ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Acta Neurobiol Exp 2006, 66: 23-31

Acute effects of maprotiline on learning, anxiety, activity and analgesia in male and female mice

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Abstract. The acute effects of maprotiline (2.5, 5, 10, 15, 20 or 25 mg/kg) on learning, anxiety, activity and analgesia in male and female mice were evaluated. In addition to inhibitory avoidance learning, anxiety and locomotor activity were measured in the same animals using an elevated plus-maze. A study of the acute effects of maprotiline (15, 20 or 25 mg/kg) on analgesia was carried out in naive animals of both sexes. Maprotiline impaired inhibitory avoidance at doses of 15, 20 or 25 mg/kg. The highest dose produced an anxiolytic effect in females, and the doses of 20 and 25 mg/kg reduced locomotor activity. Analgesia was observed with the highest dose. The impairment of inhibitory avoidance by maprotiline would seem to be independent of the drug's influence on anxiety, is not shadowed by an instrumental performance deficit and, at least in the case of the highest dose, could be influenced by the drug's effects on analgesia. It is hypothesized that acquisition is the memory process principally affected by maprotiline, and in particular stimuli processing. The lack of sex differences in the effects of maprotiline on inhibitory avoidance supports the generalization of findings previously obtained only in males.

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Key words: maprotiline, inhibitory avoidance learning, anxiety, locomotor activity, analgesia, male, female, mice

INTRODUCTION

Maprotiline is a tetracyclic antidepressant that selectively inhibits norepinephrine reuptake, and has a high antihistaminergic activity and a modest anticholinergic activity (Gareri et al. 2000). It also has a low serotonin reuptake inhibitory effect (Harvey et al. 2000, Redrobe and Bourin 1997). This compound has fewer side effects than classic tricyclic antidepressants (Grüter and Pöldinger 1982), but what it does have in common is the impairment of memory (Gareri et al. 2000). Clinical studies have attributed a variety of roles to memory in its relationship with antidepressants: memory impairment is a symptom of depression that is reduced as well as other symptoms by antidepressant therapy (Antikainen et al. 2001); antidepressants have "memory impairment" among their possible side effects (Riedel and Van Praag 1995); and memory impairment is also a factor in differentiating dementia from depressive pseudodementia because antidepressant therapy has clearly different outcomes in these syndromes (Yousef et al. 1998).

Recently, it has been hypothesized that memory impairment would be a central issue in the therapeutic action of antidepressants (Parra 2003, Parra et al. 2000). In our laboratory, we are at present testing some aspects of this hypothesis in intact animals. Most of the experiments carried out so far have dealt with the effects of three antidepressants, amitriptyline, fluoxetine and maprotiline on inhibitory avoidance (frequently known as passive avoidance) in mice. We have previously reported that acute and chronic amitriptyline treatment produced an impairment of inhibitory avoidance (Everss et al. 2005, Parra et al. 2002), and chronically but not acutely administered fluoxetine had the same effect (Monleón et al. 2001, 2002). With respect to maprotiline, acute and chronic effects of the drug (5, 10, and 20 mg/kg) were evaluated in male mice (Parra et al. 2000). Results showed that acute administration of maprotiline impaired inhibitory avoidance at doses of 5 and 20 mg/kg but not at 10 mg/kg. The present work was designed to investigate the effects of a wider range of doses of acutely administered maprotiline (2.5, 5, 10, 15, 20 or 25 mg/kg) on the same learning task in both male and female mice. To the best of our knowledge, there are no published studies of the effect of maprotiline on memory in female animals except for one from our laboratory (Vinader-Caerols et al. 2002). We consider that there are important reasons to evaluate the impact of antidepressant drugs in both male and female mice: (i) the gender differences in the epidemiology of depression, with a greater incidence in women than in men (American Psychiatric Association 1994, Kornstein 1997); (ii) the gender differences in the efficacy of some antidepressants such as maprotiline and fluoxetine (Martényi et al. 2001); (iii) the sex differences reported in inhibitory avoidance (e.g. Monleón et al. 2001, 2002); and finally (iv) differences in pharmacokinetics and pharmacodynamics between men and women have been reported for several drugs, including antidepressants (Frackiewicz et al. 2000, Gandhi et al. 2004).

The main aim of the present work was to investigate the acute effects of maprotiline on the acquisition of inhibitory avoidance. This paradigm has been used for decades to test the pharmacological effects of drugs on memory (Gold 1986, Wilson and Cook 1994). As antidepressants have effects on anxiety, locomotor activity, and analgesia (Hascoët et al. 2000, Korzeniewska-Rybicka and Plaznik 1998), and can interfere with the performance of the inhibitory avoidance response, it was important for the purposes of this study to try to dissociate the effects of the drugs on learning and memory from those on anxiety, activity and analgesia (McGaugh 1989). Thus, behavioral measures linked to these processes were included.

METHODS

Animals

Male and female CD1 mice (CRIFFA, Lyon, France), weighing 23–27 g and 18–22 g, respectively, were used in this study. They arrived at the laboratory at 35 days of age and were housed in unisexual groups of 4–6 animals in translucent plastic cages (height 14.5 cm, width 27 cm, length 27 cm) with roofs of stainless steel bars (Panlab S.L., Barcelona, Spain). Subjects were maintained at a constant temperature (21 ± 2°C), under a modified light schedule (white lights on 7:30 P.M. – 07:30 A.M.) with food and water available *ad libitum*. The procedures of the study comply with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Drugs

Maprotiline hydrochloride (Ciba-Geigy A.G., Basel, Switzerland) was diluted in physiological saline and intraperitoneally injected at a volume of 0.01 ml/g

body weight. Doses of drug were calculated as the weight of the base. The control groups received the same volume of physiological saline.

Apparatus

An inhibitory avoidance apparatus for mice (Ugo Basile, Comerio-Varese, Italy) was employed. The cage, made of Perspex sheets, was divided into two sections (both height 15 cm, width 9.5 cm, length 16.5 cm). The chambers were separated, widthwise, by a flat-box partition, with an automatically-operated sliding door at floor level. A light (24 V, 10 W) was left on at all times in the ceiling of the starting side, while the other side remained in darkness. The starting side was white and the other side was black. The floor consisted of stainless steel bars, 0.7 mm in diameter and 8 mm apart.

An elevated plus-maze (Cibertec S.A., Madrid, Spain) was also used. The apparatus was composed of two open arms (30 × 5 cm^2 each) and two closed arms (30 × 15 × 5 cm^3 each) that extended from a common central square (5 × 5 cm^2). The maze was constructed from Plexiglas (black floor and walls) and elevated to a height of 45 cm above floor level. The tests were videotaped with a standard VHS system.

A prototype apparatus (Cibertec S.A., Madrid, Spain) was used for the analgesia experiment. This equipment consisted of a translucent Perspex box of the same dimensions as one side of the avoidance apparatus, with a similar floor (see above), and a constant current source with increasing output steps of 0.059 mA. The tests were videotaped with a standard VHS system.

Experimental procedures

INHIBITORY AVOIDANCE

Ninety-three naive CD1 mice of each sex were randomly allocated to seven groups according to their pharmacological treatment and received saline or one of the six doses (2.5, 5, 10, 15, 20 or 25 mg/kg) of maprotiline before training (saline, n=23; maprotiline, n=11–12). The drug was not administered post-training, in spite of its recommendation (McGaugh 1989), because it was found to be ineffective in a previous study by our group (Parra et al. 2000). Animals from different groups were randomly subjected to the training phase of the inhibitory avoidance task 30 min after the drug injection.

A one-trial step-through inhibitory avoidance task was used as the behavioral procedure. Training and testing began with a 90-s adaptation period in the safe chamber before the door to the other chamber was opened. During training, animals received a 5 s 0.7 mA shock when they crossed from the safe chamber into the shock chamber. During the test, mice were placed once more in the safe side of the apparatus and the procedure used in the training phase was repeated, without the shock. Latencies of step-through to the shock chamber were recorded in both phases. Crossing latencies longer than 300 s in the test phase resulted in the trial being terminated and a latency of 300 s recorded. The training-test interval was 4 days, which was chosen in order to ensure that animals were drug-free in the test phase (Wells and Gelenberg 1981).

ELEVATED PLUS-MAZE

Immediately after the training phase of the inhibitory avoidance task the same animals were tested in the elevated plus-maze. Sessions, which lasted 5 min, commenced with the subject being placed into an open arm (facing the central square). All sessions were videotaped for subsequent analysis. The maze was cleaned after each subject. The number of entries into open and closed arms (arm entry is defined as all four paws entering an arm) was scored by a trained observer who was unaware of the treatment applied. This provided a measurement of anxiety, the percentage of open arm entries [(open/open + closed) X 100], and a measurement of activity, the number of closed arm entries. These measurements were based on former studies: File (2001), Lister (1987), and Rodgers and Johnson (1995).

ANALGESIA

Forty-seven male and fifty-one female naive CD1 mice were randomly allocated to four groups according to sex and pharmacological treatment and were administered saline or 15, 20 or 25 mg/kg of maprotiline (n=11–13). Thirty minutes after injection, subjects were individually introduced into the test box and were allowed a 2-min adaptation period. Subsequently, the animal received a 5-s shock of 0.059 mA, increasing proportionately by 0.059 mA every 10 s. The test was

interrupted when the subjects removed all four paws from the grid for the first time during the shock (this was done while the test was underway; and is a different criterion to that for jump threshold, which was determined after viewing the recorded sessions; see below). The highest shock delivered was 0.77 mA.

The results were represented as flinch and jump thresholds in milliamperes. Flinch threshold was defined as the lowest shock level that elicited any detectable response, and jump threshold as the lowest shock level that elicited simultaneous removal of three paws from the grid. All tests were videotaped and later assessed.

Statistics

The inhibitory avoidance data were transformed into proportion (p=x/300) values and then to arcsin (arcsin$\sqrt{p}$) values according to Snedecor and Cochran (1980). Analysis of variance for training and test were performed separately. The data of locomotor activity and anxiety obtained with the elevated plus-maze and the data of analgesia fulfilled the criteria for normality and homogeneity, and so analysis of variance was carried out for these measurements. Newman-Keuls tests were used for post hoc comparisons. Training and test sessions within the same group were compared using the Student's *t*-test for dependent samples. All analyses were performed using the "Statistica" version 5.5 for Windows software package (StatSoft Inc.).

RESULTS

In the training phase of inhibitory avoidance, Treatment was statistically significant ($F_{6,172}$=3.96, P<0.001). The *post-hoc* analysis showed that subjects treated with 25 mg/kg of maprotiline had longer latencies than subjects treated with saline (P<0.01), 2.5 mg/kg (P<0.001), 10 mg/kg (P<0.05), or 15 mg/kg (P<0.05). No other *post-hoc* comparisons were statistically significant (see Fig. 1A). In the test phase, Treatment was statistically significant ($F_{6,172}$=5.86, P<0.0001). The *post-hoc* analysis showed that subjects treated with 15, 20 or 25 mg/kg of maprotiline had shorter latencies than those in the saline group (P<0.05, P<0.001, and P<0.01, respectively). Other significant *post-hoc* comparisons were: 25 mg/kg vs. 5 mg/kg and 10 mg/kg; 20 mg/kg vs. 2.5 mg/kg, 5 mg/kg, and 10 mg/kg (Ps<0.05) (see Fig. 1B). Sex and the Treatment × Sex interaction were not statistically significant in either the training or in the test phases. Comparisons of training *versus* test within each sex and treatment group showed that learning took place in all cases (longer latencies in the test phase than in the training, Ps<0.05); except in the group of females that received 25 mg/kg of maprotiline (P>0.05).

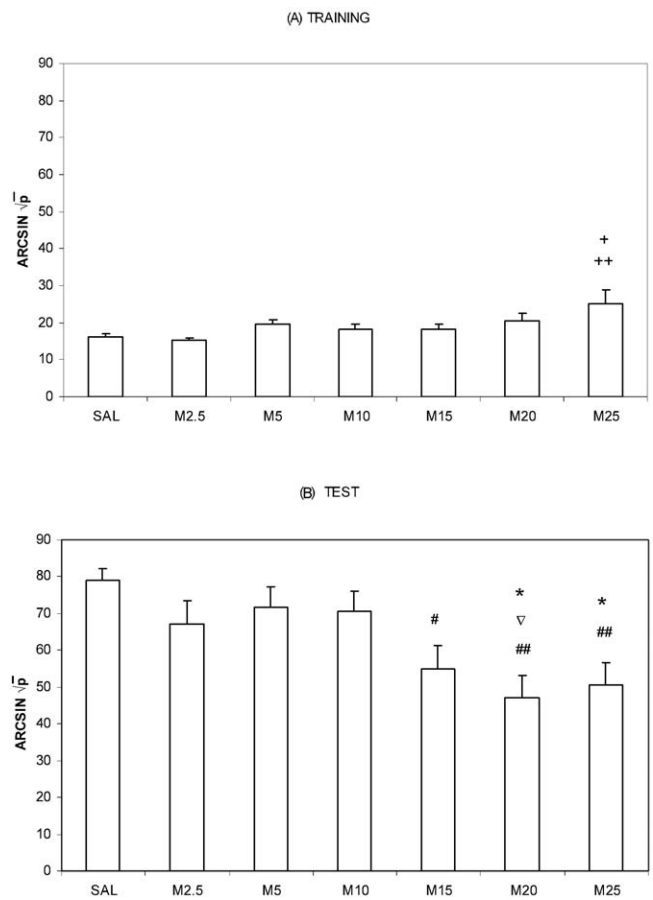

Fig. 1. Effect of pre-training administration of saline (SAL) or maprotiline (M2.5: 2.5 mg/kg; M5: 5 mg/kg; M10: 10 mg/kg; M15: 15 mg/kg; M20: 20 mg/kg; M25: 25 mg/kg) on step-through latencies of an inhibitory avoidance task in the training (A) and test (B) phases. Values are expressed as means (+SEM) of square root of proportions (p = x/300) transformed to arcsin. (+) P<0.05 vs. M10 or M15; (++) P<0.01 vs. SAL or M2.5. (#)P<0.05 vs. SAL; (##) P<0.01 vs. SAL; (*) P<0.05 vs. M5 or M10, (∇) P<0.05 vs. M2.5.

In the elevated plus-maze, the analysis of data related to anxiety revealed that the main effect Treatment and the Treatment × Sex interaction were statistically significant ($F_{6,171}$=2.43, P<0.05; and $F_{6,171}$=2.36, P<0.05; respectively). The *post-hoc* analysis of the interaction showed that the females treated with 25

mg/kg of maprotiline had a significant increase in the percentage of open arm entries (lower anxiety) *versus* any of the rest of female groups (*Ps*<0.05) and *versus* the males treated with 25 mg/kg of maprotiline (*P*<0.05), as can be seen in Fig. 2.

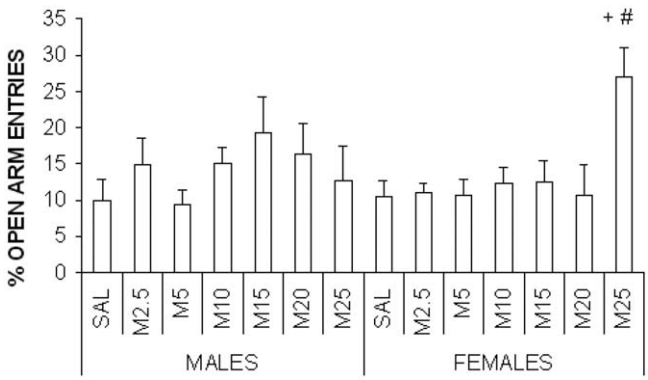

Fig. 2. Effect of administration of saline (SAL) or maprotiline (M2.5: 2.5 mg/kg; M5: 5 mg/kg; M10: 10 mg/kg; M15: 15 mg/kg; M20: 20 mg/kg; M25: 25 mg/kg) on percentage of open arm entries of an elevated plus-maze task as index of anxiety in male and female mice. Values are expressed as means (+ SEM). (+) *P*<0.05 vs. rest of the female groups; (#) *P*<0.05 vs. M25 males.

Analysis of locomotor activity showed that only the main effect Treatment was statistically significant ($F_{6,171}$=4.85, *P*<0.01). Animals treated with 20 or 25 mg/kg of maprotiline showed a significant reduction in the number of closed arm entries (*P*<0.05 and *P*<0.01, respectively) when compared to those in the control group. This reduction was also observed in the group receiving the highest dose with respect to the groups receiving 2.5 mg/kg (*P*<0.01), 5 mg/kg (*P*<0.01), or 15 mg/kg (*P*<0.05) of maprotiline (see Fig. 3).

The experiment on analgesia showed that, when males and females were considered together, Treatment was significant in jump ($F_{3,90}$=3.41, *P*<0.05) but not in flinch threshold ($F_{3,90}$=1.79, *P*>0.05). The *post-hoc* comparisons revealed that the jump threshold was greater in animals treated with 25 mg/kg of maprotiline (*P*<0.05) than in animals in the control group (see Fig. 4). Sex was not statistically significant in either jump ($F_{1,90}$=3.23, *P*>0.05) or flinch ($F_{1,90}$=0.72, *P*>0.05). The Treatment × Sex interaction was not statistically significant in either jump ($F_{3,90}$=0.24, *P*>0.05) or flinch ($F_{3,90}$=1.04, *P*>0.05).

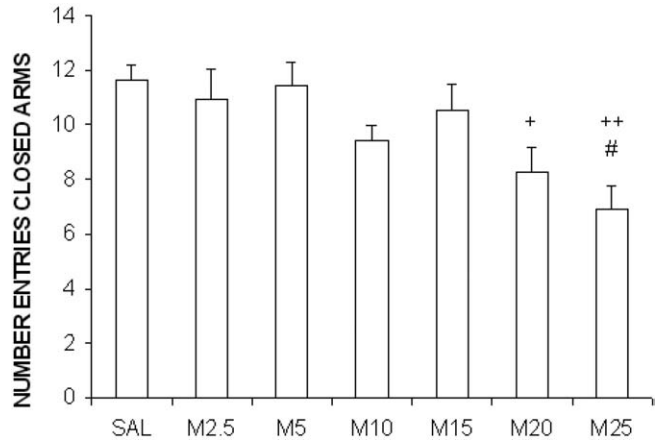

Fig. 3. Effect of administration of saline (SAL) or maprotiline (M2.5: 2.5 mg/kg; M5: 5 mg/kg; M10: 10 mg/kg; M15: 15 mg/kg; M20: 20 mg/kg; M25: 25 mg/kg) on closed arm entries of an elevated plus-maze task as index of locomotor activity in mice (taking males and females together). Values are expressed as means (+ SEM). (+) *P*<0.05 vs. SAL; (++) *P*<0.01 vs. SAL, M2.5 or M5; (#) *P*<0.05 vs. M15.

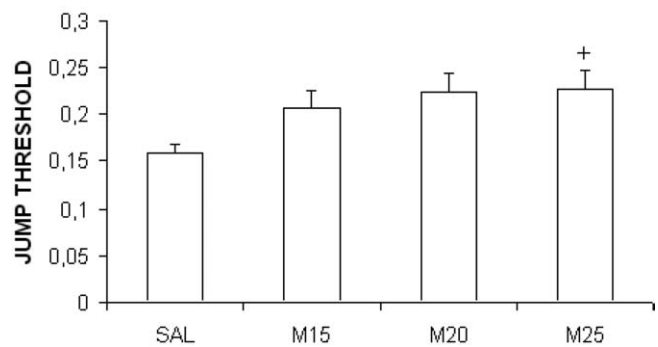

Fig. 4. Effect of administration of saline (SAL) or maprotiline (M15: 15 mg/kg; M20: 20 mg/kg; M25: 25 mg/kg) on jump threshold of a prototype of analgesia in mice (taking males and females together). Values are expressed as means (+ SEM). (+) *P*<0.05 vs. SAL.

DISCUSSION

The present results indicate that maprotiline, administered acutely before training, impairs inhibitory avoidance in male and female mice. Subjects were affected at doses of 15, 20 and 25 mg/kg. We have previously observed impairment of inhibitory avoidance learning in males (females were not included in said experiments) treated with maprotiline at doses of 5 and 20 mg/kg, but not with a dose of 10 mg/kg (Parra et al. 2000). Shimizu-Sasamata and coauthors (1993) found no effect with doses of between 1 and 10 mg/kg of

maprotiline on step-through inhibitory avoidance in rats. To our knowledge, the studies cited here are the only ones in the literature that explore the effect of maprotiline on inhibitory avoidance. Studies involving other learning paradigms reported that maprotiline impaired spatial learning, using the water maze test, with 5 and 25 mg/kg in male but not in female mice (Vinader-Caerols et al. 2002). In rats, no effect was observed in active avoidance learning with acute administration of 5, 10 or 20 mg/kg of maprotiline before the acquisition session (Archer et al. 1984).

In the measurement of anxiety, the highest dose of maprotiline showed an anxiolytic effect only in females. Rodgers and coauthors (1997) reported an anxiolytic effect with a dose as low as 5 mg/kg, and no effect with higher doses. In the case of locomotor activity, a reduction in activity was observed with 20 and 25 mg/kg of maprotiline, which is in agreement with results previously observed (Brocco et al. 2002, Korzeniewska-Rybicka and Plaznik 1998, Szymczyk and Zebrowska-Lupina 2000, Vinader-Caerols et al. 2002). In the analgesia experiment, only the highest dose of maprotiline (25 mg/kg) significantly increased the jump threshold, thereby producing an analgesic effect. These results confirm the findings of Korzeniewska-Rybicka and Plaznik (1998), who reported an analgesic effect in the flinch-jump test in rats with the same dose of maprotiline. Parra and coauthors (2000) reported the absence of antinociceptive effects with doses of 5, 10 or 20 mg/kg of maprotiline in male mice, which echo the results reported here.

In order to clarify the mechanisms responsible for the effects of maprotiline on inhibitory avoidance two important issues need to be addressed. A possible instrumental performance deficit should be ruled out and the learning processes involved should be delineated. With respect to instrumental performance, the decrease in activity observed with the doses of 20 and 25 mg/kg did not appear to influence the performance of these animals in the test phase of inhibitory avoidance learning as they crossed the compartment in less time than the controls in the test phase. This is contrary to what was expected, bearing in mind the influence of maprotiline on locomotor activity. Furthermore, there is a pharmacokinetic reason for discarding the locomotor influence of maprotiline in the avoidance test phase, as the four days between injection of the drug and the behavioral test were sufficient for the drug to have been eliminated. Moreover, with one of the doses (15 mg/kg) an avoidance deficit was observed but no motor effect was detected. In the training phase the increased latencies of the 25 mg/kg group can be interpreted as evidence of a deficit in instrumental performance. This alteration of responsiveness would challenge our interpretation if the effect of the drug had facilitated inhibitory avoidance, but this was not the case.

Regarding the learning processes, several questions are raised with respect to the acquisition, consolidation and retrieval of memory. The acquisition process involves, at least, sensory perception, emotional evaluation and stimuli association. As far as we know maprotiline does not produce sensory deficits. In relation to emotional evaluation, and considering anxiety as an emotional process, the lack of effects observed (anxiolysis was detected only in females receiving the highest dose) suggests that maprotiline's effect on avoidance does not involve anxiety. Also in relation to emotional evaluation, it can be hypothesized that electric shock would produce a lower degree of punishment in subjects receiving the 25 mg/kg dose, in which both avoidance and analgesia were affected. However, in two groups of mice avoidance was impaired without the detection of any effects on analgesia (15, and 20 mg/kg). Nevertheless, it cannot be ruled out that alterations in the animal's sensitivity to pain at the lower doses might be revealed by a more sensitive test. Effects on analgesia can directly affect memory formation because if the punishment is diminished the memory trace is softer (Campbell and Church 1969). We hypothesize that the acquisition of inhibitory avoidance is impaired by an impoverished stimuli association, because the involvement of other processes related to learning and memory should be excluded. Among these is the consolidation process, which, according to a previous report (Parra et al. 2000), does not seem to be affected. In this study, maprotiline (5, 10, and 20 mg/kg) did not impair inhibitory avoidance when administered immediately after training. Retrieval is not thought to be affected, as Arenas and coauthors (2006) failed to detect any effect when 25 mg/kg of maprotiline was administered 30 min before the test phase. That study assessed state-dependent learning (Overton 1974), which led the authors to affirm that maprotiline simultaneously produced performance facilitation, due to motor impairment, and memorization deficit.

Based on the neuropharmacology of inhibitory avoidance (Izquierdo and Medina 1997), the mechanisms of action of maprotiline (Pinder et al. 1977), and

the electrophysiological effects of antidepressants in several brain regions (Mongeau et al. 1994, 1997, 1998), and in the light of the present study, we put forward a hypothesis on the role of maprotiline in the behavioral task. Briefly, memory formation of inhibitory avoidance behavior in the rat hippocampus involves the activation of glutamate receptors, changes in second messengers, enhanced activity of protein kinases, changes in glutamate receptors subunits and increased expression of transcription factors. These events are modulated soon after training by a variety of hormonal and neural mechanisms. The neural regulatory influences on the hippocampus are constituted by three groups of fibers originated in the septum, locus coeruleus, and dorsal and medial raphe nuclei, which are cholinergic, noradrenergic and serotonergic respectively (Mongeau et al. 1997). Maprotiline possibly impairs memory through two mechanisms: a central anticholinergic action (Richelson and Nelson 1984) and the inhibition of neuronal firing in noradrenergic neurons of locus coeruleus that project to the hippocampus. Hippocampal acetylcholine plays a role in learning (Thiel et al. 1998), and a blocking of noradrenalin reuptake in locus coeruleus neurons by maprotiline could be a negative feedback signal for decreasing their firing rate. Such a negative loop has been observed with milnacipran, which is also a noradrenalin reuptake blocker (Mongeau et al. 1998). This effect was not reported with maprotiline in a past study (Mongeau et al. 1994), though it should be pointed out that the authors applied only one dose (10 mg/kg), which also proved to be ineffective in the present study.

CONCLUSIONS

The impairment of inhibitory avoidance observed in mice with acutely administered maprotiline would appear to be independent of the drug's influence on anxiety; it is not shadowed by an instrumental performance deficit and, at least at the highest dose, may be influenced by the drug's effects on analgesia. Our hypothesis is that acquisition, and more specifically stimuli processing, is the memory process that is affected by maprotiline.

The lack of sex differences in the effects of maprotiline on inhibitory avoidance should not be interpreted as a negative result, as it supports the generalization of findings previously obtained only in males.

ACKNOWLEDGEMENTS

The authors wish to thank Aránzazu Ferrer Añó for her help with the experiments. This research was partially financed by the "Generalitat Valenciana", of Valencia, Spain (Grant, GV97-SH-22-89). The Spanish "Ministerio de Ciencia y Tecnología" and European Regional Development Fund (ERDF) of the European Union have also contributed to the funding of the present study (Grant, BSO2003-07163). The analyses of inhibitory avoidance data were carried out following the suggestions of an anonymous reviewer.

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Received 4 November 2005, accepted 7 March 2006