BRAIN RESEARCH

Research report

Alpha-2 agonist-induced memory impairment is mediated by the alpha-2A-adrenoceptor subtype

Nicoletta Galeotti, Alessandro Bartolini, Carla Ghelardini*

Department of Preclinical and Clinical Pharmacology, Viale G. Pieraccini 6, I-50139 Florence, Italy

Abstract

The activation of α_2-adrenoceptors has been reported to impair memory functions in both rats and humans. The α_2-adrenoceptor subtype responsible for this detrimental effect is still unknown. The effect of the α_2-agonists clonidine and guanabenz on memory processes, in dependence to the time of administration, was evaluated in the mouse passive avoidance test. Clonidine (0.02–0.2 mg kg^{-1} i.p.) and guanabenz (0.1–0.3 mg kg^{-1} i.p.) induced amnesia in a dose-dependent manner. From time–course experiments emerged that the impairment of memory function was detectable only when clonidine and guanabenz were administered 60 min before or immediately after the training test, respectively. This detrimental effect was prevented by pretreatment with the α_2-antagonist yohimbine (1–3 mg kg^{-1} i.p.) and by the α_{2A}-antagonist BRL-44408 (0.3–1 mg kg^{-1} i.p.). By contrast, the $\alpha_{2B,C}$ antagonists ARC-239 (10 mg kg^{-1} i.p.) and prazosin (1 mg kg^{-1} i.p.) did not revert the amnesia induced by both clonidine and guanabenz. At the highest effective doses, clonidine and guanabenz were devoid of behavioral side-effects as well as maintained unaltered the motor coordination, as revealed by the rota-rod test. Furthermore, none of the compounds used modified the spontaneous motility as indicated by the Animex apparatus. These results indicate that clonidine and guanabenz impaired memory processes in a mouse passive avoidance paradigm through the selective activation of the α_{2A}-adrenoceptor subtype.
© 2004 Elsevier B.V. All rights reserved.

Keywords: Clonidine; Guanabenz; α_2-Adrenoceptor agonists; α_{2A}-Adrenoceptor subtype; Amnesia; Passive avoidance

1. Introduction

Agonists of α_2-adrenoceptors produce a wide variety of central and peripheral effects. These include an antihypertensive action, alleviation of opiate-withdrawal syndrome, antinociception, cardiovascular control, feeding, and sedation [37]. They have many clinical uses: to lower blood pressure [48], promote anesthesia [30], ameliorate symptoms in neuropsychiatric disorders such as attention deficit hyperactivity disorders [24,43]. This broad range of effects is consistent with the broad projections of the noradrenergic system along the length of the neuroaxis. Subtypes of α_2-adrenoceptors were originally discovered by Bylund [10] and Boyajian and Leslie [8], and later confirmed with the identification of different α_2-adrenoceptor subtypes in humans [31,34,39]. These receptors have distinct pattern in the nervous system: the α_{2A} is widely distributed throughout the nervous system and is localized both pre-

and post-synaptically, with high levels in the cortex and in the locus coeruleus; the α_{2B} is dense in kidney, and mostly localized to the thalamus in brain; the α_{2C} is densest in striatum, but has also been localized in cortex, on locus coeruleus dendrites, and to a small degree on presynaptic terminals in the peripheral nervous system [37].

One aspect of the α_2-adrenoceptor function receiving increasing examination is its role in cognitive functions. Clonidine and other α_2-adrenoceptor agonists have previously been shown to improve spatial working memory in animals that have depleted levels of noradrenaline. In monkeys, a 6-OHDA lesion of the prefrontal cortex, causing significant depletion of both noradrenaline and dopamine, produced a profound impairment on the delayed alternation task [9] that was significantly improved by clonidine administration [3]. Aged monkeys, with naturally occurring catecholamine depletion, are also improved by α_2-adrenoceptor agonist treatment [26,38] as were animals with noradrenaline depletion produced by reserpine [11] or MPTP [44]. Similarly, clonidine improved spatial working memory in aged rats [45] as well as reversed rat working memory deficits induced by the anxiogenic

* Corresponding author. Tel.: +39-055-4271312;
fax: +39-055-4271280.
E-mail address: carla.ghelardini@unifi.it (C. Ghelardini).

drug FG7142 [6]. The clonidine-induced beneficial effect was reversed by the α_2-adrenoceptor antagonist yohimbine [33] further suggesting a role of α_2-adrenoceptors in ameliorating memory functions. Evidence suggests that α_{2A}-adrenoceptors are involved in cognitive enhancement produced by α_2-adrenoceptor agonists in aged monkeys [2]. Recent literature on α_{2A}-adrenoceptor mutant mice further evidence the role of this receptor subtype in working memory performance and in cognitive enhancement produced by α_{2A}-adrenoceptor agonists [15]. In humans, clonidine has been used clinically to treat disorders thought to involve prefrontal cortical dysfunctions, such as mania [21], ADHD [25], and Tourette's syndrome [12]. Clonidine has also been shown to alleviate spatial working memory and attentional set-shifting defect in Parkinson's disease patients [41], to improve prefrontal cortex tasks in patients with Korsakoff's syndrome [35], and schizophrenia [14].

In spite of the fact that there is a large consensus on the ameliorative effect produced by α_2-adrenoceptor agonists on memory functions, there are also some studies indicating the induction of a detrimental effect induced by the above-mentioned compounds on cognitive processes. Clonidine treatment provoked memory disturbances in rats in a step-down [16,17] and shuttle-box [22,32] paradigms. Recent humans studies showed that systemic administration of clonidine disrupted memory accuracy in delayed matching to sample test in Alzheimer's disease patients [42] and disrupted spatial working memory in healthy subjects [27]. The infusion of the α_2-adrenoceptor agonists dexmedetomidine and clonidine impaired memory processes and reduced performance on the digit symbol substitution test in healthy young volunteers [19,20].

Although most research has focused on the ameliorative effect of cognitive processes induced by activation of α_2-adrenoceptors, the induction of a detrimental effect on memory function by α_2-agonists also deserve examination. The aim of the present study was to further elucidate the pharmacological profile of α_2-adrenoceptor agonists in a mouse passive avoidance paradigm in order to investigate their potential amnesic effect in laboratory animals. In particular, our attention was focused on the identification of the α_2-adrenoceptor subtype involved by using selective pharmacological antagonists. Since agonists of α_2-adrenoceptors can induce numerous pharmacological effects such sedation and hypotension [37], in order to exclude that the effects produced by treatments were due to the induction of side effects, some additional behavioral tests (rota-rod, Animex apparatus) were performed.

2. Materials and methods

2.1. Animals

Four-week-old male Swiss albino mice (23–25 g) from the Morini (San Polo d'Enza, Italy) breeding farm were used. Fifteen mice were housed per cage (26 cm × 41 cm). The cages were placed in the experimental room 24 h before the test for acclimatization. The animals were fed a standard laboratory diet and tap water ad libitum and kept at 23 ± 1 °C with a 12-h light/12-h dark cycle, light on at 7.00 a.m. The same mice were not used for different behavioural tests. All experiments were carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

2.2. Passive avoidance test

The test was performed according to the step-through method described by Jarvik and Kopp [28]. The apparatus consisted of a two-compartment acrylic box with a lighted compartment connected to a darkened one by a guillotine door. As soon as the mouse entered the dark compartment, it received a punishing electrical shock (0.5 mA, 1 s). The latency time for entering the dark compartment were measured in the training test and after 24 h in the retention test. The maximum entry latency allowed in the training and retention sessions was 60 and 180 s, respectively. The administration schedule of each drug used is reported in the figure legends. Between 11 and 25 mice per group were tested.

2.3. Rota-rod test

The apparatus consisted of a base platform and a rotating rod with a diameter of 3 cm and a non-slippery surface. The rod was placed at a height of 15 cm from the base. The rod, 30 cm in length, was divided into five equal sections by six disks. Thus, up to five mice were tested simultaneously on the apparatus, with a rod-rotating speed of 16 rpm. The integrity of motor coordination was assessed on the basis of the number of falls from the rod in 30 s according to Vaught et al. [49]. Those mice scoring less than three and more than six falls in the pretest were rejected (20%). The performance time was measured before (pretest) and 15, 30, and 45 min after the beginning of the test. Clonidine and guanabenz were administered 60 and 20 min, respectively, before the test. Twelve to fifteen mice per group were tested.

2.4. Spontaneous activity meter (Animex)

Locomotor activity in mice was quantified using an Animex activity meter type S (LKB, Farad, Sweden) set to maximum sensitivity. Every movement of mice, which were placed on the top of the Animex activity meter, produced a signal due to variation in inductance and capacity of the apparatus resonance circuit. Then signals were automatically converted to numbers. On the day of the experiment the mice were treated and then the cage, containing five mice, was put on the measuring platform. Activity counts were made for 10 min starting 15 min after the beginning of the test. Because of the arbitrary scale adopted to quantify movements, drug-treated mice were always compared with saline-treated ones. The test was performed 60 min after administration of

clonidine, yohimbine, prazosine, and ARC-239, 20 min after administration of guanabenz and 30 min after administration of BRL-44408. Fifteen mice per group were tested.

2.5. Drugs

The following drugs were used: α_2-adrenoceptor agonists: clonidine, guanabenz; α_2-adrenoceptor antagonist: yohimbine; α_{2A}-adrenoceptor antagonist: BRL-44408; $\alpha_{2B,C}$-adrenoceptor antagonists: ARC-239 and prazosin; muscarinic antagonist: scopolamine; nicotinic antagonist: mecamylamine; and GABA$_B$ agonist: baclofen.

Clonidine hydrochloride, guanabenz acetate, prazosin hydrochloride, BRL-44408 (2-(2H-(1-methyl-1,3-dihydro-isoindole)methyl)-4,5-dihydroimidazole), mecamylamine hydrochloride (RBI); yohimbine hydrochloride, scopo-lamine hydrobromide, baclofen (Sigma); ARC-239 ((2-(2-(4-o-methoxyphenyl)-piperazine-1-yl)-ethyl)-4,4-dimethyl-1,3 (2H,4H)-isoquinolinedione) (Neuroscience Institute, Geneva). All drugs were dissolved in isotonic (NaCl 0.9%) saline solution immediately before use. Drug concentrations were prepared in such a way that the necessary dose could be administered in a volume of $10\,ml\,kg^{-1}$ by intraperitoneal injection.

2.6. Statistical analysis

All experimental results are given as the mean ± S.E.M. Student's t-test was used to verify significance between two means. Data were analyzed with the StatView software for the Macintosh (1992). P-values of less than 0.05 were considered significant.
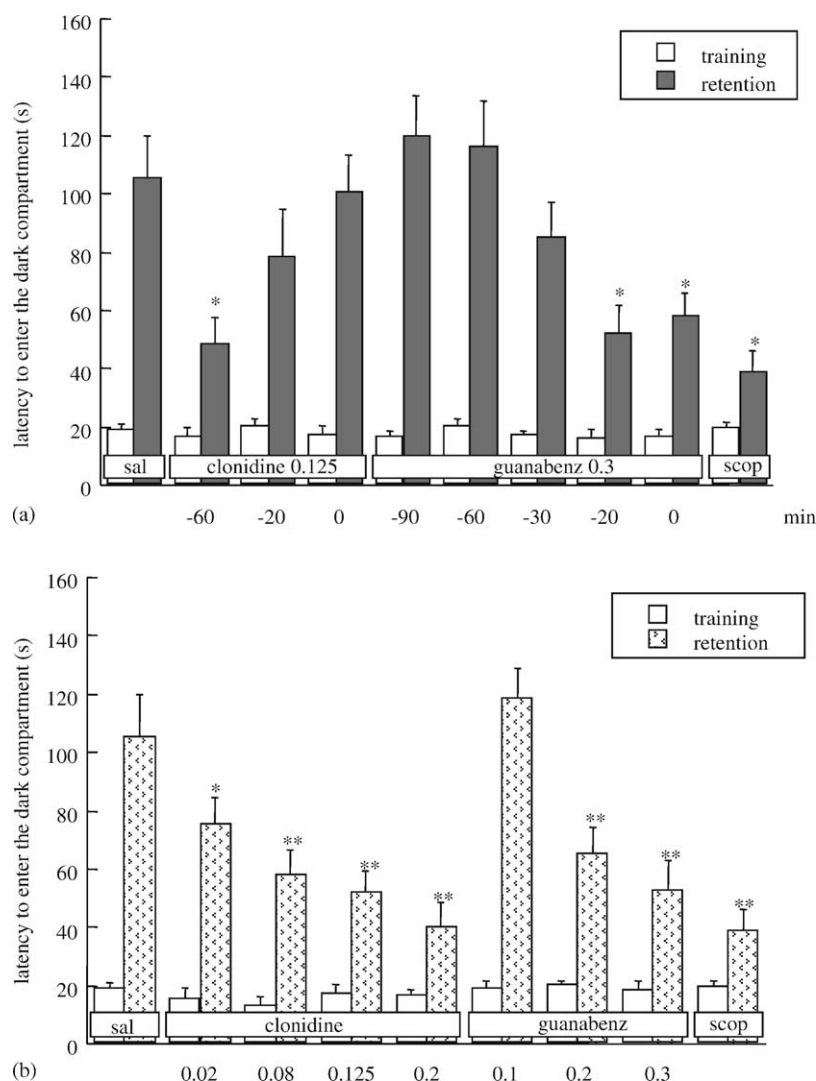

Fig. 1. (a) Time–course curve of clonidine ($0.125\,mg\,kg^{-1}$ i.p.) and guanabenz ($0.3\,mg\,kg^{-1}$ i.p.) in the mouse passive avoidance test. (b) Dose–response curve of clonidine and guanabenz in the mouse passive avoidance test. Clonidine ($0.125\,mg\,kg^{-1}$ i.p.) was injected 60 min before the test; guanabenz ($0.3\,mg\,kg^{-1}$ i.p.) and scopolamine ($1.5\,mg\,kg^{-1}$ i.p.) were administered immediately after the training session. Vertical lines represent S.E.M.; $^* P < 0.05$, $^{**} P < 0.01$ in comparison with saline-treated group (sal).

3. Results

3.1. Amnesic effect of α_2-agonists

Clonidine (0.125 mg kg^{-1} i.p.), administered 60 min before the training session, induced amnesia in the mouse passive avoidance test. A reduction of the entrance latency to the dark compartment was observed also when injected 20 min prior to the test, even if the statistical significance was not reached. By contrast, when administered immediately after the training session, no detrimental effect on mouse memory processes was detected (Fig. 1a). Similarly, guanabenz (0.3 mg kg^{-1} i.p.) induced amnesia in the same experimental conditions. A statistically significant reduction of the entrance latency was reached when administered 20 min before or immediately after the training session, whereas, when injected 90, 60, or 30 min before the first session of the test it was completely ineffective (Fig. 1a). The amnesia induced by both α_2-agonists was of the same intensity of that produced by the well-known amnesic drug scopo-

lamine (1.5 mg kg^{-1} i.p.), used as the reference drug (Fig. 1a and b).

The amnesic effect of clonidine and guanabenz was induced in a dose-dependent manner. The doses of clonidine and guanabenz of 0.002 and 0.1 mg kg^{-1}, respectively, i.p. were devoid of any effect. A statistically significant impairment of mnemonic functions was reached at 0.02 mg kg^{-1} i.p. (clonidine) and 0.2 mg kg^{-1} i.p. (guanabenz), whereas the maximum detrimental effect was obtained by administering the doses of 0.2 mg kg^{-1} i.p. (clonidine) and 0.3 mg kg^{-1} i.p. (guanabenz) (Fig. 1b).

No difference among the entrance latencies of each group in the training session of the passive avoidance test was observed (Fig. 1a and b).

3.2. Prevention by yohimbine and BRL-44408 of α_2-agonist-induced amnesia

The amnesia induced by clonidine (0.125 mg kg^{-1} i.p.) and guanabenz (0.3 mg kg^{-1} i.p.) was dose-dependently
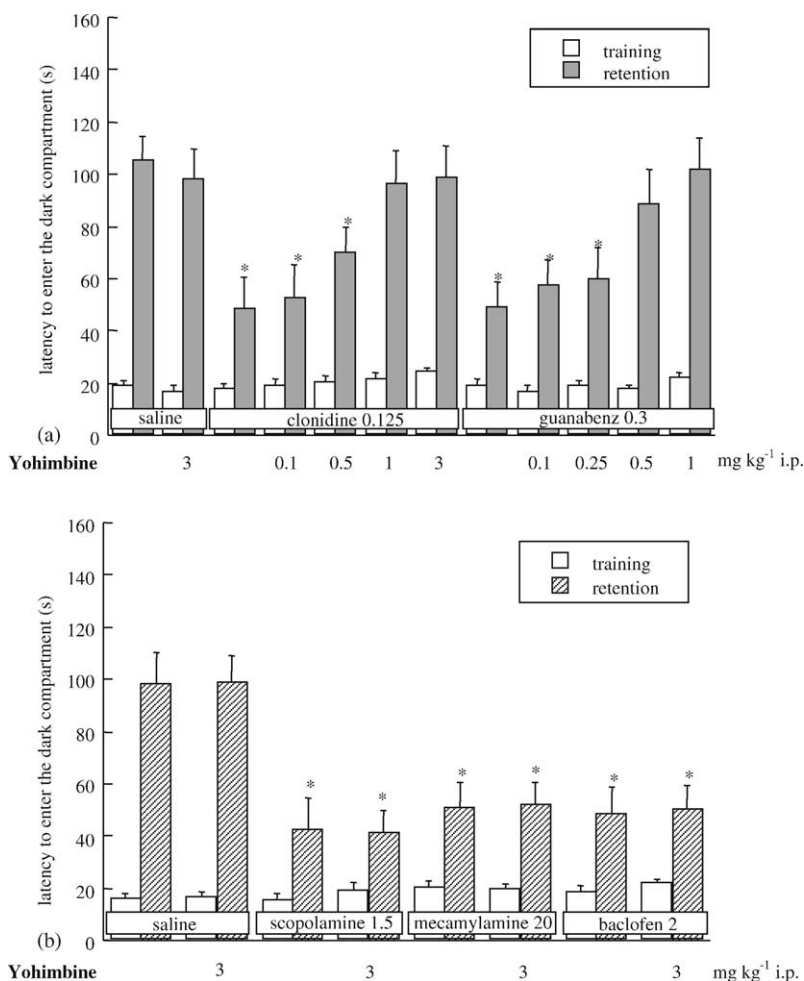
Fig. 2. (a) Prevention by yohimbine (0.1–3 mg kg^{-1} i.p.) of clonidine (0.125 mg kg^{-1} i.p.)- and guanabenz (0.3 mg kg^{-1} i.p.)-induced amnesia in the mouse passive avoidance test. (b) Lack of prevention by yohimbine of amnesia induced by scopolamine (1.5 mg kg^{-1} i.p.), mecamylamine (20 mg kg^{-1} i.p.), and baclofen (2 mg kg^{-1} i.p.) in the mouse passive avoidance test. Clonidine and yohimbine were injected 60 min before the test; guanabenz, scopolamine, mecamylamine, and baclofen were administered immediately after the training session. Vertical lines represent S.E.M.; *$P < 0.05$ in comparison with saline-treated group.

prevented, in the mouse passive avoidance test, by i.p. pre-treatment with the α_2-antagonist yohimbine. The dose of 0.1 and 0.25 mg kg^{-1} were completely ineffective; at 0.5 mg kg^{-1} yohimbine only reverted the guanabenz-induced amnesia, while the doses of 1 and 3 mg kg^{-1} enhanced the entrance latency in the retention session up to a value comparable to that produced by control animals (Fig. 2a). The α_2-antagonist, at the dose of 3 mg kg^{-1}, did not modify the amnesia induced by the muscarinic antagonist scopolamine (1.5 mg kg^{-1} i.p.), the nicotinic antagonist mecamylamine (20 mg kg^{-1} i.p.), and the GABA$_B$ agonist baclofen (2 mg kg^{-1} i.p.), as illustrated in Fig. 2b. Yohimbine, at the highest dose employed, did not produce any effect in the mouse passive avoidance test in comparison with saline-treated mice when given alone (Fig. 2a and b).

The administration of the $\alpha_{2A,C}$-antagonist BRL-44408 (0.3–1 mg kg^{-1} i.p.) antagonized the memory disruption produced by both clonidine and guanabenz without showing any memory facilitating activity when given alone (Fig. 3a). Similarly to yohimbine, BRL-44408 (1 mg kg^{-1} i.p.) was inactive in preventing amnesia induced by scopolamine, mecamylamine, and baclofen (Fig. 3b).

No difference between the entrance latencies of each group in the training session of the passive avoidance test was observed (Figs. 2 and 3).

3.3. Lack of effect by prazosin and ARC-239 of α_2-agonist-induced amnesia

The administration of the $\alpha_{2B,C}$-antagonist ARC-239 (10 mg kg^{-1} i.p.), in contrast to the $\alpha_{2A,C}$-antagonist, was
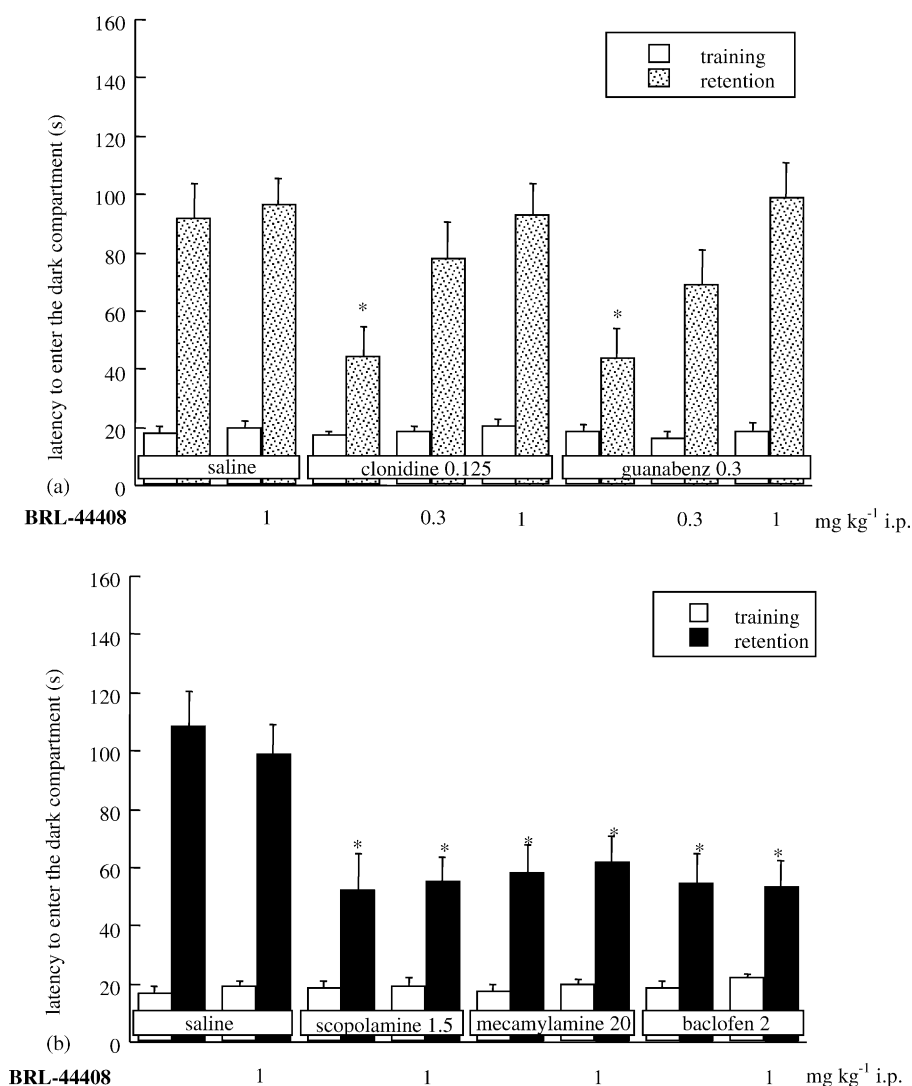

Fig. 3. (a) Prevention by BRL-44408 (0.3–1 mg kg^{-1} i.p.) of clonidine (0.125 mg kg^{-1} i.p.)- and guanabenz (0.3 mg kg^{-1} i.p.)-induced amnesia in the mouse passive avoidance test. (b) Lack of prevention by BRL-44408 of amnesia induced by scopolamine (1.5 mg kg^{-1} i.p.), mecamylamine (20 mg kg^{-1} i.p.), and baclofen (2 mg kg^{-1} i.p.) in the mouse passive avoidance test. Clonidine and BRL-44408 were injected, 60 and 30 min, respectively, before the test; guanabenz, scopolamine, mecamylamine, and baclofen were administered immediately after the training session. Vertical lines represent S.E.M.; $^*P < 0.05$ in comparison with saline-treated group.

Fig. 4. Lack of antagonism by prazosin (1 mg kg^{-1} i.p.) and ARC-239 (10 mg kg^{-1} i.p.) of amnesia induced by clonidine (0.125 mg kg^{-1} i.p.) and guanabenz (0.3 mg kg^{-1} i.p.) in the mouse passive avoidance test. Clonidine, prazosin, and ARC-239 were injected 60 min before the test; guanabenz was administered immediately after the training session. Vertical lines represent S.E.M.; $^*P < 0.05$ in comparison with saline-treated group.
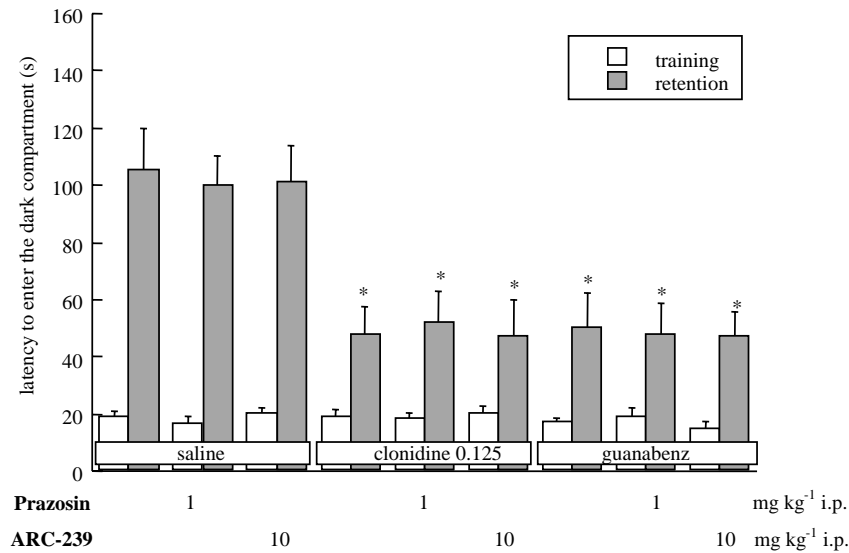
unable to prevent clonidine- and guanabenz-induced amnesia. Similarly, the α_1-antagonist prazosin, administered at the dose of 1 mg kg^{-1} i.p., did not modify the entrance latency of mice in comparison with the α_2-agonist-treated groups (Fig. 4).

3.4. Effect of α-adrenoceptor modulators on mouse behavior

The administration of the α-adrenoceptor modulators used in the present investigation elicited their effect on cognitive processes without changing animals' gross behavior, spontaneous motility or motor coordination. The spontaneous motility of mice, evaluated by means of the Animex apparatus, was not modified by the above-mentioned treatments administered at the highest active doses (Fig. 5).

The rota-rod performance, evaluated as number of falls in 30 s, of mice treated with clonidine at the doses of 0.125 mg kg^{-1} i.p., and guanabenz at the doses of 0.30 mg kg^{-1} i.p., was not impaired in comparison with saline-treated mice, indicating the lack of motor incoordination. On the contrary, clonidine and guanabenz administered
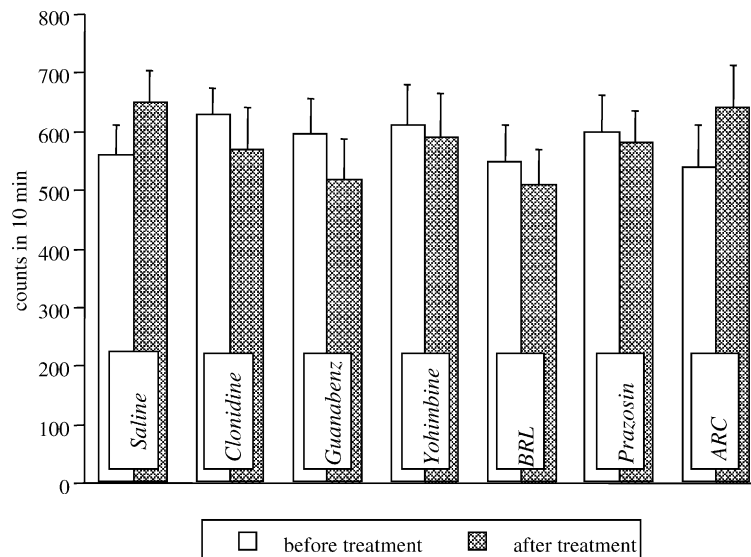

Fig. 5. Lack of alteration of spontaneous motility by clonidine (0.125 mg kg^{-1} i.p.), guanabenz (0.3 mg kg^{-1} i.p.), yohimbine (3 mg kg^{-1} i.p.), BRL-44408 (1 mg kg^{-1} i.p.), prazosin (1 mg kg^{-1} i.p.), and ARC-239 (10 mg kg^{-1} i.p.), evaluated in the mouse Animex apparatus. The test was performed 60 min after administration of clonidine, yohimbine, prazosin, and ARC-239, 30 min after administration of BRL-44408 and 20 min after administration of guanabenz. Vertical lines represent S.E.M.
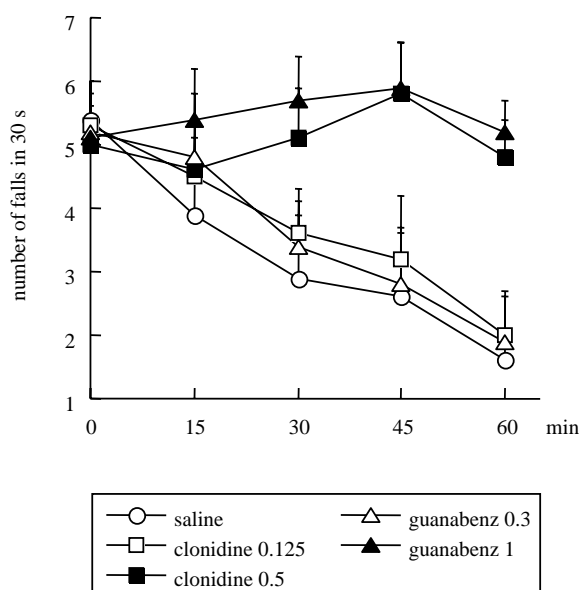
Fig. 6. Effect of clonidine (0.125–0.5 mg kg^{-1} i.p.) and guanabenz (0.3–1 mg kg^{-1} i.p.) on the motor coordination evaluated in the mouse rota-rod test. Clonidine and guanabenz were administered 60 and 20 min, respectively, before the test. Vertical lines represent S.E.M.

at higher doses (0.50 and 1.0 mg kg^{-1} i.p., respectively), produced a significant impairment of the rota-rod performance by increasing the number of falls from the rotating rod. In the control group, the number of falls in the rota-rod test progressively decreased since mice learned how to balance on the rotating rod (Fig. 6).

4. Discussion

The current study examined the effects exerted by activation of α_2-adrenoceptors on memory processes. To this purpose two chemically diverse α_2-adrenoceptor agonists, the imidazoline derivative clonidine and the guanidine derivative guanabenz, were investigated. The results showed that systemic administration of clonidine and guanabenz induced a dose-dependent amnesia in a mouse passive avoidance paradigm of intensity comparable to that exerted by scopolamine, used as reference amnesic drug. Various observations described a detrimental effect on memory processes induced by clonidine in mice [23], rats [17,22,32], and humans [20,27,42]. Data reported in the present study confirm and extend the above-mentioned literature reports, further supporting the hypothesis of a negative role for α_2-adrenoceptors in the modulation of cognitive function.

The impairment of memory processes induced by the investigated α_2-adrenoceptor agonists is time-dependent. Time–course experiments indicated that clonidine-induced amnesia was detectable when the compound was administered 60 min before the training session of the test. Similarly, guanabenz exerted its detrimental effect when administered 20 min before or immediately after the first session of the passive avoidance test. At all other administration times, clonidine and guanabenz were unable to modify the entrance latency values in comparison with the control group. In our experimental conditions, an amelioration of memory processes induced by clonidine and guanabenz was never observed at any administration time. However, it should be taken into account that an improvement in cognition of animals that have no memory impairment is difficult to demonstrate in the passive avoidance test. As a matter of fact, well-known nootropic drugs such as piracetam and aniracetam or cholinomimetics such as physostigmine and oxotremorine, do not show any memory facilitation in unamnesic animals [13,18].

The α_2-antagonist yohimbine reversed the impairment of memory function induced by clonidine and guananbenz, a profile consistent with α_2-adrenoceptors contributing to amnesia. α_2-Adrenoceptors are divided into several subtypes: α_{2A}, α_{2B}, and α_{2C} [37]. The α_{2A}-subtype is the key α_2-adrenoceptor involved in numerous effects produced by α_2-adrenoceptor activation, such as modulation of nociception, cardiovascular function, sedation, lipid metabolism, and release of noradrenaline [29]. The involvement of this receptor subtype in the mechanism of amnesic action of clonidine and guanabenz was, therefore, investigated. The administration of the α_{2A}-adrenoceptor antagonist, BRL-44408 [40], prevented the amnesia induced by clonidine and guanabenz, consistent with actions at α_{2A}-adrenoceptors. The α_2-antagonists used selectively prevented the amnesia induced by α_2-agonists since neither yohimbine nor BRL-44408 were able to reverse the memory impairment induced by the muscarinic antagonist scopolamine, the nicotinic antagonist mecamylamine or the GABA$_B$ agonist baclofen at the highest dose effective against clonidine and guanabenz amnesia. We can, therefore, exclude any unselective effect not related to a α_2-adrenoceptor blockade.

Overexpression of α_{2C}-adrenoceptors impaired navigation in the mouse Morris water maze task [7] suggesting an involvement of the α_{2C}-adrenoceptor subtype in the modulation of memory function. The anatomical distribution of α_{2C}-adrenoceptors (i.e. prefrontal cortex, striatum) suggests their involvement in mediating the effects of α_2-adenoceptors agonists on working memory [1,36]. In our experimental conditions, the $\alpha_{2B,C}$-adrenoceptor antagonists ARC-239 and prazosin [47] were unable to prevent the amnesia induced by clonidine and guanabenz indicating that the adreneceptor subtype responsible for the induction of memory impairment by the α_2-agonists in a passive avoidance paradigm does not belong to the α_{2B} and α_{2C} subtypes. Similar results have been obtained investigating the α_2-adrenoceptor subtype involved in the memory enhancing properties of α_2-adrenoceptor agonists. Experiments performed with mice with inactivation of the α_{2C}-receptor gene indicate that the beneficial effect of α_2-adrenoceptor agonists on spatial working memory is not mediated via α_{2C}-adrenoceptor subtype [46].

The involvement of α_1-adrenoceptors in the modulation of mnemonic functions has also been postulated. Systemic administration of the imidazoline/α_1-adrenoceptor agonist cirazoline impaired delayed response performance in aged monkeys [4]. Furthermore, local infusion of the α_1-adrenoceptor agonists directly into the prefrontal cortex in rats impaired performance on a delayed alternation task [5]. Prazosin is not only a $\alpha_{2B,C}$-adrenoceptor antagonist, but it is also a α_1-adrenoceptor antagonist. The inability of prazosin to reverse the detrimental effect induced by clonidine and guanabenz indicates that not even α_1-adrenoceptors are involved in the mechanism of amnesic action of the two investigated compounds.

Clonidine and guanabenz belong to two different chemical classes. Since both compounds showed a similar pharmacological profile, we can exclude that the induction of amnesia is related to the particular chemical structure of each molecule. It is plausible to suppose that the memory impairment produced by the above-mentioned compounds is dependent to their capability to activate α_2-adrenoceptors.

Agonists of α_2-adrenoceptors induce numerous pharmacological effects, such as sedation and hypotension [37], whose appearance could lead to an alteration of the results obtained. It has been, therefore, necessary to choose a range of doses of clonidine and guanabenz at which these compounds showed amnesic properties without any behavioral side effect. Clonidine and guanabenz, at the highest doses used, did not impair motor coordination as revealed by the rota-rod test, and did not modify spontaneous motility as indicated by the Animex apparatus. The observation that, in the first session of the passive avoidance test, the latency to enter the dark compartment of the light–dark box was not modified by the administration of clonidine and guanabenz further confirms the absence of behavioral side effects. Higher doses of clonidine and guanabenz were not used because they impaired the mouse rota-rod performance. All other α_2-adrenoceptor modulators used were administered at doses that did not modify the animals' spontaneous motility.

In conclusion, our results evidence that the activation of the α_{2A}-adrenoceptor subtype is a requirement for the induction of amnesia by clonidine and guanabenz in the mouse passive avoidance test. Contemporary, the lack of involvement of α_{2B} and α_{2C} subtypes has been observed.

Acknowledgements

References

[1] Aoki C, Go CG, Venkatesan C, Kurose H. Perikaryal and synaptic localization of alpha 2A-adrenergic receptor-like immunoreactivity. Brain Res 1994;650:181–204.

[2] Arnsten AFT, Contant TA. Alpha-2 adrenergic agonists decrease distractibility in aged monkeys performing the delayed response task. Psychopharmacology 1992;108:159–69.

[3] Arnsten AFT, Goldman-Rakic PS. α_2-Adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged human primates. Science 1985;230:1273–6.

[4] Arnsten AFT, Jentesch JD. The alpha-1 adrenergic agonist, cirazoline, impairs spatial working memory performance in aged monkeys. Pharmacol Biochem Behav 1997;58:55–9.

[5] Arnsten AFT, Mathew R, Ubriani R, Taylor JR, Li B-M. Alpha-1 noradrenergic receptor stimulation impairs prefrontal cortical cognitive function. Biol Psychiatry 1999;45:26–31.

[6] Birnbaum SG, Podell DM, Arnsten AFT. Noradrenergic alpha-2 receptor agonists reverse working memory deficits induced by the anxiogenic drug, FG7142, in rats. Pharmacol Biochem Behav 2000;67:397–403.

[7] Björklund M, Sirviö J, Riekkinen M, Sallinen J, Scheinin M, Riekkinen Jr P. Overexpression of alpha 2C-adrenoceptors impairs water maze navigation. Neuroscience 2000;95:481–7.

[8] Boyajian CL, Leslie FM. Pharmacological evidence for α-2 adrenoceptor heterogeneity: differential binding properties of [^{3}H]idazoxan in rat brain. J Pharmacol Exp Ther 1987;241:1092–8.

[9] Brozoski T, Brown RM, Rosvold HE, Goldman PS. Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkeys. Science 1979;205:929–31.

[10] Bylund DB. Heterogenity of α-2 adrenergic receptors. Pharmacol Biochem Behav 1985;22:835–43.

[11] Cai J-X, Ma Y, Xu L, Hu X. Reserpine impairs spatial working memory performance in monkeys: reversal by the α-2-adrenergic agonist clonidine. Brain Res 1993;614:191–6.

[12] Cohen DJ, Detlor J, Young JG, Shaywitz BA. Clonidine ameliorates gille de la tourette syndrome. Arch Gentile Psychiatry 1980;37:1350–7.

[13] Coyle MJ. A cholinergic hypothesis for Alzheimer's disease. In: Meyer L, Nordeberg GH, editors. Learning and memory molecular bases. London: Pergamon Press; 1995. p. 11–32.

[14] Fields RB, Van Kammen DP, Peters JL, Rosen J, Van Kammen WB, Nugent A, et al. Clonidine improves memory function in schizophrenia independently from change in psychosis. Schiz Res 1988;1:417–23.

[15] Franowicz JS, Kessler LE, Borja CM, Kobilka BK, Limbird LE, Arnsten AF. Mutation of the alpha2A-adrenoceptor impairs working memory performance and annuls cognitive enhancement by guanfacine. J Neurosci 2002;22:8771–7.

[16] Genkova-Papazova M, Lazarova-Bakarova M. Influence of nootropic drugs on the memory-impairing effect of diethyldithiocarbamate and clonidine in "step-down" passive avoidance in albino rats. Acta Physiol Pharmacol Bulg 1988;14:36–41.

[17] Genkova-Papazova M, Petkova-Petkova B, Lazarova-Bakarova M, Boyanova E, Staneva-Stoytcheva D. Effects of flunarizine and nitrendipine on electroconvulsive shock- and clonidine-induced amnesia. Pharmacol Biochem Behav 1997;56:583–7.

[18] Gouliaev AH, Senning A. Piracetam and other structurally related nootropics. Brain Res Rev 1994;19:180–222.

[19] Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmetedomidine infusions. Anesth Analg 2000;90:699–705.

[20] Hall JE, Uhrich TD, Ebert TJ. Sedative, analgesic and cognitive effects of clonidine infusions in humans. Br J Anasth 2001;86:5–11.

[21] Hardy M-C, Lecrubier Y, Widlocher D. Efficacy of clonidine in 24 patients with acute mania. Am J Psychiatry 1986;143:1450–3.

[22] Hawkins M, Monti JM. Effects of pretreatment with 6-hydroxydopamine or noradrenergic receptor blockers on the clonidine-induced disruption of conditioned avoidance responding. Eur J Pharmacol 1979;58:53–8.

[23] Homayoun H, Khavandgar S, Zarrindast MR. Morphine state-dependent learning: interaction with α_2-adrenoceptors and acute stress. Behav Pharmacol 2003;14:41–8.

[24] Horrigan JP, Barnhill LJ. Guanfacine for treatment of attention-deficit hyperactivity disorder in boys. J Child Adolesc Psychopharmacol 1995;5:215–23.

[25] Hunt RD, Mindera RB, Cohen DJ. Clonidine benefits children with ADD and hyperactivity: report of a double-blind placebo-crossover therapeutic trial. J Am Acad Child Psychiatry 1985;24:617–29.

[26] Jackson WJ, Buccafusco JJ. Clonidine enhances delayed matching-to-sample performance by young and aged monkeys. Pharmacol Biochem Behav 1991;39:79–84.

[27] Jäkälä P, Riekkinen M, Sirvio J, Koivisto E, Kejonen K, Vanhanen M, et al. Guanfacine, but not clonidine, improves planning and working memory performance in humans. Neuropsychopharmacology 1999;20:460–70.

[28] Jarvik ME, Kopp R. An improved one-trial passive avoidance learning situation. Psychol Rep 1967;21:221–4.

[29] Kable JW, Murrin LC, Bylund DB. In vivo gene modification elucidates subtype-specific functions of the alpha-2 adrenergic receptors. J Pharmacol Exp Ther 2000;293:1–7.

[30] Khan ZP, Ferguson CN, Jones RM. α-2 and imidazoline receptor agonists: their pharmacological and therapeutical role. Anaesthesia 1999;54:146–65.

[31] Kobilka BK, Matsui H, Kobilka TS, Yang-Feng TL, Francke U, Caron MG, et al. Cloning, sequenceing, and expression of the gene coding for the human platelet α-2 adrenergic receptor. Science 1987;238:650–6.

[32] Kostowski W, Plaznik A, Pucilowski A. Effect of chronic clonidine treatment and lesion of the locus coeruleus on the conditioned avoidance behavior in rats. Pl J Pharmacol Pharm 1980;32:305–12.

[33] Li B-M, Mao Z-M, Wang M, Mei Z-T. Alpha-2 adrenergic modulation of prefrontal cortical neuronal activity related to spatial working memory in monkeys. Neuropsychopharmacology 1999;21:601–10.

[34] Lomasney JW, Lorenz W, Allen LF, King K, Regan JW, Yang-Feng TL, et al. Expansion of the a-2-adrenergic receptor family: cloning and characterization of a human α-2-adrenergic receptor subtype, the gene for which is located on chromosome 2. Proc Natl Acad Sci USA 1990;87:5094–8.

[35] Mair RG, McEntee WJ. Cognitive enhancement in Korsakoff's psychosis by clonidine: a comparison with L-DOPA and ephedrine. Psychopharmacology 1986;88:374–80.

[36] MacDonald E, Scheinin M. Distribution and pharmacology of α_2-adrenoceptors in the central nervous system. J Physiol Pharmacol 1995;46:241–58.

[37] McDonald E, Kobilka BK, Scheinin M. Gene targeting—homing in on α_2-adrenoceptor-subtype function. Trends Pharmacol Sci 1997;18:211–9.

[38] Rama P, Linnanskoski I, Tanila H, Pertovaara A, Carlson S. Metedotimine, atipamezole, and guanfacine in delayed response performance of aged monkeys. Pharmacol Biochem Behav 1996;55:415–22.

[39] Regan JW, Kobilka TS, Yang-Feng TL, Caron MG, Lefkowitz RJ, Kobilka BK. Cloning and expression of human kidney cDNA for and a-2-adrenergic receptor subtype. Proc Natl Acad Sci USA 1988;85:6301–5.

[40] Renouard A, Widdowson PS, Millan MJ. Multiple alpha-2 adrenergic receptor subtypes. I. Comparison of [^{3}H]-RX821002-labeled rat $R_{alpha-2A}$ adrenergic receptors in cerebral cortex to human $H_{alpha-2A}$ adrenergic receptor and other populations of alpha-2 adrenergic subtypes. J Pharmacol Exp Ther 1994;270:946–57.

[41] Riekkinen M, Jäkälä P, Kejonen K, Riekkinen Jr P. The alpha-2 agonist, clonidine, improves spatial working memory performance in Parkinson's disease. Neuroscience 1999;92:983–9.

[42] Riekkinen M, Laakso MP, Jäkälä P. Clonidine impairs sustained attention and memory in Alzheimer's disease. Neuroscience 1999;92:975–82.

[43] Scahill L, Chappell PB, Kim YS, Schultz RT, Katsovich L, Shepherd E, et al. Guanfacine in the treatment of children with tic disorders and ADHD: a placebo-controlled study. Am J Psychiatry 2001;158:1067–74.

[44] Schneider JS, Kovelowski CJ. Chronic exposure to low doses of MPTP, I: Cognitive deficits in motor asymptomatic monkeys. Brain Res 1990;519:122–8.

[45] Tanila H, Rama P, Carlson S. The effects of prefrontal intracortical microinjections of an α-2 agonist α-2 antagonist and lidocaine on the delayed alternation performance of aged rats. Brain Res Bull 1996;40:117–9.

[46] Tanila H, Mustonen K, Sallinen J, Scheinin M, Riekkinn Jr P. Role of α_{2C}-adrenoceptor subtype in spatial working memory as revealed by mice with targeted disruption of the α_{2C}-adrenoceptor gene. Eur J Neurosci 1999;11:599–603.

[47] Uhlén S, Xia Y, Chhajlani V, Felder CC, Wikberg JES. [^{3}H]-MK 912 binding delineates two α_2-adrenoceptor subtypes in rat CNS one of which is identical with the cloned pA2d α_2-adrenoceptor. Br J Pharmacol 1992;106:986–95.

[48] van Zwieten PA. Centrally acting antihypertensive drugs. Present and future. Clin Exp Hypertens 1999;21:859–73.

[49] Vaught J, Pelley K, Costa LG, Sether P, Enna SJ. A comparison of the antinociceptive responses to GABA-receptor agonists THIP and baclofen. Neuropharmacology 1985;24:211–6.