THE EFFECT OF A BETA ADRENERGIC AGONIST, ISOPROTERENOL, AND AN ANTICHOLINESTERASE, ESERINE, ON ETHANOL-INDUCED INTOXICATIONE IN THE RAT

A Thesis

by

Kevin Charles Oeffinger

Submitted to the Honors Program
of Texas A&M University
in partial fulfillment of the requirement for
the Fellowship Program

April 24, 1978

Major Subject: Biology

TABLE OF CONTENTS

FIGURES LISTED

ACKNOWLEDGEMENTS

I would like to express my deep gratitude to Dr. William R. Klemm for his patience and help throughout the project. I am especially thankful for the countless times in which he stopped some of his own work to help me.

I also extend my thanks and appreciation to Joe Mikeska, Clinton Mallari and David Stevens for their help in the laboratory.

I owe my moral support to the typist, Patty Leathers. Without her help in the more frustrating times, it would have been much more difficult.

Finally, I thank the good Lord for helping me in all ways.

ABSTRACT

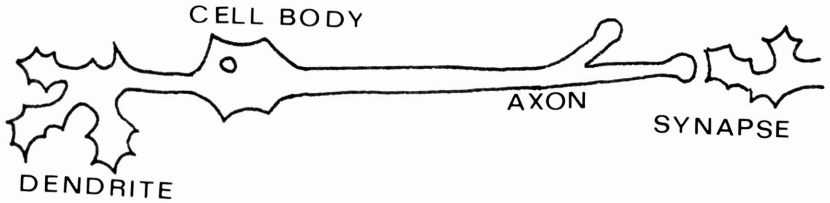
This study was designed to determine the effects of eserine and isoproterenol on ethanol-induced intoxication in the rat. The cortical EEG (recording from the frontal and occipital lobes), four behavioral tests, and a coordination test were used as indicators of intoxication. Eserine (0.2 mg/kg) blocked the ethanol-induced deactivation of the EEG, but the animals remained behaviorally intoxicated.

Isoproterenol (0.05, 0.1, 0.2 mg/kg) caused a decrease in the ethanol deactivation and behaviorally blocked intoxication. Isoproterenol by itself deactivates the EEG. Propranolol (10 mg/kg), a Beta blocker, potentiated the effect of ethanol, both by an increase in deactivation and an increase in the intoxication state. It was concluded that isoproterenol antagonizes the action of ethanol.

INTRODUCTION

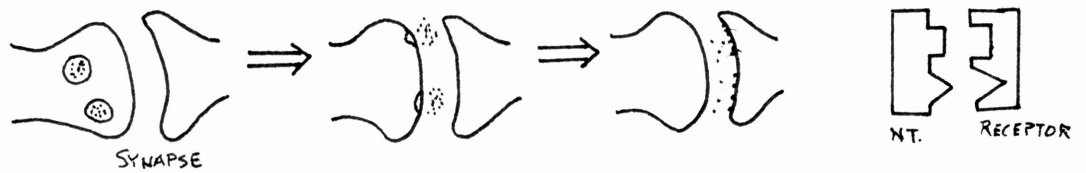
Among the various drugs of abuse, none have achieved the wide popularity of alcohol. In spite of this, mechanisms by which alcohol acts are still poorly understood. There are several important reasons to study alcohol. First, by understanding its action, one has a chance to develop effective methods for preventing alcohol addiction, or alcoholism. Second, it is possible that one might systematically develop a drug that could antagonize the intoxicating action of alcohol (i.e. a "sober-up" pill). Finally, by learning more about the mechanisms by which alcohol acts, one may better understand the normal functions of the brain.

Before the present research of ethanol is discussed, a few key principles need to be explained. In the nervous system, the neuron is the morphological and functional unit. The neuron consists of three primary structures: the cell body (soma), the axon, and the dendrite. The junction between two neurons, referred to as the synaptic cleft, is about 200 Å from the first to the second neuron.



An impulse is conducted from the dendrites, through the cell body, and down the axon. When the impulse reaches

the terminal region of the axon (the bouton), it causes the release of a chemical, the neurotransmitter, into the synaptic cleft. When the neurotransmitter is released, it binds to the receptors on the dendrite. This interaction is stereospecific.



If there is a large enough number of these bindings, then the second neuron is either hyperpolarized or depolarized, depending upon the type of neuron and transmitter. Hyperpolarization results in the inhibition of the second neuron. Depolarization results in the initiation of the impulse in the second neuron.

One can alter this action in the synapse by the use of various drugs. An agonist mimics the action of the neurotransmitter by interacting with the receptors. A blocker blocks or antagonizes the action of the neurotransmitter.

Another mode of altering the action of the neurotransmitter is to inhibit its metabolism so that it has a longer lasting effect.

Several chemicals known to be neurotransmitters. Two of these are acetylcholine and norepinephrine. Acetylcholine is the transmitter in the cholinergic system. Eserine is a drug which inhibits the metabolism of acetylcholine, thus giving acetylcholine a persistent effect.

Norepinephrine is the neurotransmitter in the noradrenergic system. This system is divided into alpha and beta receptors. This present study deals with the beta receptors. Isoproterenol is a beta agonist, so it increases the activity in the beta receptors. Propranolol, on the other hand, is a beta blocker and thus decreases the activity in the beta receptors.

Other points that need explanation concern the electroencephalogram (EEG). The EEG is a series of extracellular voltage (μv) changes that are compounded from the neural activity of many cells near the skull surface. Behavioral indications of arousal are correlated with an EEG dominated by low voltage, high frequency waves. High voltage, low frequency waves are generally indicative of a deactivated state, such as sleep or drowsiness.

The known effects of ethanol on the EEG include the fact that it normally produces a deactivated (high voltage,

low frequency) EEG (Sauerland, 1970). It has also been reported that small doses of ethanol produce a short stimulation period in both the EEG and the behavior in the animal (Dolce, 1972).

Initially, it was thought that the primary action of ethanol was on the cholinergic system. It has been shown that ethanol causes a decrease in the acetylcholine turnover rate in the cortex (Morgan, 1975; Erickson, 1973). Cortical slices prepared in vitro show a greater sensitivity in the cholinergic system to ethanol than does any of the other transmitter systems (Carmichael, 1975). Hunt found that ethanol generally depresses the release of acetylcholine in six subcortical regions, most significantly in the brainstem and in the caudate nucleus (involved in motor functions; Hunt, 1976).

This depression of acetylcholine release led many to believe that this was a direct result of ethanol. However, recent studies indicate that this is probably untrue and that the action on the cholinergic system might be indirect. Graham reported that drugs which alter the cholinergic system (atropine and hemicholinium) had no effect on the ethanol-induced behavioral depression. Graham concluded that the reported reduction in acetylcholine release may merely reflect a reduction of neuronal activity (Graham, 1974). In 1974, Klemm reported that the administration of eserine, which increases the acetyl-

choline levels by blocking its metabolism, blocked the normal deactivation of the EEG of ethanol. However, the animals were still behaviorally intoxicated. This dissociation between the EEG and behavior suggested that the primary action of ethanol was mediated via a non-cholinergic system (Klemm, 1974).

Research on the noradrenergic system has recently increased. Norepinephrine turnover decreases when ethanol is administered (Carlsson, 1973; Pohorecky, 1974). Pohorecky further showed that the effect of ethanol was greater in the telencephalon and in the brainstem. This led her to conclude that a direct inhibitory effect of ethanol on noradrnergic neurons could result in a decrease in activity (Pohorecky, 1975). Pohorecky has also reported a decrease in the firing rate in the locus coeruleus cells due to ethanol. She suggests that this slower firing rate can be equated with a slower rate of norepinephrine release (Pohorecky, 1977).

This present study was designed to further elucidate the role which the noradrenergic system, specifically the beta receptors, plays in ethanol intoxication.

METHODS

Animals

In this experiment, twenty-seven Sprague-Dawley rats (250-400mg) were divided into five groups. In the first group, ten rats were used for the Eserine study. Five of these ten rats were also used for the Isoproterenol and Ethanol study. Three separate rats were used in the third study to determine the effects of isoproterenol by itself. Two of these rats were used for the Propranolol study. Fourteen other rats were used for a behavioral assessment of isoproterenol with ethanol.

Surgery and Recording Apparatus

Chronically implanted epidural electrodes were bilaterally placed over the frontal and occipital cortex. Four to six days were allowed for surgical recovery before the recordings. A Beckman Dynograph recorder was used for the EEG recordings. Two channels recorded from the frontal and occipital lobes, while a third channel was used to monitor motion artifact. During the recording periods, the rat was free to move within a 25 x 25 cm box.

Behavior Tests

Four behavioral tests were used to determine the percent intoxication exhibited. Two platform tests were used in which the two front paws were placed on platforms 3 cm and 9 cm high respectively. Intoxication was defined as the

two front paws remaining on the platform for ten seconds. In another test, four corks were placed in an 8 x 11 cm configuration with the corks at the corners. The four paws were placed on the four corks, and intoxication was scored if the feet were not moved for ten seconds. In a fourth test, a net test was used where the rat was placed on a vertical wire screen. Intoxication was defined as remaining in the same position for ten seconds or falling off. Finally, a coordination test was used where the rat was placed upon a rotation rod, 8 cm in diameter. The number of seconds which the rat remained on the rod were recorded.

Eserine Study

In the eserine study, the normal behavior for each rat was recorded. Then, a five minute segment of the normal EEG was recorded. Upon the completion of this recording, 2 g/kg ethanol and 0.2 mg/kg were injected intraperitoneally and thirty-five minutes were allowed to lapse. After this, the extent of intoxication of the rat was tested behaviorally by the previously described behavioral tests. A five minute recording of the EEG was then taken to determine the percent deactivation.

Isoproterenol and Ethanol Study

Five of the rats used in the eserine study were also used for the isoproterenol study. The same time segments were used with the addition of two recordings. After the second EEG recording, saline (for the control) or isopro-

terenol (0,05, 0.1, or 0.2 mg/kg) was injected intraperitoneally. Then there was a fifteen minute wait and a subsequent five minute recording of EEG, followed by another ten minute wait and another five minute recording. After this, the rat was tested for its final behavior. Each rat served as its own control, so each rat was in at least two recording sessions. Two to three days were allowed between recording sessions. The EEG recordings were later scored for percent deactivation.

Illustration:

Behavior / EEG / inj. EtOH, eserine / 35 minutes / EEG / inj. isoproterenol / 15 minutes / EEG / 10 minutes / EEG / Behavior

Isoproterenol Only Study

Three separate rats were used in the study which used only isoproterenol. This study was used to determine if isoproterenol has an activating effect on the EEG. If it does, its interaction with ethanol may be indirect and the EEG changes seen are due only to isoproterenol. In this study, isoproterenol (0.1, 0.15, 0.2 mg/kg) was injected IP into the rat after its normal EEG and behavior had been recorded. Then there was a fifteen minute lapse, and then the EEG was recorded for five minutes. After another ten minute wait, there was another five minute recording. After this, the behavior was tested.

Propranolol Study

If isoproterenol is interacting with ethanol, then propranolol should have the opposite effect. Propranolol (10 mg/kg) was injected IP in place of isoproterenol as in the earlier studies with ethanol. The time segments in the propranolol study were the same as in the isoproterenol and ethanol study.

Isoproterenol Behavior Study

Fourteen rats, which had had no surgery, were used in this study to assess the effect of isoproterenol on an intoxicated rat. Seven rats were in a control group, and seven in the isoproterenol group. In the control group, each rat was tested for its normal behavior. Then, each was injected with physiological saline. After thirty minutes, the rat was behaviorally tested and then injected with 2 g/kg ethanol IP. Behavior was again recorded fifteen and thirty-five minutes after the ethanol injection. In the other group, 0.2 mg/kg isoproterenol was substituted for the saline.

RESULTS

Eserine Study

In each of the ten rats, an activated EEG was noted along with behavioral intoxification. This dissociation between cortical activity and behavior further supports the study of Klemm (1974). For results, refer to Tables 1 and 2 of the Appendix.

Isoproterenol and Ethanol Study

Each of the five rats showed a decrease in the percent of deactivation when isoproterenol was injected in comparison to the controls. Each rat also showed a general decrease in behavioral intoxication (Figures 1-10). Examples of the various recordings are shown in Figure 11. The results are expressed in Figures 1-10. A graph is used to express the changes in percent deactivation from the normal segment of each recording sission. The behavior of each rat is also expressed in percent intoxication, using the previously discussed behavioral tests and the coordination test.

Isoproterenol Only Study

When the three rats were injected with isoproterenol only, there was an increase in deactivation, with no change in behavior (Figure 12).

Propranolol Study

When propranolol was used in place of isoproterenol, a facilitation of the ethanol effect was seen. The rats showed a 40.7% and 58.9% increase in deactivation from their normal EEG's respectively (Figure 13). Also, both rats were still 100% intoxicated at the end of the recording sessions.

Isoproterenol Behavior Study

There was a significant decrease in the percent intoxication in the isoproterenol group compared to the control group (Table 3 and 4 of Appendix). The Mann-Whitley U test was used to determine significance.

FIGURE 1

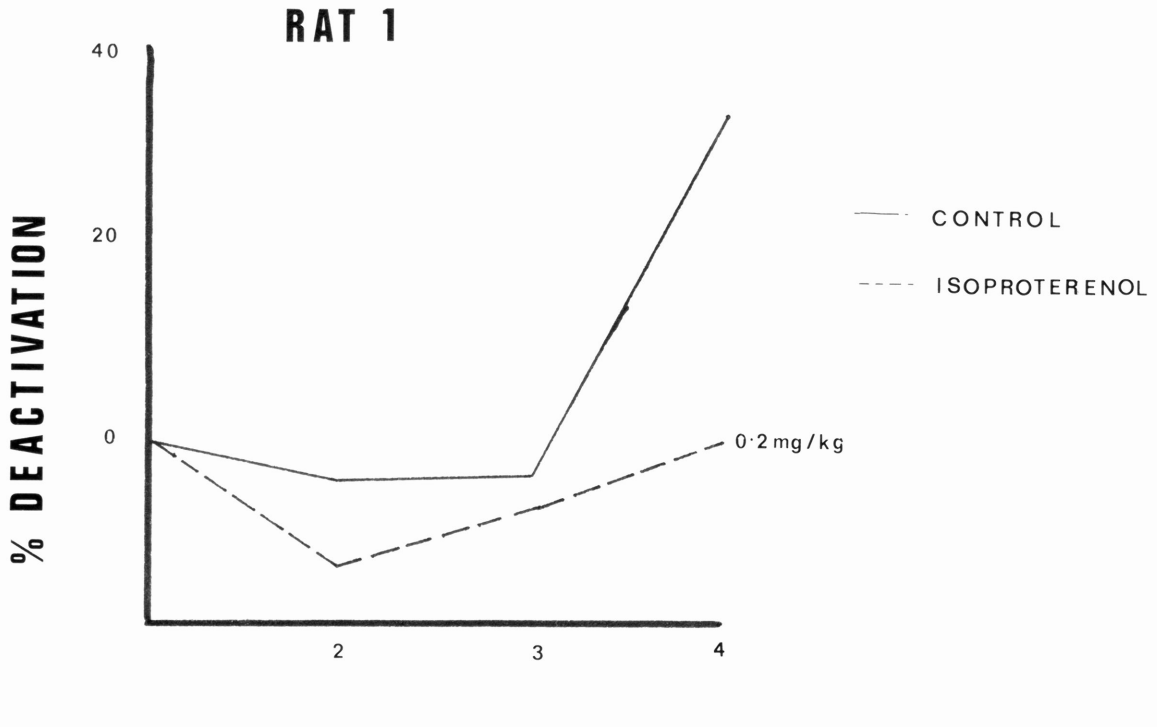


FIGURE 2

BEHAVIOR: % INTOXICATION

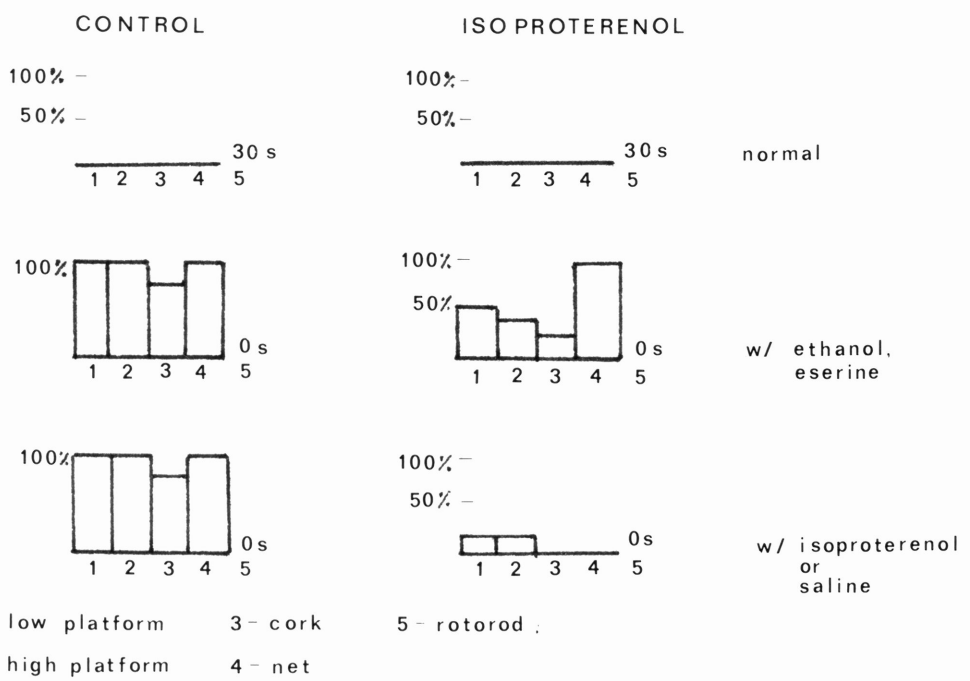


Figure 3: Graph of the % deactivation in Rat 2 in the 2nd, 3rd, and 4th EEG recording segments (control and 0.1 mg/kg isoproterenol)

Figure 4: Behavior of Rat 2 expressed in percent intoxication (control and 0.1 mg/kg isoproterenol)

FIGURE 3

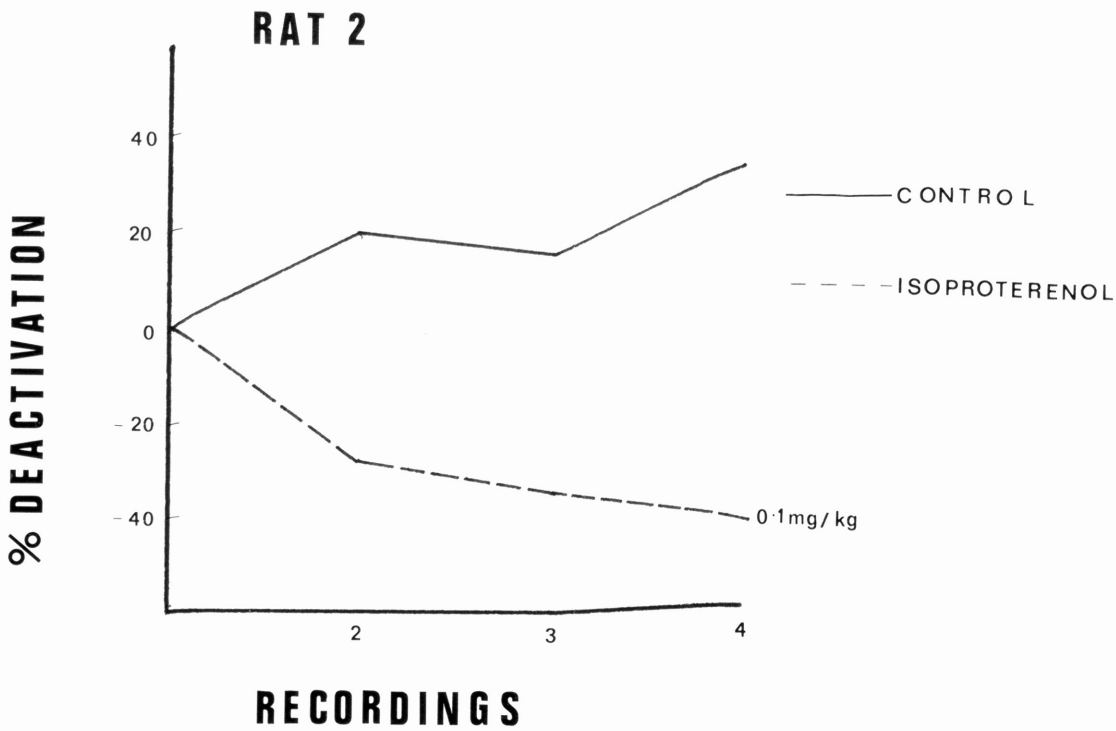


FIGURE 4

BEHAVIOR: % INTOXICATION

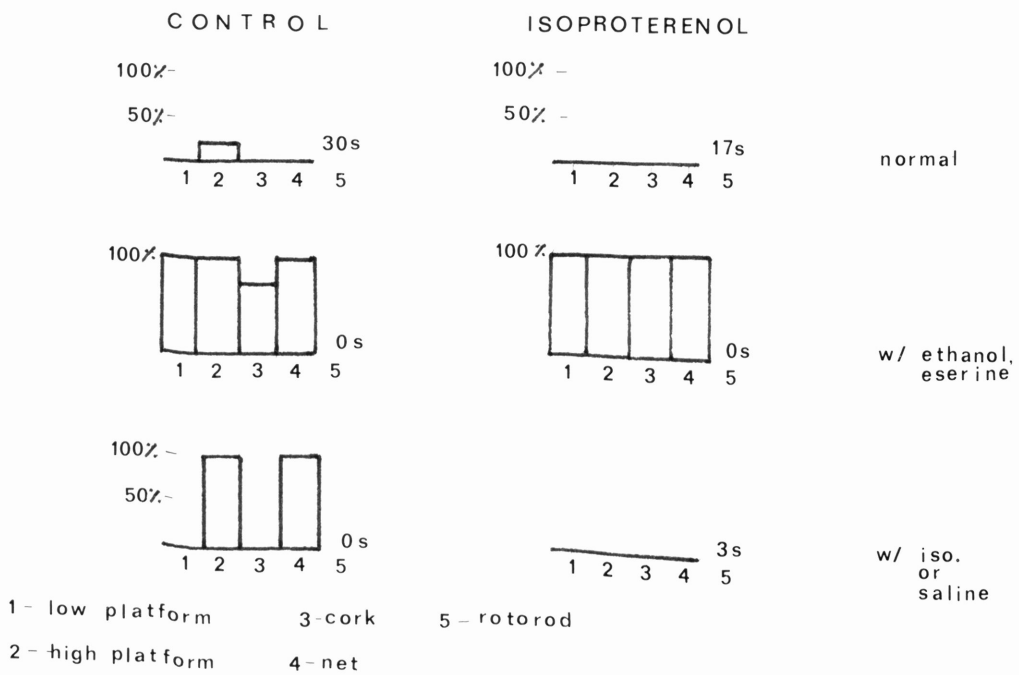


Figure 5: Graph of the % deactivation in Rat 3 in the 2nd, 3rd, and 4th EEG recording segments (control and 0.2 mg/kg isoproterenol)

Figure 6: Behavior of Rat 3 expressed in percent intoxication (control and 0.2 mg/kg isoproterenol)

FIGURE 5

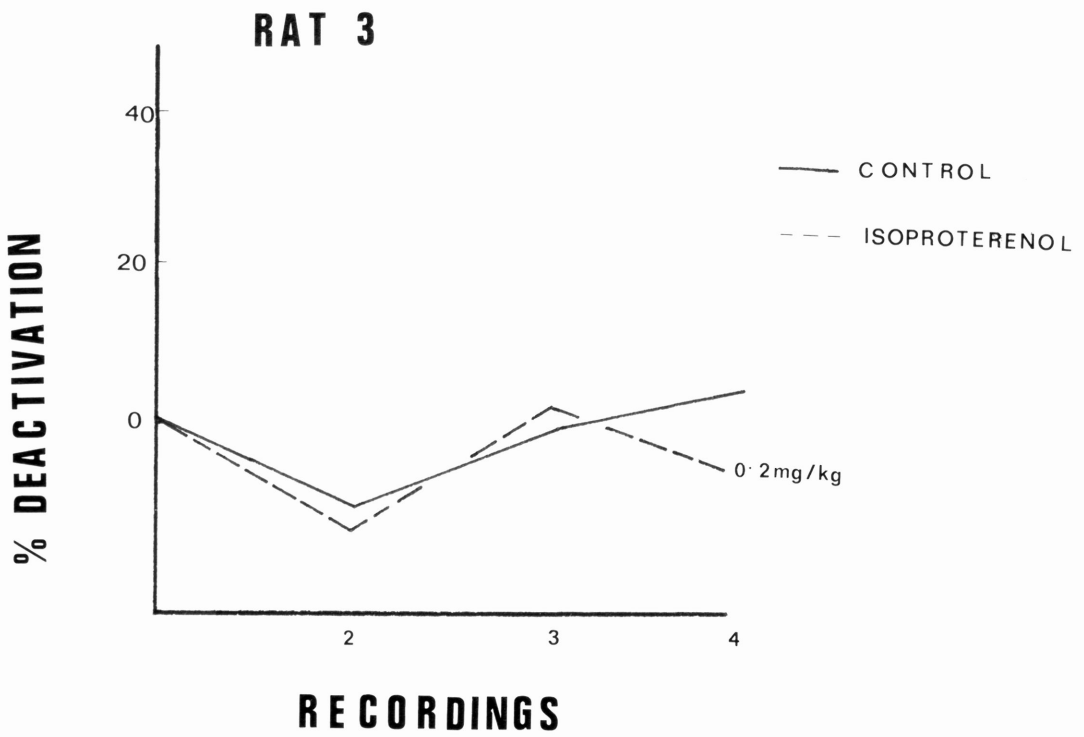


FIGURE 6

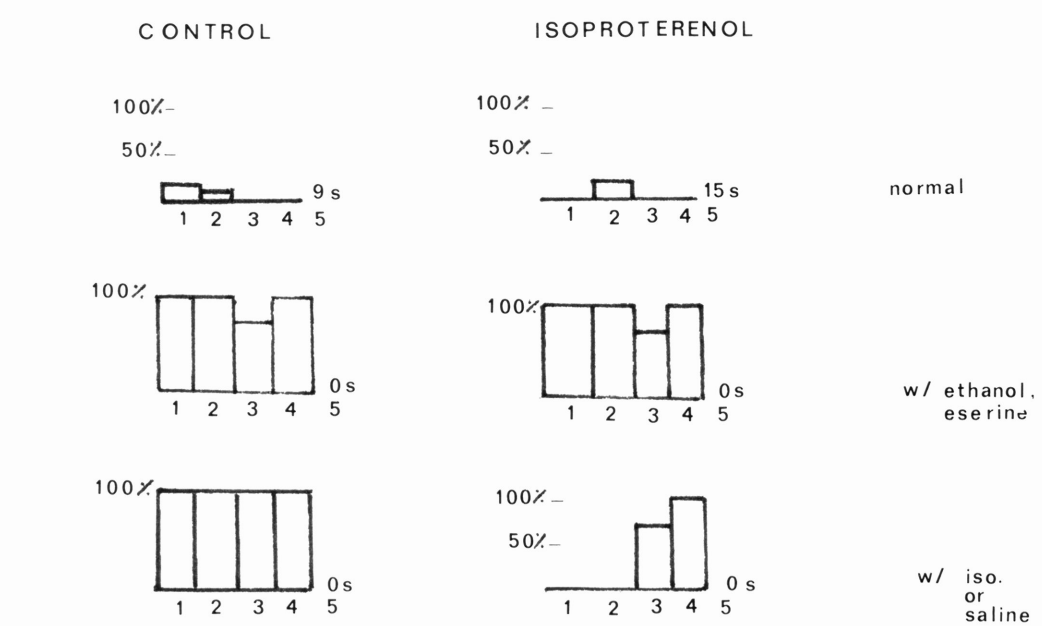


Figure 7: Graph of the % deactivation in Rat 4 in the 2nd, 3rd, and 4th EEG recording segments. Three doses of isoproterenol were used (0.05, 0.1, 0.2 mg/kg isoproterenol).

Figure 8: Behavior of Rat 4 expressed in percent intoxication. Three doses of isoproterenol were used (0.05, 0.1, 0.2 mg/kg isoproterenol).

FIGURE 7

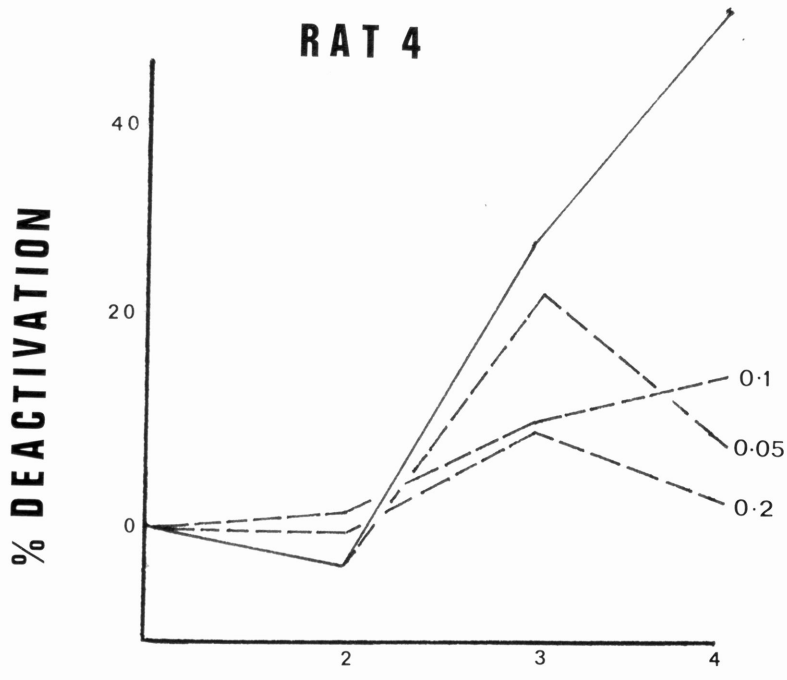


FIGURE 8

BEHAVIOR: % INTOXICATION

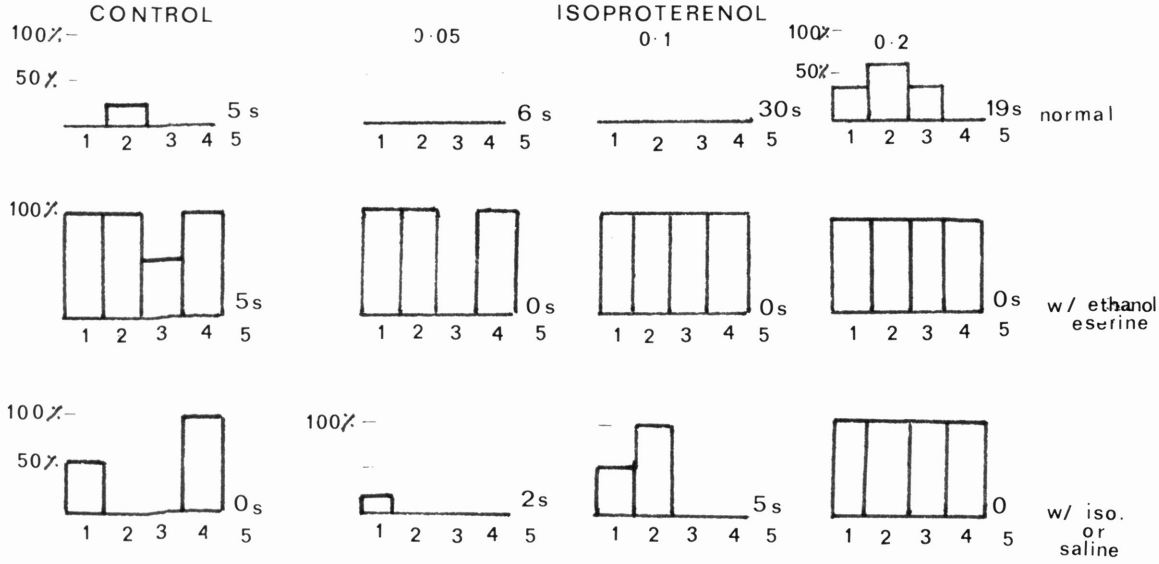


Figure 9: Graph of the % deactivation in Rat 5 in the 2nd, 3rd, and 4th EEG recording segments. Two doses of isoproterenol were used (0.1 and 0.2 mg/kg).

Figure 10: Behavior of Rat 5 expressed in percent intoxication. Two doses of isoproterenol were used (0.1 and 0.2 mg/kg).

FIGURE 9

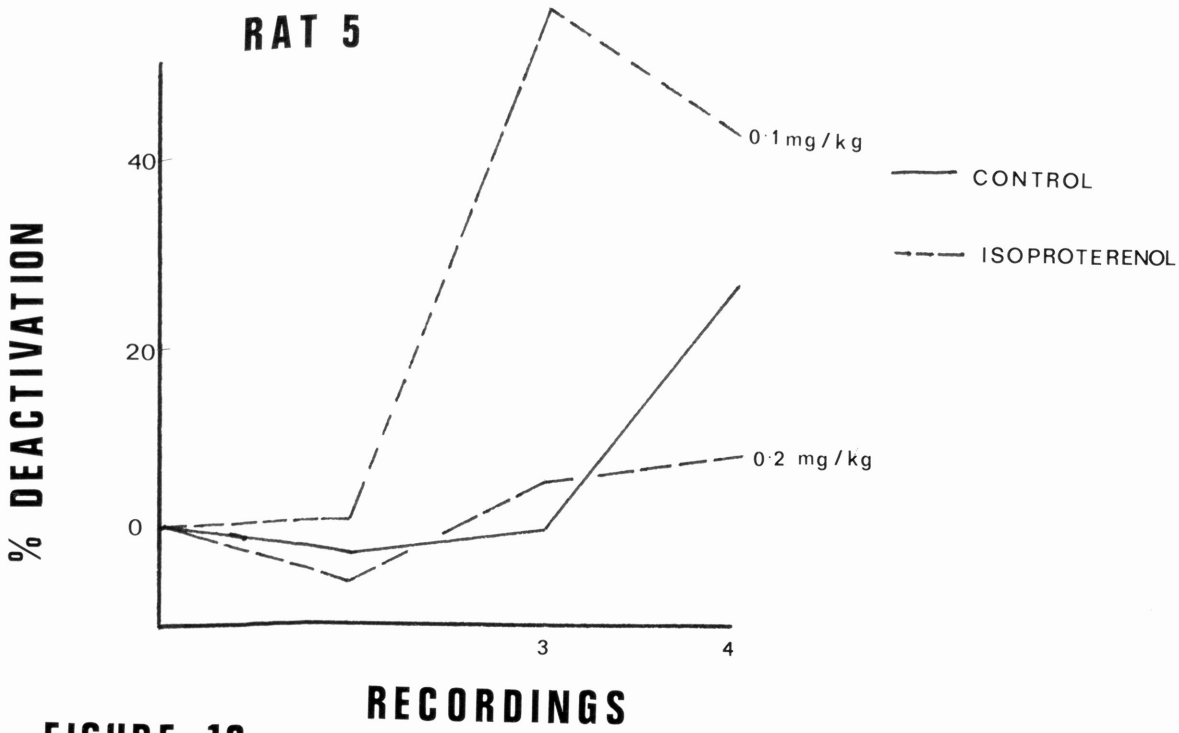


FIGURE 10

BEHAVIOR: % INTOXICATION

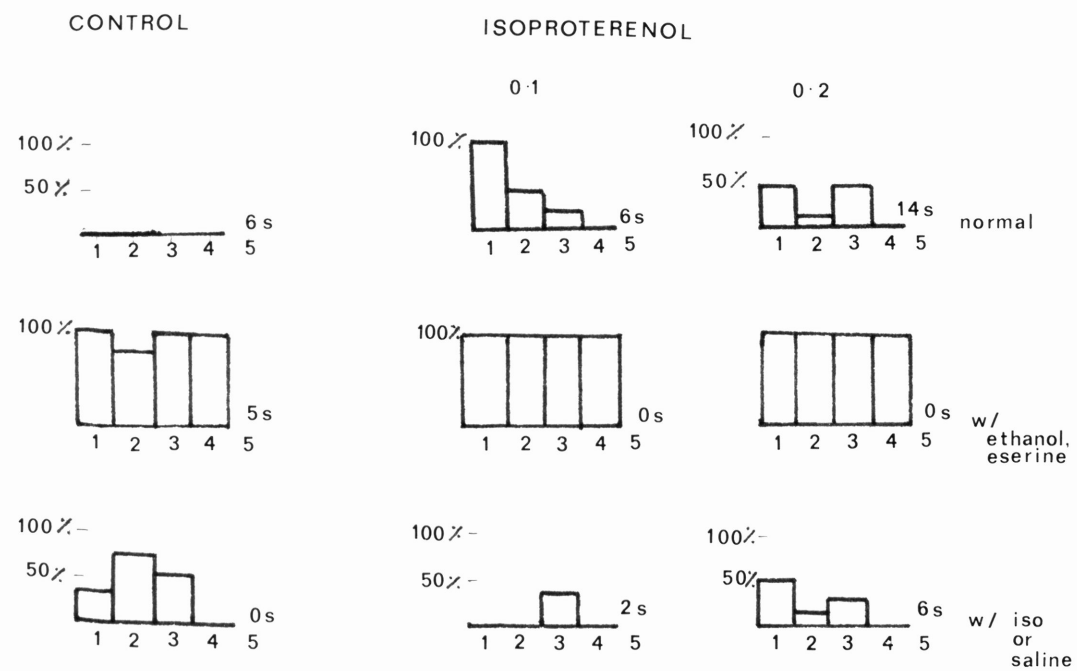


Figure 11: Examples of EEG:

1) normal

2) ethanol + eserine

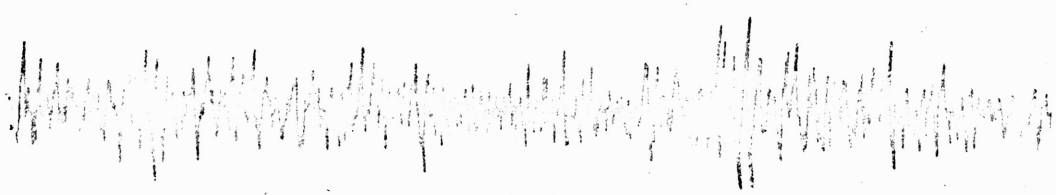
3) ethanol, eserine, and saline

4) ethanol, eserine, and isoproterenol

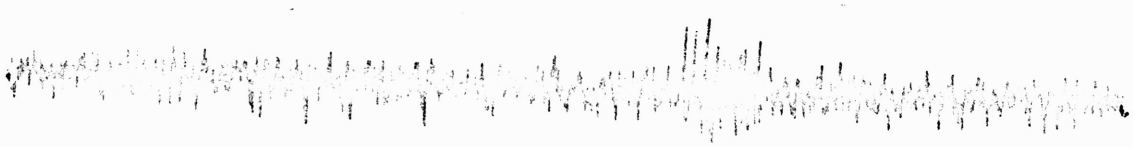
1

2

3



4



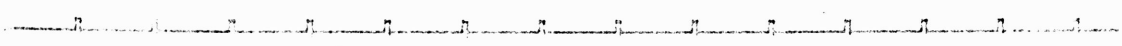


Figure 12: Graph of three rats showing the effect of three doses (0.1, 0.15, 0.2 mg/kg) isoproterenol when administered by itself on the EEG.

FIGURE 12

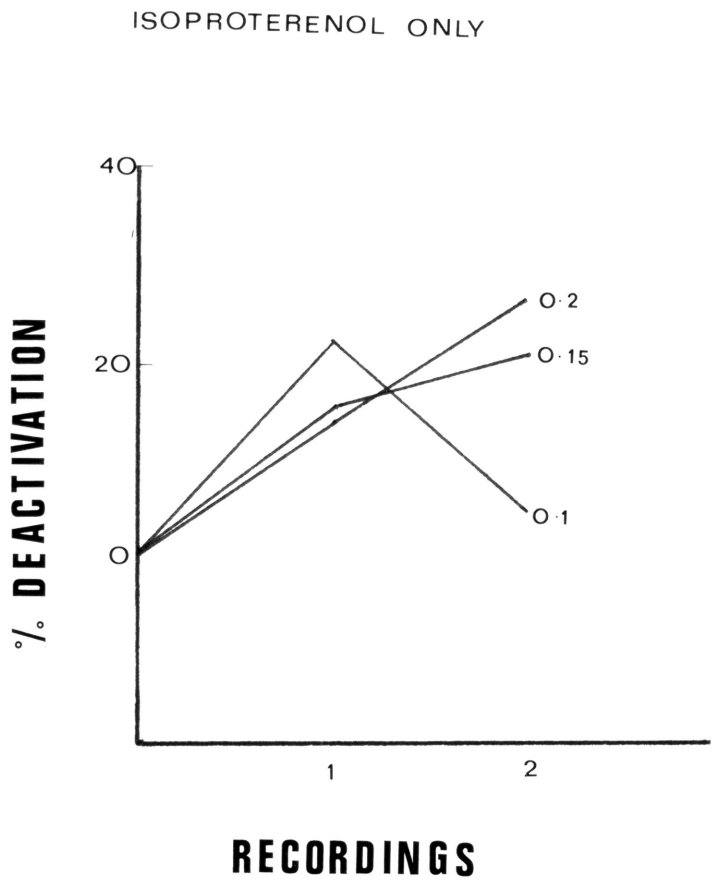
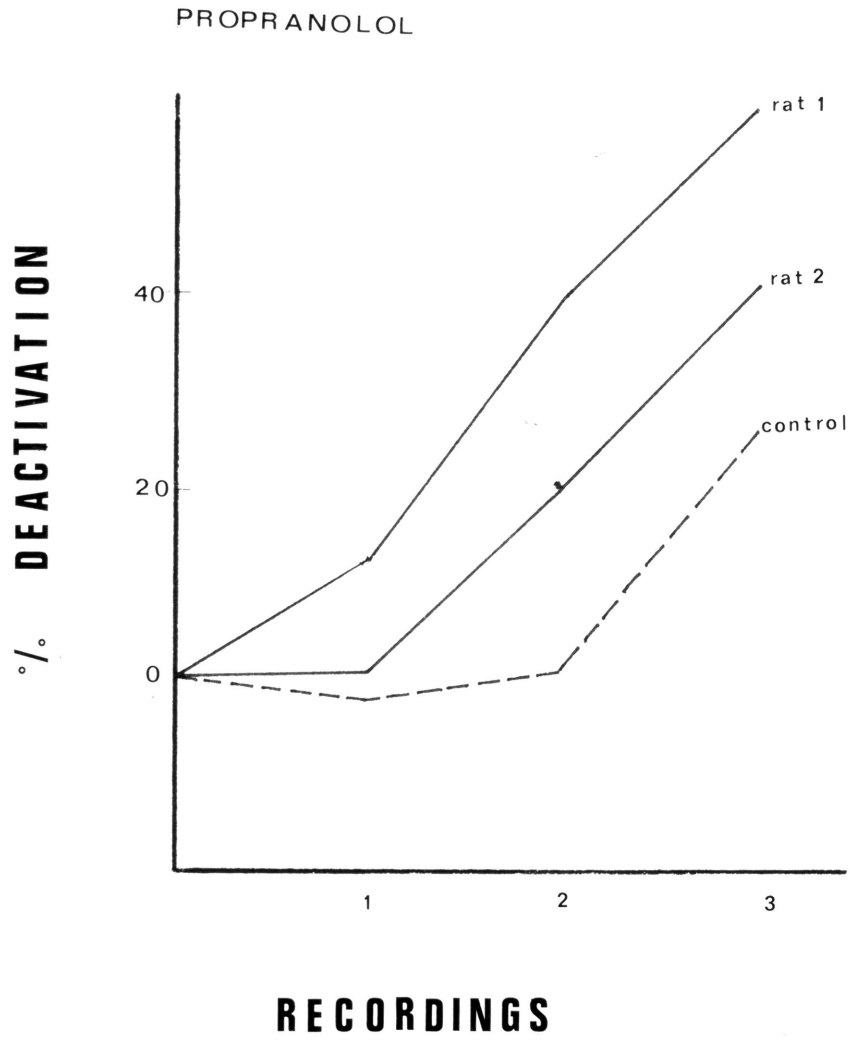

ISOPROTERENOL ONLY
40
20
0
% DEACTIVATION
0·2
0·15
0·1
1
2
RECORDINGS

Figure 13: Graph of the effect of propranolol (10mg/kg) with ethanol on two rats. Control is shown for comparison.

FIGURE 13


PROPRANOLOL
% DEACTIVATION
40
20
0
rat 1
rat 2
control
1
2
3
RECORDINGS

DISCUSSION

This study indicates that isoproterenol antagonizes the action of ethanol. How direct this antagonism is can only be determined by further experimentation, but the opposite effects of the beta blocker, suggests that the effect could be rather specific. In the five rats in the isoproterenol and ethanol study, each rat was less deactivated than the control animals. However, in Rat 5, the 0.1 mg/kg dose seemed ineffective, but the % deactivation decreased by 12.7% between the two isoproterenol recording segments. It is possible that in this case, the action of isoproterenol was not as immediate as in the other cases.

The decrease in deactivation cannot be due to an inherent activating action of isoproterenal. This was shown in the three rats where the EEG was recorded after an injection of isoproterenol only. In these rats, isoproterenol actually deactivated the EEG.

To test for the action of isoproterenol in these studies being on the beta receptors, propranolol, a beta blocker, was also used. Propranolol has the opposite effect of isoproterenol on the beta receptor. If ethanol were acting on the beta receptors, and isoproterenol is inhibiting this effect, then propranolol would be expected to potentiate the effect of ethanol. This is what occurred when propranolol was administered with ethanol. This

evidence lends further support to the hypothesis that ethanol is acting upon the beta receptor to produce some of its effect.

To further support the earlier results that isoproterenol altered the behavioral intoxication, a behavioral study was done. Isoproterenol clearly inhibited the ethanol-induced intoxication.

The question now arises as to how these results correlate with other published studies. To date, no other studies have dealt with the interaction between isoproterenol and ethanol. Several studies have shown the effect of propranolol on ethanol-induced intoxication. Smith showed that a low dose of propranolol (1mg/kg) shortened the time for the return of the righting reflex. However, larger doses (5, 10, 20 mg/kg) actually potentiated the effect of ethanol and increased the time for the return of the righting reflex (Smith, 1970). Alkana showed that propranolol significantly increased alcohol's effect in the behavior and the EEG in humans (Alkana, 1976). Wimbish reported that propranolol in high doses (40 mg/kg) enhanced ethanol-induced narcosis in mice; lower doses it had no effects (Wimbish, 1977). It should be noted, though, that propranolol has central depressant properties other than by its action on beta receptors (Leskovsky, 1965). This necessitates the use of a beta blocker other than propranolol in future research, which would not have any other significant effects other than on the beta receptors. Frankel

reported that 25 mg/kg propranolol increased motor impairment due to ethanol. There was no significant change when 1 or 5 mg/kg were used (Frankel, 1976).

As reported earlier, ethanol reduces the amounts of acetylcholine in the cortex. This may reflect decreased neuronal activity. The acetylcholine release in the cerebral cortex has been related to a diffusely spread ascending cholinergic pathway associated with the reticular formation (Morgan, 1975). A reduction in the activity of this system would explain the sedative and EEG changes worked by ethanol. It would also account for the decrease in the acetylcholine levels.

There is a substantial noradrenergic input into the reticular formation. Ethanol may decrease the activity in the beta receptors in this region. This idea needs to be expanded through further research.

So, it can be concluded that isoproterenol antagonizes the effect of ethanol in some way. This study should provide some direction for future research. First, it is necessary that more animals be used in a continuation of this study. These additional results would add support to the findings of the initial study. Then, a dose-response curve should be determined by the use of various doses of isoproterenol. Finally, the effect of ethanol on the reticular formation should be studied. By recording the multiple unit activity from various cell groups in the

reticular formation, the effect of isoproterenol on the actions of ethanol might be further elucidated.

APPENDIX

Table 1

Eserine Study: expressed in percent deactivation of EEG

Rat #	Normal	W/ EtOH, Eserine	Saline, run 1	Saline, run 2
Rat 1	8.9%	3.3%	4.4%	41.4%
Rat 2	0.0%	6.0%	7.9%	32.5%
Rat 3	3.3%	17.3%	35.2%	9.2%
Rat 4	17.2%	7.0%	14.2%	21.8%
Rat 5	0.7%	20.5%	16.2%	29.7%
Rat 6	13.7%	4.8%	12.8%	16.0%
Rat 7	3.6%	1.3%	35.3%	58.7%
Rat 8	3.7%	1.2%	3.7%	28.2%
Rat 9	23.0%	19.5%	22.0%	11.3%
Rat 10	26.7%	6.8%	30.3%	46.1%

Table 2

Behavior in Eserine Study

Rat #	Tests	Normal	W/ EtOH, Eserine	at end
Rat 1	low platform	0 sec	10 sec	10 sec
	high platform	0	10	10
	cork	0	8	10
	net	-	+	+
	rotorod	30	0	0
Rat 2	low platform	0	10	10
	high platform	0	10	10
	cork	0	10	10
	net	-	+	+
	rotorod	10	0	0
Rat 3	low platform	0	10	10
	high platform	0	10	10
	cork	0	8	0
	net	-	+	+
	rotorod	30	0	0
Rat 4	low platform	4	10	0
	high platform	0	10	0
	cork	0	10	0
	net	-	+	+
	rotorod	24	0	3
Rat 5	low platform	0	10	0
	high platform	2	10	10
	cork	0	7	0
	net	-	+	+
	rotorod	30	0	0
Rat 6	low platform	2	10	10
	high platform	1	10	10
	cork	0	7	10
	net	-	+	+
	rotorod	9	0	0

Table 2 (continued)

Rat #	Tests	Normal	W/ EtOH, Eserine	at end
Rat 7	low platform	0 sec	10 sec	5 sec
	high platform	1	10	0
	cork	0	5	0
	net	-	+	+
	rotorod	5	5	0
Rat 8	low platform	0	10	4
	high platform	0	8	8
	cork	0	10	5
	net	-	+	-
	rotorod	6	2	0
Rat 9	low platform	0	10	10
	high platform	0	10	10
	cork	0	10	10
	net	-	+	+
	rotorod	30	0	3
Rat 10	low platform	0	10	5
	high platform	0	10	7
	cork	0	10	5
	net	-	+	+
	rotorod	7	0	0

Table 3

Isoproterenol Behavior Study: Control Group

Rat #	Tests	Normal	Saline	$EtOH_1$	$EtOH_2$
Rat 1	low platform	0 sec	0 sec	0 sec	0 sec
	high platform	0	0	0	0
	cork	0	0	0	0
	net	-	-	-	-
	rotorod	17	30	0	0
Rat 2	low platform	0	0	10	8
	high platform	0	0	10	10
	cork	0	0	10	10
	net	-	-	+	+
	rotorod	17	20	0	0
Rat 3	low platform	0	0	10	10
	high platform	0	1	5	10
	cork	0	0	10	10
	net	-	-	+	+
	rotorod	30	30	0	0
Rat 4	low platform	0	0	0	0
	high platform	0	0	0	0
	cork	0	0	0	0
	net	-	-	-	-
	rotorod	13	30	30	10
Rat 5	low platform	0	0	10	10
	high platform	0	0	2	8
	cork	0	0	1	8
	net	-	-	+	+
	rotorod	12	5	0	0
Rat 6	low platform	0	0	5	10
	high platform	0	0	5	7
	cork	0	0	5	5
	net	-	-	+	+
	rotorod	24	30	0	0
Rat 7	low platform	0	0	0	10
	high platform	0	0	0	8
	cork	0	0	0	2
	net	-	-	-	+
	rotorod	12	12	2	0

Table 4

Isoproterenol Behavior Study: Isoproterenol Group

Rat #	Test	Normal	Iso.	$EtOH_1$	$EtOH_2$
Rat 1	low platform	0 sec	0 sec	7 sec	0 sec
	high platform	0	0	2	0
	cork	0	0	0	0
	net	-	-	+	-
	rotorod	30	30	0	3
Rat 2	low platform	0	0	5	3
	high platform	0	0	5	3
	cork	0	0	5	5
	net	-	-	+	+
	rotorod	23	18	0	6
Rat 3	low platform	0	0	8	6
	high platform	0	0	3	1
	cork	0	0	5	0
	net	-	-	+	-
	rotorod	27	19	0	0
Rat 4	low platform	0	0	10	5
	high platform	0	0	10	3
	cork	0	0	7	3
	net	-	-	+	-
	rotorod	30	30	0	0
Rat 5	low platform	0	0	7	3
	high platform	0	0	2	2
	cork	0	0	0	0
	net	-	-	-	-
	rotorod	25	7	0	0
Rat 6	low platform	0	0	0	3
	high platform	0	0	0	0
	cork	0	0	0	0
	net	-	-	-	+
	rotorod	5	4	0	0
Rat 7	low platform	0	0	0	0
	high platform	0	0	0	1
	cork	0	0	1	2
	net	-	-	-	-
	rotorod	14	30	0	0

REFERENCES

Alkana, R. L., E. S. Parker, H. B. Cohen, H. Birch, and E. P. Noble. Reversibility of ethanol intoxication in humans: an assessment of the efficacy of propranolol. Psychopharmacology 51: 29-37 (1976).

Carlsson, A., T. Magnusson, T. H. Svensson, and B. Waldeck. Effect of ethanol on metabolism of brain catecholamines. Psychopharmacology 30: 27-36 (1973).

Carmichael, F. J. and Y. Israel. Effects of ethanol on neurotransmitter release by rat brain cortical slices. J. Pharm. exp. Ther. 193: 824-834 (1975).

Dolce, G. and H. Decker. The effects of ethanol on cortical and subcortical electrical activity in cats. Res. Comm. Chem. Pathol. Pharmacol. 3: 523-534 (1972).

Erickson, C. K. and D. T. Graham. Alteration of cortical and reticular acetylcholine release by ethanol in vivo. J. Pharm. exp. Ther. 185: 583-593 (1973).

Frankel, D., H. Kalant, J. M. Khanna, and A. E. Leblanc. Interaction of propranolol and phentolamine with ethanol in the rat. Can. J. Physiol. Pharmacol. 54: 622-625 (1976).

Graham, D. T. and C. K. Erickson. Alteration of ethanol-induced CNS depression: ineffectiveness of drugs that modify cholinergic transmission. Psychopharmacology 34: 173-180 (1974).

Hunt, W. A. and T. K. Dalton. Regional brain Ach levels in rats acutely treated with ethanol or rendered ethanol-dependent. Brain Research 109: 628-631 (1976).

Klemm, W. R. Dissociation of EEG and behavioral effects of ethanol provides evidence for a noncholinergic basis of intoxication. Nature 251: 234-236 (1974).

Leskovsky, G. and L. Tardos. Some effects of propranolol on the central nervous system. J. Pharm. Pharmacol. 17: 518-520 (1965).

Morgan, E. P. and J. W. Phillis. The effects of ethanol on acetylcholine release from the brain of unanaesthetized cats. Gen. Pharmacol. 6: 281-284 (1975).

Pohorecky, L. A. Effects of ethanol on central and peripheral noradrenergic neurons. J. Pharm. exp. Ther. 189: 380-391 (1974).

Pohorecky, L. A. and L. S. Jaffe. Noradrenergic involvement in the acute effects of ethanol. Res. Comm. Chem. Path. Pharmacol. 12: 433-446 (1975).

Pohorecky, L. A. and J. Brick. Activity of neurons in the locus coeruleus of the rat: inhibition by ethanol. Brain Research 131: 174-179 (1977).

Sauerland, E. K. and R. M. Harper. Effects of ethanol on EEG spectra of the intact brain and isolated forebrain. Exp. Neurol. 27: 490-496 (1970).

Smith, A. A., K. Hayashida, and Y. Kim. Inhibition by propranolol of ethanol-induced narcosis. J. Pharm. Pharmacol. 22: 644-645 (1970).

Wimbish, G. H., R. Marty, and R. B. Forney. Combined effects of ethanol and propranolol on sleep time in the mouse. Life Sciences 20: 65-72 (1977).