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The Effects of Serotonin Uptake Blockade
on Voluntary Ethanol Consumption in Rats:
Studies on the Mechanism of Action

Kathryn J. Gill

A Thesis

in

The Department

of

Psychology

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ABSTRACT

The Effects of Serotonin Uptake Blockade
on Voluntary Ethanol Consumption in Rats:
Studies on the Mechanism of Action

Kathryn J. Gill

Previous research has demonstrated that the serotonin uptake blocker, zimeldine, reduced voluntary ethanol consumption in rats and humans. However, the mechanism of action of this compound is not well understood. It has been suggested that zimeldine interferes with the processes which mediate the reinforcement derived from ethanol ingestion. On the other hand, there is considerable experimental evidence which has suggested that serotonin plays a general inhibitory role in consummatory behavior. The experiments in this thesis were therefore designed to test several hypothesis related to the effects of zimeldine on food and fluid intake.

In the first study zimeldine was administered to rats consuming solutions of saccharin, dextrose and ethanol. The drug produced a significant reduction in the absolute consumption of and preference for all three fluids as well as a loss of body weight. The second experiment examined the effects of zimeldine on the diurnal-nocturnal patterns of, and relationships between, food and fluid intake.

Zimeldine appeared to primarily affect food intake, with secondary decreases in the fluid most closely associated with prandial drinking. In the third experiment, the effects of zimeldine on locomotor activity were determined, using two behavioral measures. The drug appeared to have no overt sedative actions which could account for its inhibitory effects on feeding. In the final experiment, a more detailed analysis of zimeldine's effects on food intake was carried out. The data provided some support for the hypothesis that zimeldine specifically enhanced the onset of satiety. The results were discussed in terms of the effects of serotonin uptake blockade on motivational processes in general.

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TABLE OF CONTENTS

TABLE OF CONTENTS (continued)   Page

LIST OF FIGURES

LIST OF FIGURES. (continued)

INTRODUCTION

The social and medical harm associated with alcohol use and abuse is well established. As outlined by Hofmann (1983), the magnitude of the medical problem alone is staggering, and arises as a direct consequence of the tissue damage and metabolic aberrations produced by alcohol (i.e. gastritis, hypertension, liver cirrhosis, Wernicke-Korsakoff syndrome) as well as a consequence of intoxication (i.e. traffic accidents, labour accidents, suicide attempts). The social harm caused by alcohol, while not as easily quantifiable, is also enormous and includes aggression, family violence, lost work hours and absenteeism (Chick, 1984; LeDain, 1973).

Recently, there have been two international symposia devoted to the discussion of "pharmacological treatments for alcoholism" (Edwards & Littleton, 1984; Naranjo & Sellers, 1985). It is very clear from reading the published proceedings of both these symposia, that at present there are no clinically effective pharmacological treatments for alcoholism. Overall, the pharmaceutical industry has been taken to task for ignoring and neglecting this area of drug development (Naranjo, 1985; Edwards, 1984; Teeling-Smith, 1984). While there are some compounds for the treatment of alcohol withdrawal sypmtoms (i.e. benzodiazepines, chloromethiazole), there are no available medicines which tackle problems related to the

development and maintenance of the alcohol dependence syndrome (Teeling-Smith, 1984).

In Clare's (1984) article on the treatment of alcoholism, he stated that the alcohol abuser and clinician have different needs at various stages of the treatment process. Following the initial phases of therapy (and detoxification where necessary), the clinician requires a pharmacological tool as an adjunct to therapy, which would help patients avoid relapse by reducing the desire to drink over and above a moderate level. Virtually all patients in rehabilitation programs relapse one or more times during treatment (Hofmann, 1983). The agents currently used to combat this tendency for relapse are the "alcohol sensitizing" compounds, Antabuse and Temposil. These compounds, which inhibit the the metabolism of alcohol, in effect, punish the patient for consuming alcohol through the development of the aversive "acetaldehyde syndrome". This syndrome is typified by facial flushing, headache, tachycardia, sweating and nausea. These effects are due to the accumulation of acetaldehyde, the primary metabolite of ethanol (Fuller, 1984; Peachey & Annis, 1985). There are numerous problems associated with the use of these compounds, which limit their usefulness i.e. variability in the intensity of the reaction following alcohol ingestion (depending primarly on the individual's sensitivity to acetaldehyde), problems with patient

compliance, and the development of adverse side effects
(Hofmann, 1983; Peachey & Annis, 1985). In addition, the
use of these compounds is indicated only when a patient
has agreed that total abstinence is the goal of therapy
(Naranjo, Sellers, Wu & Lawrin, 1985). A more serious
problem however, is that there is little evidence that
alcohol sensitizing drugs reduce alcohol intake or prevent
relapse (Fuller, 1984; Naranjo et al., 1985; Peachey &
Annis, 1985).

There has been an appeal, by both clinicians and basic
researchers, to intensify the search for new compounds for
the treatment of alcohol abuse (Edwards, 1984; Naranjo,
1985). There has been a call for the development of
pharmacological interventions which would reduce alcohol
craving, prevent the development of tolerance and physical
dependence, reverse organic brain damage and reduce
ethanol-induced memory impairments. In addition, agents
which would moderate ethanol intake and reduce the
reinforcement derived from intoxication have been
considered to be important areas of drug development (Amit
& Sutherland, 1975; Clare, 1984, Littleton, 1984;
Teeling-Smith, 1984).

Until several years ago, the serotonin uptake blocker,
zimeldine, appeared to hold considerable promise as a new
treatment for alcohol abuse. The drug was found to have a
potent inhibitory effect on voluntary ethanol consumption
in rats (Rockman, Amit, Carr, Brown & Ogren, 1979;

Rockman, Amit, Carr & Ogren, 1979) and was hypothesized to act by reducing the positive reinforcing effects of ethanol. In human trials, the drug was shown to increase the number of abstinent days in heavy social drinkers and to produce a slight reduction in the number of daily drinks (Naranjo, Sellers, Roach, Woodley, Sanchez-Craig & Sykora, 1984). Additional evidence for zimeldine's effects in humans was provided by a double-blind cross-over study in which subjects were administered zimeldine in combination with an acute dose of ethanol. Subects reported a redaction in ethanol-induced euphoria and a reduced desire to drink during the week following the experimental sessions in which zimeldine had been paired with ethanol administration (Amit, Brown, Sutherland, Rockman, Gill & Selvaggi, 1985). Zimeldine has also been reported to antagonize ethanol-induced memory impairments in human subjects (Weingartner, Rudorfer, Buchsbaum, & Linnoila, 1983).

The initial reports of the effects of zimeldine in humans were highly encouraging. However, the data were preliminary, and extensive clinical testing was clearly called for. At the time that the above studies were being conducted, zimeldine was also undergoing extensive clinical testing as a treatment for depression. Zimeldine proved to be an effective antidepressant (Aberg & Holmberg, 1979). However, chronic administration of this compound was found to be associated with the development

of serious adverse side-effects (hepatic and neurologic toxicity) and in September 1983, the drug was withdrawn from the market in Europe, and clinical trails in North America ceased. Despite this setback, several groups of researchers have continued testing the effects of various serotonin uptake blockers on alcohol intake, in both animals and humans (Naranjo et al, 1985; Amit et al, 1985).

One of the problems which has plagued this area of research however, is the lack of understanding the mechanism of action of these compounds. (Amit, Sutherland, Gill & Ogren, 1984). In addition to being of considerable theoretical interest in terms of the interaction between the serotonin system and ethanol, an understanding of the mechanism of action of zimeldine may possibly aid in the development of new compounds for the treatment of alcohol-related problems. The difficulty inherent in this enterprise is a reflection of a larger problem; that is, the present lack of understanding of the factors involved in regulating ethanol consumption. Rational approaches to the development of pharmacological treatments should be based on an understanding of the central psychobiological mechanisms underlying ethanol intake (Dietrich & Baker, 1984; Naranjo et al., 1985). To this end, considerable effort has been made in recent years to determine what role, if any, various central neurotransmitters play in regulating ethanol intake (Holman, 1984). Furthermore, a

host of endogenous peptides have been implicated in some of ethanol's actions (e.g. Kulkosky, 1985; Samson & Doyle, 1985). Overall, the results of studies examining the role of neurotransmitters and peptides have been inconsistent and the picture is far from clear. For example, depletion of brain norepinephrine through the use of neurotoxins or synthesis inhibitors has been reported to reduce voluntary ethanol intake in rats (Amit, Levitan & Lindros, 1976; Brown & Amit, 1977; Davis, Smith & Werner, 1978) or to have no effect (Corcoran, Lewis & Fibiger, 1983; Gill, Amit & Ogren, 1984). Thus, despite extensive research it is clear that the neurobiological underpinnings of ethanol's actions have not been delineated (Amit et al., 1984; Dietrich & Baker, 1984; Holman, 1984; Naranjo et al., 1985).

Studies on the mechanism of action of zimeldine have continued. One issue, generally ignored by researchers in the area related to serotonin and ethanol-intake, is the large body of research devoted to the relationship between serotonin and consummatory behavior, in general. There is ample evidence that 5-HT is involved in the regulation of both food and fluid intake (Blundell, 1984). In light of this body of data, it was clear that the specificity of zimeldine's effects needed to be more thoroughly investigated. Therefore, the present series of experiments was designed to specifically test the

hypothesis that zimeldine's effects on ethanol intake were mediated through more global effects on consummatory behavior. The following sections will review areas of the literature pertinent to the present investigation.

Serotonin and Ethanol: Biochemical and Behavioral Interactions

One of the first observations to spark interest in the interactions between serotonin and ethanol, was the finding by Myers and Veale (1968), that the 5-HT synthesis inhibitor, p-chlorophenylalanine (PCPA), reduced voluntary ethanol consumption in rats. This work led researchers to examine a number of related areas, such as the effects of ethanol on 5-HT levels and metabolism (e.g. Frankel, Khanna, Kalant & Leblanc, 1974), the differences in endogenous 5-HT levels between high and low ethanol preferring strains of rats (e.g. Ahtee & Eriksson, 1972), as well as the effects of pharmacological manipulations of the 5-HT system on voluntary ethanol intake (e.g. Geller, 1973). This field of research has thus far yielded very inconsistent data, some controversy and has, overall, failed to firmly link the serotonin system to the regulation of ethanol intake.

There is disagreement with regards to the effects of both acute and chronic ethanol admininstration on 5-HT metabolism. For example, acute doses of ethanol have been found to elevate brain 5-HT levels in rats (Pohorecky, Jaffe & Berkley, 1974) or to have no effect (Frankel et

al., 1974). Attempts to examine the functional status of
the 5-HT system following ethanol administration, through
measurement of the 5-HT metabolite, 5-hydroxyindole acetic
acid (5-HIAA), has led to similar discrepancies (Frankel
et al., 1974; Hunt & Majchrowicz, 1974; Pohorecky, Newman,
Sun & Bailey, 1978). More recently, Murphy, Cunningham
and McBride (1985) reported that acute ethanol admin-
istration had no effect on 5-HT release.

During chronic exposure to ethanol, brain 5-HT levels
have been reported to be elevated (Pohorecky et al., 1974)
decreased or unchanged in rats (Frankel et al., 1974; Hunt
& Majchrowicz, 1974). Badawy and his coworkers on the
other hand, have consistently reported elevations in brain
5-HT and 5-HIAA content following chronic ethanol
administration. The enhancement of 5-HT synthesis and
turnover was proposed to be due to an increased
availability of circulating tryptophan, secondary to an
ethanol-induced inhibition of liver tryptophan pyrrolase
activity (Badawy, Evans & Punjani, 1981; Badawy, Punjani &
Evans, 1979). However, such results are not consistently
reported in the literature. Hunt and Majchrowicz (1983)
suggest that the reasons for the discrepancies may be
related to the biphasic action of ethanol on
neurotransmitter release. Therefore, perhaps more
extensive studies of the dose and time dependent effects
of ethanol, will reveal more consistent effects on
serotonin metabolism.

In humans, acute ethanol administration has been shown to produce a shift in the metabolism of 5-HT (Davis, Brown, Huff & Cashaw, 1967). The normal breakdown product of serotonin, 5-HIAA, is produced through a series of oxidations, culminating with the action of the enzyme aldehyde dehydrogenase. However, following ethanol administration there appeared to be a shift to the reductive pathway, and thus an increase in the production of the 5-HT metabolite, 5-hydroxytryptophol (5-HTOL). This alteration in 5-HT metabolism from the oxidative to the reductive pathway may be due to a competitive inhibition of aldehyde dehydrogenase by acetaldeyhyde (produced during the oxidation of ethanol) and/or by shifts in the redox state of the brain (Davis et al., 1967; Beck, Borg, Eriksson & Lundman, 1982). Several studies have shown altered cerebrospinal fluid concentrations of 5-HTOL (Beck, Borg, Holmstedt, Kvande & Sdroder, 1980; Beck et al., 1982) as well as blood platelet uptake of 5-HT (Kent, Campbell, Pazdernik, Hunter, Gunn & Goodwin, 1985) in alcoholics compared to control subjects. These investigators have suggested that the abnormal metabolism of 5-HT apparent in alcoholics, may contribute to the pathophysiology of alcoholism. However, no firm hypothesis as to the relationship between the two has been suggested.

Another approach to the relationship beween serotonin and ethanol has been the study of 5-HT metabolism in rats

demonstrating a natural preference for ethanol drinking. For example, Daoust, Chretien, Moore, Saligaut, Lhuintre and Boismare (1985) recently demonstrated that although the rates of striatal synaptosomal 5-HT uptake were similar in ethanol preferring and non-preferring rats, the steady state accumulation of 5-HT in preferring rats was higher. Differences in regional brain 5-HT content, have previously been demonstrated in other preferring and non-preferring strains of rats. Ahtee and Eriksson (1972, 1973) demonstrated that 5-HT and 5-HIAA levels were higher in the genetically selected strain of ethanol preferring (AA) rats than in the low preferring (ANA) rats. In addition, 5-HT content and turnover in the hypothalamus, thalamus and midbrain regions appeared to be most affected. Comparison of this work to a more recent genetic selection program by T.-K. Li and his colleagues, yields an opposite spectrum of results. In their preferring (P) rats, lower levels of 5-HT were observed in the cortex, hippocampus, striatum, thalamus and hypothalamus compared to the non-preferring (NP) rats (Murphy, McBride, Lumeng & Li, 1982). Recently, Lumeng, Wong, Threlkeld, Reid and Li (1986) reported that $5-HT_1$ receptor binding in membranes isolated from the frontal cortex and hippocampus of P rats was significantly higher than in NP rats. This increased receptor binding was accounted for by an increased number of 5-HT receptors rather than a change in receptor affinity. In a very

thorough turnover study, this group also demonstrated that following a variety of acute and chronic ethanol treatments, no alterations in 5-HT metabolism could be detected in any brain region of the P strain of rats (Murphy, McBride, Lumeng & Li, 1983).

As previously mentioned, much of the interest in 5-HT was stimulated by the Myers and Veale (1968) study, in which direct manipulation of 5-HT levels produced a reduction in ethanol consumption. This study led to a very controversial area of research. The decrease in ethanol preference produced by PCPA appeared to be very long lasting (Veale and Myers, 1970) and the drug affected both saccharin and water intake (Stein, Wayner & Tilson, 1977). This led several researchers to suggest that PCPA given by the oral route induced a conditioned taste aversion (CTA) and that the effects were not specific to ethanol (Nachmann, Lester & LeMagnen, 1970; Holman, Hoyland & Shillito, 1975). When PCPA was given intraperitoneally, at doses producing comparable 5-HT depletion to that produced by oral administration, no reductions in ethanol preference were observed (Holman et al., 1975).

Other attempts to affect ethanol consumption by lowering brain 5-HT content have been somewhat more consistent. Intracerebroventricular (ICV) application of the neurotoxin, 5,6-dihydroxytryptamine (5,6-DHT), produced an increase in ethanol consumption (Ho, Tsai,

Chen, Begleiter & Kissin, 1974; Myers & Melchior, 1975).
Kiianmaa (1976) reported however, that despite sizable
decreases in brain 5-HT produced by the neurotoxin 5,6-DHT
or electrolytic lesion of the midbrain raphe nuclei, there
was no effect on ethanol consumption in the AA strain of
rats. Strain specificity however, was also demonstrated
by Melchior and Myers (1976), who found that 5,6-DHT
produced long lasting increases in ethanol intake in
Sprague-Dawley and Holtzman rats and little effect in the
Long Evans and Wistar strains. In agreement with the
ethanol elevating effect of some neurotoxins, Geller,
Hartmann and Messiha (1975) reported that the 5-HT
antagonist, cinanserin, produced an increase in ethanol
selection in Sprague-Dawley rats.

As would be predicted by the data presented above,
manipulations which increase cerebral 5-HT release or
turnover, should be expected to produce a reduction in
ethanol intake. This prediction has been born out by
numerous studies employing agents which increase 5-HT
neurotransmission. Zabik, Binkerd and Roache (1985)
reported that tryptophan and the 5-HT agonist, quipazine,
reduced ethanol consumption in rats given access to
ethanol as their only source of fluids. In addition, ICV
administration of 5-HT, as well as systemic or cerebral
administration of the serotonin precursor 5-HTP, have been
shown to decrease ethanol consumption (Geller, 1973; Hill,
1974; Myers & Martin, 1973; Zabik, Liao, Jeffreys &

Maikel, 1978)-- Geller, Hartmann and Messiha, (1981) demonstrated that the reduction in ethanol consumption produced by 5-HTP could be blocked by the decarboxylase inhibitor, RO4-4602. This agent blocks the conversion of 5-HTP to 5-HT. Thus., according to these investigators, these data provided further support for the notion that central 5-HT is involved in voluntary ethanol intake.

In a study employing chronic forced choice ethanol intake, Zabik et al., (1978) found that 5-HTP produced a pronounced rejection of ethanol such that 25% of the subjects died, due to persistant refusal to consume the ethanol solution. 5-HTP was subsequently found to produce strong CTA's to a number of novel, flavoured solutions including ethanol. However, only those rats which received ethanol solutions, exhibited a persistant refusal to consume the paired fluid on test days (Zabik & Roache, 1983). Subsequently, Zabik et al., (1985) reported that the 5-HTP induced CTA to ethanol could be blocked by pretreatment with the peripheral 5-HT blocker, Xylamidine Tosylate, suggesting that the CTA inducing effects of the drug were mediated peripherally. Thus far, this peripheral receptor blocker has not been tested against 5-HTP's effects on voluntary ethanol consumption. This would be an interesting and necessary test of the notion that the effects of 5-HTP on voluntary ethanol intake are indeed mediated centrally, as suggested by Geller et al., (1981). There is considerable data to suggest that

peripheral 5-HT is involved in the actions of serotonergic compounds (Carter & Appel, 1976). This issue will be dealt with in more detail in a later section of this thesis.

In summary, it would appear that the most consistent relationship between 5-HT and ethanol intake has been established by studies employing agents which are direct acting agonists or which increase the synthesis and release of 5-HT. All of these manipulations have been shown to decrease voluntary ethanol intake in rats. Directly related to this body of research has been the study of the effects of 5-HT uptake blockers on ethanol intake. Much of the initial work was carried out in this laboratory using the drug, zimeldine. An overview of the properties of zimeldine as well as behavioral studies related to its effects on voluntary ethanol intake are presented in the following sections.

Zimeldine

5-HT uptake blockade results in a prolonged activity of released 5-HT within the synaptic cleft and enhanced 5-HT neurotransmission (Meek, Fuxe & Anden, 1970; Ogren, Lundstrom & Moore, 1981). Zimeldine (ZIM) has consistently been shown to be a specific and potent inhibitor of 5-HT uptake and to potentiate 5-HT receptor mediated activity (Ogren et al., 1981a; Ogren, Ross, Hall, Holm & Renyi, 1981; Pawlowski & Mazela, 1984).

Zimeldine is the generic name for (Z)-3-(4-Bromophenyl)-N,N-Dimethyl-3(3-Pyridyl)-Allylamine (Astra Alab AB, Sweden). This bicylic compound, initially developed for the treatment of depression, has been shown to possess an antidepressant action comparable to tricyclics in several studies (Aberg, 1981; Georgotas, Krakowski & Gershon, 1982).

ZIM and its primary metabolite, Norzimeldine (NORZIM) are potent inhibitors of the carrier mediated reuptake of 5-HT (Ross, Ogren & Renyi, 1976; Ross & Renyi, 1977). In vitro, NORZIM has been shown to be approximately 10 times more potent on 5-HT uptake than ZIM. However, in vivo they are equipotent, due to the rapid demethylation of ZIM to NORZIM. Ross and Renyi (1977) have demonstrated that when the formation of NORZIM was inhibited through administration of the metabolic inhibitor, SKF 525A, there was a significant drop in zimeldine's potency on 5-HT uptake blockade. This indicated that the largest part of ZIM's effect on 5-HT uptake in vivo, was in fact due to NORZIM. In vitro, NORZIM appeared to have a slight NE uptake blocking capacity (Ross & Renyi, 1977). Recently, some studies have demonstrated that NORZIM behaved like a weak norepinephrine uptake inhibitor in behavioral tests (Pawlowski & Mazela, 1984). Both compunds show negligible effects on dopamine uptake in vitro and in vivo (Ogren et al., 1981b). Following oral or intraperitoneal administration, peak effects on amine uptake occurs within

2-4 hours, with ZIM and NORZIM showing plasma half-lives of approximately 6 and 17 hours, respectively (Ogren et al., 1981a; Ross & Renyi, 1977).

Various studies of the effects of ZIM on receptor binding have indicated that this compound exhibits negligible affinity for muscarinic, alpha or beta-adrenergic, histamine, dopamine, opiate or benzodiazepine receptors (Hall & Ogren, 1981). The drug also possesses virtually no postsyaptic 5-HT receptor blocking activity and little 5-HT releasing capacity (Ross & Renyi, 1977, Ogren et al., 1981b).

Acute administration of ZIM produced a marked reduction in 5-HT synthesis, release and turnover, measured respectively by decreases in the accumulation of 5-HTP after decarboxylase inhibition, attenuation of the disappearance of 5-HT after synthesis inhibition and a reduction in whole brain 5-HIAA levels (Ogren et al., 1981b; Ross & Renyi, 1977). At the doses used in the present investigation, the drug has been shown not to affect NE or dopamine synthesis or turnover in several brain regions (Ogren et al., 1981b). Chronic treatment with ZIM reduced brain and plasma levels of 5-HT. However, over repeated dosing there does not appear to be any development of tolerance to ZIM's capacity to block 5-HT uptake or enhance functional 5-HT activity (Ogren et al., 1981b; Ogren, Fuxel, Archer, Johansson & Holm, 1982; Ross, Hall, Renyi & Westerlund, 1981).

Zimeldine appears to be devoid of any pharmacokinetic interactions with sedative/hypnotic drugs' including alcohol and does not possess overt sedative actions when administered alone (Brown, Amit, Sutherland, Rockman, Selvaggi & Ogren, 1961; Cott & Ogren, 1980; Scott, Fagen & Tiplady, 1982; Seppala, Stromberg & Bergman, 1984). Only one report in the literature has suggested that there are any deleterious interactions between the ZIM and ethanol. In this study, ZIM was found to enhance ethanol-induced impairments in memory, body sway and manual tracking (Naranjo, Sellers, Kaplan, Hamilton & Khouw, 1984). However, other studies have reported that ZIM antagonized ethanol-induced impairments in body sway and memory (Seppala, Stromberg & Bergman, 1984; Weingartner et al., 1983).

Serotonin Uptake Blockade and Ethanol Intake

The first report of the effects of 5-HT uptake blockade on ethanol intake appeared in 1979, and has subsequently been followed up by numerous studies. In this study zimeldine was found to produce a dose dependent reduction in voluntary oral ethanol consumption (Rockman, Amit, Carr, Brown & Ogren, 1979). ZIM (20 mg/kg) produced a suppression of locomotor activity following the first injection, which disappeared over repeated dosing. However, the drug had no effect on body weight gain, total fluid consumption or the ingestion of an aversive tasting quinine-sucrose solution, suggesting that the drug effects

were specific to the consumption of ethanol solutions.
Two subsequent studies however, have shown that ZIM
produced a dose-dependent reduction in the voluntary oral
consumption of a morphine-sucrose solution (Rockman, Amit,
Bourque, Brown & Ogren, 1980) as well as the comsumption
of a liquid diet containing morphine (Ronnback, Zeuchner,
Rosengren, Wronski & Ogren, 1984). Rockman et al., (1980)
suggested that the inhibitory effects of ZIM on both
ethanol and morphine supported the notion that the
reinforcing effects of these drugs were mediated by a
common mechanism, perhaps via interactions with the NE
system.

In a subsequent experiment, extinction of ethanol
drinking behavior was accomplished using a paradigm in
which forced choice ethanol intake was combined with 20
days of ZIM treatment. When animals were subsequently
allowed voluntary access to ethanol, there was a slow
reacquisiton of the ethanol drinking response (Rockman et
al., 1979a). These authors suggested that these results
provided additional support for the notion that serotonin
is involved in the actions of ethanol, specifically the
positive reinforcing properties of ethanol. Amit and his
colleagues examined the effects of several specific 5-HT
uptake inhibitors (norzimeldine, fluoxetine, citalopram,
alaproclate), as well as NE uptake blockers
(desmethylimipramine, doxepin) on ethanol intake. Only
those drugs known to be more selective for 5-HT uptake

blockade appeared to have a significant inhibitory effect on voluntary ethanol consumption (Rockman, Amit, Brown, Bourgue & Ogren, 1982). Subsequent to these studies, several other research groups have confirmed the ethanol reducing properties of 5-HT uptake blockers, using compounds such as Indalpin, Fluoxetine and Fluvoxamine (Daoust, Saligaut, Chadelaud, Chretien, Moore & Boismare, 1984; Le Bourhis, Uzan, Autrere & LeFur, 1981; Murphy, Waller, Gatto, McBride, Lumeng & Li, 1985; Zabik et al., 1985).

In studies examining the mechanism of action of ZIM, partial blockade of the effects of ZIM could be produced by pretreatment with DMI, as well as the alpha-2 NE receptor agonist, clonidine. However, the serotonin receptor antagonist, methergoline, produced no blockade of ZIM's actions (Rockman et al., 1979b; Rockman et al., 1982; Amit et al., 1984). In a similar series of studies, employing NORZIM, a different pattern of results was obtained. DMI and clonidine had no effect, whereas methergoline (1 mg/Kg) significantly attenuated the NORZIM induced reduction in ethanol intake (Amit et al., 1984). These results appear paradoxical and are not readily reconciled with the demonstration that NORZIM accounts for much of the in vivo activity of ZIM (Ross & Renyi, 1977). There are few known differences between the two compounds which could account for the differential actions following DMI, clonidine or methergoline. Complicating the picture

further is the study by Murphy et al., (1985) in which they reported the inability of a variety of NE and 5-HT receptor antagonists to block the inhibitory effects of fluoxetine and fluvoxamine on ethanol intake. Other attempts to block the actions of both ZIM and NORZIM have yielded negative results. Prior depletion of central 5-HT by the neurotoxin, p-Chloroamphetamine (2 x 10 mg/kg), failed to alter the actions of these compounds, despite substantial reductions in whole brain 5-HT levels (Amit et al., 1984; Gill, Amit & Ogren, 1985).

Overall, these studies suggested that 5-HT uptake blockers are not acting directly through a 5-HT receptor mechanism (Amit et al., 1984; Murphy et al., 1985). The inability to block the activity of these compounds by a variety of methods suggested that some non-specific or indirect action, perhaps the induction of a CTA, was responsible for reductions in ethanol intake. ZIM produced CTA's to a variety of novel, flavoured solutions including ethanol (Gill, Shatz & Amit, 1986). However, when animals were pretreated with ZIM (using a time frame similar to that employed in voluntary consumption studies), a CTA did not develop. These results suggested that it is unlikely that the development of a CTA accounted for ZIM's effects on voluntary ethanol consumption.

It is clear from the data reviewed above that the mechanism of action of 5-HT uptake blockers on ethanol

intake is not well understood. In a review of the effects
of Zimeldine on voluntary ethanol consumption, Amit,
Sutherland, Gill and Ogren (1984) outlined several
mechanisms through which 5-HT uptake blockers may be
acting to reduce ethanol intake. Among those listed was
the suggestion that ZIM induces "anorexia". In the
following section a review of the role of 5-HT in feeding
behavior is presented. Similarities between the effects
of serotonergic manipulations on food and ethanol intake
have been noted.

Serotonin and Feeding

. There is considerable experimental evidence to suggest
that manipulations of the serotonergic system induce
changes in feeding behavior. In initial work, ICV
infusion of the enzyme inhibitor PCPA, produced a severe
depletion of serotonin and a concomitant hyperphagia; with
increases of up to 175% in baseline food intake for
several days, following a single administration of the drug
(Hoebel, Zelman, Trulson, MacKenzie, DuCret & Norelli,
1978). Saller and Stricker (1976) reported that central
admimistration of the 5-HT neurotoxin 5,7-DHT induced
hyperphagia and increased body weight gain in rats.
Similarly, 5-HT antagonists such as cyproheptadine have
been reported to increase food intake and are used
clinically as appetite stimulants in humans (Hoebel,
1977). As outlined in the section on serotonin and
ethanol, there is some evidence that depletion of cerebral

5-HT by central administration of neurotoxins, also increased voluntary ethanol intake (Melchior & Myers, 1975).

On the other hand, agents that acutely increase the levels of brain serotonin (i.e the precursor 5-HTP), increase release (fenfluramine), act as direct acting agonists (quipazine), or 5-HT reuptake blockers (fluoxetine) have all been reported to decrease food intake (Barrett & McSharry, 1975; Blundell & Latham, 1978; Goudie, Thornton & Wheeler, 1976; Samanin, Mennini & Garattini, 1980). This work, taken as a whole, has suggested that serotonin plays a role in the processes which mediate satiety; with reductions in 5-HT producing overeating and increases producing anorexia (Blundell, 1984). It should be noted that all the serotonergic agents listed above (e.g. 5-HTP, quipazine, fluoxetine) have been shown to reduce voluntary ethanol intake.

One of the most studied 5-HT anorexic agents is fenfluramine (Rowland & Carleton, 1986). Silverstone and Kyriakides (1982) have extensively documented the influence of fenfluramine (FEN) on appetite and food intake in humans. The drug reduced subjective ratings of appetite, increased the latency to start feeding, slowed the rate of eating and produced a total reduction in caloric intake. Similar effects on food intake have been demonstrated in animals (Blundell, 1984; Blundell & Latham, 1982; Hoebel, 1977). Fenfluramine's effects on

the 5-HT system has been established by the work of
Samanin and Garattini (1982) who found that acute
administration of the drug increased the release of 5-HT
and inhibited its reuptake. Additional evidence for 5-HT
involvement comes from work which showed that FEN's
effects on food intake could be blocked by 5-HT
antagonists such as methergoline and methysergide (Barrett
& McSharry, 1975; Blundell, Latham & Lesham, 1973;
Jesperson & Scheel-Kruger, 1973; Thurlby, Garattini &
Samanin, 1985). Davies, Rossi, Panksepp, Bean and
Zolovick (1983), examining free feeding patterns in rats,
reported that FEN reduced meal size without having any
effect on meal frequency. However, these authors further
reported that FEN significantly attenuated the rate of
gastric emptying following stomach loading, suggesting
that peripheral signals from the upper gastro-intestinal
tract might be involved in the control of FEN induced
satiation. These results indicated that FEN may have an
action on free feeding via mechanisms independent of
central 5-HT.

Serotonin containing neurons are abundant in the
periphery; with large quantities located in the enteric
cells of the gut (Fletcher & Burton, 1984). A role for
peripheral 5-HT in feeding has been suggested by the
demonstration that systemic administration of 5-HT (1, 2,
4 mg) which does not cross the blood brain barrier,
produced a dose dependent reduction in food intake. This

effect, observed in food deprived as well as in free feeding animals, appeared to be due to a selective reduction in bout size and duration (Fletcher & Burton, 1984, 1986a). The anorexic effects of the 1 and 2 mg doses of 5-HT were attenuated by pretreatment with methysergide (3 mg/kg) but not by methergoline (1 mg/kg).

Administration of 5-HTP has been reported to reduce operant responding for water and food reinforcement (Carter & Appel, 1976; Carter, Dykstra, Leander & Appel, 1978), reduce food intake (Blundell & Lesham, 1975; Goudie et al., 1976), and to produce a CTA (Ervin, Carter, Webster, Moore. & Cooper, 1984). Treatment with 5-HTP (50 mg/kg) significantly reduced responding for water reinforcement; an effect which could be blocked by pretreatment with RO4-4602, at doses sufficient to inhibit peripheral but not central decarboxylase (Carter & Appel, 1976; Ervin et al., 1984). As was noted in the previous section on serotonin and ethanol, Geller et al., (1981) interpreted the RO4-4602-induced blockade of 5-HTP's effects on ethanol intake to suggest that central 5-HT mediated voluntary ethanol consumption. Carter and Appel (1976) and Ervin et al., (1984) however, suggested that their data support the notion that the effects of 5-HTP are mediated entirely in the periphery. As outlined previously, Zabik et al., (1985) have demonstrated that the CTA to ethanol solutions produced by 5-HTP could be

blocked by the peripheral 5-HT antagonist, xylamidine tosylate.

The experiments reported above have dealt with the behavioral effects of 5-HT and 5-HTP when administered through a peripheral route. These experiments raised the possibility that many 5-HT manipulations (i.e. agonists, releasing agents and uptake blockers) are acting mainly through peripheral mechanisms, possibly by reducing the rate of gastric clearance, through general malaise or aversion. Despite this, several investigators have found that central administration of anorexic agents also reduce food intake.

Traditional divisions of the central systems controlling feeding into excitatory and inhibitory centers in the lateral hypothalamus (LH) and ventromedial hypothalamus (VMH), are currently held to be inadequate and simplistic (Stricker, 1983; Stricker & Zigmond, 1984; Smith, 1982) or are supported (Hoebel & Leibowitz, 1981; Hoebel, 1984). While the purpose here is not to review this controversy, some reference to the VMH must be made in assessing the role of central 5-HT in feeding.

The VMH is associated with two major neural tracts: a serotonergic input originating from the raphe nuclei of the pontine-midbrain area and a noradrenergic input from the ventral noradrenergic bundle originating in the dorsal pons, which connects the reticular formation with the septum (Morley, 1980). Both Hoebel and Leibowitz (1981)

and Morley (1980) in reviewing the literature on brain

monoamines and feeding, have suggested that the medial

serotonergic system facilitates satiety through an

interaction with NE in the VMH and associated

Paraventricular Nucleus (PVN). Several studies have

demonstrated that NE had specific facilitory effects on

feeding when injected into the PVN, whereas destruction of

the ascending NE input into the VMH and PVN by knife cuts

or lesions led to decreased food intake, weight loss, and

a blockade of NE or DMI-induced feeding. In addition,

lesions of the VMH or PVN regions produced hyperphagia,

increased meal size and obesity (Hoebel & Leibowitz, 1981;

Leibowitz, 1978; Leibowitz, Brown, Tretter &

Kirschgessner, 1985). This data suggested therefore, that

NE normally inhibited a putative satiety system

functioning in these regions. On the other hand, a

reduction in central 5-HT, produced by neurotoxins or

PCPA, has been reported to produce hyperphagia and obesity

(Hoebel et al., 1978), further suggesting that central

serotonin normally stimulated the putative satiety system.

Serotonin injected directly into the PVN inhibits

feeding. For example, microinjections of 5-HT produced a

dose dependent suppression of deprivation induced feeding

and the serotonin precursor 5-HTP suppressed NE-induced

feeding; an effect which could be reversed by

administration of RO4-4602 (Hoebel & Leibowitz, 1981;

Leibowitz & Papadakos, 1978). Other serotonergic

manipulations described previously, which are known to reduce feeding when injected peripherally (i.e. fluoxetine, quipazine, fenfluramine) also produced a dose-dependent blockade of NE-induced feeding. Taken together, these results suggested that NE and 5-HT formed inhibitory and excitatory inputs, respectively, into the VMH-PVN which controlled the activity of neurons directly producing satiety (Blundell, 1984; Hoebel & Leibowitz, 1981; Morley, 1980).

There has been a great deal of speculation about the nature of this putative satiety system within the VMH-PVN. Morley, Levine, Gosnell and Krahn (1985) have recently presented the hypothesis that Corticotrophin Releasing Hormone (CRF) may be the putative satiety agent on which NE and 5-HT act to produce their effects. Stricker (1983) presented evidence to support the hypothesis that in fact the VMH-PVN is involved in the regulation of peripheral metabolism, particularly the rate of gastric clearance and insulin secretion. Morley (1980) suggested that the peptide, Cholecystokinin (CCK) is also a likely candidate for the satiety system within the VMH-PVN. At the present time CCK is receiving a great deal of interest as a putative satiety inducing agent which appears to have both peripheral and central actions to reduce food intake (Hoebel, 1984; Morley, 1980; Morley et al., 1985; Smith, 1982). CCK is widely distributed in the gastrointestinal tract as well as the central nervous system where high

concentrations have been localized in the dorsomedial
hypothalamus and PVN (Morley, 1982). Intraventricular or
cerebral application of CCK has been shown to have a
variety of behavioral and physiological effects including
a reduction in food intake, hyperglycemia and a reduction
of gastric motility. Morley (1980) demonstrated that the
5-HT precursor, tryptophan, produced a rapid decrease in
hypothalamic CCK, suggesting a link between the 5-HT and
CCK systems. Thus in Morley's model, 5-HT induces the
release of CCK in the VMH-PVN, which is inhibitory on
feeding. While the data at the present time are
insufficient to support any of these models, further
research will no doubt yield some interesting results. It
should be noted that CCK has recently been shown to reduce
voluntary ethanol intake (Kulkosky, 1985).

The literature reviewed above suggested that 5-HT
affects consummatory behavior; however there is
considerable discussion about whether the effects are
mediated centrally or peripherally and some suggestion
that these effects are non-specific (Stricker, 1983).
Nevertheless, several investigators support the notion
that 5-HT plays a specific role in feeding (Blundell,
1984; Hoebel and Liebowitz, 1981; Morley, 1980).
Furthermore, a more detailed analysis of the effects of
various pharmacological manipulations has indicated that
serotonin may be involved in the dietary selection of
particular nutrients (Li & Anderson, 1983, Wurtman &

Wurtman, 1977, 1979); thus arguing against an overall non-specific inhibition of behavior.

The Present Investigation

As is apparent from the previous discussion, the similarities between the effects of 5-HT manipulations on food and on voluntary ethanol consumption are numerous. The interpretation of the effects of zimeldine on ethanol intake has rested on the hypothesis that the drug produced a blockade of the positive reinforcing properties of ethanol (Rockman et al., 1979a). It may be possible however, that ZIM's actions are mediated through more global effects on consummatory behavior, rather than specific effects on ethanol reinforcement.

In the first experiment, the specificity of zimeldine's effects were examined by administering the drug to groups of animals consuming solutions of ethanol and dextrose as well as non-nutritive saccharin. In the second study, zimeldine's direct effect on food intake was determined using a drinkometer paradigm, in which food and fluid intake were monitored continuously. Changes in total food and fluid intake, the temporal patterns of intake as well as the frequency and duration of food and fluid bouts were determined. The third study examined the actions of zimeldine in two measures of locomotor activity. This experiment was conducted in order to determine whether sedation could account for zimeldine's effects on consummatory behavior. In the final study,

zimeldine's effects on the consumption of highly

reinforcing sucrose food pellets were examined, in order

to determine whether the drug had specific effects on

satiation.

EXPERIMENT 1

Blundell and Lesham (1975) reported that admin-
istration of the serotonin precursor 5-HTP produced
anorexia in rats. These authors proposed that an
inhibitory serotonergic system was involved in the control
of food intake. Goudie et al. (1976) argued however, that
treatment with 5-HTP could lead to the formation of 5-HT
in many areas of the brain, (due to the presence of the
enzyme L-amino-acid decarboxylase), which in turn could
displace catecholamines leading to a non-specific
disruption of feeding. Goudie et al., reasoned that if
the anorectic properties of 5-HTP were in fact
specifically mediated by serotonin, it should be possible
to potentiate the effects of this drug by 5-HT uptake
blockade. In their report, the 5-HT uptake blocker
fluoxetine not only potentiated the effects of 5-HTP but
also had a potent anorexic action of its own.

Wurtman and Wurtman (1977) confirmed the anorexic
properties of fluoxetine and further reported that the
drug specifically supressed the consumption of
carbohydrates relative to protein. These investigators
suggested that a carbohydrate rich meal normally increased
the synthesis and release of central 5-HT, through an
indirect route involving insulin which is released during
the ingestion of a meal. Insulin alters plasma amino acid
patterns and enhances the entry of tryptophan into the
brain relative to other amino acids with which it normally

competes (Wurtman, 1978). In their model, enhanced synthesis and release of 5-HT exerts a negative feedback effect on further selection of diets containing carbohydrates. Thus, when synaptic levels of serotonin are high, as for example after administration of drugs which increase serotonin release (fenfluramine) or inhibit 5-HT uptake (fluoxetine), animals would tend to reduce their elective carbohydrate consumption.

These studies were considered to be particularly significant to the investigation of the mechanism of action of Zimelidine on ethanol intake. If one considers voluntary ethanol consumption as a potential source of "carbohydrates", then there is a possibility that the decrease in ethanol consumption seen after treatment with both fluoxetine and zimeldine could be due to this mechanism. While ethanol is not strictly speaking a carbohydrate, it is a ready source of energy, and is known to interact with carbohydrate metabolism; producing hypoglycemia in fasted rats (Field, Williams & Mortimore, 1963), hyperglycemia and enhanced gluconeogenesis in AA rats (Forsander & Poso, 1986), and a potentiation of the plasma insulin response to glucose (Metz, Berger & Mako, 1969).

Rockman et al. (1979a) however, demonstrated that zimeldine did not alter the consumption of a sucrose-quinine solution. This finding would argue against an "anorexia" hypothesis. However, subsequent

studies demonstrated that ZIM reduced the consumption of morphine-sucrose solutions as well as morphine added to a liquid diet (Rockman et al., 1980; Ronnback et al., 1984). A feature common to all these studies, was the presence of carbohydrates in the fluids consumed. Therefore, the present experiment was designed to compare the effects of zimeldine on the consumption of ethanol as well as the carbohydrate, dextrose. A solution containing saccharin was included as a non-nutritive control.

METHOD

Subjects

Sixty naive male Long Evans rats (Charles River, Canada) weighing 125-150 grams at the start of the experiment were used. Rats were individually housed in standard stainless steel cages and were maintained in a temperature and humidity controlled environment on a 12 hour dark-light cycle. Fluids were presented in two Richter tubes mounted on the front of the cages. Food and water were available ad libitum.

Procedure

Ethanol Screening: Following 5 days acclimation to the animal colony, the animals were divided into three groups and a screening procedure was initiated where rats received ethanol, dextrose or saccharin solutions presented in an ascending series of concentrations on alternate days in a free choice with water. Initially rats were presented with either a 2% (v/v) ethanol, 3%

(w/v) dextrose or a 0.1% (w/v) saccharin solution. On each presentation the concentration of the ethanol and dextrose solutions were increased by 1% and the saccharin solution by 0.05%. Once final concentrations of 10% ethanol, 14% dextrose and 0.6% saccharin were reached, rats were switched to a daily presentation schedule. Quinine sulphate (0.015%, w/v) was added to both the dextrose and saccharin solutions in order to reduce consumption to a level comparable to that of the ethanol consuming group. The concentration of 14% dextrose was chosen to be approximately iso-caloric to the 10% ethanol solution. The position of the water tubes was alternated daily in order to control for position bias. Animals were weighed and handled daily. Those animals in each group consuming less than 50 % of their total daily fluid intake as ethanol, dextrose or saccharin were eliminated from the study.

Injection Period: Following a 2 week baseline period, the remaining animals in each group were matched for baseline intake and were assigned to either a vehicle (2 ml/kg) or zimeldine (20 mg/2 ml/kg) group. Animals were injected intraperitoneally, approximately 2 hours prior to the onset of the dark cycle, for 5 consecutive days. Following the injection period, consumption was monitored for an additional 5 day period. Zimeldine was dissolved in saline immediately prior to injection.

Zimeldine at a dose of 20 mg/kg has previously been shown
to reduce voluntary ethanol intake (Rockman et al.,
1979a).

RESULTS

The data shown in Figures 1-3 are expressed as the
mean preference ratio (calculated as percent of total
daily fluid intake) for the ethanol, dextrose and
saccharin consuming groups respectively.

Analysis of Variance (with repeated measures) yielded
significant drug by days interaction effects as follows:
ethanol, $F(14,140) = 2.63$, $p < 0.002$; dextrose, $F(14,140) =$
5.14, $p < 0.001$; saccharin, $F(14,140) = 4.5$, $p < 0.001$. During
the injection period the preference for all three fluids
was reduced in those rats treated with zimeldine, compared
to their respective vehicle injected controls. Preference
remained low during the post-injection period. The
absolute consumption (mls.) as well as total fluid
consumption, for all groups injected with ZIM were also
significantly (p< 0.05) reduced during the injection
period. In addition, those animals treated with ZIM lost a
mean of 2.4 ± 1 grams of body weight during the injection
period compared to the normal body weight gain of 12.5 ± 2
grams in the control animals. This difference was
significant (p< 0.05).

Figure 1. Ethanol.preference during the baseline, injection and post-injection periods for those animals treated with vehicle or ZIM (20 mg/kg).

Figure 2. Dextrose preference during the baseline, injection and post-injection periods for those animals treated with vehicle or ZIM (20 mg/kg).
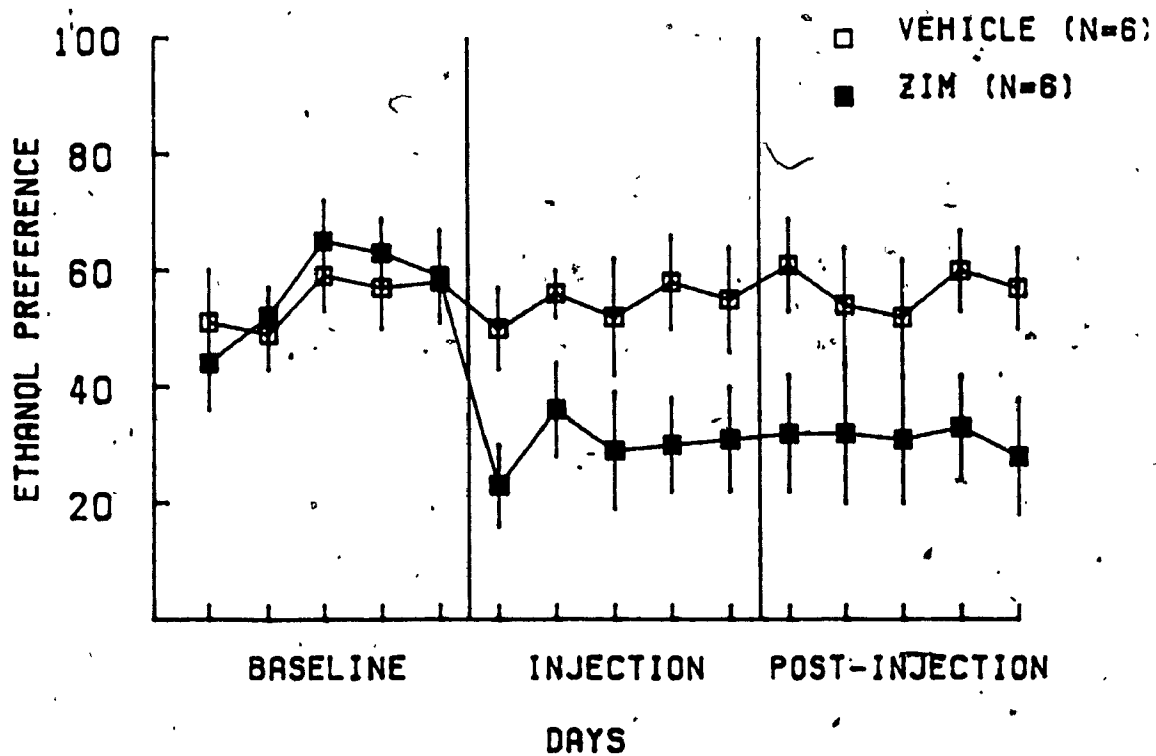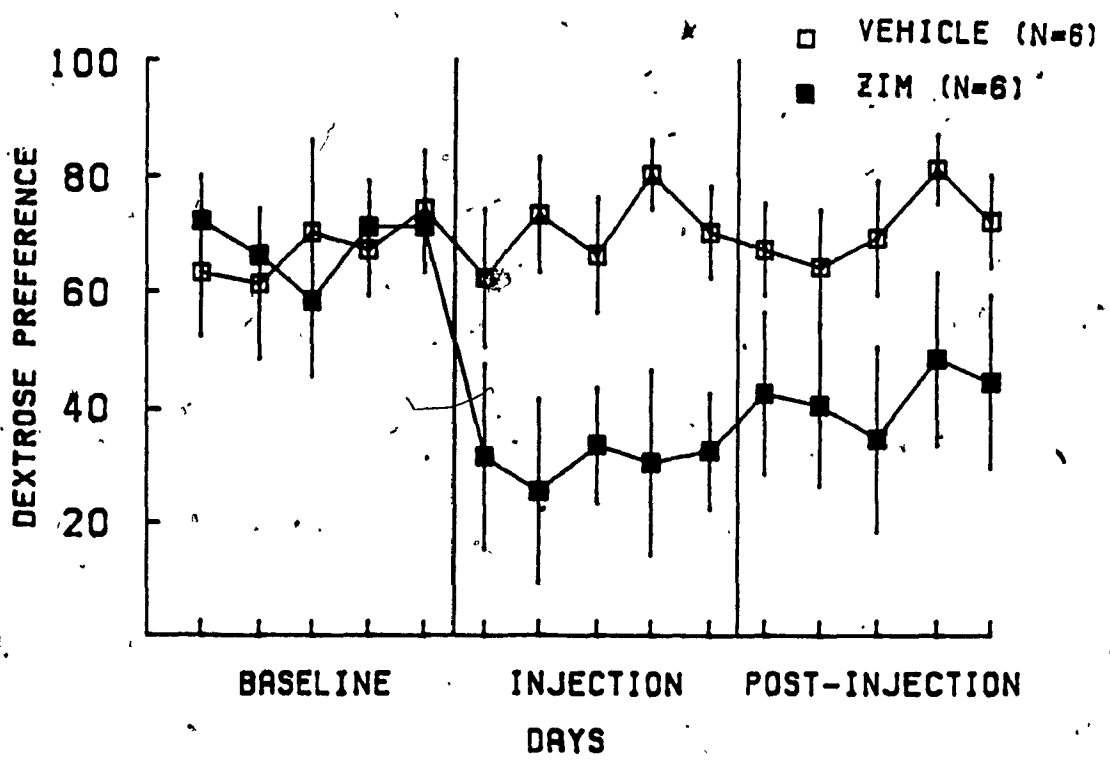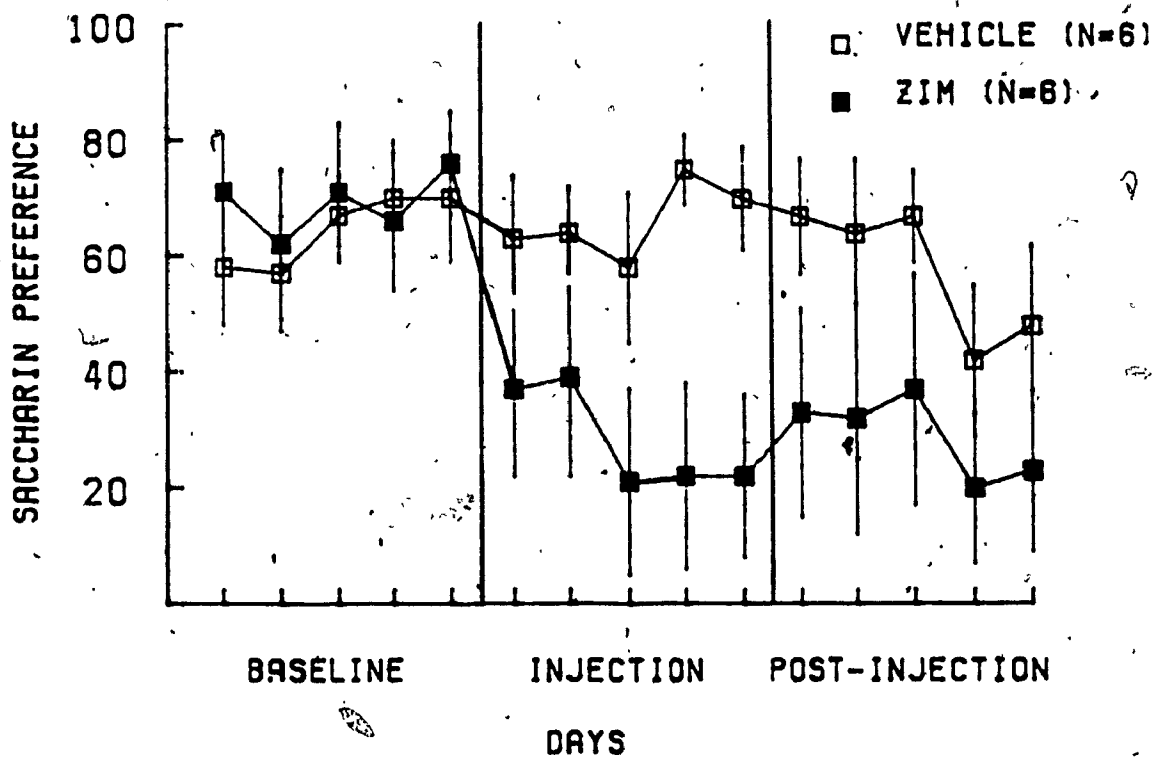
Figure 3. Saccharin preference during the baseline, injection and post-injection periods for those animals treated with vehicle or ZIM (20 mg/kg).

DISCUSSION

Zimeldine induced significant reductions in the voluntary consumption of ethanol as well as dextrose solutions. However, saccharin consumption was also reduced by the drug treatment. Given the non-nutritive nature of saccharin, it appears that the consumption of highly preferred solutions in general, rather than only those solutions containing ethanol or carbohydrates were reduced following zimeldine treatment.

These data do not appear to support Wurtman and Wurtman's (1977, 1979) hypothesis that serotonin is specifically involved in the control of carbohydrate consumption. However, one could argue that saccharin was not the correct flavour choice for the non-nutritive control solution in this study. The flavour of sweet substances may be innately associated with the consequences of carbohydrate consumption. Evidence to support this hypothesis has been provided by Nicolaidis (1981), who has shown that oral saccharin administration produces an immediate plasma hyperglycemic response in rats. Thus, rats may respond to saccharin as though it were a carbohydrate-containing solution (Montgomery & Burton, 1986; Mook, 1974). While the validity of this argument cannot be adequately dealt with by the data presented in this experiment, recently zimeldine has been shown to produce a supression in the consumption of a variety of flavoured solutions. Fluid deprived animals

Were given a two bottle choice between water and one concentration of sodium chloride (0.5, 1.0%), saccharin (0.05, 0.1%) or ethanol (2, 4%). Zimeldine (20 mg/kg) produced similar degrees of fluid suppression in all groups (unpublished observations). Thus, it would appear that ZIM has a general fluid suppressant action, that is independent of carbohydrates.

The amount of fluid consumed by animals has, in general, been found to be highly correlated to dry food intake (Fitzsimmons & LeMagnen, 1969). It may be possible therefore, that the general fluid suppressant action of zimeldine is an effect secondary to a reduction in food consumption. The significant difference in body weight between ZIM treated animals and controls would support this interpretation. This notion was examined in the following experiment.

EXPERIMENT 2

While the food reducing or anorexic effects of ZIM have not been systematically studied, there is some evidence to suggest that chronic ZIM treatment produces a weight reduction in humans (Simpson, Lawton, Watt & Tiplady, 1981; Gottfries, 1981). Non-depressed subjects attending a weight loss clinic received ZIM (2 x 100 mg/day) for an 8 week period. These subjects lost an average of 2.5 Kg of body weight, which was significant compared to controls (Simpson et al., 1981). Studies examining the efficacy of ZIM as an antidepressant, have reported significant weight loss (Aberg & Holmberg, 1979) or no changes in weight (Coppen, Rama Rao, Swade & Wood, 1979; Dewilde, Mertens & Gustafsson, 1983) following chronic treatment.

Within the animal literature, fluoxetine has been most extensively studied with regards to its specific effects on food intake. In an initial report, fluoxtine (10 mg/kg) significantly reduced food intake in 18 hour deprived rats and potentiated the anorexic actions of the serotonin precursor 5-HTP (Goudie et. al., 1976). The anorexic action of the drug was found to be of short duration, lasting approximately the first 2 hours of a 6 hour food access period. Similarly, Rowland, Antelman and Kocan (1982) reported that fluoxetine (10 & 15 mg/kg) significantly reduced food intake in 20 hour food deprived rats. During an 8 day treatment period no tolerance to

the anorexic effects of fluoxetine developed and animals
exhibited a significant body weight loss compared to
saline controls. Wurtman and Wurtman (1977) found that
fluoxetine (5 & 10 mg/kg) produced significant reductions
in food intake only during the first hour of access to
food in rats maintained on a schedule of 16 hours
deprivation. It should be noted that the drug appeared to
have a short duration of action and in some studies the
animals consumed sufficient food in the latter portions of
t'he test sessions to maintain normal food intake - an
unusual finding considering the extremely long half-life
of this compound (Goudie et al., 1976). In a very brief
report, Sugrue, Charlton, Mireylees and McIndewar (1978)
found that 30 mg/kg of ZIM reduced food intake by 54.3 %
in 18 hour food deprived rats; an effect which could be
blocked by methergoline (1 mg/kg). No attempt was made to
monitor fluid intake in any of these studies.

A more recent trend within the feeding literature has
been the use of "microstructural" analyses of the action
of anorexic agents. For example, Blundell and Latham
(1978) extensively studied the effects of a variety of
anorexic agents (amphetamine, pimozide, fluoxetine) in
free feeding animals using a paradigm in which food intake
was monitored continuously. This type of study has
produced a more detailed description of the temporal
patterns of meals, meal frequency and bout duration in
free feeding animals, and are considered to provide a more

accurate assessment of the types of changes in feeding induced by anorexic agents (Blundell & Latham, 1982; Fletcher & Burton, 1986). Therefore, modelled on this type of "microstructural" analysis, the following experiment was designed in order to assess the effects of an acute dose of ZIM on food, ethanol and water intake.

This study was carried out in two phases. In the first phase, high ethanol preferring rats were used as subjects. Based on the results of the first phase, a replication of the experiment was carried out using low ethanol preferring rats, whose main fluid of choice was water. The methods and procedure for both phases of this study were identical. The data were analysed in terms of zimeldine's effects on total food and fluid intake, the temporal patterns of intake as well as effects on bout frequency and duration.

METHOD

Subjects:

Fifty male Long Evans rats (Charles River, Canada) weighing between 125-150 grams at the beginning of the experiment were used. Rats were housed individually in standard stainless steel cages and were maintained on a 12 hour light-dark cycle. The light cycle changed at 8:00 p.m.-a.m. Fluids were presented in two Richter tubes mounted on the front of the cages. Standard rat chow and water were available ad libitum.

Procedure

Ethanol Screening: Following acclimatization to the animal colony, animals were screened for ethanol intake by presenting an ascending series of concentrations on alternate days in a free choice with water. Initially rats received access to a 2% (v/v) ethanol solution prepared from 95% ethanol diluted with tap water. On each subsequent ethanol presentation the concentration was increased by 1%. The position of the ethanol and water tubes was alternated daily in order to eliminate position bias. On the intervening water day, the animals had access to two tubes of water.

Once a final concentration of 8% ethanol was reached the schedule was switched to daily ethanol presentations and baseline intake was monitored for two weeks. Animals were handled and weighed every 2 days.

Drinkometer Procedure: Following the screening and baseline periods, rats were placed in operant chambers set up for continuous monitoring of food, water and ethanol consumption. Each operant box (Grason-Stadler rat chamber) was equipped with a single lever for food pellet delivery and two plastic drinking tubes fitted with steel ball-bearing spouts which were connected to Grason-Stadler drinkometer circuits. Each lever press resulted in the delivery of a single 45 mg standard Noyes pellet. Animals were not shaped to bar press for food. Those

animals which did not learn to lever press within one 24 hour period were eliminated from the study.

The cumulative number of lever presses and licks on the fluid dispensers were recorded on counters. In order to continuously monitor feeding and drinking behavior over a 24 hour period, all circuits were connected to a multi-pen recorder. The time, duration and frequency of individual food or drinking bouts, as well as the number of pellets consumed per food bout, were determined directly from the recording chart.

In order to avoid scoring inadvertent lever presses or closures of the drinkometer circuits as bouts, a minimum criterion was established for bout definition. In order to be scored as a bout, contact with the lever or drinking tube must have lasted a minimum of 18 seconds. Additional licks or bar presses within 5 minutes of the last event were counted as part of the same bout.

The amount of fluid consumed per bout was estimated by converting bout duration scores to volume equivalents by calculated calibration factors, based on the assumption that a constant volume of fluid was consumed per unit time. Thus the total volume of fluid consumed during the 24 hour period was redistributed among the individual drinking bouts, relative to the duration of each bout. The validity of the underlying assumption was supported by the constancy (for each drinkometer circuit) of the calculated calibration factor over days. In addition, the

ratio of lick counts/ml consumed was constant (for each drinkometer circuit) over days, indicating that little fluid spillage occurred during the 24 hour periods. If any drinkometer failed to yield a constant calibration factor (within a 10% error margin), data for the rat were dropped from the analysis. Of 22 rats run through the entire procedure, 3 were eliminated on this basis. An additional rat was eliminated due to equipment failure on test day. This resulted in group sizes of $n=8$ for the high ethanol preferring rats.(Group 1-HIGH) run in phase 1 of this study and $n=10$ for the low ethanol preferring rats (Group 2-LOW) run in phase 2.

Ethanol and water consumption were measured and fluids changed daily at 6 p.m., 2 hours prior to the onset of the dark cycle. Animals were maintained in the operant chambers for an 8-12 day period prior to testing.

Injection Period: Once stable baseline intake was established, each animal was treated with vehicle solution (2 ml/kg) on 2 consecutive days. This was followed by a test day where animals received ZIM (20 mg/2 ml/kg). All injections were given intraperitoneally, at 6 p.m.

RESULTS

The results for both groups of animals are presented concurrently. All statistical tests were within-group analyses. Analyses of Variance (ANOVA) with repeated measures were carried out using the statistical package BMDP2V.

Total Food and Fluid Consumption

Total food, ethanol and water consumption on the last vehicle injection day (baseline day) were compared to intake on the ZIM injection day (test day). The data for each group are presented in Table 1. The absolute amounts of ethanol consumed (gm/kg) as well as the mean ethanol preference ratio (calculated as percent of total daily fluid intake) are also listed. As outlined in the introduction, animals in Group 1 were selected for high ethanol preference, indicating that the largest portion of their daily fluid intake was consumed as ethanol. This group exhibited a mean ethanol preference ratio of $90 \pm 4\%$ on baseline day. No shift in this preference ratio was observed on test day. There was however, a 46 % reduction of ethanol consumption in terms of gm/kg ($t(7) = 7.05$, $p < 0.001$). There was also a marked 47 % decrease in total food consumption ($t(7) = 7.55$, $p < 0.001$). No changes in water intake were observed.

The animals in Group 2, initially selected on the basis of low ethanol preference exhibited a mean preference ratio of $24 \pm 6 \%$ on baseline day indicating

TABLE 1

Total Food and Fluid Consumption

	Group 1		Group 2	
	Baseline	Test	Baseline	Test
Food (pellets)	487±30	259±23 *	616±37	342±55 *
Water (mls)	2.9±1	2.1±0.9	30±3.7	18±3.8 *
Ethanol (mls)	31±2.9	17±1.9 *	8.6±1.3	7.4±1.1
Ethanol (gm/kg)	4.3±.48	2.3±.32 *	1.1±.17	.97±.16
Ethanol Preference	90±4%	87±6%	24±4%	35±6%

Data are expressed as group mean ± SEM.

* Significantly different from baseline day, by Students t-test for dependent samples.

that the major portion of their daily fluid intake was
consumed as water. There was no statistically reliable
shift in the ethanol preference ratio on test day
(t(9)=-1.7, p>0.05). Water consumption however, was
significantly reduced (t(9)= 4.82, p<0.01), as was food
intake (t(9)= 8.63, p<0.001). The decreases from baseline
were 40 % and 44 %, for water and food respectively.

Temporal Patterns of Food and Fluid Intake

In order to examine the temporal changes in intake
over the 24 hour baseline and test day periods, hourly
consumption of food, water and ethanol were collapsed into
4 hour time blocks. Time block 1 commenced at 6 p.m., and
represents group mean consumption during the four hour
period immediately following the vehicle or drug
injections. Lights were turned off at the midpoint of
time block 1 and were turned on again during time block 4.

Baseline and test day consumption across the 6 time
blocks for Group 1-HIGH are presented in Figure 4.
Baseline consummatory behavior followed a distinct pattern
with the majority of intake occurring during the dark
cycle. There was a strong diurnal reduction of
consumption during time blocks 5 and 6. On test day there
was a reduction in both food and ethanol intake during the
first 12 hours following the ZIM injection. Consumption
gradually increased during the latter part of the dark
cycle. However, animals showed a normal reduction during
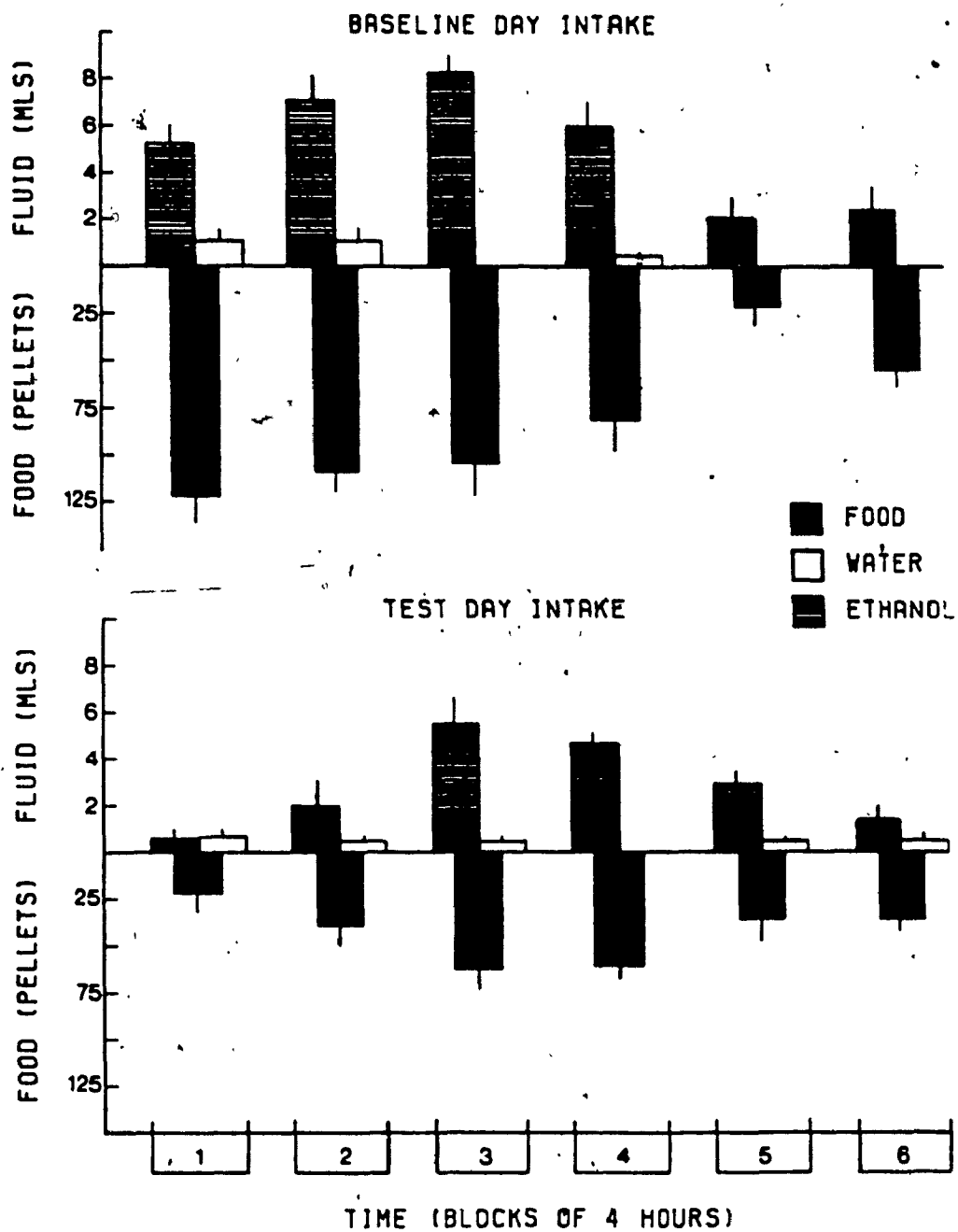the light cycle (time blocks 5 & 6). Water consumption

Figure 4. Temporal patterns of food, water and ethanol consumption for Group 1-HIGH, on baseline and test days.

was initially very low in this group and there did not appear to be any consistant changes due to ZIM treatment.

Statistical analyses (2 way ANOVA with repeated measures) on the days factor (baseline vs test days) and time factor (time blocks 1-6) for food, water and ethanol, confirmed this visual inspection of the data. The results are listed below:

Food: The analysis yielded a significant days effect $[F(1,7)= 59.54, p<0.001]$, time effect $[F(5,35)= 5.08, p<0.01]$, as well as a significant day x time interaction $[F(5,35)= 8.88, p<0.01]$. Post hoc (Tukey) tests indicated that test day food intake was significantly $(q(2,35)=3.89, p<0.01)$ below baseline during time blocks 1 to 3.

Water: No significant days or day x time interaction effects were found.

Ethanol: The analysis yielded a significant days effect $[F(1,7)= 57.92, p<0.001]$, time effect $[F(5,35)= 12.54, p<0.001]$ as well as a significant day x time interaction $[F(5,35)= 3.37, p<0.05]$. Post hoc (Tukey) tests indicated that test day ethanol intake was below baseline during time blocks 1 and 2 $(q(2,35)= 3.89, p<0.01)$.

The data for Group 2-LOW are presented in Figure 5. Baseline intake and the temporal distribution of food and fluid across the time blocks were very similar to those of Group 1. The majority of food and fluid were consumed during the dark cycle with a sharp decline in activity
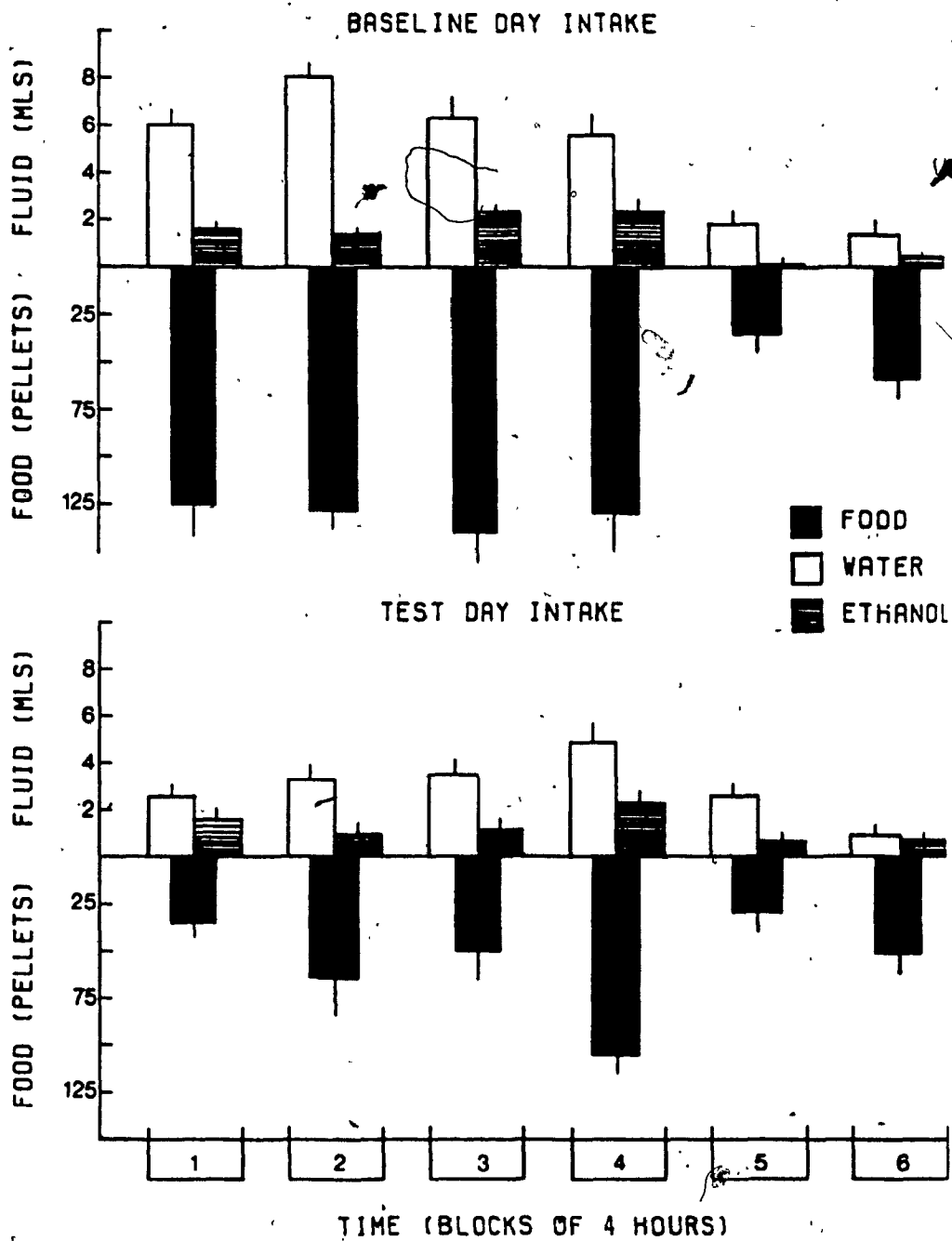
Figure 5. Temporal patterns of food, water and ethanol consumption for Group 2-LOW, on baseline and test days.

during time blocks 5 and 6. On test day, water and food intake appeared to be suppressed during the first three time blocks. Recovery occurred in time block 4, twelve hours after ZIM administration. The animals maintained a normal diurnal pattern of intake on test day. Statistical analyses of these data by ANOVA yielded results as follows;

Food: A significant days effect $[F(1,9)= 75.8, p<0.001]$, time effect $[F(5,45)= 11.28, p<0.001]$ and day x time interaction $[F(5,45)= 5.26, p<0.01]$ were found. Post hoc (Tukey) tests indicated that test day food intake was significantly below baseline during time blocks 1 to 3 $(q(2,45)= 3.82, p<0.01)$.

Water: The analysis yielded significant days $[F(1,9)= 21.9, p<0.01]$, time $[F(5,45)= 11.03, p<0.001]$ and day x time $[F(5,45)= 5.19, p<0.01]$ interaction effects. Post hoc Tukey tests indicated that test day intake was suppressed during time blocks 1 to 3 $(q(2,45)= 3.82, p<0.01)$.

Ethanol: No statistically reliable day or day x time interaction effects were observed.

Frequency and Duration of Bouts

The data for group mean frequency and duration of food and fluid bouts on Baseline vs Test day are presented in Table 2. Data were analysed by Students t-tests for dependent samples.

In Group 1-HIGH, ZIM treatment did not appear to affect food bout frequency $(t(7)= 1.35, p>0.05)$. Food

TABLE 2

Frequency and Duration of
Food and Fluid Bouts

	Bout Frequency		Bout Duration (Min)	
	Baseline	Test	Baseline	Test
GROUP 1				
Food	10±.71	8.6±.98	7.3±.77	4.9±.40 *
Water	5.3±1.4	4.1±1.3	0.47±.13	0.45±.14
Ethanol	11.6±1.4	7.9±.9 *	2.0±.30	1.8±.24
GROUP 2				
Food	12.3±1	9.4±.87 *	7.1±.62	5.6±.61 *
Water	17±1.4	12±1.8 *	1.6±.17	1.5±.26
Ethanol	6±1	6.2±1.1	1.1±.17	0.9±.11

Data are expressed as group mean ± SEM.

* Significantly different from baseline by Students t-test for dependent samples.

bout duration on the other hand, was significantly reduced
on test day (t(7)= 3.47, p<0.05). It would appear
therefore, that the reduction in food intake produced by
ZIM cannot be accounted for by a reduction in the number
of meals but rather is produced as a result of a reduction
in the size of individual meals. It is possible however,
that there was a rebound increase in the frequency of
meals during the latter part of the night cycle, thus
accounting for the overall lack of effect on total food
bout frequency. In order to test this hypothesis a food
bout frequency by time blocks analysis was carried out
using ANOVA with repeated measures. These data, shown in
Figure 6 (top panel) demonstrate that there was no rebound
increase in the number of food bouts. The analysis
yielded no significant days (F(1,7)= 1.82, p>0.2) or day x
time interaction effects (F(5,35)= 1.73, p>0.15). There
was a significant reduction in the number of ethanol
drinking bouts on test day compared to baseline (t(7)=
3.91, p<0.01).

The analyses of Group 2-LOW indicate a slightly
different pattern of results. There was a significant
reduction in food bout duration (t(9)= 2.91, p<0.02) as
well as frequency (t(9)= 2.49, p<0.05). A temporal
analysis of food bout frequency (Figure 6, bottom panel)
yielded a significant days effect [F(1,9)= 5.9, p<0.035].
Thus the strong food suppressant effects of ZIM,
particularly apparent in time blocks 1-3 (see Figure 5)

GROUP 1- HIGH

BOUT FREQUENCY

GROUP 2- LOW

⊡ VEHICLE
■ ZIMELDINE
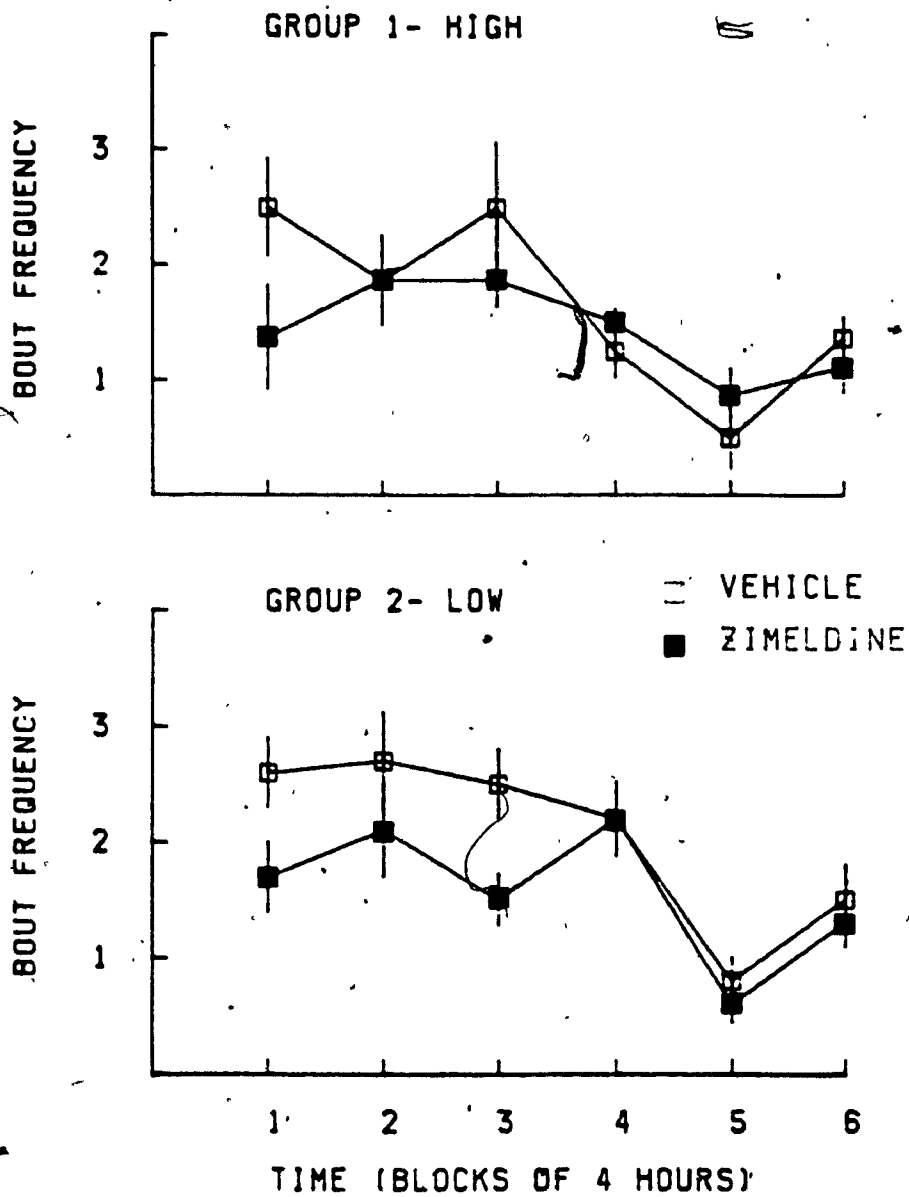
BOUT FREQUENCY

TIME (BLOCKS OF 4 HOURS)

Figure 6. Frequency of food bouts across the 6 time blocks, on baseline and test days, for Group 1 and Group 2.

can be accounted for by a reduction in the number and size
of individual meals. On test day there was also a
significant reduction in the number of water drinking
bouts (t(9)= 2.9, p<0.02).

DISCUSSION

Zimeldine treatment produced a significant reduction
in food intake. The reduction was very robust, and was
seen irrespective of whether the subjects were high or low
ethanol preferring animals. In both groups, the volume of
preferred fluid consumed was also reduced following ZIM
treatment. Thus, rats in Group-1 which normally consumed
ethanol as their fluid of choice, significantly reduced
consumption on test day. Contrary to previous research
(e.g. experiment 1) there was no reduction in the ethanol
preference ratio, indicating that rats did not consume
more water in order to compensate for the loss of fluid.
This lack of effect on the ethanol preference ratio was
highly unusual. While total fluid consumption was
decreased in the ethanol consuming group in Experiment 1,
there was a larger decrease in ethanol relative to water.
The very high ethanol preference exhibited by Group 1 in
this experiment, compared to those animals in Experiment 1
(see Figure 1) may account for these differences.
Similarly in Group 2, consumption of the most preferred
fluid, in this case water, was significantly reduced and
there was no compensatory increase in ethanol intake.

Overall, the temporal patterns of food and fluid
intake appeared to be tightly linked. Feeding, almost
without exception occurred in discrete bouts, separated by
long periods of inactivity. These food bouts were often
preceeded by a short fluid bout and followed by a slightly
longer bout of drinking. Kraly (1984) has stated that
"eating is a potent stimulus for drinking" and as such
drinking appears to be related to the patterns and amount
of food consumed. As mentioned previously; food related
drinking has been found to be highly correlated with the
amount of dry food eaten (Fitzsimmons & LeMagnen, 1969).
Under the influence of ZIM, there appeared to be little
change in this basic pattern of feeding and drinking.
While food and fluid appeared to be primarily suppressed
during the first 12 hours following drug administration,
the animals maintained a normal pattern of diurnal
behavior and no evidence of rebound increases were found.

These results would seem to suggest that ZIM has a
primary effect on food intake and that preferred fluids
are decreased by virtue of their normal association with
prandial drinking. Thus as food intake is suppressed,
fluid requirement is reduced. If this were the case, then
one would expect ZIM to suppress the intake of any fluid
that is presented in association with food. However, it
should be noted that several serotonergic anorexic agents
have been found to reduce both food and fluid intake.
5-HTP reduced food intake (Goudie et al., 1976), operant

responding for water or sweet milk reinforcement (Carter, Dykstra, Leander & Appel, 1978) as well as ethanol consumption (Zabik et al., 1985). The apparent general suppression of a wide variety of oral and operant behaviors raises serious questions about the specificity of serotonergic anorexics. As previously outlined, Blundell and his coworkers have extensively examined the effects of fenfluramine on meal initiation and duration. Blundell has maintained that while non-specific effects on behavior are not entirely ruled out with regards to 5-HT manipulations, the weight of evidence points to a specific role in satiety (Blundell & Latham, 1982; Blundell, 1984). In support of his hypothesis, Blundell has demonstrated that fenfluramine and fluoxetine suppressed total food intake by reducing meal size and eating rate rather than meal frequency. These data suggested that the drug specifically enhanced the processes which normally serve to limit the size of meals and left intact those processes responsible for meal initiation (Blundell, 1984). Zimeldine had a large and consistent effect on the duration of feeding bouts. In Group 1-HIGH, the suppression in food intake was entirely accounted for by a reduction in food bout duration. In Group 2-LOW, effects on both duration and frequency of food bouts were observed. Therefore, some support for Blundell's hypothesis is provided by the results of the present experiment.

EXPERIMENT 3

The previous experiments established that zimeldine produced a significant reduction in ingestive behavior, in terms of both fluid and food intake. While it would appear that specific aspects of feeding were disrupted, particularly the duration of feeding bouts, it is difficult to assess the nature of these changes. In general, feeding may be disrupted by a number of non-specific effects of a pharmacological manipulation; including the induction of a conditioned taste aversion (CTA), general malaise, disruption of motor coordination as well as a decrease in sensory processing (Blundell, 1984). While zimeldine has been shown to produce a potent CTA to a variety of flavoured solutions (Gill et al., 1986), this type of conditioning does not appear to play a role in reducing voluntary fluid intake.

Of particular relevence to the present investigation, is a consideration of serotonin's role in motor behavior. 5-HT has a well documented, complex role in motor behaviors, appearing to have both inhibitory and excitatory effects (Gershon & Baldessarini, 1980). The "serotonergic motor syndrome" consisting of hyperactivity, forepaw treading, lateral head weaving, ataxia, and straub tail, appears to be critically related to levels of 5-HT receptor stimulation (Green & Heel, 1985; Gerson & Baldessarini, 1980). While zimeldine has been shown to potentiate the 5-HTP induced serotonin syndrome, it

produces no such effects when administered alone (Ogren et al, 1981b). In addition, zimeldine has been found to be devoid of any capacity to directly stimulate 5-HT receptors by a series of behavioral tests and in vitro binding assays (Ogren et al, 1981b).

Anatomically, serotonin neurons are highly collaterallized with a diffuse and branched terminal network, and appear to tonically modulate multiple neuronal networks throughout the brain. Consistent with its anatomical organization, 5-HT has been implicated in a wide variety of behavioral processes including pain, feeding, sleep, sexual behavior and aggression (Messing, Pettibone, Kaufman & Lytle, 1978). Due to the scope and diversity of behaviors affected by 5-HT, Trulson and Jacobs (1979) suggested that 5-HT plays a general modulatory role in behavior, rather than a specific one, by controlling the level of general arousal. Arousal was defined behaviorally as stages along a sleep-wakefulness continuum as measured through electrographic procedures. These researchers demonstrated that level of arousal was highly correlated to serotonin dorsal raphe unit activiy. Consistent with these data, is Stricker's (1983) statement that 5-HT may play a general role in "the non-specific activational component of motivated behavior" rather than a specific one in feeding.

While it is unlikely that zimeldine produces motor activation, it may have important effects on arousal and

level of activity. Enhancement of serotonergic neurotransmission has also been reported to decrease locomotor activity in rats, however the conditions of testing (i.e. familiar vs novel environments) appear to influence the results (Gershon & Baldessarini, 1980). Consistently across both human and animal research zimeldine has been reported to produce little or no locomotor depression (Cott & Ogren, 1980). In one report, (Rockman et al., 1979a) animals were treated with zimeldine (20 mg/kg) for 5 consecutive days. Locomotor activity was monitored in an open field apparatus on days 1, 3 and 5, four hours following the drug injection. Following the first drug administration, the animals exhibited a slight, though significant, reduction in activity levels. This effect disappeared over repeated drug administrations. Since it has been shown that zimeldine suppressed fluid intake over chronic treatment periods (Gill et al., 1985), it seems unlikely that a slight motor deficit following the first dosing is responsible for the suppression of consummatory behavior. While it appears unlikely that zimeldine-induced sedation is responsible for the observed effects on consummatory behavior, it is not possible to predict the degree to which even a slight sedative action can inhibit motivated behavior. Therefore, in this experiment, the effects of zimeldine were examined in two measures of locomotor activity.

EXPERIMENT 3A

In this experiment zimeldine was tested for its effects on locomotor activity in an open field apparatus as described by Rockman et al., (1979a). Animals were habituated to the locomotor activity chambers prior to being tested.

METHOD

Subjects

Sixteen naive male Long Evans rats weighing 250-275 grams at the start of the experiment were used. Animals were maintained in our animal colony under the conditions described in Experiment 1.

Apparatus

Activity was measured in open field chambers. The boxes were constructed of wood and measured 45 cm square x 39 cm high. 4 intersecting photocells were placed inside the chambers, 3.8 cm above the floor, 15.2 cm apart. Locomotor activity was automatically registered on counters connected to the photocells.

Procedure

Animals were habituated to the open field chambers 10 minutes per day, for 6 days prior to testing. For the last 2 days of the habituation period, animals were injected with vehicle solution (2 ml/kg). Average activity was calculated and animals were assigned to one of 2 groups (n = 8/group); vehicle (2 ml/kg) or zimeldine

(20 mg/2 ml/kg). All injections were given

intraperitoneally, 4 hours prior to being placed in the

open field chambers.

RESULTS

The cumulative locomotor activity counts over the 10

minute testing period were 168 ± 22 and 146 ± 28, for the

vehicle and zimeldine treated animals respectively. There

was no significant difference between the two groups.

EXPERIMENT 3B

File and Wardhill (1975) have extensively documented

the effects of various drugs on exploratory behavior and

locomotor activity using a hole board apparatus. These

investigators have concluded that a 4 hole board is a

reliable and particularly sensitive measure of locomotor

activity. Therefore, in this study the hole board

apparatus was used to examine the effects of ZIM on

locomotor activity, in a novel environment.

METHOD

Subjects

Sixteen naive Male Long Evans rats (Charles River,

Canada) weighing 250-275 grams at the start of the

experiment were used. Animals were housed singly in

stainless steel cages in a temperature and humidity

controlled environment. Food and water were available ad

libitum.

Apparatus

The hole board was constructed according to the specifications of File and Wardhill (1975). The box was constructed of wood with a floor 66 x 56 cm and walls 47 cm high. The interior of the box was painted black. Four equally spaced holes were placed in the floor. Objects, including an aluminum box, tissue paper, soap and a glass jar containing paper chips were placed beneath the holes.

Procedure

The animals were handled daily for 1 week prior to testing. On test day, the animals were divided into two groups (n = 8/group) and treated with either vehicle (2 ml/kg) or zimeldine (20 mg/2 ml/kg), intraperitoneally. Injections were given 2 hours prior to the test. Animals were placed in the center of the hole board and observed by a single observer for a 10 minute period. The observer was blind to the treatment each animal had received. A general activity measure for each animal was determined by counting the total number of head dips, as well as rearing, crossing and grooming. In order to score crossing the box was divided into 4 quadrants. A crossing was scored only when the animal had placed all four paws into the next quadrant. The total time spent head dipping was recorded on a stop watch. A head dip was scored only when the animal's eyes disappeared beneath one of the holes.

TABLE 3

Hole Board Activity

	Saline (n=8)	Zimeidine (n=8)
Grooming	6.5 ± 1.6	7.1 ± 1.6
Crossing	26 ± 4	28 ± 4
Rearing	33 ± 3	29 ± 5
Head Dips	10.2 ± 3.3	4.5 ± 2
Time Spent Head Dipping (seconds)	18.4 ± 7	7.3 ± 3

RESULTS

The results were analyzed using Students t-tests for independent samples. It is apparent from the data in Table 3 that in Long Evans rats zimeldine produced no locomotor deficit as measured by crossing or rearing. ZIM appeared to reduce the number of head dips, however there was no statistically reliable difference between the groups ($t(14)= 1.54$, $p>0.1$). Similarly, there was no difference between the groups in terms of the seconds spent head dipping ($t(14)= 1.49$, $p>0.1$).

DISCUSSION

Zimeldine, tested under the conditions described in both experiments, had no significant effect on activity levels. Thus it would appear that the drug does not have any overt sedative actions. These results do not preclude the possibility that zimeldine affects either some specific aspects of motor activity not measured in the paradigms used here or the performance of more complex motor tasks. However, it is apparent from these data that gross locomotor deficits are not likely to be responsible for the changes in consummatory behavior observed in the previous experiments.

EXPERIMENT 4

As described in Experiment 2, zimeldine appeared to have a significant anorexic action which included a general suppressant effect on fluid intake. The most consistent factor which accounted for the decrease in food intake, was a reduction in the size of individual meals. In order to further examine the effects of ZIM on meal duration and size, the following study was carried out using a paradigm where animals were presented with a single meal of highly palatable Noyes sucrose reward pellets, divided into multiple segments. ZIM's effects on the initiation of feeding as well as eating rate were determined. In the first phase of this study, a group of rats was given the opportunity to obtain a total of 34 Noyes pellets presented in 17 segments. Based on the results obtained, a second group of rats were run where 66 pellets were presented in 33 segments.

METHOD

Subjects

Sixteen male Long Evans rats (Charles River, Canada) weighing 250-275 grams, were used as subjects in this experiment. The rats were housed singly in stainless steel cages in a humidity and temperature controlled environment. Food and water were available ad libitum, in the home cages.

Apparatus

Specially equipped feeding chambers, described by Wise and Raptis (1985) were used for training and testing the animals. The boxes, constructed of aluminum with a metal grid floor, measured 25 x 25 cm. The automatic feeding dispenser consisted of a circular aluminum platter in which 36 food cups were drilled. The platter was indexed into the chamber one food cup at a time, by rubber drive wheels pulled against the cirumference of the platter by a solinoid. The system was controlled by a timer.

Procedure

Animals were trained to eat sucrose pellets during daily 20 min feeding sessions. Under the first feeding regimen (Group 1), animals were presented with 17 meal segments, each consisting of 2 pellets. Each segment was automatically introduced into the chamber, for 36 sec at 72 sec intervals. In the second regimen (Group 2), 33 meal segments were presented at 36 sec intervals. For both groups, the latency to initiate feeding as well time taken to eat both pellets (duration) in each segment were measured using two stop watches connected in series. The first stop watch was activated with the entry of the food cup into the chamber. This watch was stopped (providing the latency score) and the second activated following oral contact with the food. The second watch was stopped when both pellets in each segment had been removed from the food cup (duration score). If an animal failed to

initiate feeding on any given segment a maximum latency score of 36 sec was assigned. If any pellets were missed on any given segment, a maximum duration score of 36 sec was assigned. The animals in both groups were trained daily for a 3 week period prior to testing. Initially 10 animals were trained under the 17 segment condition. However, as the training period progressed, 4 of these animals learned to pull the next food cup into the chamber, thus consuming the pellets for the next trial ahead of schedule. These animal had to be eliminated from the study leaving a final group size of 6. None of the animals in the 33 segment condition learned to turn the food platter (n=6).

Following the training period animals were treated with vehicle solution (2 ml/kg) for 2 consecutive days followed by a test day where they received zimeldine (20 mg/2 ml/kg). All injections were given intraperitoneally, 2 hours prior to the feeding session. Latency and duration scores on the last vehicle injection day were compared to drug day. Thus each animal served as its own control.

RESULTS - GROUP 1

As outlined in the procedure, animals were not food deprived at any time during this experiment. Although food was freely available in the home cages, animals quickly learned to eat the sucrose pellets during the daily feeding sessions. As shown in Figure 7, baseline

latency scores across the 17 meal segments were very low (approx 1 sec) and all animals initiated and completed each segment of the meal. On test day, the animals appeared to initiate feeding during the first 6 segments normally. However, in the later trials the animals failed to respond to the introduction of new-meal segments. A 2-way ANOVA on the latency scores with treatment (vehicle vs drug) and trials (segments 1-17) factors was carried out. The analysis yielded a significant main effect for treatment [$F_{(1,5)}=40.66$, $p<0.01$], trials [$F_{(6,80)}= 5.8$, $p<0.001$] and a treatment x trials interaction [$F_{(6,80)}= 5.48$, $p<0.001$].

On the vehicle injection day animals consumed both pellets in each segment very quickly (approx 2-4 sec). On test day all animals consumed both pellets in each segment, up until segment 10. Thereafter, some animals failed to initiate feeding, and duration scores could not be assigned. However, for illustrative purposes, the mean duration scores for those animals still continuing to respond on the later trials were calculated and the data was plotted in Figure 8. Due to the problem of missing duration scores for those animals which did not initiate feeding on the later trials, no statistical analysis was carried out on the data presented in Figure 8.
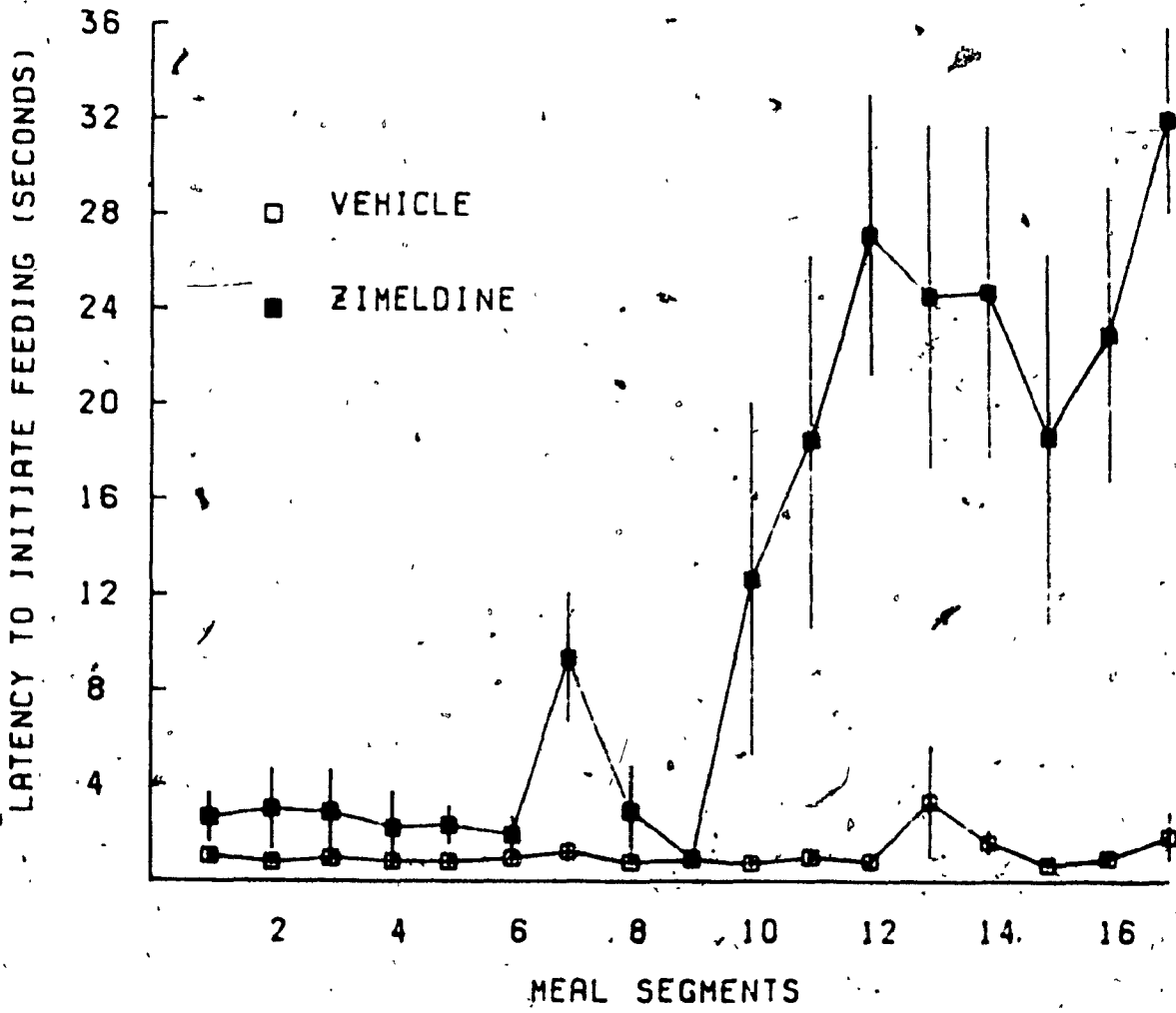
Figure 7. Latency to initiate feeding across 17 meal segments for those animals in Group 1, on baseline and test days.
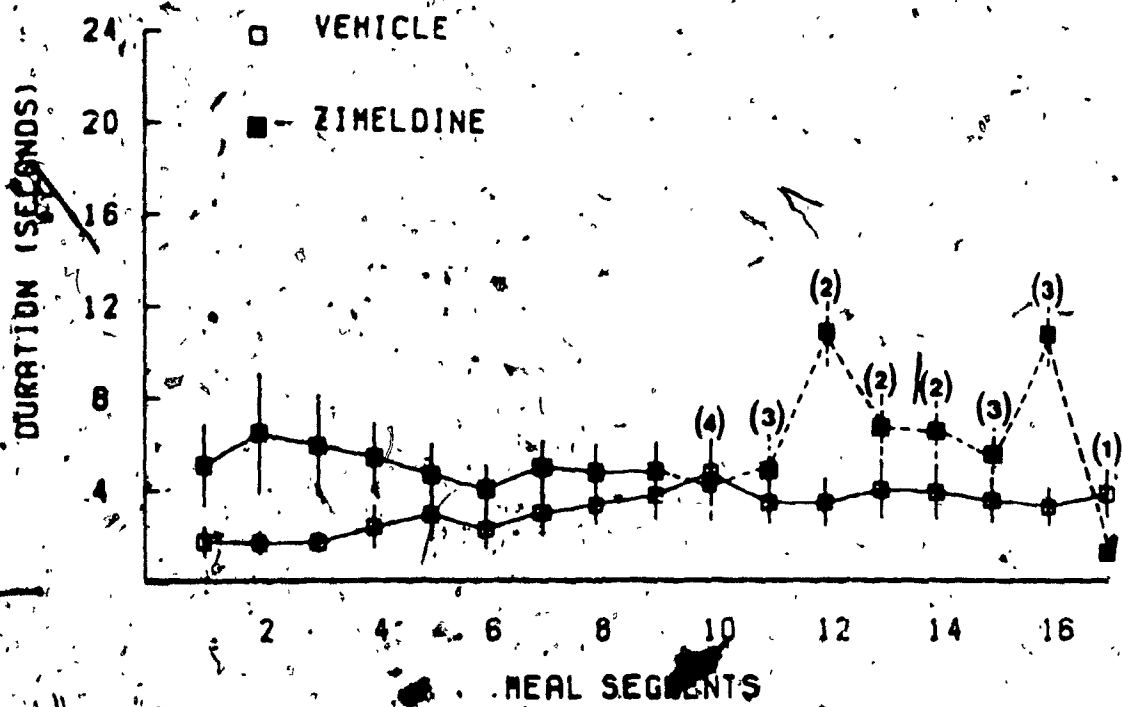
Figure 8. Mean duration scores for animals in Group 1, on
baseline test days. Numbers in brackets above data
points 10-17 on test day, represent number of animals on
which the mean is based.

Overall, zimeldine treated animals initiated feeding during the first meal segments. However, in the later trials, the animals failed to consistently respond to the introduction of new meal segments, and most animals had stopped feeding by the end of the session. This pattern of changes suggest that under drug treatment, "satiation" occured as the meal progressed. On the other hand, one could also argue that zimeldine produced a "motor deficit" which reduced the ability of the animal to maintain responding over multiple segments. However, if this were the case, perhaps one would expect a gradual increase in the response latency and duration scores across segments rather than an abrupt cessation of responding. While the data for the group as whole (Figure 7) appear to show a gradual increase in the latency scores over segments, this is not a true representation of the animal's performance. The data for individual animals in Group 1 are presented in Figures 9-11. The majority of animals appeared to abruptly cease responding following the consumption of several meal segments. Overall duration scores for those segments on which the animals initiated feeding appeared relatively normal. Informal observation of the animals supports the inference that the drug treatment reduced the animal's motivation to feed. On baseline days, the animals remained close to the food cups and nosed them continuously, engaging in little exploratory activity.
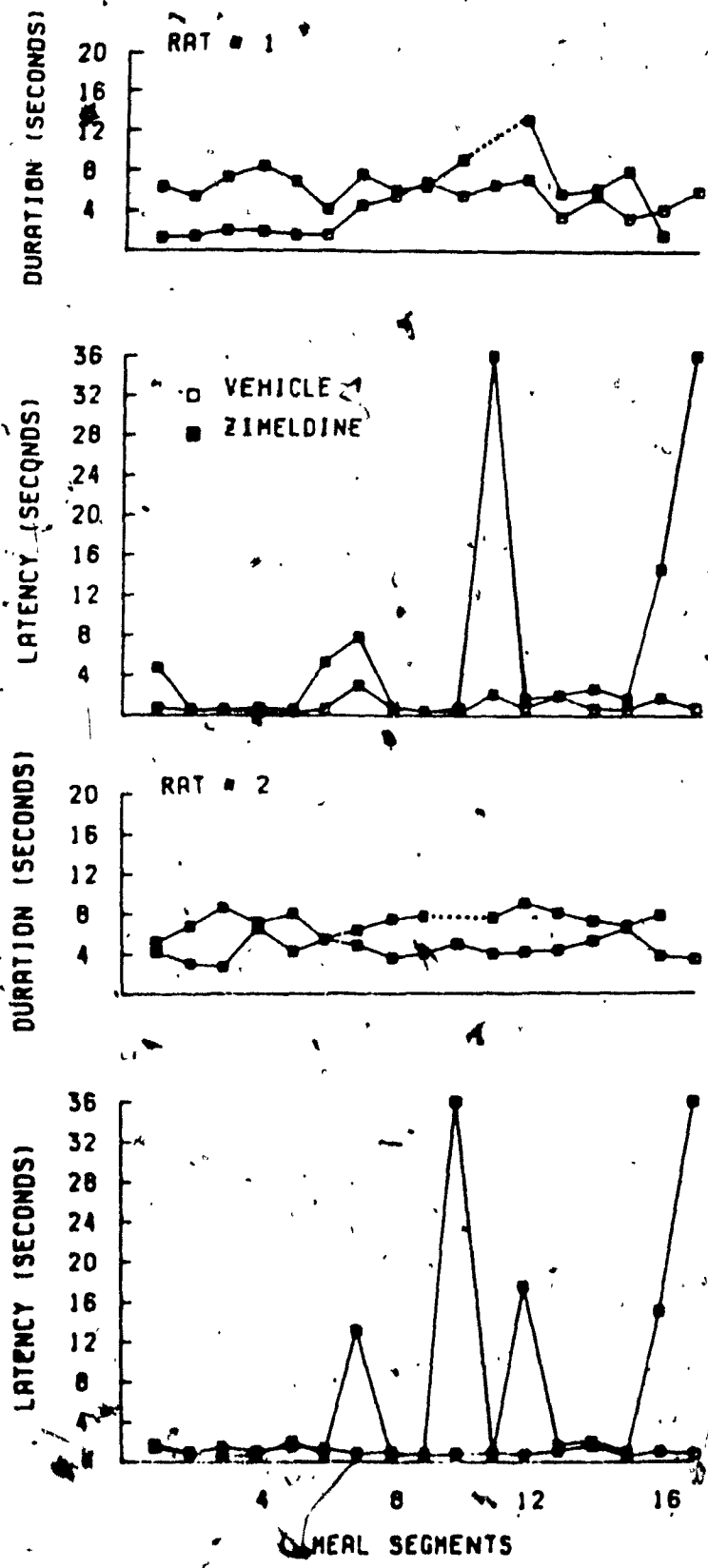
Figure 9. Latency and duration scores for rats 1 and 2, Group 1. For duration scores, dotted lines represent segments on which animals failed to initiate feeding.

Figure 10. Latency and duration scores for rats 3 and 4, Group 1. For duration scores, dotted lines represent segments on which animals failed to initiate feeding.
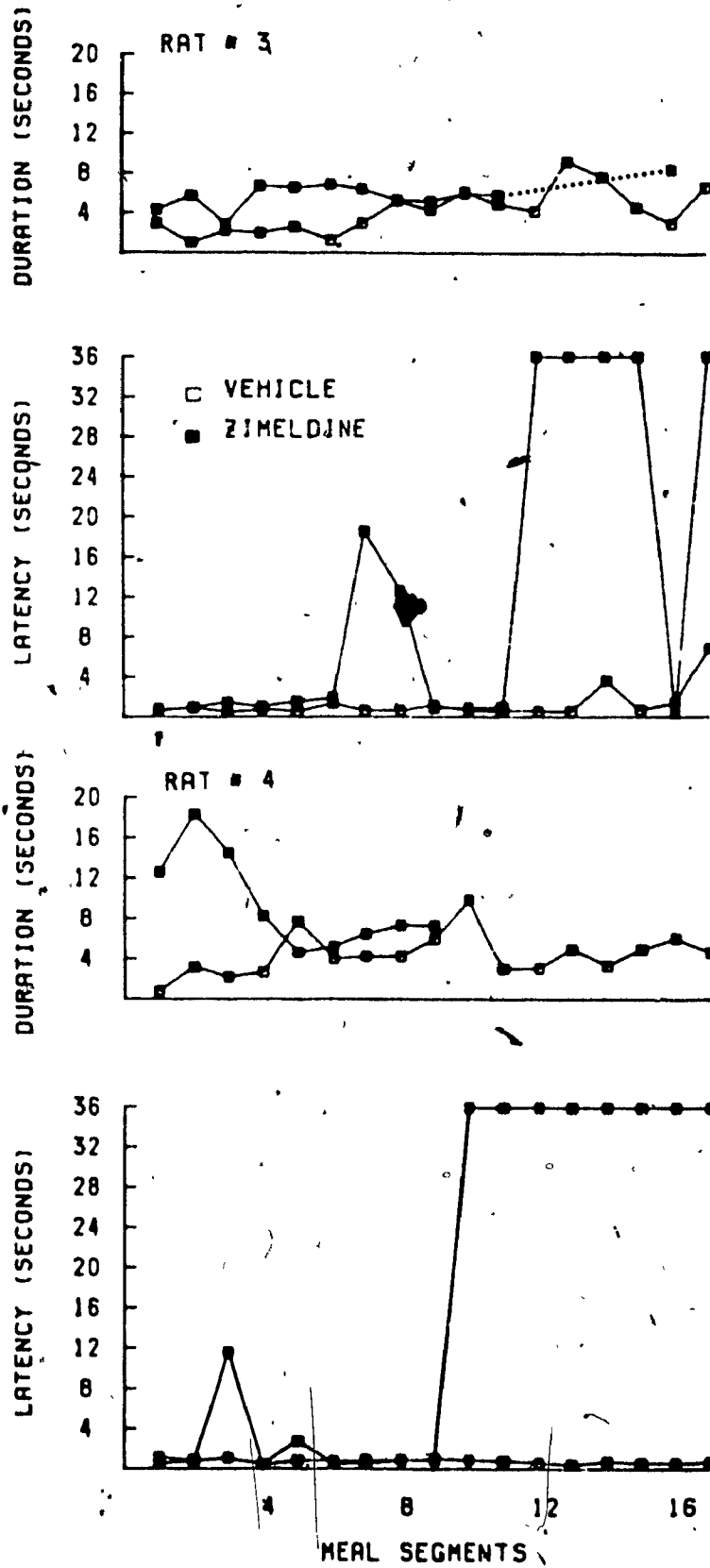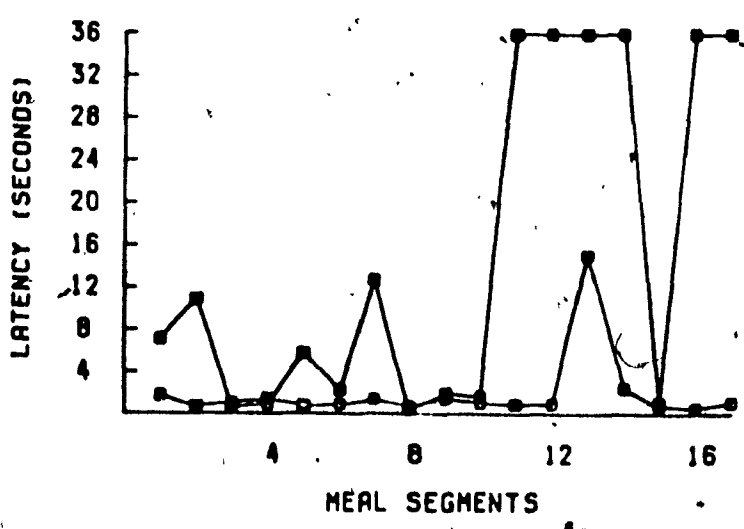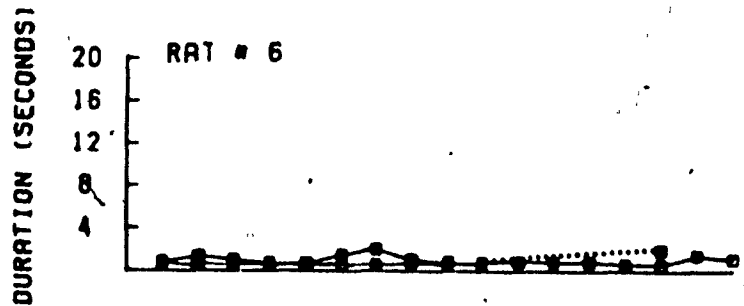
Figure 11. Latency and duration scores for rats 5 and 6, Group 1. For duration scores, dotted lines represent segments on which animals failed to initiate feeding.
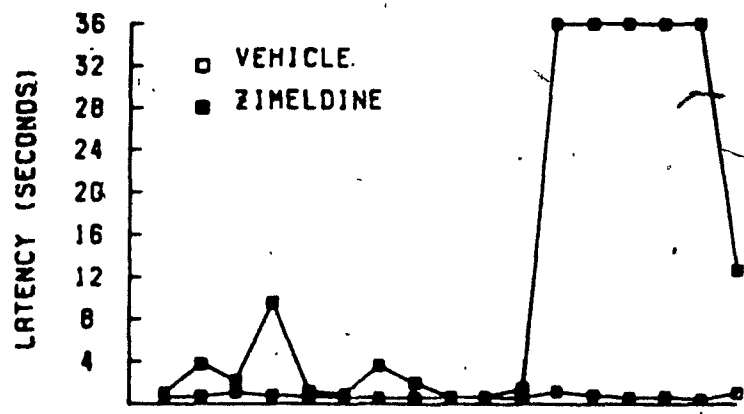
In contrast, on test day, the animals failed to nose the food cups and spent a great deal of the time between segments exploring and grooming. It should be noted that under vehicle treatment the animals in Group 1 maintained consistently low latency and duration scores across the 17 meal segments, not appearing to satiate. In order to further examine the notion that zimeldine treatment enhanced the onset of satiety, the second phase of this study was carried out as described in the prodedure section. Group 2 was given the opportunity to respond to 33 meal segments.

RESULTS - GROUP 2

The latencies to initiate feeding over the 33 segments on vehicle and drug days are presented in Figure 12. A two-way ANOVA with repeated measures yielded significant treatment $[F(1,5)= 67.3, p<0.001]$; trials $[F(32,160)= 12.37, p<0.001]$ and treatment x trials interaction $[F(32,160)= 2.72, p<0.01]$ effects. The data for individual rats are presented in Figures 13-15.

As shown in Figure 12, vehicle treated rats failed to maintain responding across all the meal segments, thus appearing to satiate. Under zimeldine treatment the shape of the curve appeared to be similar, except that it was shifted to the left, such that responding ceased after the consumption of fewer meal segments.
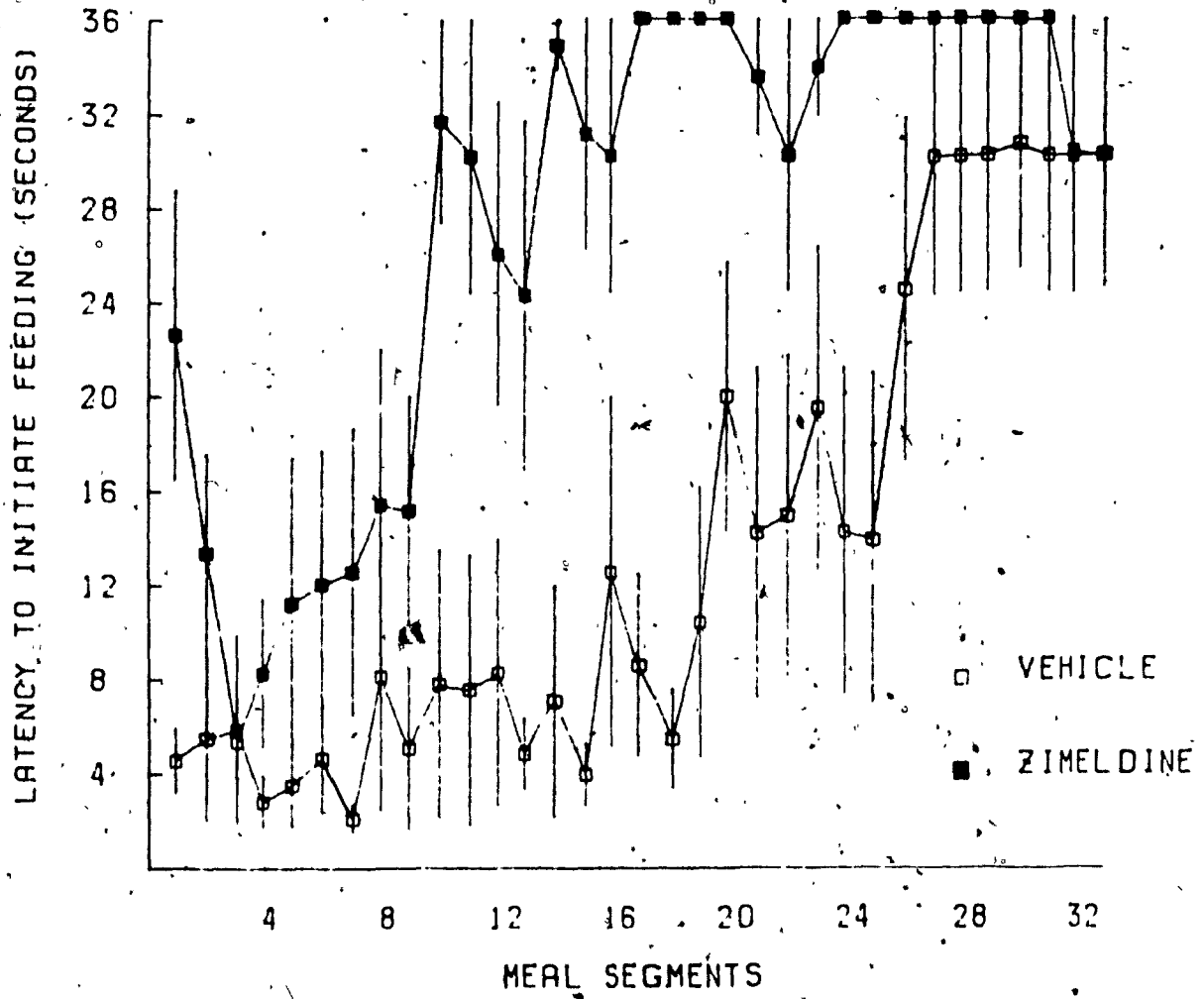
Figure 12. Latency to initiate feeding across 33 meal segments for those animals in Group 2, on baseline and test days.
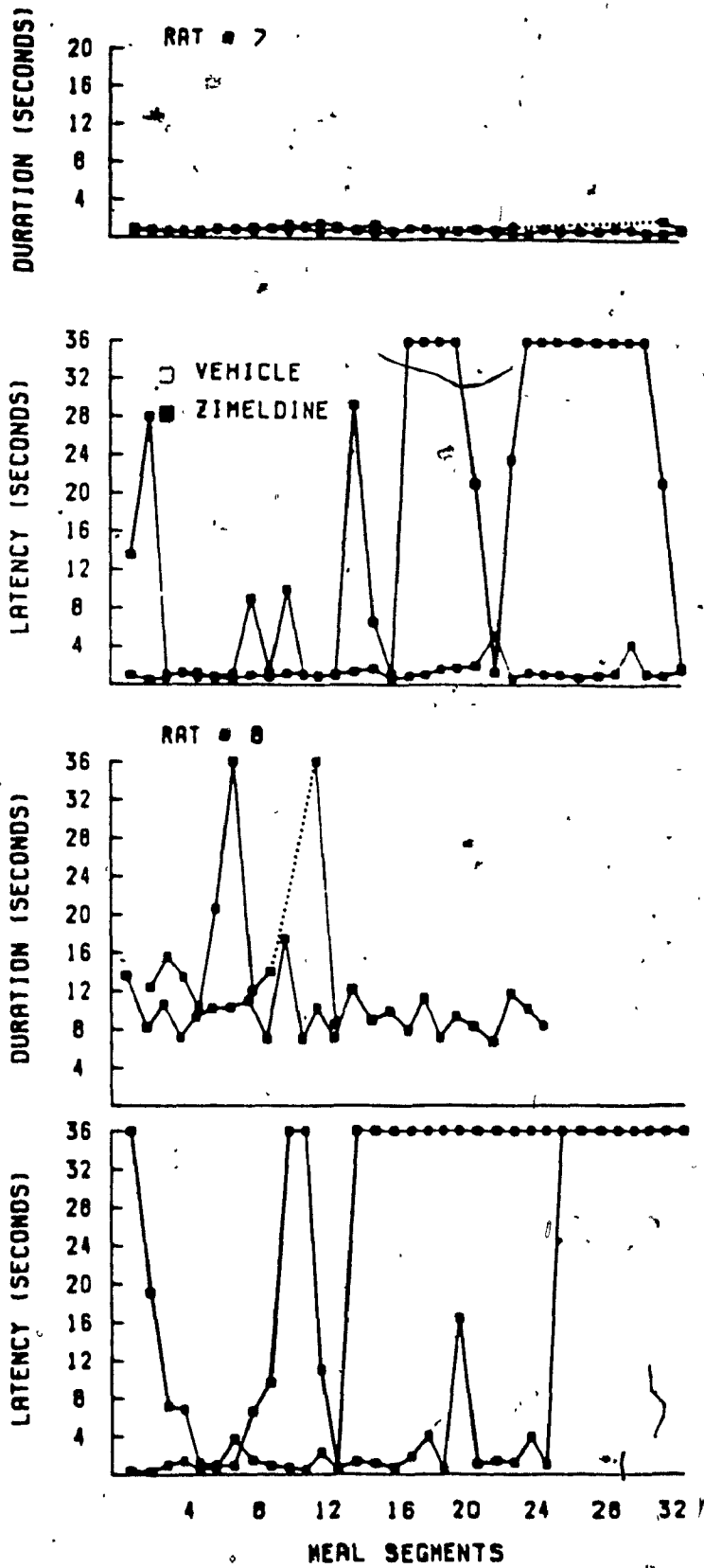
Figure 13. Latency and duration scores for rats 7 and 8, Group 2. For duration scores, dotted lines represent segements on which animals failed to initiate feeding.
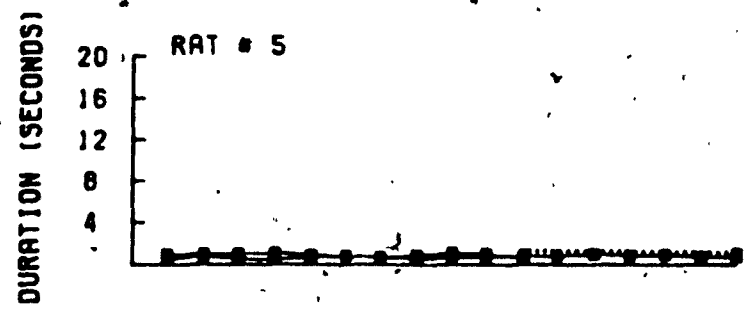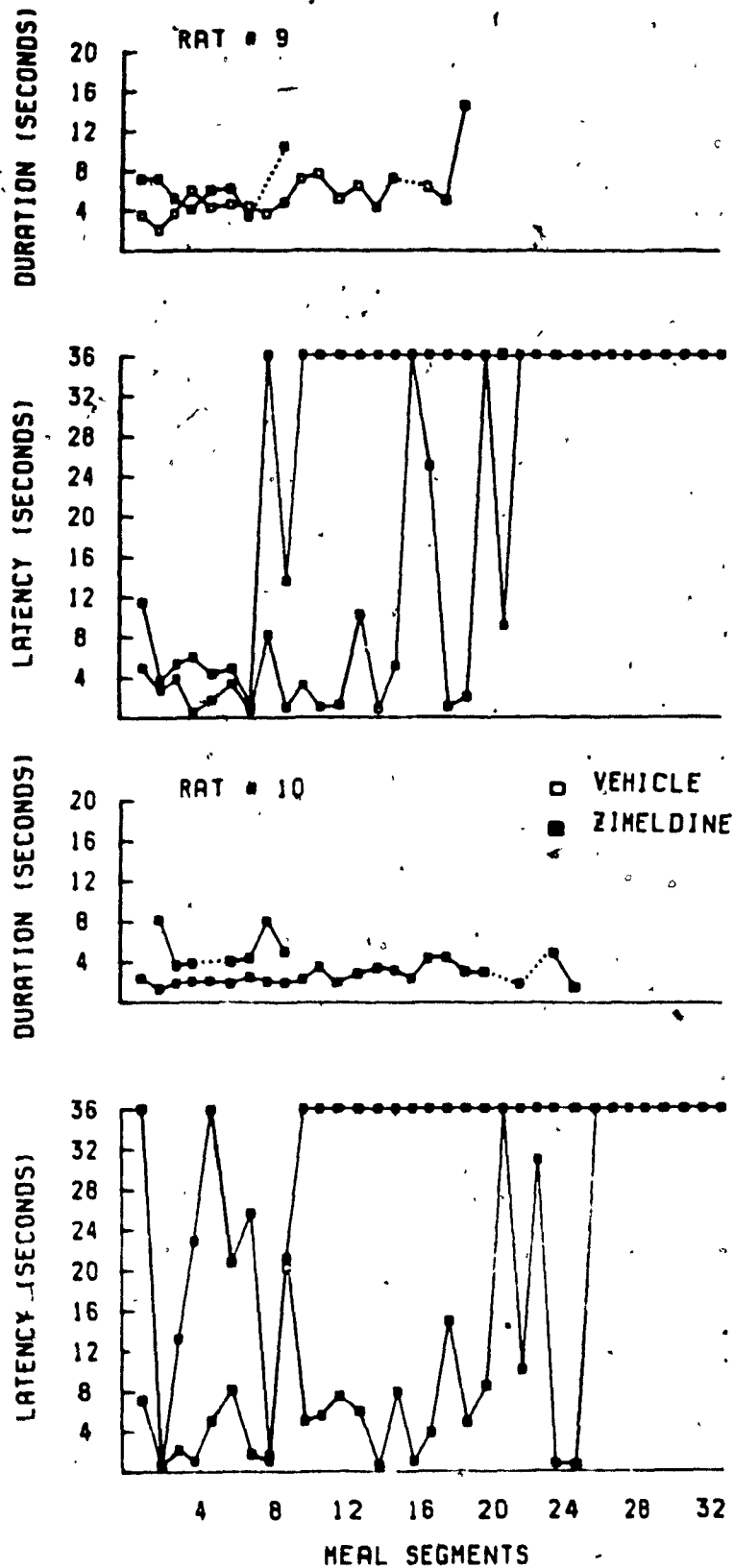
Figure 14. Latency and duration scores for rats 9 and 10, Group 2. For duration scores, dotted lines represent segments on which animals failed to initiate feeding.
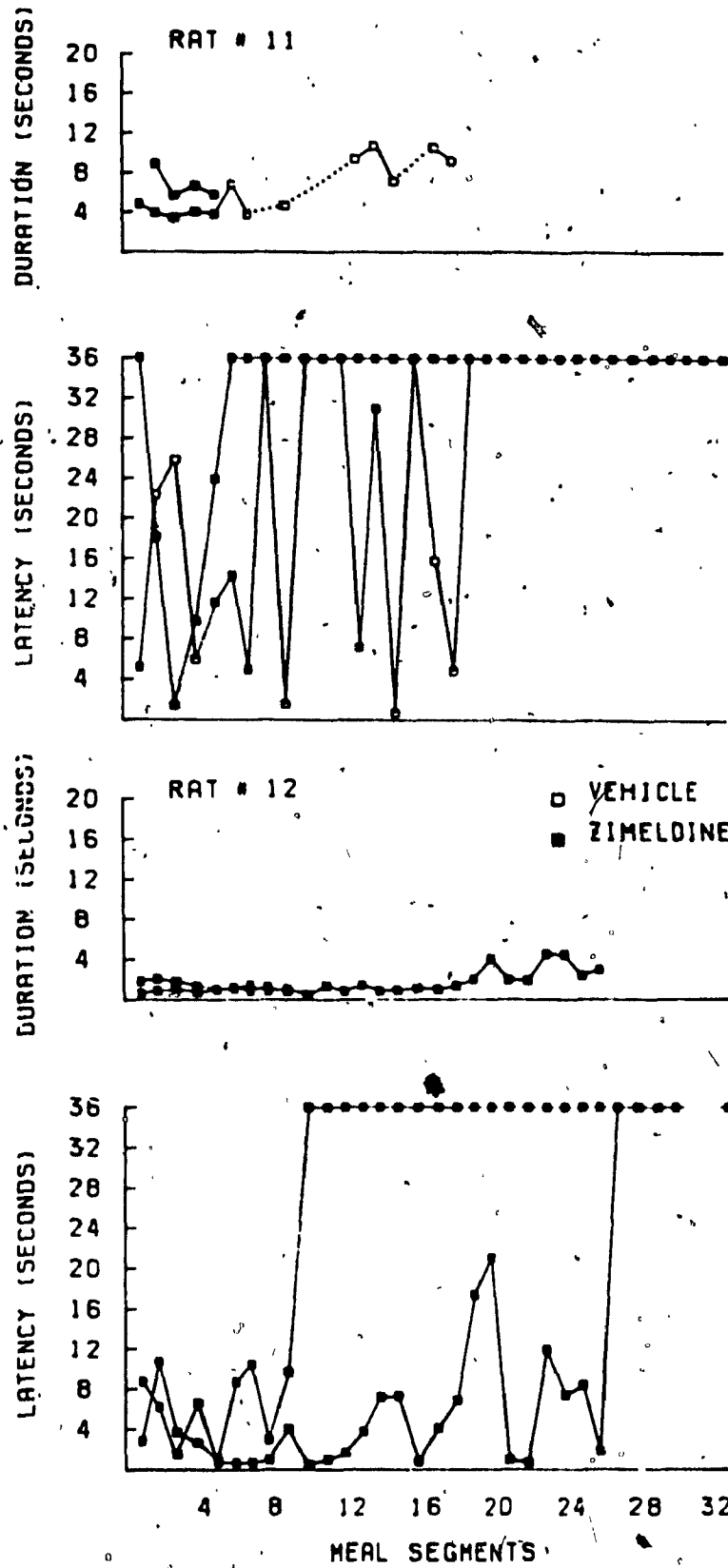
Figure 15. Latency and duration scores for rats 11 and 12, Group 2. For duration scores, dotted lines represent segments on which animals failed to initiate feeding.

DISCUSSION

There were several notable differences between Groups 1 and 2 in terms of baseline behavior on the vehicle injection day. First, the overall latencies to initiate feeding appeared higher in Group 2 (compare vehicle treated animals in Figures 7 and 12). This may have been a reflection of the different presentation schedules in effect between the two regimens (i.e. animals responded every 36 seconds in the 33 segment condition as opposed to every 72 seconds in the 17 segment condition). This change in schedule resulted in both a higher density of reinforcement (i.e. more pellets were consumed in a shorter time period) as well as a higher response demand. Second, in Group 1 (Figures 7-8), vehicle treated animals did not appear to satiate and displayed very short latency and duration scores over the entire session. However in Group 2, there is a clear indication that satiation occurred over meal segments. When examining the response patterns of individual rats in Group 2 (Figures 13-15), normal satiation appeared to be typified by an increase in sporadic responding, followed by cessation of feeding altogether. However, on trials that animals did initiate, they consumed both pellets at a normal rate. Thus, responding appeared to be all or none and no gradual increases in either the latency or duration scores were noted. The most salient feature of normal satiation in this paradigm, therefore, appeared to be the failure to

initiate responding to the introduction of new meal segments, rather than a gradual slowing of the rate of eating. Once feeding ceased, the animals engaged in exploratory activity, grooming and finally resting.

Under zimeldine treatment animals in both groups responded to the introduction of the first few meal segments. This was followed by sporadic initiation and finally cessation. However, animals ceased responding after the consumption of fewer meal segments (in both groups 1 and 2), suggesting that the drug enhanced the onset of satiety. There is some evidence that animals failed to respond to the introduction of the first meal segment. This was observed in Rats 8, 10 and 11 of Group 2. This failure to initiate was observed in 3 rats out of a total of 12, and therefore did not appear to be typical of ZIM's effects.

These data support and extend the data obtained in Experiment 2. It is clear that ZIM has potent inhibitory effects on feeding behavior. In both studies, the drug appeared to reduce meal size. These data provide some support for the hypothesis that serotonergic manipulations enhance the processes which mediate the onset of satiety.

GENERAL DISCUSSION

Zimeldine significantly reduced the consumption of solutions containing ethanol, dextrose and saccharin. In addition, zimeldine treatment reduced total fluid consumption and body weight gain. The second experiment demonstrated that zimeldine had a potent anorexic action, which was observed in both high and low ethanol preferring rats. The most parsimonious explanation for these data is that zimeldine produced a primary reduction in food consumption with secondary decreases in the consumption of fluids most closely associated with prandial drinking. It would appear therefore, that zimeldine's effects on ethanol consumption may be mediated through global effects on consummatory behavior.

The mechanism underlying these changes in feeding is of considerable theoretical interest. As outlined previously, the interpretation of behavioral changes induced by serotonergic manipulations has been a matter of some debate, particularly with regards to their specificity for food and fluid intake (Blundell, 1984). As demonstrated by Trulson and Jacobs (1979), the serotonin system appears to have an important influence on arousal, orientation to stimuli and level of general activity. Since zimeldine failed to significantly alter open field activity or exploratory activity, as demonstrated in Experiment 3, it appears unlikely that sedation accounts for the inhibitory effects of zimeldine on food and fluid

consumption. Recently, Montgomery and Burton (1986)
reported that systemic administration of 5-HT, in addition
to reducing food intake, also reduced the consumption of
and preference for sucrose, saccharin and sweet milk
solutions, while increasing the consumption of quinine,
saline and citric acid solutions. These results appeared
to rule out non-specific effects on behavior since there
was a differential effect on fluid intake, depending on
the flavour of the solution. These results have been
interpreted to suggest that 5-HT reduced the "incentive
value" of food-related stimuli (Montgomery & Burton,
1986a). Recently, zimeldine has been shown to produce a
differential suppression of water compared to the
consumption of various concentrations of saccharin in
fluid deprived rats (Gill & Amit, 1986). Zimeldine (2.5,
5, 10 & 20 mg/kg) produced a dose dependent suppression in
the intake of all solutions. However, consumption of the
highest and most preferred concentration of saccharin was
significantly more affected than that of the lowest
saccharin concentration or water. Taken together, these
data suggest that the deficits in food and fluid intake
produced by serotonergic manipulations such as zimeldine,
may result from specific changes in the "palatability" of
consumed substances.

Acknowledging the inherent difficulty in interpreting
the nature of changes in behavior produced by
pharmacological manipulations, Blundell and his colleagues

have attempted to deal with the problem, by providing a
more detailed analysis of consummatory behavior (Blundell
& Latham, 1982). The use of "microstructural" analyses
have been particularly important in relation to the
motivational aspects of consummatory behavior. Stellar
and Stellar (1985) stated that motivated behavior is goal
directed behavior which is "dependent upon specific states
of arousal or drive of the organism". In this schema,
feeding behavior is a motivated behavior which is under
multifactorial-control, with a variety of internal,
external and conditioned stimuli, contributing to the
initiation, maintenance and cessation of the behavior
(Stellar & Stellar, 1985; Blundell & Latham, 1982). The
processes which stimulate the onset of eating, i.e.
"hunger", maintain feeding once it has begun i.e.
"appetite" or "reward" and those which terminate eating
i.e. "satiation", have been proposed to correspond to
different "motivational states" and to be mediated through
different physiological and neurochemical events in the
brain (Blundell, 1984; Smith, 1982b). Thus, if feeding
can be viewed as a sequence of discrete behaviors, the
influence of various pharmacological manipulations should
be determined in relation to these different behavioral
and motivational states. The terms "hunger and
satiation" have been operationalized through a variety of
experimental measures, (e.g. latency to initiate feeding,
frequency and duration of feeding bouts, rate of eating,

interbout interval, etc). Some attempt to analyze the
effects of zimeldine in these terms has been made in the
present investigation. In Experiment 4, zimeldine reduced
the consumption of highly reinforcing sucrose Noyes
pellets, in a manner which suggested that the drug
enhanced the onset of satiety. As shown in Experiment 2,
zimeldine appeared to produce its most consistent effects
on feeding through a reduction in the duration of feeding
bouts. Thus, animals terminated feeding after the
consumption of fewer food pellets. These data would
appear to support the work carried out by Blundell and
coworkers (1978, 1982) which demonstrated that many
serotonergic manipulations affect the amount of food
consumed per meal, rather than meal frequency. However,
in Group 2-LOW, Experiment 2 (Figure 6) there was also a
significant reduction in the frequency of food bouts.
The term satiation has been defined as the "cessation of
feeding due to the consequences of feeding" (Blundell,
1984). ZIM, while decreasing the latency to termination
of feeding, also appeared to alter the subsequent
initiation of feeding. Further examination of zimeldine's
effects on satiation is clearly called for.

Perhaps it is pertinent at this point to suggest that
while the use of the construct, "satiation", has heuristic
value, it is basically a descriptive term. The process of
satiation can be described behaviorally, however it is
puzzling phenomenon which cannot be easily explained in

physiological terms. Nicolaidis (1981) refers to
satiation as a pre-absorpive event, wherein the cessation
of feeding occurs before nutrients are absorbed. The
signals which induce satiation therefore, do not appear to
arise as a consequence of nutrient repletion per se, which
necessarily must occur in the post-absorptive period
following food ingestion. Fantino (1984) suggested that
"satiation" is a process related to "negative alimentary
alliesthesia". This term has been used to denote the
change in the hedonic or reinforcing aspects of taste,
which result from the stimulation of internal sensors
(Fantino, 1984; Waldbillig & O'Callaghan, 1980). Fantino
(1984) proposed that as feeding proceeds, signals from
various peripheral (visual, olfactory, oral and
gastrointestinal) sensors are relayed to the brain through
neural and humoral pathways. These signals, following
integration in the hypothalamus, produce an alteration in
the rewarding properties of food. Numerous reports have
emphasized the possible relationships between satiation
and reward (Fantino, 1984; Smith, 1982b; Wise & Raptis,
1985). Smith (1982b) suggested that "reward" has both
immediate as well as delayed effects on feeding. The
immediate effect guides feeding once it has begun, and is
related to the palatability or pleasure derived from a
food item. The delayed effect of "reward" is one which
produces changes in subsequent feeding. Thus, a
pharmacological manipulation, such as zimeldine which

appears to reduce the size of individual meals, and in
some cases the frequency of meals, may be producing its
effects by reducing the palatability or rewarding
properties of food and fluids. However, this is highly
speculative at the present time. This discussion however,
points out the difficulties inherent in interpreting
changes in feeding behavior as well as the conceptual
difficulties associated with the use of terms such as
hunger, reward and satiation.

As discussed in the introduction to this thesis,
serotonin has been proposed to modulate food and fluid
through multiple sites of action. One site is directly in
the brain where it may affect the release of a putative
satiety agent (CCK or CRF). Serotonin may also act by
reducing the consumption of carbohydrates, indirectly
through an insulin mediated alteration in plasma amino
acid patterns, and in the periphery to inhibit the rate of
gastric clearance. Peripheral sites of action have also
been implicated for serotonergic compounds that alter
ethanol intake (Zabik et al., 1985). Similarly, in
various models of feeding control currently discussed
within the feeding literature (see Nicolaidis, 1981,
Stricker & McCann, 1985, Fantino, 1984) these same factors
(i.e. insulin, rate of gastric clearance as well as
hypothalamic factors) are implicated in food intake
regulation. Despite the conceptual difficulties discussed
above, there has been a very interesting attempt to

integrate information concerned with the hypothalamic control of feeding with the body of evidence that visceral and sensory factors also contribute to "hunger and satiation". There is little doubt that serotonin participates in the control of feeding behavior. Further clarification of its role and of the effects of agents such as zimeldine, will go hand in hand with advancement in our knowldge of the physiological controls of consummatory behavior.

In the context of the original questions posed by this thesis it is perhaps important to emphasis that while the effects of zimeldine are clearly not "specific" to the consumption of ethanol solutions, they may not be "non-specific" either. That is to say, the drug may have produced specific changes in consummatory behavior that are motivational in nature. This distinction has considerable importance with regards use of 5-HT uptake blockers for the treatment of alcohol abuse. If 5-HT uptake blockade indeed produced a reduction in the "reward" derived from food and fluids, it is possible that such compounds may have considerable therapeutic value, particulary when considering the abuse of alcohol within the context of a motivated behavior.

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