*Pharmacology Biochemistry & Behavior*, Vol. 36, pp. 299–304. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

# Behavioral and Biochemical Correlates of Chronic Administration of Quipazine

MATILDE VALENCIA-FLORES,*‡[1] EFRAIN CAMPOS-SEPULVEDA,†
JOSE ANTONIO GALINDO-MORALES,‡ MIGUEL LUJAN† AND VICTOR A. COLOTLA*

**Facultad de Psicología and †Facultad de Medicina*
*Universidad Nacional Autónoma de México, Coyoacán 04510, D.F., México*
*‡Instituto Nacional de Neurología y Neurocirugía "Dr. Manuel Velasco Suárez"*
*Insurgentes Sur 3877, Tlalpan 14410, D.F., México*

Received 5 May 1989

VALENCIA-FLORES, M., E. CAMPOS-SEPULVEDA, J. A. GALINDO-MORALES, M. LUJAN AND V. A. COLOTLA. *Behavioral and biochemical correlates of chronic administration of quipazine.* PHARMACOL BIOCHEM BEHAV **36**(2) 299–304, 1990.—In Experiment 1 groups of rats received single injections of 1, 3, 10, 20 or 40 mg/kg quipazine, and their total 24-hr food and water intake after a 24-hr deprivation period was recorded; there was a dose-related reduction of both food and water intake. In Experiment 2 a group of 15 rats received 5 mg/kg/day, SC quipazine during 29 days, and a control group received saline injections. During treatment, all animals were exposed to a 24-hr food and water deprivation schedule, alternated with 24 hr of free access. Food and water consumption was measured 2 and 24 hr after drug injection; regional 5-HT concentrations were determined at 1 and 13 treatment days by fluorometric assay. Beginning the first treatment day, food and water intake decreased, but by the 13th day the quipazine group had returned to normal ingestion levels. 5-HT concentrations were increased in cerebellum and cortex in acute conditions, but after 13 days they had decreased in cerebellar samples. In Experiment 3 we found that the effects of quipazine on food and water ingestion were recovered after 14 days of discontinuing chronic drug administration.

Food consumption Water consumption Tolerance Quipazine 5-HT Body weight Rats

THE role of serotonin (5-HT) in the regulation of food intake is well established. For instance, it has been proposed that this neurotransmitter facilitates satiety in the hypothalamic system, thereby reducing food intake (12). A fruitful approach in the understanding of the serotonergic mechanisms of eating has been the use of diverse drugs directly affecting 5-HT. Quipazine is a serotonergic agonist which reduces food intake with acute administration (1, 13, 20). The reports published to date have employed single drug administrations, with the exception of the work by Rowland, Antelman and Kocan (17), who employed a cross-tolerance paradigm to explore the chronic administration of quipazine. We replicate here the findings of Rowland *et al.* and extend the results to the recovery of the drug effect upon termination of the chronic treatment. Behavioral observations were also carried out to establish the temporal course of gross behavioral changes that could be correlated with alterations in food and water ingestion, since it is known that serotonergic compounds produce certain behavioral effects that could interfere with consumatory behavior. For instance, it has been reported that at low doses, quipazine produces sedation in rats, whereas at high doses, the compound produces the serotonergic syndrome, which consists of stereotyped head movements, intensive sniffing and rubbing the nose with the forepaws, and "piano playing" movements in the rat [e.g., (7,8)].

Finally, it has been shown that chronic administration of anorectic drugs produces changes in central 5-HT receptor numbers and sensitivity [e.g., (19,20)]. At present, we have only limited data concerning the neurochemical changes which might accompany behavioral tolerance. Thus, we assessed regional serotonin levels by biochemical assays during quipazine treatment in the present experiments.

## GENERAL METHOD

### *Subjects*

Male adult albino rats of the Wistar strain were obtained from the breeding colony of the Faculty of Medicine, National Autonomous University of Mexico. Their weights ranged between 250–300 g and were individually housed in clear plastic cages measuring 43 × 29 × 16 cm which contained a food magazine with 400 g Purina Chow pellets and a water bottle. The rats were kept in a room with a 12:12 light-dark cycle with light onset at 0600. They were initially habituated during 14 days before the beginning of the experiment to a deprivation regime of 24 hr unlimited access

[1]Requests for reprints should be addressed to Matilde Valencia-Flores, Instituto Nacional de Neurología "Dr. Manuel Velasco Suárez," Insurgentes Sur 3877, Tlalpan 14410, D.F., México.

to food and water alternated with 24 hr of total deprivation. This deprivation schedule allowed the evaluation of the temporal course of food and water intake up to 24 hr after drug administration. It also allowed determining whether there was immediate recovery in ingestion at the end of 24 hr.

*Drug*

Quipazine maleate was obtained from Miles Laboratories, Inc. (Elkhart, IN). The drug was dissolved in physiological saline and injected SC in a volume equated to body weight of 1 ml/kg. The substance was prepared daily before the beginning of each experimental session.

*Biochemical Assays*

Regional brain 5-HT concentrations were measured after different days of treatment by fluorometric assay (21). Groups of 5 rats each were sacrificed after days 1 and 13 of daily quipazine administration. Similarly, groups of 5 rats each were sacrificed after days 3, 7 and 14 of having suspended drug treatment. For the first group, the animals' sacrifice was carried out through decapitation 2 hr after drug injection and exposure to the food magazine and water bottle. The procedure employed was as follows. Rats were killed by decapitation and brains were rapidly removed and placed on aluminium foil over ice and the dissection of the regions was performed as described by Glowinski and Iversen (6). The brain areas were weighed and homogenized in ice-cold 0.4 N perchloric acid (8 ml/g of tissue). The homogenates were centrifuged for 10 min at 3000 rpm. A 2-ml aliquot of the supernatant was adjusted to pH 10.0 with sodium hydroxide solution and added 0.5 ml of 0.15 M borate buffer at pH 10.0, 1.5 g sodium chloride, and 6 ml n-butanol. Tubes were shaken for 10 min, centrifuged, and the organic phase transferred to 15-ml glass-stoppered centrifuge tubes which contained 6 ml of n-heptane and 2 ml of 0.05 M phosphate buffer, pH 7.00. After shaking for 10 min, the tubes were centrifuged and the organic phase carefully aspirated. A 1.8-ml aliquot of the aqueus phase was transferred to small tubes containing 0.1 ml of 0.1 M ninhydrin solution and the tubes heated for 60 min at 60°C. The tubes were cooled in water, the solution was transferred to a quartz cuvette and the fluorescence measured in Perkin-Elmer spectrophotofluorometer. Activation and fluorescent wavelengths were 385 nm and 490 nm. Blanks were prepared by carrying 2 ml of 0.4 N perchloric acid through the above procedure. The samples of tissues were processed by triplicate and a third tube was added 0.5 μg of 5-HT to calculate the recovery.

*Behavioral Observations*

For Experiment 3, groups of 5 rats each were observed during a 2-hr period in repeated samples of 6 min. Immediately after SC injection of quipazine or saline the animals were individually placed in the Plexiglas cages described previously in the Subjects section. Two trained observers with more than 80% interobserver reliability registered the animals' behavior every 6 min until 2 hr had elapsed. Then, the animals were sacrificed and their brains homogeneized for fluorometric analysis. The behavior categories observed were divided in active (e.g., stereotyped rhythmical head movements, grooming, locomotor activity, circling, and so on) and passive (e.g., lying down on the rear paws with the front extremities extended, immobility, sleeping, and the like). Different groups of rats were studied at days 1 and 13 of daily quipazine administration, and at days 3, 7 and 14 after termination of the drug treatment.

*Experiment 1: Determination of Quipazine Dose-Effect Curve*

Rats were randomly assigned to groups of 8 each and received a single SC injection of saline, or 1, 3, 10, 20 or 40 mg/kg quipazine. Food and water intake were measured at 1, 2, 4 and 24 hr after drug administration. Figure 1 shows the dose-effect accumulated curves for both food and water 24-hr ingestion. There was a nonsignificant increase in both measures with 1 mg/kg, but a dose-related decrease was evident with the other dosages, $F(5,42)=12.44$, $p<0.01$ (food) and, $F(5,42)=16.86$, $p<0.01$ (water). The $ED_{50}$ was determined to be 5 mg/kg. Figure 2 shows the temporal course of the drug effect in food consumption; the effect in water ingestion showed a similar pattern and is thus not shown here. This covariation of water and food intake warrants further investigation, since it cannot be ascertained from our data whether the decrease in water drinking was due to the decrease in food ingestion or whether it is due to an effect upon the central mechanisms regulating water intake, or even a peripheral effect. Thus, we assessed the behavioral alterations in another study (see Experiment 3).

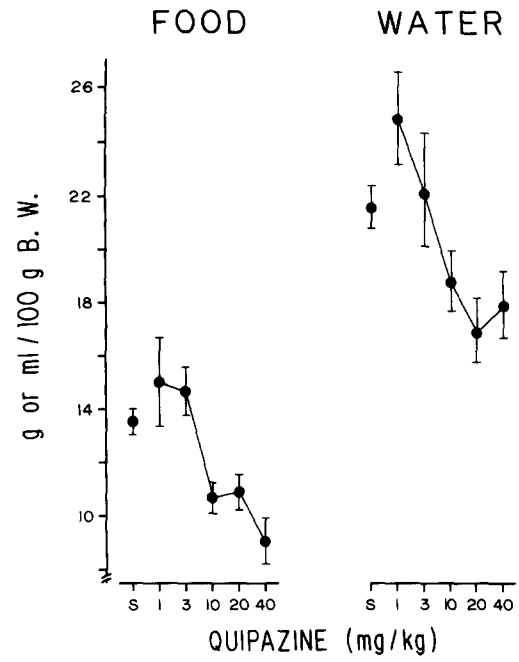


FIG. 1. Total consumption of food and water after 24 hr of SC administration of quipazine maleate. Each point represents the accumulated mean ± SEM of food and water ingestion during a 24-hr period of 6 different groups of 8 rats each. The control group (S) was injected a saline solution. With low doses it is possible to observe a nonsignificant increase in food and water ingestion.

Food intake remained inhibited as long as 4 hr after drug injection with the higher doses, $F(5,42)=6.2$, $p<0.01$, but by 24 hr was back to normal, even higher than control (saline) rats' ingestion.

*Experiment 2: Effects of Repeated Administration of a Single Dose of Quipazine*

Since almost all reports published to date on quipazine have employed only single drug injections, we undertook the present experiment to determine the effects of the repeated administration of this serotonergic drug on food and water ingestion. From Experiment 1 we found the $ED_{50}$ to be 5 mg/kg, hence this is the dose level administered to the rats in the present experiment.

One group of 20 rats was studied during 29 days of drug

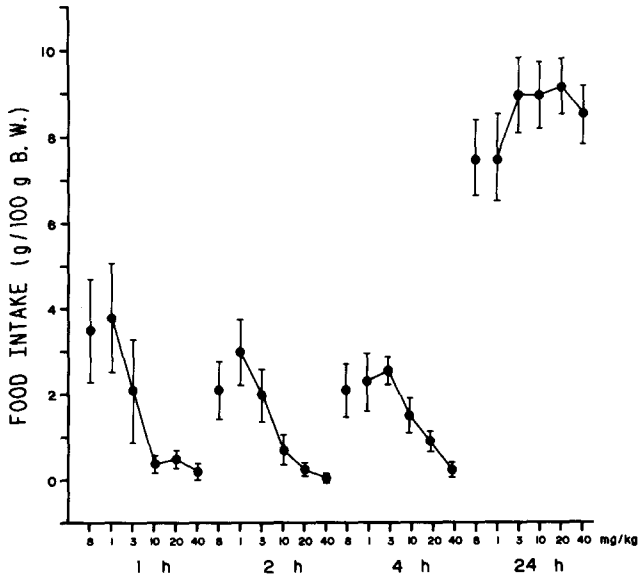


FIG. 2. Temporal course of the effects of SC injection of quipazine on food consumption. Each point represents the mean ± SEM of food ingestion relative to body weight (g/100 body weight) of 8 rats. Each curve shows the effects of quipazine at 1, 2, 4 and 24 hr of administration. Food intakes shown are not accumulative.

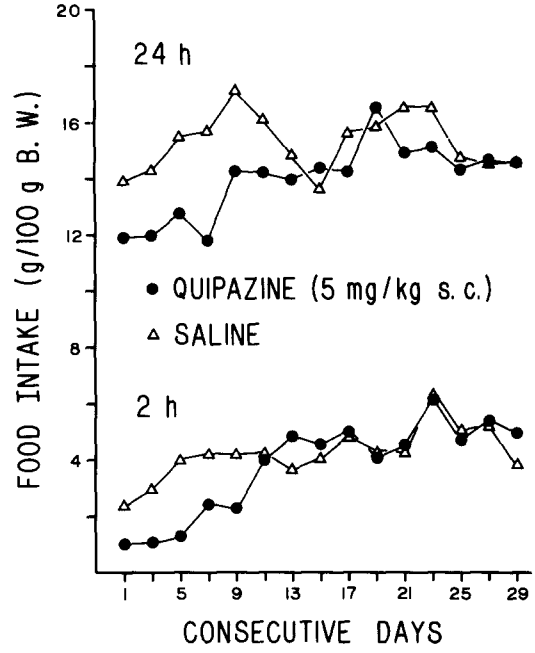


FIG. 3. Temporal course of the repeated SC administration of 5 mg/kg quipazine on food consumption. Filled circles represent mean ingestion of 20 rats under quipazine administration; open triangles represent mean consumption of 20 rats that received saline injections. In the upper part of the figure the curves show total consumption 24 hr after drug administration; the curves in the lower portion show the effect after 2 hr of drug injection.

administration, receiving 5 mg/kg/day SC quipazine; another group of 20 rats received saline injections under the same conditions. As mentioned previously, during this treatment all rats were subjected to a 24-hr free food and water-24-hr deprivation schedule; at 2 and 24 hr after drug injection food and water intake were measured. Data registered were the difference in weight of the animal's daily ration of Purina Chow pellets and the food available in the food magazine of the home cage, and were determined with an accuracy within 0.2 g. Visual inspection of the cage helped to identify food residues not eaten by the rat and left in the floor. Water intake was measured from the difference in volume previously registered in a 250-ml bottle, to the nearest ml. The rats' body weight was measured throughout the experiment.

Figure 3 displays the amount of food eaten at 2 and at 24 hr throughout the repeated administration of quipazine. During the first treatment days a decrease in food consumption is evident in the drug-treated rats, as compared to the control rats, $t = 10.03$, $p < 0.01$ (day 1), thus confirming the observations reported in Experiment 1. However, by day 11 the drug effect on food intake had disappeared and the experimental group did not differ from the saline rats in subsequent days of drug administration, $t(38) = 0.57$, $p > 0.01$ (day 11). Again, the findings for water ingestion were similar. In addition, Fig. 4 depicts the percent difference in body weight for the experimental (quipazine) and control (saline) animals. It should be noted that the body weight of the quipazine-treated rats remains lower than that of control animals (Wilcoxon Test, $Z = -3.25$, $p < 0.01$, for free-access day, upper data; $Z = -3.23$, $p < 0.01$, for deprivation day, bottom data), despite the fact that food and water ingestion had recovered to normal levels (Figs. 3 and 4). This persistence of lower body weight has not been reported frequently for other drugs decreasing food consumption, since weight loss has usually been transient. One exception is fenfluramine, which appears to sustain reduced body weight throughout a 12-week period (15).

Table 1 shows the determination of regional brain 5-HT in groups of rats ($N = 5$) sacrificed 2 hr after either quipazine or saline injection. One group received a single (acute) administration of 5 mg/kg SC quipazine, whereas the other received daily injections of the same dose during 13 days (chronic). Regional concentrations of brain 5-HT (ng/g) were significantly increased, according to ANOVA analyses, both in cortex, $F(1,1) = 11.8$, $p < 0.02$, and cerebellum, $F(1,1) = 72.24$, $p < 0.01$, in the group receiving an acute administration of quipazine, as compared to control rats, whereas chronic administration resulted in a significant decrease of 5-HT in cerebellum, $F(1,1) = 212.74$, $p < 0.005$.

*Experiment 3: Recovery of the Effect of Quipazine on Food and Water Consumption Following the Repeated Administration Treatment*

To assess the time taken for the tolerance to the drug effect on ingestion, and to correlate it with 5-HT levels, rats exposed to the chronic quipazine treatment were allowed to rest for varying periods after the drug condition before receiving single doses of the serotonin agonist.

Two groups of 20 rats each were employed. One group received daily injections of 5 mg/kg SC quipazine during 13 days, whereas the other group received equivalent volumes of saline solution. As can be observed in Fig. 5, the drug-treated rats showed initially a reduction in food intake, eating less than the control animals, but by day 13 of drug treatment this effect had been lost; water intake showed a similar pattern. These findings replicated the results obtained in Experiment 2. Next, the experimental group was divided into 4 groups of 5 rats each; one of those groups received a single quipazine injection (5 mg/kg, SC) 3 days after termination of the chronic treatment, and a control group received a saline injection at the same time. A second pair

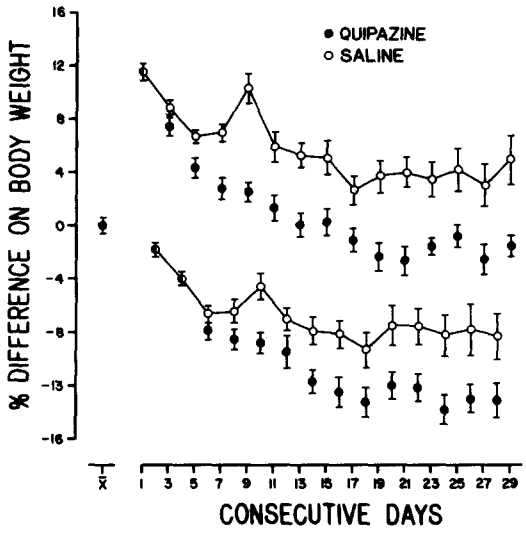


FIG. 4. Reduction in body weight of rats due to repeated administration of 5 mg/kg quipazine each day. Each point represents the change in percentage of body weight with respect to the body weight before the first drug injection. The point at 0 stands for the mean ± SEM of body weight of 20 rats; filled circles represent the values for the quipazine-treated rats, open circles are the values for control, saline rats. The curves in the lower part of the figure are the values obtained 2 hr after quipazine administration, whereas the curves in the upper portion represent the values obtained after 24 hr, in alternate days.

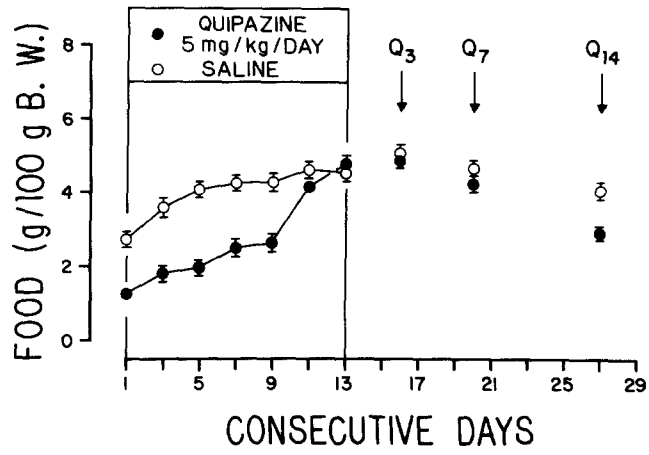


FIG. 5. Loss and recovery of quipazine effects on food intake in rats. Each point represents daily consumption of food relative to body weight (g/100 g body weight) of 20 rats receiving repeated injections of 5 mg/kg/day quipazine (filled circles) or saline (open circles) during a 13-day period (within vertical lines). Drug administration was discontinued when the rats' food consumption reached values similar to control animals. At days 3, 7 and 14 (Q3, Q7 and Q14) the experimental animals were again injected 5 mg/kg quipazine.

of groups received either saline or quipazine injections 7 days after termination of the drug treatment; and the other groups were similarly injected 14 days after the end of the repeated quipazine or saline injections. All animals were subjected to behavioral observations 2 hr after the single, acute, drug administration, and were sacrificed for biochemical assays of 5-HT concentrations. Figure 5 shows the effect of the drug challenges in food consumption: the loss of the effect on food ingestion found with repeated administration of quipazine was maintained up to 7 days after termination of the drug treatment; single injections at days 3 and 7 posttreatment did not produce the reduction in consumption found in Experiments 1 and 2. However, the loss of the effect was transient; rats receiving a drug injection 14 days after the end of the chronic treatment showed again a decrease in food intake (Mann-Whitney U-test, $p<0.05$). Table 2 displays regional concentrations of brain 5-HT after a single injection of quipazine (5 mg/kg SC) on the day 3, 7 or 14 after discontinuation of chronic drug treatment. No significant changes in 5-HT concentrations were evident, except in the cortex in day 14, when there was a significant increase in 5-HT, $F(1,1)=6.87$, $p<0.05$.

With respect to the behavioral observations, Fig. 6 shows the frequency of passive behavior in treated and control rats. Figure 6A displays the data obtained on the first day of drug administration, hence these represent data for the acute administration of quipazine. It is evident that the experimental animals are more passive than the control rats (Mann-Whitney U-test, $p<0.05$), and there is a correlation between passiveness and ingestion: the greater the decrease in eating and drinking, the more passive the animals. Panel B in Fig. 6 shows the same observations, obtained

TABLE 1

REGIONAL CONCENTRATION OF BRAIN 5-HT (ng/g)

| Administration | Region | Saline | Quipazine |
|---|---|---|---|
| Acute | Cerebellum | 398 ± 8 | 473 ± 4* |
| | Cortex | 668 ± 69 | 801 ± 13† |
| | Brain stem | 456 ± 7 | 464 ± 27 |
| | Hypothalamus | 1,398 ± 61 | 1,217 ± 15 |
| Chronic | Cerebellum | 347 ± 69 | 159 ± 13‡ |
| | Cortex | 514 ± 62 | 554 ± 104 |
| | Brain stem | 321 ± 82 | 349 ± 91 |
| | Hypothalamus | 868 ± 1 | 1,224 ± 111 |

Groups of 4 rats each were sacrificed 2 hr after saline or quipazine (5 mg/kg) administration.

All values are mean ± SEM; *$p<0.01$; †$p<0.02$; ‡$p<0.005$.

TABLE 2

REGIONAL CONCENTRATION OF BRAIN 5-HT (ng/g)

| Administration | Region | Saline | Quipazine |
|---|---|---|---|
| 3 Days | Cerebellum | 415 ± 16 | 352 ± 26 |
| | Cortex | 550 ± 134 | 460 ± 15 |
| | Brain stem | 352 ± 14 | 433 ± 43 |
| | Hypothalamus | 531 ± 266 | 1,202 ± 200 |
| 7 Days | Cerebellum | 325 ± 49 | 394 ± 52 |
| | Cortex | 463 ± 32 | 558 ± 64 |
| | Brain stem | 316 ± 49 | 350 ± 33 |
| | Hypothalamus | 558 ± 37 | 558 ± 28 |
| 14 Days | Cerebellum | 393 ± 38 | 361 ± 29 |
| | Cortex | 642 ± 23 | 726 ± 31* |
| | Brain stem | 412 ± 33 | 422 ± 17 |
| | Hypothalamus | 736 ± 15 | 832 ± 103 |

Groups of 5 rats each were sacrificed 2 hr after saline or quipazine (5 mg/kg) administration.

All values are mean ± SEM; *$p<0.05$.

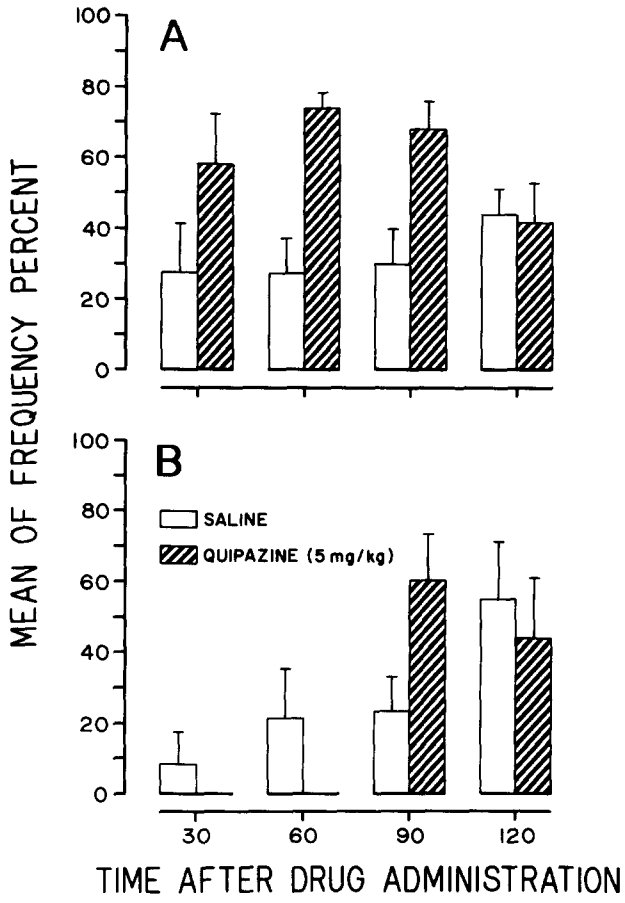


FIG. 6. Passive behavior pattern (e.g., resting with eyes closed) observed with acute administration (Panel A) and with chronic (13 days) administration (Panel B) of 5 mg/kg quipazine. Two trained observers rated the behavior of 5 rats every 6 min. Each bar represents the average frequency ± SEM of passive behavior as a percent of total behavior exhibited within a 30-min period throughout 2-hr observation time. Open bars (saline) show the normal behavior pattern of rats subjected to a 2-hr deprivation period: during the first minutes the rats engage most of the time in ingestive behavior and towards the end of the interval, already satiated, tend to rest. This pattern is altered with acute quipazine injection, but not with chronic administration, when the drug effect on eating behavior has been lost. See text for further details.

on day 13 of repeated quipazine administration. Within the first hr after injection, saline animals are more passive than treated rats; later, the experimental animals are remarkably more passive, and 2 hr after the injection the frequency of passive behavior was about the same in all animals.

## GENERAL DISCUSSION

The first experiment of the series reported here resulted in a decrease in both food and water consumption, a fact which confirms previous findings about the acute effects of quipazine on food consumption (1,13), and adds the report of the drug effects on water drinking. This experiment also allowed the determination of the $ED_{50}$ when groups of rats received varying single doses of quipazine; such $ED_{50}$ was determined to be 5 mg/kg. In addition, we found an increase in food and water intake higher than control levels 24 hr after drug adminstration at small doses, suggestive of a "rebound effect" of the drug. From our data it is impossible to ascertain whether the reduction in food intake was due to the decrease in water drinking, or vice versa, or to some other variable, such as an increase in behavior competing with eating and drinking, e.g., passive behavior. It is known that serotonergics have a remarkable generalized behavioral effect (11). Although this relationship between passive behavior and consumatory activities is discussed later in this paper, it is a matter that still requires further experimental research. On the other hand, it should be noted that with our experimental procedure it is possible to separate drug effects on eating and drinking: recent data from our laboratory (submitted) show that acute injections of fluprazine hydrochloride, a phenylpiperazine, have adipsic but not anorectic effects.

Experiment 2 and 3 confirmed the Rowland *et al.*'s finding (17) of tolerance to quipazine effects on food consumption, adding evidence for a similar effect on water intake, with repeated administration of the substance; however, the tolerance is lost 14 days after the chronic treatment is discontinued, since a single injection of quipazine brought about a reduction in food and water intake similar to the effect observed with first drug injection. The long time (14 days) taken for the recovery of such an effect strongly suggests biochemical changeovers with chronic quipazine administration. In fact, a recent experiment (10) concluded that quipazine reduces food intake by activation of 5-$HT_2$-receptors, since the drug's anorectic effect could be blocked by administration of either a nonselective 5-HT-receptor antagonist, methysergide, or the selective 5-$HT_2$-receptor antagonists, ketanserin and ritanserin.

The gradual increase in food and water intake during the repeated administration of quipazine could be due to tolerance or to the maintenance of a new weight level, according to the set point theory [e.g., (22,23)]. This is a matter awaiting empirical attention. On the other hand, the effect on ingestive behavior induced acutely by quipazine, the loss of this effect upon chronic administration, and the recovery of this phenomenon after several days of discontinuing the chronic quipazine administration, might represent changes at the receptor level. This possibility is further stressed by the observation from our laboratory that there were changes in the in vitro sensitivity of pieces of intestine obtained from animals treated acutely, chronically or after stopping the chronic administration of quipazine (14).

The regional changes in brain 5-HT reported in Table 2 suggest that the recovery of the drug effect on ingestive behaviors may be due to changes at the receptor level, since as mentioned before there was a significant decrease in 5-HT concentrations in cerebellum with the chronic treatment. Other authors (19) have suggested that the reduction of central 5-HT-receptors could account for the decreased effects of fenfluramine, but apparently, no previous report of cerebellum involvement in ingestive behavior has been published to date. Whether this might reflect a cause or an effect of this drug upon 5-HT levels remains to be seen. However, some behavioral changes as well as qualitative and quantitative alterations in the sensitivity of cerebellar Purkinje cells to iontophoretically applied 5-HT were observed in rats with dietary deficiency (15).

Measures of the animals' body weight in Experiment 2 showed a monotonic decrease in the percent difference in body weight for all animals, with a greater weight loss in the rats receiving quipazine. Of particular importance is the fact that the body weight of quipazine-treated rats continued to be low even after day 13, when the ingestive effects induced by the drug were lost, according to its effect on food and water consumption.

Finally, from Experiment 3 it is evident that quipazine is not a very selective compound, since it affects activity in general. However, it is important to underline the relationship between passive behavior and a reduction in ingestive behavior: the greater

the degree of food and water reduction the more passive were the animals. Blundell *et al.* (2–4) had demonstrated that a serotonergic drug like fenfluramine reduces the overall size of meals, and it was tentatively suggested that this drug may act via a satiety system to bring meals to a premature termination. From the pattern observed in Fig. 6, quipazine increased the frequency of incompatible behavior under acute administration and consequently it reduced feeding and drinking behavior. Conversely, under chronic administration quipazine remarkably decreased passive behavior at the beginning of the 2-hr food interval and increased passive behavior around 1 and one-half hr later. Green *et al.* (9) reported also a decrement in motor activity in rats receiving acute intraventricular administration of serotonin. These findings are at variance to the behavioral observations with other anorectic compounds, such as amphetamine: it has been known that there is a negative correlation between activity and feeding in amphetamine-treated rats (5). For instance, a recent experiment (18) assessing the role of anorexia and behavioral activation in amphetamine-induced suppression of feeding concluded that the initial suppression of intake is due to both anorexia and behavioral interference.

ACKNOWLEDGEMENTS

We are grateful to Antonio Javier Sevilla for expert technical assistance. These experiments were partially supported by Research Grant PCALBNA-020892 from the Consejo Nacional de Ciencia y Tecnología (CONACYT) and by Grant 26/85 from the Fondo Ricardo J. Zevada. V.A.C. also had support of a Sabbatical Fellowship (48370) from CONACYT.

## REFERENCES

1. Antelman, S. M.; Rowland, N.; Kocan, D. Anorectics: Lack of cross-tolerance among serotonergic drugs and sensitization of amphetamine's effect. In: Garattini, S.; Samanin, R., eds. Anorectic agents: Mechanisms of action and tolerance. New York: Raven Press; 1981.
2. Blundell, J. E.; Leshem, M. B. Analysis of the mode of action of anorexic drugs. In: Howard, A., ed. Recent advances in obesity research. London: Newman; 1975:368–371.
3. Blundell, J. E.; Latham, C. J. Pharmacological manipulation of feeding behavior: Possible influences of serotonin and dopamine on food intake. In: Garattini, S.; Samanin, S. Central mechanisms of anorectic drugs. New York: Raven Press; 1978:83–109.
4. Blundell, J. E.; Latham, C. J.; Leshem, M. B. Differences between the anorectic actions of amphetamine and fenfluramine: Possible effects on hunger and satiety. J. Pharm. Pharmacol. 28:471–477; 1976.
5. Cole, S. O. Brain mechanisms of amphetamine-induced anorexia, locomotion and stereotypy: A review. Neurosci. Biobehav. Rev. 2:89–100; 1978.
6. Glowinski, J.; Iversen, L. L. Regional studies of catecholamines in the rat brain. I. The disposition of [$^3$H]-norepinephrine, [$^3$H]-dopamine and [$^3$H]-dopa in various regions of the brain. J. Neurochem. 13:655–669; 1966.
7. Grabowska, M.; Antkiewicz, L.; Michaluk, J. A possible interaction of quipazine with central dopamine structures. J. Pharm. Pharmacol. 26:74–76; 1974.
8. Green, A. R.; Youdim, M. B. H.; Grahame-Smith, D. G. Quipazine: Its effects on rat brain 5-hydroxytryptamine metabolism, monoamine oxidase activity and behaviour. Neuropharmacology 15:173–179; 1976.
9. Green, R. A.; Gillin, J. C.; Wyatt, R. J. The inhibitory effect of intraventricular administration of serotonin on spontaneous motor activity of rats. Psychopharmacologia 51:81–84; 1976.
10. Hewson, G.; Leighton, G. E.; Hill, R. G.; Hughes, J. Quipazine reduces food intake in the rat by activation of 5-HT-$_2$-receptors. Br. J. Pharmacol. 95:598–604; 1988.
11. Hoebel, B. G. The psychopharmacology of feeding. In: Iversen, L. L.; Iversen, S. D.; Snyder, S. H., eds. Handbook of psychopharmacology. vol. 8. Drugs, neurotransmitters, and behavior. New York: Plenum; 1977:55–129.
12. Hoebel, B. G. Neurotransmitters in the control of feeding and its rewards. Monoamines, opiates and brain-gut peptides. In: Stunkard, A. J.; Stellar, E., eds. Eating and its disorders. New York: Raven Press; 1984:15–38.
13. Hong, E.; Sancillio, L. P.; Vargas, R.; Pardo, E. Similarities between the pharmacological actions of quipazine and serotonin. Eur. J. Pharmacol. 6:274–280; 1969.
14. Jiménez, P.; Solís, P.; Valencia, M.; Campos, E.; Galindo, J. A.; Colotla, V. A.; Luján, M. Cambios en la sensibilidad del receptor serotonérgico periférico, inducido por la administración repetida de quipazina. Posible relación con la pérdida del efecto anoréxico. Congreso Nacional de Ciencias Fisiológicas, 30:1987.
15. Lee, R. S.; Strahlendorf, H. K.; Strahlendorf, J. C. Enhanced sensitivity of cerebellar Purkinje cells to iontophoretically-applied serotonin in thiamine deficiency. Brain Res. 327:249–258; 1985.
16. Munro, J. F. The management of obesity. In: Anorexia nervosa and obesity. Royal College of Physicians, Symposia No. 42:100–109; 1973.
17. Rowland, N.; Antelman, S. M.; Kocan, D. Differences among serotonergic anorectics in a cross-tolerance paradigm: Do they all act on serotonin systems? Eur. J. Pharmacol. 81:57–66; 1982.
18. Salisbury, J. J.; Wolgin, D. L. Role of anorexia and behavioral activation in amphetamine-induced suppression of feeding: Implications for understanding tolerance. Behav. Neurosci. 99:1153–1161; 1985.
19. Samanin, R.; Mennini, T.; Ferraris, A.; Bendotti, C.; Borsini, F. Hyper- and hyposensitivity of central serotonin receptors: [$^3$H]Serotonin binding and functional studies in the rat. Brain Res. 189:449–457; 1980.
20. Samanin, R.; Caccia, S.; Bendotti, C.; Borsini, F.; Borroni, E.; Invernizzi, R.; Pataccini, R.; Mennini, T. Further studies on the mechanism of serotonin-dependent anorexia in rats. Psychopharmacology (Berlin) 68:99–104; 1980.
21. Snyder, S. H.; Axelrod, J.; Zweig, M. A sensitive and specific fluorescence assay for tissue serotonin. Biochem. Pharmacol. 14: 831–835; 1965.
22. Stunkard, A. J. Anorectic agents: A theory of action and lack of tolerance in a clinical trial. In: Garattini, S.; Samanin, R., eds. Anorectic agents: Mechanisms of action and tolerance. New York: Raven Press; 1981:191–210.
23. Wolgin, D. L. Tolerance to amphetamine anorexia: Role of learning versus body weight settling point. Behav. Neurosci. 97:549–562; 1983.