Pharmacology Biochemistry & Behavior, Vol. 22, pp. 671–676, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

Comparison of Anorexia and Motor Disruption by Cyclazocine and Quipazine[1]

JUDITH W. HENCK, DALE H. REZABEK AND RICHARD H. RECH[2]

Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI 48824

Received 17 August 1984

HENCK, J. W., D. H. REZABEK AND R. H. RECH. *Comparison of anorexia and motor disruption by cyclazocine and quipazine*. PHARMACOL BIOCHEM BEHAV 22(5) 671–676, 1985.—The mixed narcotic agonist-antagonist cyclazocine and the 5-HT agonist quipazine disrupt food-rewarded fixed ratio-40 (FR-40) operant behavior in rats as a dose-dependent decrease in the number of reinforcers obtained and a reciprocal increase in the number of 10-second intervals between responding ("pausing"). This disruption has been shown to result in part from interaction with 5-HT neuronal systems, and may be a consequence of: (1) disruption of cognitive processes, (2) motivational impairment, or (3) motor deficits. To identify which of these components is (are) involved in the disruption of operant responding, female Sprague-Dawley rats were tested for food consumption, spontaneous locomotor activity, or rotarod performance following intraperitoneal injection of cyclazocine, quipazine, or both. Cyclazocine decreased food consumption at doses larger than those required to disrupt operant behavior, while quipazine decreased consumption at doses disruptive to operant responding. Little effect was exerted by either drug on spontaneous locomotor activity, while rotarod performance was disrupted only by very large doses of either drug relative to effects of FR-40 behavior. These data indicate that neither drug appears to disrupt operant behavior by causing gross motor deficits. Thus, cyclazocine may disrupt operant responding by impairing cognition, while quipazine may act through food satiation mechanisms.

Cyclazocine Quipazine Rat Feeding Motor activity Rotarod Operant behavior

CYCLAZOCINE, a mixed narcotic agonist-antagonist, and quipazine, a 5-hydroxytryptamine (5-HT) agonist, have been shown to disrupt food-rewarded fixed ratio-40 (FR-40) operant behavior in rats [6, 14, 28, 29, 36]. The pattern of disruption consists of a dose-dependent decrease in the number of reinforcers obtained and a reciprocal increase in "pausing" (interresponse time greater than 10 seconds). This pattern is characteristic of drugs which appear to exert disruptive behavioral effects via interactions with brain 5-HT neurons and/or receptors (see [35] for a comprehensive review).

Cyclazocine disruption of FR-40 behavior is attenuated by the 5-HT antagonist metergoline, as well as by the narcotic antagonist naloxone, indicating that this disruption involves both serotonergic and opioid components [14]. Disruption of FR-40 behavior by quipazine is antagonized by the 5-HT antagonists metergoline, pizotifen and cinanserin [6,28]. Interaction of quipazine with naloxone is complex: naloxone has been shown to potentiate the disruptive effects of low doses of quipazine on FR-40 behavior and attenuate the disruptive effects elicited by higher doses [29, 36]. Thus, both cyclazocine and quipazine appear to disrupt operant behavior, at least in part, via direct or indirect interactions with 5-HT neurons and opioid systems.

Operant behavior is believed to require the integrity of cognitive processes. However, the possibility exists that disruption of food-rewarded operant behavior may be due to motivational impairment; i.e., rats will not work for food reinforcement if they are not motivated to eat. Treatments or procedures which lead to increased 5-HT in the synaptic cleft or that directly activate 5-HT receptors are known to decrease food consumption [2]. Serotonergic modulation of feeding may involve both central [21] and peripheral [34] components. Quipazine decreases food intake at doses which produce no other obvious behavioral changes [41]. This anorexia is completely reversed by metergoline, suggesting that quipazine decreases food intake via interaction with 5-HT receptors. Behavioral disruption resulting from administration of large doses of quipazine involves both serotonergic and catecholaminergic components. However, doses of quipazine required to act on catecholamine mechanisms are considerably larger than those required to produce anorexia [40].

Cyclazocine has been shown to disrupt operant behavior in part through an interaction with serotonergic systems [14]. Therefore, at least some part of this effect of cyclazocine may relate to anorexigenic properties. However, cyclazocine is a mixed narcotic agonist/antagonist which is active at several types of opiate receptors. The role of opiate receptors in food consumption is very complex and is dependent on such factors as receptor subtype and the state of deprivation of the test animal [30–33, 42, 43, 49]. Therefore, it is somewhat difficult to predict the effect of cyclazocine administration on food consumption.

The present study examined the effects of cyclazocine

[1]Supported in part by NIDA Grant DA01836 and NIGMS Training Grant 07392.

[2]Requests for reprints should be addressed to Dr. Richard H. Rech, Dept of Pharmacology and Toxicology, Michigan State University, East Lansing, MI 48824.

and quipazine on food intake in an attempt to correlate anorexia with disruption of operant responding. In addition, generalized motor abilities of rats administered cyclazocine or quipazine were examined to assess whether a component of the disruption of FR-40 behavior may relate to motor disturbances.

METHOD

Subjects

Female Sprague-Dawley rats (Harlan Sprague-Dawley, Inc., Indianapolis, IN), approximately ten weeks of age at the beginning of the experiment, were acclimated to the laboratory environment for at least two weeks prior to testing in a room with a 12-hour light-dark cycle (lights on from 1300 to 0100 hours). All rats were randomly assigned to treatment groups upon arrival and were housed three/cage. None had previous drug treatments prior to the start of the experiment. All rats received food (Wayne Lab Blox, Chicago, IL) and tap water ad lib with the exception of those animals undergoing one-week food consumption testing.

Test Materials

Cyclazocine base (a gift from Sterling-Winthrop Research Institute, Rensselaer, NY) and metergoline (a gift from Farmitalia Carlo Erba, Milan, Italy) were suspended in 0.5% methyl cellulose, Quipazine maleate (Miles Laboratories, Elkhart, IN) was dissolved in distilled water; doses were converted to the weight of quipazine hydrochloride to facilitate comparison with earlier studies. All drug doses were injected intraperitoneally. For all experiments cyclazocine was administered 30 minutes prior to testing, quipazine 15 minutes, and metergoline 180 minutes.

Behavioral Procedures

Food consumption. Groups of rats, consisting of 6 rats/group, were deprived of food overnight and trained to consume food (Wayne Lab Blox) only during a 30-minute period between 1400 and 1600 hours. Prior to the consumption period each rat was weighed and then placed in a 14×16×6.5″ clear plastic cage devoid of bedding in a quiet, well-lighted room. A measured amount of food (more than that required by the rat) was placed in each cage, and the amount of food consumed was calculated by subtracting the amount remaining after 30 minutes from the initial amount. Food consumption was monitored on 6 consecutive days to establish a baseline. On the seventh day rats were administered cyclazocine (2, 4, 8, 16 or 32 mg/kg), quipazine (0.5, 1, 2, 4 or 8 mg/kg), metergoline (1 mg/kg), or various combinations of these drugs. Consumption by drug-treated rats was compared to that of a group of controls administered distilled water.

Spontaneous locomotor activity. Additional groups of 6 rats each were tested for spontaneous locomotor activity during a 30-minute testing period between 1300 and 1700 hours. Rats were placed in a 14×16×6.5″ clear plastic cage containing bedding. Within the cage was a 5″ diameter cylinder, around which activity was directed. Activity counts were monitored via a Stoelting Company electronic activity monitor model 31400 situated in a dark, sound-attenuating box. All experiments were controlled by electromechanical programming circuits. Prior to testing of spontaneous locomotor activity rats were administered cyclazocine (1, 2, 4, 8, 16 or 32 mg/kg), quipazine (0.5, 1, 2, 4, 8 or 16 mg/kg), metergoline (1 mg/kg), or various combinations of these drugs. The number of activity counts per minute was recorded for each animal. Spontaneous locomotor activity of drug-treated rats was compared to that of a group of controls administered distilled water.

Rotarod performance. As an assessment of sensory and motor coordination, additional groups of 6 rats each were trained on 2 consecutive days to walk on a rotating cylinder (11 rpm) for 180 seconds. On the third day rats were administered cyclazocine (8, 11.2, 16 or 32 mg/kg), quipazine (8, 11.2 or 16 mg/kg), metergoline (1 mg/kg), or various combinations of these drugs. The amount of time each rat was capable of staying on the rotarod (up to 180 seconds) was monitored. Rotarod performance of drug-treated rats was compared to that of a group of controls administered distilled water.

Statistical Analysis

Data from control and drug-treated rats were compared using an analysis of variance. Dose-response relationships of the various drug combinations were examined by multifactorial analysis of variance and the least significant difference test [46]. The level of significance for all cases was $p<0.05$. ED_{50} values were calculated by probit analysis.

RESULTS

Control rats consume 5.7±0.4 g of rat chow during the course of 30 minutes. Figure 1 depicts the amount of food consumed following various doses of cyclazocine alone or in combination with quipazine or quipazine plus metergoline. Cyclazocine alone decreased food consumption in a dose-related manner (ED_{50}=10.94 mg/kg; 4.20–44.16 mg/kg, 95% confidence interval). A subthreshold dose of quipazine (0.5 mg/kg) potentiated the decrease in feeding caused by 16 mg/kg cyclazocine. This potentiation was partly reversed by 1 mg/kg metergoline. Paradoxically, quipazine combined with 4 mg/kg cyclazocine reversed the reduction in food consumption produced by this dose of cyclazocine alone.

Quipazine also decreased food consumption (Fig. 2) in a dose-related manner (ED_{50}=1.41 mg/kg; 0.02–7.24 mg/kg, 95% confidence interval). A dose of 1 mg/kg cyclazocine, considered to be subthreshold in this paradigm, had no effect on the quipazine dose-response curve.

Spontaneous locomotor activity was unaffected by any dose of cyclazocine tested (Fig. 3); therefore, an ED_{50} could not be determined. Administration of 0.5 mg/kg quipazine, a dose we had previously found to be subthreshold in this paradigm, resulted in a bimodal effect when combined with various doses of cyclazocine. Combination of 0.5 mg/kg quipazine with 1 or 2 mg/kg cyclazocine resulted in inhibition of motor activity when compared to controls, while combination of 0.5 mg/kg quipazine with 32 mg/kg cyclazocine resulted in enhanced motor activity. Both inhibitory and excitatory effects were reversed by 1 mg/ kg metergoline.

Quipazine decreased spontaneous locomotor activity to approximately half that of controls at a dose of 16 mg/kg (Fig. 4); an ED_{50} could not be calculated. When combined with 1 mg/kg cyclazocine (a dose demonstrated to be subthreshold in this paradigm), quipazine decreased locomotor activity at doses of 0.5, 1, 4 and 8 mg/kg; this effect was reversed by metergoline. However, combination of 1 mg/kg cyclazocine with 2 or 16 mg/kg quipazine, alone or after pretreating with 1 mg/kg metergoline, did not result in an additive effect.

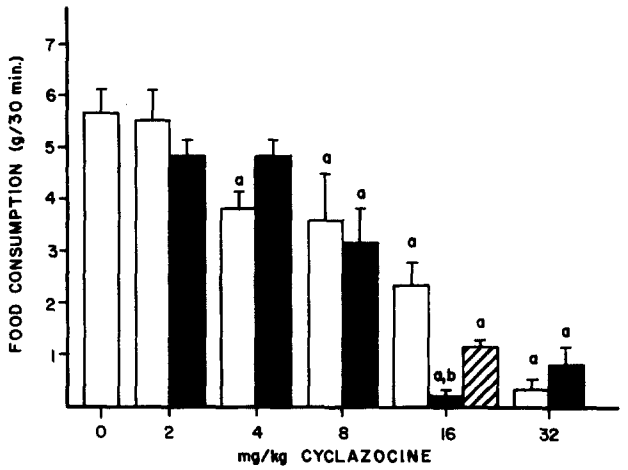

FIG. 1. Food consumption of rats administered cyclazocine alone or in combination with quipazine and metergoline. Open bars indicate food consumed during a 30-minute period by rats administered cyclazocine alone, filled bars indicate consumption following combination of cyclazocine and 0.5 mg/kg quipazine, and striped bars indicate consumption following combination of cyclazocine, 0.5 mg/kg quipazine and 1 mg/kg metergoline. Each bar represents the mean±S.E. food consumption for 6 subjects. Bars marked by "a" are significantly different from control ($p<0.05$) by ANOVA and the least significant difference test; those marked by "b" are significantly different from cyclazocine alone. Cyclazocine decreased food consumption in a dose-related manner, with an ED_{50} of 10.94 mg/kg (4.20–44.16 mg/kg, 95% confidence interval).

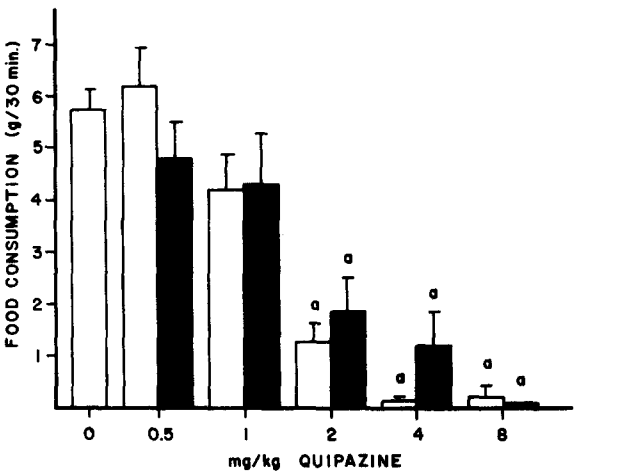

FIG. 2. Food consumption of rats administered quipazine alone or in combination with cyclazocine. Open bars indicate food consumed during a 30-minute period by rats administered quipazine alone and filled bars indicate consumption following combination of quipazine and 0.5 mg/kg cyclazocine. Quipazine decreased food consumption in a dose-related manner, with an ED_{50} of 1.41 mg/kg (0.02–7.24 mg/kg, 95% confidence interval). See Fig. 1 legend for further details.

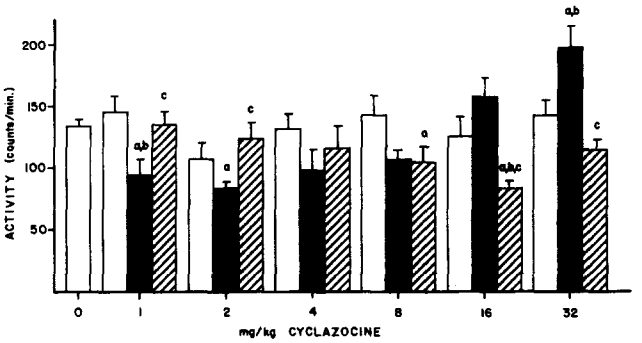

FIG. 3. Spontaneous locomotor activity of rats administered cyclazocine alone or in combination with quipazine and metergoline. Open bars indicate activity counts/minute obtained during a 30-minute test period by rats administered cyclazocine alone, filled bars indicate activity following combination of cyclazocine and 0.5 mg/kg quipazine and 1 mg/kg metergoline. See Fig. 1 legend for further details. Bars marked "c" are significantly different from the cyclazocine/quipazine combination.

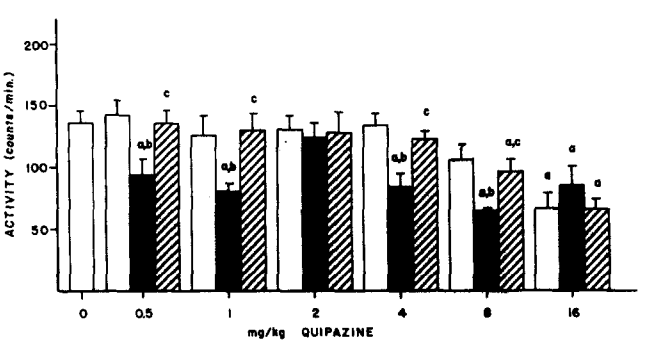

FIG. 4. Spontaneous locomotor activity of rats administered quipazine alone or in combination with cyclazocine and metergoline. Open bars indicate activity counts/minute during a 30-minute test period by rats administered quipazine alone, filled bars indicate activity following combination of quipazine and 0.5 mg/kg cyclazocine, and striped bars indicate activity following quipazine, 0.5 mg/kg cyclazocine and 1 mg/kg metergoline. See Fig. 2 legend for further details. Bars marked by "b" are significantly different from quipazine alone, while those marked by "c" are significantly different from the quipazine/cyclazocine combination.

A dose of 32 mg/kg cyclazocine was required to significantly disrupt rotarod performance (Fig. 5). The ED_{50} was calculated as 22.39 mg/kg (15.49–114.80 mg/kg, 95% confidence interval). A dose of 8 mg/kg quipazine alone had been previously determined to exert no disruptive effect on rotarod performance. However, combination of this dose of quipazine with cyclazocine doses of 8 mg/kg and greater resulted in a markedly decreased ability of these subjects to remain on the rotarod. Disruption of rotarod performance by the cyclazocine/quipazine combination was reversed by metergoline, rotarod performance being comparable to that of controls following administration of a combination of 8, 11.2, 16, or 32 mg/kg cyclazocine with 8 mg/kg quipazine and 1 mg/kg metergoline.

Quipazine alone disrupted rotarod performance (Fig. 6), with an ED_{50} of 11.35 mg/kg (9.13–14.62 mg/kg, 95% confidence interval). A subthreshold dose of 8 mg/kg cyclazocine combined with 8 or 11.2 mg/kg quipazine resulted in potentiation of this disruption; this potentiation was reversed by

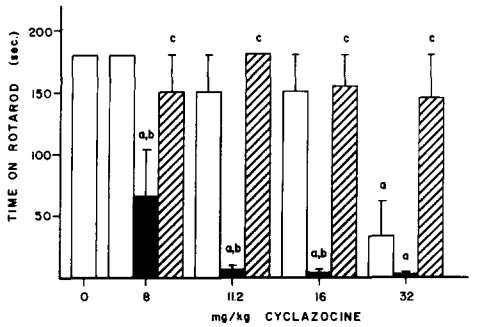

FIG. 5. Rotarod performance of rats administered cyclazocine alone or in combination with quipazine and metergoline. Open bars indicate mean time that the group remained on the rotarod (up to 180 seconds) for rats administered cyclazocine alone, filled bars indicate time following combination of cyclazocine and 8 mg/kg quipazine, and striped bars indicate time following combination of cyclazocine, 8 mg/kg quipazine and 1 mg/kg metergoline. See Fig. 1 and 3 legends for futher details. Cyclazocine reduced rotarod performance with an ED_{50} of 22.39 mg/kg (15.49–114.80 mg/kg, 95% confidence interval).

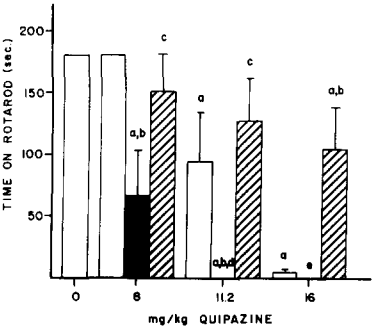

FIG. 6. Rotarod performance of rats administered quipazine alone or in combination with cyclazocine and metergoline. Open bars indicate time remaining on the rotarod (up to 180 seconds) for rats administered quipazine alone, filled bars indicate time following combination of quipazine and 8 mg/kg cyclazocine, and striped bars indicate time following combination of quipazine and 8 mg/kg cyclazocine and 1 mg/kg metergoline. See Fig. 2 and 4 legends for further details. Space marked by "d" indicates time spent on rotarod=0 seconds, while that marked by "e" indicates that this combination was not tested due to potential lethality. Quipazine reduced rotarod performance with an ED_{50} of 11.35 mg/kg (9.13–14.62 mg/kg, 95% confidence interval).

pretreatment with metergoline. Combination of 8 mg/kg cyclazocine with 11.2 mg/kg quipazine resulted in the death of 1 of 6 rats; therefore, a combination of 8 mg/kg cyclazocine with 16 mg/kg quipazine was not attempted. However, pretreatment with 1 mg/kg metergoline negated the adverse effects of this potentially lethal combination.

DISCUSSION

Food intake of female rats was reduced by relatively large doses of cyclazocine (ED_{50}=11.94 mg/kg, 4.20–44.16, 95% confidence interval). FR-40 operant behavior was disrupted with an ED_{50} of 1.79 mg/kg (1.12–2.69, 95% confidence interval [14]). Although these operant studies were conducted with male rats, while the present studies were conducted with females, we believe that the comparison of the ED_{50} values is valid. Pilot studies in our laboratories have indicated that the reduction of food consumption by males following cyclazocine or quipazine is comparable to that in females (Henck, unpublished observation). Harris [13] has reported disruption of a FI-5 min schedule of food presentation to male rats by cyclazocine in the range of 0.3–1.0 mg/kg, while Adam-Carriere *et al.* [1] have reported a dose-dependent decrease in number of reinforcements obtained by female rats following cyclazocine administration on a DRL schedule of food presentation, with an ED_{50} between 1 and 3 mg/kg. Comparable performance between males and females on various operant schedules has been reported [1, 5, 12, 50].

Some portion of the behavioral disruption after cyclazocine is likely to be dependent on opioid receptor interactions: mu receptor antagonism, as well as kappa and sigma receptor agonism [10, 17, 37, 47, 53, 54]. Effects of cyclazocine in animals [8, 14, 15] and humans [20] are attenuated by the narcotic antagonist naloxone. Endogenous opioid peptides do appear to influence appetite [11, 24–26, 30], and treatment with naloxone can decrease food intake under some circumstances [3, 7, 16, 33, 44]. That this may be due to an interference with a general opioid-mediated reward system has been refuted [45]. Cyclazocine might be expected to depress feeding in rats, since morphine can enhance it in satiated animals [43, 48, 49]. However, morphine has been reported to decrease intake in food-deprived rats [42]. Kappa agonists also appear to enhance food intake in satiated rats [22, 30, 31, 43] and decrease it in food-deprived subjects [31]. Sigma agonists (N-allyl-normetazocine, phencyclidine) decrease intake in free-feeding dogs [52] and in food-deprived rats (Henck, unpublished observations). Thus the effects of drugs interacting with opioid receptors to influence appetite are complex.

The disruption of operant responding by cyclazocine involves serotonergic as well as opioid mechanisms [14]. Since quipazine increased the anorectic effects of a larger dose of cyclazocine, and this potentiation was partly antagonized by metergoline, cyclazocine may affect feeding to some degree by an influence on 5-HT mechanisms. On the contrary, quipazine antagonized the disruption of FR-40 behavior induced by a much smaller dose of cyclazocine; this antagonism was also reversed in part by metergoline pretreatment [36]. Therefore, while the anorexia after a large dose and the FR-40 disruption after a small dose of cyclazocine both appear to be mediated by 5-HT effects, they probably involve different neuronal systems. The system mediating effects on FR-40 behavior is much more sensitive and presumably involves cognitive processes.

The potency of quipazine to decrease food intake (ED_{50}=1.41 mg/kg, 0.02–7.24, 95% confidence interval) was in the same range as that to disrupt FR-40 responding (ED_{50}=1.80 mg/kg, 1.17–2.58, 95% confidence interval [28,36]). Therefore, the effects of quipazine on operant behavior may relate primarily to a motivational component for food intake. Both the anorectic and FR-40 disruptive effects of quipazine are antagonized by pretreatment with metergoline and other 5-HT antagonists [6, 28, 40, 41], supporting a 5-HT agonistic mechanism [2, 9, 21]. Although quipazine also acts on catecholamine systems, this occurs at much larger doses [27,41]. Part of the quipazine anorectic action may be mediated via peripheral 5-HT effects [18, 34,

38]. A subthreshold dose of cyclazocine did not significantly influence the anorectic dose-response pattern of quipazine, and it did not potentiate the FR-40 effects of quipazine [36], suggesting again that the same mechanism is responsible for both quipazine effects (i.e., lack of motivation for food).

We observed no change in locomotor activity after doses of 1–32 mg/kg cyclazocine, while others have reported increases [15] or decreases [51] in this dose range. Combination of cyclazocine with a small dose of quipazine reduced (2 mg/kg of the opiate) or increased (32 mg/kg of the opiate) locomotor activity relative to control. Since both of these effects were blocked by metergoline, they appear to relate to increased 5-HT activity at some brain loci. Effects of other opiates have yielded complex patterns in altering motor activity [4, 19, 36] not easily explained by a unitary hypothesis.

Relatively large doses of quipazine alone (16 mg/kg) were required to decrease motor activity. Combination of quipazine with a small dose of cyclazocine caused a decrease in motor activity at 0.5, 1.0, 4.0 and 8.0 mg/kg, but not at 2 mg/kg quipazine. These effects were again reversed by metergoline, suggesting a 5-HT mediation. This contrasts with the report by Samanin *et al.* [39]: 10 and 20 mg/kg of quipazine increased activity of rats being tested also for antinociception. Here the stress of painful stimuli may have potentiated effects of quipazine on dopaminergic mechanisms. Quipazine (15 mg/kg) also interacts with later stages of morphine's actions to potentiate the cataleptogenic activity [23]. Neither cyclazocine nor quipazine singly have effects on locomotor activity at doses that markedly disrupt the FR-40 operant pattern.

Large doses of either cyclazocine or quipazine were required to impair rotarod performance (32 and 11.2 mg/kg, respectively). A subthreshold dose of quipazine (8 mg/kg) greatly potentiated the disruptive effects of cyclazocine and the potentiation after this combination was reversed by metergoline. Likewise, a subthreshold dose of cyclazocine (8 mg/kg) potentiated quipazine for impairing rotarod performance, and metergoline once more acted as an antagonist. These interactions further reinforce the hypothesis that these agents influence behavior in large measure by actions on serotonergic mechanisms. Nevertheless, neither agonist affects rotarod performance at doses that cause marked deficits in FR-40 responding.

The results of this study indicate that cyclazocine may affect operant responding not by reducing the motivation to obtain food, but rather by disruption of cognition. Conversely, quipazine may disrupt operant responding through satiation mechanisms for food appetite. Neither drug appears to affect operant responding by disruption of motor abilities.

ACKNOWLEDGEMENT

The authors wish to express their appreciation to Diane Hummel and Katharine Stoudt for help in preparation of the manuscript.

REFERENCES

1. Adam-Carriere, D., Z. Merali and R. Stretch. Effects of morphine, naloxone, *d,l*-cyclazocine and *d*-amphetamine on behaviour controlled by a schedule of interresponse time reinforcement. *Can J Physiol Pharmacol* **56:** 707–720, 1978.
2. Blundell, J. E. and C. J. Latham. Pharmacological manipulation of feeding behavior: Possible influences of serotonin and dopamine on food intake. In: *Central Mechanisms of Anorectic Drugs*, edited by S. Garattini and R. Samanin. New York: Raven Press, 1978, pp. 83–109.
3. Brands, B., J. A. Thornhill, M. Hirst and C. W. Gowdey. Suppression of food intake and body weight gain by naloxone in rats. *Life Sci* **24:** 1773–1778, 1979.
4. Cervo, L., C. Rochet, S. Romandini and R. Samanin. Evidence of a preferential role of brain serotonin in the mechanisms leading to naloxone-precipitated jumping in morphine-dependent rats. *Psychopharmacology (Berlin)* **74:** 271–274, 1981.
5. Commissaris, R. L., W. H. Lyness, J. J. Cordon, K. E. Moore and R. H. Rech. The effects of *d*-lysergic acid diethylamide (LSD), 2,5-dimethoxy-4-methylamphetamine (DOM) and *d*-amphetamine on operant responding in control and 6-hydroxydopamine-treated rats. *Pharmacol Biochem Behav* **13:** 621–626, 1980.
6. Commissaris, R. L. and R. H. Rech. Antagonism of the behavioral effects of 2,5-dimethoxy-4-methylamphetamine (DOM) and quipazine by metergoline. *Pharmacol Biochem Behav* **15:** 659–662, 1981.
7. Cooper, S. J. Naloxone: Effects on food and water consumption in the non-deprived and deprived rat. *Psychopharmacology (Berlin)* **71:** 1–6, 1980.
8. Dykstra, L. A. Effects of morphine, pentazocine and cyclazocine alone and in combination with naloxone on electric shock titration in the squirrel monkey. *J Pharmacol Exp Ther* **211:** 722–732, 1979.
9. Fuller, R. W., H. D. Snoddy, K. W. Perry, B. W. Roush, B. B. Molloy, F. P. Bymaster and D. T. Wong. The effects of quipazine on serotonin metabolism in rat brain. *Life Sci* **18:** 925–934, 1976.
10. Gilbert, P. E. and W. R. Martin. The effects of morphine- and nalorphine-like drugs in the nondependent, morphine-dependent and cyclazocine-dependent chronic spinal dog. *J Pharmacol Exp Ther* **198:** 66–82, 1976.
11. Grandison, L. and A. Guidotti. Stimulation of food intake by muscimol and beta endorphin. *Neuropharmacology* **16:** 533–536, 1977.
12. Gupta, R. C., R. H. Rech, K. L. Lovell, F. Welsch and J. E. Thornburg. Brain cholinergic, behavioral and morphological development in rats exposed *in utero* to methylparathion. *Toxicol Appl Pharmacol*, in press, 1985.
13. Harris, R. A. Interactions between narcotic agonists, partial agonists and antagonists evaluated by schedule-controlled behavior. *J Pharmacol Exp Ther* **213:** 497–503, 1980.
14. Henck, J. W., D. J. Mokler, R. L. Commissaris and R. H. Rech. Cyclazocine disruption of operant behavior is antagonized by naloxone and metergoline. *Pharmacol Biochem Behav* **18:** 41–45, 1983.
15. Holtzman, S. G. and R. E. Jewett. Stimulation of behavior in the rat by cyclazocine: Effects of naloxone. *J Pharmacol Exp Ther* **187:** 380–390, 1973.
16. Holtzman, S. G. Suppression of appetitive behavior in the rat by naloxone: Lack of effect of prior morphine dependence. *Life Sci* **24:** 219–226, 1979.
17. Holtzman, S. G. Stimulus properties of opioids with mixed agonist and antagonist activity. *Fed Proc* **41:** 2328–2332, 1982.
18. Hong, E., L. F. Sancilio, R. Vargas and E. G. Pardo. Similarities between the pharmacological actions of quipazine and serotonin. *Eur J Pharmacol* **6:** 274–280, 1969.
19. Iwamoto, E. T. Opioid hypermotility in rats: Differential effects of putative μ, κ and σ receptor agonists. *Soc Neurosci Abstr* **5:** 561, 1979.
20. Jasinski, D. R., W. R. Martin and J. D. Sapira. Antagonism of the subjective, behavioral, pupillary, and respiratory depressant effects of cyclazocine by naloxone. *Clin Pharmacol Ther* **9:** 215–222, 1967.
21. Kruk, Z. L. Dopamine and 5-hydroxytryptamine inhibit feeding in rats. *Nature* **246:** 52–53, 1973.

22. Lowy, M. T. and G. K. W. Yim. Stimulation of food intake following opiate agonists in rats but not hamsters. *Psychopharmacology (Berlin)* **81:** 28–32, 1983.
23. Malec, D. and R. Langwinski. Effect of quipazine and fluoxetine on analgesic-induced catalepsy and antinociception in the rat. *J Pharm Pharmacol* **32:** 71–73, 1980.
24. Margules, D. L., B. Moisset, M. J. Lewis, H. Shibuya and C. B. Pert. Beta-endorphin is associated with overeating in genetically obese mice (ob/ob) and rats (Fa/Fa). *Science* **202:** 988–991, 1978.
25. McCay, L. D., N. J. Kenney, N. K. Edens, R. H. Williams and S. C. Woods. Intracerebroventricular beta-endorphin increases food intake of rats. *Life Sci* **29:** 1429–1434, 1981.
26. McLean, S. and B. G. Hoebel. Local injection of morphine or an opiate peptide into the hypothalamic paraventricular nucleus elicits feeding. *Soc Neurosci Abstr* **6:** 532, 1980.
27. Medon, P. J., J. L. Leeling and B. M. Phillips. Influence of quipazine, a potential anti-Parkinsonian agent on the uptake of ^{3}H-dopamine and ^{3}H-serotonin into rat striatal tissue *in vitro*. *Life Sci* **13:** 685–691, 1973.
28. Mokler, D. J., R. L. Commissaris, M. R. Warner and R. H. Rech. Blockade of the behavioral effects of lysergic acid diethylamide, 2,5-dimethoxy-4-methylamphetamine, quipazine and lisuride by 5-hydroxytryptamine antagonists. *J Pharmacol Exp Ther* **227:** 557–562, 1983.
29. Mokler, D. J., R. L. Commissaris, J. W. Henck and R. H. Rech. Naloxone alters the effects of LSD, DOM and quipazine on operant behavior of rats. *Pharmacol Biochem Behav*, in press, 1984.
30. Morley, J. E. and A. S. Levine. Dynorphin-(1–13) induces spontaneous feeding in rats. *Life Sci* **29:** 1901–1903, 1981.
31. Morley, J. E., A. S. Levine, M. Grace and J. Kniep. An investigation of the role of kappa opiate receptor agonists in the initiation of feeding. *Life Sci* **31:** 2617–2626, 1983.
32. Morley, J. E., A. S. Levine, G. K. Yim and M. T. Lowy. Opioid modulation of appetite. *Neurosci Biobehav Rev* **7:** 281–305, 1983.
33. Ostrowski, N. L., N. Rowland, T. L. Foley, J. L. Nelson and L. D. Reid. Morphine antagonists and consummatory behaviors. *Pharmacol Biochem Behav* **14:** 549–559, 1981.
34. Pollock, J. D. and N. Rowland. Peripherally administered serotonin decreases food intake in rats. *Pharmacol Biochem Behav* **15:** 179–183, 1981.
35. Rech, R. H. and R. L. Commissaris. Neurotransmitter basis of the behavioral effects of hallucinogens. *Neurosci Biobehav Rev* **6:** 521–527, 1982.
36. Rech, R. H., D. J. Mokler, R. L. Commissaris and J. W. Henck. Behavioral interactions of opioid agonists and antagonists with serotonergic systems. *NIDA Research Monograph 43: Problems of Drug Dependence, 1983,* pp. 179–184, 1984.
37. Rosecrans, J. A., W. T. Chance and R. M. Spencer. The discriminative stimulus properties of cyclazocine: Generalization studies involving nalorphine, morphine and LSD. *Res Commun Chem Pathol Pharmacol* **20:** 221–237, 1978.
38. Rowland, N., S. M. Antelman and D. Kocan. Differences among 'serotonergic' anorectics in a cross-tolerance paradigm: Do they all act on serotonin systems? *Eur J Pharmacol* **81:** 57–66, 1982.
39. Samanin, R., S. Bernasconi and A. Quattroni. Antinociceptive action of quipazine: Relation to central serotonergic receptor stimulation. *Psychopharmacology (Berlin)* **46:** 219–222, 1976.
40. Samanin, R., C. Bendotti, F. Miranda and S. Garattini. Decrease of food intake by quipazine in the rat: Relation to serotoninergic receptor stimulation. *J Pharm Pharmacol* **29:** 53–54, 1977.
41. Samanin, R., C. Bendotti, G. Candelaresi and S. Garattini. Specificity of serotoninergic involvement in the decrease of food intake induced by quipazine in the rat. *Life Sci* **21:** 1259–1266, 1977.
42. Sanger, D. J. and P. S. McCarthy. Differential effects of morphine on food and water intake in food deprived and freely-feeding rats. *Psychopharmacology (Berlin)* **72:** 103–106, 1980.
43. Sanger, D. J. and P. S. McCarthy. Increased food and water intake produced in rats by opiate receptor agonists. *Psychopharmacology (Berlin)* **74:** 217–220, 1981.
44. Sanger, D. J., P. S. McCarthy and G. Metcalf. The effects of opiate antagonists on food intake are stereospecific. *Neuropharmacology* **20:** 45–47, 1981.
45. Sanger, D. J. and P. S. McCarthy. A comparison of the effects of opiate antagonists on operant and ingestive behavior. *Pharmacol Biochem Behav* **16:** 1013–1015, 1982.
46. Steel, R. G. D. and J. H. Torrie. *Principles and Procedures of Statistics*. New York: McGraw-Hill, 1980.
47. Teal, J. J. and S. G. Holtzman. Discriminative stimulus effects of cyclazocine in the rat. *J Pharmacol Exp Ther* **212:** 368–376, 1980.
48. Tepperman, F. S. and M. Hirst. Concerning the specificity of the hypothalamic opiate receptor responsible for food intake in the rat. *Pharmacol Biochem Behav* **17:** 1141–1144, 1982.
49. Thornhill, J. A., M. Hirst and C. W. Gowdey. Changes in core temperature and feeding in rats by levorphanol and dextrorphan. *Can J Physiol Pharmacol* **57:** 1028–1032, 1979.
50. Tilson, H. A., T. G. Baker, J. H. Chamberlain, W. J. Marquis and R. H. Rech. Behavioral and neuropharmacological analysis of amphetamine and 2,5-dimethoxy-4-methylamphetamine in rats. *Psychopharmacology (Berlin)* **44:** 229–239, 1975.
51. Tortella, F. C., A. Cowan and M. W. Adler. EEG and behavioral effects of ethylketocyclazocine, morphine and cyclazocine in rats: Differential sensitivities towards naloxone. *Neuropharmacology* **19:** 845–850, 1980.
52. Vaupel, D. B. and E. C. Morton. Anorexia and hyperphagia produced by five pharmacologic classes of hallucinogens. *Pharmacol Biochem Behav* **17:** 539–545, 1982.
53. White, J. M. and S. G. Holtzman. Three-choice drug discrimination in the rat: Morphine, cyclazocine and saline. *J Pharmacol Exp Ther* **217:** 254–262, 1981.
54. Zukin, R. S. and S. R. Zukin. Demonstration of [^{3}H]cyclazocine binding to multiple opiate receptor sites. *Mol Pharmacol* **20:** 254–264, 1981.