# EFFECT OF CYPROHEPTADINE ON BAR-PRESSING FOR FOOD REWARD IN RATS

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**Summary :** Lever pressing rate under a continuous reinforcement schedule for food reward in rats was reduced significantly by cyproheptadine in the dose of 5 and 10 *mg/kg* body weight. Under fixed ratio schedule of reinforcement, the responding was also suppressed significantly by 5 and 10 *mg/kg* body weight doses of cyproheptadine. However, high dose (20 *mg/kg*) of cyproheptadine administered subsequent to the low doses, failed to inhibit the bar pressing rate under either continuous or fixed ratio schedules.

Although a higher dose of cyproheptadine also reduced bar-pressing rates initially, the response showed tendency to return to normal level after 6 days, because of tolerance.

**Key words:** cyproheptadine food reward serotonin (5-HT) continuous reinforcement schedule fixed ratio reinforcement schedule

## INTRODUCTION

Systemic administration of cyproheptadine, a serotonin antagonist (9) in various doses is known to stimulate appetite and to increase body weight in humans (2, 8), cats (3) and rats (1, 7). This implies that brain serotonin exerts an inhibitory influence on the control of food intake. Further, recently it has been reported that serotonin releasing agents like fenfluramine reduce food intake as well as lever pressing activity for food reward (5). These studies also provide evidence that serotonin exerts inhibitory influence on feeding. From this, it is logical to imply that with cyproheptadine, a serotonin antagonist, the lever pressing activity for food reward, which is a tool to assess the motivation for feeding behaviour should increase. However, Chakrabarty *et al.* (4) reported that a dose of cyproheptadine reduced lever pressing activity for food reward in rats trained under continuous reinforcement schedule and attributed this to a sedative effect on the rats. In view of this and little information available on the effect of cyproheptadine on food motivation, the present work was planned to investigate further the effects of various

doses of cyproheptadine on food motivation in rats trained under continuous as well as intermittent schedules.

## MATERIALS AND METHODS

Male albino rats weighing 150–200 g were randomly divided into three groups (CR; $FR_2$, $FR_4$) of six each for behavioural testing. Animals were housed at controlled temperature (24 ± 1°C) with 14.00 hr light and 10.00 hr dark schedule.

After adaptation to the laboratory conditions, each rat was deprived of food 18 hr prior to each session. Tap water was, however, allowed *ad libitum*.

*Study of operant behaviour :*

An operant chamber (Takei & Co) was utilized to train rats on different reinforcement schedules. Food reward consisting of 45 *mg* pellet was automatically delivered from the feeder into a food cup located below the lever. The animal was trained to press the lever to obtain the food reward.

Under continuous reinforcement (Group CR), rat received a pellet for each bar press. The schedule was altered for intermittent reinforcement by adjusting the pellets in the feeder so as to provide the animal a reward for every two bar presses (Group $FR_2$, 2 : 1) or every four bar presses (Group $FR_4$, 4 : 1).

Animals were initially trained so that all rats in CR, $FR_2$ and $FR_4$ groups were reinforced on continuous, 2 : 1 and 4 : 1 fixed ratio schedules respectively. Each training session lasted for 30 min at the same time of the day. Total number of lever responses for the duration of the session was recorded.

The animals at the end of the initial training lasting for 6 days attained a maximum and almost constant asymptote of the number of bar presses per session in their respective schedules.

Following the behavioural acquisition, cyproheptadine hydrochloride (CPH) (MSD, Bombay, India) dissolved in distilled water was administered subcutaneously as a salt in the dose of 5.0 *mg/kg* to all rats in each group. Thirty minutes after cyproheptadine injection, rats were again tested daily under their corresponding reinforcement session to 60 min fordays.

Every animal in each group was subsequently subjected to same behavioural testing for 6 days, after administration of cyproheptadine in the dose of 10.0 *mg/kg* followed by 20.0 *mg/kg*.

*Group D* : An additional group of 12 rats was trained on CR, $FR_2$ and $FR_4$ (4 rats each) schedules. These animals were further studied after administration of CPH in the dose of 20 *mg/kg* without prior exposure to lower doses.

## RESULTS

*Behavioural acquisition :*

In intermittent reinforcement schedules (Groups $FR_2$ and $FR_4$) response rates were higher than that in continuous reinforcement schedule (Group CR) (Figs. 1, 2 and 3).

*Response after cyproheptadine :*

*Group CR* : At lower doses of CPH (5 and 10 *mg/kg*) the response rates were significantly reduced and remained at low levels throughout the 6 days of testing

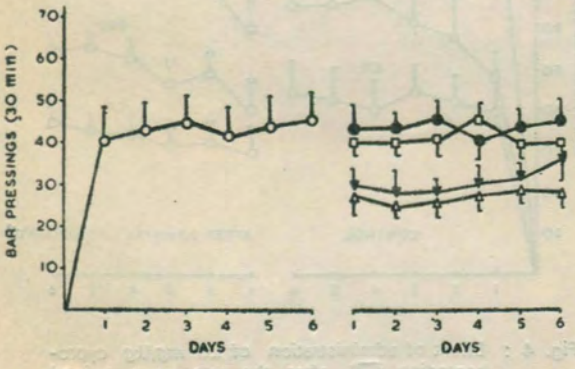


Fig. 1 : Effect of administration of cyproheptadine in successive doses of 5 *mg/kg* (Δ), 10 *mg/kg* (▼) and 20 *mg/kg* (□) body weight, on bar pressing rates recorded for 30 min for 6 consecutive days. The rats were previously trained under continuous reinforcement schedule ( O ) for 6 days. A group of 6 rats trained under the same schedule recieved distilledwater (●) during the testing period. Each point represents mean of responses recorded in 6 rats. Vertical bars represent SE of the mean.

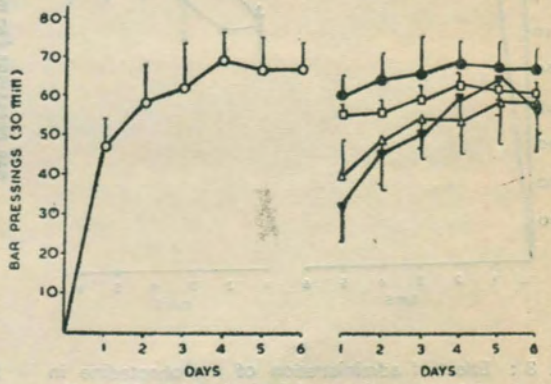


Fig. 2 : Effect of administration of cyproheptadine in successive doses of 5 *mg/kg* (Δ), 10 *mg/kg* (▼) and 20 *mg/kg* (□) body weight, on bar pressing rates recorded for 30 min for 6 consecutive days. The rats were previously trained under 2 : 1 variable reinforcement schedule ( O ) for 6 days. A groups of 6 rats trained under the same schedule received distilled water (●) during the testing period. Each point represents mean of responses recorded in 6 rats. Vertical bars represent SE of the mean.

($P<0.001$ for 5 *mg/kg* and $P<0.001$ for 10 *mg/kg*). However, when this group was exposed subsequently to high dose (20 *mg/kg*) the response rate reverted to control level ($P<0.2$), (Fig. 1).

*Group $FR_2$ and $FR_4$* : Cyproheptadine was effective in significantly reducing the bar pressing response at lower doses (5 and 10 *mg/kg*), the P value being $<0.1$; $<0.05$ in $FR_2$ group and $<0.001$; $<0.01$ in $FR_4$ group after 5 and 10 *mg/kg* CPH dose respectively. However, this inhibition was not consistent throughout the period of drug administration. The animal showed tendency to regain their normal rates after few days of treatment. Increasing the dose (20 *mg/kg*) did not potentiate the inhibitory response in both ($FR_2$ and $FR_4$ groups) groups ($P = NS$). On the other hand the animals showed normal bar-pressings at this high dose (Figs. 2 and 3).

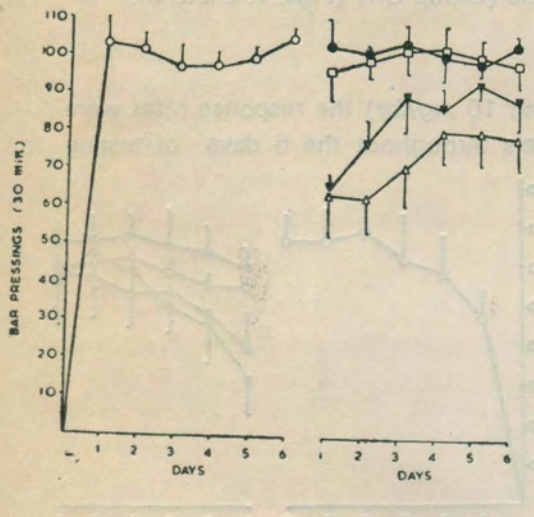


Fig. 3 : Effect of administration of cyproheptadine in successive doses of 5 *mg/kg* (Δ), 10 *mg/kg* (▼) and 20 *mg/kg* (□) body weight, on bar pressing rates recorded for 30 min for 6 consecutive days. The rats were previously trained under 4 : 1 variable reinforcement schedule (O) for 6 days. A group of 6 rats trained under the same schedule received distilled water (●) during the testing period. Each point represents mean of responses recorded in 6 rats. Vertical bars represent SE of the mean.

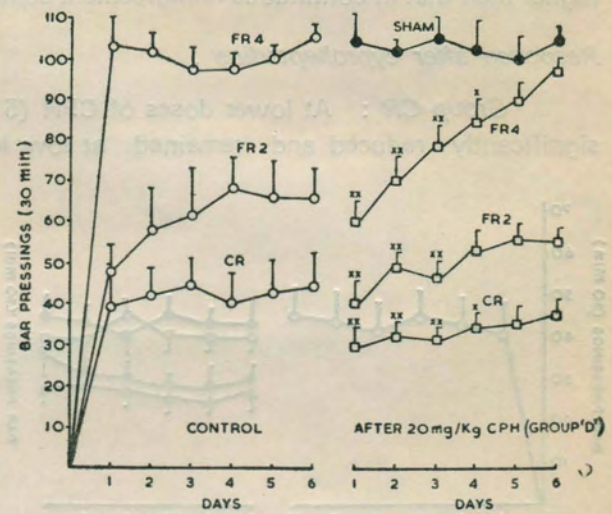


Fig. 4 : Effect of administration of 20 *mg/kg* cyproheptadine (□) after the rats were trained under CR, $FR_2$ and $FR_4$ schedules (O) for six days. Significant reeduction (XX = $P<0.001$ ; X = $P<0.01$) in bar-pressings was observed initially. Other values (□) are not significant. Only sham group under $FR_4$ schedule is included in this figure. Values for sham group under CR and $FR_2$ (excluded in this figure) are same as in Fig. 1 and Fig. 2.

*Group D* : When animals were exposed to high dose of CPH, without prior testing with low doses, CPH reduced the bar-pressing rates initially, but even in these rats, the response showed tendency to return to normal levels after 6 days (Fig. 4).

*Sham group* : Throughout the testing period, another group of 6 rats trained under corresponding schedules received only distilled water and showed no difference in bar-pressing rates to control rates.

## DISCUSSION

Bar-pressing rates under CR, $FR_2$ and $FR_4$ schedules are effectively inhibited by 5 *mg/kg* and 10 *mg/kg* doses of CPH. Higher dose subsequent to low dose could not reduce bar-pressing rates significantly. Behavioural (4) and electro-encephalographic studies (3), after administration of CPH in animals have shown its sedative effect. This drug is not only a serotonin but also a histamine antagonist (9). Present study cannot exclude this effect of CPH in producing drowsiness which is attributed to decreased levels of bar-pressings (4) in rats.

Effect of CPH on responding under different reinforcement schedules of food reward appears to be in conflict with its effect on food intake seen in other studies (1, 7).

Lever pressings in our study were almost restored to normal level after administration of increasing doses of CPH. These findings suggest development of tolerance to CPH. It may be argued that the tolerance to the drug developing over long period on administration of successive higher doses would be indistinguishable from decreasing depression with increasing doses. But independant administration of high dose (20 *mg/kg*) to separate groups of animals has demonstrated that higher dose as such reduced bar pressing rates initially, but the response showed tendency to return to normal level after 6 days especially in $FR_4$ schedule. These results provide further evidence in support of the development of tolerance to this drug. Such tolerance was not observed by Chakrabarty *et al.* (4) since they studied the effect of a single dose of CPH on rats trained under CR schedule alone.

Fuxe *et al.* (6) have shown that partial blocking of 5-HT receptors in limbic system by agents like 5-7, dihydroxytryptamine (5-7, DHT) also leads to decreased lever pressing activity. CPH in low doses may also produce similar actions like 5-7 DHT, by partial blocking of 5HT receptors. As the neuropharmacological mode of action of CHP is far from clear, 5HT depleting effects of varying doses of CPH on limbic system needs

further investigation. Such scrutiny will help in understanding the basis of varying effects of CPH in different doses, on operant behaviour.

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