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An Evaluation of the Purported Anti-Craving
Effects of Ibogaine, and
Comparative Studies Employing Harmaline

Michael Gintowt

A Thesis
in
The Department
of
Psychology

Presented in Partial Fulfillment of the Requirements
For the Degree of Master of Arts
Concordia University
Montreal, Quebec, Canada

August 1989

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ABSTRACT

An Evaluation of the Purported Anti-Craving
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Employing Harmaline

Michael Gintowt

The purpose of this thesis was to determine whether there was any empirical evidence which would support the anecdotal claims that ibogaine, a naturally occurring alkaloid, could rapidly interrupt cocaine or ethanol abuse in humans. The described experiments, employing rats, were designed to evaluate those claims by determining the effect of treatment with ibogaine on both cocaine and ethanol self administration. The effects of a similar alkaloid, harmaline, on ethanol self administration were also evaluated. Additionally, the effects of both ibogaine and harmaline on locomotion in general, and ethanol induced locomotor depression in particular, were examined. The obtained results suggested that ibogaine had no effect on cocaine self administration; these results were consistent with the literature concerning ibogaine, which tended, because of reported effects on serotonergic (as well as most other neurotransmitter) systems, to support the notion that ibogaine may affect ethanol, but not cocaine consumption. In ethanol drinking rats, both ibogaine and harmaline administration resulted in reduced body weight. Only the highest dose of ibogaine, and two of three doses of harmaline, resulted in reduced total fluid intake. Although the highest dose of ibogaine resulted in reduced absolute

ethanol and total fluid consumption, the lack of effect on ethanol preference suggested that the reduction was on consumption in general, and not specific to ethanol. Harmaline administration resulted in no significant reductions in ethanol intake. Ibogaine was observed to have a locomotor depressant effect which lasted 30-40 minutes. Harmaline had a similar depressant effect which was still observable after 110 minutes. The locomotor depression produced by either drug did not interact with the locomotor depression caused by 2 gm/kg ethanol. The locomotion data suggested that locomotor deficits induced by ibogaine were probably not responsible for the weight reduction effect of ibogaine. The partial behavioral profile obtained for harmaline, and to some extent ibogaine, is consistent with the hypothesis that harmaline (and ibogaine) may be a partial benzodiazepine inverse agonist. It was concluded that the data, although of considerable theoretical interest, did not support the notion that ibogaine may have potential clinical usefulness in the treatment of cocaine or alcohol abuse in humans.

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INTRODUCTION

Alcohol abuse is recognized as a major problem in society today. Death and disability from alcohol related heart, liver and other disease, and accidents are prevalent (Hofmann, 1983). Disruption of family structure, spouse and child abuse, suicide attempts and loss of employment are some of the other consequences of alcohol abuse (Chick, 1984).

Cocaine abuse is another major, growing problem which has reached epidemic proportions in North America (Adams, Gfroerer and Blanken, 1985). The personal and social costs resulting from involvement with cocaine are enormous (Gold, Washton and Dackis, 1985). Furthermore, a simple treatment for cocaine abuse is not yet available (Kleber, 1985).

The effectiveness of ibogaine (a naturally occurring alkaloid) administration in the treatment of cocaine abuse was first described in United States Patent number 4,587,243, dated May 6, 1986, titled "Rapid Method for Interrupting the Cocaine and Amphetamine Abuse Syndrome" (Appendix A). As described in the patent, a single administration of ibogaine effectively blocked the craving and use of cocaine and amphetamine for up to six months, and a series of four treatments was effective for approximately three years. In support of these claims, the "inventor" (H. Lotsof 1986) of the treatment presented three short case

histories. In all the cases of ibogaine treatment described, the subjects experienced no withdrawal symptoms, and no desire for their favorite drug.

A similar patent was granted for the rapid interruption of heroin addiction by a single administration of ibogaine. Mr. Lotsof (personal communication) also described the unexpected cessation of tobacco use and alcohol abuse in some subjects.

There are ethical and legal obstacles to testing these unusual claims in humans. Consequently, in the experiments to be described, rats were used to determine whether there were any ibogaine/ethanol or ibogaine/cocaine interactions which would either support or argue against the anti-craving claims made for ibogaine.

Unfortunately, very little has been published concerning the behavioral pharmacology of ibogaine. Consequently, a similar but better understood alkaloid, harmaline, was employed in some of the experiments to be described in this thesis. Similar behavioral effects of these two drugs would have suggested that perhaps ibogaine and harmaline belong to the same class of drugs, and may therefore have similar neuropharmacological properties, such as receptor affinity. Although a comparison of the two drugs could not result in any definitive statement regarding the

neuropharmacology of ibogaine, the comparison was expected to result in the generation of plausible hypotheses which could serve to guide further research. This reasoning was successfully applied by Trouvin, Jacqmin, Rouch, Lesne, and Jacquot (1987). These authors observed that tabernanthine (structurally almost identical to ibogaine) induced tremor was similar to harmaline induced tremor. Subsequent pharmacological manipulations and receptor binding studies (described on page 11) suggested that the overt tremorigenic manifestations of the two drugs were mediated by apparently similar, benzodiazepine receptor-mediated mechanisms.

Naranjo (1973) described the similarities between ibogaine and harmaline, both in physical effects and as facilitators of psychotherapy in humans. Other commonalities in the usage and pharmacology of ibogaine and harmaline are described in a later section of this thesis. Given the apparent similarity between the two drugs, it was hypothesized that ibogaine and harmaline would have similar behavioral effects in rats.

No mechanism for the purported effects of ibogaine on drug dependency has yet been proposed. A pharmacological mechanism was suggested by the following: 1) The rapidity and effectiveness of the reported anti-craving effects of ibogaine, and 2) the

claim that, prior to treatment, at least some of the successfully treated subjects did not even express a desire to stop their drug habit. Consequently, existing pharmacological treatments for drug abuse are described next.

Pharmacological Treatment of Cocaine Abuse in Humans

Ibogaine treatment for cocaine abuse is the most recent of a series of proposed pharmacological interventions. For example, Dackis, Gold, Sweeney, Byron and Climko (1986) conducted a controlled, double blind study which suggested that a single dose of bromocriptine (a selective D-2 receptor agonist) reduced cocaine craving in humans. The reported effect, however, was weak, and the results of their study therefore do not imply that bromocriptine has a useful role in the interruption of cocaine dependency.

Amantadine, an indirect dopamine agonist, was also subjected to a controlled evaluation of its ability to reduce cocaine craving. Results indicated that it was no more effective than placebo (Gawin, Morgan, Kosten & Kleber, 1989).

Antidepressant treatment has also been tried in the treatment of cocaine abuse (Small & Purcell, 1985;

Gawin & Kleber, 1986; Kosten, Schuman, Wright & Gawin, 1987), but these studies were limited in terms of number of subjects, treatment outcome measures, or control groups. Addressing these problems, Gawin, Kleber, Byck, Rouansville, Koster, Jatlow & Morgan (1989) conducted a double blind, six week study comparing desipramine with placebo and lithium on their ability to maintain abstinence. Fifty nine per cent of the desipramine group were abstinent for at least three to four weeks, compared to 17% for placebo and 25% for lithium ($p < .03$). Another study (O'Brien, Childress, Arndt, McLellan, Woody and Maany, 1988) yielded results which also suggested that desipramine was more effective than placebo in reducing cocaine use. The results of this study were not as dramatic, however, possibly because the subjects were also on a methadone maintenance program.

In summary, a generally effective pharmacological treatment for cocaine abuse does not yet appear to exist. Desipramine may become useful as an adjunct to cocaine abuse treatment, but confirmatory evidence is lacking. The evaluation of the claims made for the outcome of ibogaine treatment was therefore warranted.

Another purpose of the experiments described in this thesis was to determine whether the alkaloid ibogaine has potential use as a therapeutic agent for

the treatment of alcohol dependence. Given the present lack of an effective pharmacological treatment for alcohol abuse (Peachey and Annis, 1985), it was considered appropriate to evaluate the ability of ibogaine to interrupt alcohol consumption in rats.

Non-pharmacological treatment of alcohol abuse is difficult and not usually successful, with relapse rates ranging from 40-80%, depending on the treatment used and the outcome measure employed (Riley, Sobell, Leo, Sobell and Klajner, 1987). Although Alcoholics Anonymous (A.A.) is helpful for some individuals, overall relapse rates do not appear to be superior to other treatment approaches (Alford, 1980). Moreover, A.A. has not been demonstrated to be a generally effective treatment for alcoholism (Miller & Hester, 1980).

Pharmacological Treatments for Alcoholism

The most commonly used pharmacological intervention for alcoholism is either Antabuse or Temposil, the trade names for disulfiram and citrated calcium carbamide (Miller & Hester, 1980). These drugs inhibit liver aldehyde dehydrogenase, the enzyme responsible for metabolizing acetaldehyde, the primary metabolite of alcohol (Marchner, 1984). If an

individual pretreated with Temposil or Antabuse drank alcohol, the resulting increase in blood levels of acetaldehyde caused a severe physical reaction which included chest pains, pounding heart, sweating, nausea, vomiting, difficulty in breathing, headache and weakness (Miller & Hester, 1980). The rationale behind Antabuse or Temposil treatment was that the anticipation of a severely unpleasant reaction to alcohol would deter drinking. Those who did drink, despite Antabuse or Temposil pretreatment, experienced the aversive reaction, which reinforced the expectation that further drinking would have painful consequences (Miller & Hester, 1980).

One problem with the use of these alcohol sensitizing drugs is lack of patient compliance, mostly due to side effects and lack of motivation (Peachey and Annis, 1985). Another problem with this treatment is that success rates are comparable to those attained using placebo (Fuller, 1988). This suggests that the overall effectiveness of alcohol sensitizing drug treatment is low.

The effect of serotonin (5HT) uptake inhibitors on ethanol consumption has been the subject of research aimed at finding new pharmacological treatments for alcoholism.

The first report of decreased ethanol consumption following 5HT uptake blockade with Zimeldine (Rockman, Amit, Carr, Brown and Ogren, 1979) was followed by other experiments which examined the effects of other 5HT uptake inhibitors (Norzimeldine, fluoxetine, citalopram and alaproclate), which were also found to reduce voluntary ethanol consumption in rats (Rockman, Amit, Brown, Bourque, and Ogren, 1982). Serotonin uptake inhibitors were later found to have general anorectic effects, decreasing food and water consumption (Gill and Amit, 1987). This suggested that the effect of 5HT inhibitors on ethanol consumption was secondary to the general effects of 5HT uptake inhibitors on consummatory behavior.

In conclusion, an effective pharmacological intervention for the treatment of alcoholism has not yet been found. Given the present degree of progress in this area of research, the claims made for the effects of ibogaine warranted investigation.

Ibogaine

Ibogaine is the main alkaloid found in the rootbark of the Taberanthé Iboga bush, native to West Central Africa. The root is chewed by the natives in order to combat fatigue, sleep, and hunger; during initiation ceremonies, the high doses employed result in profound, personally relevant visions (Shultes and Hoffmann, 1973).

Early research focussed on the cardiovascular action of ibogaine (Schneider and Rinehart, 1957). Schneider and McArthur (1956) demonstrated an ibogaine-induced potentiation of morphine analgesia, measured by the tail flick. Schneider and Sigg (1956-57) studied the EEG response to ibogaine in cats and dogs. The electroencephalogram showed a typical arousal response, which was blocked by pretreatment with atropine. This suggested that the arousal caused by ibogaine may have been at least partly mediated by a muscarinic cholinergic mechanism.

Dhahir (1971) studied the toxicity, tissue distribution, excretion, cardiovascular action, and other properties of ibogaine, using rats and mice. Dhahir (1971) also determined that concurrent ethanol administration (2 gm/kg, i.p.) significantly reduced the fatal dose (LD50) of ibogaine. Also pertinent to

this study was his observation that chronic ibogaine treatment caused a reduction in rate of weight gain, so that by the eighth day of treatment, the ibogaine treated rats (40 mg/kg, i.p) weighed significantly less than control animals. Dhahir (1971) also noted that methysergide, a 5HT₂ receptor blocker, antagonized the hypotensive effect of ibogaine.

Sloviter, Drust, Damiano and Connor (1980) compared a number of hallucinogens on their behavioral and pharmacological effects in rats. Ibogaine was found to produce the same behavioral syndrome (characteristic of serotonin receptor activation) as LSD and the other hallucinogens studied. Depletion (79%) of 5HT with the 5HT synthesis inhibitor p-chloro-p-phenylalanine did not prevent the behavioral response elicited by ibogaine, suggesting that ibogaine may be a 5HT receptor agonist. d-2-bromo-LSD (BOL), a 5HT receptor antagonist, prevented the behavioral syndrome produced by ibogaine, which again suggested that ibogaine may be a 5HT receptor agonist.

Sloviter et al. (1980) also measured rat whole brain norepinephrine, dopamine and serotonin levels ten minutes after ibogaine (40 mg/kg, i.p.) administration. Dopamine levels were significantly elevated (by 39%) compared to control animals, while levels of the other two neurotransmitters remained unchanged.

More recently, Dzoljic, Kaplan and Dzoljic (1988) observed that intracerebroventricularly administered ibogaine attenuated some of the symptoms of naloxone precipitated morphine withdrawal. This suggested that ibogaine may act directly or indirectly at opiate receptors.

Given the relative lack of data concerning ibogaine, it may be useful to consider available data concerning tabernanthine. Tabernanthine is an alkaloid structurally almost identical to ibogaine, with cardiovascular and tremorigenic effects similar to those of ibogaine (Zetler, Singbartl & Schlosser, 1972). Prioux-Guyonneau, Mocaer-Cretet, Cohen and Jacquot (1984) demonstrated that tabernanthine (20 mg/kg, i.p.) significantly increased the synthesis and elimination of dopamine and norepinephrine in the rat brain. Additionally, Trouvin, Jacqmin, Rouch, Lesne and Jacquot (1987) determined that tabernanthine is a benzodiazepine receptor inverse agonist. This was demonstrated by the ability of tabernanthine to displace 3H-flunitrazepam from rat brain homogenates, and by the inhibition of tabernanthine-induced tremor by flunitrazepam or RO-15 1788 (a benzodiazepine receptor antagonist). Therefore, given the almost identical structures of tabernanthine and ibogaine, it

is possible that ibogaine is also a benzodiazepine inverse agonist.

In summary, the work of Sloviter et al.. (1980), and some of the findings of Dhahir (1971) provided some evidence that ibogaine had effects on 5HT receptor functioning. Given the similarities between ibogaine and tabernanthine, it is possible that ibogaine affects dopamine and norepinephrine activity (Prioux-Guyonneau et al., 1984) as well as acting as a benzodiazepine receptor inverse agonist (Trouvin et al., 1987). This profile is complicated by data which suggested that cholinergic activity (Schneider and Sigg, 1956-57) and opiate receptor activity (Schneider and McArthur, 1957; Dzoljic et al., 1988) may also be involved in the effects of ibogaine.

The lack of consistency, and the paucity of data regarding ibogaine were factors which argued for the utilization, in this thesis, of a comparable drug. Harmaline was chosen because of the apparent similarities between ibogaine and harmaline, and to capitalize upon the data base regarding harmaline, which is described below.

Harmaline and the
Beta-Carbolines

The beta-carbolines (BC's) are psychoactive indolic compounds which were first isolated from plant sources in the Amazon (Holmstedt, 1982). A species of vine (*Banisteriopsis*) is used by South American Indians in the preparation of a brew, variously called ayahuasca, yage, and caapi. It is consumed by shamans in order to experience visions which facilitate the diagnosis of disease, communication with spirits, and other shamanic activities (Harner, 1980). Like iboga, ayahuasca is also used in rites of passage into manhood (Naranjo, 1979). The main active ingredients of ayahuasca were isolated and found to be several beta-carbolines, notably harmine, tetrahydroharmine, harmaline and N,N-Dimethyltryptamine (McKenna and Towers, 1985).

Initial research activity on harmaline was devoted to an analysis of its tremorigenic properties, in the hope of elucidating the mechanism of the tremor produced by Parkinson's Disease (Hara, 1953; Ahmed and Taylor, 1959; Agarwal and Bose, 1967). Later, it was found that harmaline induced a rhythmic activation of neurons in the inferior olivary nucleus (Biscoe, Duggan, Headley and Lodge, 1973). This activity caused

spinal motor neurons to discharge, resulting in the fine, generalized tremor which is characteristic of harmaline administration (DeMontigny and Lamarre, 1973). Data concerning harmaline induced tremor may be pertinent to the present investigation because of an observed attenuating effect of low dose, intraperitoneally administered ethanol on harmaline induced tremor (Rappaport, Gentry, Schneider and Dole, 1984). If orally consumed ethanol has similar effects on harmaline induced tremor, and if tremor is assumed to be aversive, then ethanol may become a negative reinforcer by virtue of its ability to reduce tremor.

Acetaldehyde, the primary metabolite of ethanol, was reported to combine with catecholamines to form tetrahydroisoquinoline (TIQ) alkaloids (Cohen and Collins, 1970) and tetrahydropapaveroline (Davis and Walsh, 1970). Cohen and Collins (1970), and Davis and Walsh (1970) suggested that these condensation products may be responsible for the addictive properties of alcohol. Similarly, beta-carbolines were shown to be formed in vitro and in vivo from condensation reactions between serotonin and acetaldehyde (Dajani and Saheb, 1973; McIssac, 1961). Since TIQ mediation of the positive rewarding properties of ethanol is an idea that has been largely discredited (Smith, Brown, and Amit, 1980; Amit, Smith,

Brown and Williams, 1982.), and there has been little recent research on the possible role of TIQ's in ethanol consumption, further discussion will be limited to beta-carbolines.

In vivo formation of beta-carbolines

The first identification of a BC in living animal tissue was by Farrell and McIsaac (1961), who identified 6-methoxy-1-methyl-tetrahydrobetacarboline in bovine pineal gland. The same researchers then pretreated rats with iproniazide (a monoamine oxidase inhibitor) and disulfiram, to block metabolism of methoxytryptamine and acetaldehyde, respectively. The animals were then injected with labelled 5-methoxytryptamine, and ethanol. Radiolabelled 6-methoxytetrahydroharman was subsequently found in the urine of the rats, and it was concluded that ethanol administration resulted in the formation of beta-carbolines (Farrell and McIssac, 1961).

Rommelspacher, Damm, Strauss and Schmidt (1984) injected rats with ethanol, and observed corresponding increases in brain and urinary harman, a beta-carboline.

Rommelspacher, Damm, Schmidt and Schmidt (1985) examined the urinary excretion of harman by alcoholics

and non-alcoholics. They found elevated blood levels of acetaldehyde and urinary harman in the alcoholics. The difference was still significant two weeks after admission to a clinic, where alcohol was unavailable. Since tobacco smoke contains significant amounts of harman (Rommelspacher and Susilo, 1982), smoking may have been a confounding variable, uncontrolled in this study.

Kari, Peura and Araksinsen (1979, 1980) analyzed blood and plasma levels of 1-methyl-tetrahydrocarboline (1-Me-THBC) in human volunteers. After alcohol intake, 1-Me-THBC was found in all nine volunteers, where none was found before the experiment.

Taken together, the above findings suggested that beta-carbolines may be formed in vivo, and that ethanol consumption may have resulted in increased formation and excretion of beta-carbolines. The significance of BC formation remains a matter of speculation. They may or may not be related to the aversive or reinforcing properties of ethanol. Their formation may be purely artifactual, and have little to do with the effects of ethanol or the underlying susceptibility to the effects of ethanol. Nevertheless, the possible endogenous formation of BC's following ethanol consumption suggested that BC administration may have some influence on subsequent alcohol consumption. If BC

formation was related to the positive reinforcing aspects of ethanol consumption, then BC administration would be expected to be reinforcing. Therefore, BC administration could also lessen the motivation to consume ethanol. Alternately, if beta carboline formation was related to other, possibly aversive effects of ethanol (e.g. disturbed body balance and incoordination), then BC administration would be expected to potentiate the aversive properties of ethanol, and result in reduced ethanol consumption.

The effect of beta-carbolines on ethanol consumption.

Myers and Oblinger (1977) and Myers and Melchior (1977) reported increased voluntary ethanol consumption following chronic intracerebroventricular infusions of TIQ's and tetrahydrobetacarboline (THBC, tetrahydronorharman). Others, however were able to only partly replicate (Duncan and Deitrich, 1980), or failed to replicate (Smith, Brown and Amit, 1980) their findings.

Tuomisto, Airaksinen, Peura and Eriksson (1982) repeated the experiments of Myer's group, studying the effect of THBC and 1-Me-THBC on ethanol consumption in rats. The beta-carbolines were administered by chronic ventricular infusion, and the concentration of ethanol was increased by 2% every day, from three to 30%. After

six days of drug infusion, the high dose (47nmoles/hour) experimental group (1-Me-THBC) consumed significantly more alcohol than the control group. In contrast, the low dose (0.47 nmoles/hour) THBC group showed significantly reduced drinking during the last six days of the experiment. Despite the statistical significance of the results, the researchers attributed this discrepancy in the direction of results to variability. It appears that these unexpected results were dismissed because they were not in accord with the theoretical bias entertained by Tuomisto et al.(1982).

In a follow-up experiment, Airaksinen, Mahonen, Tuomisto, Peura, and Eriksson, (1983) evaluated only the high dose of 1-Me-THBC, and a related BC, 6-Methoxy-THBC. As in their previous study, 1-Me-THBC infusions resulted in increased voluntary intake of ethanol after one week had elapsed. They speculated that the time delay for the observed effect could have been due to a decreased aversiveness of the stronger taste of ethanol (because of the higher concentrations of ethanol), or to a learned association between drinking and the relief of unsubstantiated, but "possible dysphoric effects of 1-Me-THBC".

The use of increasing concentrations of ethanol introduced confounding variables related to learning and adaptation to novel stimuli. These sources of

variance make the results of Airaksinen et al (1982, 1983) difficult to interpret. Interestingly, the same authors cited one of their own, unpublished studies in which no effect of 1-Me-THBC was found on ethanol consumption when a constant concentration (11%) of ethanol was maintained throughout the experiment. This finding suggested that the initially observed increase in ethanol consumption was possibly dependent upon the increasing concentration of ethanol, and not upon the administration of beta-carbolines.

Rommelspacher, Buchau and Weiss (1987), using an almost identical paradigm (continuous infusions, increasing concentrations of ethanol), evaluated the effect of harman, harmalan, and THBC on ethanol consumption in rats. They found that 27 nmoles/hour of harman, and 72 nmoles/hour of THBC significantly increased alcohol consumption. Confirming the findings of Airaksinen et al. (1982, 1983), they found that the effect was not observable until one week had elapsed. The results of the experiment were confounded by the increasing concentration of ethanol; therefore, no conclusions can be made from their results.

Bosin, Krogh and Zabik (1987) investigated the effect of intraperitoneal carboxylated THBC (CTHBC) and carboxylated 1-Methyl-Tetrahydrobetacarboline (CMeTHBC) injections on forced choice ethanol (12%) consumption

in fluid deprived rats. They found that doses of 25 and 50 mg/kg, but not 100mg/kg CMETHBC, significantly reduced ethanol consumption. Their results were in direct opposition to the results of the other researchers cited above, who all found that BC's increased ethanol consumption (except the low dose of THBC used by Tuomisto et al., 1982). The intraperitoneal administration employed in the study by Bosin et al. (1987), as opposed to the intraventricular administration employed in the studies described above, may have been the primary factor responsible for the attenuating effect of BCs on ethanol consumption. Considering that CTHBC did not cross the blood brain barrier, these results suggested the possible involvement of peripheral mechanisms. Bosin et al.(1987) presented data showing that CTHBC lowered blood levels of tryptophan, perhaps by displacing tryptophan from albumin binding sites. They speculated that the free tryptophan was then able to enter the brain and raise central serotonin levels. Indeed, brain levels of serotonin were elevated after CTHBC administration. These elevated serotonin levels were the purported CNS effect of the peripheral action of CTHBC. This reasoning was proposed as an explanation for the observed reductions in ethanol consumption, despite the fact that CTHBC did not affect ethanol

intake. While CMETHBC did reduce ethanol intake, the investigators did not present data on the effect of CMETHBC on blood and brain tryptophan and serotonin, nor did they indicate whether it crossed the blood brain barrier. If the peripherally induced elevation of central serotonin was responsible for the CMETHBC induced reduction in ethanol consumption, then CTHBC should have had a similar effect on ethanol consumption. Therefore, there is little evidence that peripheral serotonergic mechanisms either did or did not mediate any of the effects of beta carbolines on ethanol consumption.

Geller, Purdy and Merritt (1973) examined the effect of intraperitoneal injections of 1-methyl-6-methoxyTHBC (MMeTHBC) on free choice ethanol consumption in the rat. They found that MMeTHBC caused a reduction in ethanol consumption, with a compensatory increase in water intake. Messiha, Larson and Geller (1977) administered THBC (40mg/kg, i.p.) to rats and observed a decrease in voluntary ethanol consumption. A single administration of THBC resulted in a marked drop in ethanol consumption, with no changes in liver alcohol dehydrogenase or aldehyde dehydrogenase (the enzymes responsible for the metabolism of ethanol and acetaldehyde, respectively) levels. THBC treatment for

five days resulted in a significant decrease in liver alcohol dehydrogenase.

To summarize the experiments presented in this section, it appears that certain beta-carbolines have a distinct potentiating effect on ethanol consumption, but only when infused intracerebroventricularly over long periods, and only when the concentration of ethanol is increased daily (Meyers et al., 1977; Tuomisto, et al., 1982; Airaksinen et al., 1983; Rommelspacher et al., 1987). This experimental design, with its lack of control over confounding variables, permits no conclusion regarding the effect of beta-carbolines on voluntary ethanol consumption. The results of Bosin et al. (1987), who observed a BC-induced decrease in ethanol consumption, and the results of Geller et al. (1973, 1977) do support the notion that certain beta carbolines may be useful in the treatment of alcohol dependence.

The possible reduction of ethanol intake following beta carboline administration (Bosin et al., 1987; Geller et al., 1973, 1977) may have been mediated by serotonergic mechanisms. The involvement of 5HT systems in consummatory behavior is well established (Blundell, 1984), although the precise nature of that involvement is unclear (Amit, Sutherland, Gill and Ogren, 1984). The next section reviews evidence that serotonergic

mechanisms may mediate some of the effects of beta carbolines.

Beta-carbolines and Serotonin

There are several lines of evidence which indicate that harmaline, the beta carboline used in this thesis, interacts with serotonin receptors.

Glennon (1981) determined that harmaline had a fairly high affinity ($pA=5.82$) for serotonin receptors, using the isolated rat fundus preparation. Muller, Fehske, Borbe, Wollert, Nanz and Rommelspacher (1981) found that harmaline had moderate affinity ($IC_{50}=115$ micromM) for serotonin receptors, as indicated by the ability of harmaline to displace 3H serotonin from the cortex of the calf brain.

Sjolund, Bjorklund and Wicklund (1977), investigating harmaline induced tremor, found that when serotonergic afferents to the inferior olive were lesioned, there was a significant attenuation of harmaline induced tremor. Furthermore, the reappearance of the harmaline induced tremor appeared to parallel the regrowth of new serotonergic axon sprouts in the inferior olive. They concluded that harmaline interferes with an inhibitory serotonergic input to the inferior olive.

There is additional, although indirect, evidence of serotonergic mediation of some of harmaline's effects. Research investigating the effects of harmine may be relevant. Harmine is an alkaloid which is structurally almost identical to harmaline, and which has a similar pharmacological and behavioral profile (Muller et al., 1981; Glennon, 1981; Fuentes and Longo, 1971). Schulka, Garg and Kulkarni (1986) found that cyproheptadine, a serotonin receptor blocker, abolished harmine-induced tremor in mice. Kulkarni and Kaul (1979) observed that the 5HT agonist quipazine resulted in a prolongation and shortened latency to harmine induced tremor. Therefore, with a 5HT antagonist and a 5HT agonist having opposite effects on harmine induced tremor, the case for serotonergic mediation of the tremor is strengthened.

Several subtypes of 5HT receptor, including the 5HT₂ receptor, have been described (Hamon, Nelson, Helmut and Glowinski, 1980). The head twitch response has been used as behavioral assay of 5HT₂ receptor activation (Peroutka, Lebovitz and Snyder, 1981), and harmine was found to enhance the head twitch response in animals pretreated with 5HTP (Corne, Pickering and Warner, 1963). This suggests that harmine may activate 5HT₂ receptor sites.

Mendelson and Gorzalka (1986) examined the effects of harmine on lordosis in the female rat, a behavior that has been associated with 5HT₂ function. They found that harmine facilitated lordosis, and that harmine attenuated the inhibitory effects of the selective 5HT₂ antagonists pirenperone and ketanserin on lordosis. They concluded that harmine may bind at post-synaptic 5HT₂ receptors. This conclusion was supported by the observed enhancement of harmine induced tremor by pretreatment with reserpine or p-chlorophenylalanine, which results in receptor sensitization (Kelly and Naylor, 1974). Acknowledging that harmine has affinity for other receptors (e.g. opiate, cholinergic), Mendelson and Gorzalka (1986) conceded that the harmine induced facilitation of lordosis could have been mediated by other neurotransmitter systems.

The discriminative effects of LSD are probably mediated by 5HT neurons (Colpaert, Niemegeers and Janssen, 1982). Therefore, the ability of both harmaline and THBC to substitute for LSD in a food motivated stimulus discrimination task (White, Nielson and Appel, 1982) implies serotonergic involvement in the effects of harmaline. White et al. (1982) also found that the 5HT antagonist pizotofen attenuated the generalization between THBC and LSD. The effect of

pizotofen on harmaline generalization was not determined. Furthermore, THBC was found to inhibit 3H LSD binding to the rat frontal cortex. The authors concluded that THBC's have discriminative stimulus properties similar to those of LSD, and have effects that are probably mediated by activation of 5HT receptors. When THBC was used as the drug controlling behavior in an identical paradigm (Schechter, 1986), fenfluramine (a 5HT releasing agent) substituted for the THBC, while LSD partially substituted for THBC. This again suggested that THBC may significantly affect serotonergic mechanisms. The generalizability of these conclusions regarding THBC to harmaline must be made cautiously, for although harmaline displaces 3Hserotonin, THBC is approximately 30 times more potent in that respect (Muller, et al., 1981).

THBC was also used in other studies which examined directly the question of whether THBC was a serotonin uptake inhibitor. In general, THBC's were found to be more potent uptake inhibitors of serotonin than of norepinephrine, dopamine, gamma-aminobutyric acid (GABA), or choline, both in vitro and in vivo (Kellar, Elliot, Holman, Vernikos-Danellis and Barchas, 1976; Buckholtz and Boggan, 1977; Rommelspacher, Strauss and Rehse, 1978; Freidman, Meller, and Mallock, 1981). As a competitor of 3Hserotonin uptake in mouse brain

suspension, harmaline was found to be a relatively less effective 5HT uptake inhibitor, being 15 times less potent than THBC (Buckholtz and Boggan, 1977).

There has been more research on the neurotransmitter effects of THBC and other beta-carbolines than of harmaline in particular. Research has consistently found that THBC's, depending on the dose and particular structure, affect both serotonin release and uptake (Holman 1982). This conclusion regarding THBC action partially confirms the results of the few binding studies done with harmaline. The results of the experiments described in this section are generally consistent in indicating that serotonergic mechanisms may be responsible for some of the effects of harmaline and other beta carbolines. However, not all the data are consistent with the conclusion that the effects of harmaline are mediated by serotonin.

Much of the data presented in this section concerned THBC, which is 30 times more potent than harmaline in displacing 3Hserotonin from 5HT receptors (Muller et al., 1981). Muller et al. (1981) also showed that harmaline has a greater affinity for opiate and muscarinic adrenergic receptors than for 5HT receptors. Harmaline is also a potent inhibitor of monoamine oxidase (MAO-A), the enzyme responsible for the

degradation of serotonin (Buckholtz and Boggan, 1977). The time course of the MAO-A inhibition was determined by Kim, Hassler, Kurokawa and Bak (1970), who observed that harmaline administration caused rat striatal 5HT to increase by 82% after one hour, then decrease to baseline levels after three hours. This finding suggested that serotonergic activation may be responsible only for some of the acute effects of harmaline. Longer term effects of harmaline are therefore not easily explained in terms of serotonergic activation.

Furthermore, Shukla, Garg and Kulkarni (1986) demonstrated that the serotonergic mediation of harmine induced tremor in mice was modulated by a noradrenergic mechanism. Shukla et al. (1986) found that clonidine, a noradrenergic alpha-2 agonist, exhibited a dose dependent protection against harmine induced tremor. This effect of clonidine was antagonized by behaviorally ineffective doses of fluoxetine and quipazine, which suggested that both 5HT and noradrenergic systems are involved in the action of harmine.

In conclusion, the case for a simple serotonergic mediation of the effects of harmaline is complicated by inconsistent data, and data which suggest that other neurotransmitter systems may be the primary site of

action for harmaline. Harmaline and other beta-carbolines have been shown to both interact specifically with the GABAergic system, and to have powerful effects on consummatory behaviors, as outlined in the following two sections.

Beta-carbolines and GABA

The first report of an interaction between harmaline and benzodiazepine (BZ) was by Mao, Guidotti and Costa (1975), who reported that harmaline-induced tremor could be antagonized by pretreatment with BZ. These authors suggested that the observed anti-tremorigenic effect of BZ was the result of increased GABA release from the inhibitory afferents to the Purkinje cells in the cerebellum.

Robertson (1980) injected mice with several doses of harmaline, noted the degree of tremor produced, and then analyzed regional brain concentrations of harmaline in the same mice. He found that although harmaline had a relatively low affinity (as determined by 3Hflunitrazepam displacement) for the BZ receptor ($IC_{50}=600$ microm), brain concentrations of harmaline were sufficient to occupy a significant percentage of BZ binding sites. He concluded that the BZ receptor mediates harmaline induced tremor.

This conclusion was challenged, however, by the observation that the tremorigenic potency of BC's did not correlate well with their BZ receptor affinities (Skolnick, Williams, Cook, Caine, Rice, Mendelson, Crawley and Paul, 1982). These authors suggested that harmaline acts indirectly, and not directly at BZ receptors. Furthermore, harmaline induced tremor lasts only three hours (Fuentes and Longo, 1971). Since the three hour duration of harmaline induced MAO-A inhibition (Kim et al., 1970) happens to coincide with the duration of tremor, it may be that the two phenomena are related.

The beta-carbolines are a unique class of compounds because small structural changes result in large differences of pharmacological action at the GABA/BZ receptor complex. Specific beta-carbolines act as full or partial BZ agonists, antagonists, or inverse agonists. The concept of an inverse agonist was introduced to explain the activity of beta-carboline-3-carboxylate (BCCE) (Haefely, 1983). Binding experiments confirmed that BCCE had a high affinity for BZ receptor sites (Braestrup, Neilson and Olsen, 1980; Neilson and Braestrup, 1980), but when tested in vivo, it did not act as a benzodiazepine. Not only did it antagonize the effects of BZ, but when administered alone, it resulted in convulsions, an

effect opposite to the anticonvulsant effect of BZ. Proconvulsant and anxiogenic effects (i.e. opposite effects to those of BZ) of BCCE were described by several investigators (e.g. Braestrup, Schmiechen, Neef, Neilson and Peterson, 1982; Cowen, Green, Nutt and Martin, 1981). Another BZ full inverse agonist, FG 7142, induced extreme anxiety (the opposite effect of BZ) in human volunteers (Dorow, Horowski, Paschelke, Amin & Braestrup, 1983). Agonists, antagonists, and inverse BZ agonists, both full and partial, are each associated with a specific effect on food and fluid consumption (Cooper, 1987). In the next section, evidence is presented which suggests that harmaline is a BZ partial inverse agonist, and should therefore be expected to have an attenuating effect on consummatory behavior.

Beta-carbolines and Consummatory Behavior

The full BZ agonists, such as benzodiazepine, chlordiazepoxide, oxazepam, and others, all have a characteristic hyperphagic effect (Cooper, 1987), and the term "voraciousness" has been used to describe the feeding induced by diazepam (Mereu, Fratta, Chessa, and Gessa, 1976). Nonbenzodiazepines which act as BZ agonists, such as zopiclone, also increase food

consumption in both deprived and non-deprived rats (Cooper and Mooles, 1985). The beta-carboline ZK 93423, a full BZ agonist, proved effective in increasing food consumption in non-deprived rats (Cooper, 1987).

Detailed temporal (microstructural) analysis of feeding patterns in rats revealed that midazolam (a BZ receptor agonist) treatment resulted in an increase in the total duration of feeding, due to an increase in the duration of feeding bouts. Neither the rate nor the frequency of feeding were affected (Cooper, 1987). These results suggested that the onset of satiety was delayed, and that BZ receptor agonists interact with factors which influence the maintenance of feeding.

The motivational effects of BZ treatment were investigated by Berridge and Treit (1986), who analyzed taste reactivity in rats following chlordiazepoxide treatment. The BZ selectively enhanced the ingestive responses (licking, head poking, etc.) to oral infusions of palatable fluids, yet did not affect rejection of aversive fluids. Interestingly, these results were similar to the pattern of results obtained following systemic administration of serotonin (Montgomery and Burton, 1986). If BZ agonists increase food consumption, then BZ inverse agonists should be expected to have the opposite effect.

As expected, FG 7142 (and other full inverse agonists) cause a reduction in the consumption of palatable food by non-deprived rats (Cooper, Barber, Gilbert and Moores, 1985). This reduction was antagonized by BZ receptor agonists, and is therefore likely to be mediated by an action at BZ sites. Microstructural analysis of the feeding following FG 7142 administration revealed that the frequency of feeding bouts was unchanged, but their duration was reduced. These results reinforce the idea that drugs which are active at the BZ receptor affect the maintenance of feeding activity within bouts of feeding (Cooper, 1987).

Cooper (1986) found that FG 7142 administration resulted in reduced intake of water, saccharine and quinine solutions in fluid deprived rats. Saccharine consumption was most reduced, as was its preference, whereas the aversion to quinine was not attenuated at low doses. In addition, aversion to quinine was abolished at high doses of FG 7142. Cooper (1987) concluded that FG 7142, in contrast to BZ agonists, may cause a decrease in the attractiveness, or palatability, of food substances.

FG 7142 caused a reduction in feeding bout duration, but not frequency. This same pattern of results was found by researchers who manipulated the

serotonergic system. For example, reductions in feeding bout duration were observed by Gill and Amit (1987) following Zimeldine treatment, and by Blundell and Lathan (1982) following fenfluramine and fluoxetine treatment. One possible interpretation of these results is that the effects of BZ inverse agonists on feeding may be due to an increase in activity of serotonergic systems. GABA is an important inhibitory neurotransmitter, and a reduction in GABA release would be expected to result in a disinhibition of any secondary serotonergic cell bodies or synapses. If harmaline were a BZ inverse agonist as well as a serotonin agonist or uptake blocker, there would be two mechanisms whereby harmaline could cause a reduction in food intake.

Harmaline causes tremor and hyper-reactivity (Fuentes and Longo, 1971), effects which are opposite to the effects of benzodiazepine. Additionally, harmaline induced tremor is attenuated by diazepam (Robertson, 1980). These observations are consistent with the classification of harmaline as a partial BZ inverse agonist. The failure of harmaline to readily induce states of anxiety in humans is an effect which does not permit the classification of harmaline as a full BZ inverse agonist. On the contrary, human

subjects report ataxia and muscle relaxation (Naranjo, 1973), both indicative of BZ agonist properties.

There is experimental evidence which suggests that GABA/BZ and 5HT systems interact. Agarwal, Lapierre, Rastogi and Singhal (1977) demonstrated that daily administration of diazepam significantly increased levels of tryptophan hydroxylase, tryptophan, serotonin and 5-HIAA (a metabolite of serotonin) in several brain regions, including the hypothalamus. Withdrawal of benzodiazepine caused a rebound reduction of serotonin levels. These results suggested that manipulations of the GABAergic system affects serotonin levels, either directly or indirectly.

More direct evidence of a functional link between GABA/BZ and serotonin was provided by Pratt, Jenner, Reynolds and Marsden (1979), who demonstrated that clonazepam depressed firing of 5HT neurons. Additionally, intraperitoneal administration of the benzodiazepines diazepam or chlordiazepoxide depressed unit activity in the raphe of freely moving cats (Preussler, Howell, Frederickson and Trulson, 1981).

Autoradiographic studies indicate that BZ receptors are found in areas which are components of the forebrain serotonin system, such as the hippocampus, basolateral and cortical amygdaloid nuclei, and dorsal raphe (Iverson, 1984). A functional link between BZ and

5HT in those same brain regions was suggested when iontophoretically applied GABA inhibited the firing of 5HT neurons, an effect which was enhanced by benzodiazepines (Gallager, 1978).

In summary, there are convergent lines of evidence which suggest that harmaline may act as a partial BZ inverse agonist, and, as such, would be expected to have certain anorectic properties. There is also indirect evidence (Holman, 1982; Buckholtz and Boggan, 1977) that harmaline may act as a non-specific serotonin uptake blocker and/or serotonin receptor agonist, increasing the expectation that harmaline may possess anorectic, and other, taste related effects on food and fluid consumption. The intimate association of the GABAergic and serotonergic systems suggests that harmaline may have indirect (via GABA) as well as direct (5HT receptor activation or uptake inhibition) effects on serotonergic systems. Given that both serotonin (Blundell, 1984) and GABA (Cooper, 1986, 1987) manipulations affected consummatory behavior, harmaline administration was expected to affect ethanol consumption in rats.

The use of harmaline in this thesis was justified on the grounds that the behavioral effects of harmaline were similar to those of ibogaine. The commonalities

between these two drugs, and the implications thereof, are described in the following section.

Similarities between
Ibogaine and Harmaline

The experiments described in this thesis were conducted for the purpose of evaluating the claim (Lotsof, 1986) that ibogaine administration could result in the interruption of cocaine, and possibly, alcohol abuse in humans. As described in the section on ibogaine, there has been very little research on the behavioral effects of ibogaine; additionally, the neuropharmacology of ibogaine appears to be complex. Harmaline was similarly evaluated for two reasons: 1) If harmaline and ibogaine administration resulted in similar behavioral effects, it would have been possible, drawing upon the available data concerning harmaline, to hypothesize that ibogaine may possibly have neuropharmacological properties similar to those of harmaline. 2) Since the known neuropharmacological effects of harmaline are consistent with the hypothesis that harmaline would affect consummatory behavior, and since there have been no reports on the effects of harmaline on consummatory behavior, it was deemed appropriate to investigate the effects of harmaline on

consummatory behavior. It was considered possible that harmaline could have attenuating effects on ethanol consumption, which would be of theoretical, if not practical, interest.

Some of the similarities between ibogaine and harmaline were noted in the literature which describes the effects of these two drugs, in their crude and pure forms, on humans. Ibogaine is the main alkaloid in the Iboga root, and harmaline is one of the main active constituents of ayahuasca (Holmstedt, 1982). The ingestion of both iboga and ayahuasca results in a numbness of the extremities, and visions. Local uses of the two drugs (described in the sections on ibogaine and harmaline) are very similar, with one exception: iboga in low doses is used as a stimulant. It is unknown whether ibogaine is the alkaloid responsible for Iboga-induced psychomotor stimulation. Naranjo (1973) administered both harmaline and ibogaine to dozens of individuals. He grouped the two drugs together, and apart from other hallucinogens, because both had unique and similar physical, emotional, and imagery effects in humans.

In addition to having similar behavioral effects in humans, ibogaine and harmaline appear to share at least some pharmacological properties. Tabernanthine is an alkaloid whose chemical structure is identical to that

of ibogaine, except for the shifting of the methoxy group to the next position. Both tabernanthine and harmaline have tremorigenic properties that are attenuated by diazepam (Trouvin et al. 1987). This suggests that benzodiazepine receptors may mediate some of the effects of both harmaline and tabernanthine. Given the similar structures of tabernanthine and ibogaine, it may be that some of the effects of ibogaine are also mediated by BZ receptors.

Finally, Sloviter et al. (1980) suggested that ibogaine may have 5HT receptor agonist properties, as does harmaline (Glennon, 1981; Muller et al., 1981; Sjolund et al., 1977). The previously described findings regarding harmine, THBC, and other beta carbolines, are consistent with the notion that the beta carbolines, as a class (which includes harmaline), affect serotonergic systems.

The first experiment to be described was conducted in order to evaluate (using rats) the claim that a single administration of ibogaine could interrupt cocaine abuse in humans. Given that this was a highly unusual claim, with no known theoretical mechanism of action, or comparable effects of other drugs, it was not considered likely that ibogaine would affect cocaine self administration in rats.

Experiment 1
The Effect of Ibogaine on
Cocaine Self Administration in Rats.

The purpose of this experiment was to determine whether a single dose of ibogaine would result in the interruption of intravenous cocaine self administration in rats. The intravenous self administration of cocaine by rats is a phenomenon that has been used as a model of human cocaine use (e.g. Collins, Weeks & Cooper, 1984; Johanson, 1985). There are no formal reported observations which support the claim by Lotsof (1986) that a single dose of ibogaine interrupted cocaine abuse in humans. Additionally, there is no known pharmacological mechanism which could account for the observations of Lotsof(1986). Consequently, it was not considered likely that ibogaine would interrupt cocaine self administration in rats, and a minimal number of rats were used in this experiment. For the same reason, rats were used as their own controls: if an effect of ibogaine on cocaine self administration were to be observed, an additional experiment, using an independent control group, was planned.

The dose of ibogaine (100mg/kg), and the intragastric route of administration were chosen in

order to approximate the conditions described by Lotsof (1986).

METHOD

Subjects

Subjects were eight male Long Evans rats weighing 175-200 gms. at the start of the experiment. They were housed individually in stainless steel cages in a temperature regulated room, and maintained on a 12:12 light:dark cycle commencing at 0800 hrs. Food and water were available ad libitum.

Materials

Operant boxes (20 x 20 x 22 cm) equipped with a lever activated syringe pump and cue light (12 sec.) were used. The plexiglass boxes had wire floors, and the lever press responses were recorded by means of a strip chart event recorder. A lever press activated the pump which delivered 0.1 ml of either 0.9% saline or cocaine HCl dissolved in saline. The concentration of the cocaine HCl was adjusted so that each 0.1 ml infusion would deliver 0.5mg/kg cocaine. The infusion was delivered via tubing mounted on a rotating swivel assembly which enabled the rat to move about freely.

Ibogaine HCl was supplied by NDA International, Inc., and its identity was confirmed by infrared spectroscopy (Dickel, Holden, Maxfield, Paszek and

Taylor, 1958). The ibogaine was suspended in 0.9% saline solution.

Procedure

Following one week of acclimatization to the laboratory environment and handling, the rats were anaesthetized with sodium pentobarbitol (65mg/kg), and implanted with chronic indwelling jugular catheters (Dow Silastic, 0.25 mm i.d.). The catheter was passed subcutaneously to the top of the skull where it was secured to a stainless steel elbow tube mounted in dental acrylic. The entire head piece was secured to the skull with four stainless steel screws. The animals were given one week to recover from the surgery.

The rats were then placed in the operant boxes for daily three hour sessions. All sessions were between 1100 and 1400 hrs. For five experimental rats, a lever press resulted in a cocaine infusion; three operant control rats received saline infusions with each lever press. The rats were allowed a seven day period for the establishment of cocaine reinforced responding, as determined by significantly elevated response rates relative to operant control rats.

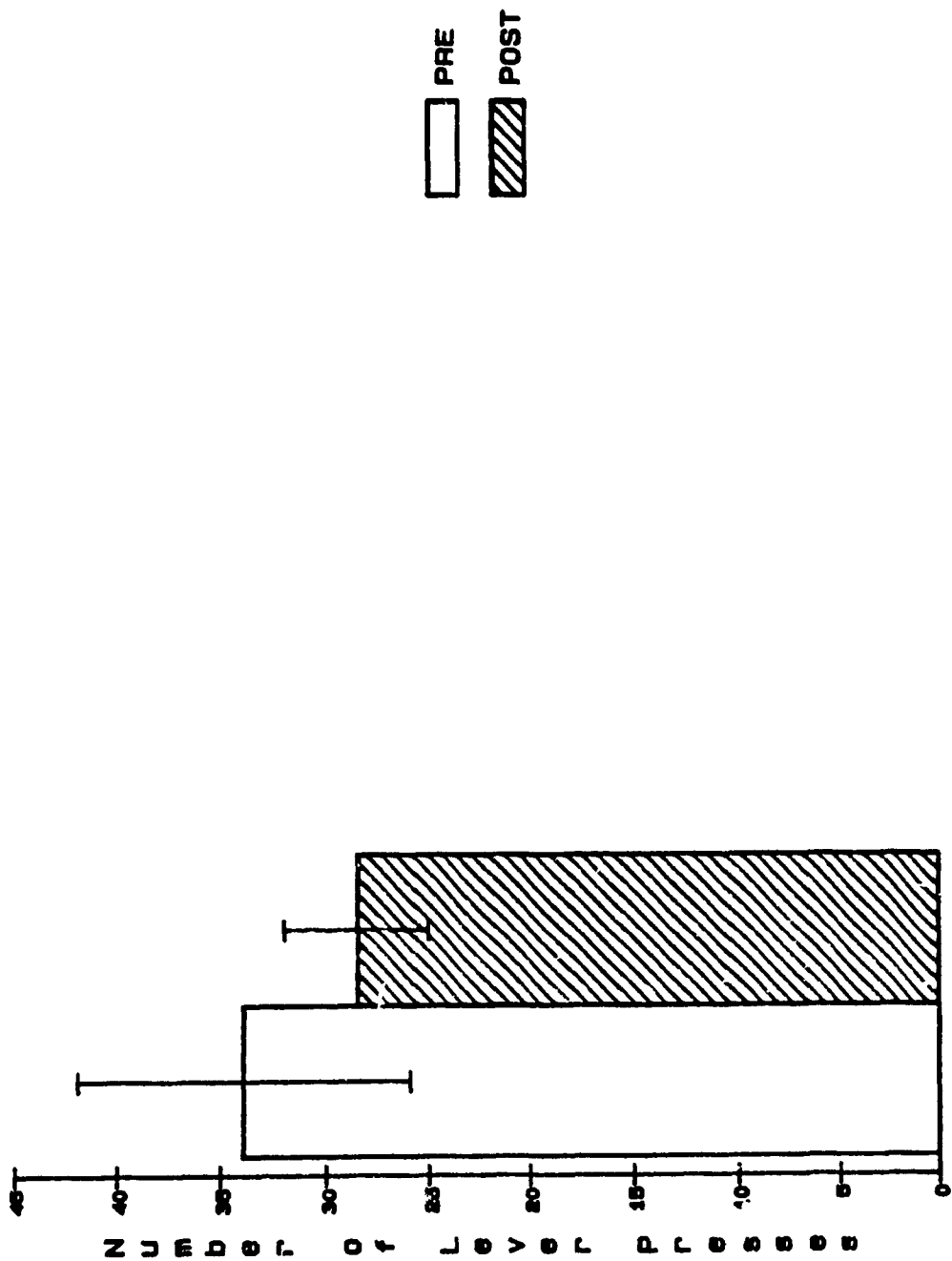
Ibogaine HCl (100mg/kg) was administered intragastrically to all the rats at 1800 hrs of day seven. The following day, all rats were placed in their operant boxes for their daily session. On day nine, after the daily session (1800 hrs), 180mg/kg ibogaine

or saline was administered to the same rats. Ibogaine was administered intragastrically, via a sterile rubber feeding tube. Daily sessions in the operant boxes continued as usual for five days following the first dose of ibogaine.

RESULTS

The mean number of lever presses during the four days preceding, and the four days following the first ibogaine administration, were compared to each other in the five rats responding for cocaine. A correlated groups t-test revealed that there was no significant difference between the two means ($t=1.059$, n.s.). Rats receiving cocaine pressed significantly more than rats pressing for saline, as determined by an independent groups t-test: $t=-2.829$, $p<.025$. The results are presented in Figure 1.

Figure 1
Lever Presses for Cocaine
Ibogaine (100mg/kg)



DISCUSSION

This experiment yielded results which do not support the notion that high dose ibogaine administration may interrupt cocaine self administration. The second, higher dose of ibogaine was in fact administered when it was observed that the first dose had no effect on subsequent cocaine self administration. Therefore, the fact that cocaine self administration was not affected by two administrations of ibogaine suggested that the claims made for ibogaine were either not based in fact, or that the mechanism involved was non-pharmacological in nature (e.g. due to suggestion, placebo effect, etc). Given the lack of theoretical or empirical support for the claim that ibogaine could interrupt cocaine self administration, the question was not pursued further by additional experimentation.

Although this experiment did not support the primary claim made for ibogaine, it was nevertheless possible that ibogaine could affect ethanol consumption. This possibility, although not emphasized by Lotsof (1986), had some theoretical basis (see earlier in this thesis). The succeeding experiment was therefore conducted to evaluate the possibility that

ibogaine may attenuate ethanol self administration in rats.

Experiment 2
The Effect of Ibogaine on
Voluntary Ethanol Consumption in Rats.

As in Experiment 1, the dose of ibogaine and route of administration were chosen to approximate the conditions reported by Lotsof (1986) following his observations of the outcome of human ibogaine self administration. There is no formal literature which either supports or refutes the claim that ibogaine may interfere with ethanol self administration in humans or animals. The results of Experiment 1 suggested that two administrations of ibogaine were not effective in attenuating cocaine self administration in rats. Therefore, in this experiment, ibogaine was administered to ethanol drinking animals for five consecutive days. In this laboratory, a five day schedule has been used in experiments which investigated the effects of other drugs on ethanol self administration in rats. Ethanol consumption was also recorded for 15 days post treatment, in order to determine whether ibogaine administration had any prolonged or delayed effect on ethanol consumption. Water and food consumption were recorded in order to determine whether ibogaine administration had effects

specific to ethanol consumption or to consummatory behavior in general.

METHOD

Subjects.

Subjects were 32 male Long-Evans rats, weighing 175-200 gms. at the start of the experiment. They were housed individually in stainless steel cages in a temperature regulated room. They were kept on a 12:12 light:dark cycle, commencing at 0800 hrs. Food and water were always available ad libitum.

Materials.

Ethanol solutions (2-10%, v/v) were prepared by mixing 95% ethanol with tap water. Ethanol solutions and water were presented in glass Richter tubes mounted on the front of each cage. Ibogaine HCl was supplied by NDA International, Inc., and its identity was confirmed by I.R. spectroscopy (Dickel, et al., 1958). The ibogaine was administered by a sterile rubber feeding tube attached to a 5cc syringe. The ibogaine HCl was suspended in a 0.9% saline solution, at a concentration of 15mg/ml.

Procedure.

After four days of acclimatization to the animal room, the rats were given 2% ethanol solution in a free choice with water. The next day, water only was given in the two tubes. The third day, the positions of the

tubes were reversed, and the concentration of ethanol was increased by one percent. This alternate day and alternate side exposure to increasing concentrations of ethanol was repeated until a concentration of 10% was reached. The rats were then presented with 10% ethanol for seven consecutive days (baseline period), during which time there were daily tube position reversals. Fluid consumption and body weight were recorded every other day.

Based on average ethanol consumption during the last six days of the baseline period, the 12 highest drinking rats were selected for the experiment. Mean ethanol consumption of these rats was 2.92 gm/kg/day. Either ibogaine (120mg/kg, i.g.), or an equivalent volume of saline (i.g.) was administered to each of two randomized groups. Drug and saline administrations were carried out between 1600 and 1800 hrs, for five consecutive days. Tube positions were reversed daily during the treatment and post treatment periods.

Data was collected at three points during both the baseline period (days 3, 5 and 7), and the treatment period (days 9, 11 and 12). Data from the 18 day post treatment period was also collected on alternate days. In order to compare approximately equal length periods, only the first three data points (days 14, 16 and 18)

from the post treatment period were used in the statistical analysis.

RESULTS

A three way analysis of variance (with repeated measures) was applied to the data, comparing the saline and ibogaine groups across the baseline, treatment, and post treatment periods. A significant drug/period interaction ($F(2,20) = 6.324$, $p=0.007$) indicated that there was a reduction in total fluid consumption during the treatment period. There was no significant reduction in ethanol consumption, expressed as percent of total fluid (%TF) intake. When ethanol consumption was expressed as gms/kg (Figure 2), a significant reduction in consumption was revealed by a drug/period interaction: $F(2,20)=3.577$, $p=0.046$. There were significant period effects for total fluid consumption and for ethanol consumption (gm/kg) as follows: $F(2,20)=5.697$, $p=0.011$; $F(2,20)=4.870$, $p=0.018$. The ethanol preference results, which showed no significant reductions, are depicted in Figure 3.

The saline treated rats had a mean weight gain of 7.33 gms, while the ibogaine treated rats lost an average of 5.0 gm during the five day treatment period. This difference was significant, as determined by an independent sample t-test: $t(6) = -4.44$, $p < 0.05$.

Figure 2
Ethanol Consumption (gms/kg)
Ibogaine 120 mg/kg

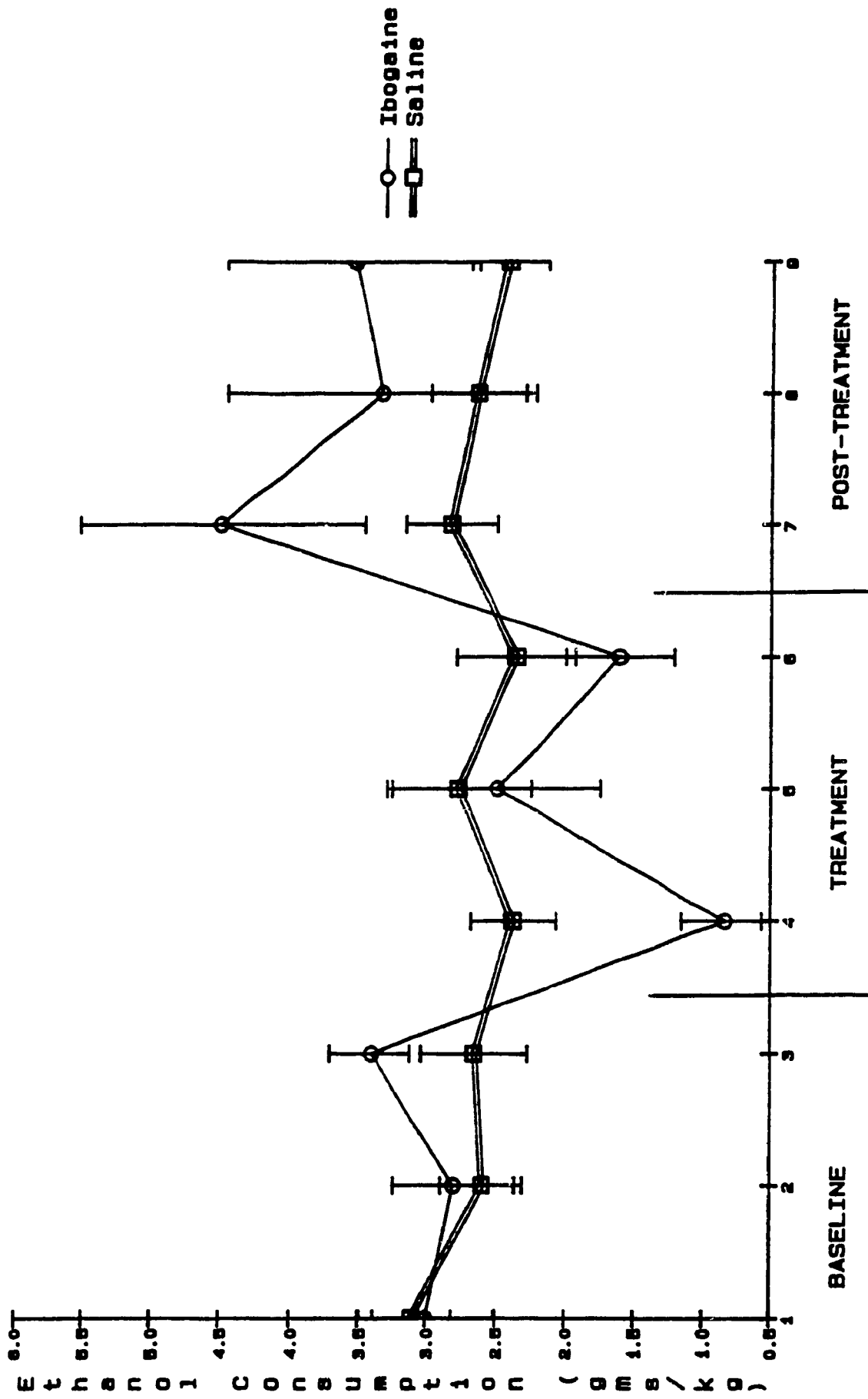
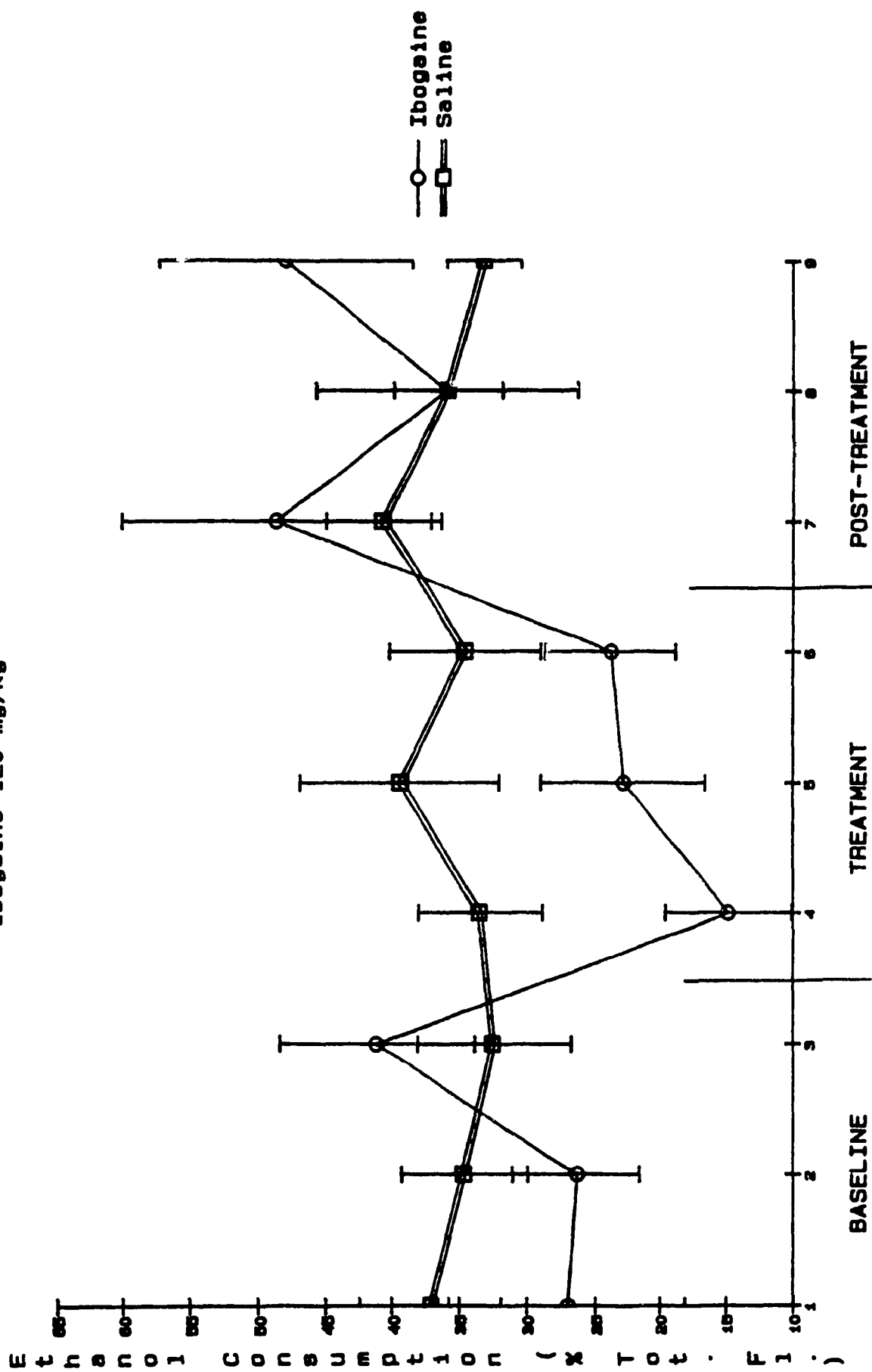


Figure 3
Ethanol Consumption (% Total Fluid)
Ibogaine 120 mg/kg



Ibogaine administration was observed to result in ataxia, as well as tremor when the rat tried to move, and unusual postures, characterized by splaying of the forelimbs, and Straub tail. The second and subsequent administrations of ibogaine resulted in the rats remaining motionless for at least two hours. They were, however, capable of movement when stimulated. Movement appeared normal after three hours.

DISCUSSION

The results obtained in this experiment suggested that five consecutive days of ibogaine administration may reduce absolute (gm/kg) ethanol consumption in rats. However, the observations that preference for ethanol was not significantly reduced, and that total fluid consumption and body weight were also reduced in the ibogaine treated rats, suggested that the effect was not specific to ethanol.

Despite the fact that ethanol preference was not significantly reduced in ibogaine treated rats, it was clear that ibogaine treatment did have some effect on consummatory behavior. Consequently, the experiment was extended, using additional doses of ibogaine, in order to further investigate the effects of ibogaine.

Experiment 3
The Effect of I.P. Ibogaine
on Ethanol Intake in Rats.

The gavage procedure utilized in Experiment 2 appeared to be stressful to the animals. They quickly learned to bite, struggle, or otherwise avoid insertion of the feeding tube. Also, the gavage procedure was wasteful of ibogaine, which is difficult to obtain in Canada. Dhahir (1971) determined that the LD50 of intraperitoneally administered ibogaine was approximately half the intragastric dose. Consequently, in this and all further experiments, the intraperitoneal route of administration was used. The doses of ibogaine chosen for this experiment range from low (no observable motor effects) to high (resulting in extreme ataxia).

METHOD

Subjects.

Subjects were 75 male Long Evans rats, weighing 175-200 gms. at the start of the experiment. They were housed individually in stainless steel cages in a temperature regulated room. They were kept on a 12:12 light:dark cycle, commencing at 0800 hrs. Food and water were always available, ad libitum.

Materials.

Ethanol solutions (2-10%, v/v) were prepared by mixing 95% ethanol in tap water. Ethanol solutions and water were presented in glass Richter tubes mounted on the front of each cage. Ibogaine HCl was dissolved in distilled water to a concentration of 8mg/ml.

Procedure.

After four days of acclimatization to the animal room, the rats were given 2% ethanol solution in a free choice with water. The next day, water only was given in the two tubes. The third day, the positions of the tubes were reversed, and the concentration of ethanol was increased by one percent. This alternate day and alternate side exposure to increasing concentrations of ethanol was repeated until a concentration of 10% was reached. The rats were then presented with 10% ethanol for seven consecutive days, during which time there were daily tube position reversals and recording of fluid consumption and body weight. Mean ethanol consumption for each rat over the last five days of the 10% baseline period was calculated, and the 30 highest drinking rats (by %TF) were selected for the experiment. The rats were then divided into five groups of six rats each, matched on average ethanol

preference, in such a way that each group was composed of a range relatively high and low drinking rats.

During the five day treatment period, rats were injected daily with either 15, 30, 60, or 80mg/kg ibogaine, or an equivalent volume of 0.9% saline. Injections were done between 1600 and 1800 hrs. During the treatment period and the five day post treatment period, tube position reversals and data collection were done daily.

RESULTS

A three way (dose x period x days) analysis of variance with repeated measures was applied to the data, which consisted of measurements taken during the baseline, treatment, and post treatment periods. No significant reductions in total fluid consumption (mls.) or ethanol consumption were observed, whether expressed as gm/kg or percent of total fluid (%TF), in any of the groups. Although there were no significant dose/period interaction effects, there were significant period effects for total fluid (mls.), and ethanol consumption (expressed both as gm/kg and %TF), as follows: Total fluid: $F(2,50)=14.238$, $p<.001$; Ethanol gm/kg: $F(2,50)=13.832$, $p<.001$; Ethanol %TF: $F(2,50)=8.894$, $p<.001$. Figures 4 and 5 show ethanol consumption in grams per kilogram, and Figures 6 and 7

show ethanol consumption as percent of total fluid intake.

Figure 4
Ethanol Consumption (gm/kg)
Ibogaine 15 mg/kg & 30 mg/kg

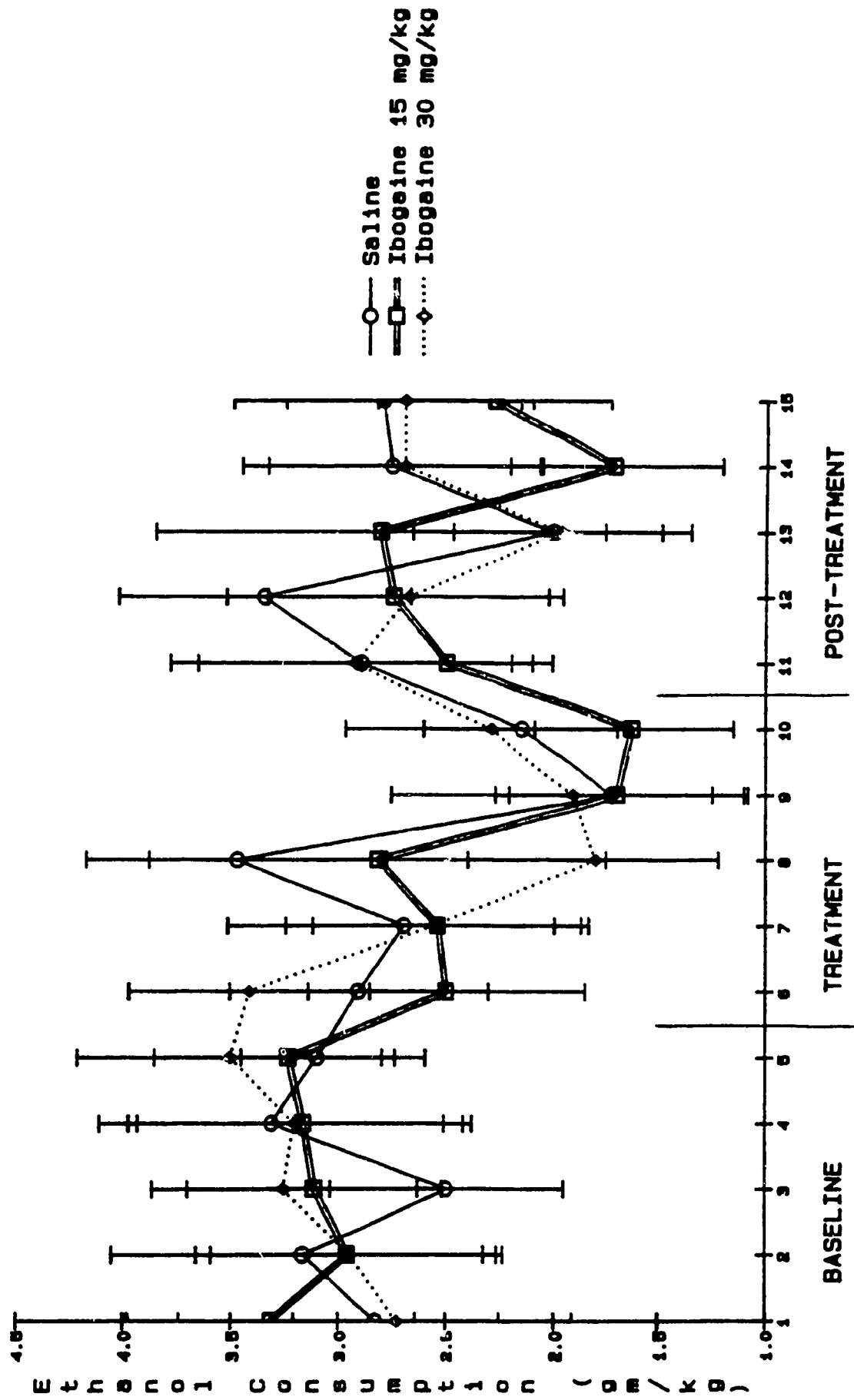


Figure 5
Ethanol Consumption (gm/kg)
Ibogaine 60 mg/kg
Ibogaine 80 mg/kg

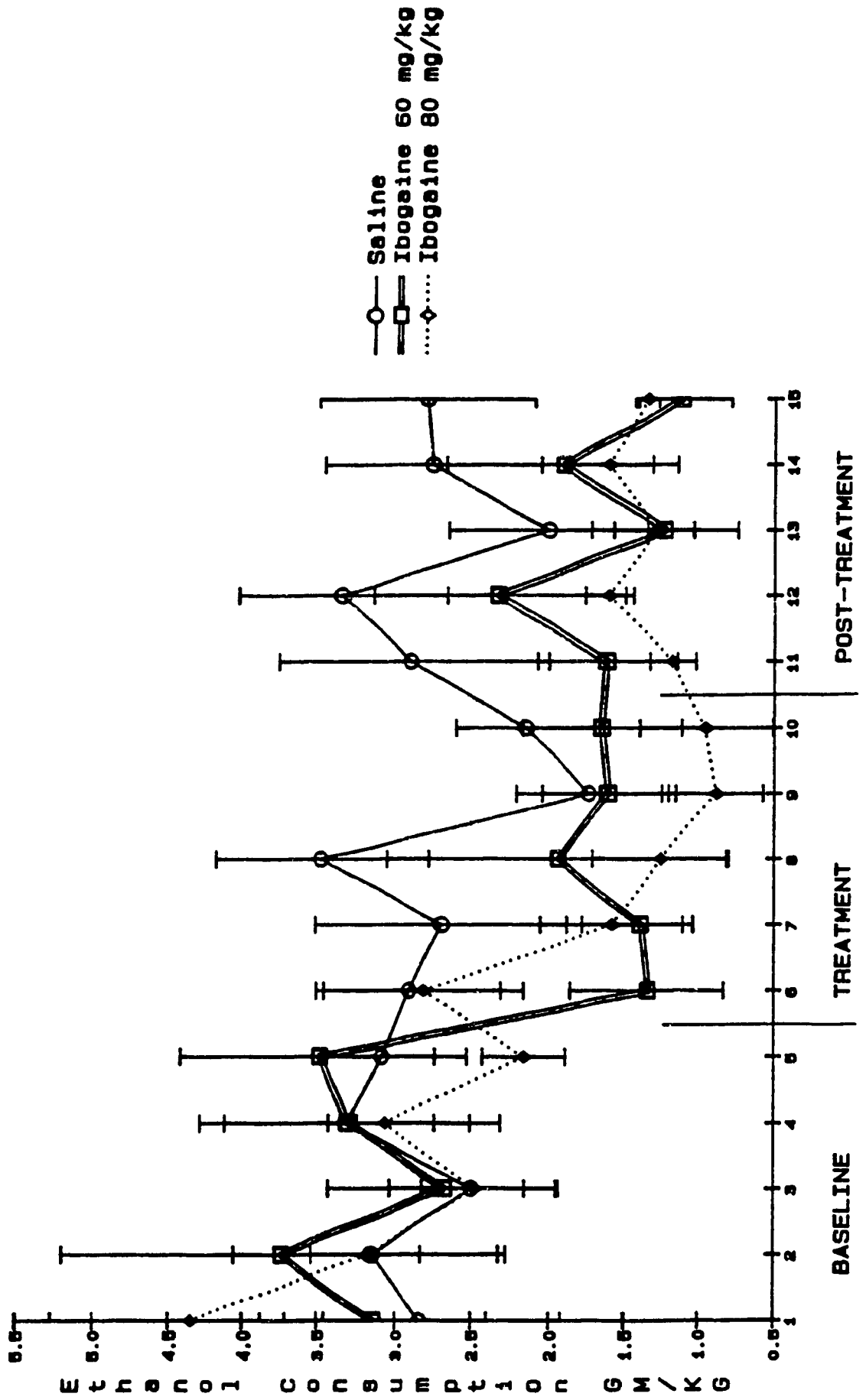


Figure 6
Ethanol Consumption (XTF)
Ibogaine 15 & 30 mg/kg

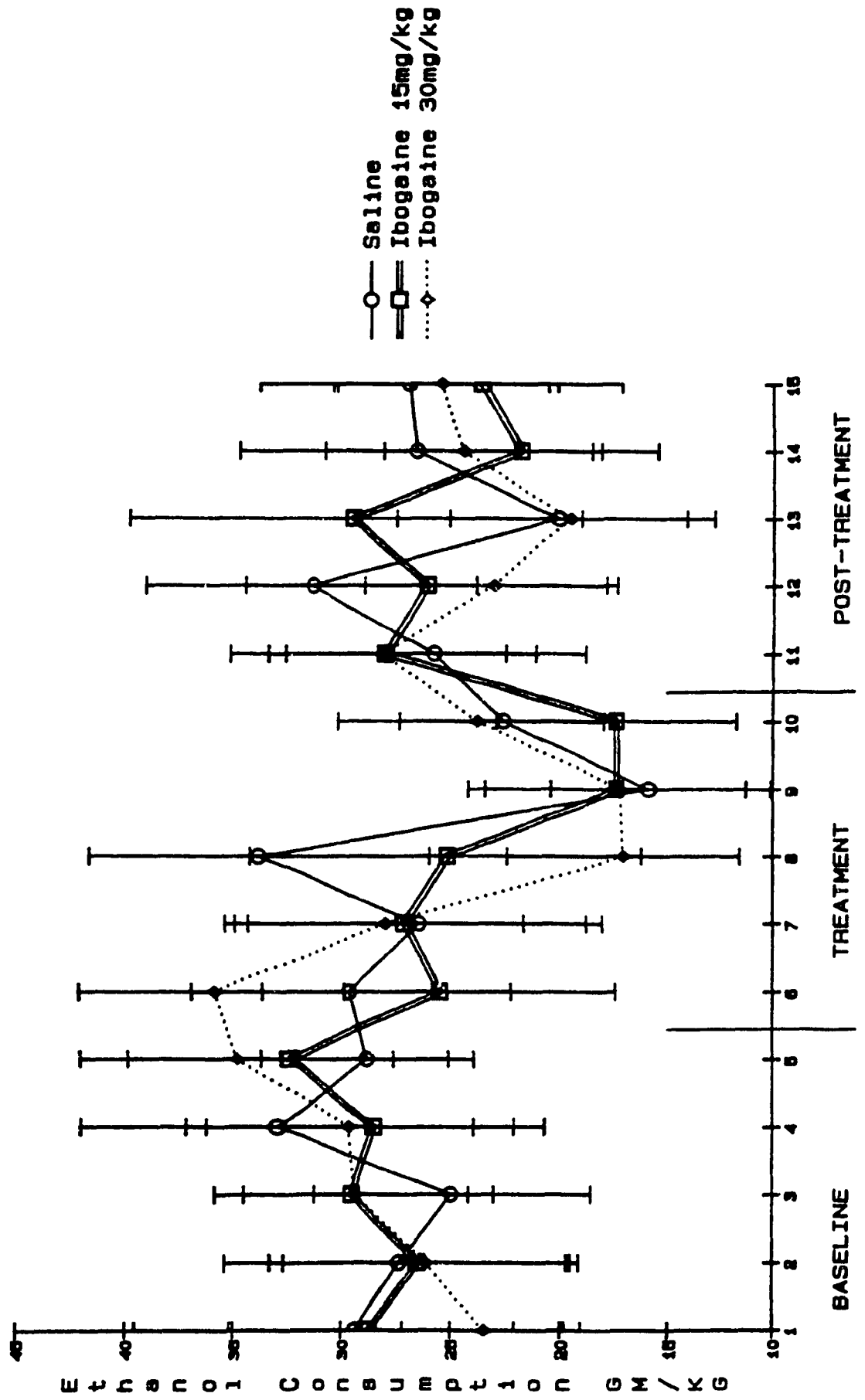
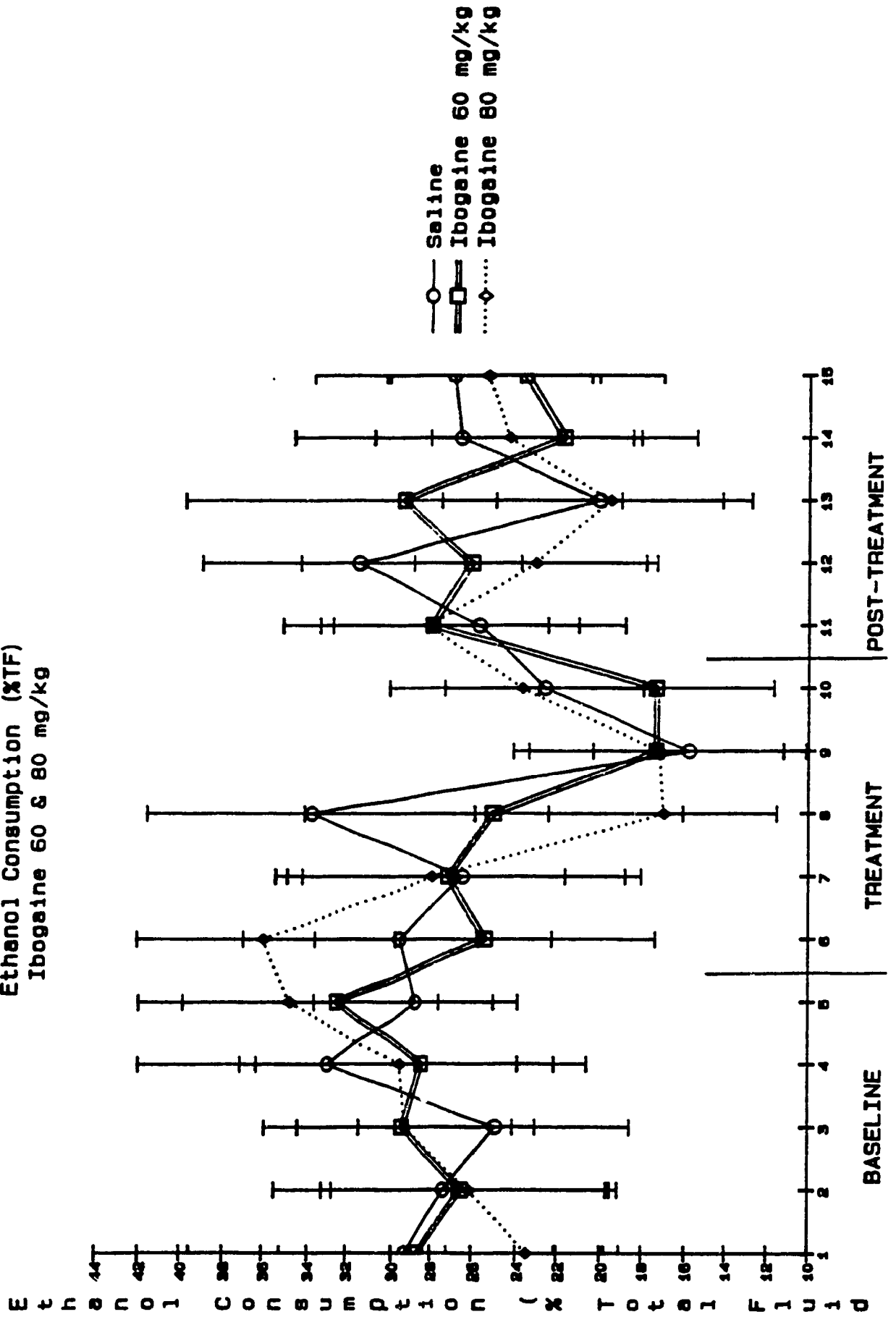


Figure 7
Ethanol Consumption (%TF)
Ibogaine 60 & 80 mg/kg



The change in body weight between the last baseline day and the last treatment day was calculated for each rat. The saline group had an average net gain of 18.2 gms. There was a dose related decrease in body weight in the ibogaine treated animals, revealed by one-way analysis of variance: $F(4,25)=11.382$, $p<.001$. Application of the Dunnett test further revealed that the difference in weight was significant ($p<.05$) for the 30, 60, and 80mg/kg doses of ibogaine.

DISCUSSION

The results of this experiment indicated that although administration of most doses of ibogaine resulted in reduced body weight, there were no significant reductions (i.e. no dose/period interaction effects) in ethanol consumption, as measured by either gm/kg or preference ratio.

The period effect revealed by the statistical analysis indicated that ethanol consumption was reduced during the treatment period. It appears that the period effect was due to the decrease in drinking which occurred in all groups on days nine and ten. All groups reduced their ethanol consumption on days 9 and 10, which indicated that there was an environmental influence, such as a disturbance caused by changes in

ventilation. Ethanol consumption on days 9 and 10 did not reach zero. Therefore, it was possible to observe further decreases in ethanol consumption by the experimental groups. The observed non-significant decreases in ethanol consumption did not persist into the post treatment period.

There are at least two possible interpretations of these results. First, ibogaine may not have a specific attenuating effect on ethanol consumption. Second, the dose range employed in this experiment may have not included the effective dose. However, the highest dose used, 80mg/kg, had profound motor effects which were similar to those observed after intragastric administration of 120mg/kg. Also, 80mg/kg was the highest dose that could be administered in a single injection, because the solubility of ibogaine is such that a relatively large injection volume was required (4-5 ml.).

The significant weight loss associated with three of the four doses of ibogaine was not paralleled by comparable reductions in total fluid consumption. This suggested that ibogaine may have specific effects on food intake.

The results of this experiment partially supported the hypothesis that ibogaine would have some attenuating effect on consummatory behavior. This

hypothesis was arrived at by first deducing an anorectic effect of harmaline. That deduction was based on the experimental literature on harmaline. The similarities between the effects of ibogaine and harmaline administration in humans were then noted, and the deduced anorectic effect of harmaline was extended to include ibogaine. Therefore, in order to confirm that administrations of ibogaine and harmaline would have similar effects on consummatory behavior in general, and alcohol intake in particular, the effect of harmaline on ethanol consumption was examined in the next experiment.

Experiment 4
The Effect of Harmaline on
Ethanol Consumption in Rats.

The apparent similarities between harmaline and ibogaine were described earlier in this thesis. The present experiment was conducted in order to determine whether harmaline had the same effect as ibogaine on food, water, and ethanol intake. Earlier in this thesis, harmaline was tentatively classified as a partial benzodiazepine inverse agonist (see pp. 31-34). Since this class of compounds has been shown to have attenuating effects on consummatory behavior (Cooper, 1987), this hypothesized classification of harmaline was expected to be supported by the observation of a general anorectic effect following harmaline administration.

The doses of harmaline chosen for this experiment ranged from low (10mg/kg) to very high (40mg/kg), as determined from the available literature (Fuentes and Longo, 1971; DeMontigny & Lamarre, 1973).

Comparison between this experiment and the previous experiment was facilitated by the utilization of an identical experimental procedure.

METHOD

Subjects.

Subjects were 60 male Long Evans rats, weighing 175-200 gm. at the start of the experiment. They were housed individually in stainless steel cages in a temperature regulated room. They were kept on a 12:12 light:dark cycle, commencing at 0800 hrs. Food and water were always available, ad libitum.

Materials.

Ethanol solutions (2-10%, v/v) were prepared by mixing 95% ethanol with tap water. Ethanol solutions and water were presented in glass Richter tubes mounted on the front of each cage. Harmaline HCl was dissolved in 0.9% saline, to a concentration of 8mg/ml.

Procedure.

After four days of acclimatization to the animal room, the rats were given 2% ethanol solution in a free choice with water. The next day, water only was given in the two tubes. The third day, the positions of the tubes were reversed, and the concentration of ethanol was increased by one percent. This alternate day and alternate side exposure to increasing concentrations of ethanol was repeated until a concentration of 10% was reached. The rats were then presented with 10% ethanol

for seven consecutive days, during which time there were daily tube position reversals and recording of fluid consumption and body weight. Mean ethanol consumption for each rat over the last five days of the 10% baseline period was calculated, and the 30 highest drinking rats (by %TF) were selected for the experiment. The rats were then divided into four groups of six rats each, matched on average ethanol preference.

During the five day treatment period, rats were injected daily with either 10, 20, or 40mg/kg harmaline, or an equivalent volume of 0.9% saline. Injections were done between 1600 and 1800 hrs. During the treatment period and the five day post treatment period, tube position reversals and data collection were done daily.

RESULTS

There was a significant reduction in total fluid intake during the treatment period, for the 10 and 40mg/kg doses of harmaline, as revealed by a three way analysis of variance dose/period interaction:
 $F(6,40)=4.524$, $p=0.001$, and post hoc Tukey test:
 $Q=3.403$ (10mg/kg) and $Q=6.057$ (40mg/kg);
 $Q(\text{crit})=2.904$. There were no significant reductions in ethanol intake, whether measured as gm/kg or as

preference ratio. The analysis of variance revealed significant period effects for total fluid and ethanol consumption (both gm/kg and %TF) as follows: Total Fluid: $F(2,40)=3.434$, $p=.041$; Ethanol gm/kg: $F(2,40)=9.894$, $p<.001$; Ethanol %TF: $F(2,40)=10.040$, $p<.001$. Ethanol consumption, expressed as gm/kg and %TF, are presented graphically in Figures 8 and 9, respectively.

During the treatment period, significant weight loss was observed in the harmaline treated animals, as revealed by analysis of variance: $F(3,20)=10.884$, $p<.001$. A Dunnett test revealed that the weight loss was significant ($p<.05$) only for the 40mg/kg dose of harmaline.

Figure 8
Ethanol Consumption (GMS/KG)
Harmaline 10, 20 & 40 mg/kg

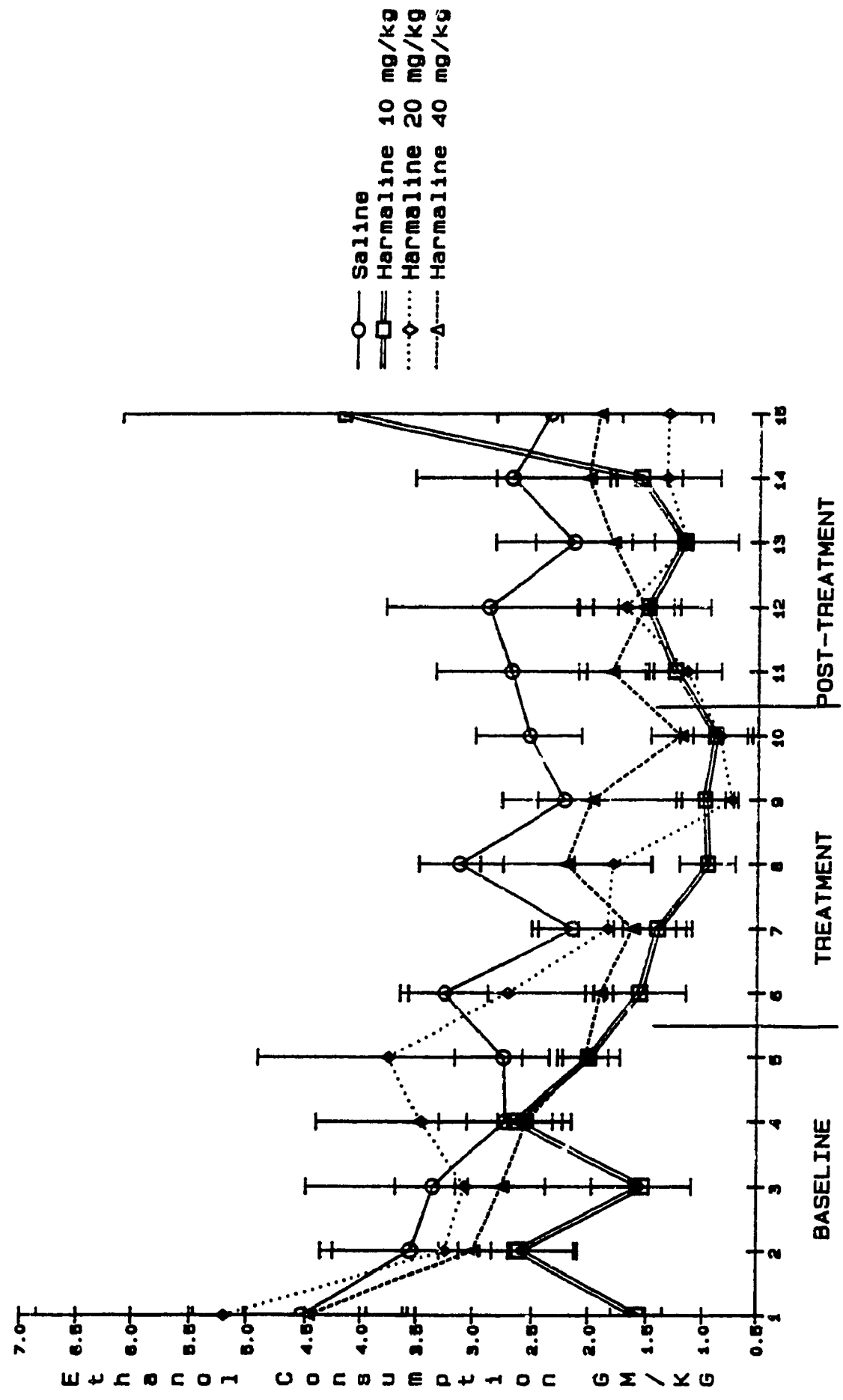
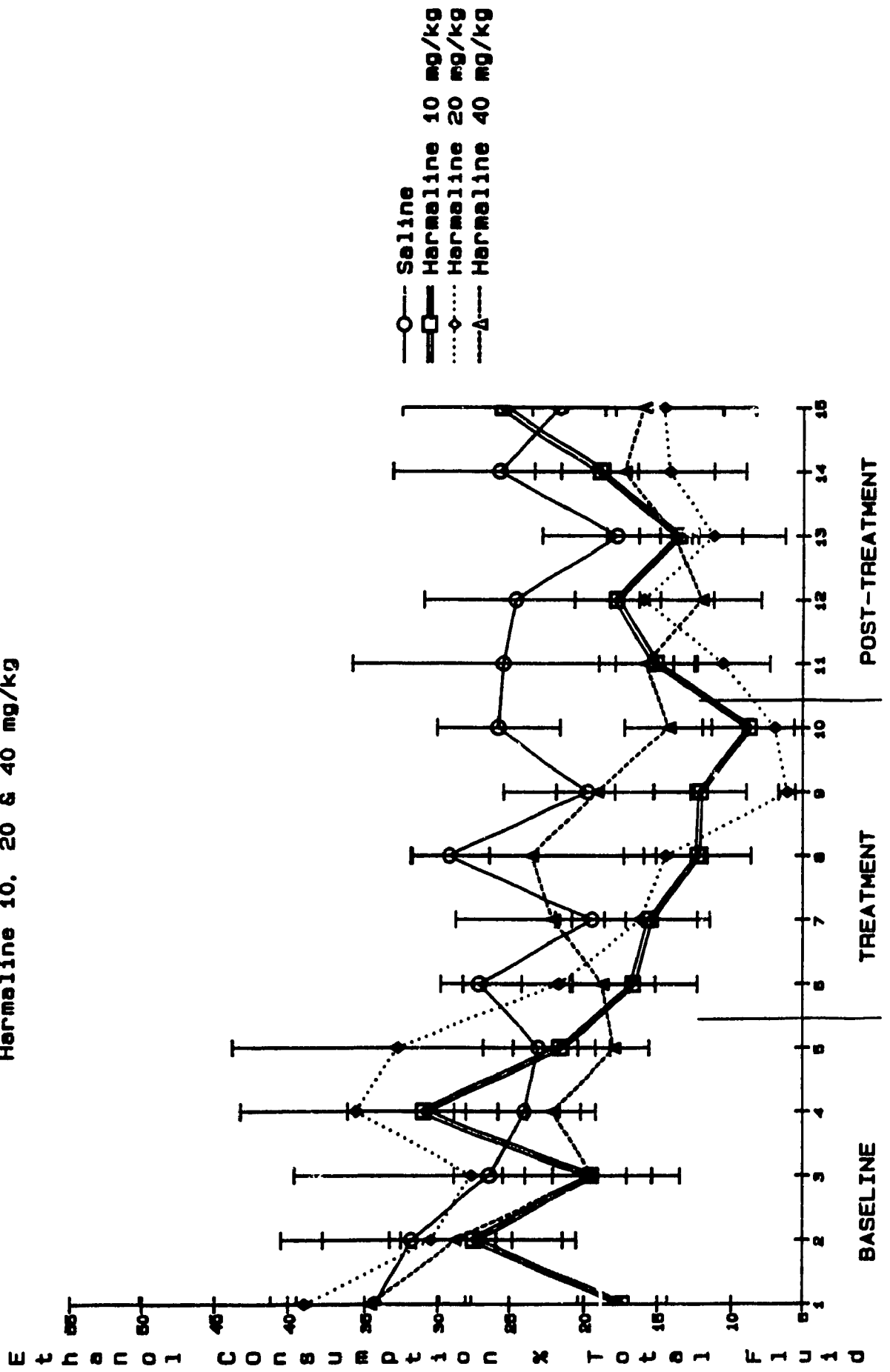


Figure 9
 Ethanol Consumption (% Total Fluid)
 Hermaline 10, 20 & 40 mg/kg



DISCUSSION

The results of this experiment suggested that harmaline administration, at the doses tested, did not significantly reduce ethanol consumption. There was significant weight loss and reduced total fluid intake during the treatment period with the 40 mg/kg group. The 10mg/kg dose resulted in reduced total fluid intake. This suggested that harmaline may have a general anorectic effect, as hypothesized.

Harmaline administration resulted in a pronounced reduction in total fluid intake and weight, at two of the doses tested. In contrast, ibogaine administration (Experiment 3) resulted in non-significant reductions in total fluid intake, but significant weight loss for all but one dose tested. These results suggested that harmaline and ibogaine may have differential effects on food and fluid consumption.

The significant period effects for ethanol consumption (measured both in gm/kg and %TF), did not suggest an attenuating effect of harmaline on ethanol consumption, because saline injections apparently also contributed to the observed period effect.

Although only short duration motor effects of ibogaine and harmaline were observed, the possibility remained that the anorectic effect of these drugs may

be related to a locomotor deficit of some sort. Consequently, in the following experiment, the effects of ibogaine and harmaline administration on locomotion and ethanol induced locomotor depression were investigated.

Experiment 5

The Effect of Ibogaine and Harmaline on Locomotion and Ethanol Induced Locomotor Depression

The experiments previously reported did not support the hypothesis that ibogaine and harmaline may attenuate ethanol consumption. Given that ethanol has caloric value, the robust effect of ibogaine administration on food intake suggested that ibogaine, under certain conditions, would be able to affect ethanol intake. In order to further examine this question, the effect of ibogaine and harmaline on a behavior other than drinking was examined. It was felt that the extended time required in order to conduct drinking experiments could be more efficiently used by developing an additional perspective to the understanding of the effects of these drugs.

All observable behavior, by definition, is characterized by some degree of locomotion. Without knowledge of the locomotor effects of ibogaine and harmaline, it would have been difficult to interpret the effects of these drugs on behaviors such as runway performance, passive avoidance, etc., that could have been chosen for investigation.

Ethanol drinking has been described as a motivated behavior, with ethanol itself serving as the reinforcer (Amit & Sutherland, 1987). Motivated behavior has also been described in terms of the activation of neurobiological approach mechanisms which underly locomotion towards reinforcers (Glickman and Schiff, 1967; Wise & Bozarth, 1987). These approach mechanisms can in turn be quantified by open field locomotor behavior, which measures (although not exclusively) forward locomotion. It should be noted that the relation between locomotor activity and reinforcement mechanisms is a controversial subject. Given both the theoretical relationship between reinforcement and locomotion, and the difficulty inherent in interpreting the results of other experimental paradigms without knowledge of basic locomotor effects, locomotion was chosen as the behavior to be examined in this experiment.

The experiment which follows was designed to determine firstly if there was an interaction of ibogaine or harmaline with the locomotor depressant effects of ethanol, and secondly, to determine the effects of ibogaine or harmaline alone on locomotor behavior.

METHOD

Subjects.

Subjects were 168 male Long Evans rats, weighing 175-200 gms. at the start of the experiment. They were housed individually in stainless steel cages, in a temperature regulated room, and provided with food and water ad libitum.

Apparatus.

Eight wooden boxes (40 x 40 x 40cm) were used. They were painted black inside, and equipped with a 2 x 2 horizontal photocell array 2.5 cm from the floor of the box. The photocells were connected to a counter in an adjoining room, where the activity counts were recorded. A single 25 watt red light bulb illuminated the activity room.

Materials

Ibogaine HCl was dissolved in distilled water to a concentration of 8 mg/ml. Harmaline HCl was dissolved in saline to a concentration of 5mg/ml. Ethanol (20% v/v) was prepared by dissolving 95% ethanol in 0.9% saline solution.

Procedure.

Following two days of handling and acclimatization to the laboratory environment, the rats were habituated

to the activity boxes, by placing them in the boxes for twenty minutes daily, for four days.

On the fifth day, the rats were randomly assigned to two pretreatment groups (saline or ibogaine), and two treatment groups (saline or ethanol). There were seven rats in each group. Rats from each of the four groups were run at the same time to control for time of day effects. Box assignment for each group was rotated in order to control for any effects due to a particular box. The experiment consisted of four runs, carried out over two days. Runs were done at approximately the same time each day, and the boxes were washed in between each run.

Immediately before each run, the rats were injected with either ibogaine or saline, and placed in the boxes for 70 minutes; activity counts were recorded after 50 and 70 minutes. Injections (saline or ethanol) were then given to the rats, the counters were reset to zero, and the cumulative activity counts were recorded after another 40 minute period.

Using six independent groups of new animals, the above described sequence was repeated six times, one for each dose of ibogaine (15, 60 and 80mg/kg, i.p.), and for each dose of harmaline (10, 20 and 40mg/kg, i.p). The dose of ethanol used was always 2gm/kg, i.p.

RESULTS

The results of ibogaine treatment are presented in Figures 10, 11 and 12. The 60 and 80mg/kg doses of ibogaine had a pronounced depressant effect on locomotion. Two-way analysis of variance revealed pretreatment effects for the first 50 minutes are as follows (for each increasing dose of ibogaine):

$F(1,24)=.037$, n.s.; $F(1,24)=8.714$, $p=.006$;

$F(1,24)=23.043$, $p<.001$.

During the last 20 minutes of the pretreatment period, there were no significant differences in locomotion between any of the groups.

Figure 10
 Activity Counts
 Ibogaine 15 mg/kg; Ethanol 2 gm/kg

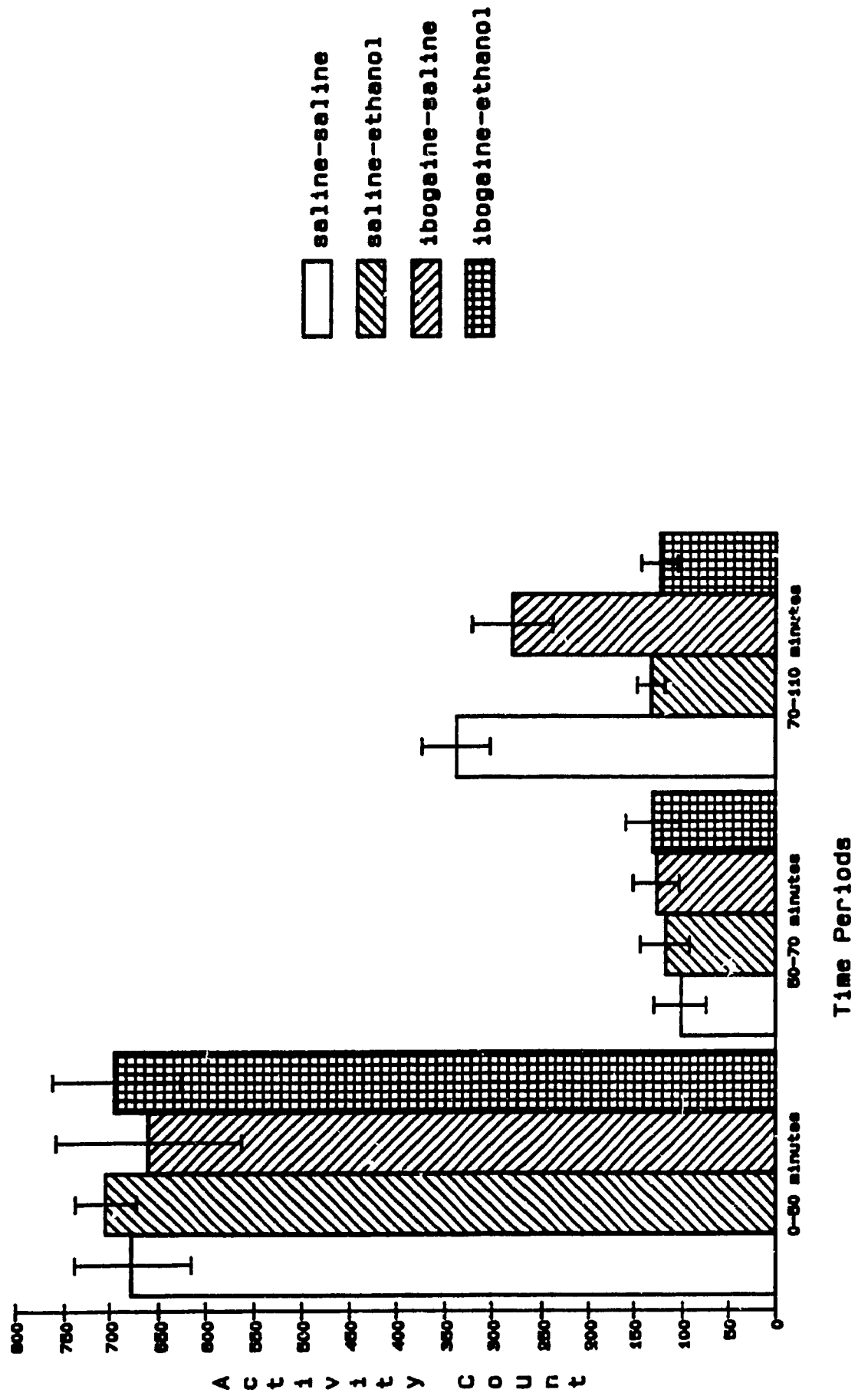


Figure 11
 Activity Counts
 Ibogaine 60 mg/kg; Ethanol 2 gm/kg

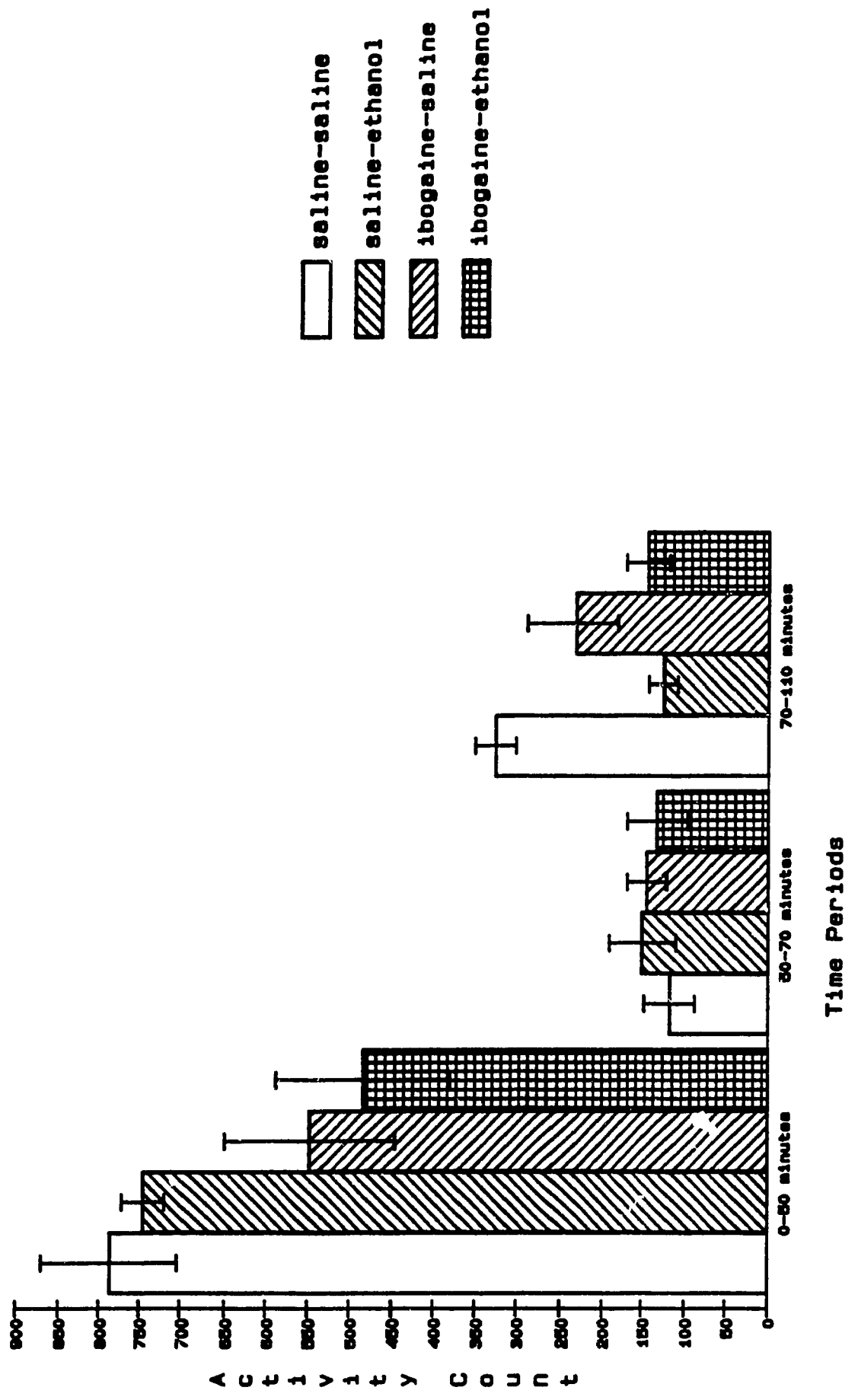
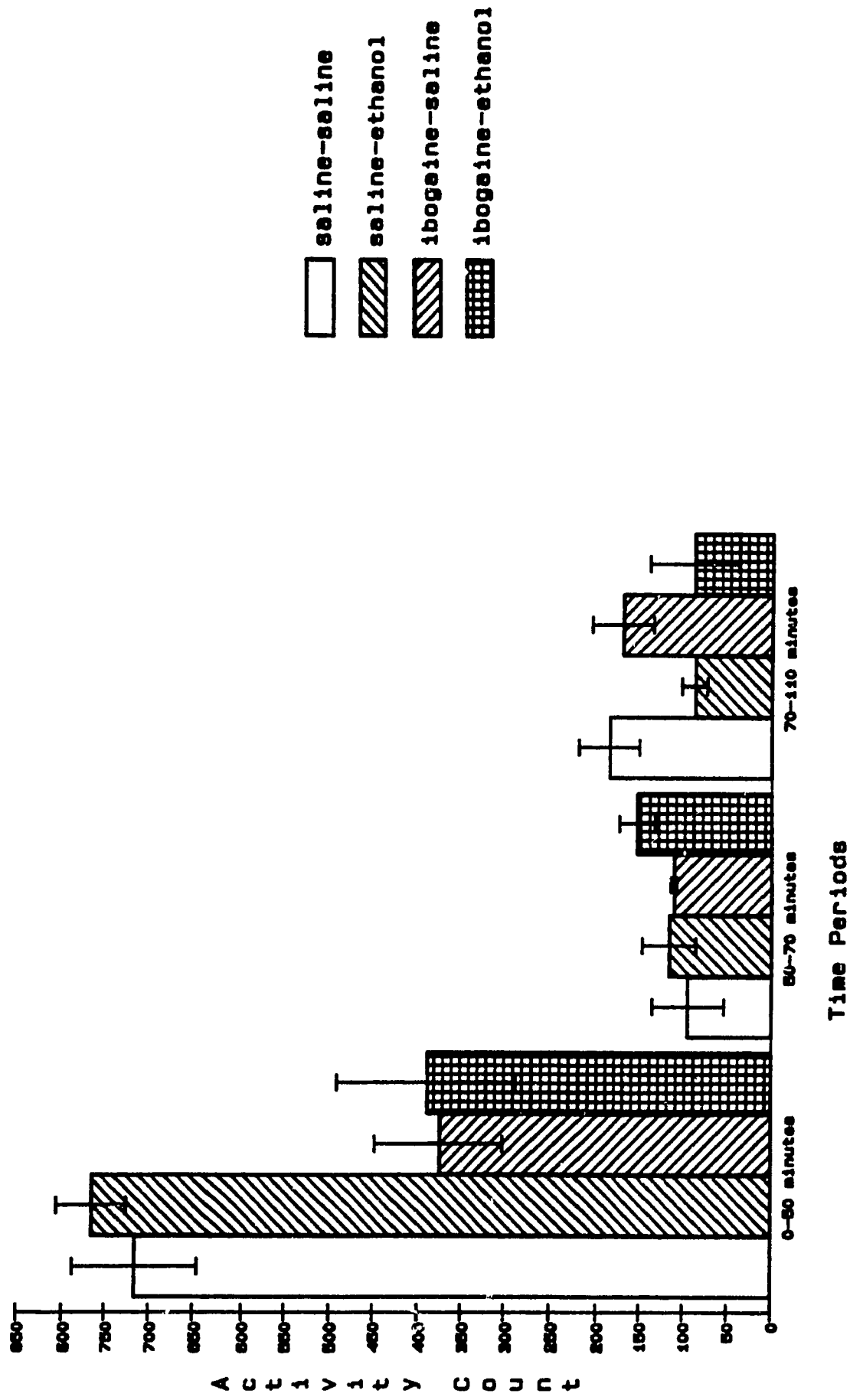


Figure 12
 Activity Counts
 Ibogaine 80 mg/kg; Ethanol 2 gm/kg



Activity following ethanol administration (70-110 minutes) was reduced in both saline and ibogaine pretreated animals. A two-way analysis of variance of the last 40 minute period revealed significant treatment (ethanol) effects for the three doses of ibogaine, as follows (in order of increasing dose of ibogaine): $F(1,24)=37.063$, $p<.001$; $F(1,24)=19.175$, $p<.001$; $F(1,24)=6.075$, $p=.02$. There were no significant pretreatment/treatment interaction effects.

Harmaline administration resulted in reduced locomotion during the first 50 minutes, as revealed by two-way analysis of variance pretreatment effects (in order of increasing dose): $F(1,24)=4.471$, $p=.042$; $F(1,24)=17.6$, $p<.001$; $F(1,24)=27.528$, $p<.001$. These results are presented in Figures 13, 14 and 15.

During minutes 50-70 of the pretreatment period, a significant pretreatment effect was obtained only for the 40mg/kg dose of harmaline: $F(1,24)=10.489$, $p=.003$.

Activity was reduced for all groups receiving ethanol injections, as revealed by treatment effects (in order of increasing dose of harmaline) as follows: $F(1,24)=23.243$, $p<.001$; $F(1,24)=8.425$, $p=.007$; $F(1,24)=5.936$, $p=.021$. Additionally, analysis of variance revealed that during the last 40 minute

period, there was a pretreatment effect for the 20mg/kg dose of harmaline: $F(1,24)=13.921$, $p=.001$.

The 20 and 40 mg/kg doses had nonsignificant pretreatment effects during the last 40 minutes: $F(1,24)=.058$, $p=n.s$; $F(1,24)=4.073$, $p=.052$. There were no significant pretreatment/treatment interaction effects.

Figure 13
 Activity Counts
 Harmaline 10 mg/kg. Ethanol 2gm/kg

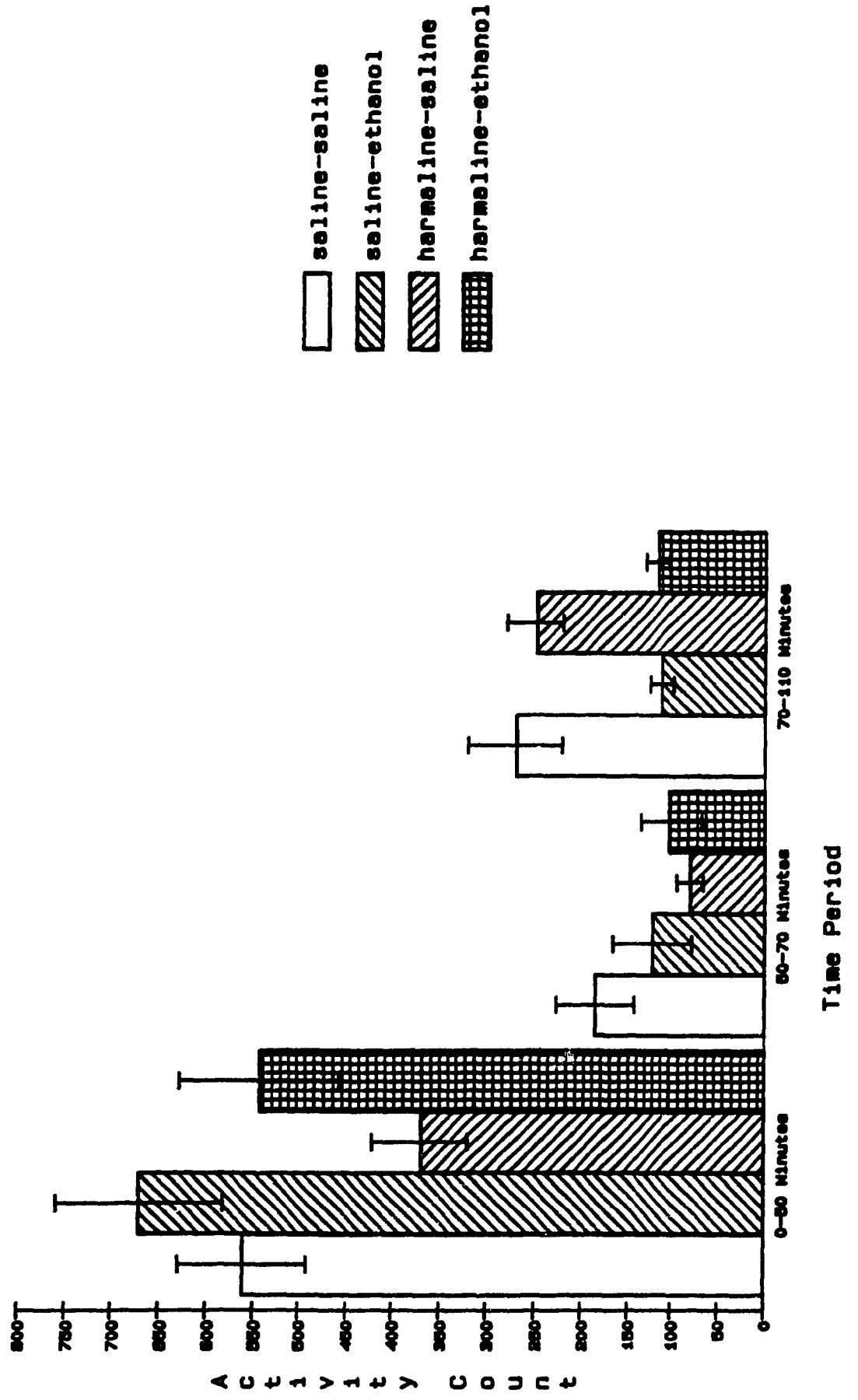


Figure 14
Activity Counts
Harmaline 20 mg/kg; Ethanol 2 gm/kg

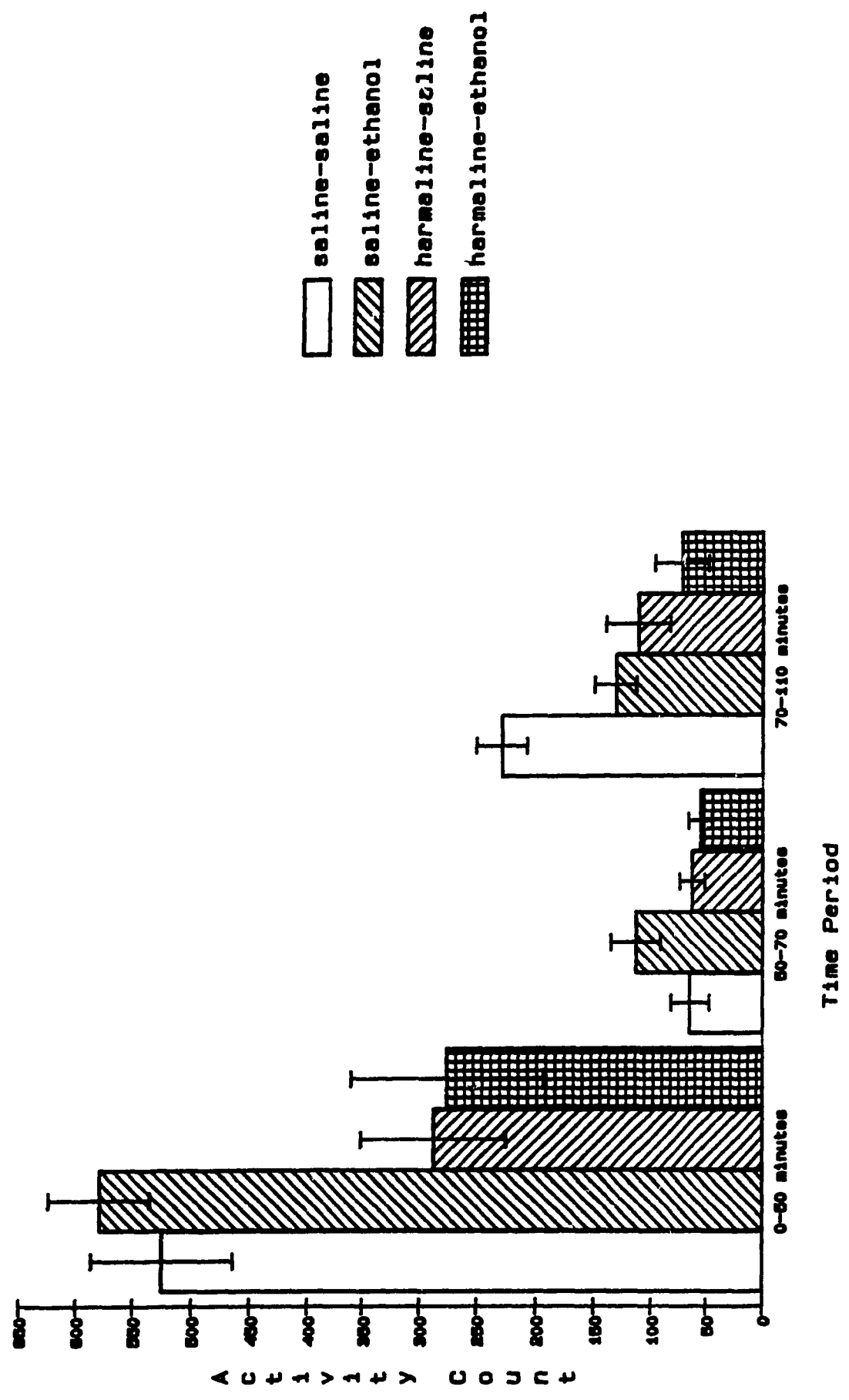
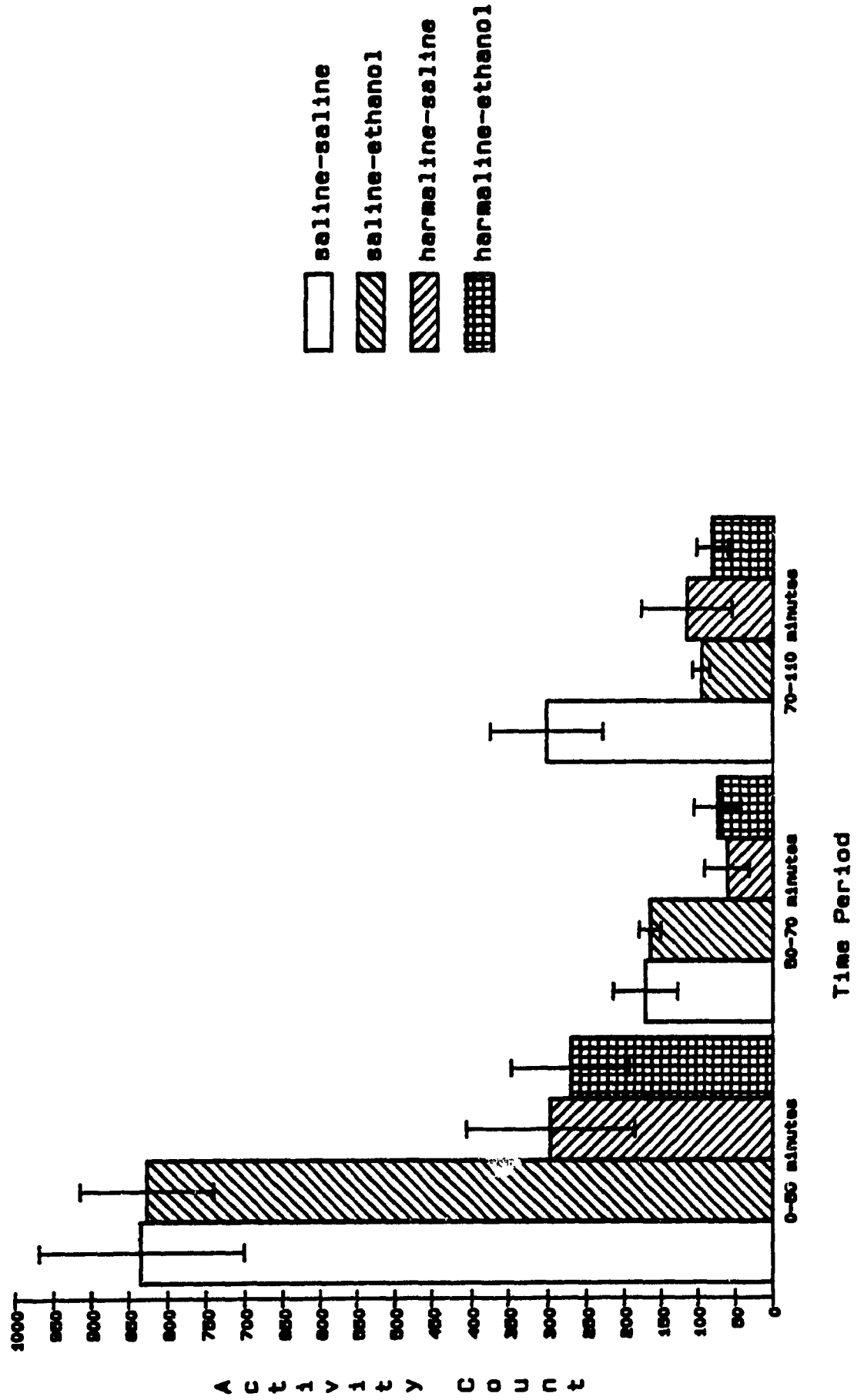


Figure 15
 Activity Counts
 Harmaline 40 mg/kg; Etherol 2 gm/kg



DISCUSSION

Both ibogaine and harmaline administration resulted in locomotor depressant effects, which lasted no more than 50 minutes. In contrast, the two higher doses of harmaline (20 and 40mg/kg) appeared to have a prolonged depressant effect, still detectable after 110 minutes. The depressant effects of ibogaine and harmaline were dose dependent.

The lack of observed interaction effects between ibogaine or harmaline and ethanol, suggested that they neither potentiated nor attenuated the depressant effects of ethanol.

GENERAL DISCUSSION

The purpose of this thesis was to determine whether the anecdotal reports concerning anti-craving claims made of ibogaine (Lotsof, 1986) could be substantiated through controlled experiments. In addition, harmaline, an apparently similar drug (e.g., Naranjo, 1973), was employed for comparative purposes. The obtained results suggested that ibogaine had no observable effect on cocaine self administration in rats, and no specific effect on ethanol preference in ethanol drinking rats. Only the highest dose (120mg/kg, i.g.) of ibogaine reduced absolute ethanol intake non-specifically, as part of its reducing effect on total fluid intake. For all other doses of ibogaine, absolute ethanol intake, ethanol preference, and total fluid intake were unaffected. However, it is of interest to note that ibogaine administration reduced body weight in a dose dependent manner.

Harmaline administration was found to reduce body weight and total fluid intake, but not ethanol intake. Both ibogaine and harmaline were observed to result in locomotor depression, which neither attenuated nor potentiated the locomotor depression caused by ethanol. The locomotor depression caused by harmaline was of

longer duration than that resulting from ibogaine injections.

In Experiment 1, it was found that administration of high dose ibogaine, intragastrically administered, had no subsequent effect on cocaine self administration in rats. Although only one dose of ibogaine was employed, it was the equivalent (as determined by its ability to cause ataxia) of the large dose (400-750mg) which supposedly eliminated cocaine craving in cocaine dependent humans (Lotsof, 1986). It would seem that the obtained data did not support the claim (Lotsof, 1986) that ibogaine may be useful as a pharmacological adjunct to the treatment of cocaine abuse in humans. Given lack of empirical and theoretical support for an attenuating effect of ibogaine on cocaine self administration, and since there was at least a theoretical possibility that ibogaine could reduce ethanol intake, the focus of this research project then shifted to ethanol.

Experiment 2 revealed that high dose, intragastrically administered ibogaine resulted in reduced ethanol consumption (gm/kg), as well as reduced total fluid intake and body weight in rats. Ethanol preference was not significantly reduced. It was concluded that the reduced absolute ethanol intake

reflected an attenuating effect of ibogaine on consummatory behavior in general.

The effect of ibogaine on consummatory behavior was examined further (Experiment 3) by using several doses of ibogaine, administered intraperitoneally. Although ibogaine was found to have a pronounced, dose dependent effect on body weight, there were no corresponding reductions in total fluid or ethanol intake.

In Experiment 4, it was observed that 10 and 40mg/kg (but not 20mg/kg) harmaline significantly reduced total fluid intake. Harmaline administration, like ibogaine, resulted in dose related weight reductions. The results of Experiment 4 suggested that harmaline, in a similar fashion to ibogaine, had a general attenuating effect on consummatory behavior. Such an attenuation of consummatory behavior is characteristic not only of 5-HT inhibitors (e.g. Blundell, 1984), and psychomotor stimulants (e.g. Wise & Bozarth, 1987), but also of benzodiazepine inverse agonists (Cooper, 1976). Therefore, the earlier proposed hypothesis that harmaline may be a partial benzodiazepine inverse agonist, could be interpreted to be consistent with the results of Experiment 4. This interpretation was supported by the results of Experiment 5, which suggested that harmaline had depressant properties, and is therefore not a typical

stimulant. The results of Experiment 4 suggested that harmaline had attenuating effects on total fluid consumption, and that the dose response of that effect was biphasic, observed with low and high, but not intermediate doses of harmaline. The attenuating effect of harmaline on body weight gain increased proportionally with increasing doses of harmaline. These disparate dose response patterns were difficult to reconcile, and a plausible interpretation of the results may only be possible following further experimentation, possibly employing additional doses of harmaline. At present, given the observed attenuating effect of harmaline on body weight gain and total fluid consumption, one may conclude that harmaline had a general attenuating effect on consummatory behavior.

In Experiment 5, the effects of these drugs on locomotion in general and ethanol induced locomotor depression in particular were examined. Both drugs had similar depressant effects, but the time course of the effect differed for the two drugs. Neither drug affected ethanol-induced locomotor depression, and the depressant effect of ibogaine did not last more than 50 minutes. This suggested that the earlier observed ibogaine induced reductions in body weight and total

fluid consumption were probably not due to locomotor depression.

In contrast, the depressant effects of harmaline were still in evidence after 110 minutes. Until the time course of the depressant effect of harmaline is determined, one cannot be certain that locomotor depression was not responsible for the general anorectic effect of harmaline.

Ibogaine and harmaline administration both resulted in dose related weight reductions. Additionally, the highest doses of each drug were both associated with reduced total fluid consumption, and both drugs had locomotor depressant effects which did not appear to interact with the depressant effects of ethanol. Therefore, within the experimental paradigms employed in these experiments, it appeared that ibogaine and harmaline had similar behavioral profiles. The effects induced by ibogaine were consistent with the hypothesis that ibogaine, like harmaline, may be a partial benzodiazepine receptor inverse agonist. The minimal effect of these drugs on ethanol consumption was inconsistent with the known effects of typical 5HT reuptake inhibitors.

In conclusion, the results of these experiments did not support the notion that either ibogaine or harmaline may have a practical application in the

treatment of human cocaine or alcohol abuse. The results did suggest, however, the possibility that ibogaine may be useful as a weight reducing agent which does not have typical stimulant properties. Further experimentation is required to determine the mechanism whereby ibogaine and harmaline caused reduced body weight.

Future research employing ibogaine or harmaline may help to further understand the mechanisms governing appetitive behavior.

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APPENDIX A

United States Patent (19)

Lotsof

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(45) **Date of Patent:** May 6, 1986

[34] **RAPID METHOD FOR INTERRUPTING THE COCAINE AND AMPHETAMINE ABUSE SYNDROME**

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[22] **Filed:** Jul. 15, 1985

[51] **Int. Cl.⁴** A61K 31/55

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[58] **Field of Search** 514/210, 214

[56] **References Cited**

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[57] **ABSTRACT**

The administration to a cocaine or amphetamine abuser of ibogaine, ibogaine HCl or other non toxic salts of ibogaine, an alkaloid of the family Apocynaceae, has been discovered to unexpectedly interrupt the physiological and psychological aspect of the cocaine and/or amphetamine abuse syndrome. A single treatment was effective for about 6 months, and a series of 4 treatments was effective for approximately 3 years. The treatments consisted of the oral administration of ibogaine or its salts in dosage ranges of 6 mg/kg to 19 mg/kg. The minimum effective dose was 400 mgs and dosage increases above 1000 mgs were found to be unnecessary. Treatments were effective in 100% of the cases.

9 Claims, No Drawings

RAPID METHOD FOR INTERRUPTING THE COCAINE AND AMPHETAMINE ABUSE SYNDROME

BACKGROUND OF THE INVENTION

The present invention relates generally to improvements in the treatment of cocaine and/or amphetamine abuse and it relates particularly to an improved method for interrupting the physiological and psychological aspects of the cocaine and/or amphetamine habituation.

Treatment procedures heretofore employed or proposed for the interruption of the cocaine and/or amphetamine habituation syndrome, including the administration of antidepressants and/or tranquilizers, have been generally ineffective.

HISTORICAL BACKGROUND

Ibogaine is one of at least 12 alkaloids found in the Tabernanthe iboga shrub of West Africa. The indigenous peoples have used the drug as a ritual, ordeal or initiation potion in large dosages as a stimulant in smaller doses. One of the first European references to the drug was made by Professor Baillon on the Mar. 6th, 1889 session of the Linnaean Society in Paris during which he described samples obtained by Griffon de Behay from Gabon and the French Congo.

Early isolation, and identification of ibogaine was accomplished by Dybowski and Landrin (*Compt. rend. ac. sc.* 133:748, 1901), Haller and Heckel (*ibid.* 133:850), Lambert and Heckel (*ibid.* 133:1236) and Landrin (*Bull. sc. pharm.* 11:1905).

Interest in the drug seemed to lie fallow until it was picked up by Raymond-Hamet and his associates Rothlin, E. and Raymond-Hamet published the "Effect of Ibogaine on the Isolated Rabbit Uterus" in 1938 (*Compt. rend. soc. biol.* 127:592-4). Raymond-Hamet continued to study the drug for a period of 22 years. He singularly published 9 papers. Pharmacological Action of Ibogaine (*Arch. intern. pharmacodynamie*, 63:27-39, 1939), Two Physiological Properties Common to Ibogaine and Cocaine (*Compt. rend. soc. biol.* 133:426-9, 1940), Ibogaine and Aphedrine (*Ibid.* 134:541-4, 1940), Difference Between Physiological Action of Ibogaine and That of Cocaine (*Ibid.* 211:285-8, 1940), Mediate and Intermediate Effects of Ibogaine On The Intestine (*Compt. rend. soc. biol.* 175:176-79, 1941), Pharmacologic Antagonism of Ibogaine (*Compt. rend.* 212:768-771, 1941), Some Color Reactions of Ibogaine (*Bull. soc. chim. Biol.* 25:205-10, 1943), Sympathicosthenic Action of Ibogaine On The Vessels of The Dog's Paw (*Compt. rend.* 223:757-58, 1946), and Interpretation of The Ultraviolet Absorption Curves of Ibogaine and Tabernanthine (*Ibid.* 229:1359-61, 1949).

Vincent, D. began his work on ibogaine by a collaboration with Sero, I., Inhibiting Action of Tabernanthe iboga On Serum Cholinesterase (*Compt. rend. Soc. Biol.* 136:612-14, 1942). Vincent participated in the publication of five other papers: The Ultraviolet Absorption Spectrum of Ibogaine (Brustler, B., Vincent, D., & Sero, I., *Compt. rend.*, 216:909-11, 1943), Detection of Cholinesterase Inhibiting Alkaloids (Vincent, D. & Beauyard, P., *Ann. pharm. franc.* 3:22-26, 1945), The Cholinesterase of The Pancreas. Its Behavior in the Presence of Some Inhibitors in Comparison With The Cholinesterases of Serum and Brain (Vincent, D. & Lagreu, P., *Bull. soc. chim. Biol.* 31:1043-45, 1944), and two papers, which he and Raymond-Hamet worked on

together: Action of Some Sympathicosthenic Alkaloids On the Cholinesterases (*Compt. rend. soc. biol.*, 150:1384-1386, 1956) and On Some Pharmacological Effects of Three Alkaloids of Tabernanthe iboga, Baillon: Ibogaine, Iboluteine and Tabernanthine (*Compt. rend. soc. biol.*, 154:2223-2227, 1960).

The structure of ibogaine was investigated by Dickel et al. (*J.A.C.S.* 80, 123, 1958). The first total synthesis was cited by Buchi et al. (*J.A.C.S.* 87, 2073, 1965) and (*J.A.C.S.* 88, 3099, 1966).

In 1956 Salmouraghi and Page elucidated ibogaine's relations to serotonin (*J. Pharm. & expt. ther.* 120 (1), 20-25, 1957.9). About the same time J. A. Schneider published three important papers. The first, Potentiation Action of Ibogaine on Morphine Analgesia was done in collaboration with Marie McArthur (*Experientia* 12:322-324, 1956). The second was *Neuropharmacological Studies of Ibogaine: An Indole Alkaloid With Central-Stimulant Properties* (Schneider, J. A. & Sigg, E. B., *Annals of N.Y. Acad. of sciences*, Vol 66:765-776, 1957) and third was *An Analysis of the Cardiovascular Action of Ibogaine HCL* (Schneider, J. A. & Rinehard, R. K., *Arch. int. pharmacodyn.*, 110:92-102, 1957).

Ibogaine's stimulant properties were further investigated by Chen and Bohner in *A Study of Central Nervous System Stimulants* (*J. Pharm. & Expt. Ther.*, 123 (3):212-215, 1958). Gerson and Lang published *A Psychological Study of Some Indole Alkaloids* (*Arch. intern. pharmacodynamie*, 135:31-56, 1962).

R. D. Bunag, in 1963, evaluated certain aspects of the relationship between ibogaine and Substance P (Bunag, R. D.; Walaszek, E. J. *The Cardiovascular Effects of Substance P in the Chicken* *Ann. N.Y. Acad. Sci.* 104, Part 1, 437-48, 1963.)

In 1969, Claudio Naranjo reported on the effects of both ibogaine and harmine on human subjects in his paper, *Psychotherapeutic Possibilities of New Fantasy-Enhancing Drug* (*Clinical Toxicology*, 2 (2):209-224, June 1969).

Dhahir, H. I., as his 1971 doctoral thesis, published *A Comparative Study of The Toxicity of Ibogaine and Serotonin* (University Microfilm International 71-25-341, Ann Arbor, Mich.). The paper gives an overview of much of the work accomplished with ibogaine.

Additionally studies of interest include: The Effects of Some Hallucinogens on Aggressiveness of Mice and Rats (Kostowski et al., *Pharmacology* 7:259-263, 1972), Cerebral Pharmacokinetics of Tremor-Producing Harmala and Iboga Alkaloids (Zetler et al., *Pharmacology* 7 (4):237-248, 1972), High Affinity 3H-Serotonin Binding to Caudate Inhibition by Hallucinogens and Serotonergic Drugs (Whitaker, P. & Seeman, P., *Psychopharmacology* 59:1-5, 1978, *Biochemistry*), Selective Labeling of Serotonin Receptors by d-(3H) Lysergic Acid Diethylamide in Calf Caudate (*Proc. natl. acad. sci., USA*, Vol. 75, No. 12, 5783-5787, Dec 1978, *Biochemistry*) and A Common Mechanism of Lysergic Acid, Indolealkylamine and Phenethylamine Hallucinogens Serotonergic mediation of Behavioral Effects in Rats (Sloviter, Robert et al., *J. Pharm. & Expt. Ther.*, 214 (2) 231-238, 1980).

SUMMARY OF THE INVENTION

It is a principal object of the present invention to provide an improved method for the treatment of cocaine and/or amphetamine abuse.

Another object of the present invention is to provide an improved method for interrupting the physiological and psychological aspect of the cocaine and/or amphetamine habituation.

Still another object of the present invention is to provide a method of the above nature characterized by its high degree of success, the absence of the great pain and discomfort accompanying earlier treatments, the ease and convenience of application the absent of undesirable or persistent side effects and the persistent effectiveness of the treatment.

The above and other object of the present invention will become apparent from a reading of the following description which sets forth preferred embodiments thereof

A feature of the present invention is based on the discovery that an alkaloid of the family Apocynaceae and its therapeutically active derivatives and salts, particularly, ibogaine and its therapeutically active, non-toxic derivatives and salts for example, ibogaine hydrochloride and other non-toxic salts of ibogaine, possess the unexpected unique ability to disrupt the cocaine and/or amphetamine habituation syndrome. Examples of other salts of ibogaine which may be used are ibogaine hydrobromide, and any other non-toxic salt of ibogaine

For the purpose of definition, the cocaine and/or amphetamine abuse syndrome is meant to consist of all the symptomology demonstrated by users in their use of and search of cocaine or amphetamine. The interruption of the syndrome was accomplished in three out of three (100%) of the tests subjects who were habituated to amphetamine or cocaine. None of the test subjects were seeking to terminate their use, and all three enjoyed stimulant use.

A single treatment with ibogaine or ibogaine HCL of doses ranging from 6 mg/kg to 19 mg/kg administered orally, disrupted the subject's use of cocaine and/or amphetamine for about six months

A treatment lasts about thirty hours during which time ibogaine exerts a stimulant effect. Apparently, an abreactive process is involved during ibogaine therapy but is not noticeable until the patient wakes from natural sleep occurring after primary and secondary effects of ibogaine are diminished. When effective, ibogaine left the abuser with no desire to use stimulants and no noticeable signs of physical or psychological withdrawal. Subjects appeared relaxed, coherent, with a sense of direction and feelings of confidence

Ibogaine was one of five substances we studied. The other four—mescaline, psilocybin, LSD and DMT though different in duration of action and intensity—have similar psychotropic effects that are well documented and will not be discussed here. Ibogaine, unlike the others, is not a euphoriant hallucinogen and did not leave the subjects open to swells of emotion. While under the influence of ibogaine, emotional responses to traumatic repressed thoughts and feelings appeared to be negated

Another effect of ibogaine administration that was found interesting was that even after twenty-six to thirty hours of wakefulness, subjects slept three to four hours and awoke fully rested. This pattern continued, diminishing slowly, over a three to four month period.

The effects of oral administration of ibogaine are first noticed in fifteen to twenty minutes. Initially, a numbing of the skin is accompanied by an auditory buzzing or oscillating sound. Within twenty-five to thirty-five min-

utes the auditory transcends across the sensory mechanisms to include the visual: objects appear to vibrate with great intensity. It is at this time that the dream enhancement or hallucinatory effects begin. In many cases an acute stage of nausea follows the hallucinatory phase. The visions end abruptly and the numbness of the skin begins to abate.

This is followed by six to eight hours of a high energy state during which the subjects see "lightning" or flashes of light dance about them. Thoughts which seem to amplify the meaning of the visions seen during the primary phase of ibogaine intoxication continue during this period.

Between twenty-six and thirty-six hours, the level of stimulation diminishes and the test subject falls asleep.

Thus, three stages of ibogaine intoxication have been observed. First, an hallucinatory period lasting for three to four hours during which time the person receiving ibogaine manifests repressed material visually. Second, a high energy period accompanied by flashes of light, the appearance of a vibration to all objects, and the awareness of thoughts appropriate to the visual material seen by the subject. Third, a diminishing energy period free of vibration or light flashes and culminating in sleep

In the administration of acceptable dosage forms, any one of a variety of preparations may be compounded, for example: capsules, tablets, pills, powder, solutions, etc. In addition to the active agent, there may be present additional substances used in the manufacture of pharmaceutical preparations such as binders, fillers and other inert ingredients.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples are given merely by way of illustration and are not intended to limit the scope of the present invention.

EXAMPLE 1

Male, age 19, weight 143 lbs. The subject was using both cocaine and amphetamine. Cocaine use consisted of two to three grams of pharmaceutical grade cocaine HCl. The routes of administration were nasal, I.V. injection and smoking in combination with marijuana and hashish in cigarettes. Amphetamine use consisted of 300 mg to 500 mg per week, generally taken over a one or two day period. The principal forms of amphetamines used were d-amphetamine tannate, d-amphetamine sulfate and d-desoxyephedrine HCl. Drug use at the above levels has been consistent for two months.

All treatments were by oral ingestion in capsules. The first treatment consisted of 400 mg of ibogaine HCl. This curtailed amphetamine and cocaine use for six months at which time a series of treatments was administered.

Treatments within the series were spaced at seven day intervals. The first dose was 500 mg of ibogaine. The second was 500 mg plus 250 mg fifteen minutes later, the third was 600 mg and the final dose was 1000 mg

The series was considered complete when the subject ceased to experience the hallucinatory stage and no longer desired to use additional ibogaine. This occurred upon administration of the third and fourth doses in the series, respectively.

The subject remained amphetamine free for six months and cocaine free for eighteen months.

EXAMPLE 2

Male, age 20, weight 135 lbs. Subject was using two to four grams of d-desoxyephedrine HCl a week. The route of administration was I.V. injection. The general pattern of use consisted of three to four days of continuous use followed by a day or two of "crashing." After treatment with a single 500 mg dose of ibogaine the subject remained stimulant free for six months.

EXAMPLE 3

Female, age 23, weight 95 lbs. Cocaine use consisted of two to three grams of pharmaceutical grade cocaine HCl administered nasally or by I.V. injection. Amphetamine use consisted of 500 mg to 1000 mg of d-desoxyephedrine HCl or de-amphetamine sulfate taken orally. The above figures represent weekly totals. A single dose of 500 mg of ibogaine curtailed cocaine and amphetamine use for six months at which time we lost contact with this subject.

MODE OF ACTION -

There are a number of mechanisms and relationships of action by which ibogaine may interrupt the amphetamine and/or cocaine abuse syndrome. These include memory coding by RNA and protein, immune mechanisms, neurohormonal adaptations, involvement in systems including catecholamines, acetylcholine, serotonin, adrenergic compounds, hypothalamic-pituitary neuro-hormones, opiate receptor outside the CNS as well as adaptations taking place outside the central nervous system. The mode of action may also include structure-activity relationships, receptor within the brain or other binding sites, psychological causes, systems involving endorphins, metabolic imbalances, prevention of access of drugs to the site of action, or occupation and saturation of receptor sites as well as interaction with systems involving Substance P and mechanisms controlling spindling.

While the exact mechanism or mechanisms of action by which ibogaine interrupts the cocaine and/or amphetamine abuse syndrome is not clear, it is known that it functions by interaction with one or more of the

above systems. It is not intended, however, that the present invention be limited to any particular theory or mechanism of action.

The advantage of this invention is that it allows for the rapid interruption of physiological and psychological withdrawal and the elimination of the subject's desire to use stimulants for about six months. The invention itself is non-addicting, and in a series of treatments will remove its own potential for abuse.

While there have been described preferred embodiments of the present invention it is apparent that numerous alterations, omissions and additions may be made without departing from the spirit thereof.

I claim:

- 1. The method of treating cocaine and/or amphetamine abuse comprising internally administering to the abuser a composition including ibogaine or a therapeutically active compound thereof.
- 2. The method of claim 1 wherein said composition is orally administered.
- 3. The method of claim 1 or 2 wherein said compound includes a non-toxic salt of ibogaine.
- 4. The method of claim 1 or 2 wherein there is administered a dosage of said composition containing ibogaine or one or more non-toxic salts thereof or a mixture thereof of between 6 mg and 19 mg per kg weight of the abuser.
- 5. The method of claim 3 or 4 wherein the administered dosage of said composition contains ibogaine or its non-toxic salt or a mixture thereof of between 400 mg and 1000 mg.
- 6. The method of claim 3, 4 or 5 wherein a plurality of doses of said composition are administered, the administration of successive doses being separated by a plurality of days.
- 7. The method of claim 3 wherein said ibogaine is in the form of the hydrochloride or hydrobromide salt thereof.
- 8. The method of claim 4 wherein said dosage is in capsule, tablet, pill, powder or solution form.
- 9. The method of claim 4 wherein said dosage is admixed with binders, fillers or other inert ingredients.

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