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Pharmacology, Biochemistry and Behavior 75 (2003) 755–762
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
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Zuclopenthixol facilitates memory retrieval in rats: possible involvement of noradrenergic and serotonergic mechanisms

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Received 11 November 2002; received in revised form 24 March 2003; accepted 16 May 2003

Abstract

Although disturbed memory function often coexists with psychosis, the cognitive effects of antipsychotic medications with diverse pharmacodynamic properties are rarely investigated. The neurocognitive profile of zuclopenthixol, a thioxanthene dopaminergic antagonist and a conventional neuroleptic agent, has yet to be investigated despite the effect of the drug on a variety of neurotransmitter systems involved in mediation of learning and memory processes. In this study, the effect of zuclopenthixol was tested on memory retrieval 24 h after training using an inhibitory avoidance task in rats. Acute administration of zuclopenthixol (0.7 and 1.4 mg/kg ip) before retrieval testing increased step-through latency during the test session. The same doses of zuclopenthixol did not affect the ambulatory activity of rats in the openfield test and therefore the facilitatory effect of the drug on memory function could not be confounded with any motoric properties. This study also investigated the effect of zuclopenthixol on cortical and hippocampal monoaminergic neurotransmitters' levels together with acetylcholinesterase enzyme (AChE) activity, both of which are known to be important in control of cognitive function. Administration of zuclopenthixol (0.7 and 1.4 mg/kg ip) neither affected dopamine (DA) level nor AChE activity in rat cortex and hippocampus. On the other hand, the lower dose of zuclopenthixol elevated cortical norepinephrine (NE) level, while the higher dose elevated both cortical and hippocampal NE level together with hippocampal serotonin (5-HT) level. These results may suggest the involvement of adrenergic and serotonergic mechanisms in the facilitatory effect of zuclopenthixol on retrieval memory. Zuclopenthixol may therefore be a better alternative than other commonly used antipsychotic medications reported to impair cognitive function of schizophrenic patients.

Keywords: Psychosis; Zuclopenthixol; Cognition; Norepinephrine; Serotonin; Rat

1. Introduction

Most psychotic patients demonstrate poor cognitive performance as one of the disease manifestations (Bell et al., 2001). Psychotic patients may also exhibit memory impairment due to commonly used antipsychotic medications (Castner et al., 2000). Therefore, the effect of antipsychotic therapy on memory function is of particular importance in management of psychosis. Nevertheless, few clinical and experimental studies investigated the effect of antipsychotics on cognitive function (Chua et al., 2001; Goldberg and Weinberger, 1994; Ichihara et al., 1989; Kern et al., 1999; Skarsfeldt, 1996; Williams et al., 1996). Such few and yet controversial reports regarding the effect of antipsychotics on cognition lead researchers to underscore the need to investigate the neurocognitive profile of antipsychotic agents with diverse pharmacodynamic actions (Byerly et al., 2001; Lebert et al., 2000; Moore and O'Keeffe, 1999). Zuclopenthixol acetate, {(*Z*)-4-[3-(2-chlorothioxanthene-9-ylidene)propyl]-1-piperazine ethanol acetate ester}, is a conventional neuroleptic agent that has yet to be investigated to test its effect on cognitive function. Zuclopenthixol acts as a thioxanthene dopaminergic antagonist with high affinity for both dopaminergic D-1 and D-2 receptor subtypes (Amdisen et al., 1987). It also possesses some affinity for α_1-adrenergic and a lower affinity for α_2-adrenergic receptors. In addition, it has some affinity for serotonergic 5-HT2, histamine-H_1, and muscarinic receptors (Nyberg et al., 1995). Respectable number of studies has indicated that cholinergic, dopaminergic, adrenergic, serotonergic, and histaminergic neurotransmitter systems play an important role in control of learning and memory processes (GoldmanRakic, 2000; Passani et al., 2000; Robbins et al., 1997). In addition, the mediation of such neurotransmission by

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doi:10.1016/S0091-3057(03)00153-9

some antipsychotics has been related to their effect on cognitive function (Sharma and Mockler, 1998). BuTAC, a novel potential antipsychotic, with selective partial agonistic mode of action at cholinergic muscarinic M2 and M4 receptors, was shown to have favorable effects on aspects of learning and memory of experimental animals (Rasmussen et al., 2001). In addition, both experimental and clinical research showed that treatment with the typical neuroleptic chlorpromazine, among other dopaminergic antagonists, suppressed AChE activity or enhanced its inhibition by other drugs in different brain areas (Chemnitius et al., 1996; Michalek et al., 1983; Nasello et al., 1995). Moreover, the effect of risperidone on 5-HT2A-mediated neurotransmission has been hypothesized as the possible basis for its positive effect on cognitive function (Honey et al., 1999). Furthermore, the facilitatory effect of haloperidol on retrieval memory of a step-through passive avoidance task of rats was suggested to be mediated through augmenting noradrenergic transmission (Chugh et al., 1991).

The neurocognitive profile of zuclopenthixol has yet to be evaluated despite the effect of the drug on a variety of neurotransmitter systems mediating cognitive processes. Therefore, this study aimed at investigating the effect of zuclopenthixol on cognitive function using step-through passive avoidance paradigm in rats. The one-trial passive avoidance task used in this study has been referred to be an optimal method to study the effects of neuroleptics on memory processes (Ichihara et al., 1988). Two dose levels of the drug (0.7 and 1.4 mg/kg ip) equivalent to antipsychotic doses available for clinical use were attempted. Measuring the effect of nootropic "memory facilitating" doses of the drug, if any, on ambulatory activity of animals was also aimed to rule out any confounding effect on the memory task. This study also investigated the effect of zuclopenthixol (0.7 and 1.4 mg/kg ip) on cortical and hippocampal monoaminergic neurotransmitters' levels together with AChE activity, both of which are known to be important in mediation of learning and memory processes.

2. Methods

2.1. Drugs and animals

Zuclopenthixol acetate (Clopixol Acuphase ampoules, 50 mg/ml, in vegetable oil, H.Lundbeck, Denmark) was used. 5-Hydroxytryptamine oxalate, acetyl thiocholine iodide, cholinesterase (bovine erythrocytes), dopamine hydrochloride, norepinephrine acid tartarate, and *o*-phthaldialdehyde (fluorescence grade) were all purchased from Sigma-Aldrich, Chemie, Germany. The rest of the chemicals used in this experimental work were of the highest commercial grade.

Zuclopenthixol in vegetable oil was dissolved in 0.2 ml ethanol and completed to the final volume with saline (NaCl, 0.9%) to give ethanol concentration of 20% v/v. Control animals received saline containing ethanol (20% v/v) and vegetable oil (2.8% v/v). Preparation and kinetics of zuclopenthixol were adopted from Manzaneque and Navarro (1999). All drugs or vehicle were administered intraperitoneally in a volume of 1 ml/kg body weight. Control animals received respective solvent injections, and they were run concurrently with drug-treated groups.

Male albino rats of Wistar strain weighing 200–300 g were obtained from National Research Center Laboratories, Cairo, Egypt. They were kept in a temperature of 23–25 °C with alternating 12-h light and dark cycles (lights on at 6 a.m.) and allowed free access to food and water. Animal chow and water were available ad libitum. On the day of the experiment, animals were brought to the experimental room and allowed to habituate to the environmental conditions for a period of approximately 60 min before the beginning of the experiment. Handling and experimentation were conducted in accordance with the international ethical guidelines concerning the care and use of laboratory animals, and the experimental protocol was approved by Ain Shams University College of Pharmacy Review Committee for the use of Animal Subjects.

2.2. Apparatus for Experiment 1

A step-through passive avoidance apparatus was used (UGO BASILE, Italy). The apparatus is made of Perspex sheets and is divided into two compartments. One compartment is white and illuminated by a light fixture, featuring a 24-V, 10-W bulb, fastened to the compartments lid. The second compartment is dark and made of black Perspex panels. The two compartments are separated by an automatically operated sliding door. The floor consists of 40 bars (0.3-cm-diameter) spaced 1.2 cm apart. The bars of the dark compartment floor are wired to a constant current high-precision eight-pole scrambling circuit located in the controller.

2.3. Procedure for Experiment 1

Habituation session: Only one habituation session was performed in which each animal was first gently placed in the dark compartment for 5 min and returned to home cage for another 5 min. The animals were then gently placed in the light compartment, and the latency to enter the dark compartment with all four feet was measured in seconds. Animals with a step-though latency that was longer than 20 s, in the habituation session, went through the previous habituation procedures several times, with 5 min between trials, until they enter the dark compartment in less than 20 s (Wright et al., 1996). Animals entering the dark compartment in less than 4 s were noted to be hyperactive and therefore were excluded from the experiment. Such excluded animals were replaced by other naïve ones. The habituation session was performed on these naïve animals for the

purpose of reaching equal number of animals (eight) with latencies between 4 and 20 s in each group.

Training session: Training session followed the habituation session where each rat was trained by gently placing it in the light compartment, and when the animal stepped through the dark compartment putting all its paws on the grid floor, the door automatically closed and electric shock (2 mA) was delivered for 3 s. The electrical shock was only delivered during this training session. The animal was then returned to its home cage.

Test session: Twenty-four hours after training, each rat was introduced to the light compartment, and the latency to step-through to the dark compartment was recorded as a passive avoidance behavior indicating memory level. Electrical shock was not delivered during this test session. An upper cut-off time of 300 s was set, and all tests were run between 10:00 and 3:00 h.

Two groups of rats ($n=8$) showing a step-through latency of 4–20 s during the habituation session went through the training session. Twenty-four hours after training and 30 min before retrieval testing, animals were injected with 0.7 or 1.4 mg/kg ip of zuclopenthixol. Another group of rats ($n=8$) demonstrating a latency of 4–20 s during the habituation session were trained, and then 24 h later, were injected with saline, with the same content of ethanol (20% v/v) and vegetable oil (2.8% v/v) in the test solution 30 min before retrieval testing.

2.4. Apparatus for Experiment 2

Activity monitor based on the traditional infrared (IR) photocell principle is used (Opto-Varimex-Mini Model B, Columbus Instruments, OH, USA). It consists of a control unit ($35 \times 29 \times 10$ cm), two units of sensors ($50.8 \times 8.9 \times 2.5$ cm each), and a Plexiglas cage ($45 \times 25 \times 20$ cm). Interruption of 15 infrared beams (wavelength = 875 nm, diameter = 0.32 cm, spaced 2.65 cm apart) reflected total activity of the animal. This system has two outputs: (1) Total output that provides one pulse every time a light beam is broken. It is activated when the beam is broken and becomes inactive when the beam is restored. (2) Ambulatory output that provides one pulse every time a new light beam is broken. It acts just like the total output, but does not respond to the same beam being broken and restored repeatedly. This keeps ambulatory output from responding to rapid beam interruptions caused by scratching, grooming, digging, or other stereotypic nonambulatory movements. By recording the counts accumulated by the total and ambulatory counters, it is possible to compare amounts of ambulatory and stereotypic movements.

2.5. Procedure for Experiment 2

Animals showing delayed latency to step-though during retrieval testing were introduced in the locomotor activity detector. This experiment followed retrieval testing where the ambulatory activity of each animal placed in the cage was recorded during a 5-min session and compared with a respective control. This test was performed since drugs that decrease the ambulatory component of movement would prolong the latency to step-through and therefore their potential facilitatory effect on cognitive function could be confounded with their effect on locomotion.

2.6. Procedure for Experiment 3

For determination of both cortical and hippocampal 5-HT, NE, and DA levels, two groups of rats ($n=6$) received 0.7 or 1.4 mg/kg ip of zuclopenthixol 30 min before decapitation. One more group of animals ($n=6$) served as their normal controls receiving respective solvent injection, and they were run concurrently with drug-treated groups. Animals were decapitated and skulls were split on ice and salt mixture. Cortices and hippocampi were separated, weighed (0.360 ± 0.032 and 0.102 ± 0.010 g, respectively), and homogenized in ice-cold *n*-butanol solution (10 ml/g tissue) according to Miller et al. (1970). Homogenization was performed using ice-cold Teflon homogenizer (Glas-Col Terre Haute, USA) for 1 min to make a 10% homogenate, which was then centrifuged at 1000 rpm for 5 min. Supernatant (2.5 ml) was transferred to a tube containing 1.6 ml of 0.2 N acetic acid and 5 ml *n*-heptane. After mixing with a vortex mixer for 30 s, the tubes where centrifuged at 1000 rpm for 5 min. The aqueous phases were used for the estimation of 5-HT, NE, and DA levels employing the fluorometric method reported by Ciarlone (1978), which

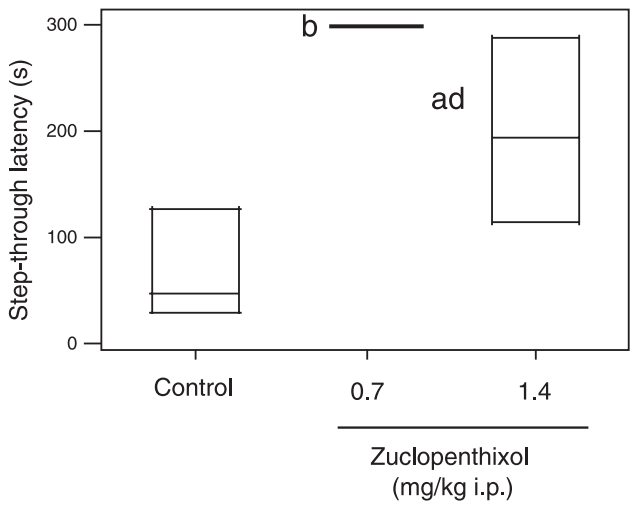

Fig. 1. Effect of zuclopenthixol (0.7 and 1.4 mg/kg ip) on retrieval memory of passive avoidance task in rats. Zuclopenthixol was administered 30 min before retrieval testing. Eight animals were used per group. Step-through latency values are shown as medians (horizontal bar) and first and third interquartiles (vertical column). Significantly different from normal: [a]$P<.05$, [b]$P<.01$. Significantly different from zuclopenthixol, 0.7 mg/kg: [d]$P<.05$ (Mann–Whitney *U* test).

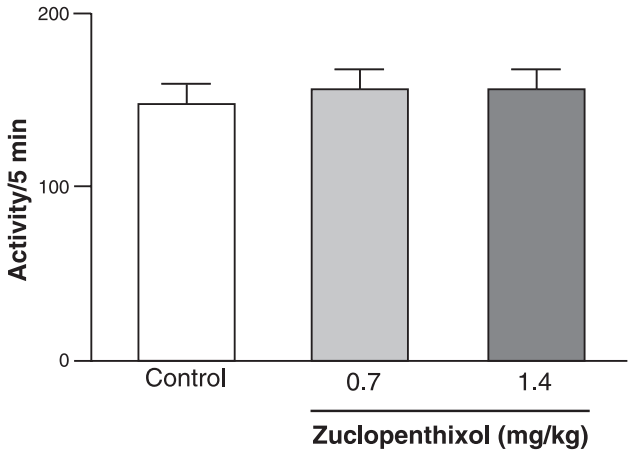

Fig. 2. Effect of zuclopenthixol on ambulatory activity of rats. Animals that received 0.7 and 1.4 mg/kg ip of zuclopenthixol with the resultant increase in step-through latency during retrieval testing were introduced into the locomotor activity detector. Means of ambulatory activity 5 min ± S.E. are shown.

can assess monoamine level, in brain tissues, in concentrations as low as 30 ng.

2.7. Procedure for Experiment 4

For determination of both cortical and hippocampal AChE activity, two groups of rats ($n = 6$) received 0.7 or 1.4 mg/kg ip of zuclopenthixol 30 min before decapitation. One more group of animals ($n = 6$) served as their normal controls receiving respective solvent injection, and they were run concurrently with drug-treated groups. Animals were decapitated and skulls were split on ice and salt mixture. Cortices and hippocampi were separated, weighed, and homogenized in phosphate buffer, pH 8.0 (1 ml/20 mg tissue), for 1 min to make a 2% homogenate. Estimation of AChE activity in cortical and hippocampal homogenates was performed employing the spectrophotometric assay of Ellman (1961), which is appli-

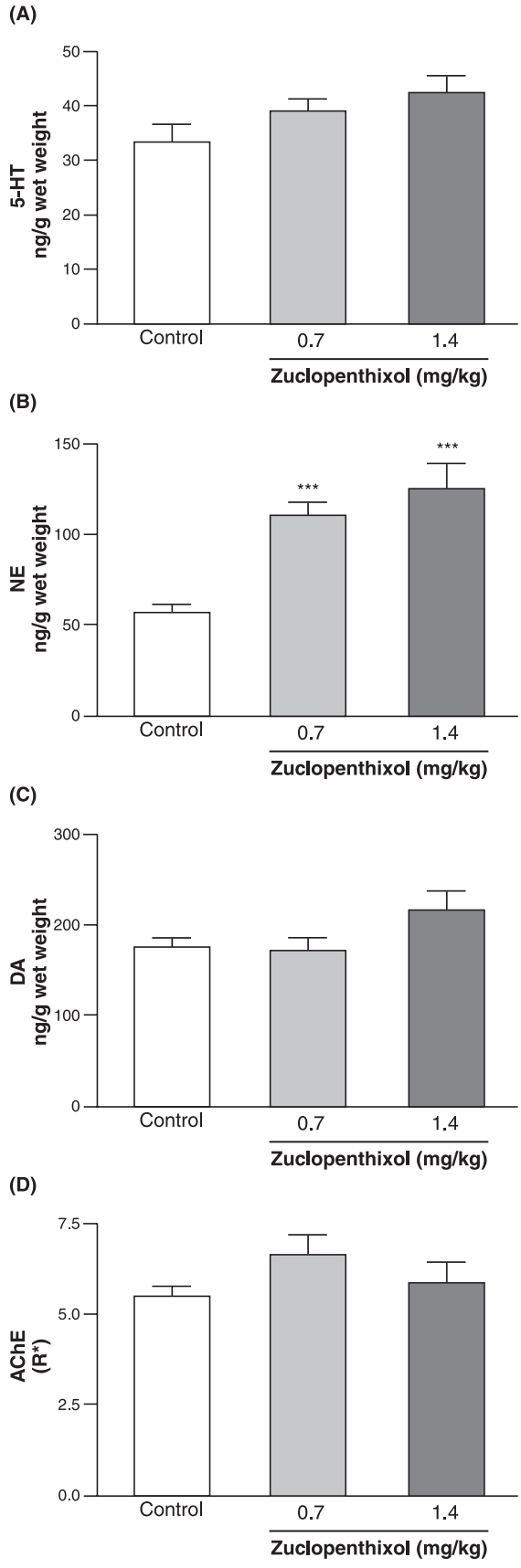

Fig. 3. (A) Effect of zuclopenthixol on 5-HT level in rat cortex. Zuclopenthixol (0.7 and 1.4 mg/kg ip) was administered 30 min before decapitation. Six animals were used per group. The values represent the mean ± S.E. Data were analyzed using one-way ANOVA followed by Tukey HSD test. (B) Effect of zuclopenthixol on NE level in rat cortex. Zuclopenthixol (0.7 and 1.4 mg/kg ip) was administered 30 min before decapitation. Six animals were used per group. The values represent the mean ± S.E. Data were analyzed using one-way ANOVA followed by Tukey HSD test. Significantly different from normal rats, *** $P < .00$. (C) Effect of zuclopenthixol on DA level in rat cortex. Zuclopenthixol (0.7 and 1.4 mg/kg ip) was administered 30 min before decapitation. Six animals were used per group. The values represent the mean ± S.E. Data were analyzed using one-way ANOVA followed by Tukey HSD test. (D) Effect of zuclopenthixol on AChE activity in rat cortex. Zuclopenthixol (0.7 and 1.4 mg/kg ip) was administered 30 min before decapitation. Six animals were used per group. The values represent the mean ± S.E. Data were analyzed using one-way ANOVA followed by Tukey HSD test. * R is rate of acetyl thiocholine hydrolysis in μmole/min/g tissue.

cable to very low concentrations of the enzyme (as low as 0.3 units/ml).

2.8. Data analysis for Experiments 1, 2, 3, and 4

The step-through latencies were analyzed by Kruskal–Wallis nonparametric one-way analysis of variance (ANOVA). If the overall H value was found statistically significant, comparisons among groups were made according to Mann–Whitney U tests. Probability values of less than 0.05 were considered statistically significant. Ambulatory activity data were analyzed using student's t test. Comparisons between means of monoamines and AChE data were analyzed by one-way ANOVA. If the overall F value was found statistically significant, comparisons among groups were made according to Tukey HSD test. Probability values of less than .05 were considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 8.

3. Results

3.1. Experiment 1: effect of zuclopenthixol (0.7 and 1.4 mg/kg ip) on retrieval memory of passive avoidance task in rats

Kruskal–Wallis one-way ANOVA revealed a significant overall drug effect [$H(2) = 10.06$, $P < .01$]. Further statistical analysis with Mann–Whitney U test showed that zuclopenthixol in a dose of 0.7 and 1.4 mg/kg caused a significant increase in step-through latency during retrieval testing ($U = 8.5$, $P < .01$; $U = 10.0$, $P < .05$, respectively) (Fig. 1). Worth mentioning is that the lower dose of zuclopenthixol used was more efficacious than the higher dose in delaying the latency to step-through during retrieval testing ($U = 15.0$, $P < .05$).

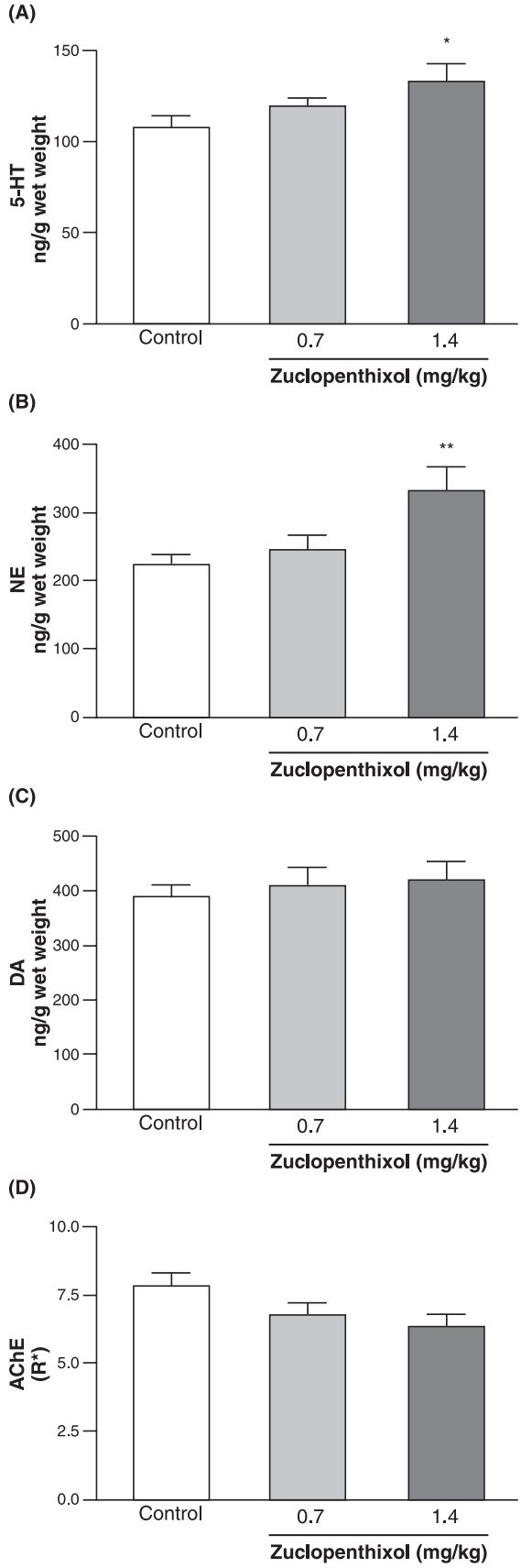

Fig. 4. (A) Effect of zuclopenthixol on 5-HT level in rat hippocampus. Zuclopenthixol (0.7 and 1.4 mg/kg ip) was administered 30 min before decapitation. Six animals were used per group. The values represent the mean ± S.E. Data were analyzed using one-way ANOVA followed by Tukey HSD test. Significantly different from normal rats, * $P < .05$. (B) Effect of zuclopenthixol on NE level in rat hippocampus. Zuclopenthixol (0.7 and 1.4 mg/kg ip) was administered 30 min before decapitation. Six animals were used per group. The values represent the mean ± S.E. Data were analyzed using one-way ANOVA followed by Tukey HSD test. Significantly different from normal rats, ** $P < .01$. (C) Effect of zuclopenthixol on DA level in rat hippocampus. Zuclopenthixol (0.7 and 1.4 mg/kg ip) was administered 30 min before decapitation. Six animals were used per group. The values represent the mean ± S.E. Data were analyzed using one-way ANOVA followed by Tukey HSD test. (D) Effect of zuclopenthixol on AChE activity in rat hippocampus. Zuclopenthixol (0.7 and 1.4 mg/kg ip) was administered 30 min before decapitation. The values represent the mean ± S.E. Data were analyzed using one-way ANOVA followed by Tukey HSD test. * R is the rate of acetyl thiocholine hydrolysis in μmole/min/g tissue.

3.2. Experiment 2: effect of zuclopenthixol (0.7 and 1.4 mg/kg ip) on ambulatory activity

Fig. 2 shows that zuclopenthixol (0.7 and 1.4 mg/kg), injected 30 min before placing the animals in the IR/photocell activity detector, did not affect the ambulatory activity of animals.

3.3. Experiment 3: effect of zuclopenthixol (0.7 and 1.4 mg/kg ip) on both cortical and hippocampal 5-HT, NE, and DA levels

One-way ANOVA showed a significant effect of treatment on cortical NE, hippocampal NE, and hippocampal 5-HT levels [$F(2,15)=27.22$, $P<.00$; $F(2,15)=5.50$, $P<.05$; and $F(2,15)=4.67$, $P<.05$, respectively]. On the other hand, one-way ANOVA revealed that zuclopenthixol treatment did not affect cortical 5-HT, cortical DA, or hippocampal DA levels [$F(2,15)=3.22$, $P=.069$; $F(2,15)=2.43$, $P=.122$; $F(2,15)=0.58$, $P=.571$, respectively]. The Tukey HSD post hoc test showed that treatment of the animals with zuclopenthixol (0.7 mg/kg) elevated cortical NE level by 88.2% ($P<.00$) without affecting its hippocampal level. The same dose did not affect either cortical or hippocampal 5-HT levels. The higher dose of zuclopenthixol used (1.4 mg/kg) caused about twofold increase in cortical NE level ($P<.00$) while elevating its hippocampal level by 48.8%. ($P<.01$). The higher dose of zuclopenthixol also elevated hippocampal 5-HT level by 25.1% ($P<.05$) without affecting its cortical level (Figs. 3A–C and 4A–C).

3.4. Experiment 4: effect of zuclopenthixol (0.7 and 1.4 mg/kg ip) on both cortical and hippocampal AChE activity

One-way ANOVA revealed that zuclopenthixol treatment (0.7 and 1.4 mg/kg) neither affected cortical nor hippocampal AChE activity [$F(2,15)=.67$, $P=.526$; $F(2,15)=1.97$, $P=.174$, respectively] (Figs. 3D and 4D).

4. Discussion

Our findings demonstrated that administration of zuclopenthixol (0.7 and 1.4 mg/kg ip) caused a significant increase in step-through latency during retrieval testing. These results would suggest a facilitatory effect of zuclopenthixol on memory function. This effect of the drug could not be confounded with the use of ethanol as the drug solvent, since five times the volume of ethanol used in this study was given to animals as a vehicle for zuclopenthixol with no effect on their mobility (Manzaneque and Navarro, 1999). In addition, the ambulatory activity of control animals (receiving saline containing the same concentration of ethanol) was within the normal range. The resultant facilitation of cognitive function by zuclopenthixol could not also be confounded with any effect of the drug on locomotion since zuclopenthixol did not affect the ambulatory activity of animals in the open field test. The effects of other neuroleptics on cognitive function using the passive avoidance paradigm were investigated in a number of studies. In one study, pretest administration of haloperidol (0.3 and 0.5 mg/kg ip) enhanced memory retrieval of a step-through passive avoidance task in rats (Chugh et al., 1991). Other researchers reported that pimozide (0.1 and 0.2 mg/kg ip) enhanced acquisition of passive avoidance response of mice (Ichihara et al., 1989). The same study though demonstrated that SCH-23390 (0.05 and 0.1 mg/kg ip) failed to affect the acquisition of the passive avoidance response. On the other hand, post-training intraperitoneal injection of clozapine (0.1–7.5 mg/kg) induced dysfunction of memory acquisition as well as retrieval of a passive avoidance task in mice (Ninan and Kulkarni, 1996). Moreover, clozapine, sertindole, and olanzapine impaired retention memory of mice in a one-trial passive avoidance paradigm (Rasmussen et al., 2001). From another perspective, risperidone (0.1 mg/kg) did not affect the acquisition or retention of avoidance behaviors in rats (Drago et al., 1997).

When the effect of zuclopenthixol (0.7 and 1.4 mg/kg) on monoamines' level and AChE activity was investigated, our results demonstrated that the drug did not affect either DA level or AChE activity in cortices and hippocampi of rats. Therefore, the effect of the drug on both DA level and AChE activity may not be involved in its nootropic properties. Results also showed that zuclopenthixol (1.4 mg/kg) elevated hippocampal 5-HT level. Such higher dose of the drug also elevated both cortical and hippocampal NE levels. On the other hand, 0.7 mg/kg of zuclopenthixol only enhanced cortical NE level. The resultant increase in hippocampal 5-HT level after the administration of 1.4 mg/kg of zuclopenthixol could be due to the antagonistic action of the drug on α_2-adrenergic receptors located on the serotonergic nerve terminals. In rat hippocampus, direct blockade of inhibitory α_2-heteroreceptors located on 5-HT terminals was suggested to be responsible for an increase in 5-HT release (De Boer et al., 1994; Mongeau et al., 1993; Numazawa et al., 1995; Tao and Hjorth, 1992). Such elevated hippocampal 5-HT neurotransmission may partially explain the facilitatory effect of the higher dose of zuclopenthixol on memory function. Nevertheless, opponent views exist regarding the role of serotonin in cognition (Meneses, 1999). The increase of noradrenergic function may provide an explanation for the facilitatory effect of zuclopenthixol on memory function since both dose levels of the drug enhanced NE levels. Augmented cortical noradrenergic function could particularly be crucial for mediation of the positive effect of the drug on retrieval memory since the lower dose showed higher efficacy in the memory task, and yet it only elevated cortical NE without changing either NE or 5-HT level in the hippocampus. The antagonistic action of zuclopenthixol on both α_1- and α_2-adrenergic receptors may underlie enhanced cortical NE level since blockade of these receptors was reported to cause compen-

satory activation of noradrenergic neurons with the resultant increase in intracellular NE level (Anden et al., 1970). The central presynaptic α_2-adrenoceptors were also reported to modulate the synthesis and release of NE in rat cortical synaptosomes (Garro et al., 1999). In addition, blockade of α_2-adrenergic receptors was reported to cause elevation of dialysate levels of NE in frontal cortex of rats (Millan et al., 2000). Alternatively, the enhanced cortical NE level may be explained by the antagonistic action of zuclopenthixol on serotonergic 5-HT2 receptors since the antagonistic effects of haloperidol, clozapine, olanzapine, risperidone, and ziprasidone on these receptors were found to result in an increase in NE release in prefrontal cortex (Westerink et al., 2001). Since memory retrieval of inhibitory avoidance task in cortical structures of the rat was found to be strongly modulated by β-noradrenergic receptors (Aguzzoli et al., 2001), elevated cortical NE level may further be suggested to affect β-adrenergic receptor function. In this study, the resultant increase in cortical NE level due to zuclopenthixol administration and the suggested relevance of this action to the nootropic effect of the drug could substantiate other reports demonstrating a facilitatory effect of cortical NE on cognitive function in experimental animals (Bymaster et al., 2002; Friedman et al., 1999; McCormick et al., 1991). It is therefore suggested that pharmacological modulation of cortical noradrenergic pathways may provide a valuable strategy for therapeutic intervention in schizophrenic patients exhibiting impaired memory function.

In conclusion, in psychotic patients, zuclopenthixol would be expected not only to have a good efficacy in controlling behavioral and psychotic symptoms, but also to preserve the cognitive function of such patients from further deterioration that could result with the use of other types of antipsychotic medications. Zuclopenthixol could also constitute a valuable therapeutic option in psychotic elderly patients, exhibiting further deterioration of cognitive function due to the normal aging process. Zuclopenthixol may not be expected to facilitate memory function of psychotic patients unless this experimental effort is substantiated by clinical investigation of its neurocognitive profile after chronic administration. Furthermore, clinical studies should investigate the effect of the drug on various types of memory function since one antipsychotic agent may have opposing effects on different memory types (Rosengarten and Quartermain, 2002; Terry et al., 2003). In this study, behavioral experiments were conducted on trained rats, and biochemical assays were performed on naïve ones, since performing all experiments on the same animals could confound the results of the biochemical assay by an interaction between conditioned fear and zuclopenthixol. Conditioned fear was reported to alter monoamine and acetylcholine brain levels (Evans and Kerkut, 1979; Hashimoto et al., 1999; Wedzony et al., 1996). Therefore, future research should establish the cause–effect relationship by attempting to identify whether defects in the adrenergic and serotonergic neurotransmission prevent the memory-facilitating effect of zuclopenthixol. Since a desirable cognitive effect has been reported for glutamate (Ohno and Watanabe, 1996), future studies should also be directed toward investigating the effect of zuclopenthixol on glutamatergic neurotransmission in brain areas implicated in control of learning and memory processes. In addition, it is suggested that pharmacotherapeutic efficacy in schizophrenia treatment could be broadened to include impact of antipsychotic medications on neurocognitive abilities. Research efforts should be directed toward conducting large rigorous trials investigating the cognitive effects of antipsychotics with diverse pharmacodynamic actions.

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