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**THE EFFECTS OF
CHLORDIAZEPOXIDE AND RO15-4513
ON COCAINE SELF-ADMINISTRATION**

**BY
GARY JOHN VICKERS**

**A THESIS SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND
RESEARCH IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE
DEGREE OF MASTER OF SCIENCE.**

**DEPARTMENT OF PSYCHOLOGY
CARLETON UNIVERSITY
OTTAWA ,CANADA
NOVEMBER, 1993**

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ABSTRACT

The anxiolytic chlordiazepoxide and the anxiogenic RO15-4513 were tested for the ability to alter cocaine self-administration. The progressive ratio schedule using the dependent measure breaking point was used to assess the motivation to respond for infusions of cocaine. A small dose of chlordiazepoxide caused an increase in responding while the effects of larger doses were masked by sedation which was shown to rapidly undergo tolerance. This sedation effect may account for different results among laboratories. Pretreatment with a non-sedative dose of chlordiazepoxide produced increases in breaking points at the highest concentrations of cocaine tested while pretreatment with RO15-4513 caused decreases which reached statistical significance at the lower doses. The results suggest anxiety modulates responding for cocaine but counter the proposal that the benzodiazepines would make useful therapeutic agents in cocaine abuse treatment. The finding that neural systems other than the monoamines alter motivation to self-administer cocaine points to new research directions.

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INTRODUCTION

Attention grabbing headlines reflect a world wide concern with illegal drugs. One generation removed from the recreational drug use of a more idealistic time we find ourselves faced with the serious social problems of rampant drug abuse. In response, a war on drugs has been undertaken and in the minds of many, cocaine is the focus of this effort. This drug seems to generate emotion even in the scientific press. It has been labelled an emergency (Khalzian, 1991), an epidemic (W.H.O.,1987), the deadliest addiction (Vandegaer,1989) and the drug of greatest national concern (Pollin,1984).

The research presented in this paper demonstrates the effects of benzodiazepine anxiolytic and anxiogenic agents acting via the gamma-aminobutyric acid (GABA) receptor complex on the motivation to self-administer cocaine. Investigation of the contribution of the GABA system to cocaine abuse is a somewhat novel approach. A short discussion of the scope of the cocaine problem, the evolution of scientific methods to address it and the present state of understanding will give an historical perspective to the current experiments.

Although the medical problems produced by alcohol and tobacco products generate staggering numbers (Williams, Chang and Van Truong, 1992) cocaine may exact even greater per capita negative health consequences on the smaller illicit abuser population. A compilation of surveys on Canadian use (Williams, Chang and Van Truong,1992) shows 4.5% of males and 2.7% of females had tried cocaine or crack at least once by 1990 and current users in 1989

amounted to 1.4% of the population. Results from the province of Ontario alone show use increasing from the early 1980s and peaking at about 2% between the years 1987 and 1991. In the United States, by 1985 twenty two million report using cocaine at least once while six million of those were current users (NIDA 1987).

For those who do try cocaine some dramatic animal research data bodes ill. Monkeys given a choice between food and cocaine, chose cocaine almost exclusively (Aiger and Balster, 1978) or given unlimited access self-administer until the advent of coma or even death (Johanson, Balster and Bonese, 1976). In experiments where responding for cocaine is suppressed by the graduated application of electric shock, responding recovers quickly at all but the highest levels (Bergman and Johanson, 1981). This is not encouraging in light of the fact that society's greatest deterrent to abuse is threat of punishment by incarceration. Most dramatic, rats given unlimited access show a 90% mortality rate after thirty days; nearly three times the rate following free access to heroin (Bozarth and Wise, 1985). These results point to the intensity of reward associated with cocaine and its negative correlate, risk of addiction.

HUMAN HEALTH CONSEQUENCES

The health consequences of cocaine use are extensive. Occasionally, use results in death from ventricular fibrillation, cardiac arrest, stroke, apnoea or hypertension (Arif, 1987) but more generally acute use generates hypertension, tachycardia, anorexia, pupillary dilation, and euphoria (Clouet, Asghar and Brown 1988). When withdrawn, irritability, hypersomnia, anxiety and depression result (Vandegaer, 1989). Serious permanent injury takes the form of fatty liver damage (Shuster et al., 1988), changes in myocardial oxygen consumption and vasodilation,

ventricular arrhythmias (Wilkerson, 1988) and premature arteriosclerotic lesions (Langner, Bement and Peiry, 1988). Exposure during pregnancy may cause adverse developmental effects (Dow-Edwards, 1988) and smoking the crack or free base forms leads to pulmonary edema, decreased lung capacity and bronchitis (Pollach, Brotman and Rosenbaum, 1989). Indirect negative consequences include nasal septum perforation, possible infection (eg. HIV) and increased risk of suicide (Vandegaer, 1989). Clearly the facts of cocaine abuse stand by themselves and need no hyperbole. Unfortunately no existing treatment can claim more than marginal success. Inasmuch as this situation denotes an incomplete understanding of the problem it points to an important role for the basic sciences.

ANIMAL MODEL TECHNIQUES

A useful research technique in addressing human problems is to reproduce the aberrant behavior or disease process in a experimental subject. Cocaine use is readily modeled in animals and a number of species self-administer the drug: monkeys, (Bedford, Baily and Wilson, 1978); baboons, (Griffiths, Brady and Snell, 1978); dogs (Risner and Goldberg, 1983) and rats (Roberts, Corcoran and Fibiger 1977). In general the animal is required to perform some operant response in order to obtain an intravenous infusion of drug solution. While more exotic schedules are sometimes employed the most commonly used is the simple fixed ratio 1 (FR 1) in which a single response is followed by reward. In this paradigm experimental treatments can only effect the rate of infusion. Unfortunately, as a dependent variable rate suffers from inherent flaws.

Interpretation of treatment induced changes in rate has generated some conflict. One camp takes the position that increased rate reflects a blockade of cocaine reward and an effort by the animal to overcome that effect (Yokel and Wise, 1975, 1976; Roberts and Vickers, 1984). On the

other hand, convincing arguments have been offered to support the view that increased rate reflects increased reward value in some situations (Wilson and Schuster, 1973). It is worth noting that the cocaine dose response curve clearly shows that rate is an inverse function of unit dose (Wilson, Hitomi and Schuster, 1971) and that an increased rate of responding following dopamine receptor blockade can be reproduced by decreasing the concentration of the infused solution (Roberts et al. 1977). It is also conceivable to attribute an increase in responding to simple stereotypy or a decrease to a motor deficit. This ongoing difficulty decreases the value of rate as a dependent variable.

In substance abuse research, concepts like drug craving and addiction which imply motivation cannot be measured by an FR schedule. To overcome this problem, Hodos (1961) developed what is known as the progressive ratio schedule. An FR requirement was escalated at the beginning of each session until the subject failed to meet the response demand. The dependent measure, breaking point, was the value of the highest requirement successfully completed. This technique proved sensitive to manipulation of reward and deprivation and offered a method to measure motivation. Because of this obvious advantage it has been used to generate dose response curves and assess the relative reinforcing strengths of various drugs (Griffiths et al., 1975; Bedford et al., 1978; Thompson, 1977; Griffiths et al. 1978; Griffiths et al., 1979 Hoffmeister, 1979; Risner and Silcox, 1981; and Risner and Goldberg, 1983).

The marriage of this schedule to computer technology has produced improvements allowing response requirement escalation following each drug infusion (Roberts, Loh and Vickers, 1989; Roberts, 1989; Roberts, Bennett and Vickers, 1989). In this method the response requirement for each subsequent reward increases in an exponential like sequence

derived from the equation, $\text{ratio} = (5 \times e^{0.2 \times \text{infusion number}} - 5)$ rounded to the nearest integer. On this schedule the first response is rewarded and then subsequent response requirements escalate through the series: 2, 4, 6, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, 737, 901, 999. Breaking point is defined as the ordinal value of the final ratio completed prior to a one hour period in which a subsequent response contingency is not met. This approach has the advantage of providing a breaking point after each session. A dose response relationship is observed with breaking point and importantly, treatments which block the neurochemical actions of cocaine (ie. dopamine antagonists) decrease motivation to self-administer as reflected in decreased breaking points (Roberts et al., 1989b). This outcome is more intuitive than the difficult to interpret increases in rate seen following these treatments on FR schedules.

COCAINE: SITE OF ACTION AND PHYSIOLOGICAL EFFECTS

The well known and powerful behavioral effects of cocaine derive from relatively straightforward neurochemical actions. The main effects are on the major monoamine neuronal systems. Cocaine blocks the reuptake of released norepinephrine (Whitby, Herting and Axelrod, 1960), serotonin (Ross and Renyi, 1969) and dopamine (Scheel-Kruger et al., 1977), which results from inhibition of the transporter sites (Ritz et al., 1987). This is the drugs' most potent effect which leads to a prolonged presence of the neurotransmitter in the synapse and therefore classification as an indirect agonist.

Investigation of the dopamine system has yielded the most interesting results. Pharmacological intervention reveals that a host of D1 and D2 receptor antagonists (pimozide, sulpiride, SCH23390, metoclopramide, thioridazine, haloperidol, chlorpromazine, and

flupenthixol) decrease breaking point or increase responding on an FR schedule (Roberts and Vickers, 1984; DeWit and Wise, 1977; Roberts et al., 1977; Koob and Creese, 1987). Pretreatment with the D3 receptor antagonist (+)- AJ 76 has also been shown to decrease breaking points and delay onset of responding (Richardson et al., 1993). Clozapine presents an interesting anomaly. This drug unexpectedly decreases FR responding (Roberts and Vickers, 1984) and increases breaking points on a PR schedule (Loh et al., 1992). This effect may be related to an unusually strong affinity for the D4 receptor.

Although it is agreed that the mesocorticolimbic dopamine system is the relevant pathway, the specific locus of action is under contention. Compelling evidence points to the nucleus accumbens as the necessary site (Roberts et al., 1977, 1980; Roberts and Koob, 1982; Pettit et al., 1984) while others tout the medial prefrontal cortex as an alternate (Goeders and Smith, 1983, 1984; Isaac et al., 1984).

The noradrenergic system is apparently not linked to cocaine self-administration. Complete destruction of both the dorsal and ventral noradrenergic bundles is without impact (Roberts et al., 1977) while pharmacological treatment with either the norepinephrine alpha blocker phenoxybenzamine or the beta blocker propranolol does not effect intake (De Wit and Wise, 1977; Wilson and Schuster, 1974). Investigation of the serotonergic system has produced confusing results. While depletion of forebrain serotonin by chemical destruction of the amygdala or the medial forebrain bundle increases breaking points (Loh and Roberts, 1990) receptor blockade with a wide range of antagonists fails to effect intake (Lacosta and Roberts, 1992; Peltier and Schenk, 1991). In addition, the administration of the uptake inhibitor fluoxetine has been shown to increase, decrease or not affect the intake of cocaine (Carroll et al., 1990; Peltier and Schenk,

1991; Richardson et al. in press).

In summary, pharmacological and lesion evidence clearly indicate that the dopamine system plays a major role in cocaine reward while the contributions of the other systems remain less evident.

ALTERNATE APPROACHES

Research seeking a drug therapy to counter cocaine abuse has focused almost exclusively on the monoamines directly affected by cocaine. Medically the goal has been to discover a compound which would benignly block reward. This approach fails to assess the possibility that pharmacological manipulation of secondary neural systems which indirectly affect the main monoaminergic systems could decrease the motivation to self-administer cocaine. It is also possible that alteration of aversive drug effects, as opposed to reward, may also achieve the same outcome.

For most self-administered drugs the relationship between a measure of a subjects' motivation to acquire an infusion and the concentration of the drug in the reward solution is best described as an inverted U. This quality is shared by cocaine (Roberts, Loh and Vickers, 1989b) and is interpreted as evidence that the drug produces a spectrum of rewarding and aversive effects whose relative expression varies with dose. The downturned portion of the curve is generally thought to reflect a relative increase in aversive over rewarding qualities. Anxiety appears to be the aversive quality associated with cocaine and is increasingly expressed at larger doses (Yang et al., 1991). These observations suggest that anxiety may have an impact on the motivation to ingest cocaine. In the past some therapeutic approaches have taken advantage of

Presently our knowledge of cocaine is limited to understanding reward and the role of monoaminergic systems. Pharmacological manipulation of the GABA system offers insight into the lesser known anxiogenic cocaine effect and possible alternate routes to therapy. A group of drugs known as the benzodiazepines which act on the GABA system are well known anxiety modifiers. The class contains both anxiolytic and anxiogenic compounds (for review see; Hommer et al. 1987). Investigation of a possible influence of the GABA system on cocaine intake offers a unique research opportunity in a new direction.

COCAINE AND ANXIETY

The aversive anxiety component of cocaine is well studied but not often mentioned in research seeking a pharmacological solution to cocaine abuse. A discussion of the findings also serves to illustrate some interesting interactions between cocaine and the direct and indirect benzodiazepine agonists.

Researchers have developed paradigms in which experimentally induced conflict can be studied. Typically in such designs subjects respond for food or water on a variable interval schedule. During selected time periods a second schedule is introduced which runs in conjunction with the first and delivers a stressor event contingent on responding. This event is usually a shock delivered to the tongue or feet. During this period a conflict situation occurs in which a subject is thought to balance a desire for the reward with an aversion for the negative consequence of responding. The result is a decrease in responding as compared to non-shock periods which can be manipulated by altering the parameters of the shock schedule. This shock suppression effect is countered by clinically useful anxiolytic substances like the GABA receptor agonist benzodiazepines and is augmented

by anxiogenic compounds or events. In lick suppression testing, cocaine also augments shock induced suppression (Fontana and Commissaris, 1989).

In open field studies cocaine causes defensive withdrawal behavior, an effect shared with restraint, anxiogenic GABA inverse agonists and corticotrophin releasing factor (Yang et al., 1992). Blood testing shows the cocaine effect is associated with increased levels of blood corticosterone. Interestingly the effect is countered by chlordiazepoxide.

In humans, panic attack featuring intense anxiety often occurs during episodes of increased cocaine use (Aronson and Craig, 1986). Lerner et al., (1986) demonstrated that the combination of amphetamine and chlordiazepoxide, at levels where neither are active alone, can unexpectedly produce anxiolytic effects in conflict situations. This unexpected outcome of a stimulant/sedative combination may explain why ethanol, which shares many benzodiazepine qualities (Sudzak et al., 1986), is the substance of greatest co-abuse with cocaine (Pollack et al., 1989).

It seems that cocaine has a response suppressant, anxiogenic quality which is countered by anxiolytics. This fact appears well known to street abusers.

ACTIONS OF COCAINE AND GABA AGENTS ON DOPAMINE

Much of the information gathered about cocaine has been the result of the use of compounds which augment or inhibit dopaminergic transmission in the mesocorticolimbic system.

Pharmacological manipulation of the GABA system indirectly mimics these effects.

Thanks mainly to the dialysis technique we know a great deal about the neurochemical effects of the various chemicals of interest. Cocaine increases dopamine release in the ventral tegmental area, the nucleus accumbens and the frontal cortex (Moghaddam and Brunney, 1989). A similar action is produced by benzodiazepine inverse agonists. The beta carbolines FG7142 and

beta CCM (Giorgi et al.,1988) and the benzodiazepine RO15-4513 (Bradberry et al.,1991 and Giorgi et al., 1987b) increases dopamine turnover in prefrontal cortex and FG7142 increases dopamine release (Bradberry et al., 1991). On the contrary GABA agonists decrease dopamine turnover and release in the nucleus accumbens (Findlay et al., 1992; Imperato et al. 1990; Zetterstrom and Fellenz, 1990) and decrease dopamine utilization in prefrontal cortex (Tam and Roth, 1990).

The ability of this group of chemicals to counter or mimic cocaine neurochemical actions points to possible effects on cocaine reinforcement.

ANXIETY AGENTS AND COCAINE REINFORCEMENT

Surprisingly few studies have looked at the impact of anxiety altering agents on cocaine reinforced behavior. One such study employed a straight alley apparatus in which subjects were rewarded with several infusions of cocaine for successfully entering the goal box (Ettenberg and Geist, 1991). In general, for the more traditional reinforcers, running times in this apparatus decrease over trials but this was found not to be the case with cocaine. Closer observation revealed stop and retreat behavior in close proximity to the goal box. The researchers reasoned that a conditioned anxiety component of the reinforcer was creating a conflict situation. They tested the idea by administering the anxiolytic diazepam and found a dose dependent reduction in the goal box related conflict behavior. The authors suggest that this result shows cocaine as having concurrent reinforcing and aversive qualities with the anxiolytics acting solely on the aversive component.

The effects of anti-anxiety drugs have been more extensively studied in the cocaine self administration model. Chlordiazepoxide (Goeders et al.,1989) and alprazolam (Goeders,1992)

decrease responding for cocaine on an FR schedule. Direct intracranial administration of small amounts of chlordiazepoxide increases responding (Guerin and Goeuvers, 1992; Goeders, 1992). This latter finding was interpreted as an apparent effort by the animal to overcome blockade of reinforcement. The combined evidence purports to show anxiolytics counter the reinforcing effect of cocaine. This conclusion is in contrast to that of Ettenberg and Geist which clearly suggests that chlordiazepoxide enhances the attractiveness of cocaine.

Finally, one rather unusual experiment has been reported. Using a second order schedule [FR10(FI3min)] in which ten successful completions of a fixed interval schedule results in cocaine reward, Nader and Barrett (1990) have demonstrated that chlordiazepoxide pretreatment decreased responding. This result is interesting but difficult to explain and unfortunately even the authors fail to try.

The foregoing information combined with a dearth of experimentation suggests a research opportunity. When considering the subjective reward value of cocaine used in conjunction with anxiolytics the discordant conclusions of Ettenberg and Geist and the Goeders' group lead to opposed predictions. Unfortunately the design of the former study makes it inappropriate to address this question and the latter series employs a rate measure with all the associated problems discussed previously. Fortunately the progressive ratio schedule was designed to overcome these interpretive problems.

Further, in the few studies which address the issue of the effect of the benzodiazepines on cocaine intake, all have exclusively used direct benzodiazepine receptor agonists. The benzodiazepine family includes a group of inverse agonists which generally produce behavioural effects opposite to those of the direct agonists (Nutt, 1988). Employing both direct and inverse

benzodiazepine agonists as pretreatments makes it possible to more fully understand the interactions of cocaine self-administration and benzodiazepine receptor activation.

THE EXPERIMENTS

OBJECTIVES

The purpose of the experiments was to examine the effect of direct and inverse benzodiazepine receptor agonists on the self administration of cocaine. We investigated the effects of the anxiolytic chlordiazepoxide and the anxiogenic RO15-4513 on breaking points on a progressive ratio schedule in which responding was maintained by cocaine. Specifically, experiment 1 was run to provide a dose response curve for the effects of chlordiazepoxide on breaking point. Experiment 2 was designed to further investigate the sedation, and time course of the tolerance which seemingly developed to that phenomenon, observed in experiment 1. Experiments 3 and 4 were designed to determine the effects of the direct benzodiazepine agonist chlordiazepoxide and the inverse benzodiazepine agonist RO15-4513 on breaking points supported by four different concentrations of cocaine.

SUBJECTS

Male Wistar rats (Woodlyn Farms, Guelph, Ontario) weighing 350-400 grams at the beginning of each experiment served as subjects. Following selection and preparation all subjects were housed singly in operant chambers for the duration of the experiments. Except for a brief period of food deprivation for training purposes animals were fed ad libitum throughout. Lights were maintained on a 12 hour reversed day /night cycle (switched off/on at 10.00 am/pm). All testing occurred during the dark phase. In experiments 1, 3, and 4 a group consisted of

eight subjects. In experiment 2 the group contained nine subjects.

BAR RESPONSE TRAINING

Following 24 hour food deprivation the subjects underwent training in order to acquire a bar press response. The training chamber was identical to the operant chamber in which they eventually were housed. A bar press resulted in delivery of a 45 mg Noyes food pellet on an FR1 schedule. To complete training an animal was required to demonstrate at least 100 such responses on two consecutive sessions. The response was readily learned by most animals and those that could not were removed from the experiment.

SURGERY

When successfully bar trained, subjects underwent surgical implantation of a chronically indwelling jugular cannula. The cannula consists of a freely rotating fluid delivery swivel joined at one end to 36 cm. of silastic tubing. The first 28 cm. are protected by an overlay of plastic tubing (PE 260) and stainless steel spring. A small piece of marlex mesh (approx. 2cm X 3cm) is attached to the distal end and the tubing exits at right angles and is attached to the marlex by silastic cement. The tubing extends for 8 cm at which point a smaller piece of silastic tubing is inserted in the first and cemented in place. The smaller tubing is trimmed to 3 cm. For a full description and illustration see Roberts and Goeders (1989).

The animals were deeply anesthetized using sodium pentobarbitol (Somnotol, 60mg/kg,IP) and a small incision was made over the mid-scapular region and a second ventrally over the right jugular vein. Implantation consisted of placing the marlex saddle into a pocket formed below the scapular incision and drawing the tubing through a subcutaneous connection to the ventral incision and there inserting the smaller tubing into an opening in the jugular vein and pushing

the tip to the entrance of the heart. The tubing was then secured, the wounds sutured closed and the animal allowed to recover.

OPERANT APPARATUS

Following surgery the animal was placed in a chamber that served as testing facility and permanent housing. The apparatus was a cubical plexiglas box ,25 cm. on each side sitting on a wire grid floor above a removable waste pan containing wood chips. On one wall was mounted a bar activated switching device for counting responses and a time out light. A water bottle was affixed to the opposite wall. The cannula leash extended through a hole in the ceiling and was attached to a counter-balanced arm. The system allowed for free movement of the animal without interference by the drug delivery cannula.

COCAINE TRAINING

On the day following surgery the animal began daily 5 hour cocaine self-administration sessions. The initial exposures were designed to facilitate acquisition of responding appropriate to progressive ratio schedule requirements. The task and setting closely resembled food training except that a bar depression resulted in delivery of a single 0.1 ml infusion (1.5 mg/kg) of a standard cocaine solution (5 mg/ml in saline) delivered over a 5 second period. The response also initiated a twenty second time out signalled by the light. Bar presses during this period were without consequence. The time out and a programmed "binge protector" which didn't allow closely spaced repeated infusions protected the animal against overdose during both fixed ratio and progressive ratio responding. Once stable fixed ratio 1 responding, characterized by an evenly spaced uninterrupted response pattern, was demonstrated for a period of at least three days subjects were switched to a progressive ratio schedule. On this schedule the first response is

rewarded and then subsequent response requirements escalate through the series: 2, 4, 6, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, 737, 901, 999. A response requirement defines the number of bar presses required to attain a given infusion of cocaine. For example, following the third infusion of cocaine, six additional bar presses are needed to receive the fourth infusion. Progressive ratio training continued until a subject achieved a stable breaking point pattern. A breaking point is defined as the ordinal value of the last infusion received prior to a one hour period in which a subsequent response requirement is not met. This procedure typically required about 5 sessions. The animal was then ready to take part in an experiment. During participation in the experiments animals were replaced due to cannula malfunction or death.

DRUGS

Chlordiazepoxide hydrochloride was purchased through Hoffmann-La Roche limited (Mississauga, Ont.) and Ro15-4513 was obtained from Research Biochemicals Inc. (Natick, Md.). Cocaine hydrochloride was supplied by the National Institute on Drug Abuse (Rockville, Md.). Drugs were prepared fresh for each treatment day. Chlordiazepoxide was dissolved in a 0.9% saline solution. Ro15-4513 was first placed in a small volume of 0.9% saline to which a drop of tween 80 was added. The solution was then sonicated to effect dispersal. A further amount of saline was added to bring the solution up to volume and the liquid was mechanically swirled to achieve an even suspension. Drug injections were delivered intraperitoneally in a volume of 1.0 ml/kg. of body weight. Cocaine hydrochloride was dissolved in a 0.9% saline solution and delivered intravenously in 0.12 ml over a period of 5 seconds. The standard solution contains 5 mg/ml.

EXPERIMENT 1

This experiment was designed to examine the effect of a range of doses of chlordiazepoxide on breaking point using a progressive ratio schedule reinforced by the standard dose of cocaine (approx. 1.5mg/kg/inj.). Because chlordiazepoxide had not been used in the context of the progressive ratio schedule before the aim was to obtain information by which to select an appropriate dose to use in subsequent experiments.

Figure 1 shows a typical event record and cumulative record for a subject responding for infusions of cocaine (1.5 mg/kg) on a progressive ratio schedule. Also included for the sake of comparison is an event record of the same subject responding on a training fixed ratio 1 schedule.

METHODS

Following successful pre-experimental preparation and establishing a stable baseline on the progressive ratio schedule each subject underwent five pretreatments consisting of injections of the vehicle (saline, 1ml/kg ,i.p.) and four doses of chlordiazepoxide: 2.5, 5.0, 10.0, 20.0 mg/kg, i.p.). Each of the five pretreatment test days was preceded by a minimum of three consecutive baseline sessions. Drug injections were given thirty minutes prior to the test session.

In order to counter any possible order of presentation effect for dose, two subjects began the series of pretreatments at each of the four doses of chlordiazepoxide. Following the initial pretreatment test dose subjects received subsequent doses in an ascending order until receiving the 20 mg/kg dose. Subjects then received a pretreatment with the vehicle and on the following test session re-entered the drug series at the 2.5 g/kg level again receiving pretreatments in an ascending order until all five doses had been administered.

FIGURE 1

Temporal response patterns of cocaine self-administration under FR1 and PR schedules of reinforcement. The horizontal lines represent 5 hour sessions. Upward deflections represent drug infusions (1.5 mg/kg). Panel A is a computer reconstructed event record of FR1 responding. Panel B is a computer reconstructed cumulative event record. Upward movements of the pen represent lever responding.

A one-way ANOVA appropriate for a repeated measures design was used to determine if mean group breaking point varied across dose. When indicated, paired *t*-tests were subsequently used for comparisons of selected group pairs. The probability level for statistical significance was set at $p < 0.05$.

RESULTS

Figure 1 illustrates the relationship between mean group breaking point and the dose of chlordiazepoxide used as a pretreatment. The most readily apparent effect is an increase in breaking point produced by pretreatment with the lowest dose of chlordiazepoxide (2.5 mg/kg). This is followed by a dose dependent decrease in breaking points as a result of pretreatment with the higher doses. A closer inspection however, reveals a direct relationship between dose and an increase in the variability of scores. This situation was readily predictable from direct observation of the subjects just prior to the beginning of a session. From the 5.0 mg/kg dose upward, naive subjects increasingly displayed sedation. At the 20.0 mg/kg dose the effect was marked. Because the level of the starting dose was staggered across subjects each group contained scores derived from naive as well as subjects with varying degrees of drug experience. It was also apparent from perusal of the data that the higher scores in a group were associated with greater drug experience. The effect was most obvious in the highest drug dose where some naive subjects were unable to respond within one hour of initiation of the session while experienced subjects sometimes responded at levels double their baseline scores. Sedation and tolerance appeared to play a role in the outcome of this experiment.

This observation was confirmed by statistical analysis. The Mauchly sphericity test for homogeneity of variance proved significant ($W=0.00568$) showing that the assumption of

equality was violated. However, because sedation was not evident at the 2.5 mg/kg dose level either through direct observation or through outcome, ie. mean responding increased, it was decided to compare the results of that dose to the saline control group. A paired *t*-test revealed the breaking points of the drug group to be significantly elevated over the saline control group ($t=3.41$, $df=7$, $p=0.011$). Because of the ability to alter breaking points and the absence of the negative side effect this dose was chosen for use in experiments 3 and 4.

FIGURE 2

The dose response relationship between chlordiazepoxide pretreatment and breaking points on a progressive ratio schedule supported by cocaine infusion (1.5 mg/kg/inj.). Symbols (□) represent the mean breaking point (+/- S.E.M.) for the day of pretreatment with chlordiazepoxide (2.5, 5.0, 10.0, 20.0 mg/kg, IP) or saline (1.0 ml/kg). Each mean represents the test scores of eight subjects. An asterisk (*) indicates a statistically significant difference in breaking point compared to the saline pretreatment group ($P < .05$).

EXPERIMENT 2

In experiment 1 the outcome strongly suggested that doses of chlordiazepoxide in excess of 2.5 mg/kg caused sedation. At doses which produced this effect subjects receiving their first drug injection showed strong sedative effects characterized by low breaking points. Subjects receiving their final injections at these doses sometimes achieved breaking points of twice baseline levels. This not only suggested that sedation affected the outcome of experiment 1 but that tolerance develops to the effect within four administrations. Because the presence of sedation and the range of scores was greatest at the 20.0 mg/kg dose we decided to repeatedly administer this dose to a group of subjects. The purpose of experiment 2 was to determine if the decrease in breaking point observed to be the effect of an initial injection of the high dose of chlordiazepine in experiment 1 undergoes behavioural tolerance with repeated administrations.

Given that increases in breaking point occurred following pretreatment with the 2.5 mg/kg dose in experiment 1 it was also of interest to determine the effect of the 20 mg/kg dose following the development of tolerance if and when it occurred.

METHODS

After collecting breaking point data from subjects for three consecutive baseline sessions each received a pretreatment injection of chlordiazepoxide (20.0 mg/kg ip.) thirty minutes before the beginning of session 4. This procedure was repeated prior to test sessions 6, 8 and 10. On the intervening 5th, 7th, 9th and 11th test sessions control injections of the saline vehicle (1.0 ml/kg) were administered.

An analysis of variance procedure appropriate for a two factor repeated measures design was used to compare the effect of treatments across days. Where allowed groups were compared

using paired *t*-tests. The probability level for statistical significance was set at $p < 0.05$.

RESULTS

Figure 3 shows the result of repeated chlordiazepoxide pretreatments (20.0 mg/kg) on the mean breaking point for the group across days. The overall analysis of the breaking point data revealed a significant interaction between day and treatment ($F=3.02$, $df(3,25)$, $p=0.049$). A repeated measures one-way ANOVA comparison of data collected on saline injection days did not reach significance which indicated baseline stability. However individual comparisons between group means showed that scores obtained on the first day of chlordiazepoxide pretreatment were significantly depressed compared to those reached on the following saline pretreatment day ($t=4.26$, $p<0.033$, $df=8$). Similarly these same scores were also significantly lower than those recorded following the fourth repetition of the drug pretreatment ($t=-2.56$, $p=0.034$, $df=8$). Also of importance, breaking point scores from the final drug injection day were not significantly different from those of the following saline pretreatment day. These results clearly show the development of tolerance to the sedative effects of the drug treatment over the short (4 day) trial period. Although not to the level of significance, the final pretreatment resulted in a small elevation of the mean breaking point reminiscent of the effect caused by the 2.5 mg/kg dose in experiment 1.

FIGURE 3

The effect of repeated pretreatment with chlordiazepoxide (20.0 mg/kg) on breaking points on a progressive ratio schedule supported by cocaine infusion. Closed squares (■) represent days on which subjects received pretreatment injections of chlordiazepoxide (20.0 mg/kg, IP, -30 min.). Open squares (□) following the first drug injection, represent days on which subjects received pretreatment injections of saline (1 ml/kg). An asterisk (*) indicates a statistically significant difference from both the first saline day and the last drug day, $P < .05$. The group contained nine subjects.

EXPERIMENT 3

In this experiment we studied the ability of a direct benzodiazepine agonist to alter the motivation to self-administer cocaine as measured by breaking point. We determined the effect at four different concentrations of cocaine in order to cover the range of concentrations commonly used in the literature to support self-administration. In the past it has been suggested that differences in reward strength may explain contrasting results from various laboratories.

METHODS

Following successful pre-experimental preparation each rat was required to demonstrate stable baseline progressive ratio responding for four different concentrations of cocaine (0.625, 1.25, 2.5, 5.0 mg/ml) for a minimum of three consecutive baseline sessions. Prior to the test session which immediately followed each block of baseline sessions, a subject received a pretreatment injection of chlordiazepoxide (2.5 mg/kg, i.p., -30 min.) in order to evaluate the effect of the drug on responding for cocaine at that concentration. On the day following a test session a subject began another block of baseline sessions in which responses were rewarded with infusions of the concentration of cocaine next in the series. This pattern was repeated until each subject had undergone successful baseline and pretreatment sessions at each of the four concentrations of cocaine.

In order to counter any possible order of presentation effect for the concentrations of cocaine, the sequence in which subjects encountered the concentrations was balanced. Two subjects proceeded through the series in the order 0.625, 1.25, 2.5, 5.0; a further two in the order 1.25, 2.5, 5.0, 0.625; two more in the order 2.5, 5.0, 0.625, 1.25; and finally two in the order 5.0, 0.625, 1.25, 2.5.

A two factor repeated measures ANOVA was used to compare treatments (baseline vs. drug) across concentrations. When appropriate, selected groups were compared using paired *t*-tests. The probability level for statistical significance was set at $p < 0.05$.

RESULTS

Figure 4 shows the effect of concentration of cocaine reward on breaking point as well as the effect of the chlordiazepoxide pretreatment on responding at each of the individual concentrations. The effect of concentration proved significant ($F=9.23$, $df(3,21)$, $p < 0.001$). Individual comparisons among the baseline means showed that the lowest concentration of cocaine supported breaking points significantly lower than the two highest concentrations ($t=-5.4$, $df(7)$, $p = 0.001$) and ($t=-3.62$, $df(7)$, $p = 0.008$). Similarly responding for the second weakest concentration of cocaine was also significantly less than the two highest concentrations ($t=-3.38$, $df(7)$, $p=0.012$) and ($t=-2.63$, $df(7)$, $p=0.034$). Also responding at the two highest concentrations differed significantly from one another ($t=-2.81$, $df(7)$, $p=0.026$). This clearly demonstrates an ability of the progressive ratio schedule to discriminate strength of reward.

EXPERIMENT 3A

Surprisingly, chlordiazepoxide did not affect responding at any reward strength in experiment 3. It was our belief that by reducing the aversive anxiety component of the reward this drug would increase the attractiveness of cocaine. The negative results pointed to the possibility that the relatively few injections delivered on the progressive ratio schedule in

combination with our chosen dose range might not produce significant anxiety. If this were true an effect might be expected to appear at a yet higher concentration. In this experiment we decided to investigate that possibility and extended the range used in experiment 3 by training animals to self-administer a higher concentration of cocaine (2.25 mg/kg/inj.).

Method

Following successful pre-experimental preparation, breaking point data were gathered from eight subjects on three baseline sessions for which a solution of cocaine 1.5X larger than the highest dose used in experiment 3 was used to support responding. On the subsequent fourth session animals received a pretreatment of chlordiazepoxide (2.5mg/kg,i.p.,-30 min.).

A paired *t*-test was used to compare the median baseline vs. drug day scores.

RESULTS

The mean breaking point for this group on the day on which they received the chlordiazepoxide pretreatment was greater than baseline scores. The drug treatment produced an increased breaking point in every subject tested. This increase proved statistically significant as the drug day mean was significantly elevated over baseline ($t=-6.35$, $df(7)$, $p= <0.001$). These results are illustrated in figure 4 to the right of the vertical dashed line.

FIGURE 4

The effect of pretreatment with chlordiazepoxide (2.5 mg/kg) on breaking points on the progressive ratio schedule supported by five concentrations of cocaine. Closed squares (■) represent mean baseline breaking points (+/- S.E.M.) for a group of rats (n=8) responding at four concentrations of cocaine. Open squares (□) represent mean breaking points (+/- S.E.M.) following pretreatment with chlordiazepoxide (2.5 mg/kg). All scores were derived from the same group of subjects participating in a repeated measures latinized square design. An asterisk (*) denotes a statistically significant difference from the baseline breaking point at the same concentration. ($P < 0.05$)

EXPERIMENT 4

This experiment was designed as a companion to experiment 3. The design and procedure were identical to experiment 3 except that the pretreatment drug was the anxiogenic benzodiazepine inverse agonist RO15-4513. Benzodiazepine agonists and inverse agonists are known to cause opposed behavioural effects (Nutt, 1988). For example, in contrast to the well known anti-anxiety effects of the direct agonist benzodiazepines, members of the related inverse agonist class cause fear and anxiety in humans (Dorow et al., 1983) and augment suppression in punished responding situations (Giorgi, 1987b). In this experiment we investigated the effect of the inverse benzodiazepine agonist RO15-4513 on breaking points supported by four different concentrations of cocaine.

METHODS

The methods used in this experiment were identical to those used in experiment 3 except that the pretreatment drug was the anxiogenic RO15-4513. Subjects were required to successfully baseline and receive pretreatment at four different concentrations of cocaine: 0.625, 1.25, 2.5, 5.0.. Following a minimum of three consecutive baseline sessions at each concentration the animals were injected with RO15-4513 (5 mg/kg, I.P.) thirty minutes prior to the initiation of the next session. In order to counter any possible order of presentation effect associated with the various concentrations of cocaine we used a sequence balancing procedure identical to that used in experiment 3.

A two factor (concentration x treatment) repeated measures ANOVA was used to statistically analyze the experimental results. Where appropriate, selected group means were

compared using paired *t*-tests. The probability level for statistical significance was set at $p < 0.05$.

RESULTS

Figure 5 illustrates the effect of pretreatment with RO15-4513 on breaking points supported by various doses of cocaine. The effect of altering the concentration of the cocaine reward solution on breaking point can also be seen in the figure. Statistical analysis showed that the main effect of concentration ($F = 13.22$, $df(3,21)$, $p < 0.001$) was statistically significant. The simple main effect of this variable for baseline sessions also proved to be statistically significant ($F = 15.25$, $df(3,21)$, $p < 0.001$) which confirmed that the breaking point measure is sensitive to variation in reward strength.

The main effect of treatment was also statistically significant ($F = 16.79$, $df(1,7)$, $p = 0.005$) but the treatment by concentration interaction was not statistically significant. Figure 4 shows that the RO15-4513 pretreatment caused decreases in breaking points at each of the concentrations of cocaine tested. The differences in breaking points reached significance at the two lowest doses of cocaine suggesting that the action of RO15-4513 is greatest at levels where reward strength are most tenuous. This outcome may be the result of the ability of the inverse agonists to mimic the dopaminergic effects of stress (Giorgi et al., 1988) or stem from a reaction similar to the intense anxiety reaction shown to occur in man (Dorow et al., 1983) following treatment with this class of drugs. At the higher concentrations of cocaine the reward quality of that drug may modulate the effect but at the lowest concentrations where reward strength is less the negative effects of the pretreatment predominate and decreases in breaking point become more dramatic.

FIGURE 5

The effect of pretreatment with RO15-4513 (5.0 mg/kg) on breaking points on the progressive ratio schedule supported by four concentration of cocaine. Closed squares (■) represent mean breaking points (+/- S.E.M.) of a group of animals responding for five concentrations of cocaine. Open squares (□) represent mean breaking point (+/-S.E.M.) at each concentration following pretreatment with RO15-4513. All scores were derived from a group of animals (n=8) participating in a repeated measures latinized square design. An asterisk (*) denotes a significant difference from mean baseline breaking point at the same concentration. ($P < 0.05$).

DISCUSSION

Our research shows that pretreatment with the anxiolytic chlordiazepoxide increases the motivation to self-administer cocaine while pretreatment with the anxiogenic RO15-4513 produces the opposite effect. This outcome suggests that anxiety modulates responding for cocaine. It is known that in addition to reward cocaine causes anxiety which is a concomitant aversive component. Our results support the conclusion that reducing anxiety augments the reward value of cocaine while increasing anxiety reduces the attractiveness. These findings however are at odds with the conclusions of Goeders and his colleagues who report that anxiolytic benzodiazepine pretreatment diminishes the reinforcing efficacy of cocaine which implies that the anxiolytics may be good therapeutic candidates to counter abuse. Our experiments provide some evidence to reconcile these opposed conclusions.

As the literature provided no information on the effects of benzodiazepines on responding for cocaine on a progressive ratio schedule our first task was to derive the appropriate dose response curve. The lowest pretreatment dose of chlordiazepoxide (2.5 mg/kg) produced a small but significant increase in breaking point while the higher doses produced a dose dependent decrease. While this might be interpreted as a decrease in the reward efficacy of cocaine direct observation offered an alternate conclusion. It was apparent that these doses, especially the 20.0 mg/kg level, caused increasing sedative effects in the subjects. The effect was most notable in naive animals. Because we used a balanced order of presentation for the doses in experiment 1, means for each dose level contained scores from subjects with drug experience which varied from naive to a maximum of 4 injections. The sedation, along with the apparent development of

tolerance to the effect, led to a large variability in scores at higher doses. While some subjects failed to respond others responded significantly above their baseline values. Casual perusal of the data revealed an apparent relationship between breaking point and level of experience.

Experiment 2 was designed to address these concerns and indeed an initial injection of a large dose of chlordiazepoxide (20.0 mg/kg) caused marked depression of responding which rapidly underwent tolerance within four repetitions. In fact, following the development of tolerance, a small increase in responding occurred which leads to the conclusion that even at high doses chlordiazepoxide does not decrease the reinforcing efficacy of cocaine. Sedation was not noticed at the 2.5 mg/kg level and this was confirmed independently by the fact that breaking points increased following this pretreatment.

The findings on sedation are germane to the work of Goeders (1988) which provides two dose response curves describing the effect of chlordiazepoxide on responding for two concentrations of cocaine on a fixed ratio schedule (see Fig. 6). This experiment and the present work share many similarities but it is the points of disagreement which are most instructive. He reports that small doses slightly increase responding while higher ones decrease responding dose dependently. Although the schedules used to derive the curves were different the results from our two labs are remarkably similar.

Because his subjects were required to press 4 times in a 300 second interval for reward he concludes that sedation could not have been a factor. Unfortunately subjects were placed in isolation chambers and direct observation was not possible. Still some indirect evidence of sedation does exist. In his experiment order of presentation of dose was randomized which means that scores at each dose came from subjects with a variety of drug experience. This procedure

FIGURE 6

The effect of chlordiazepoxide pretreatment on intravenous cocaine self-administration expressed as the total number of infusions. Points are means ($\pm$ S.E.M). Figure 1 taken from Goeders et al., 1989. The closed circles (●) represent drug intake with 0.5 mg/kg/infusion cocaine and open squares (□) represent intake with 1.0 mg/kg/infusion cocaine. Points above V are effects of pretreatment with vehicle and points above S are for saline substitution.

was similar to ours. Also his figure shows that at higher doses the variability of scores increased as evidenced by increased S.E.M. bars. As the design and outcome are similar to ours it suggests a like mechanism, sedation, may be responsible for both results.

There is additional evidence. Figure 7 is a reproduction of the event records of a selected subject in Goeders' experiment. The event records show a dose dependent increase in delay to first response. Much of the decrease in responding is the result of this delay. At the highest pretreatment doses responding does not start until about 45 minutes. This is reminiscent of our work which showed responding in the first hour was most affected by sedation.

Additionally the author points to the fact that the ability of chlordiazepoxide to decrease responding is attenuated by increasing the concentration of cocaine reward solution. This means that a given dose of chlordiazepoxide suppresses responding for a low dose of cocaine to a greater extent than a higher one. This is taken as evidence that reward is being affected. However, if sedation is present it may be that the higher concentration of cocaine simply counters sedation resulting in higher response rates.

Goeders (1992) reports an interesting experiment in which subjects pressed in the first hour of a session for intravenous cocaine (0.25 or 0.50 mg/kg), concentrations about equivalent to our two middle levels, and for food in the second hour. While pretreatment with the anxiolytic alprazolam initially caused "non-specific" decreases in responding for both, it eventually caused a dose dependent decrease in responding for cocaine only. This seems to indicate that anxiolytics specifically decrease cocaine reward, however we may be seeing a first hour effect. Given the evidence and observations that sedation may occur primarily in the first hour the use of the

FIGURE 7

Event records depicting the effect of chlordiazepoxide pretreatment on cocaine self-administration (1.0 mg/kg) selected from a representative rat. Figure 3 taken from Goeders et al., 1989. The upper trace of each pair of lines indicates cocaine infusions while the lower trace represents lever presses.

control technique by which half of the subjects pressed for food in the first hour and cocaine in the second would have yielded more convincing results.

There is a second factor which may help explain the discrepant conclusions between our two labs. While we used the progressive ratio schedule Goeders' group employed a fixed ratio schedule and measured rate of responding. Rate as a dependent measure has some inherent flaws.

Goeders (1992) reports that some subjects increased responding as a result of the alprazolam pretreatment while pressing for the 0.25 mg/kg level of cocaine. This was interpreted as an attempt to overcome blockade of cocaine reward. In Goeders (1991) a similar increase in responding was observed following intracranial injection of chlordiazepoxide. This was also thought to result from an effort to overcome blockade. This introduces an unusual situation in which on various occasions both increases and decreases of a single dependent variable are offered as proof for the same conclusion, ie. a decrease in the reward value of cocaine caused by anxiolytic pretreatment.

Finally it is interesting that Goeders et al.(1989) show subjects respond less for a larger, presumably more rewarding, concentration of cocaine than for a lower concentration (see fig. 5, above V). Given this fact it is difficult to interpret a chlordiazepoxide induced decrease in responding as a lowering of the efficacy of cocaine reinforcement.

The demonstration that sedation may act as a confound in earlier experiments involving anxiolytics and the problems with rate as a dependent measure bolsters our conclusions. Anxiolytics increase the reward value of cocaine. This seems readily apparent to cocaine abusers who commonly co-abuse sedative drugs (Pollack et al., 1989). In addition there is supporting evidence from Ettenberg and Geist (1990).

These authors report an experiment in which cocaine was given as reward for entering a goal box in a straight alley maze. Rather than decreasing with repetition, as is common in this design, running times increased. The effect was the result of stops and retreats in the vicinity of the goal box which was apparently the result of a conditioned conflict situation arising from the rewarding and anxiogenic co-effects of cocaine. These stops and retreats were dose dependently reversed by diazepam. This suggests that when the aversive anxiogenic effects of cocaine are countered by a benzodiazepine, the attractiveness of the cocaine reward increases.

There are a number of mechanisms with the potential to explain these experimental results. Goeders (1991), and Goeders et al.(1989) have offered evidence of a complex interrelationship between cocaine and the numbers of cocaine and benzodiazepine receptors in both the mesocorticolimbic and nigrostriatal dopamine systems. This interaction has been suggested to hold the explanation for his observation of decreased reinforcing efficacy of cocaine (Goeders et al., 1992; Goeders et al., 1988). Unfortunately this approach does not offer a specific testable mechanism.

It is possible that the underlying neurochemical actions of the benzodiazepines cause the observed changes in responding for cocaine. Benzodiazepine direct agonists cause a decrease in dopamine turnover in the prefrontal cortex (Tam and Roth, 1989) and decrease the amount of dopamine available at various other mesocorticolimbic system sites (Findlay et al.,1992; Imperato et al. 1990). On the other hand the inverse agonists mimic the effect of cocaine by increasing the amount of dopamine available to receptors at sites along the same system (Giorgi et al., 1988; Bradberry et al.,1991).

This information would lead one to predict an increase in responding for cocaine on a CRF

schedule, ie. an effort to overcome blockade, and a decrease in the motivation to self-administer which would yield decreased breaking points on a progressive ratio schedule following anxiolytic pretreatment. The synergistic action of the inverse agonists should augment the strength of an individual infusion of cocaine and produce a decreased rate of responding and an increase in breaking point. As these predictions don't match the outcomes of our lab or that of the Goeders' group the neurochemical actions of the benzodiazepines do not make a useful explanation.

Our results can be most readily be explained in terms of anxiety. Cocaine produces both reward and anxiety. Reward obviously encourages responding while anxiety has an aversive negative impact. We believe the reward value of an injection of cocaine, and therefore the motivation to self-administer, is a summation of the positive and negative components. This would predict that adding anxiety in the form of an anxiogenic would decrease breaking points and indeed this occurred following pretreatment with RO15-4513. This effect was most marked at the lowest concentrations of cocaine. This would be expected given that the reward value of an infusion would be lowest at these concentrations and the superimposition of an anxiogenic would have the greatest negative impact.

Conversely, anxiolytics decrease anxiety and would therefore be expected to increase the attractiveness of cocaine and the motivation to self-administer. As expected anxiolytic pretreatment had the greatest effect at the highest concentrations of cocaine tested. It is at these levels that anxiety would be most noticeable. Responding for low doses of cocaine where the anxiety component would be expected to be negligible was unaffected. This approach also explains the observation that the 2.5 mg/kg and the 20.0 mg/kg chlordiazepoxide pretreatments had a similar effect on responding for the 1.5 mg/kg/infusion level of cocaine. It was at this level

that the effect of chlordiazepoxide first became apparent. If the amount of anxiety produced by an infusion of cocaine is small and can be overcome by a small dose of anxiolytic a larger dose should not be expected to have a greater effect. For the purpose of explaining our results the anxiety model has the greatest predictive value.

There is a final question to be answered concerning an anxiety explanation. The direct agonist benzodiazepines are known to reverse response suppression (Rawlins et al., 1980) and the inverse agonists augment response suppression (Giorgi, 1987b). Perhaps the explanation could simply be made in those terms. It would appear however that explanations couched in terms of either anxiety or response suppression are virtually equivalent.

Animal research suffers from some drawbacks. Because there is no direct communication with the subjects we are limited to describing behavioural outcomes and it is impossible to infer intermediate causes from effects. Fortunately both anxiolytics and anxiogenics have been tested in man so that we know directly the subjective states they cause. The ability of the direct agonist benzodiazepines to reduce anxiety is well known and the inverse agonists cause fear and anxiety in man. In science we often extrapolate findings from animals to man and in this case it seems appropriate to reverse the process. It seems evident that the cause of altered responding in animals following benzodiazepine treatment results from the modulation of anxiety.

In summary we report that the anxiolytic chlordiazepoxide increases motivation to self-administer cocaine while the anxiogenic RO15-4513 has the opposite effect. The effect of the direct benzodiazepine agonist is seen at higher concentrations of cocaine where anxiety is most prevalent while the greatest impact of the inverse agonist occurs at the lowest levels where cocaine reward value is least.

These results clearly do not support the contention that the anxiolytics would be good therapeutic candidates to counter cocaine abuse. In contrast to earlier work we caution that anxiolytics increase the attractiveness of cocaine. Neither do we espouse the use of anxiogenics as therapeutic agents even though they were shown to decrease responding for cocaine. There is an obvious moral objection to controlling the use of cocaine by inducing fear and anxiety. It is also possible that these effects would simply be overcome by simultaneous abuse of the anxiolytic benzodiazepines.

The value of this research lies in pointing new directions. Previous work has focussed on the three monoamine systems directly affected by cocaine and methods to reduce reward. It is now obvious that manipulations of independent systems can alter the motivation to self-administer cocaine in novel ways and alternate approaches may now be pursued.

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