Pharmacology Biochemistry and Behavior, Vol. 60, No. 2, pp. 337–343, 1998

0091-3057/98 $19.00 + .00

ELSEVIER

PII S0091-3057(97)00591-1

Ameliorating Effect of *p*-Hydroxybenzyl Alcohol on Cycloheximide-Induced Impairment of Passive Avoidance Response in Rats: Interactions with Compounds Acting at 5-HT_{1A} and 5-HT_2 Receptors

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Received 25 April 1997; Revised 3 October 1997; Accepted 16 October 1997

HSIEH, M. T., C. R. WU AND C. C. HSIEH. *Ameliorating effect of* p-*hydroxybenzyl alcohol on cycloheximide-induced impairment of passive avoidance response in rats: Interactions with compounds acting at 5-HT_{1A} and 5-HT_2 receptors*. PHARMACOL BIOCHEM BEHAV **60**(2)337–343, 1998.—The effect of *p*-hydroxybenzyl alcohol (HBA) on cycloheximide (CXM)-induced impairment in the step-through passive avoidance task was investigated in rats and compared to the effect of the nootropic piracetam. HBA and piracetam significantly counteracted the CXM-induced shortening of retention latencies. The effect of HBA was a bell-shaped dose–response curve with a maximal effect of 5 mg/kg. The counteractive effect of HBA was not depressed by either scopolamine or mecamylamine. The serotonin (5-HT) releaser, *p*-chloroamphetamine, and presursor, 5-hydroxytryptophan, significantly antagonized the counteractive effect of HBA on the CXM-induced shortening of retention latencies. Furthermore, the counteractive effect was also inhibited by the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) and the 5-HT_2 receptor agoinst 1-(2,5-dimethoxy-4-iodophenyl)-2 aminopropane [(±)-DOI], but potentiated by the 5-HT_1 receptor antagonist (±)-pindolol and the 5-HT_2 receptor antagonist ritanserin. There results suggest that the beneficial effect of HBA on CXM-induced impairment is amplified by treatment with serotonergic receptor antagonists but reduced by serotonergic 5-HT_{1A} and 5-HT_2 receptor agonists, and insensitive to cholinergic manipulations. © 1998 Elsevier Science Inc.

p-Hydroxybenzyl alcohol Cycloheximide Cholinergic receptor Serotonergic receptor Passive avoidance task Piracetam

p-HYDROXYBENZYL alcohol (HBA) is a phenolic compound and is prepared from phenol and formaldehyde by hydroxymethylation. Early studies pointed out that HBA had sedative and anticonvulsive effects by acting at central GABA receptors (5), and possessed antioxidant and free radical scavenging activity (16). More recently, HBA attenuated the drug-induced acquisition impairment in the passive avoidance task, which acted through suppressing the dopaminergic and serotonergic activities (30,31).

In general, memory processes are divided into three stages: learning acquisition, memory consolidation, and retrieval. According to biochemical studies, memory consolidation needs the participation of protein, especially new protein transcription and synthesis (8). Thus, protein synthesis inhibitors such as cycloheximide impair memory consolidation in rodents (2,6). Furthermore, recent studies have pointed out that memory consolidation involves the activation, by neurotransmitters such as acetylcholine, dopamine, and serotonin, of recep-

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tor-linked enzymes responsible for synthesis of intra- and intercellular messages (15,18). In a series of studies, Nabeshima et al. pointed out that cycloheximide induced memory consolidation deficits mainly via disturbances in the cholinergic system and increased serotonergic activity in experimental animals (21,22). Therefore, cycloheximide-induced impairment appears to be a useful model for evaluating the mechanisms of the ameliorating drugs on memory consolidation.

In the present study, we attempted to clarify the role of the cholinergic and serotonergic neuronal systems on HBA-induced recovery from the cycloheximide-induced impairment in the passive avoidance task. We investigated whether the ameliorating effects of HBA were antagonized by cholinergic receptor antagonists, a serotonergic releaser, precursor, and agonists. We also employed the nootropic piracetam as positive control, because it enhances resistance to the learning and memory impairment induced by various drugs and increases the activities of central neurotransmitters such as acetylcholine and the monoamines (9).

METHOD

Animals

Male Sprague–Dawley rats, weighing 200–250 g, were housed in groups of six with free access to food (supplied and designed by Fwusow Industry Co. Ltd., Taiwan) and water and kept in a regulated environment (23 ± 1°C), wherein a 12-L:12-D cycle (light period: 0800 to 2000 h) was maintained. The rats were randomly assigned into each group supported the below experiments. The number of subjects in each group was 12 to 18 and is depicted in the figures. Then, the below drugs were administered and the behavioral assays were operated by double-blind method.

Step-Through Passive Avoidance Apparatus

Memory processes including acquisition, consolidation, and retrieval were assessed with a step-through passive avoidance task. The step-through passive avoidance task was used to measure the above three stages depending on drug-treated period. This apparatus was consisted of two compartments having a steel-rod grid floor (36 parallel steel rods, 0.3 cm in diameter set 1.5 cm apart). One of the compartments (48 × 20 × 30 cm) was equipped with a 20-W lamp located centrally at a height of 30 cm, and the other was dark compartment of same size, connected through a guillotine door (5 × 5 cm). The dark room was used during the experimental sessions that were conducted between 0900 and 1700 h.

Passive Avoidance Behavior with a Brief Shock

At the beginning of a training trial, the guillotine door connecting the light and dark compartment was closed. After each rat was placed in the light compartment with its back to the guillotine door, the door was opened and simultaneously the time (step-through latency, STL) taken by the rat to enter the dark compartment was measured with a stopwatch. Once the rat entered the dark compartment, the door was closed. An inescapable scrambled foot shock (1.0 mA for 2 s) was then delivered through the grid floor by MCU-101 Controller (Muromachi Kikai Co., Tokyo). The rat was removed from the dark compartment 5 s after administering the shock. The rat was then put back into its home cage until the retention trial, which was carried out 24 h later. The rat was once again placed in the light compartment, and as in the case of the training trial, the guillotine door was opened and the STL was recorded and used as a measure of retention (29). An upper cutoff time of 300 s was set.

In the first series of experiments, CXM (1.5 mg/kg, SC) was administered immediately after the training trial. HBA (0.5, 1, 5, 10, and 25 mg/kg, PO) were administered to CXM-treated rats 1 h before the training trial. Piracetam (50, 100, and 300 mg/kg, PO) was also administered to CXM-treated rats 1 h before the training trial.

In the second series of experiments, HBA (5 mg/kg, PO) was administered to CXM-treated rats 1 h before the training trial. SCOP (0.3 mg/kg, IP), MECA (1 mg/kg, IP), PCA (1 mg/kg, IP), 5-HTP (10 mg/kg, IP), PIN (10 mg/kg, IP), 8-OH-DPAT (0.025 mg/kg, IP), DOI (0.2 mg/kg, IP), and RIN (0.25 mg/kg, IP) were also given simultaneously with CXM.

Motor Activity With Nonshock Rats

To evaluate the effect of various drug combinations on motor activity in passive avoidance task, the same experimental steps were followed as described in the above section with the exception that rats received no foot shock during the training period. Twenty-four hours later, the retention trial was also carried out and the STL was recorded (14). The rats were given 1.5 mg/kg CXM in combination with the above-mentioned drugs.

Pain Threshold to Electric Stimulation

The threshold of flinch, jump, or vocalization produced by electric shock was measured by using the passive avoidance apparatus. Each rat was placed in the dark compartment of the passive avoidance task apparatus and the shock intensity was manually raised stepwise from 0.5 to 1.0 mA in increments of 0.1 mA until either a flinch, jump, or vocalization was observed. Duration of shock was 2 s, and the intershock interval was 15 s. The point at which the rat exhibited these responses was recorded (28). The rats were orally given doses of 0.5, 1, 5, 10, and 25 mg/kg HBA or 50, 100, and 300 mg/kg piracetam, 1 h before the training trial.

Drug Administration

p-Hydroxybenzyl alcohol (HBA), piracetam, cycloheximide (CXM), scopolamine hydrobromide (SCOP), mecamylamine (MECA), *p*-chloroamphetamine hydrochloride (PCA) and (±)-pindolol (PIN) were all purchased from Sigma Chemical Co. and dissolved in 0.9% saline. 1-(2,5-dimethoxy-4-iodophenyl)-2 aminopropane [(±)-DOI] was purchased from Research Biochemicals Inc. and also dissolved in 0.9% saline. 5-Hydroxytryptophan (5-HTP, Sigma Chemical Co.) was suspended in 0.5% carboxymethylcellulose (CMC, Hwa Hsing Chemical Co. Ltd.) in 0.9% saline. 8-Hydroxy-2-(di-n-propylamino) tetralin hydrobromide (8-OH-DPAT, Sigma Chemical Co.) was dissolved in 0.9% saline containing 0.5% ascorbic acid. Ritanserin (RIN, Research Biochemicals Inc.) was dissolved in distilled water along with 3 drops of lactic acid, and sodium bicarbonate was used to adjust the pH of the solution to about 4. These drugs were administered in a volume of 1 ml/kg body weight. HBA and piracetam were administered PO 1 h before the training trial. CXM (SC) and the other above drugs (IP) were administered immediately after training to avoid any direct acute effect on behavior in the training or retention trial.

Statistics

Because the data distribution from the passive avoidance task was truncated at 300, nonparametric Kruskal–Wallis

analysis followed by two-tailed Mann–Whitney *U*-tests were used to analyze the data. The *U*-value was then transformed into a *Z*-value. In addition, the data collected during motor activity and shock sensitivity was analyzed using a one-way analysis of variance, followed by Duncan's multiple range test. The criterion for statistical significance was $p < 0.05$ in all the above statistical evaluations.

RESULTS

Effects of HBA and Piracetam on CXM-Induced Impairment

CXM (1.5 mg/kg) injected immediately after the training trial significantly reduced the STL in the retention test ($H = 19.86$, $p < 0.0001$). The effects of pretraining administration of HBA at various doses on CXM-induced shortening of retention latencies are shown in Fig. 1. A Kruskal–Wallis test yielded a significant overall effect of HBA on the decremental effect of CXM ($H = 33.46$, $p < 0.0001$). Further, Mann–Whitney *U*-tests indicated that HBA at 1, 5, 10, and 25 mg/kg significantly counteracted CXM-induced shortening of retention latencies ($U = 51$, $Z = 2.09$, $p < 0.05$; $U = 6$, $Z = 4.18$, $p < 0.001$; $U = 21$, $Z = 3.48$, $p < 0.001$; $U = 44$, $Z = 2.41$, $p < 0.05$). The dose–effect curve was bell shaped, with a maximal effect occurring at 5 mg/kg. The nootropic, piracetam at 100 and 300 mg/kg, also significantly counteracted the CXM-induced shortening of retention latencies ($U = 15$, $Z = 3.0$, $p < 0.01$; $U = 1$, $Z = 3.86$, $p < 0.001$) (Fig. 1).

Effect of Cholinergic Receptor Antagonists on the Counteractive Effects of HBA on CXM-Induced Impairment

SCOP, a muscarinic receptor blocker, injected immediately after the training trial at 0.3 mg/kg did not cause memory disruption itself and did not abolish the counteractive effect of HBA at 5.0 mg/kg on CXM-induced impairment of passive avoidance response ($U = 77.0$, $Z = 0.63$, $p > 0.05$) (Fig. 2A). MECA, a nicotinic receptor blocker, injected immediately after the training trial at 1.0 mg/kg also did not cause memory disruption itself and did not abolish the counteractive effect of HBA at 5.0 mg/kg on CXM-induced impairment of passive avoidance response ($U = 56.0$, $Z = 0.62$, $p > 0.05$) (Fig. 2B).

Effects of Serotonergic Agonists and Antagonists on the Counteractive Effect of HBA on CXM-Induced Impairment

PCA, a 5-HT releaser, injected immediately after the training trial at 1.0 mg/kg did not cause memory disruption itself but markedly antagonized the counteractive effect of HBA at 5.0 mg/kg on CXM-induced impairment of passive avoidance response ($U = 17.0$, $Z = 3.32$, $p < 0.001$) (Fig. 3A). 5-HTP, a precursor of 5-HT, injected immediately after the training trial at 10 mg/kg, also did not cause memory disruption itself but markedly antagonized the counteractive effect of HBA at 5.0 mg/kg on CXM-induced impairment of passive avoidance response ($U = 39.0$, $Z = 2.31$, $p < 0.05$) (Fig. 3B).

8-OH-DPAT, a selective 5-HT_{1A} agonist, injected immediately after the training trial at 0.025 mg/kg, did not cause memory disruption itself but did abolish the counteractive effect of HBA at 5.0 mg/kg on CXM-induced impairment of passive avoidance response ($U = 13.0$, $Z = 3.65$, $p < 0.001$) (Fig. 4A). (±)-Pindolol, a 5-HT_1 antagonist, injected immediately after the training trial at 10 mg/kg, also did not prolong CXM-induced shortening of retention latencies itself ($U =$

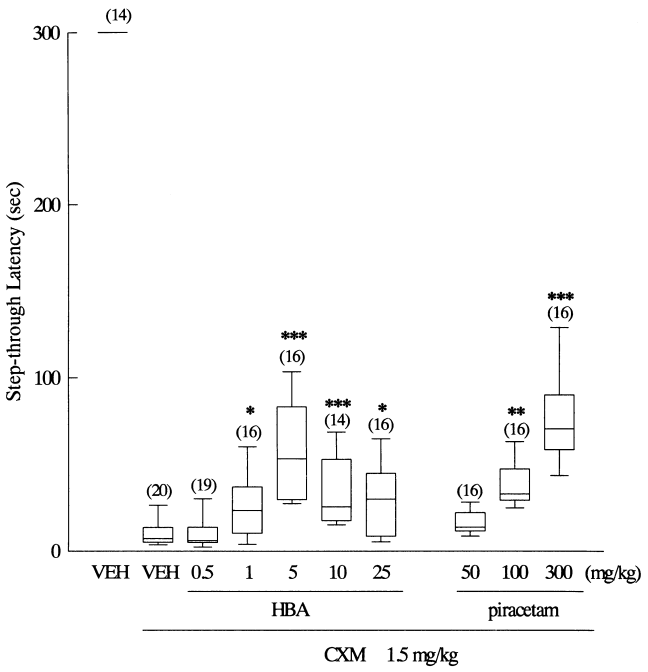

FIG. 1. Effects of *p*-hydroxybenzyl alcohol (HBA) and piracetam on CXM-induced impairment of passive avoidance response in rats. Each column represents the medians, 50% of the values and the range inside the 5th and 95th percentile. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ compared with CXM group.

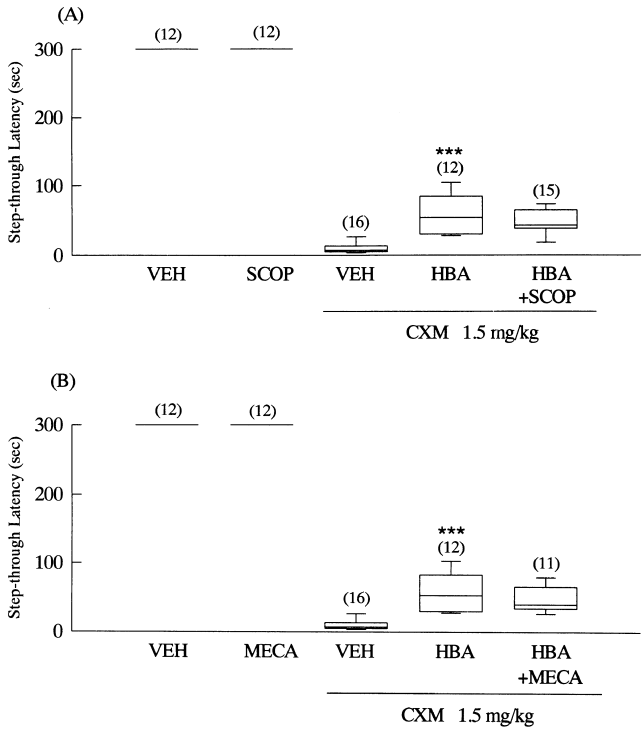

FIG. 2. Effects of (A) scopolamine (SCOP) and (B) mecamylamine (MECA) on *p*-hydroxybenzyl alcohol (HBA)-induced recovery from CXM-induced impairment of passive avoidance response in rats. Each column represents the medians, 50% of the values and the range inside the 5th and 95th percentile. $***p < 0.001$ compared with CXM/VEH group.

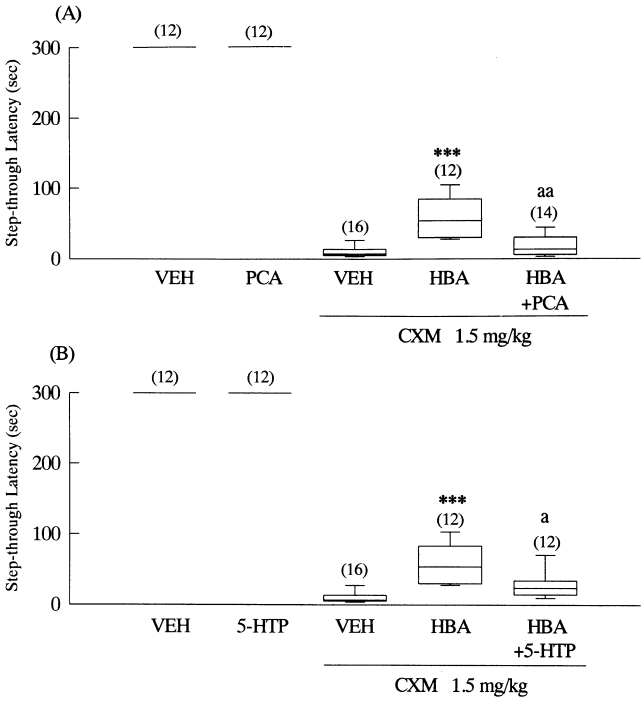

FIG. 3. Effects of (A) *p*-chloroamphetamine (PCA) and (B) 5-hydroxytryptophan (5-HTP) on *p*-hydroxybenzyl alochol (HBA)-induced recovery from CXM-induced impairment of passive avoidance response in rats. Each column represents the medians, 50% of the values and the range inside the 5th and 95th percentile. $^{*}p < 0.01$ compared with CXM/VEH group. $^{a}p < 0.05$, $^{aa}p < 0.01$ compared with CXM in combination with the HBA group.

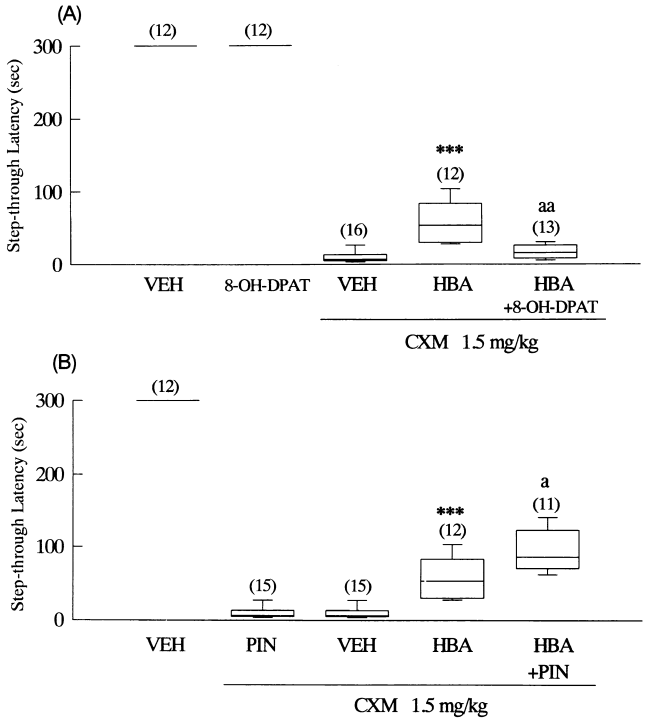

FIG. 4. Effects of (A) 8-hydroxy-2-(di-n-propylamino) tetralin hydrobromide (8-OH-DPAT) and (B) pindolol (PIN) on *p*-hydroxybenzyl alcohol (HBA)-induced recovery from CXM-induced impairment of passive avoidance response in rats. Each column represents the medians, 50% of the values and the range inside the 5th and 95th percentile. $^{***}p < 0.001$ compared with CXM/VEH group. $^{a}p < 0.05$, $^{aa}p < 0.01$ compared with CXM in combination with HBA group.

116.5, $Z = 0.14$, $p > 0.05$) but potentiated the counteractive effect of HBA at 5.0 mg/kg on CXM-induced impairment of passive avoidance response ($U = 28.0$, $Z = 2.34$, $p < 0.05$) (Fig. 4B).

DOI, a 5-HT_2/5-HT_{1C} agonist, injected immediately after the training trial at 0.2 mg/kg, did not cause memory disruption itself but abolished the counteractive effect of HBA at 5.0 mg/kg on CXM-induced impairment of passive avoidance response ($U = 13.0$, $Z = 3.41$, $p < 0.001$) (Fig. 5A). Finally, ritanserin, a selective 5-HT_2 receptor antagonist, injected immediately after the training trial at 0.25 mg/kg, also did not prolong CXM-induced shortening of retention latencies itself ($U = 75.0$, $Z = 0.64$, $p > 0.05$) but potentiated the counteractive effect of HBA at 5.0 mg/kg on CXM-induced impairment of passive avoidance response ($U = 1.0$, $Z = 4.72$, $p < 0.001$) (Fig. 5B).

Effects of HBA in Combination With Drugs on CXM-Treated Step Through Latencies in Nonshocked Rats

HBA and piracetam had no effect on the STL of nonshocked rats given CXM, except that HBA at 25.0 mg/kg prolonged the STL in the training trial ($p < 0.05$) (Table 1). HBA, in combination with the above-mentioned drugs, also had no effect on the STL of nonshocked rats given CXM (Table 2).

Pain Threshold to Electric Stimulation

As shown in Table 3, the flinch and vocalization thresholds of HBA at 0.5, 1, 5, 10, and 25 mg/kg were not different from the threshold for vehicle-treated rats ($p > 0.05$). Piracetam at 50, 100, and 300, mg/kg doses also did not significantly alter flinch and vocalization thresholds in rats ($p > 0.05$).

DISCUSSION

In the present study, piracetam and HBA counteracted a CXM-induced shortening of STL in passive avoidance retention; the maximal effect brought about by HBA was close to that produced by piracetam. These results confirm a dose–response analysis of the effect of HBA in a previous study (31).

Acquisition and performance of the passive avoidance task can be altered by the sensory, motivational, or motor effects. However, several aspects argue against the possibility that the passive avoidance response in drug-treated animals can be related to sensitivity to nociceptive stimuli or motor effects during training. Although our previous study indicated that HBA at 25 mg/kg did not alter horizontal activity in rats (31), Huang reported that HBA at 100 mg/kg reduced motor activity in mice (11). Therefore, the behavior observed in the passive avoidance task and the vocalization threshold of rats that received HBA or piracetam were demonstrated. The vocalization threshold of rats that received HBA or piracetam were normal in the training or retention trial, but HBA at 25 mg/kg prolonged the STL in the training trial. It appears from the present results and the previous report (11,31) that HBA at 25 mg/kg only altered attention in the passive avoidance task but selectively decreased motor activity at 100 mg/kg in the open-field test. The data demonstrated that the beneficial effect of

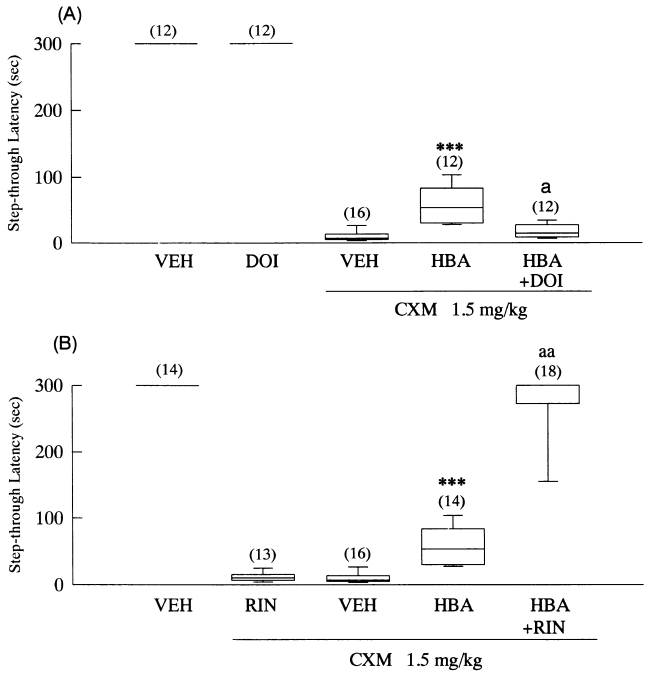

FIG. 5. Effect of (A) 1-(2,5-dimethoxy-4-iodophenyl)-2 aminopropane (DOI) and (B) ritanserin (RIT) on *p*-hydroxybenzyl alcohol (HBA)-induced recovery from CXM-induced impairment of passive avoidance response in rats. Each column represents the medians, 50% of the values and the range inside the 5th and 95th percentile. ***$p < 0.001$ compared with the CXM/VEH group. [a]$p < 0.05$, [aa]$p < 0.01$ compared with CXM in combination with the HBA group.

HBA on the CXM-induced impairment in the passive avoidance task was dose dependent. At these doses (1–10 mg/kg), this counteractive effect of HBA was mainly related to memory-related process, but at 25 mg/kg, this counteractive effect of HBA may have been partially attenuated via alteration of exploratory behavior and motor activity during the training trial.

TABLE 1

EFFECTS OF *p*-HYDROXYBENZYL ALCOHOL (HBA) AND PIRACETAM ON THE STEP-THROUGH LATENCY OF NONSHOCKED RATS GIVEN CXM

Drug	Dose (mg/kg)	Step-Through Latency (s)	
		Training Trial	Testing Trial
Control		5.946 ± 0.368	8.903 ± 1.870
CXM	1.5	7.192 ± 1.256	7.403 ± 0.744
CXM + HBA	0.5	7.454 ± 0.985	5.658 ± 0.648
	1.0	7.442 ± 0.565	5.179 ± 0.708
	5.0	9.952 ± 0.710	7.459 ± 1.282
	10.0	10.128 ± 1.142	7.372 ± 0.968
	25.0	10.515 ± 1.323*	6.362 ± 0.749
CXM + piracetam	50	7.574 ± 0.786	7.942 ± 1.074
	100	7.454 ± 0.985	8.211 ± 0.986
	300	7.442 ± 0.565	8.867 ± 1.245

The results are expressed as mean ± SE for eight rats for each group.

*$p < 0.05$ compared with CXM group.

TABLE 2

EFFECTS OF *p*-HYDROXYBENZYL ALCOHOL (HBA) IN COMBINATION WITH VARIOUS DRUGS ON THE STEP-THROUGH LATENCY OF NONSHOCKED RATS GIVEN CXM

Drug	Step-Through Latency (s)	
	Training Trial	Testing Trial
Control	5.946 ± 0.368	8.903 ± 1.870
CXM	7.192 ± 1.256	7.403 ± 0.744
CXM + HBA 5.0	9.952 ± 0.710	7.459 ± 1.282
CXM + HBA 5.0 + PCA	8.217 ± 1.125	7.824 ± 0.814
CXM + HBA 5.0 + 5-HTP	8.924 ± 0.982	6.571 ± 1.057
CXM + HBA 5.0 + 8-OHDPAT	9.502 ± 1.165	6.431 ± 0.812
CXM + PIN	10.283 ± 1.294	7.438 ± 0.875
CXM + HBA 5.0 + PIN	9.858 ± 0.976	7.262 ± 0.769
CXM + HBA 5.0 + DOI	7.656 ± 1.240	7.957 ± 0.926
CXM + RIN	9.482 ± 1.201	8.435 ± 0.864
CXM + HBA 5.0 + RIN	9.641 ± 0.967	9.128 ± 1.147

The results are expressed as mean ± SE for eight rats for each group.

Several investigators suggested that the cholinergic and serotonergic systems play complementary roles in the passive avoidance procedure and spatial memory paradigms. CXM-induced impairment of passive avoidance response has been found to act through the disturbance in the cholinergic neuronal system and the increase in the serotonergic neuronal system (21). Therefore, we further clarified the role of the cholinergic and serotonergic neuronal system on the HBA-induced recovery from CXM-induced impairment of passive avoidance response. The muscarinic receptor antagonist SCOP and nicotinic receptor antagonist MECA, which the used doses in the present study were below the efficacy dose in cognitive function and consistent with other reports (25,27), did not shorten the STL of the retention trial by themselves and did not inhibit the counteractive effects of HBA in amnesia. However, the serotonin releaser PCA and precursor 5-HTP, which the used doses in the present study were below the efficacy dose in cognitive function and consistent with other reports (21,24), did

TABLE 3

EFFECTS OF *p*-HYDROXYBENZYL ALCOHOL (HBA) ON THRESHOLDS OF RESPONSES TO ELECTRIC FOOT SHOCK IN RATS

Drug	Dose (mg/kg, PO)	Threshold (mA)	
		Flinch	Jump/ Vocalization
Control		0.75 ± 0.03	0.88 ± 0.01
HBA	0.5	0.78 ± 0.02	0.86 ± 0.01
	1.0	0.74 ± 0.02	0.86 ± 0.01
	5.0	0.78 ± 0.02	0.88 ± 0.01
	10.0	0.77 ± 0.02	0.86 ± 0.02
	25.0	0.77 ± 0.03	0.89 ± 0.02
Piracetam	50.0	0.77 ± 0.03	0.88 ± 0.01
	100.0	0.75 ± 0.03	0.87 ± 0.01
	300.0	0.78 ± 0.02	0.88 ± 0.02

The results are expressed as mean ± SE for eight rats for each group.

not impair the STL of the retention trial itself but significantly antagonized the counteractive effect of HBA. In fact, there is some evidence in the literature showing that the serotonergic systems play an important role in aversive behavior. The activity of serotonergic systems inhibited the behavioral response in the light–dark test box (4). Therefore, the present data similar to our previous study (12,31) suggest that HBA could counteract the CXM-induced shortening of retention latency via the serotonergic but not the cholinergic system.

Furthermore, 5-HT receptors are classified into several subtypes. 5-HT_1 and 5-HT_2 receptor subtypes have been reported to play an important role in learning and memory (17). The increase in serotonergic activity by 5-HT_2 receptors may decrease cholinergic activity and contribute to the CXM-induced impairment of passive avoidance response (21). Furthermore, activation of the serotonergic system by 5-HT_2 receptors inhibits the acetylcholine release in hippocampal slices (20). The counteractive effect of HBA on the CXM-induced impairment of passive avoidance response was significantly antagonized by the 5-HT_2/5-HT_{1C} receptor agonist DOI and potentiated by the 5-HT_2 receptor antagonist ritanserin, which the used doses in the present study were below the efficacy dose in cognitive function and consistent with other reports (17,26). Although Nabeshima et al. indicated that 5-HT_{1A} receptors did not participate in the CXM-induced impairment of passive avoidance response (21), 5-HT_{1A} receptors could participate in processing of stress-related information (10) and 5-HT_{1A} receptor agonists could induce the impairment of passive avoidance response via a postsynaptic mechanism (19). We also found that the counteractive effect of HBA was also inhibited by 5-HT_{1A} agonist 8-OH-DPAT and potentiated by 5-HT_1 antagonist (±)-pindolol, which the used doses in the present study were below the efficacy dose in cognitive function and consistent with other reports (1,26). On the other hand, (±)-pindolol is also a potent β-blocker, but our previous study has indicated that HBA attenuated the PCA-induced acquisition impairment in the passive avoidance task via blocking the serotonergic and α_1-receptors (13). Therefore, it appears that the counteractive effect of HBA on the CXM-induced impairment might act through decreased activity at postsynaptic 5-HT_{1A} and 5-HT_2 receptors. Furthermore, Riekkinen has reported that 5-HT_{1A} and 5-HT_2 receptor agonists impair the passive avoidance response and act through noncholinergic heteroreceptors (26). Our previous studies pointed out that HBA did not attenuate the SCOP-induced acquisition impairment and the beneficial effects of HBA on the PCA-induced acquisition impairment might act through 5-HT_{1A} and 5-HT_2 receptors (13,31). From these reports and our present data, this counteractive effect of HBA on the CXM-induced shortening of the retention latency might act through decreased activity at noncholinergic heteroreceptors, postsynaptic 5-HT_{1A}, and 5-HT_2 receptors. Moreover, recent studies pointed out other 5-HT receptor subtypes such as 5-HT_3 and 5-HT_4 receptors also play an important role in learning and memory (3,7). The role of 5-HT_3 and 5-HT_4 receptors in the counteractive effect of HBA might be further studied. On the other hand, Nabeshima et al. pointed out that piracetam-like nootropics could attenuate CXM-induced amnesia by interacting with GABAergic neuronal system and enhancing protein synthesis (23). HBA prevented the DNA degradation (16) and possessed central $GABA_A$ activity (5). Hence, the beneficial effect of HBA on the CXM-induced impairment of passive avoidance response can partially due to prevent the CXM-induced blockade on RNA translation.

Taking all these observations into consideration, it appears that the counteractive effect of HBA on the CXM-induced memory consolidation impairment of passive avoidance response can be amplified by 5-HT_{1A} and 5-HT_2 receptor antagonists but reduced by 5-HT_{1A} and 5-HT_2 receptor agonists, and not sensitive to cholinergic manipulations. The interaction among serotonergic system, GABAergic system, and protein synthesis in the HBA-induced recovery from CXM-induced memory consolidation impairment will be worthy of investigation in the future.

ACKNOWLEDGEMENTS

The present study was supported by a grant from the National Science Council of the Republic of China (NSC-86-2314-B-039-007-M13, NSC-87-2314-B-039-005) and China Medical College (85-003).

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