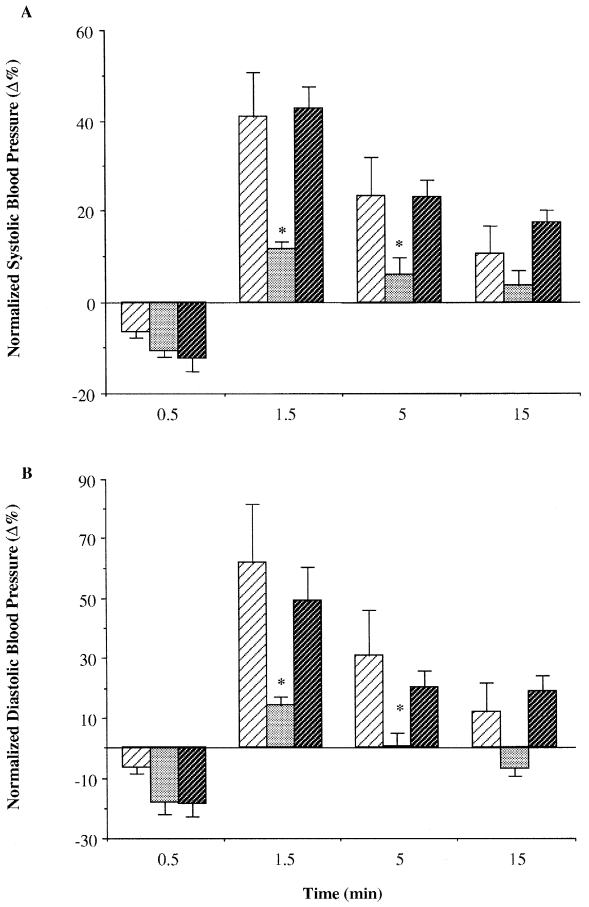

Fig. 4. Changes in systolic (A) and diastolic blood pressure (B) elicited by i.v. injection of tacrine (2 mg kg^{-1}, widely hatched columns) ($n = 6$), atropine (2 mg kg^{-1}, shaded columns) ($n = 6$) and methylscopolamine (0.2 mg kg^{-1}, closely hatched columns) ($n = 7$). Values are expressed in mean percentages from baseline (Δ%) ± S.E.M. Statistical significance was accepted for $P < 0.05$. Cardiovascular parameters are significantly different from those for the tacrine group: $* P < 0.05$ and $** P < 0.01$ (ANOVA followed by a Scheffe post-hoc test).

which was accompanied by a reduction of the blood pressure variability. For this reason and in order to compare the tacrine, methylscopolamine and atropine groups, we expressed the mean blood pressure changes as percentages of baseline (Δ%). The two-way ANOVA showed that there was a significant time by group interaction ($P < 0.001$).

At T0.5 min, there were no differences between the three groups (Fig. 4).

At T1.5 min the mean increase in systolic and diastolic blood pressure was significantly smaller in the atropine group ($+12 \pm 2\%$ and $+14 \pm 3\%$, respectively), when compared to those in the tacrine ($+41 \pm 10\%$ and $+62 \pm 20\%$, respectively) and the methylscopolamine group ($+43 \pm 5\%$ and $+49 \pm 11\%$, respectively) (Kruskal–Wallis test, $P < 0.05$) (Fig. 4). The mean bradycardia was not significantly different between the atropine ($-26 \pm 2\%$), methylscopolamine ($-15 \pm 3\%$) and tacrine ($-13 \pm 7\%$) groups.

The increases in mean plasma levels of noradrenaline and adrenaline were also smaller in the atropine group ($+41 \pm 40\%$ and $+135 \pm 21\%$, respectively), than in the tacrine ($+520 \pm 201\%$ and $+613 \pm 167\%$, respectively) and the methylscopolamine ($+486 \pm 248\%$ and $+426 \pm 68\%$, respectively) groups (Kruskal–Wallis test, $P < 0.05$).

Despite the fact that the rise in vasopressin plasma level was reduced in the atropine group, the difference between the three groups fell short of significance at any time (Fig. 5). This may have been related to the large standard deviations and the small size of the sample.

At T5 min the mean increase in systolic and diastolic blood pressure remained significantly smaller in the atropine group ($+6 \pm 4\%$ and $+1 \pm 5\%$, respectively) than in the tacrine ($+23 \pm 8\%$ and $+31 \pm 15\%$, respectively) and the methylscopolamine ($+23 \pm 4\%$ and $+20 \pm 5\%$,

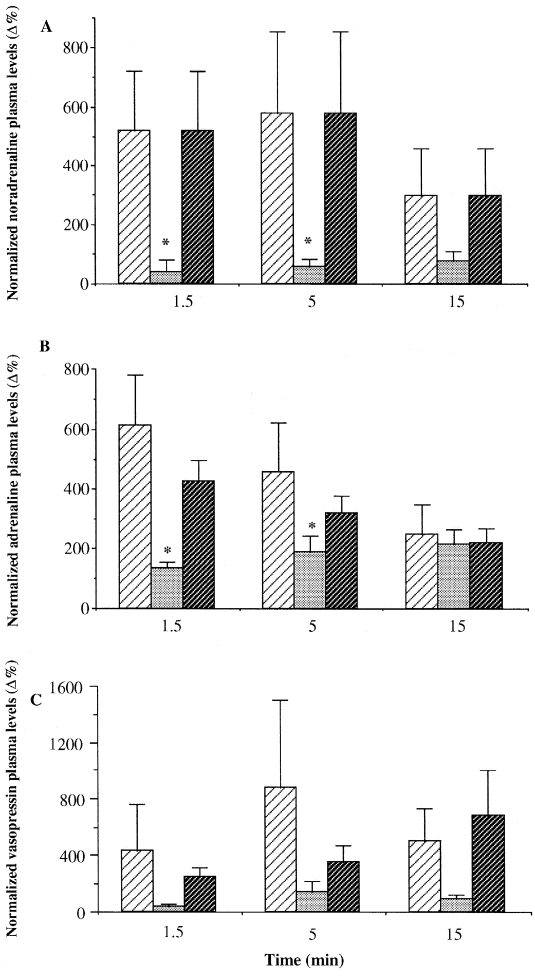

Fig. 5. Changes in noradrenaline (A), adrenaline (B) and vasopressin (C) plasma levels elicited by i.v. injection of tacrine (2 mg kg^{-1}, widely hatched columns) ($n = 6$), atropine (2 mg kg^{-1}, shaded columns) ($n = 6$) and methylscopolamine (0.2 mg kg^{-1}, closely hatched columns) ($n = 7$). Values are expressed as mean percentages of baseline (Δ%) ± S.E.M. Statistical significance was accepted for $P < 0.05$. Cardiovascular parameters are significantly different from those of the tacrine group: $* P < 0.05$ and $** P < 0.01$ (Kruskal–Wallis test).

respectively) groups (ANOVA, Scheffe's test, $P < 0.05$) (Fig. 4). The mean bradycardia was not significantly different between the atropine ($-18 \pm 2\%$), methylscopolamine ($-15 \pm 4\%$) and tacrine ($-14 \pm 5\%$) groups. The plasma levels of noradrenaline and adrenaline were also significantly lower in the atropine group ($+57 \pm 26\%$ and $+189 \pm 54\%$, respectively), than in the tacrine ($+580 \pm 273\%$ and $+459 \pm 162\%$, respectively) and the methylscopolamine groups ($+582 \pm 221\%$ and $+320 \pm 58\%$, respectively—ANOVA, Scheffe's test, $P < 0.05$) (Fig. 5).

At T15 min there were no significant differences for any cardiovascular parameters or plasma levels between the three groups (Figs. 4 and 5).

4. Discussion

The present results demonstrated that tacrine, injected i.v. in conscious dogs, induces a significant increase in blood pressure mediated by central muscarinic receptors. This effect is secondary to an increase in sympathetic outflow and vasopressin release. A long-lasting bradycardia was also observed.

4.1. Tacrine induced an increase in blood pressure

Tacrine induced a significant dose-dependent increase in systolic and diastolic blood pressure with a magnitude comparable, both in anesthetized and conscious animals, to what was reported for physostigmine (Varagic, 1955; Brezenoff, 1973; Brezenoff and Rusin, 1974; Caputi et al., 1980b; Özkutlu et al., 1993; Ally et al., 1995) and other cholinergic agents injected centrally, like neostigmine (Buccafusco and Brezenoff, 1979; Xiao and Brezenoff, 1988), acetylcholine (Rascol et al., 1990; Brefel et al., 1995), carbachol or oxotremorine (Pazos et al., 1986; Özkutlu et al., 1993) and choline (Ulus et al., 1995). It is noteworthy that the pressor effect of tacrine occurred within a few seconds and was maximal at 1.5 min, much earlier than what has been reported for other acetylcholinesterase inhibitors such as neostigmine or physostigmine (peak effect at 5 min) (Brezenoff and Giuliano, 1982). Similar results have also been observed recently in the rat (Lazartigues et al., 1996b). The dose of 2 mg kg^{-1} was chosen because it proved to induce significant and reproducible effects in the dose–response protocol, moreover, it induced only digestive disorders (defecation) but not the behavioral modifications observed with highest doses. This dose, injected by i.v. route, is in the range of the recommended maximal oral daily dose of tacrine for the treatment of Alzheimer's disease in humans (120 mg) considering that tacrine's bioavailability is about 20% (Davis and Powchik, 1995). It is possible that some patients, for example elderly and hypertensive ones, could be even more sensitive to acetylcholinesterase inhibitors. Indeed (Cain, 1986) and (Allain et al., 1996) reported hypertensive responses in patients suffering from Alzheimer's disease, during treatment with oral physostigmine and tacrine, respectively.

The pressor response to i.v. tacrine is mediated by central muscarinic cholinoceptors, as demonstrated by the total blocking effect of atropine, and the lack of effect of methylscopolamine, which does not cross the blood–brain barrier. This observation is consistent with the ability of physostigmine, but not neostigmine to induce a pressor response when injected systemically (Brezenoff and Giuliano, 1982).

Central muscarinic receptors mediating the cardiovascular effects of cholinergic drugs are located in various brain areas: pons medulla (Caputi et al., 1980a; Lee et al., 1991), hypothalamus (Buccafusco and Brezenoff, 1979; Xiao and Brezenoff, 1988) or more rostral brain structures (Hori et al., 1995). These areas are likely to be involved in the tacrine-induced pressor response. However, tacrine has also been reported to act on several other brain areas (Mesulam et al., 1987; Bassant et al., 1995) which could be involved in its cholinergic pressor effects.

The question remains as to which muscarinic receptor subtype is actually implicated in the pressor response to i.v. tacrine in the dog. Recently, a study, also conducted in Beagle dogs in our laboratory, showed that the pressor response to i.c. acetylcholine can be blocked by low doses of pirenzepine (Pelat et al., 1997a), suggesting the involvement of central M_1 cholinoceptors in this species. However, Lazartigues et al. (1996b) reported that, in the rat, the pressor response to i.v. tacrine is mediated mostly by central muscarinic M_2 cholinoceptors and it is possible that different subtypes of muscarinic receptors participate in the pressor response to cholinomimetics according to species or strain (Buccafusco, 1996).

4.2. Tacrine induced an increase in catecholamines and vasopressin plasma levels

The present data also demonstrate that tacrine induced an increase in the plasma levels of noradrenaline and adrenaline, suggesting a rise in sympathetic tone following tacrine administration. These results are in agreement with other reports showing that section of the spinal cord (Krstic and Djurkovic, 1978a), ganglionic blockade (Ozawa and Uematsu, 1976) or peripheral α_1-adrenoceptor blockade (Ulus et al., 1995) reduces the pressor response to cholinomimetic drugs.

Our data also suggest the involvement of vasopressin in the pressor effect of tacrine. It is well-known that nicotinic and muscarinic receptors are involved in the control of vasopressin release (Bisset and Chowdrey, 1984; Rascol et al., 1990; Ulus et al., 1995). This is in agreement with the reports from Rascol et al. (1990) and Brefel et al. (1995) showing that vasopressin plasma levels increase after the

central administration of acetylcholine in the dog. The authors assumed that this vasopressin release participates in the pressor effect of cholinergic drugs. This is also in agreement with the report from Lazartigues et al. (1996b) showing that in the rat, the pressor response to tacrine is significantly reduced following the systemic administration of a vasopressin V_1 receptor antagonist.

4.3. Tacrine-induced bradycardia

In the present study, i.v. tacrine induced long-lasting bradycardia. Similar results were reported by Brefel et al. (1995) following central acetylcholine administration. The effects of cholinomimetic drugs on heart rate are still being debated in the literature (Brezenoff and Giuliano, 1982). It is probable that some of the discrepancies reported are species- or drug-related or result from the use of different anesthetics (Brezenoff and Giuliano, 1982). The tacrine-induced bradycardia was not abolished by methylscopolamine and atropine, showing that muscarinic mechanisms are not involved. Nicotinic mechanisms are probably not involved because Brefel et al. (1995) showed that acetylcholine-induced bradycardia was not abolished following mecamylamine pretreatment. This bradycardia could involve baroreflex mechanisms but this explanation is difficult to reconcile with the observation that the bradycardia persisted after the pressor response had disappeared.

5. Conclusion

The present data demonstrate that tacrine, an acetylcholinesterase inhibitor used in the treatment of Alzheimer's disease, induced significant cardiovascular effects in dogs. These effects consisted in a long-lasting increase in blood pressure and bradycardia. The pressor response involves the central cholinergic system via muscarinic receptors and is mediated by an increase in vasoactive hormones (noradrenaline, adrenaline and vasopressin). The experimental demonstration of such effects suggests that some patients at risk, particularly the older ones or those suffering from hypertension, may present with troublesome cardiovascular adverse events with tacrine or one of the other anticholinesterase agents currently under development for the treatment of Alzheimer's disease dementia.

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