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Acute and chronic treatment with 5–HT reuptake inhibitors differentially modulate emotional responses in anxiety models in rodents

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Abstract. This study investigated behavioural effects of very potent 5–HT reuptake inhibitors after acute treatment (cianopramine and citalopram), as well as after chronic treatment (cianopramine), in two behavioural models of anxiety: 1) the light/dark choice procedure in mice and 2) the elevated plus-maze test in rats. In addition, the responses of mice to novelty in a free exploration paradigm were assessed after acute administration of both drugs. A single injection of cianopramine or citalopram increased neophobic reactions in the free exploration test. Furthermore, these drugs increased the avoidance reaction to a brightly illuminated chamber in the light/dark choice procedure as well as to open arms in the elevated plus-maze test. In contrast, after chronic treatment (10 mg/kg IP, once daily for 21 days) of cianopramine, anxiogenic-like effects were no longer produced in the light/dark choice paradigm whereas in the elevated plus-maze test, anxiolytic-like effects appeared. These results shed more light on the 5–HT hypothesis of anxiety, insofar as the increased availability of 5–HT resulting here from reuptake inhibition seems to initially result in an increased emotional reactivity which, however, subsequently disappears during chronic treatment.

Key words: Cianopramine – Citalopram – 5–HT reuptake inhibitors –Light/dark choice procedure – Elevated plus-maze test – Anxiety – Neophobia – Acute and chronic treatments

Serotonin (5–HT) reuptake blockers constitute a novel class of psychoactive drugs for which the clinical efficacy in depressive disorders is now well established (Åsberg et al. 1986). There is also growing evidence for possible beneficial therapeutic effects in other psychiatric disorders, such as obsessive-compulsive disorder (Insel et al. 1985; Goodmann et al. 1986), panic disorder (Westenberg and den Boer 1988) and social phobia (Westenberg 1992). However, several studies reported intriguing observations early in treatment (Saletu and Grünberger 1985; Gorman et al. 1987; Van Praag 1988; Westenberg and den Boer 1988; Humble et al. 1989; Giesecke 1990; Montgomery 1991; Westenberg 1992). These authors noted activating effects at the beginning of treatment with a 5–HT reuptake blocker, described as racing thoughts, anxiety, nervousness, tremor, insomnia, jitteriness, emotional discomfort and agitation; this effect disappeared with subsequent treatment. It is hypothesized that the acute increased availability of 5–HT resulting from reuptake inhibition would initially produce anxiogenic-like effects until adaptive changes of the 5–HT receptors occurred, thereby eliminating such effects (Westenberg and den Boer 1988).

Acute administration of established antidepressants in animals has been reported to produce anxiogenic-like effects in some studies (File 1985; Linnoila et al. 1987; Bodnoff et al. 1989; Handley and McBlane 1992) and no specific effects in others (Chopin and Briley 1987), or has even elicited anxiolytic-like responses (Handley and McBlane 1992). In addition, they have been found to produce anxiolytic-like effects following repeated administration (Bodnoff et al. 1988, 1989; Fontana et al. 1989; Cadogan et al. 1992).

The present experiments address this issue by assessing the role of two potent 5–HT reuptake inhibitors, cianopramine (a dibenzapine derivative) (Da Prada et al. 1982) and citalopram (a bicyclic phthalane derivative) (Hyttel 1977) in regulating emotional responses in rodent models of anxiety. Their effects were evaluated using the light/dark choice procedure in mice and the elevated plus-maze test in rats. In these paradigms, several benzodiazepines and non-benzodiazepine anxiolytics have been shown to reduce anxiety-like responses towards aversive stimuli (Belzung et al. 1987; Treit 1991; Griebel et al. 1992), while benzodiazepine receptor inverse agonists and direct 5–HT receptor agonists potentiated these responses (Belzung et al. 1987; Pellow et al. 1987; Griebel et al. 1990, 1991). Both drugs were given acutely (cianopramine and citalopram) in one experiment and

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cianopramine was administered chronically in another experiment. In addition, a free-exploration test was used to evaluate neophobia in mice after acute treatment with cianopramine and citalopram. In this procedure, psychostimulant drugs (Misslin and Ropartz 1981), as well as some 5–HT receptor agonists (Griebel et al. 1990, 1991), have previously been shown to enhance neophobia. Finally, the motor impairing effects of cianopramine and citalopram were evaluated on mice using a locomotor activity test and forced motor performance tests.

Materials and methods

Animals

Male Swiss albino mice (Ibm: MoRo), 10 weeks old at time of testing, were used in the free exploration test, in the light/dark choice procedure, in the animal activity monitor and in the forced motor performance tests. In the elevated plus-maze test, male Wistar rats (Ibm: RoRo) weighing 110–200 g at time of testing were used. All animals were housed in groups of five and maintained under standard laboratory conditions (21–23° C, relative humidity 55%) with free access to food and water. They were kept on a 12:12-h light – dark cycle with light onset at 6 p.m. and 6 a.m. for mice and rats, respectively. Animals were bred and provided by Biological Research Laboratories (Füllinsdorf, 4414, Switzerland).

Drugs

Cianopramine and citalopram (Hoffmann-La Roche, Basel, Switzerland) were dissolved in physiological saline and administered intraperitoneally in a volume of 10 ml/kg and 5 ml/kg body weight in mice and rats, respectively. In acute treatments, drugs were injected 30 min before testing was begun.

Experiment 1: effects of a single acute injection of cianopramine and citalopram in a locomotor activity test and in forced motor performance tests in mice

Locomotor activity. The apparatus (Model RXYZCM(16); Omnitech Electronics, Inc.) consisted of a polyvinylchloride box (20 × 20 × 30 cm) equipped with sensors for monitoring horizontal and vertical activity.

The subjects were individually tested under red light in 10-min sessions in the apparatus described above. All mice were initially placed in the centre of the area at the start of the test session. Total distance (cm) travelled (indicator of ambulatory activity), movement time (seconds spent ambulating) and the number of rearing movements were recorded. Mice were randomly allocated to the experimental groups: a) cianopramine experiment: vehicle control (saline; $n = 16$) and drug (1, 3.2, 10 and 30 mg/kg in saline; $n = 8$ per dose); b) citalopram experiment: vehicle control (saline; $n = 16$) and drug (1, 3.2, 10, 30 mg/kg in saline; $n = 8$ per dose). Testing was carried out between 2 p.m. and 5 p.m.

Forced motor performance in the rotarod and the horizontal wire tests. The rotarod test (ROT) situation consisted of placing the mice on a horizontal metal rod (3 cm in diameter, 27 cm high) rotating twice per minute. Six individual stations on the rod were separated by Plexiglas walls. The horizontal wire test (HWT) consisted of individually taking mice by the tail and allow them to grasp a horizontally strung wire (20 cm above the bench level, 1 mm in diameter, 15 cm long) with their forepaws.

Animals were allowed to become familiarized with the ROT test situation until they remained on the rod for 2 consecutive minutes within a period of 5 min. At different times after drug administration, animals were placed on the rotarod and inability to remain on the rod for 1 min was scored as a sign for sedative/myorelaxant activity.

In the HWT, a training trial was also performed before injection to allow the mice to become familiarized with the test situation. At different times after drug administration, the animals were tested again for HWT performance directly after ROT testing; inability to grasp the wire with the forepaws or inability to actively grasp, the wire within 3 s with at least one hindpaw is used as a criterion for sedative and/or myorelaxant effects of the substance. Groups of six mice were used to evaluated each dose over time at 2, 5, 10, 15, 30, 45, 60 and 120 min following injection. Doses of 1, 3.2, 10 and 32 mg/kg IP were tested for cianopramine and citalopram. ED_{50} values were calculated by probit analysis for each time point.

Experiment 2: effects of a single acute injections of cianopramine and citalopram in the free exploration test in mice

Apparatus. The apparatus consisted of a polyvinylchloride box (30 × 20 × 20 cm) covered with Plexiglas and subdivided into six equal square exploratory units, which were all interconnected by small doors. It could be divided in half lengthwise by closing three temporary partitions.

Procedure. Approximately 24 h before testing, each subject was placed in one half of the apparatus with the temporary partitions in place, in order to be familiarized with it. The floor of this half was covered with sawdust and the animal was given unlimited access to food and water. Next day, the subject was exposed to both familar and novel compartments by removal of the temporary partitions. It was then observed, under red light, for 10 min via a closed circuit TV camera by an observer located in an adjacent room. The time spent in the novel half (novelty preference), the number of units entered (locomotion) and the number of rears made by the animals were recorded. Mice were randomly allocated into the following groups: a) cianopramine experiment: vehicle control (saline; $n = 10$) and drug (1, 3.2, 10, 30 mg/kg in saline; $n = 10$ per group); b) citalopram experiment: vehicle control (saline; $n = 10$) and drug (3.2, 10, 30 mg/kg in saline; $n = 10$ per group). Testing was carried out between 2 p.m. and 5 p.m.

Experiment 3: effects of acute treatment of cianopramine and citalopram in the light/dark test in mice and the elevated plus-maze test in rats

Light/dark test. The apparatus consisted of two polyvinylchloride boxes (20 × 20 × 14 cm) covered with Plexiglas. One of these boxes was darkened. A light from a 100 W desk lamp, 25 cm above the other box, and four neon tubes fixed on the ceiling provided the room illumination. The light intensity on the centre of the illuminated box was 4400 lux. An opaque plastic tunnel (5 × 7 × 10 cm) separated the dark box from the illuminated one.

The subjects were individually tested in 5-min sessions in the apparatus described above. The floor of each box was cleaned between test sessions. Testing was performed between 2 p.m. and 5 p.m. At the start of the test session, mice were placed in the tunnel facing the dark box. The amount of time spent by mice in the lit box (TLB) and the number of transitions through the tunnel were recorded over a 5-min period via a closed circuit TV camera by an observer located in an adjacent room, after the first entry in the dark box. A mouse whose four paws were in the new box was considered as having changed boxes. Mice were randomly divided into the following groups: a) cianopramine experiment: vehicle control (saline; $n = 30$) and drug (0.32, 1, 3.2, 10 mg/kg in saline; $n = 15$ per dose); b) citalopram experiment: vehicle control (saline; $n = 34$) and

drug (0.32 mg/kg; $n=14$; 1 mg/kg; $n=13$; 3.2 mg/kg; $n=15$; 10 mg/kg; $n=18$ and 30 mg/kg in saline; $n=15$).

Elevated plus-maze test. All parts of the apparatus were made of grey polyvinylchloride plastic. It consisted of a maze elevated to a height of 50 cm with two open (50 × 10 cm) and two enclosed arms (50 × 10 × 50 cm), arranged so that the arms of the same type were opposite each other, connected by an open central area (10 × 10 cm).

The rats were placed in the centre of the maze and observed for 5 min via a closed circuit TV camera by an observer located in an adjacent room. The illumination in the experimental room consisted of four neon tubes fixed on the ceiling. The light intensity on the central platform was 225 lux. The time spent in open arms, the number of open-arm entries, the number of closed-arm entries (defined as entry of all four limbs into an arm of the maze), and the number of attempts towards open arms followed by avoidance responses during the observation period was recorded and the maze was thoroughly cleaned after removal of each rat. The results were expressed as mean ratio of open arm to total arm entries, mean ratio of time spent in open arms to total time for individual rats, mean total number of entries made by the rats, and mean total of attempts. Testing was carried out between 8 a.m. and 12 a.m. Rats were randomly divided into the following groups: a) cianopramine experiment: vehicle control (saline; $n=20$) and drug (0.32 mg/kg; $n=8$; 1 mg/kg; $n=10$; 3.2 mg/kg; $n=9$ and 10 mg/kg in saline; $n=8$); b) citalopram experiment: vehicle control (saline; $n=17$) and drug (3.2 mg/kg; $n=8$; 10 mg/kg; $n=9$ and 30 mg/kg in saline; $n=8$).

Experiment 4: effects of chronic treatment of cianopramine in the light/dark choice procedure in mice and the elevated plus-maze test in rats

Light/dark choice paradigm. Mice were assigned randomly to treatment with either saline ($n=13$; group A) or cianopramine 10 mg/kg ($n=15$; group B) for 20 days administered once daily. The 10 mg/kg dose of cianopramine was choosen because experiment 3 revealed that this dose produced reliable anxiogenic-like effects. Twenty four hours after the last injection, and 30 min before testing was carried out, group A were challenged with an acute saline dose and group B with an acute cianopramine dose (10 mg/kg) (for more details, see experiment 3).

Elevated plus-maze test. Rats were assigned randomly to treatment with either saline ($n=10$; group C) or cianopramine 10 mg/kg ($n=9$; group D) for 20 days administered once daily. The 10 mg/kg dose of cianopramine was choosen because experiment 3 revealed that this dose produced reliable anxiogenic-like effects. Twenty four hours after the last injection, and 30 min before testing was carried out, group C were challenged with an acute saline dose and group D with an acute cianopramine dose (10 mg/kg) (for more details, see experiment 3).

Statistical analysis

Data from the locomotor activity test, in experiment 1, as well as results from experiments 2 and 3 were analysed by a combined analysis of variance and a Bonferroni's a posteriori t-test (this test was used because variances are not assumed to be equal). In experiment 4 data were analysed by an unpaired t-test.

Results

Experiment 1: effects of a single injection of cianopramine and citalopram in the locomotor activity test and forced motor performance tests in mice

Locomotor activity test. Analysis of variance revealed significant differences among the groups with respect to the movement time [cianopramine: $F(4,43)=8.04$, $P<0.0001$; citalopram: $F(4,43)=4.81$, $P<0.002$], total distance [cianopramine: $F(4,43)=5.68$, $P<0.0009$; citalopram: $F(4,43)=4.49$, $P<0.004$] and rearings [cianopramine: $F(4,43)=10.89$, $P<0.0001$; citalopram: $F(4,43)=3.43$; $P<0.01$]. Figure 1 shows that cianopramine induced an increase in the movement time at 10 mg/kg and a decrease of all behavioural parameters at the highest dose tested (30 mg/kg). Citalopram significantly enhanced all these parameters at 10 mg/kg.

Forced motor performance tests. No significant effects in the rotarod and horizontal wire tests were observed up to 30 mg/kg citalopram and 10 mg/kg cianopramine (Table 1). Only a dose of 30 mg/kg cianopramine impaired the animals in these forced motor performance tasks.

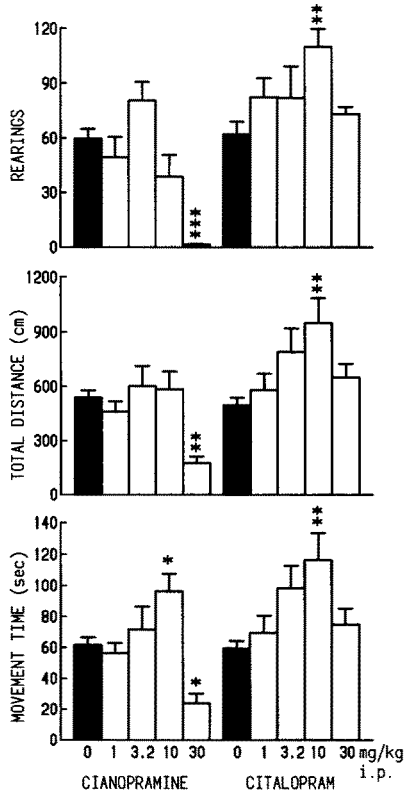

Fig. 1. Activity monitoring: mean (± SEM) ambulation time, total distance travelled and number of rearings exhibited by mice given a 10-min test in the activity monitor 30 min after IP administration of various doses of cianopramine (1–30 mg/kg) or citalopram (1–30 mg/kg). * $P<0.05$, ** $P<0.01$ and *** $P<0.001$ (Bonferroni's t-test)

Table 1. Effects of cianopramine and citalopram in the rotarod and horizontal wire tests in mice

	Cianopramine ED_{50} in mg/kg IP		Citalopram ED_{50} in mg/kg IP	
	ROT	HWT	ROT	HWT
2 min	>30	>30	>30	>30
5 min	10–30	10–30	>30	>30
10 min	10–30	10–30	>30	>30
15 min	10–30	10–30	>30	>30
30 min	10–30	11.5	>30	>30
45 min	10	11.5	>30	>30
1 h	10.7	11.5	>30	>30
2 h	10–30	≥30	>30	>30

ROT, Rotarod test; HWT, horizontal wire test
Calculated ED_{50}s (i.e. 10.7 mg/kg) or evaluated ED_{50} dose range (i.e. >30 mg/kg or 10–30 mg/kg) are presented

Experiment 2: effects of a single injection of cianopramine and citalopram in the free exploration test in mice

Analysis of variance revealed significant differences among groups for novelty preference [cianopramine: $F(4,45)=31.7$, $P<0.0001$; citalopram: $F(3,36)=5.9$, $P<0.002$], locomotion [cianopramine: $F(4,45)=21.1$, $P<0.0001$; citalopram: $F(3,36)=3.6$, $P<0.02$] and rearing behaviour [cianopramine: $F(4,45)=19.4$, $P<0.0001$; citalopram: $F(3,36)=9.8$; $P<0.0001$]. Figure 2 shows that cianopramine significantly diminished all behavioural parameters at 10 and 30 mg/kg. The absence of a dose-dependent effect could be related to the administration of logarithmic increasing doses. Citalopram only decreased novelty preference and rearings at the highest dose tested (30 mg/kg).

Experiment 3: effects of acute treatment of cianopramine and citalopram in the light/dark test in mice and the elevated plus-maze test in rats

Light/dark test. Analysis with an overall ANOVA revealed significant differences among groups for the time spent by mice in the lit box [cianopramine: $F(4,85)=4.7$, $P<0.001$; citalopram: $F(5,103)=12.4$, $P<0.001$] and for the number of tunnel crossings (transitions) [cianopramine: $F(4,85)=4.7$, $P<0.001$; citalopram: $F(5,103)=5.9$, $P<0.0001$]. Post-hoc comparisons indicated that the drugs decreased both behavioural parameters in a dose-dependent manner, the effect being significant at the highest doses tested (Fig. 3).

Elevated plus maze test. Acute administration with both drugs significantly affect the percentage of time spent by rats in the open arms [cianopramine: $F(4,50)=5.1$, $P<0.001$; citalopram: $F(3,38)=5$, $P<0.005$], the proportion of entries into open arms [cianopramine: $F(4,50)=7.6$, $P<0.0001$; citalopram: $F(3,38)=5.4$, $P<0.003$], total number of entries into each arm (total activity) [cianopramine: $F(4,50)=4.3$, $P<0.004$; citalopram: $F(3,38)=4.9$, $P<0.005$] and number of attempts towards open arms [cianopramine: $F(4,50)=2.5$, $P<0.05$; citalopram: $F(3,38)=4.6$, $P<0.007$]. Post-hoc comparisons indicated that both drugs significantly reduced percentage of time spent in open arms and proportion of entries into these arms (cianopramine: 1–10 mg/kg; citalopram: 10 and 30 mg/kg). In addition, the drugs decreased total activity at the highest dose tested (cianopramine: 10 mg/kg; citalopram: 10 and 30 mg/kg). In contrast, both drugs increased number of attempts towards open arms, at 3.2 mg/kg with respect to cianopramine and 10 and 30 mg/kg for citalopram (Fig. 3).

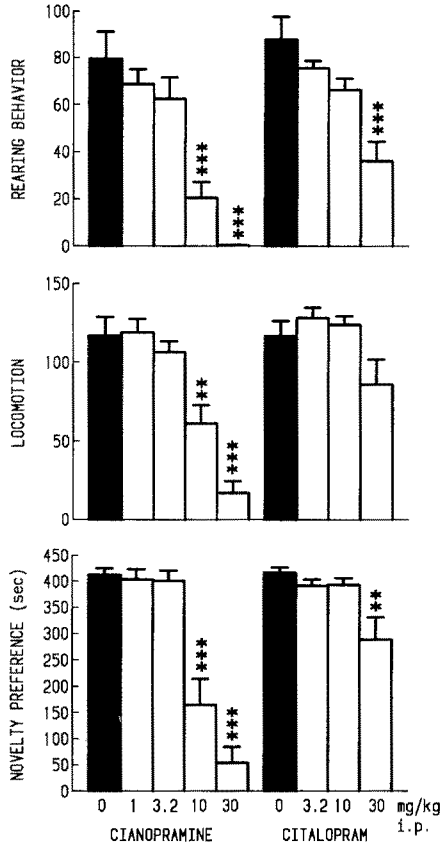

Fig. 2. Free-exploration test: mean (± SEM) time spent by animals in the novel compartment (novelty preference), locomotion and number of rearings exhibited by mice given a 10-min test 30 min after IP administration of cianopramine (1–30 mg/kg) or citalopram (3.2–30 mg/kg). ** $P<0.01$ and *** $P<0.001$ (Bonferroni's t-test)

Experiment 4: effects of chronic treatment of cianopramine in the light/dark choice procedure in mice and in the elevated plus-maze test in rats

Light/dark test. Chronic administration of 10 mg/kg cianopramine (group B) did not affect the behaviour of mice in the light/dark test compared to the chronic saline treated group (A). Analysis with an unpaired t-test revealed no significant differences between chronic saline group and chronic cianopramine group for both behav-

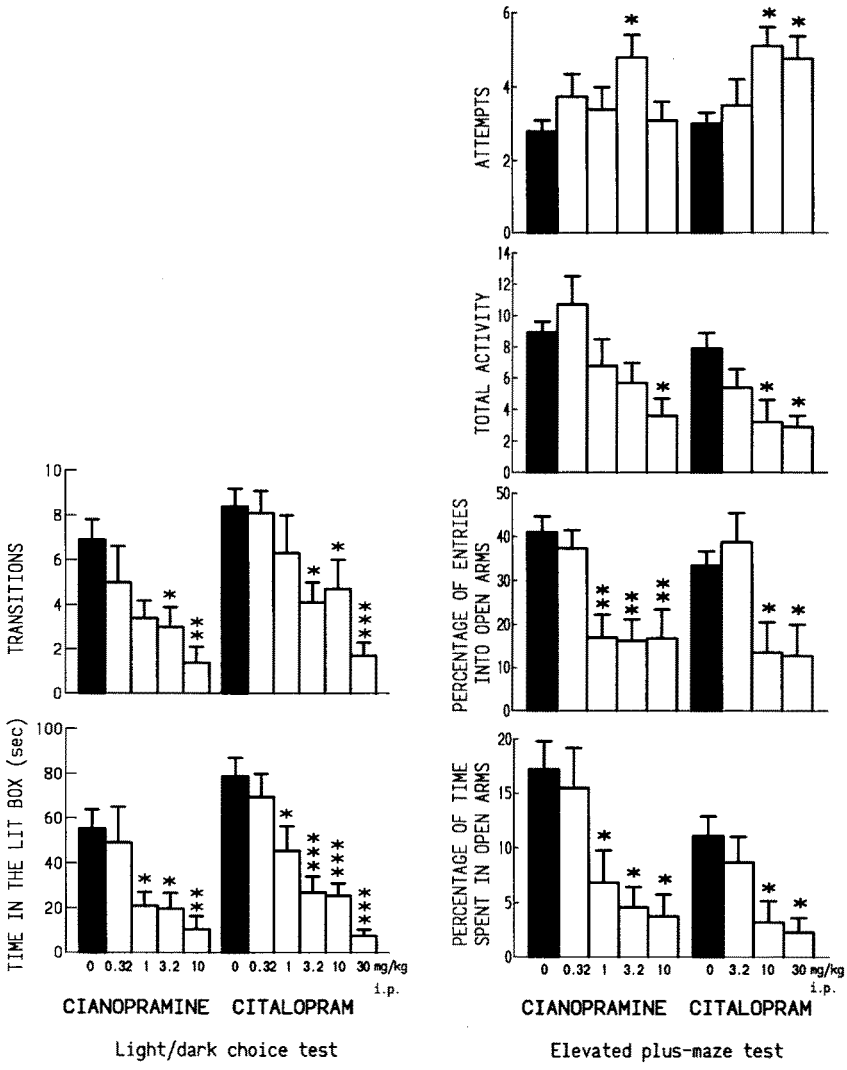

Fig. 3. a Acute treatment in the light/dark choice procedure: mean (± SEM) time spent by animals in the lit area and number of tunnel crossings (transitions) between the lit area and the dark box in mice given a 5-min test 30 min following IP administration of cianopramine (0.32–10 mg/kg) or citalopram (0.32–30 mg/kg). **b** Acute treatment in the elevated plus-maze test: mean (± SEM) percentage of entries into the open arms *(% Number)*, percentage of time spent on the open arms *(% Time)*, total number of arm entries *(total activity)* and number of attempts towards open arms performed by rats given a 5-min test 30 min after IP administration of cianopramine (0.32–10 mg/kg) or citalopram (3.2–30 mg/kg). * $P<0.05$, ** $P<0.01$ and *** $P<0.001$ (Bonferroni's t-test)

ioural parameters [time in the lit box: $T=0.23$ and transitions: $T=0.14$; $P>0.05$] (Fig. 4).

Elevated plus-maze. Figure 4 shows that chronic administration of 10 mg/kg cianopramine (group D) significantly increased the proportion of time spent by rats in open arms [$T=2.2$, $P<0.04$] and percentage of entries into these arms [$T=2.8$, $P<0.01$] as compared with the chronic saline group (C). In contrast, chronic cianopramine treatment significantly decreased number of attempts towards open arms [$T=2.66$, $P<0.01$]. Finally, the drug did not affect total activity [$T=0.58$, $P>0.05$].

Discussion

At doses which not decrease animals motor performances (below 30 mg/kg), acute administration of both cianopramine and citalopram in the light/dark choice test in mice resulted in significant, dose-related decreases in the number of illuminated box entries and time spent in the lit area. In the elevated plus-maze test in rats, a single dose of both drugs significantly decreased the percentage of open arm entries and time spent in open arms. At the same time, the number of attempts towards open arms was sharply increased. At the highest doses tested (> 10 mg/kg), some impairment of forced motor performances was observed and the drugs reduced entries in both open and closed arms, indicating a reduction of total activity in the maze. It should be noted that these effects on motor performances could be related to the ability of the drug to inhibit the reuptake of noradrenaline (NA) (Maître et al. 1980, 1982; Pawlowski et al. 1981; Da Prada et al. 1982), and Pawlowski and coworkers (1985) have argued that, at doses up to 20 mg/kg, cianopramine also slightly inhibits reuptake of NA in rats in vivo. In the free exploration paradigm in mice, acute administration of non-impairing doses of both drugs tended to increase emotional avoidance responses towards novel places (neophobia) insofar as they markedly reduced exploratory variables such as time spent by mice in the novel compartment and number of rearing responses. Taken together, these data, which are opposite to those of anxiolytic-like properties of minor tranquilizers in animals, resemble those observed after administration of inverse agonists at the benzodiazepine

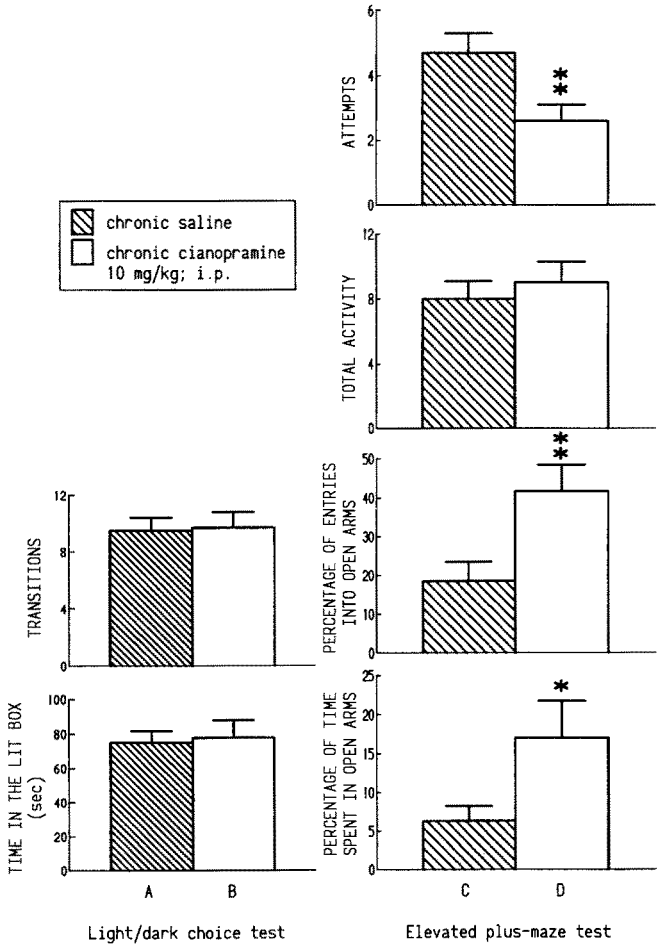

Fig. 4. Effects of repeated administration of cianopramine on the behavior of mice confronted with the light/dark choice paradigm and of rats confronted with the elevated plus-maze test. Groups A and C were challenged with saline, and groups B and D with cianopramine (10 mg/kg) once for 20 days. At day 21, and 30 min before the test, groups A and C received a saline injection, and groups B and D were challenged with a dose of 10 mg/kg cianopramine. Columns and vertical bars represent mean and SEM. * $P<0.05$ and ** $P<0.01$ (unpaired t-test)

receptor (Pellow 1986; Belzung et al. 1987; Rago et al. 1988) and some 5–HT receptor agonists such as mCPP or eltoprazine (Pellow et al. 1987; Griebel et al. 1990, 1991). These effects were interpreted as reflecting anxiogenic effects of these compounds (File et al. 1982; Pellow and File 1986).

Our data also confirm and extend previous reports on the anxiogenic-like effects observed following acute treatment with some antidepressants in animals (File 1985; Linnoila et al. 1987; Bodnoff et al. 1989). For instance, some studies demonstrate that a single injection of fluoxetine produced an anxiogenic-like action in several unconditioned conflict paradigms such as the holeboard test in mice (Linnoila et al. 1987), the elevated plus-maze test in mice and rats (Linnoila et al. 1987; Handley and McBlane 1992) or in a behavioural model based upon novelty-induced suppression of feeding in rats (Bodnoff et al. 1987). It must be emphasized, however, that these data are somewhat at variance with a recent report which pointed to an opposite effect of fluoxetine (i.e. anticonflict) in the Vogel conflict test in rats (Handley and McBlane 1992). The model used in this latter study is substantially different from animal models in which 5–HT reuptake inhibitors showed an anxiogenic-like activity and a related possibility of this discrepancy is that different animal models represent qualitatively different types of "anxiety" or fear, only some of which are reliably potentiated by 5–HT reuptake inhibitors. Finally, our data would also be in agreement with the increase in anxiety observed clinically after the initial administration of 5–HT reuptake inhibitors, especially in patients with prominent anxiety symptoms such as panic attacks (Gorman et al. 1987; Van Praag 1988; Westenberg and den Boer 1988; Humble et al. 1989; Giesecke 1990; Westenberg 1992). These authors noted an exacerbation of panic symptoms early in the treatment. This phenomenon was explained by postulating hypersensitivity of postsynaptic 5–HT receptors in such patients. Increasing 5–HT availability would under those circumstances initially lead to additional stimulation of an already hyperactive system, and hence to clinical deterioration (Van Praag 1988).

In the present investigation, repeated treatment (10 mg/kg, once daily, 3 weeks) with cianopramine produced a loss of the anxiogenic-like effects of this drug in the light/dark test. The animals of the drug-treated group reached the same level of performance as seen in the control group. More evident was the shift observed in the elevated plus-maze test in rat. Following repeated administration, cianopramine displayed an anxiolytic-like profile manifested by an increase of both entries and time spent by rats in the open arms, and by a decrease of the number of attempts towards these arms. Thus, rats, exposed to the elevated plus-maze seemed to show a greater sensitivity to a chronic cianopramine treatment than mice confronted with the light/dark paradigm. These results corroborate the findings from previous reports in rats showing that a variety of tricyclic antidepressants (desipramine and amitriptyline) as well as a monoamine oxidase inhibitor (phenelzine) and some atypical antidepressant drugs (paroxetine, fluoxetine and mianserin) acquire anxiolytic properties following chronic administration in the elevated plus-maze test in rats (Cadogan et al. 1992), in the conditioned suppression of drinking conflict paradigm (Fontana et al. 1989) or in an animal model of anxiety involving novelty-suppressed feeding in food-deprived rats (Bodnoff et al. 1988, 1989). These data can also be added to clinical observations relating an improvement of symptoms of anxiety after several weeks of antidepressant medication (Westenberg and den Boer 1988). It has been suggested that these behavioural and clinical effects might be due in part to adaptative changes of the 5–HT receptors (Westenberg and den Boer 1988): enhancement of 5–HT availability, after a single injection of 5–HT reuptake inhibitors, would lead to stimulation of the central 5–HT system, and hence increase anxiety level; conversely, repeated treatment with these drugs would decrease the responsiveness of 5–HT receptors and thus improve anxiety states (Van Praag 1988). Evidence in favour of this hypothesis is supported by the recent report of Maj and

Moryl (1992), which showed that the selective 5–HT reuptake inhibitors sertraline and citalopram, given repeatedly, decrease the responsiveness of 5–HT_{1A} (presynaptic) and 5–HT_2 receptors. However, it should be noted that several recent studies using in vivo brain microdialysis have shown that, at low doses, acute 5–HT reuptake inhibitors appear to have little effect on terminal 5–HT release and significantly raised the extracellular concentrations of 5–HT in the raphe nuclei (Adell and Artigas 1991; Invernizzi et al. 1992). Furthermore, Chaput et al. (1991) showed that long-term administration of the selective 5–HT reuptake blocker paroxetine attenuates the negative feedback exerted by terminal 5–HT autoreceptors on 5–HT release, thereby increasing extracellular 5–HT in terminal regions. These findings are somewhat surprising in view of the belief that 5–HT reuptake inhibitors increase the availability of the transmitter at terminal regions and that this effect is involved in the anxiogenic-like effects of these drugs (Bodnoff et al. 1988, 1989; Van Praag 1988). It must be emphasised, however, that behavioural investigations were performed in animals under stressful experimental conditions or in panic disorder patients, and presumably the effects of 5–HT reuptake inhibitors in such animals or patients could be substantially different from those observed in microdialysis or electrophysiologic experiments.

In conclusion, these data show that cianopramine and citalopram increased arousal as well as emotional responses when given acutely. In contrast, after chronic treatment of cianopramine, anxiogenic-like effects were no longer produced in the light/dark test whereas in the elevated plus-maze test anxiolytic-like effects, in fact, appeared. This reverse effect is likely due to adaptative changes of brain 5–HT receptors.

References

Adell A, Artigas F (1991) Differential effects of clomipramine given locally or systematically on extracellular 5-hydroxytryptamine in raphe nuclei and frontal cortex. An in vivo brain microdialysis study. Naunyn-Schmiedeberg's Arch Pharmacol 343:237–244

Åsberg M, Eriksson B, Måtensson B, Träskman-Bendz L, Wägner A (1986) Therapeutic effects of serotonin uptake inhibitors in depression. J Clin Psychiatry 47:23–35

Belzung C, Misslin R, Vogel E, Dodd RH, Chapouthier G (1987) Anxiogenic effects of methyl-β-carboline in a light/dark choice situation. Pharmacol Biochem Behav 28:29–33

Bodnoff SR, Suranyi-Cadotte B, Aitken DH, Quirion R, Meaney MJ (1988) The effects of chronic antidepressant treatment in an animal model of anxiety. Psychopharmacology 95:298–302

Bodnoff SR, Suranyi-Cadotte B, Quirion R, Meaney MJ (1989) A comparison of the effects of diazepam versus several typical and atypical antidepressant drugs in an animal model of anxiety. Psychopharmacology 97:277–279

Cadogan AK, Wright IK, Coombs I, Marsden CA, Kendall DA, Tulloch I (1992) Repeated paroxetine administration in the rat produces an anxiolytic profile in the elevated X-maze and a decreased ^{3}H-ketanserin binding. Neurosci Lett 42:S8 (suppl)

Chaput Y, de Montigny C, Blier P (1991) Presynaptic and postsynaptic modifications of the serotonin system by long-term administration of antidepressant treatments. An in vivo electrophysiologic study in the rat. Neuropsychopharmacology 5:219–229

Chopin P, Briley M (1987) Animal models of anxiety: the effects of compounds that modify 5–HT neurotransmission. TIPS 8:383–389

Da Prada M, Keller HH, Burkard WP, Schaffner R, Bonetti EP, Launay JM, Haefely W (1982) Some neuropharmacological effects of Ro 11–2465 – a novel tricyclic antidepressant with potent inhibitory activity on the uptake of 5–HT. In: Advances in biochemical psychopharmacology vol 31 (Typical and atypical antidepressants: Molecular mechanisms) pp 235–248

File SE (1985) Animal models for predicting clinical efficacy of anxiolytic drugs: social behaviour. Neuropsychobiology 13:55–62

File SE, Bond AJ, Lister RJ (1982) Interaction between effects of caffeine and lorazepam in performance tests and self-ratings. J Clin Psychopharmacol 2:102–106

Fontana DJ, Carbary TJ, Commissaris RL (1989) Effects of acute and chronic anti-panic drug administration on conflict behavior in the rat. Psychopharmacology 98:157–162

Giesecke ME (1990) Overcoming hypersensitivity to fluoxetine in a patient with panic disorder. Am J Psychiatry 147:532–533

Goodmann WK, Price LH, Rasmussen SA, Charney DS, Woods SW, Heininger GR (1986) Evidence for abnormal serotonergic function in obsessive compulsive disorder. Neurosci Abstr 12:317.6

Gorman JM, Liebowitz MR, Fyer AJ (1987) An open trial of fluoxetine in the treatment of panic attacks. J Clin Psychopharmacol 7:329–332

Griebel G, Saffroy-Spittler M, Misslin R, Vogel E, Martin JR (1990) Serenics fluprazine (DU 27716) and eltoprazine (DU 28853) enhance neophobic and emotional behaviour in mice. Psychopharmacology 102:498–502

Griebel G, Misslin R, Pawlowski M, Vogel E (1991) *m* – Chlorophenylpiperazine enhances neophobic and anxious behaviour in mice. NeuroReport 2:627–629

Griebel G, Misslin R, Pawlowski M, Guardiola-Lemaître B, Guillaumet G, Bizot-Espiard J (1992) Anxiolytic-like effects of a selective 5–HT_{1A} agonist, S20244, and its enantiomers in mice. NeuroReport 3:84–86

Handley SL, McBlane JW (1992) Opposite effects of fluoxetine in two animal models of anxiety. Br J Pharmacol 107:446P (suppl)

Humble M, Koczkas C, Wistedt B (1989) Serotonin and anxiety: an open study of citalopram in panic disorder. In: Stefanis CN, Soldatos CR, Rabavilas AD (eds) Psychiatry today: VIII World Congress of Psychiatry Abstracts. Elsevier, New York, p 151

Hyttel J (1977) Neurochemical characterization of a new potent and selective serotonin uptake inhibitor: Lu 10–171. Psychopharmacology 51:225–233

Insel TR, Mueller EA, Alterman I, Linnoila M, Murphy DL (1985) Obsessive-compulsive disorder and serotonin: is there a connection? Biol Psychiatry 20:1174–1188

Invernizzi R, Belli S, Samanin R (1992) Citalopram's ability to increase the extracellular concentrations of serotonin in the dorsal raphe prevents the drug's effect in the frontal cortex. Brain Res 584:322–324

Linnoila M, Eckhardt M, Durcan M, Lister R, Martin P (1987) Interactions of serotonin with ethanol: clinical and animal studies. Psychopharmacol Bull 23:452–457

Maître L, Moser P, Baumann PA, Waldmeier PC (1980) Amine uptake inhibitors: criteria of selectivity. Acta Psychiatr Scand 61 [Suppl. 280]:97–110

Maître L, Baumann PA, Jaekel J, Waldmeier PC (1982) 5–HT uptake inhibitors: psychopharmacological and neurobiochemical criteria of selectivity. Adv Biochem Psychopharmacol 34 [Serotonin in biological psychiatry]:229–246

Maj J, Moryl E (1992) Effects of sertraline and citalopram given repeatedly on the responsiveness of 5–HT receptor subpopulations. J Neural Transm [GenSect] 88:143–156

Montgomery SA (1991) Clinical significance of 5–HT uptake inhibitors. Hum Psychopharmacol 6:S3–7

Pawlowski L, Kwiatek H, Górka Z (1981) Is Ro 11–2465 (cyanimipramine) an antagonist of postsynaptic serotonin receptors? J Neural Transm 52:61–72

Pawlowski L, Nowak G, Górka Z, Mazela H (1985) Ro 11–2465 (cyan-imipramine), citalopram and their *N*-desmethyl metabolites: effects on the uptake of 5-hydroxytryptamine and noradrenaline in vivo and related pharmacological activities. Psychopharmacology 86:156–163

Pellow S (1986) Anxiolytic and anxiogenic drug effects in a novel test of anxiety: are exploratory models of anxiety in rodents valid? Methods Find Exp Clin Pharmacol 8:557–565

Pellow S, File SE (1986) Anxiolytic and anxiogenic drug effects on exploratory activity in an elevated plus-maze: a novel test of anxiety in the rat. Pharmacol Biochem Behav 24:525–529

Pellow S, Johnston AL, File SE (1987) Selective agonists and antagonists for 5-hydroxytryptamine receptor subtypes, and interactions with yohimbine and FG 7142 using the elevated plus-maze test in the rat. J Pharm Pharmacol 39:917–928

Rago L, Kiivet RA, Harro J, Pold M (1988) Behavioral differences in an elevated plus-maze: correlation between anxiety and decreased number of GABA and benzodiazepine receptors in mouse cerebral cortex. Naunyn-Schmiedeberg's Arch Pharmacol 337:675–678

Saletu B, Grünberger J (1985) Classification and determination of cerebral bioavailability of fluoxetine: pharmacokinetic, pharmaco-EEG and psychometric analyses. Clin Psychiatry 46:45–52

Treit D (1991) Anxiolytic effects of benzodiazepines and 5–HT_{1A} agonists: animal models. In: Rodgers RJ, Cooper SJ (eds) 5–HT_{1A} agonists, 5–HT_3 antagonists and benzodiazepines: their comparative behavioural pharmacology. Wiley, Chichester, pp 107–131

Van Praag HM (1988) Serotonin disturbances in psychiatric disorders: functional versus nosological interpretation. Adv Biol Psychiatry 17:52–57

Westenberg HGM (1992) Serotonin in anxiety and related disorders. 2nd International Symposium on Serotonin, Houston, September 15–18, p 24 (abstract)

Westenberg HGM, den Boer JA (1988) Clinical and biochemical effects of selective serotonin-uptake inhibitors in anxiety disorders. Adv Biol Psychiatry 17:84–99