ELSEVIER

Pharmacology, Biochemistry and Behavior 70 (2001) 427–436

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Dissociable effects of histamine H1 antagonists on reaction-time performance in rats

Arjan Blokland*, Bart Scholtissen, Annemiek Vermeeren, Jan Ramaekers

Maastricht Brain and Behaviour Institute, Faculty of Psychology, Section Neurocognition, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands

Received 11 May 2001; received in revised form 24 July 2001; accepted 25 July 2001

Abstract

The most pronounced side effect of antiallergic histaminergic drugs (H1 antagonists) is sedation. These effects have been linked with the effects of histaminergic drugs on central H1 receptors. In the present study, we investigated the dose–response relationship of different antihistamines on the performance in a reaction-time task that has been developed for rats. The dose–response relationship of diphenhydramine, cetirizine and terfenadine were examined for the various behavioural measures in this task (i.e., reaction time, motor time, premature responses and number of trials completed). In addition, the effects of scopolamine were assessed to evaluate the cholinergic profile in this task. Diphenhydramine did not reliably affect the reaction time, but increased the motor time and the proportion of premature responses, and decreased the number of trials completed in a session. A low dose of cetirizine decreased the reaction time, whereas an increase in reaction time was found for the high dose. The motor time was increased after both doses of cetirizine. Terfenadine did not affect the responding of rats in the reaction-time task at the doses tested. The effects of scopolamine were very similar to those of diphenhydramine. The reaction-time task used in this study was able to dissociate different types of antihistamines on aspects of psychomotor function, which were likely to be related to central muscarinic or H1 antagonism. These findings suggest that the reaction-time task may be a sensitive tool for assessing effects of drugs on psychomotor function.

Keywords: Histamine; Scopolamine; Reaction time; Side effect; Psychomotor function; Sedation

1. Introduction

Although the role of histamine as a neurotransmitter in the central nervous system has been known for a long time, its role in behaviour has received minor attention. Histaminergic neurons project from the tuberomammillary nuclei to various regions of the brain, including the cerebral cortex. Indeed, different studies have indicated that histaminergic drugs affect several aspects of cognitive functioning (see Passani et al., 2000; White and Rumbold, 1988).

It has been suggested that the histamine 1 receptor (H1) is involved in arousal mechanisms (e.g., Lin et al., 1996; Schwartz et al., 1979; White and Rumbold, 1988). It may, therefore, not be surprising that the sedative effects of antiallergic drugs have been linked to the blockade of central H1 receptors (Kay, 2000). Second-generation antihistamines cross the blood–brain barrier less readily and are less sedative when compared with first-generation antihistamines. Moreover, the latter have been found also to have cholinergic, adrenergic and serotonergic properties (Simons, 1994).

Previous studies evaluating the sedative effects of antihistamines in animals predominantly measured changes in motor behaviour, EEG recordings and drug interactions. In the present study, we evaluated the effects of histamine H1 antagonist in a choice reaction-time paradigm in rats in which rats are required to react to a stimulus (Amalric and Koob, 1987; Blokland, 1998; Döbrössy and Dunnett, 1997). This test is very similar to reaction-time tasks used in human studies (Houx and Jolles, 1993), and has been shown as a useful tool to assess side effects of histaminergic drugs in man.

Four main response variables can be distinguished in the reaction-time task for rats that allow dissociating different aspects of behaviour. Reaction time predominantly measures the speed of information processing and response

* Corresponding author. Tel.: +31-43-388-1903; fax: +31-43-388-4125.

E-mail address: a.blokland@psychology.unimaas.nl (A. Blokland).

0091-3057/01/$ – see front matter
PII: S0091-3057(01)00627-X

initiation of a rat to a stimulus, whereas the motor time predominantly reflects sensorimotor function. In addition, the number of responses emitted before the imperative stimulus could be regarded as an index of response inhibition/impulsivity. Finally, the number of trials completed provides an index of food motivation.

The aim of the present study was to evaluate whether the reaction-time task for rats was able to show effects of H1 antagonists. In addition, it was assessed whether the effects of different H1 antagonists could be dissociated based on their ability to cross the blood–brain barrier (first- and second-generation antihistamines). We selected the classical antihistamine diphenhydramine because of its well-known sedative and anticholinergic properties. On basis of these data, it was expected that diphenhydramine should have clear sedative effects. On the other hand, second-generation H1 antihistamines should not affect reaction-time responding because they do not affect central H1 receptors (Rombaut and Hindmarch, 1994). To evaluate the cholinergic profile, we also assessed the effects of scopolamine in this task.

2. Materials and methods

2.1. Animals

The study was approved by the Local Ethical Committee of the Maastricht University (The Netherlands). Twenty-two male Lewis rats (250–300 g at the start of the experiments) were used. They were housed individually in standard Makrolon (Type III) cages and had ad-libitum access to water and food. During the behavioural testing, the rats were given 12-g laboratory chow per day in order to reduce their weight to 85% of their free feeding weight.

2.2. Apparatus

The rats were tested in six identical operant chambers (inner dimensions $40 \times 30 \times 33$ cm) that were equipped with two retractable levers, and cue lights just above the levers. A food tray (5×5 cm and 2.5 cm above the grid floor), which was positioned equidistant between the two levers, could be accessed by pushing a hinged panel. The levers (4 cm wide) projected 2 cm into the conditioning chamber, and were located 6 cm from both sides of the food tray and 12 cm above the grid floor. A house light and a loudspeaker were fixed in the ceiling of the conditioning chamber. The operanda and manipulanda in the chambers were controlled by a personal computer and the data were stored on disk at the end of a session. The accuracy of the sampling of the events in the Skinner boxes was 1 ms.

2.3. Behavioural procedures

After the rats were food deprived, the rats were trained to perform the choice reaction-time task (Blokland, 1998). In this task (see Fig. 1), a rat had to poke its nose into the central panel and keep its nose until a tone was switched on. This was either a high tone (10 kHz, 80 dB), which predicted insertion of the left lever, or a low tone (2.5 kHz, 80 dB), which predicted the insertion of the right lever. The tone was switched off immediately after the rat released the hinged panel. The variable period (randomly chosen from 0.6 to 1.5 s, steps of 0.1 s) between nose poke and tone was called the hold duration. When a rat did not succeed in pushing the panel for the entire hold duration, the same interval was started again upon pushing the panel. The intertrial interval was 10 s. Fifty percent of the responses were reinforced. This was done to increase the vigour of the animals (cf. Blokland, 1998). The reinforcement (45 mg food pellet, Bioserve), which was given upon pressing the lever, was given independent of the reaction time. A session lasted 30 min or when a rat had completed 60 trials. Pretraining was completed when the rats showed a stable performance with respect to the variable reaction time and premature responses. After the rats showed a stable performance for 1 week in the operant task, the effects of the drugs were examined.

2.4. Behavioural measures

2.4.1. Reaction time

The mean latency between the onset of the tone and the release of the panel was taken as the reaction time. It is generally accepted that response latencies shorter than 100 ms are unlikely to be true reaction times but should be considered as nonvalid responses. On the other hand, response latencies longer than 1500 ms should not be considered as a task-related reaction time. In addition, the mean reaction time per hold duration was calculated.

2.4.2. Motor time

The mean latency between the release of the panel and the lever press was taken as the motor time. It was assumed that motor times longer than 2 s did not reflect ‘true’ motor time.

2.4.3. Premature responses

The total number of times the rat released the panel before the hold duration had elapsed. It should be noted that after a premature response the rats had to start the same trial again by pushing the hinged panel. Thus, premature responses were independent of nonvalid trials.

2.4.4. Nonvalid trials

These were the total number of trials in which the reaction times were either shorter than 100 ms or longer than 1500 ms. These responses were made after the tone was presented and, therefore, do not include premature responses.

2.4.5. Number of trials

These were the total number of trials the rats completed in a session of 30 min, maximum of 60.

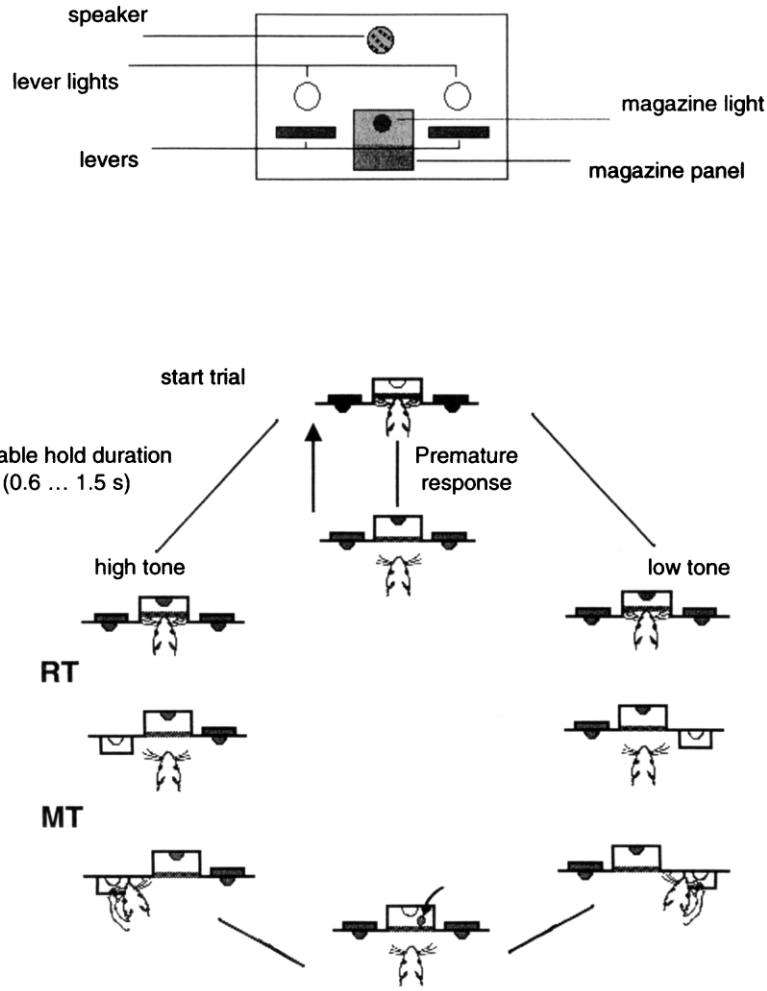

Fig. 1. Schematic illustration of the series of contingencies at the stages in the reaction-time task.

2.5. Drug testing

For drug testing, the group of animals was divided into two equal groups of 11 rats. The effects of diphenhydramine (Sigma; 0, 10, 30 mg/kg) and terfenadine (Sigma; 0, 0.1, 0.3, 1 mg/kg) were tested in one group, and the effects of cetirizine (Salsbury Chemicals, USA; 0, 3, 10 mg/kg) and scopolamine (Sigma; 0, 0.1, 0.3, 1 mg/kg) were tested in the other group. Except for terfenadine, which was dissolved in 2.5% dimethylacetamide in polyethylene glycol (PEG300), all drugs were dissolved in saline. Each dose was tested twice and the order of dose was chosen randomly. Drug sessions took place on each Monday, Wednesday and Friday, whereas on each Tuesday and Thursday the rats were not injected before behavioral testing. The drugs were injected in a volume of 2 ml/kg ip 30 min before behavioural testing started. First, the effects of diphenhydramine and cetirizine were tested in the two separate groups ($n = 11$ for each group). After the effects of these drugs were tested, the rats were given three drug-free sessions in which the rats showed a performance comparable to the predrug performance. Subsequently, the effects of terfenadine and scopolamine were assessed in the same two groups ($n = 11$ for each group). Since the vehicle of terfenadine was different from saline, it was tested whether the performance after the vehicle deviated from that of the saline sessions of the same rats in the diphenhydramine sessions. It appeared that the performance in both testing conditions were not different and were therefore pooled.

2.6. Statistical analyses

Since the rats did not always complete the maximum number of trials in a session of 30 min, the results of the premature responses were analysed on the proportion of responses. All data were statistically analysed using a general linear model procedure using a within-subjects design (factor dose as repeated measures). For the analysis of the mean reaction time per hold duration, the mean reaction time of two successive intervals was calculated. The mean reaction time per hold duration was tested using a general linear model procedure with dose and hold duration as repeated measures. A pairwise post hoc test (LSD test, α=.05) was used to evaluate the dose effects in more detail. The within-subjects analysis that was used does not neces-

sarily depend on the within-group variance (reflected as the S.E.M. in figures). Although the within-group variance at a given dose may be high, the within-subjects variance can be low. Thus, apparent overlapping S.E.M.s could sometimes reveal a statistical reliable effect when the within-subject variation between two dose conditions is low. Only differences from vehicle are reported. The relation between mean reaction time and proportion premature responses was evaluated using the Pearson correlation coefficient.

3. Results

3.1. Diphenhydramine

Although the medium dose of diphenhydramine appeared to increase the mean reaction time, this was not confirmed statistically, $F(2,20) = 1.75$, n.s. (see Fig. 2A). Post hoc test did not reveal differences between the vehicle and other doses. Also, the mean reaction time per hold duration analysis did not reveal treatment effects, dose: $F(2,20) = 1.21$, n.s.; Dose × Hold duration: $F(8,80) = 0.50$, n.s. (see Fig. 2B). Analysis of the mean motor time indicated that there was a clear increase in the time needed to press the lever after the rats had retracted their nose from the food tray, $F(2,20) = 11.48$, $P < .01$ (see Fig. 2C). Post hoc analysis revealed that the mean motor time was higher after both doses of diphenhydramine when compared to vehicle. There was a dose-dependent increase in the proportion of premature responses, $F(2,20) = 3.88$, $P < .05$ (see Fig. 2D), which was mainly due to the effects of the highest dose (post hoc analysis). Although the repeated measures analysis did not reveal a treatment effect for the number of trials completed in a session of 30 min, $F(2,20) = 2.49$, n.s.

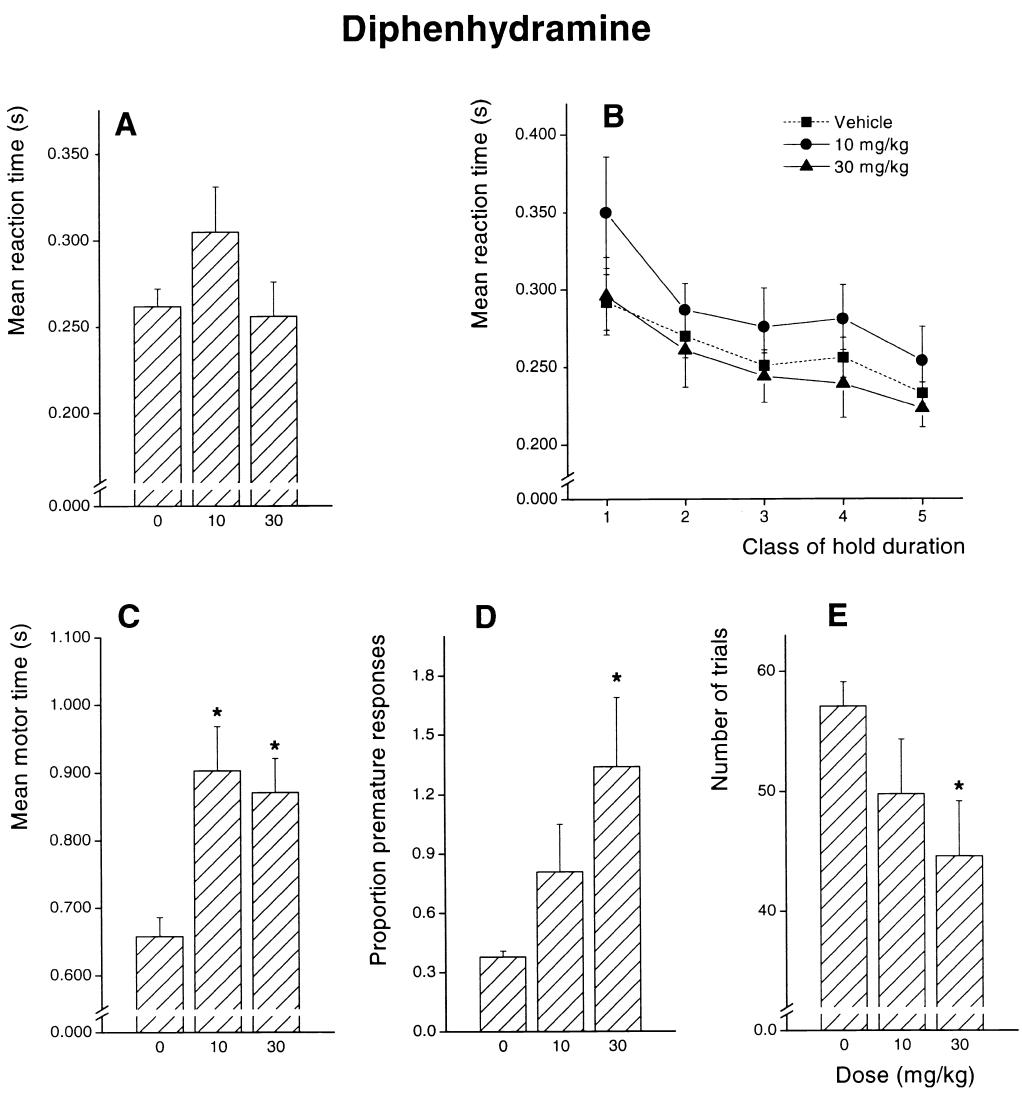

Fig. 2. Effects of diphenhydramine (0, 10, 30 mg/kg ip) on the performance in a reaction-time task in rats. (A) Mean reaction time, (B) mean motor time, (C) proportion of premature responses, (D) total number of trials completed in a session, (E) mean reaction time per class of hold duration (Class 1 corresponds with the hold duration of 0.6 and 0.7 s; Class 5 with 1.4 and 1.5 s). Data represent mean(+S.E.M.) of two sessions in each dose condition. * $P < .05$.

(see Fig. 2E), post hoc analysis indicated that the number of trials was lower in rats given the high dose compared to the vehicle condition.

3.2. Cetirizine

As can be seen from Fig. 3A, the low dose of cetirizine decreased the mean reaction time whereas the high dose increased the reaction time of the rats, $F(2,20)=11.41$, $P<.01$; post hoc test. This effect was also found for the mean reaction time per hold duration, $F(2,20)=11.87$, $P<.01$ (see Fig. 3B), although the Dose × Hold duration effect, $F(8,80)=2.24$, $P<.05$, indicated that the mean reaction time was more affected at the short hold durations for the high dose of cetirizine. The mean motor time of the rats was increased after both doses of cetirizine, $F(2,20)=3.59$, $P<.05$ (see Fig. 3C). Cetirizine affected the proportion of premature responses, $F(2,20)=6.36$, $P<.05$ (see Fig. 3D). Fig. 3D may give the impression that the proportion of premature responses was increased after administration of the low dose of cetirizine. However, post hoc analysis only revealed a marginal effect of the low dose when compared to the vehicle ($P<.07$). Although the repeated measures analysis revealed a treatment effect for cetirizine on the number of completed trials, $F(2,20)=4.17$, $P<.05$ (see Fig. 3E), post hoc analysis showed no differences between the dose and vehicle conditions.

3.3. Terfenadine

The statistical analysis revealed a clear dose effect of terfenadine on the mean reaction time, $F(3,30)=6.47$,

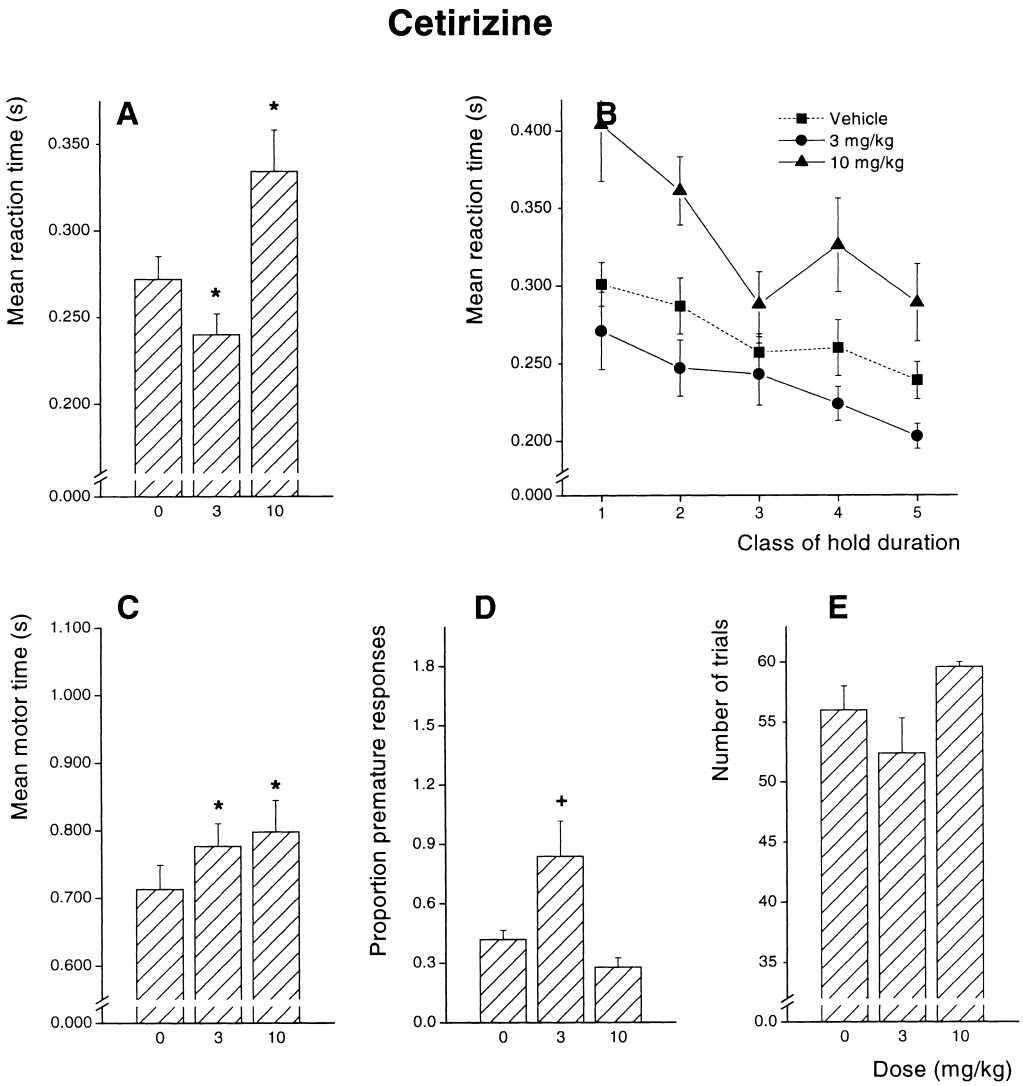

Fig. 3. Effects of cetirizine (0, 3, 10 mg/kg ip) on the performance in a reaction-time task in rats. (A) Mean reaction time, (B) mean motor time, (C) proportion of premature responses, (D) total number of trials completed in a session, (E) mean reaction time per class of hold duration (Class 1 corresponds with the hold duration of 0.6 and 0.7 s; Class 5 with 1.4 and 1.5 s). Data represent mean (+S.E.M.) of two sessions in each dose condition. $^{+}$ $.05<P<.10$; * $P<.05$.

$P < .01$ (see Fig. 4A). Examination of the within-subjects contrasts showed that the effects were mostly determined by a cubic component, which can also be seen from Fig. 4A. Post hoc analysis indicated that the rats responded faster after administration of the highest dose. Analysis of the mean reaction time per hold duration also showed effects of dose, $F(3,30) = 6.52$, $P < .01$ (see Fig. 4B), but no interaction with hold duration, Dose × Hold duration $F(12,120) = 0.89$, n.s.. The effects of terfenadine on motor time revealed a dose effect, $F(3,30) = 6.47$, $P < .01$ (see Fig. 4C), which was predominantly due to an effect on the cubic within-subjects contrast. Post hoc analysis did not show differences between the different doses and the vehicle condition. The proportion of premature responses was not affected by terfenadine, $F(3,30) = 1.66$, n.s. (see Fig. 4D), although the post hoc test indicated that the at the highest dose the rats made less premature responses. No effects of terfenadine were found on the measure number of trials, $F(3,30) = 0.59$, n.s. (see Fig. 4E).

3.4. Scopolamine

One rat made insufficient trials (< 20) in the sessions in which a dose of 1 mg/kg was administered. Since we used a repeated measure analysis, the data of this rat were excluded from the analysis.

Treatment with scopolamine affected the mean reaction time, $F(3,27) = 3.79$, $P < .05$ (see Fig. 5A). Post hoc analysis showed that only the reaction time after the highest dose was faster when compared with the vehicle condition. Scopolamine (1 mg/kg) also decreased the mean reaction time per hold duration, dose: $F(3,27) = 2.97$, $P < .05$ (see Fig. 5B),

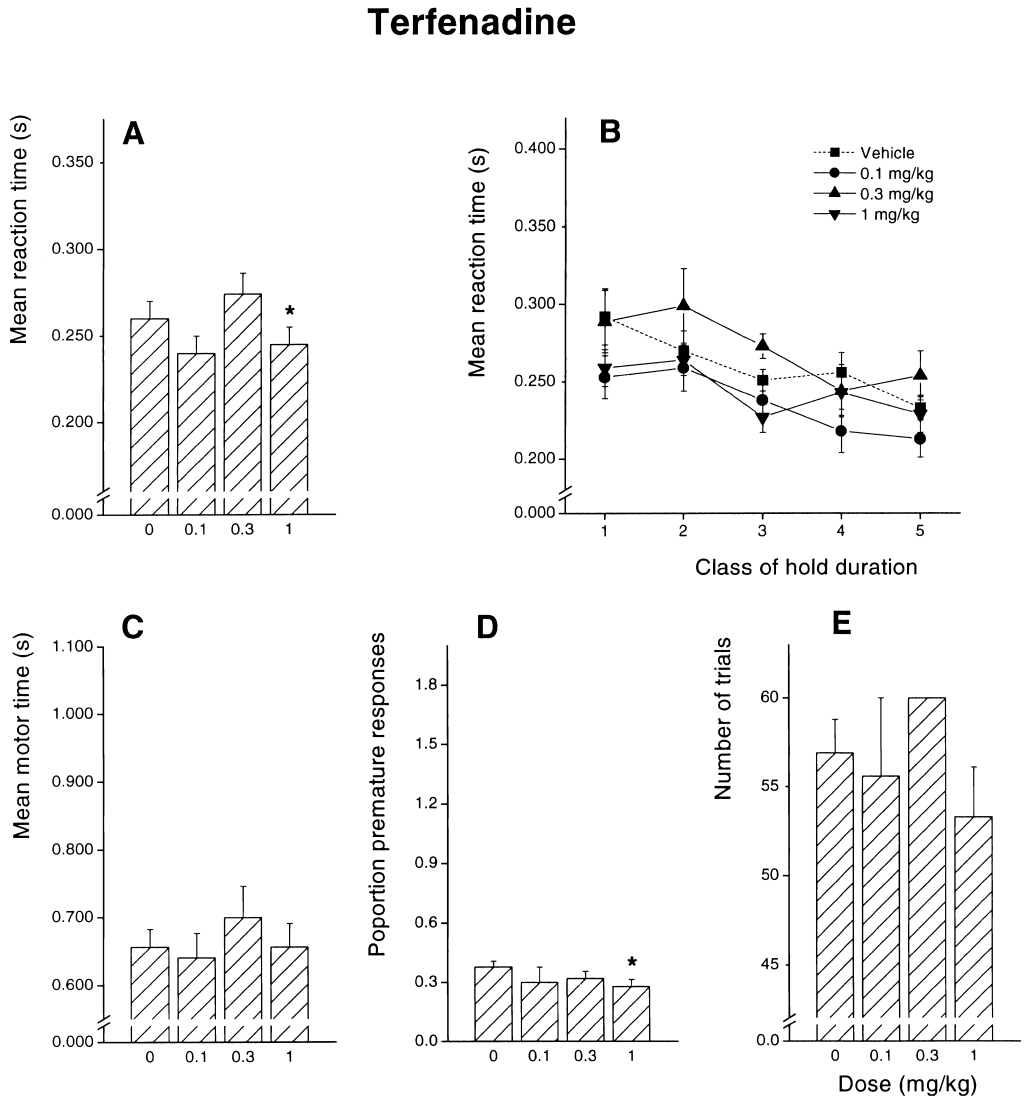

Fig. 4. Effects of terfenadine (0, 0.1, 0.3, 1 mg/kg ip) on the performance in a reaction-time task in rats. (A) Mean reaction time, (B) mean motor time, (C) proportion of premature responses, (D) total number of trials completed in a session, (E) mean reaction time per class of hold duration (Class 1 corresponds with the hold duration of 0.6 and 0.7 s; Class 5 with 1.4 and 1.5 s). Data represent mean(+S.E.M.) of two sessions in each dose condition. * $P < .05$

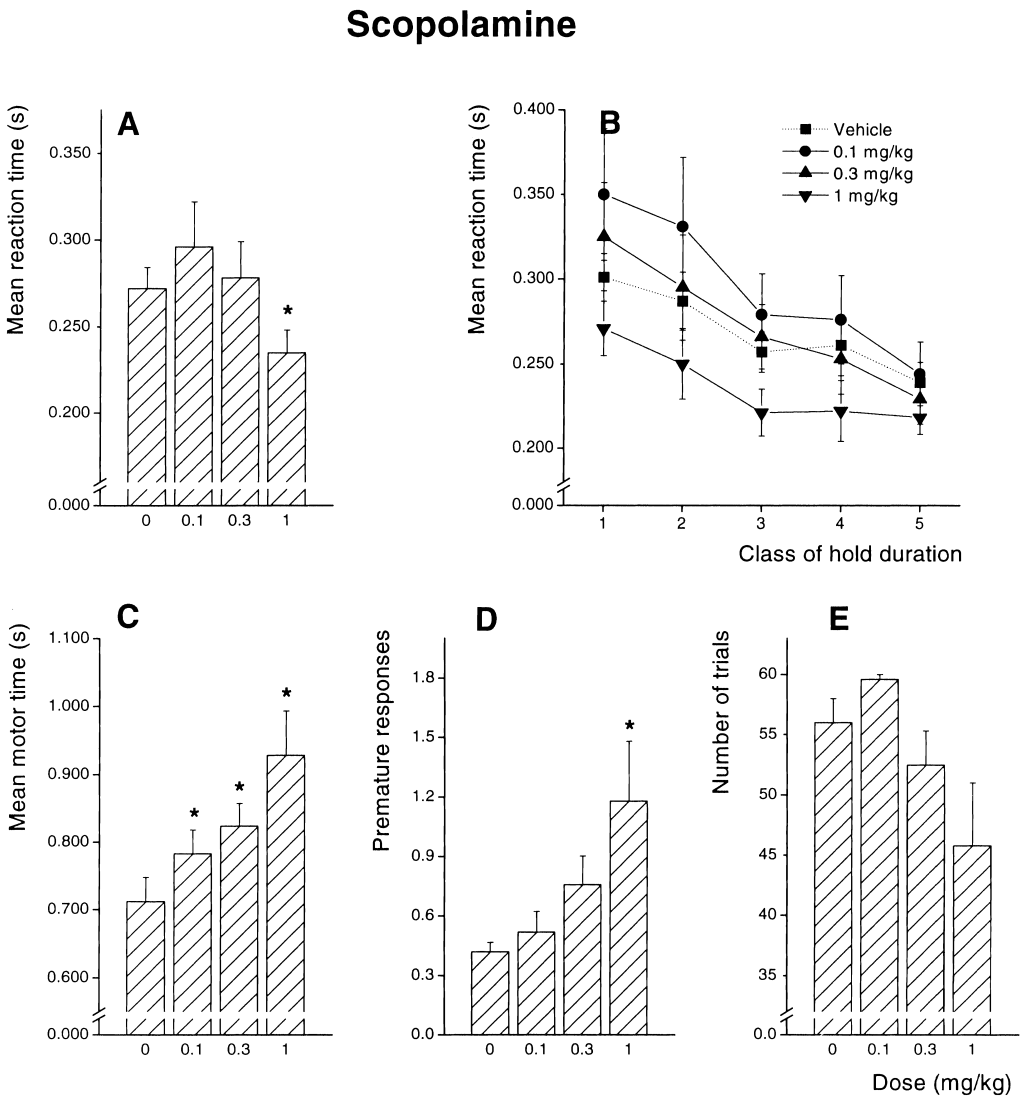

Fig. 5. Effects of scopolamine (0, 0.1, 0.3, 1 mg/kg ip) on the performance in a reaction-time task in rats. (A) Mean reaction time, (B) mean motor time, (C) proportion of premature responses, (D) total number of trials completed in a session, (E) mean reaction time per class of hold duration (Class 1 corresponds with the hold duration of 0.6 and 0.7 s; Class 5 with 1.4 and 1.5 s). Data represent mean(+S.E.M.) of two sessions in each dose condition. * $P<.05$.

while the effect was independent of the hold duration, Dose × Hold duration: $F(12,108)=1.15$, n.s.. There was a clear dose-dependent effect of scopolamine on the mean motor time, $F(3,27)=12.03$, $P<.01$ (see Fig. 5C). Post hoc test showed that the mean motor time was slower at all doses tested. A similar dose-dependent increase was found for the measure premature responses, $F(3,27)=5.04$, $P<.01$ (see Fig. 5D), although the post hoc test indicated that only the highest dose increased this responding. The number of trials completed was affected by scopolamine, $F(3,27)=5.11$, $P<.01$ (see Fig. 5E), although the post hoc analysis did not reveal differences between the different doses and vehicle (vehicle vs. 1.0 mg/kg, $P<.07$). However, it should be noted that one animal did not complete sufficient trials in the 1-mg/kg condition, indicating that the present mean value of number of completed trials is an underestimation.

3.5. Relation between reaction time and premature responses

For each drug, the correlation between the mean reaction time and proportion premature responses was calculated for each dose and drug separately (see Fig. 6). This analysis only revealed a positive relation between these measures for the highest dose of terfenadine ($r=.66$, $P<.05$). No other correlations were observed (r's $<.52$, n.s.). Evaluation of correlations per drug (all doses)

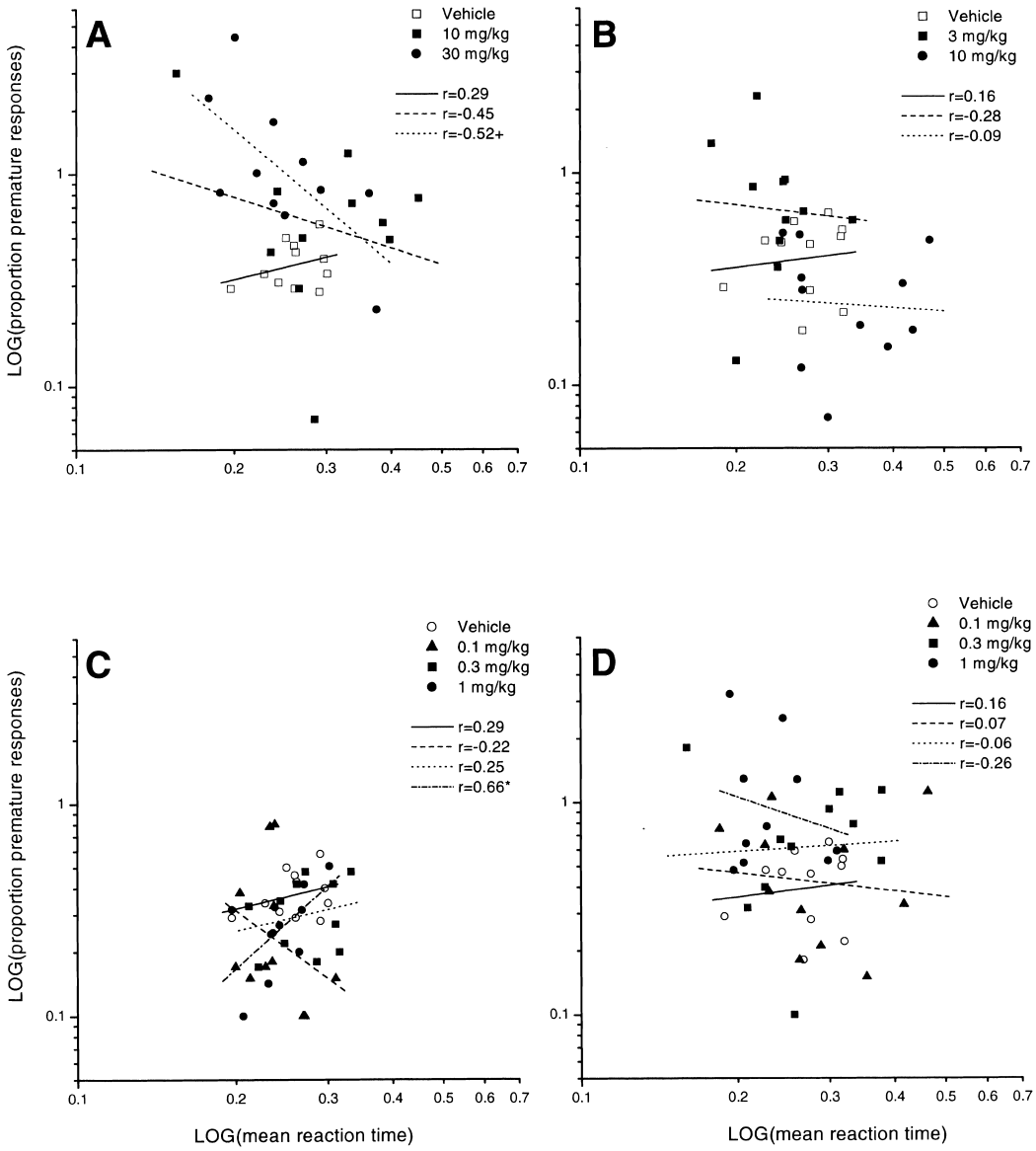

Fig. 6. Correlations between log(mean reaction time) and log(proportion premature responses) of individual rats performing a reaction-time task. (A) Diphenhydramine, (B) cetirizine, (C) terfenadine, (D) scopolamine. Lines represent the linear fit of the respective data points. Order of lines (i.e., top to bottom) corresponds with the order of doses applied. $^{+}$ $.05 < P < .10$; * $P < .05$.

revealed weak negative correlations for diphenhydramine and cetirizine ($r = -.39$ and $-.36$, P's $< .05$), but not for terfenadine and scopolamine (r's $< .19$, n.s.).

4. Discussion

In the present study, we evaluated the effects of different antihistamines on the choice reaction-time performance of rats. It appeared that the three antihistamines had different effects in this task (see Table 1). Diphenhydramine, a first-generation antihistamine, did not affect the reaction time of rats but had a clear effect on the mean motor time. This finding suggests that diphenhydramine does not affect the speed of information processing and response initiation but predominantly affects (sensori)motor functions. In contrast, cetirizine affected the reaction time more readily than the mean motor time, suggesting a greater effect on the speed of

Table 1
Overview of the effects of the different drugs on different measures in the reaction-time task in rats

	Reaction time	Motor time	Premature responding	Trials
Diphenhydramine	=	++	++	+
Cetirizine	++	+	+	=
Terfenadine	=	=	=	=
Scopolamine	+	+	+	=/+[a]

=: no effect,+: effect.

[a] One animal did not complete sufficient trials after administration with the highest dose of scopolamine and was not included in the analysis.

information processing or motor initiation than on the execution of a motor response. The other second-generation antihistamine terfenadine did not have clear effects on the reaction-time performance of the rats at the doses tested, at least, when compared with diphenhydramine and cetirizine.

The other measures of reaction-time responding indicated that diphenhydramine increased the proportion of premature responses, whereas the number of completed trials in a session was decreased. Previously, it has been reported that diphenhydramine increased the rate of responding in a fixed-interval task in monkeys (McKearney, 1982). Our finding that diphenhydramine increased the proportion of premature responses is in line with such a finding. On the other hand, diphenhydramine did not affect responding of rats in a DRL 72-s schedule of reinforcement (O'Donnell and Seiden, 1983). This apparent opposite effect could be related to the different response rates in both tasks resulting in opposite drug effects. After administration with a low dose of cetirizine, the proportion of premature responses was (marginally) increased but returned to baseline values after administration of the highest dose of cetirizine. The number of trials was not affected by cetirizine treatment. Terfenadine treatment did not affect the performance on these measures. Thus, also on these measures, the different antihistamines seemed to have different effects.

Second-generation antihistamines are claimed to cross the blood–brain barrier less readily and to have less negative side effects in man. Nevertheless, it has been argued that even second-generation antihistamines cross the blood–brain barrier and therefore may lead to sedation at higher doses (Mann et al., 2000; Ramaekers and Vermeeren, 2000). In the present study, we observed a specific effect of cetirizine on the reaction time that is likely to reflect a central effect, i.e., central H1 antagonism. In humans, therapeutic doses of cetirizine also have been found to impair a number of psychomotor functions (Hindmarch and Shamsi, 1999; Ramaekers et al., 1992). On the other hand, terfenadine has not been reported to have sedative effects at therapeutic doses. Our findings are in line with these observations.

The reaction-time task for rats has predominantly been used to investigate the functions of the basal ganglia and the effects of dopaminergic (DA) drugs on movement initiation (e.g., Amalric and Koob, 1987; Amalric et al., 1995; Baunez et al., 1995; Blokland, 1998). These studies clearly showed that DA antagonism (mainly by the D2 receptor, see Smith et al., 2000) impairs response initiation in rats. Central administration with histamine has been found to increase the DA release in the nucleus accumbens, which was reversible after administration with a H1 antagonist (Fleckenstein et al., 1993). Consequently, it could be argued that the effects of H1 antagonist in the present task could be mediated via DA mechanisms.

In this study, we also tested scopolamine to examine the cholinergic profile of this task. This was done since diphenhydramine also acts as a muscarinic antagonist (Kubo et al., 1987). The effects of scopolamine and diphenhydramine on the different behavioural measures were very similar providing further support for the notion that diphenhydramine exert its effects also via muscarinic antagonism. On the other hand, cetirizine, which is a more specific H1 antagonist, had a different behavioural profile when compared with scopolamine and diphenhydramine. Since affinity of diphenhydramine to H1 and muscarinic receptors is comparable, this strongly suggests that the cholinergic effects on the reaction-time responding can be observed at a lower threshold than the H1 antagonism.

In a previous study, it has been shown that intrastriatal scopolamine injections reduce the number of trials completed and increased the number of premature responses (Blokland and Honig, 1999). These effects are comparable with the effects of peripheral applied scopolamine in the present study. It is likely that the effects on the number of trials and premature responses are mediated by striatal mechanisms. In contrast, the effects of peripheral scopolamine on motor time and reaction time appear to be mediated by other brain structures.

The effects of diphenhydramine and scopolamine have directly been compared on the cognitive performance in man (Curran et al., 1998). It was shown that both drugs impaired arousal-related processes, e.g., early event-related potential components in a recognition task and critical flicker fusion threshold. On the other hand, in contrast to scopolamine, diphenhydramine did not affect episodic memory performance. Such a difference would suggest a different effect of both substances on the cholinergic system, i.e., diphenhydramine did not affect the cholinergic system in such a manner to affect memory performance.

Inspection of the different figures suggests that there is an inverse relation between the proportion premature responses and the mean reaction time. Such a relation has previously been indicated in a study in which the effects of amphetamine were assessed in the same task (Blokland, 1998). Thus, if rats make more premature responses, the chance that the retraction of the nose coincides with the end of the hold duration increases, leading to a faster mean reaction time. However, the data obtained with scopolamine argue against such a simple explanation since there was no inverse dose–response relationship between the mean reaction time and proportion premature responses. Although the present data do not support such a relation, it is assumed both measures are negatively correlated if the number of premature responses exceeds a certain threshold (cf., high dose of amphetamine; Blokland, 1998).

In conclusion, the reaction-time task used in the present study revealed typical behavioural effects of three different antihistamines. The present findings corroborate data obtained in human studies indicating that diphenhydramine is a sedative drug and ceterizine affects aspects of information processing or motor initiation. Terfenadine did not have adverse effects at the doses tested. This suggests that the

reaction-time paradigm used can be a useful tool to examine effects of drugs on different aspects of psychomotor function.

Acknowledgments

The research of AB has been made possible by a fellowship of the Royal Netherlands Academy of Arts and Sciences.

References

Amalric M, Koob GF. Depletion of dopamine in the caudate nucleus but not in nucleus accumbens impairs reaction-time performance in rats. J Neurosci 1987;7:2129–34.

Amalric M, Moukhles H, Nieoullon A, Daszuta A. Complex deficits on reaction time performance following bilateral intrastriatal 6-OHDA infusion in the rat. Eur J Neurosci 1995;7:972–80.

Baunez C, Nieoullon A, Amalric M. In a rat model of parkinsonism, lesions of the subthalamic nucleus reverse increases of reaction time but induce a dramatic premature responding deficit. J Neurosci 1995;15:6531–41.

Blokland A. Reaction time responding in rats. Neurosci Biobehav Rev 1998;22:847–64.

Blokland A, Honig W. Intra-striatal haloperidol and scopolamine injections: effects on choice reaction time performance in rats. Eur Neuropsychopharmacol 1999;9:223–32.

Curran HV, Pooviboonsuk P, Dalton JA, Lader MH. Differentiating the effects of centrally acting drugs on arousal and memory: an event-related potential study of scopolamine, lorazepam and diphenhydramine. Psychopharmacology 1998;135:27–36.

Döbrössy MD, Dunnett SB. Unilateral striatal lesions impair response execution on a lateralised choice reaction time task. Behav Brain Res 1997;87:159–71.

Fleckenstein AE, Lookingland KJ, Moore KE. Activation of mesolimbic dopaminergic neurons following central administration of histamine is mediated by H1 receptors. Naunyn-Schmiedeberg's Arch Pharmacol 1993;347:50–4.

Hindmarch I, Shamsi Z. Antihistamines: models to assess sedative properties, assessment of sedation, safety and other side-effects. Clin Exp Allergy 1999;29(Suppl 3):133–42.

Houx PJ, Jolles J. Age-related decline of psychomotor speed: effects of age, brain health, sex, and education. Percept Motor Skills 1993;76:195–211.

Kay GG. The effects of antihistamines on cognition and performance. J Allergy Clin Immunol 2000;105:S622–7.

Kubo N, Shirakawa O, Kuno T, Tanaka C. Antimuscarinic effects of antihistamines: quantitative evaluation by receptor-binding assay. Jpn J Pharmacol 1987;43:277–82.

Lin JS, Hou Y, Sakai K, Jouvet M. Histaminergic descending inputs to the mesopontine tegmentum and their role in the control of cortical activation and wakefulness in the cat. J Neurosci 1996;16:1523–37.

Mann RD, Pearce GL, Dunn N, Shakir S. Sedation with "non-sedating" antihistamines: four prescription-event monitoring studies in general practice. BMJ 2000;320:1184–6 (see comments).

McKearney JW. Stimulant actions of histamine H1 antagonists on operant behavior in the squirrel monkey. Psychopharmacology 1982;77:156–8.

O'Donnell JM, Seiden LS. Differential-reinforcement-of-low-rate 72-second schedule: selective effects of antidepressant drugs. J Pharmacol Exp Ther 1983;224:80–8.

Passani MB, Bacciottini L, Mannaioni PF, Blandina P. Central histaminergic system and cognition. Neurosci Biobehav Rev 2000;24:107–13.

Ramaekers J, Vermeeren A. All antihistamines cross blood–brain barrier. BMJ 2000;321:572.

Ramaekers JG, Uiterwijk MM, O'Hanlon JF. Effects of loratadine and cetirizine on actual driving and psychometric test performance, and EEG during driving. Eur J Clin Pharmacol 1992;42:363–369.

Rombaut NEI, Hindmarch I. Psychometric aspects of antihistamines: a review. Hum Psychopharmacol 1994;9:157–69.

Schwartz JC, Barbin G, Baudry M, Garbarg M, Martres MP, Pollard H, Verdiere M. Metabolism and functions of histamine in the brain. Curr Dev Psychopharmacol 1979;5:173–261.

Simons FE. H1-receptor antagonists. Comparative tolerability and safety. Drug Saf 1994;10:350–80.

Smith AD, Smith DL, Zigmond MJ, Amalric M, Koob GF. Differential effects of dopamine receptor subtype blockade on performance of rats in a reaction-time paradigm. Psychopharmacology 2000;148:355–60.

White JM, Rumbold GR. Behavioural effects of histamine and its antagonists: a review. Psychopharmacology 1988;95:1–14.