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Antidepressant activity of memory-enhancing drugs in the reduction of submissive behavior model

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Abstract

The present study tests the activity of nootropic drugs in a behavioral test linked to depression. This test measures the reduction of submissive behavior in a competition test as the relative success of two food-restricted rats to gain access to a feeder. Nootropic drugs tested include piracetam (2-oxo-1-pyrrolidineacetamide), aniracetam (1-(4-methoxybenzoyl)-2-pyrrolidinone), the Ampakine™, Ampalex™, 1-(quinoxalin-6-ylcarbonyl)piperidine, and analogs were compared to the antidepressants, fluoxetine ((±)-*N*-methyl-gamma-(4-[trifluoromethyl]phenoxy)-benzenepropanamine) and desimpramine (5*H*-dibenz[*b*,*f*]azepine-5-propanamine, 10,11-dihydro-*N*-methyl-, monohydrochloride), while the anxiolytic diazepam (7-chloro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one) served as a control. Drugs were given intraperitoneally for 3 weeks. The antidepressant and nootropic drugs reduced submissive behavior over time. The effect was dose dependent as measured for fluoxetine and Ampakines. The reduction of submissive behavior by Ampakines gradually faded after cessation of treatment and had a more rapid onset of activity (during the 1st week of treatment) than fluoxetine (after 2 weeks). The results suggest that Ampakines may have antidepressant activity. The potential of depression treatment with memory-enhancing drugs is hypothesized and the link between cognition and depression is discussed. © 2002 Published by Elsevier Science B.V.

Keywords: Affective disorder; Cognition; Glutamate receptor; Nootropic

1. Introduction

Depression is commonly associated with cognitive dysfunction that can be observed as impaired learning and memory (Grasby, 1999; Martignoni et al., 1992; Mineka et al., 1998; Willner, 1984a) but the significance of this association is unclear. The gradual development and extended time course of depression suggests an underlying neuroplastic process similar to that seen in learning and memory formation. The idea that impaired cognition is an element of depression is also consistent with psychotherapeutic treatments directed at changing cognitive processes (Beck et al., 1989; Haaga and Beck, 1995) and by some studies showing that long-term antidepressant therapy improves cognitive function in depressed patients (Bulbena and Berrios, 1993; Finkel et al., 1999; O'Brien et al., 1993; Sternberg and Jarvik, 1976). The relationship of cognitive impairment to the development of depression is unknown but the studies cited suggest a direct relationship between the relief of depression and improvement of the associated cognitive dysfunction. The present study is based on the hypothesis that impaired cognition is an element of depression and treatment with drugs enhancing cognitive performance can help to alleviate depression.

We have studied the effects of cognition-enhancing drugs in the "Reduction of Submissive Behavior Model" of depression (Malatynska et al., 2002). Dominant–submissive behavior is measured in this competition test as the relative success of two food-restricted rats to gain access to a sweetened milk supply. Submissive behavior for one subject can be objectively measured as the amount of time spent at the feeder relative to that by the paired dominant animal. The behavioral test is referred to here as the Reduction of

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Submissive Behavior Model because it measures the reduction of submissive behavior produced by antidepressant drugs and distinguishes them from the anxiolytic drug, diazepam (Malatynska et al., 2002). The Reduction of Submissive Behavior Model used here was described elsewhere (Malatynska et al., 1995, 2002) and it is a modification of the original method validated by Malatynska and Kostowski (Danysz et al., 1988; Kostowski et al., 1986; Malatynska and Kostowski, 1984). For a review on the relation of submissive behavior to depression, see Gardner (1982). A link between human depression and subordinate behavior of animals was also studied by Blanchard et al. (1988) and Blanchard and Blanchard (1989). They demonstrated that subordinate animals show increased defensive behavior, weight loss and major alterations in sleep, eating and active behaviors. Fonberg (1974) suggested similarities between the behavior of submissive dogs and depressed patients. Submissive cats can become dominant after treatment with imipramine, showing that submissive cat behavior is reversible by antidepressant treatment (Zagrodzka et al., 1985).

The nootropic drugs used in this study include piracetam, aniracetam and three Ampakines™. These drugs share some features including the ability to improve the performance of human subjects and animals in tests of learning and memory. Piracetam and aniracetam improve spatial learning performance (Martin et al., 1992; Sarter, 1986; Schindler, 1989) and can enhance certain forms of long-term potentiation (Satoh et al., 1986, 1988; Xiao et al., 1991). The Ampakines used in this study facilitate long-term potentiation and cognition in spatial (Staubli et al., 1994), olfactory (Larson et al., 1995) and delayed non-match to sample learning tasks (Hampson et al., 1998). They are chemically related to the nootropic drug aniracetam and share its ability to increase α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-mediated excitatory postsynaptic potential responses and decrease AMPA receptor deactivation and desensitization (Arai et al., 1996). Clinical studies with Ampalex show that it is well tolerated at doses up to 1200 mg and can improve performance in some memory tasks (Lynch et al., 1996, 1997). CX691 and CX731 are second-generation Ampakines having AMPA receptor modulatory activity but are about 100-fold more potent than Ampalex in spatial memory tasks using rats (unpublished observations).

The studies were extended to test the cognitive effects of the drugs under investigation in a water maze test modified from the Morris water maze paradigm to introduce an element of stress to the spatial memory task. Several studies (Abel and Hannigan, 1992; De Quervain et al., 1998) have shown that different forms of stress (e.g. forced swim and inescapable shock) impair subsequent performance in the water maze task. The hypothesis being tested is that antidepressant drugs (desipramine and fluoxetine) but not the benzodiazepine diazepam can enhance spatial memory similar to that observed for the Ampakine tested. The element of stress is added to the conventional paradigm by subjecting the animals to an inescapable condition (absence of the hidden platform) prior to the testing with the hidden platform for retention of its location.

2. Materials and methods

2.1. Subjects

Animals used in this study were adult (160–180 g) male Sprague–Dawley rats obtained from an in-house breeding program at the Evansville Center for Medical Education (Evansville, IN). Breeding pairs were obtained from Charles River Laboratories (Portage, MI). All studies were conducted under a protocol approved by the Indiana University Institutional Animal Care and Use Committee and in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the US National Institutes of Health.

2.2. Drugs

Aniracetam (1-(4-methoxybenzoyl)-2-pyrrolidinone), piracetam (2-oxo-1-pyrrolidineacetamide), desipramine (5*H*-dibenz[*b*,*f*]azepine-5-propanamine, 10,11-dihydro-*N*-methyl-, monohydrochloride), and diazepam (7-chloro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one) were purchased from Sigma (St. Louis, MO). Fluoxetine ((±)-*N*-methyl-gamma-(4-[trifluoromethyl]phenoxy)-benzenepropanamine) was a gift from Eli Lilly (Indianapolis, IN) or purchased from RBI (Natick, MA). The Ampakines, CX516 (Ampalex™, 1-(quinoxalin-6-ylcarbonyl)piperidine) and its analogs CX691 and CX731, were synthesized at Cortex Pharmaceuticals. 2-Hydroxypropyl-β-cyclodextrin was purchased from Aldrich (Milwaukee, WI).

Desipramine and fluoxetine were dissolved in sterile distilled water. Diazepam (5 mg) was added to 0.5 ml of HCl (1 mM) and left overnight on a shaker. The solution was diluted with 4.5 ml sterile water. Aniracetam, piracetam and the Ampakines were dissolved in a 25% solution of 2-hydroxypropyl-β-cyclodextrin (HPCD) in normal saline. All drugs were given by i.p. injection once a day during the treatment period (including weekends). On weekdays, drugs were administered 1 h before behavioral testing.

2.3. Reduction of Submissive Behavior Model procedure

The testing apparatus and the Reduction of Submissive Behavior Model procedure are described in detail elsewhere (Malatynska et al., 2002). The apparatus was constructed at OmniTech (Columbus, OH) according to a design by Malatynska and Kostowski (1984). The transparent Plexiglas apparatus consists of two identical chambers ($24 \times 17 \times 14$ cm) connected by a $4.5 \times 4.5 \times 52$ cm passage. In the middle of the passage, a 10-ml glass beaker

is placed into a hole cut in the floor of the passage. Prior to behavioral testing, the beaker is filled with sweetened milk (10 g sucrose/cup) through a hinged door in the ceiling of the passage.

The animals were randomly assigned to pairs prior to testing. They were group-housed four to a cage between testing sessions so that paired animals were always separated. Behavioral testing was performed once a day for a 5-min period on weekdays. During the testing period, an animal received one point when he was observed drinking milk during each 5-s interval of the 5-min period. Four different observers contributed to scoring different animal pairs and all were blinded to the treatment animals received. The design of the apparatus permits only one animal to drink at a time but it is possible for both animals to have consumed milk during an interval. At the end of the 5-min period, the animals were returned to their home cages and given free access to food for 1 h. The animals were also given free access to food from Friday afternoon following testing to Sunday afternoon when they were once again food-deprived. The animals showed normal weight gain during the course of the study.

2.4. Scoring and statistical analysis

Each animal of the pair was scored on each testing day for 2 weeks. The 2nd-week data for the two animals of a pair were tested for significant differences using the two-tailed *t*-test assuming unequal variance. The member of a pair having a significantly lower drinking score ($p < 0.05$) was defined as ''submissive'' and his partner as ''dominant''. Any pairs not showing significant dominant–submissive relationship were dropped from the study. Submissive animals were treated with drugs or vehicle and dominant animals were treated with vehicle for the next 3 to 4 weeks. These treatments are described in the figure legends.

The data used for subsequent analyses are referred to as dominance level values. They are calculated as the difference in daily drinking scores between paired rats. The daily dominance level values were averaged over each week starting with the 2nd week of testing for each pair selected. The *n* used for statistical purposes in the study was the averaged weekly dominance level value for a single pair of animals. The effect of treatment on dominance level values for animal pairs within a treatment group was tested for statistical significance by comparing dominance level values during the 2nd week of testing (control period) to values measured during subsequent weeks of testing (treatment period) by analysis of variance (ANOVA) followed by post hoc unpaired *t*-tests for significance between control and treatment data. A *P*-value of less than 0.05 was used as the cut-off for significance. This approach gives information for the time of effect onset and effect for a selected period. Effect onset is defined as the period (weeks) at which the drug-induced reduction of the dominance level becomes significant relative to the control value measured after the 2nd week before treatment is initiated. The relative effect of two treatments is determined for the same treatment period. This is typically done for the 3rd week of treatment after all drugs have passed the onset of activity.

2.5. Water-maze test

The water maze test used here was an adaptation of the Morris water maze task (Morris, 1984). The purpose of this test was to determine if desipramine and fluoxetine would enhance spatial memory performance under stressful conditions with chronic (16 days) treatment. CX691 was used as a positive control since it improves spatial memory performance, diazepam was used as a negative control since it impairs spatial memory performance, and two saline-treated groups were used to test the effect of stress on spatial memory performance. The stress used was 7 days of forced swimming for 30 min in a water bath at 23 °C in the absence of a submerged escape platform.

The study was conducted using a plastic water bath ($80 \times 45 \times 41$ cm). The water bath was filled with an opaque solution of milk of magnesia to a depth of 29 cm. During the 2 days of latency testing, the platform (25 cm high with a surface area of 615 cm^2) was placed in the same quadrant of the water bath (halfway through the width and 2/3 through the length dimension).

The rats were divided into six groups of seven animals each except for desipramine that consisted of four animals. Two groups of animals were given identical saline injections throughout the 16-day study. On day 8, one of these saline-treated groups was subjected to forced swimming (stressed control) while the other was not (unstressed control). The other four groups of animals (stressed treatment) were treated with daily i.p. injections of diazepam (1.0 mg/kg), CX691 (2.0 mg/kg), desipramine (10 mg/kg) or fluoxetine (10 mg/kg) throughout the 16-day study. These injections were given 1 h prior to immersion on days when the water bath was used. The diazepam dose was selected for its ability to produce anxiolytic activity in the plus-maze without inducing motor impairment, while the antidepressants were tested at doses producing an effect in the Reduction of Submissive Behavior Model and other behavioral tests linked to depression. The stressed treatment animals were all subjected to forced swimming on days 8 to 15 without the escape platform excluding the weekend (days 10 and 11).

On day 15, all groups, including the unstressed controls that had not experienced the water bath, were placed in the bath with the submerged escape platform present for 5 min. The time required to find the platform was measured and recorded as the animal's latency. Animals not finding the platform within the 5-min period were assigned a score of 300 s. This test was repeated on day 16 and the value measured was calculated as a percent of the previous (day 15) day's value. The data were subjected to ANOVA, where group was the independent measure and percent change in latency (day 16 relative to day 15) the dependent measure.

3. Results

3.1. Reduction of submissive behavior model results

Submissive animals from pairs with established dominant–submissive relationships were injected with vehicle, piracetam (50 mg/kg) or aniracetam (15 mg/kg). Their dominant partners were always injected with vehicle. Pairs in which both the dominant and submissive partners were injected with vehicle show the stability of dominant–submissive relationship for up to 4 weeks. Pairs in which the submissive partner was treated with drugs showed a decrease in the dominance level that became significant after the 4th week of treatment with piracetam and after the 2nd week of treatment with aniracetam (Fig. 1). The effect of aniracetam appeared to diminish during the 3rd week though remained significantly different relative to the control value at 2 weeks. This may reflect the relatively low dose of aniracetam used here compared to doses used in spatial memory tasks (Martin et al., 1992).

Submissive animals treated with Ampakines increased their time spent on the feeder. This resulted in a strong reduction or reverse of dominance level values in pair of rats (Fig. 2). This effect became significant after the 2nd week of treatment with 5 mg/kg CX516 and after 1 week of treatment with 2 mg/kg CX691 and 1 mg/kg CX731. The rank order of Ampakines potency was CX516 < CX691 < CX731

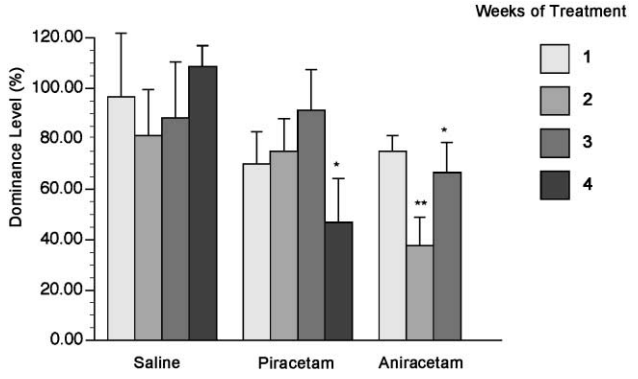

Fig. 1. Stability of control dominance level and the effect of aniracetam and piracetam in the RSBM. The figure shows the dominance level data for saline-treated rats (dominant and submissive rats given i.p. injections of vehicle, $n=6$), piracetam-treated rats (submissive rats were injected with 50 mg/kg piracetam ($n=5$) while dominant rats were injected with vehicle) and aniracetam-treated rats (submissive rats were injected with 15 mg/kg aniracetam ($n=6$) while dominant rats were injected with vehicle). The once-daily injections were given to five pairs of male rats in each group for 3 to 4 weeks (weeks 3–6). The dominance level value is defined as the difference in feeding scores between dominant and submissive rats of a pair. The dominance level in the 2nd week (initial dominance level) of each treatment group was normalized to 100% and the dominance level values for pairs in the subsequent weeks of treatment were calculated accordingly. The bars marked by $*=P<0.05$, $**=P<0.01$ as compared with initial dominance level before normalizing. Error bars are ± 1 standard error of the mean.

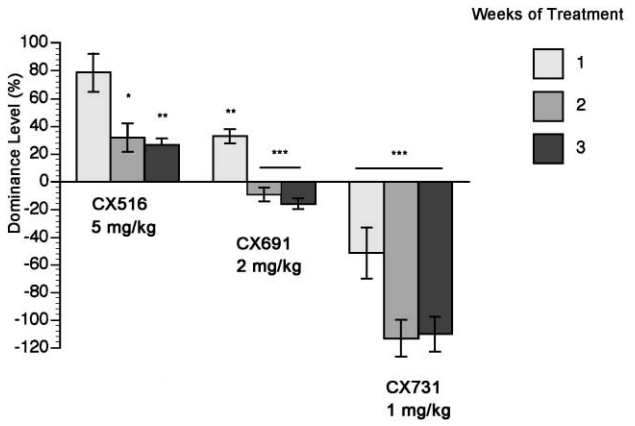

Fig. 2. Reduction of dominance level by Ampakines. The figure shows the dominance level data for CX516 (5 mg/kg, $n=4$), CX691 (2 mg/kg, $n=4$), and CX731 (1.0 mg/kg, $n=4$) treated rats (submissive rats were injected with Ampakine, dominant rats were injected with vehicle). Single daily injections were given to three pairs of male rats in each group for 3 weeks (weeks 3–5). The bars marked by $*=P<0.05$, $**=P<0.01$, $***=P<0.001$ as compared with initial dominance level (see legend of Fig. 1 for definition).

based on *t*-test comparisons between the dominance values for the 2nd week of treatment while ignoring the difference in dose levels. For CX516 relative to CX691, $P=0.039$ with 6 *df* (1-tail) while for CX691 relative to CX731 $P=0.022$ with 6 *df* (1-tail). This result is strongly reinforced by the 2.5-fold higher dose of CX516 relative to CX691 and the 2-fold high dose of CX691 relative to CX731.

The effect of CX691 on dominance level values in pairs of rats competing for food gradually fades after cessation of treatment. This is shown in Fig. 3 for CX691 at 0.1 mg/kg. Treatment was discontinued for week 6 of the study (4th week after treatment start). The figure shows the time-dependent loss of effect relative to the last week of treatment. The average dominance level approaches the original control level after treatment was discontinued for 3 weeks and is no longer significantly different from the control value measured at 2 weeks prior to initiation of treatment.

The potency and dose dependence of CX691 and CX731 activity in the Reduction of Submissive Behavior Model is compared with that of fluoxetine in Figs. 4 and 5. Fluoxetine at a dose of 2-mg/kg produced a weaker effect than at 5-mg/kg from week to week but both doses required 3 weeks of treatment for the change in dominance level to reach significance. The 10 mg/kg dose of fluoxetine produced a greater response at each week tested and the effect reached significance ($p<0.001$) after 2 weeks of treatment. CX691 (0.01, 0.1 and 2 mg/kg) and CX731 (0.01, 0.1 and 1.0 mg/kg) are more efficacious inhibitors of submissive behavior than fluoxetine, with CX731 having stronger effect than CX691. The reduction of the dominance level value for CX691 became significant ($p<0.01$) after 2 weeks of treatment at the lowest 0.01 mg/kg dose and after the 1st week of treatment ($p<0.001$) at both 0.1 and 2 mg/kg. The effect

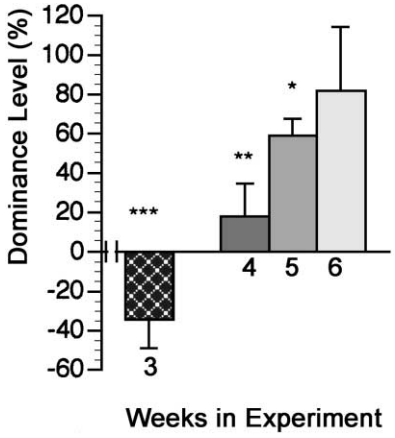

Fig. 3. The effect of CX 691 treatment discontinuation on rats in the RSBM. The figure shows the dominance level data for CX 691 (0.1 mg/kg, $n=5$) after the 3rd week of administration (bar with pattern). Submissive rats were injected with CX 691 while dominant rats were injected with vehicle. The once-daily injections were given to three pairs of male rats in each treatment group for 3 weeks. The CX691 treatment was ceased after the 3rd week (week 5 in experiment) but rats continued to be tested for the next 3 weeks (solid bars, weeks 6–8). The bars marked by $*=P<0.05$, $**=P<0.01$, $***=P<0.001$ as compared with initial dominance level (see legend of Fig. 1 for definition).

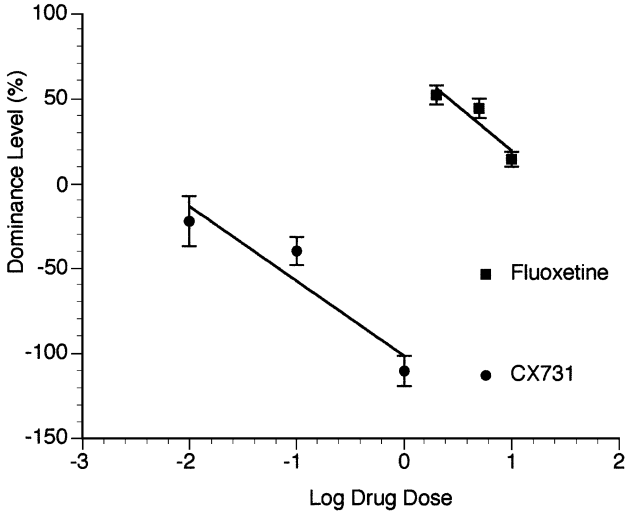

Fig. 5. Dose–response figures for fluoxetine, CX691 and CX731. The figure shows dose–response curves for fluoxetine, CX691 and CX731 using a logarithmic scale for dose. The fitted lines show that CX731 is substantially more potent than fluoxetine in the Reduction of Submissive Behavior Model but there is insufficient data to estimate ED_{50} values since the asymptotes are not defined. The absence of defined asymptotes also prevents estimation of relative efficacy. CX691 also appears to be more potent than fluoxetine but the points measured are not monotonic. The intercepts for the fitted lines of CX731 and fluoxetine are significantly different but the slope values are not (parallel line test).

of CX731 became significant ($p<0.001$) after the 1st week of treatment at all doses studied, 0.01, 0.1 and 1 mg/kg.

The data for fluoxetine and CX731 are plotted in Fig. 5 using semilogarithmic coordinates. The dose–response data for both compounds are linear ($r^2=0.9$) consistent with occurring near the midrange of the dose–response curve. This conclusion cannot be confirmed from the data presented because neither the minimal nor the maximal effect levels are defined. The statistical test for parallel lines shows no significant difference in slope allowing the estimate of a 4500-fold difference in potency. This estimate can only be a rough approximation until further studies have extended the dose–response curves to approach maximum effect.

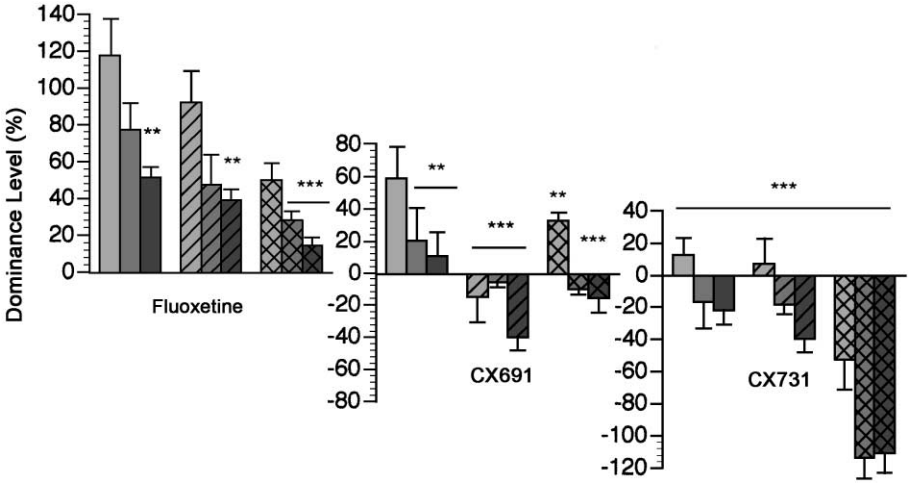

Fig. 4. Dose dependence of fluoxetine, CX691 and CX731 activity in the RSBM. Submissive rats were injected i.p. with fluoxetine at 2.0 mg/kg ($n=3$), 5.0 mg/kg ($n=3$) and 10 mg/kg ($n=5$), with CX691 at 0.01 mg/kg ($n=6$), 0.1 mg/kg ($n=5$) and 2.0 mg/kg ($n=4$), and with CX731 at 0.01 mg/kg ($n=5$), 0.1 mg/kg ($n=5$) and 1 mg/kg ($n=4$) for 3 weeks. The data are calculated as the percentage of the initial dominance level value (the dominance level value calculated for the 2nd week of experiments) for each pair of rats. Solid bars represent the lowest dose, striped bars the intermediate dose and crosshatched bars represent the highest dose for each drug studied. The bars marked by $**=P<0.01$, $***=P<0.001$ as compared with initial dominance level.

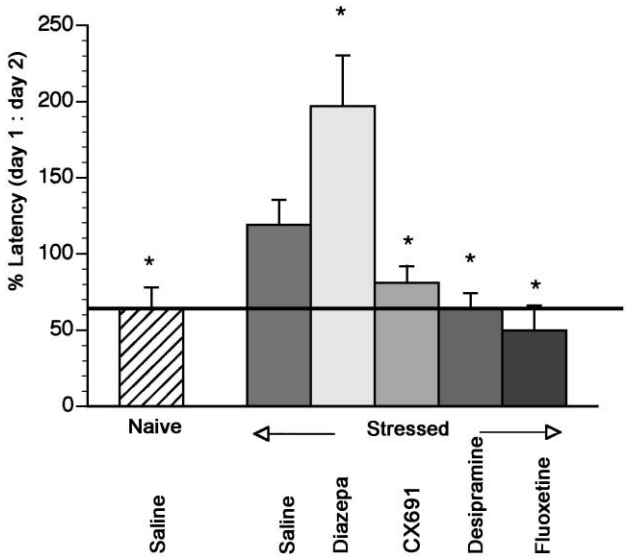

Fig. 6. Water-maze performance after chronic treatment with antidepressants and CX691. The latency of platform finding was measured (in seconds) on two consecutive days for two groups of animals (stressed and unstressed). Stressed rats were subjected to inescapable swimming on five consecutive days (solid bars). A separate unstressed saline-treated group (striped bar) is compared to the stressed saline-treated control group where both were given daily saline injections (white bars) in parallel to the drug-treated animals (gray bars). The latency on the 1st day of the experiment was normalized to 100% and the percent of day 2 latency was calculated relative to day 1. The treatment groups consisted of rats injected for 16 days with diazepam (1.0 mg/kg, $n=7$), CX691 (2.0 mg/kg, $n=7$), desipramine (10 mg/kg, $n=4$) or fluoxetine (10 mg/kg, $n=7$). All injections were made 1 h before the rats were placed in the maze. The bars marked by (*) differ from stressed saline-treated controls at $P<0.05$.

3.2. Water maze results

The effect of five 30-min periods of inescapable swimming was to increase the latency of the stressed saline-injected group for platform finding between the training and testing sessions with the platform by 44% relative to the unstressed saline-injected (naïve) group. This is shown in Fig. 6 for the two groups of saline-injected animals (naïve relative to stressed). As expected, 1.0 mg/kg diazepam treatment increased the latency between them and the saline-treated stressed animals. CX691 significantly reduced the latency of platform finding consistent with its ability to enhance performance in spatial memory tasks. The two antidepressants, desipramine and fluoxetine, also significantly reduced the latency of platform finding under these conditions.

4. Discussion

The major finding of this study is that a group of drugs known to improve performance in animal models of learning and memory act like antidepressant drugs in the Reduction of Submissive Behavior Model of depression. This finding is consistent with clinical observations that depressed patients often show impaired cognition in learning and memory tasks and improve at these tasks as their depression is relieved. The importance of this finding is that it provides a link between cognitive impairment and depression and suggests that drugs developed to improve cognition may be useful for the treatment of this disease.

The drug characteristics observed in this study include dependence on dose and treatment duration, potency, efficacy and reversibility. As shown in Fig. 4, there is a dose dependence for fluoxetine, CX691 and CX731 activity in the Reduction of Submissive Behavior Model. This finding also shows that the two Ampakines are more potent than fluoxetine (Figs. 4 and 5). They are also more potent than piracetam and aniracetam. The order of potencies seen, piracetam < aniracetam < CX516 < CX691 ≤ CX731, is consistent with their ability to improve performance in spatial memory tasks. The reversibility of activity is shown for the 0.1 mg/kg dose of CX691 after discontinuation of treatment (Fig. 3). These observations are consistent with a drug-induced effect requiring a time-dependent behavioral change that may mimic the delayed onset of therapeutic activity seen in clinical studies of antidepressants.

Ampakines show a substantially more rapid onset of action and appear to be more potent and efficacious than fluoxetine. At the highest dose tested (10 mg/kg), fluoxetine did not produce a significant effect in the Reduction of Submissive Behavior Model until after 2 weeks of treatment. The delayed effect of fluoxetine is consistent with its delayed effect on depression. Both CX691 and CX731 produced significant effects during the 1st week of treatment at 0.1 and 0.01 mg/kg, respectively. The delay seen for these drugs is consistent with the delay in their effects on learning and memory in spatial (Staubli et al., 1994), olfactory (Larson et al., 1995) and delayed non-match to sample learning tasks (Hampson et al., 1998). However, there are serious limitations to our ability to measure differences in potency between fluoxetine and the Ampakines. The range of doses used does not cover more than a small fraction of the dose–response curve and fail to define the maximum effect. It is impossible to estimate the ED_{50} values of drugs without this information.

The reversal of dominance, in contrast to the less dramatic reduction of submissive behavior, between the initially dominant and submissive animals as a result of drug treatment, is a measure of drug efficacy in the Reduction of Submissive Behavior Model. The observation of negative dominance level values in this test means that the submissive animals became dominant (i.e. had higher milk drinking scores than the previously defined dominant animals). Treatment with Ampakines over time can result in negative dominance level values. The reversal of social status for paired animals was also seen for a few fluoxetine-treated animal pairs but the group scores remained positive (Fig. 4). The same was observed for other antidepressants (Malatynska et al., 2002). Thus, Ampakines appear to be

more efficacious than fluoxetine in this study. Antidepressants such as imipramine, desimpramine, amitryptline and fluoxetine do not significantly differ in their efficacy to reduce submissive behavior in the Reduction of Submissive Behavior Model (Malatynska et al., 2002). This is consistent with clinical studies that show little difference in antidepressant efficacy based on the percentage of responding patients.

The effect of Ampakines in the Reduction of Submissive Behavior Model is not due to stimulant activity. CX516 does not increase exploratory activity and has no effect on arousal-dependent behaviors at doses up to 50 mg/kg (Davis et al., 1997; Larson et al., 1995). Ampakines, including CX691 and CX731, show a dose-dependent inhibition of amphetamine-induced locomotor activity that correlates with their potency at increasing steady-state currents at AMPA receptors (Johnson et al., 1999).

Submissive behavior is not dependent on a loss of appetite or change in the palatability of the milk. In our previous study (Malatynska et al., 2002), we showed that submissive animals consumed the same amount of milk during the 5-min period as dominant animals if both were placed in the apparatus alone. The reduced competition for the food source by the submissive animal is a reaction to the presence of its dominant partner.

The relevance of cognitive impairment to depression is supported by the description of depression in the Diagnostic and Statistical Manual of Mental Disorders, fourth ed. (American Psychiatric Association, 1994) and studies showing that depressed patients are impaired in tests of learning and memory. Bipolar and unipolar forms of depression, with or without psychotic symptoms, often show evidence of psychomotor retardation, speech and verbal fluency dysfunction, impaired executive function and disorders of declarative or explicit memory (Martinez-Aran et al., 2000). The relationship between ‘‘cognitive impairment’’ and depression has been widely studied but the meaning of cognitive impairment varies between studies (Martinez-Aran et al., 2000). A variety of tests and rating scales are used to measure cognition. These range from fairly simple measures of learning and memory to more esoteric scales of thought quality. Not all studies of depressed patients identify cognitive impairment as a corollary of depression. This may reflect the presence of several confounding variables including the kind of depression present (e.g. major depression, dysthymia, bipolar disorder), number of episodes experienced by the patient, treatment history and treatment at the time of testing.

The efficacy of electroconvulsant therapy (ECT) would appear to contradict the hypothesis that improving cognition is a therapeutic approach to depression since ECT is associated with cognitive impairment seen as a loss of memory for recent events (Fink, 2001). Clinical studies (Calev et al., 1991) show that depression and ECT independently impair cognition and that the recovery from depression produced by ECT is not a consequence of the amnesic action of the treatment. There is evidence that pretreatment non-memory cognitive impairment associated with depression is relieved after ECT in conjunction with the remission of depression symptoms (Calev et al., 1995). The nature of ECT makes it difficult to fit into any neurological hypothesis of depression since the induced seizures lack specificity for any neurotransmitter mechanism. The ability of ECT to improve depression is not easily incorporated into a hypothesis that links improve cognition with recovery from depression.

The idea that some antidepressants can enhance learning and memory in animal behavioral tests is not new (Kumar and Kulkarni, 1996; Nowakowska et al., 2000) and is also seen for depressed human subjects. Antidepressants have produced cognitive improvement in conjunction with the remission of depression in some (Bulbena and Berrios, 1993; Finkel et al., 1999; O’Brien et al., 1993; Sternberg and Jarvik, 1976) but not all studies (McNair et al., 1984). These observations suggested that antidepressants might have similar effects to the nootropic drugs. There is a clear association between stress and depression (Brown et al., 1999; File, 1996) that is used in many animal models of depression (Thiebot et al., 1992; Willner, 1984b). The observation that repeated stress impaired learning in the water maze test (Fig. 6) is consistent with other studies showing similar effects of stress (Abel and Hannigan, 1992; De Quervain et al., 1998). The difficulty of the task is increased by the training period without the platform. This impairment was increased by the benzodiazepine, diazepam (Fig. 6). This is also consistent with diazepam effects on learning and memory (McNamara and Skelton, 1997; Zanotti et al., 1994). Our finding that fluoxetine and desipramine, in addition to the CX691, improves performance in the water maze for animals subjected to stress suggests a common denominator in their activities even if their acute mechanisms of action are different.

The presence of dementia is a significant risk factor for depression (Newman, 1999; Simpson et al., 1999). Patients with vascular dementia or Alzheimer’s disease are substantially more likely to be depressed than cognitively intact individuals. Whether depression precedes dementia or is a consequence of it remains unclear, but there is a strong association between the two conditions (Chen et al., 1999; Yaffe et al., 1999).

The results of the present study support a hypothesis for understanding mood disorders and the therapeutic action of antidepressants based on cognition. The efficacy of electroconvulsant therapy, with its known risk of amnesia effects, studies showing that not all depressed patients show cognitive impairment and the limited information on cognitive enhancement by conventional antidepressants are potential evidence against this hypothesis. The ability of the Reduction of Submissive Behavior Model to link two apparently distinct classes of drugs, antidepressants and cognitive enhancers to the same endpoint provides a means of testing this hypothesis.

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