Psychopharmacology (1982) 77:66–73

Psychopharmacology
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An Analysis of Some Effects of Ethanol on Performance in a Passive Avoidance Task

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Abstract. In a one-trial step-through passive avoidance task, pretraining administration of ethanol was shown to decrease the latencies to step through at both training (day 1) and testing (day 2) for both rats and mice. A detailed analysis of these effects showed that they differed from those reported previously by others. The mechanisms underlying these effects of ethanol were also examined. The decreased day 1 latency to step through seen in rats may have been caused by an ethanol-induced hypermotility. However, ethanol did not increase the locomotor activity of mice, although it also reduced the day 1 latency to step through of this species. In addition, it was found that the ethanol-induced impairment of passive avoidance responding (i.e. the decreased day 2 latency to step through) was not state-dependent and that it was unlikely that it could be explained by a drug-induced impairment of task acquisition, long-term memory formation or memory recall. It also seemed unlikely that the impairment could be explained by an ethanol-induced decrease in shock sensitivity. Other mechanisms which may be involved are discussed.

Key words: Ethanol – Passive avoidance – Learning and memory – Locomotor activity – Shock sensitivity

Whilst the acute administration of ethanol has been shown to alter performance in a variety of learning tasks (Cappell and Herman 1972; Wallgren and Barry 1970 for reviews), these effects do not seem to have been examined in any detail. In particular, there is little evidence to indicate whether these alterations in performance are the results of effects of ethanol on learning and memory processes or if performance changes are predominantly brought about by ethanol-induced changes in motivation. In the present study an attempt was made to identify the mechanisms underlying the ethanol-induced changes in performance in a commonly used learning task, i.e. step-through passive avoidance responding.

Pretraining administration of ethanol has generally been shown to impair passive avoidance responding (Holloway 1972; MacInnes and Uphouse 1973; Parker and Alkana 1977). This was also found in the present study, and the possibility that impairment of learning and memory processes might be involved was investigated by altering various aspects of the training and/or testing procedure. In addition, as passive avoidance responding is an aversively motivated task and as ethanol has been reported to have analgesic effects (Bass et al. 1978; Brick et al. 1976), the possibility that the impairment by ethanol of passive avoidance responding could be explained by an ethanol-induced change in motivation via a reduction in pain sensitivity was also investigated.

As well as impairing passive avoidance responding (i.e. reducing the day 2 latency to step through), ethanol was found to markedly decrease the latency to step through to the dark chamber during training (day 1 latency to step through). The results of previous studies (Holloway 1972; MacInnes and Uphouse 1973) have also indicated that ethanol can have such an effect. In addition, a number of workers have reported that ethanol increases locomotor activity (Carlsson et al. 1972; Matchett and Erickson 1977), so the possibility that such a behavioural effect could account for the reduced day 1 latency to step through was investigated.

The present study was therefore undertaken to investigate further the effects of ethanol on passive avoidance responding and to gain more information regarding the possible behavioural mechanisms which underlie these effects.

Materials and Methods

Sydney White mice (20–40 g) and Sprague-Dawley rats (200–400 g) of both sexes were used. The mice were housed in groups of 20 and the rats in groups of four or five. All animals were experimentally naive and were only tested once. Food and water were provided ad libitum, except during experimental testing.

Ethanol (E) solutions were prepared by diluting 99.5% (v/v) absolute ethanol with 0.9% saline (S). The concentration of ethanol administered varied with the dose, because generally each animal was injected with 1 ml solution per 100 g body weight. However, in the experiments with mice, an injection volume of 2 ml solution per 100 g body weight was used to administer the 1.5, 2.0 and 4.0 g ethanol/kg body weight doses. In many experiments, the animals were treated only before training. However, in some experiments, the animals were treated before both training and testing: In these experiments, the animals fell into one of four treatment groups, which are designated SS, SE, EE or ES (the first letter indicating treatment before training and the second letter, treatment before testing). The drug treatments which animals were subjected to in each experiment are detailed in the results section. Unless otherwise stated, mice were treated 20 min, and rats 30 min before training and/or testing. These treatment times were also used when locomotor activity was examined. All injections were IP.

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0033-3158/82/0077/0066/$01.60

α-Methyl-*p*-tyrosine methyl ester (AMPT; Sigma, St. Louis, MO, USA) was dissolved in distilled water and administered IP 4 h before behavioural testing. The injection volume was 0.1 ml/100 g body weight. This drug was only used in experiments on locomotor activity.

Apparatus

Passive Avoidance: Mice. The passive avoidance equipment consisted of two compartments (light and dark chambers). The light chamber was constructed entirely of clear plastic and had inside dimensions of 7.5 × 9 × 14 cm. It was illuminated by a 25 W incandescent light positioned between the observer and the compartment. The dark chamber had a wooden roof and sides and the interior was painted black (inside dimensions 34 × 21.5 × 15.5 cm). The floor consisted of 44 stainless steel bars which were 3 mm in diameter and placed 5 mm apart. A foot shock of constant current DC pulses could be delivered to the bars by an active scanning-type shock generator and scrambler (R. S. Hales, Sydney). The light and dark compartments were connected by a 5 × 5 cm hole and this could be covered by a sliding metal door.

Passive Avoidance: Rats. The equipment used for rats differed from that used for mice in that the inside dimensions of the light chamber were 20 × 14.5 × 14 cm and the floor of the dark chamber consisted of 18 stainless steel bars which were 6.3 mm in diameter and spaced 19 mm apart.

Locomotor Activity. An open field was used for both mice and rats. This consisted of a black polypropylene box (inside dimensions 42 × 25 × 15.5 cm), the floor of which was marked with rectangles measuring 6.4 × 6.1 cm. The locomotor activity of mice was also examined using Animex activity meters (Farad, Hägersten, Sweden; Svensson and Thieme 1969). In this case, the mice were tested either in black polypropylene boxes (26 × 13 × 10 cm) or in clear plastic boxes (39 × 26 × 8 cm).

Procedure

Passive Avoidance. A similar basic procedure was used for both mice and rats. Any modifications of this procedure are outlined in the results section.

The standard day 1 (training) procedure was to place the animal in the light chamber so that it faced away from the hole leading into the dark chamber. The animal's latency to step through into the dark chamber was then measured with a stop-watch. The end-point taken was when the animal had all four paws on the grid floor of the dark chamber. Escape back into the light chamber was prevented by covering the connecting hole with the sliding metal door. A 5-s foot shock (1 mA constant current pulses) was delivered, after which the animal was removed from the dark chamber. Mice or rats which did not step through into the dark chamber within 180 or 120 s, respectively, were discarded. Such animals were generally distributed equally among all treatment groups.

The animals were tested (day 2), usually 24 h later, using the same procedure except that no shock was delivered. If the animal did not step through into the dark compartment within a predetermined time (300 s for mice, 180 s for rats), the trial was terminated and the latency to step through was recorded as 300 or 180 s, respectively.

The apparatus was cleaned with water after each animal was trained or tested.

Locomotor Activity. In the open field, the same procedure was used for both mice and rats. Locomotor activity was measured by counting line-crossings made by all four paws. Only forward locomotion was considered. The animals were tested individually. In the Animex activity meters, mice were either tested singly in the small black polypropylene boxes or in groups of three in the larger clear plastic boxes.

Analysis of the Results. All results are presented as the mean ± SEM, as this allows the effects of the various manipulations and treatments to be most clearly seen.

Because a cut-off latency was used on day 2, the results of the passive avoidance experiments were analysed using nonparametric statistical methods as described by Gibbons (1976) and Siegel (1956). In general, if a Kruskal-Wallis one-way analysis of variance indicated that further analysis was warranted, one of two types of analysis was carried out. For comparisons between two independent groups, Mann-Whitney *U*-tests were used. However, if a number of groups were to be compared with each other, Dunn's technique of multiple comparisons, as described by Gibbons (1976), was used.

The locomotor activity results were analysed using one-way analysis of variance, followed, if warranted, by the Newman-Keuls test (Winer 1971).

Results

Effects of Ethanol on Day 1 Latency

Male mice treated with 1.0 or 1.5 g ethanol/kg body weight exhibited significantly shorter latencies to step through to the dark chamber of the passive avoidance equipment during training than was the case for saline-treated controls (Fig. 1). However, the day 1 latencies of mice treated with 0.5 or 2.0 g ethanol/kg body weight were not significantly different from those of saline-treated animals. A dose of 2.5 g ethanol/kg body weight produced severe ataxia, which prevented the mice from being trained in the passive avoidance task. Doses of 1.0 and 1.5 g ethanol/kg body weight were also tested in female mice and were also found to significantly reduce the day 1 latency to step through (data not shown). [These and other results not detailed here have been described in full in Bammer G. (1980). An analysis of some effects of ethanol on two aversively-motivated learning tasks. Ph. D. thesis, University of Sydney, N.S.W., Australia, and are available on request.]

A similar experiment was conducted with rats and the effects of ethanol on the day 1 latency to step through are shown in Fig. 2. In this species, the day 1 latency was significantly reduced by doses of 1.5 and 2.0 g ethanol/kg body weight. These results were found for both male and female rats, though only the results obtained with male rats are shown.

The possibility that an ethanol-induced stimulation of locomotor activity could explain the reduced day 1 latency was examined. In male mice, neither of the doses of ethanol which decreased the latency to step through significantly altered locomotor activity as measured by counting line-crossings in an open field (Table 1). These doses of ethanol were also found to have no significant effect on locomotor activity when this was measured for up to 1 h using the Animex activity meters (data not shown).

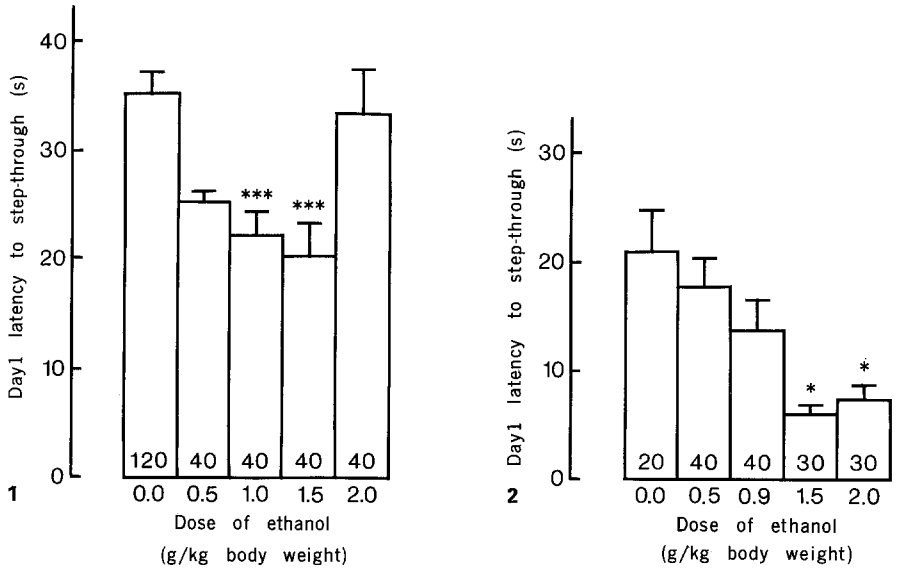

Fig. 1
Effects of ethanol on the day 1 latency to step through of male mice. Number of subjects is indicated at the base of each bar. ***$P < 0.001$ for difference from saline control (multiple comparisons)

Fig. 2
Effects of ethanol on the day 1 latency to step through of male rats. Number of subjects is indicated at the base of each bar. *$P < 0.05$ for difference from saline control (multiple comparisons)

Table 1. Effects of ethanol on the locomotor activity of male mice ($N = 10$ per group)

Time tested	Number of line-crossings		
	Dose of ethanol (g/kg body weight)		
	0	1.0	1.5
1st min	66 ± 6	72 ± 6	68 ± 16
Total in 2 min	123 ± 13	119 ± 12	125 ± 29
Total in 5 min	233 ± 35	202 ± 21	212 ± 57

In male rats, on the other hand, 1.5 g ethanol/kg body weight (the only dose tested) did significantly increase locomotor activity during minute 1 of exposure to an open field. During minute 2 of exposure, the locomotor activity of the ethanol-treated animals was no longer significantly different from that of saline-treated animals. In addition, the ethanol-induced stimulation was not blocked by 80 or 150 mg AMPT/kg body weight (Table 2).

Effects of Ethanol on Day 2 Latency

Pretraining treatment of male mice with 1.5 or 2.0 g ethanol/kg body weight significantly impaired passive avoidance responding, as there was a significant reduction in the day 2 latency to step through (Fig. 3). This reduction was found regardless of whether the animals were treated with the same dose of ethanol (EE group) or with saline (ES group) before testing. Lower doses of ethanol (0.5 and 1.0 g/kg body weight) had no significant effect and for each dose there was no significant difference between the EE and ES groups for the day 2 latency. Furthermore, none of the doses of ethanol used significantly altered the day 2 latency if administered only before testing (SE group, data not shown). A dose of 1.5 g ethanol/kg body weight administered to female mice had similar effects to those seen in males (data not shown, 2.0 g ethanol/kg body weight was not tested).

In male rats, 1.5 and 2.0 g ethanol/kg body weight also significantly decreased the day 2 latency to step through in both the EE and ES groups (Fig. 4). This was also found for female rats (data not shown). Lower doses of ethanol (0.3, 0.5 and 0.9 g/kg body weight) did not significantly alter passive avoidance responding. In another experiment, a significant impairment ($P < 0.05$, Mann-Whitney U-test) of passive avoidance responding was also seen in a male SE group treated with 1.5 g ethanol/kg body weight (other doses not examined). These animals ($N = 20$ per group) had a mean day 2 latency of 98 ± 18 s compared with 165 ± 11 s for the SS group.

Further Analysis of Ethanol-Induced Impairment of Passive Avoidance Responding

The ethanol-induced impairment of passive avoidance responding (reduced day 2 latency) was examined in some detail in a number of experiments using male mice.

Administering Ethanol at Various Times Before Training. From Fig. 5 it can be seen that administration of 2.0 g ethanol/kg body weight at times from 2 to 60 min before training significantly impaired passive avoidance responding. However, administration of ethanol immediately before training or at times longer than 60 min before training did not significantly alter passive avoidance responding. These animals were not given drug before testing.

Administering Ethanol After Training. Administration of 2.0 or 4.0 g ethanol/kg body weight immediately, 2, 5, 15 or 60 min after training did not significantly alter the day 2 latencies when compared with those of saline-treated animals (data not shown). No other drug treatment was administered to these animals either before training or before testing.

Altering the Length of the Training-Testing Interval. In this experiment, mice were tested for retention of the passive avoidance response at various times after training. Each mouse was tested only once. Administration of 2.0 g ethanol/kg body weight 20 min before training significantly impaired passive avoidance responding regardless of whether the training-testing interval was 5 min or 1 week. The results obtained for a number of training-testing intervals are shown in Fig. 6. Similar results (data not shown) were obtained for training-testing intervals of 2, 4, 8 and 12 h.

Table 2. Effects on the locomotor activity of male rats of ethanol (1.5 g/kg body weight) with and without prior treatment with α-methyl-*p*-tyrosine (AMPT). ($N = 9$ or 10 per group)

Treatment with 80 mg AMPT/kg body weight				
Time tested	Number of line-crossings			
	Drug treatment			
	Saline-saline	AMPT-saline	Saline-ethanol	AMPT-ethanol
1st min	47 ± 3	48 ± 4	87 ± 6**	73 ± 8**
2nd min	23 ± 3	21 ± 1	30 ± 8	27 ± 7

Treatment with 150 mg AMPT/kg body weight				
Time tested	Number of line-crossings			
	Drug treatment			
	Saline-saline	AMPT-saline	Saline-ethanol	AMPT-ethanol
1st min	42 ± 3	39 ± 3	68 ± 10*	59 ± 4*
2nd min	26 ± 3	27 ± 5	34 ± 7	17 ± 4

Difference from both controls (Newman-Keuls test), $*P < 0.05$; $**P < 0.01$

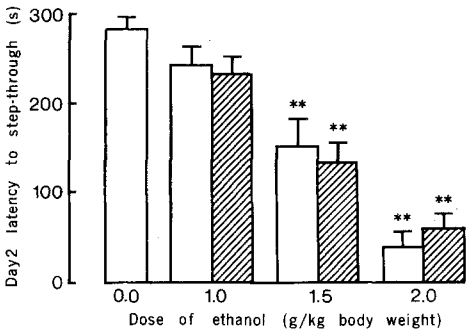

Fig. 3. Effects of ethanol on the day 2 latency to step through of male mice ($N = 20$). Open bars represent the SS or EE groups, whereas hatched bars represent the ES groups. ** $P < 0.01$ for difference from the SS group (multiple comparisons)

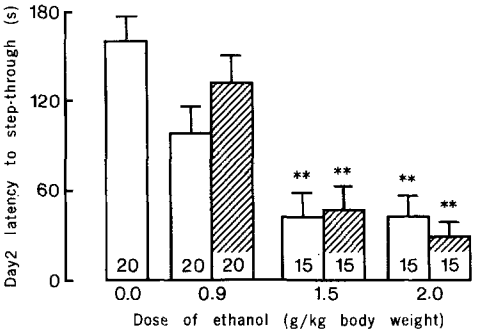

Fig. 4. Effects of ethanol on the day 2 latency of step through of male rats. Number of subjects is indicated at the base of each bar. Open bars represent the SS or EE groups, whereas hatched bars represent the ES groups. ** $P < 0.01$ for difference from the SS group (multiple comparisons)

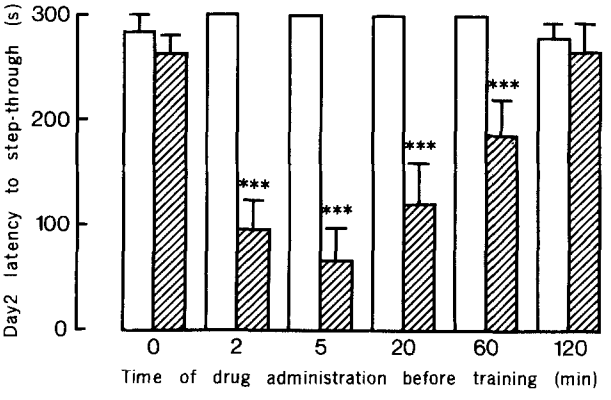

Fig. 5. Effects on the day 2 latency to step through of administering 2.0 g ethanol/kg body weight at various times before training to male mice ($N = 10$). Open bars represent saline-treated animals and hatched bars represent ethanol-treated animals. *** $P < 0.001$ for difference from appropriate saline control (Mann-Whitney *U*-test)

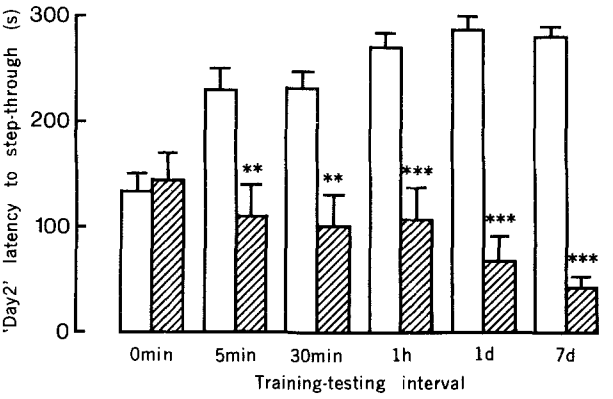

Fig. 6. Effects of 2.0 g ethanol/kg body weight on the 'day 2' latency to step through when training-testing intervals of various lengths were used ($N = 20$). Open bars represent saline-treated animals and hatched bars represent ethanol-treated animals: ** $P < 0.01$ for difference from saline control given the same training-testing interval; *** $P < 0.001$ for difference from saline control given the same training-testing interval (Mann-Whitney *U*-tests)

Table 3. Effects of ethanol (2 g/kg body weight) on passive avoidance responding when animals were trained to criterion ($N = 10$)

Drug treatment	Number of trials to criterion	Day 2 latency to step through (s)
Saline	3 ± 0.1	286 ± 14
Ethanol	3 ± 0.4	76 ± 38*

* $P < 0.05$ for difference from saline control (Mann-Whitney U-test)

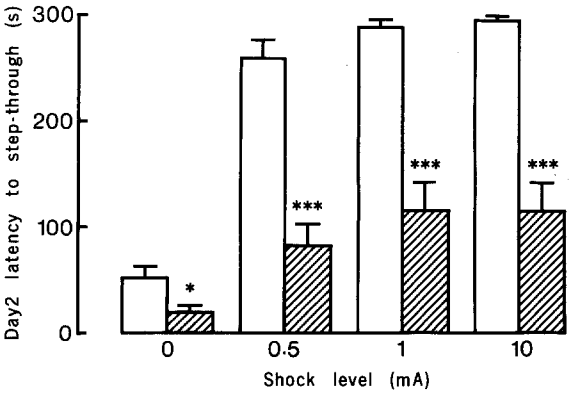

Fig. 7. Effects of 2.0 g ethanol/kg body weight on the day 2 latency to step through when the intensity of the shock administered during training was varied ($N = 20$). Open bars represent the SS groups and hatched bars represent the ES groups: *$P < 0.05$ for difference from saline control trained with the same shock intensity; ***$P < 0.001$ for difference from saline control trained with the same shock intensity (Mann-Whitney U-tests). See text for other statistics

However, if the animals were tested immediately after training, there was no significant difference between saline- and ethanol-treated animals. It should be noted that in this case the mean test ('day 2') latency to step through of the saline-treated animals was significantly shorter ($P < 0.001$; Mann-Whitney U-test) than when a 24-h training-testing interval was used.

Training to Criterion Instead of One-Trial Training. Mice were trained to criterion by returning them to the light chamber of the passive avoidance equipment immediately after foot shock in the dark chamber. This was repeated until they stayed out of the dark chamber for 300 s. In this experiment, the mice were given drug only before training. There was no significant difference between saline- and ethanol-treated animals in the mean number of trials to criterion. However, although the ethanol-treated animals acquired the passive avoidance task on day 1, they still exhibited a significant impairment of passive avoidance responding when tested 24 h later (Table 3).

Using Various Shock Intensities. In this experiment, the shock levels used were 0, 0.5, 1 or 10 mA and the results presented in Fig. 7 are for the SS group and for the ES group treated with 2.0 g ethanol/kg body weight. It can be seen that animals which were not shocked during training had shorter mean day 2 latencies to step through than those of animals which were shocked during training. This was seen in animals of both drug treatment groups and the differences were statistically significant in both groups at the $P < 0.001$ level (multiple comparisons). In both treatment groups, animals shocked with 1 or 10 mA had longer day 2 latencies than animals shocked with 0.5 mA, although these differences were not always statistically significant. The day 2 latencies of animals shocked with 1 mA did not differ significantly from those of animals shocked with 10 mA. Furthermore, for all shock levels, including the no-shock condition, the ES groups had significantly shorter mean day 2 latencies to step through than the SS groups. Results similar to those obtained for the ES groups were also found for EE groups (data not shown).

Discussion

Alterations in both the day 1 and day 2 latencies to step through were produced by a narrow range of doses of ethanol. In mice, 1.0 and 1.5 g ethanol/kg body weight had the most pronounced effects in reducing the day 1 latency, whereas a reduction in the day 2 latency was most clearly seen when either 1.5 or 2.0 g ethanol/kg body weight was administered before training. In rats, on the other hand, 1.5 and 2.0 g ethanol/kg body weight administered before training had the most marked effects in decreasing both the day 1 and day 2 latencies. Although there seemed to be some species-specific differences in the effects of ethanol on passive avoidance responding, there did not seem to be differences between sexes within each of the species.

Effects of Ethanol on Day 1 Latency

In this study ethanol was found to produce a marked decrease in the day 1 latency to step through. Although other workers have found indications of such an effect, it has not been as pronounced as reported here. Holloway (1972), for example, found that the reduction in the day 1 latency produced by 1.5 g ethanol/kg body weight was not statistically significant and MacInnes and Uphouse (1973) found that ethanol doses of 1.5 g/kg body weight or higher significantly decreased the initial day 1 latency to step through in only one of the three mouse strains which they studied. It would seem, therefore, that the effects of ethanol on the day 1 latency to step through may be sensitive to the precise experimental conditions used.

It was hypothesised that the ethanol-induced reduction in the day 1 latency to step through could be explained by an ethanol-induced stimulation of locomotor activity. Indeed, a number of workers have reported that ethanol increased locomotor activity (e.g. Carlsson et al. 1972; Matchett and Erickson 1977). However, it should also be noted that others have found similar doses of ethanol to be ineffective in altering locomotor activity (Castellano et al. 1976; Eriksson and Wallgren 1967) or to decrease it (Chesher 1974; Oliverio and Eleftheriou 1976). It was shown in this study that ethanol (1.0 and 1.5 g/kg body weight) did not alter locomotor activity in mice; though 1.5 g ethanol/kg body weight did produce a brief period of hypermotility in rats. The time at which this hypermotility occurred, i.e. immediately after exposure to the open field and 30 min after ethanol treatment, corresponded to the time at which the reduced day 1 latency was seen. It therefore seems unlikely that an ethanol-induced stimulation of locomotor activity can explain the drug's effect on the day 1 latency of mice, although it may be a valid explanation of the effect in rats.

It is also interesting to compare the ethanol-induced hypermotility found in rats in this study with that reported by

Carlsson et al. (1972). The two effects seem to differ, for, whereas Carlsson et al. (1972) observed an increase in locomotor activity which lasted for 30 min, the hypermotility reported in this study lasted for only 1 min. Although locomotor activity was only measured over 2 min in this study, previous experiments by one of us (Chesher 1974), in which the same strain of rats was used, showed that this dose of ethanol did not stimulate locomotor activity when measured over longer time periods. In addition, the stimulation of activity observed by Carlsson et al. (1972) could be prevented by prior administration of AMPT, whereas this drug was ineffective in the experiments presented here.

The reduced day 1 latency to step through of mice cannot be explained by an effect of ethanol on locomotor activity. Two possible explanations which may warrant further examination are as follows: (1) that ethanol increases sensitivity to light, thus making the light chamber more aversive and reducing the latency to step through to the dark chamber, and (2) that ethanol reduces sensitivity to odour so that, whereas odours in the dark chamber which have not been removed by the cleaning process (washing with water) may increase the latency to step through of saline-treated animals, these odours do not have this effect on ethanol-treated animals. There is evidence (Archer 1975 for review) that odours left in equipment by one animal may affect the performance of subsequently tested animals and especially that odours from stressed animals are avoided. In addition, Whittier and McReynolds (1965) have cited evidence that odours may not be removed if the equipment is only washed with water. There is little evidence to support either of the above contentions, although some results from human studies (Wallgren and Barry 1970 for review) suggest that ethanol both increases sensitivity to light and decreases sensitivity to odour.

It is also possible that effects of ethanol on general exploratory activity, rather than on just locomotor activity, may be responsible for decreasing the day 1 latency to step through. However, evidence from the literature indicates that the effects of ethanol on exploratory activity are not clear-cut and seem to depend, at least in part, on the behaviour taken as a measure of such activity. For example, File and Wardill (1975) found that, whereas ethanol increased head-dipping it did not significantly affect rearing. Eriksson and Wallgren (1967), on the other hand, suggested that ethanol reduced exploratory activity as it significantly reduced the time spent in behaviours other than locomotor activity (including rearing) in an open field. It would seem that the effects of ethanol on exploratory activity would warrant further examination per se, as well as as a possible explanation for the effects of ethanol on the day 1 latency to step through in a passive avoidance task.

Effects of Ethanol on Day 2 Latency

The results of this study indicate that administration of ethanol before training was the factor of major importance in decreasing the day 2 latency to step through. In male rats, but not in mice, administration of ethanol before testing was also shown to decrease the day 2 latency, though this effect was not as pronounced as that induced by administering the same dose of ethanol before training. It is possible that the impairment produced in rats by administering ethanol before testing may be explained by the ethanol-induced hypermotility already discussed, as this may have produced response disinhibition.

The impairment of passive avoidance responding seen in animals treated with ethanol before training does not seem to be the result of changes in the drugged state between training and testing, because similar day 2 latencies to step through were found in the EE and ES groups. These results differ from those of both Holloway (1972) and MacInnes and Uphouse (1973). Holloway (1972) found evidence for an asymmetrical state-dependent effect of ethanol, in that ES-treated rats had a significantly shorter mean day 2 latency to step through than EE-treated rats, and MacInnes and Uphouse (1973) found that the effects of ethanol differed with the strain of mouse and the dose of ethanol used. It can be concluded that, although administration of ethanol before training commonly impairs passive avoidance responding, the precise nature of this effect may be variable and is likely to be sensitive to the experimental conditions used.

The ethanol-induced impairment of passive avoidance responding may have been due to effects on learning and memory processes. This possibility was explored in experiments in which various aspects of the training and/or testing procedure were altered. It was shown that ethanol did not affect passive avoidance responding when administered to mice before testing, although it did impair responding when administered to male rats. This suggests that, in mice at least, ethanol did not affect the ability to recall a previously learnt task. The effect observed in rats may be explained by an ethanol-induced impairment of recall ability or, as already indicated, by response disinhibition brought about by the ethanol-induced hypermotility.

It was also shown that ethanol did not affect passive avoidance responding when administered immediately or at short intervals after training. This suggests that ethanol did not impair the formation of long-term memory. These findings are in agreement with those of Parker and Alkana (1977) and Prado de Carvalho et al. (1978). It is interesting to note, however, that Alkana and Parker (1979) reported that administration of ethanol after training could facilitate retention of passive avoidance responding. The design of the experiments reported here was such that a facilitation of passive avoidance responding could not be observed if it occurred. This was primarily because of the comparatively high level of shock used, as this ensured that control animals generally exhibited perfect retention.

The results of two of the experiments performed as part of this study also indicated that ethanol did not impair the ability of male mice to acquire the passive avoidance response. In particular, when mice were trained to criterion instead of being given a single training trial, it was shown that there was no significant difference between ethanol- and saline-treated animals in the number of trials needed to achieve criterion. Furthermore, even though ethanol-treated animals were shown to have acquired the passive avoidance response, their performance was still impaired when tested 24 h later. This is consistent with results from single training trial experiments in which animals were tested immediately after training (Fig. 6). Under these conditions, the latencies to step through during testing of ethanol-treated animals did not differ significantly from those of saline-treated animals. These results contrast with the findings of MacInnes and Uphouse (1973), which indicated that ethanol impaired acquisition of passive avoidance responding.

Although it seems unlikely that the ethanol-induced impairment of passive avoidance responding in mice can be explained by effects of this drug on task acquisition (and

hence immediate memory formation), formation of long-term memory or memory recall ability, the results of this study do not rule out the possibility that ethanol may have affected the formation of short-term memory (using the terminology of McGaugh 1966). Indeed, the effects of ethanol were shown to be time-specific. An examination of the effects of administering ethanol to mice at various times before training revealed that a decrease in the day 2 latency to step through was only observed if animals were trained with substantial levels of ethanol present in the blood and/or brain. In particular, no impairment of passive avoidance responding was seen if animals were trained in the passive avoidance task (1) immediately after ethanol administration, before the drug had had time to be distributed throughout the body or (2) 2 h after ethanol administration by which time metabolism of the ethanol would have greatly reduced blood and brain levels. In addition, the results depicted in Fig. 6 indicate that a significant impairment of passive avoidance responding was already evident 5 min after training. These results indicate that ethanol may have impaired the formation of short-term memory, which would be consistent with the findings in humans reviewed by Ryback (1971). However, the evidence presented here is by no means conclusive.

It is also possible that ethanol impaired performance in the passive avoidance task by an alteration in motivation, rather than by an effect on learning and memory processes. Such an alteration in motivation could be produced by a drug-induced reduction in shock sensitivity similar to that reported by Bass et al. (1978) and Brick et al. (1976). It was found that administration of foot shock during training significantly increased the day 2 latencies to step through of animals in all treatment groups compared with the latencies seen when no foot shock was used during training (see Fig. 7). This indicates that ethanol-treated animals had at least some sensitivity to foot shock. In addition, it would be expected that increasing the level of shock would increase the response to shock if this was submaximal. As an increase in the level of foot shock from 1 to 10 mA did not significantly alter the day 2 latency of either saline- or ethanol-treated animals, it seems likely that both groups were displaying maximum shock sensitivity to the 1 mA shock. Although this evidence is not conclusive, it does suggest that the ethanol-induced impairment of passive avoidance responding was unlikely to have been caused by an ethanol-induced decrease in shock sensitivity.

The results of this study do not, however, rule out the possibility that ethanol impaired passive avoidance responding by altering the endocrinological response to stress and hence the association between foot shock and the passive avoidance situation. The consensus of evidence, reviewed by Schenker (1970) and Stokes (1971) and supported by the more recent studies of Kakihana (1976) and Pohorecky et al. (1978), indicates that ethanol activates the endocrine systems involved in the reaction to stress. One possible explanation for the ethanol-induced impairment of passive avoidance responding is therefore that, because ethanol itself produces endocrinological effects associated with stress, there is a weakened association between the stress caused by foot shock and the passive avoidance situation. Further investigations may shed more light on the usefulness of this explanation.

It is also puzzling to note that the mice which were treated with ethanol prior to training (ES), but which received no foot shock, still exhibited a significantly shorter day 2 latency to step through than did the saline controls (SS). This finding suggests that the aversive nature of the foot shock may not be the predominant factor in the nature of the ethanol effect on passive avoidance responding. One possible explanation for this phenomenon is that ethanol may impair habituation to a novel environment. Evidence to support this view has been obtained in our laboratory utilising the hole-board test (unpublished data). On the other hand, File (1976) found no effect of ethanol on habituation, though the highest dose of ethanol studied was only 0.8 g/kg body weight, which was below the effective doses used in this study. A further investigation in this area would also be profitable.

In conclusion, the results both of this and of earlier studies (Holloway 1972; MacInnes and Uphouse 1973) indicate that the effects of ethanol on passive avoidance responding are complex. They seem to be sensitive to species, strain and procedural differences and the behavioural mechanisms underlying the effects remain to be fully elucidated. The results of this study do, however, give some indication of which mechanisms are unlikely to be involved in the effects of ethanol on passive avoidance responding. In particular, it was found that, although the decreased day 1 latency to step through seen in ethanol-treated rats may have been caused by an ethanol-induced hypermotility, this mechanism could not explain the reduced latency of mice. In addition, the ethanol-induced impairment of passive avoidance responding did not seem to be caused by drug-induced impairment of response acquisition or of long-term memory formation or of memory recall or by an ethanol-induced decrease in shock sensitivity.

Acknowledgements. The authors would like to thank Dr. D. H. Overstreet for his comments on an earlier version of the manuscript and Ivan Fox for his assistance with the illustrations. The first author gratefully acknowledges financial assistance from an Australian Government Postgraduate Research Award. Portions of this work were presented at the tenth annual meeting of the Australian Society for Clinical and Experimental Pharmacology, Flinders Medical Centre, Adelaide, November, 1976, and at the British Pharmacological Society meeting, National Institute for Medical Research, Mill Hill, January, 1977.

References

Alkana RL, Parker ES (1979) Memory facilitation by post-training injection of ethanol. Psychopharmacology 66:117–119

Archer J (1975) Rodent sex differences in emotional and related behavior. Behav Biol 14:451–479

Bass MB, Friedman HJ, Lester D (1978) Antagonism of naloxone hyperalgesia by ethanol. Life Sci 22:1939–1946

Brick J, Sun JY, Davis L, Pohorecky LA (1976) Ethanol and the response to electric shock in rats. Life Sci 18:1293–1298

Cappell H, Herman CP (1972) Alcohol and tension reduction: A review. Q J Stud Alcohol 33:33–64

Carlsson A, Engel J, Svensson TH (1972) Inhibition of ethanol-induced excitation in mice and rats by α-methyl-*p*-tyrosine. Psychopharmacologia 26:307–312

Castellano C, Filibeck U, Oliverio A (1976) Effects of heroin, alone or in combination with other drugs, on the locomotor activity in two inbred strains of mice. Psychopharmacology 49:29–31

Chesher GB (1974) Facilitation of avoidance acquisition in the rat by ethanol and its abolition by α-methyl-*p*-tyrosine. Psychopharmacologia 39:87–95

Eriksson K, Wallgren H (1967) Behaviour of rats under the influence of ethyl alcohol in an open-field situation. Scand J Psychol 8:257–267

File SE (1976) A comparison of the effects of ethanol and chlordiazepoxide on exploration and on its habituation. Physiol Psychol 4:529–532

File SE, Wardill AG (1975) Validity of head-dipping as a measure of exploration in a modified hole-board. Psychopharmacologia 44:53–59

Gibbons JD (1976) Nonparametric methods for quantitative analysis. Holt, Rinehart and Winston, New York

Holloway FA (1972) State-dependent effects of ethanol on active and passive avoidance learning. Psychopharmacologia 25:238–261

Kakihana R (1976) Adrenocortical function in mice selectively bred for different sensitivity to ethanol. Life Sci 18:1131–1138

MacInnes JW, Uphouse LL (1973) Effects of alcohol on acquisition and retention of passive-avoidance conditioning in different mouse strains. J Comp Physiol Psychol 84:398–402

Matchett JA, Erickson CK (1977) Alteration of ethanol-induced changes in locomotor activity by adrenergic blockers in mice. Psychopharmacology 52:201–206

McGaugh JL (1966) Time-dependent processes in memory storage. Science 153:1351–1358

Oliverio A, Eleftheriou BE (1976) Motor activity and alcohol: Genetic analysis in the mouse. Physiol Behav 16:577–581

Parker ES, Alkana RL (1977) Effect of ethanol on memory storage processes. Soc Neurosci Abstr 3:299

Pohorecky LA, Newman B, Sun J, Bailey WH (1978) Acute and chronic ethanol ingestion and serotonin metabolism in rat brain. J Pharmacol Exp Ther 204:424–432

Prado de Carvalho L, Vendite DA, Izquierdo I (1978) A near-lethal dose of ethanol, given intraperitoneally, does not affect memory consolidation of two different avoidance tasks. Psychopharmacology 59:71–74

Ryback RS (1971) The continuum and specificity of the effects of alcohol on memory: A review. Q J Stud Alcohol 32:995–1016

Schenker VJ (1970) Effects of ethanol on the endocrines. In: Trémolières J (ed) Alcohols and derivatives. International Encyclopedia of Pharmacology and Therapeutics, Section 20, Vol 1. Pergamon, Oxford, pp 261–274

Siegel S (1956) Nonparametric statistics for the behavioral sciences. McGraw Hill-Kogakusha, Tokyo

Stokes PE (1971) Alcohol-endocrine interrelationships. In: Kissin B, Begleiter H (eds) The biology of alcoholism, Vol 1. Plenum, New York, pp 397–436

Svensson TH, Thieme G (1969) An investigation of a new instrument to measure motor activity of small animals. Psychopharmacologia 14:157–163

Wallgren H, Barry III H (1970) Actions of alcohol, Vol 1. Elsevier, Amsterdam

Whittier JL, McReynolds P (1965) Persisting odours as a biasing factor in open-field research with mice. Can J Psychol 19:224–230

Winer BJ (1971) Statistical principles in experimental design. Second edition. McGraw Hill, New York

Received August 14, 1981; Final version January 7, 1982