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# Centrally Administered Cycloheximide in Rats: Behavioural Concomitants and Modulation of Amnesic Effects by Biogenic Amines[1]

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DAY, T. A., D. H. OVERSTREET, AND G. D. SCHILLER. *Centrally administered cycloheximide in rats: Behavioural concomitants and modulation of amnesic effects by Biogenic amines.* PHARMAC. BIOCHEM. BEHAV. 6(5) 557–565, 1977. – The behavioural consequences of centrally administered cycloheximide (400 μg, intraventricularly) were examined at various times after the injection and compared with the degree of protein synthesis inhibition. Operant behaviour (FR3 responding for water reward) was significantly depressed at 1, 2, 4, 6, 8, 10 and 12 hr after the injection but not at 24 hr, while general locomotor activity was significantly depressed at all time points except 1 and 24 hr. Amnesia for a passive avoidance response was observed when the cycloheximide was administered 1, 3, 5, 7, and 9 hr before the training trial but not at 11 or 17 hr. Protein synthesis was found to be maximally inhibited (80%) at 1 and 2 hr, moderately inhibited (60%) at 4, 6, and 8 hr, less but still significantly inhibited (40%) at 12 hr and slightly elevated (15%) at 24 hr after the central injection of cycloheximide. Posttraining administration of l-tryptophan (100 mg/kg) or corticosterone (5 mg/kg) significantly reversed the amnesia produced by a central injection of cycloheximide given 5 hr before training, while imipramine (5 mg/kg), d-amphetamine (5 mg/kg) and hydrocortisone (5 mg/kg) were without significant effect. These results suggest that the disruption of passive avoidance memory by centrally administered cycloheximide may not be related to the inhibition of synthesis of memory-specific protein, but rather to a depression of central levels of biogenic amines, particularly serotonin.

Cycloheximide  Protein synthesis inhibition  Behavioural depression  Amnesia  Passive avoidance  Biogenic amines

THERE NOW exists a considerable information on the memory-disruptive effects of protein synthesis inhibitors such as puromycin and cycloheximide (CXM) [See [5] and [15] for reviews]. A number of controversies have developed, however, and it is presently unclear whether the memory-disruptive effects of these agents can be ascribed solely in the inhibition of synthesis of memory-specific protein. For example, some workers have suggested that inhibition of adrenal steroidogenesis [25] or catecholamine synthesis [10,11] may be more directly related to the amnesic properties of putative inhibitors of protein synthesis, while others [33,34] have discounted these alternative explanations.

Part of the controversy in this area may be related to the fact that the majority of previously published papers have administered the drugs peripherally so that inhibition of protein synthesis outside of the central nervous system cannot be ruled out as a factor. Recently, however, Tucker and Gibbs [36] reported a significant amnesic effect of centrally administered CXM in rats in a taste aversion paradigm. The present report has adapted the above procedure and examined the time course of effects of centrally administered CXM on several behavioural parameters and protein synthesis.

## GENERAL METHOD

### *Animals*

Male Hooded-Wistar rats, bred in the Flinders University Animal House were used. These animals were housed in

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groups under conditions of continuous light and were given free access to food and water, except where otherwise stipulated. Age and weight ranges will be described in the appropriate sections for the separate experiments.

*Central Administration of CXM*

The technique of intracerebral injection was a modified version of that described by Noble *et al.* [27]. Animals were anesthetised with ether, which was administered as required during the course of the operation by means of a small gauze mask. A midsagittal scalp incision was made, the skin reflected and the cranial bone cleaned. A small hole was then bored by means of a hand drill at a position 1.5–2.0 mm lateral to the sagittal suture and immediately posterior to the coronal suture over the left hemisphere. A 25 gauge needle, attached to a 100 μl Hamilton syringe via 10 cm of polyethylene tubing, was then lowered into the hole by means of the carrier of a stereotactic device. The needle was fitted with a stop such that it penetrated 4.0 mm below the cranial surface. Thirty μl of solution was injected directly into the ventricle, usually over a period of one min. The hole was filled with bone wax immediately after removal of the needle in order to prevent loss of the solution from the brain cavity. The incision was then closed with wound clips. The entire operation normally took five min and all animals regained consciousness within 2–3 min after completion of the operation. Experimental animals received 400 μg of CXM dissolved in 30 μl of isotonic saline (adjusted to pH 6.0–7.0), while controls received 30 μl of the saline vehicle.

Needle placement, by means of the above technique, was verified by histological examination of a number of animals. In the majority of cases the needle was found to have penetrated the left ventricle as required, and to have gone no further. In no case was there any evidence of tissue damage at the delivery site.

*Analysis of Data*

All data were analysed by means of nonparametric statistics [31] after it was determined that there were significant differences among the variances of several groups. Although the data were analysed by nonparametric statistics, they were visually displayed using means and standard errors, as this method of presentation was considered to more effectively convey the group variability.

## BEHAVIOURAL EFFECTS OF CYCLOHEXIMIDE

In preliminary experiments it appeared that a number of rats were severely depressed following the central administration of CXM at 4½ hr before the time of training for a passive avoidance task. Since this behavioural depression might complicate interpretations of CXM's effects on memory, it was decided to quantify the degree of depression. This experiment examined the effects of CXM upon locomotor activity and operant responding for a water reward over a 24-hr period following its central administration.

*Method*

*Animals.* The animals were 42 male rats, weighing 200–400 g and 100–160 days old at the beginning of the experiment. They were randomly divided into two groups of 21. Animals in the experimental groups received an intraventricular injection of 400 μg of CXM at 1, 2, 4, 6, 8, 12 or 24 hr prior to testing. The animals in the control groups were treated identically except that they only received an intraventricular injection of isotonic saline.

*Procedure.* Locomotor activity measurements were made in rectangular glass chambers (50 × 30 cm) in a quiet room illuminated solely by a red fluorescent lamp. The bases of these chambers were divided into 15 squares, each 10 × 10 cm. One count was registered each time that both of a rat's forepaws crossed one of the lines on the base of the chamber.

For assessment of operant responding the animals were initially trained to obtain their water by pressing a bar in a standard operant chamber (See [29]). They were then maintained on an FR3 schedule until a stable level of responding (less than 10% variation over three consecutive sessions) was attained. The sessions were 15-min in duration and were followed by a 15-min period of access to a water bottle in the home cage. Most animals attained stable levels of responding within 10 days. As soon as the above criterion was reached, animals were randomly assigned to one of the above time points and operated on at an appropriate time prior to the next session in the operant chamber.

At the time of testing, a cumulative measure of an animal's locomotor activity was first taken over a 5-min interval. It was then placed in an operant chamber for its normal 15-min session and the percentage change in the number of responses relative to baseline (mean of responses of the last three sessions) was calculated.

*Results and Discussion*

The effects of CXM upon locomotor activity are summarised in Fig. 1. There were no significant differences among the saline-treated groups according to the Kruskal-Wallis Test, $H(6) = 2.50$, $p > 0.05$, suggesting that the groups are comparable. In contrast, the CXM-treated rats were significantly less active than the control animals at 2, 4, 6, 8, and 12 hr after the injection ($U = 0$ at all time points, $p < 0.05$). There were no significant differences between the groups at 1 and 24 hr following the injections.

Significant differences were observed among the saline-treated groups for operant responding, $H(6) = 14$, $p < 0.05$ as can be seen in Fig. 2. There was a significant depression in behaviour at 1 and 2 hr following the operation, while the rate of responding at the other time points was somewhat elevated. These data suggest that ether, which was used as the anesthetic during the operations, has relatively long-lasting effects on behaviour which can only be picked up by using sensitive behavioural measures.

The CXM-treated animals performed at a significantly reduced rate at all time points ($U = 0$ at all points, $p < 0.05$). However, they have clearly returned to their baseline level of responding within 24 hr; this group was only significantly different from its corresponding control group because the latter exhibited an increased rate of responding.

The above results indicate that CXM clearly has significant behavioural effects for up to 12 hr following its central administration. However, the operation procedure itself may also have effects, as was seen with the more sensitive operant response measure. This latter effect is probably related to use of ether as the anesthetic, as this drug has been reported to have biochemical effects which are likely to have behavioural consequences [8,19]. Thus, it is

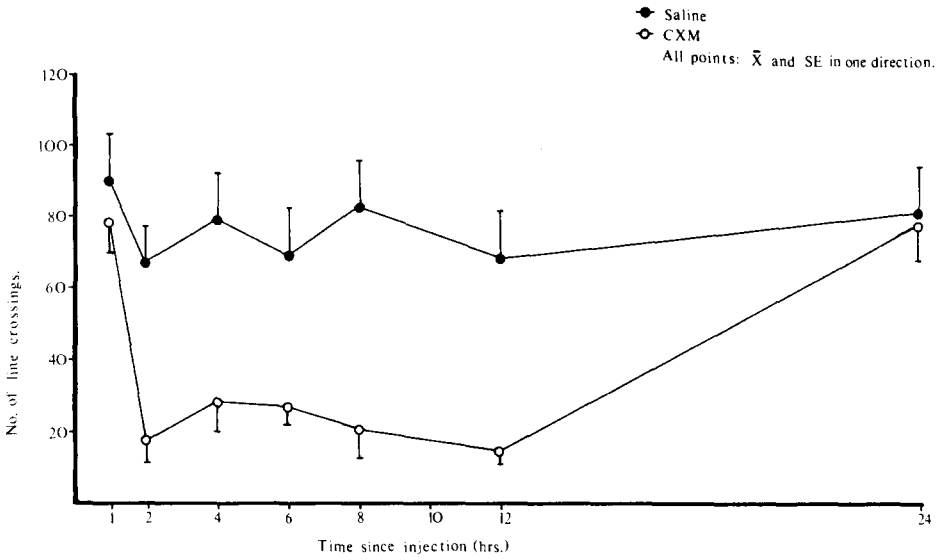


FIG. 1. Effects of centrally administered cycloheximide (CXM) or isotonic saline upon locomotor activity in male rats. CXM (400 μg) or saline were administered intraventricularly under ether anesthesia in a volume of 30 μl and locomotor activity was measured for five min at the times indicated after the injection. Each point is the mean ± SE for three rats.

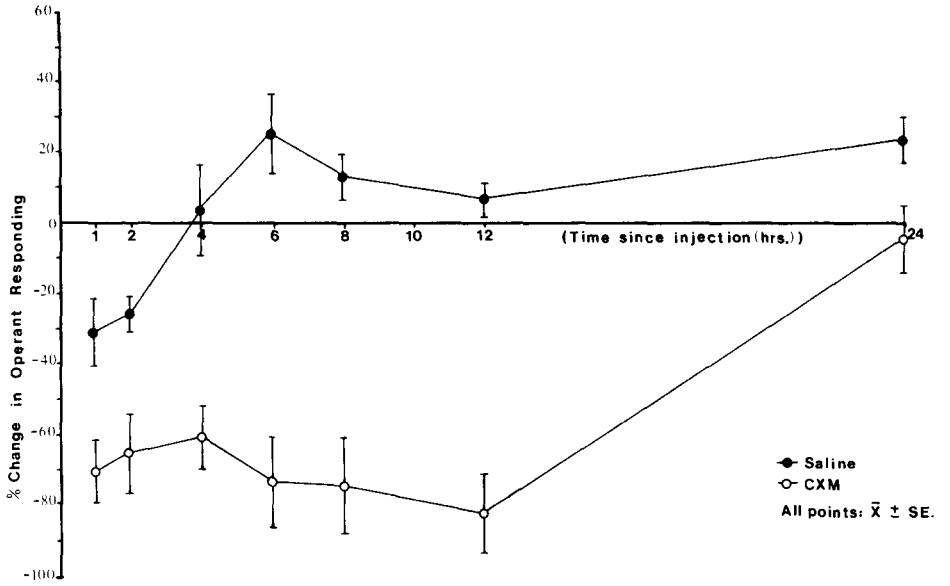


FIG. 2. Effects of centrally administered CXM or isotonic saline upon operant responding. See legend to Fig. 1 for details of administration.

possible that any disruptive effects of CXM on memory storage processes may be due to interference with acquisition of the task rather than consolidation of memory if the training is given within 12 hr of the central injection of CXM. However, it is possible that the behavioural debilitating and amnesic effects of CXM may be dissociable, as has been reported previously for mice [17,30]. One way of assessing this idea is to compare the time courses for the amnesic and behavioural depressant effects of CXM.

## AMNESIC EFFECTS OF CYCLOHEXIMIDE ON PASSIVE AVOIDANCE

The present experiment sought to determine a time course for the amnesic effects of CXM in a passive avoidance task in order to determine a suitable injection-training interval that could be used in later experiments on the reversal of CXM-induced amnesia. The time course could also be compared to the ones reported above and to the one reported earlier for amnesia of a taste aversion task [36].

*Method*

*Animals.* The animals were 84 male rats, weighing 200–320 g and 80–120 days old at the time of the experiment. They were randomly divided into two groups of 42. Experimental animals received an intraventricular injection of CXM, as described previously, at either 1, 3, 7, 9, 11 or 17 hr prior to training. These points were chosen in order to permit a direct comparison with the Tucker and Gibbs study [36]. Control animals were injected identically except that they received only physiological saline.

*Procedure.* The apparatus used for training of the passive avoidance response consisted of two compartments, each approximately 30 x 30 x 30 cm. One compartment was painted white and lighted by a 40 W globe; the other was painted black and unlighted. The floor of both compartments consisted of parallel metal rods 2 mm thick and separated by a distance of 15 mm. A shock of 0.42 mA could be delivered through the floor of the dark compartment. A small door, approximately 6 x 7 cm, allowed movement between compartments.

On the day of the experiment, animals were placed in the light box and were allowed to explore the apparatus for two min. If an animal did not move into the dark box within that period, it was eliminated from further testing. Training involved placing the animal in the light box and waiting for it to move into the dark box. Once completely inside the dark box, a shock of 0.42 mA was delivered until the animal returned to the light box. The animal was required to remain in the light box for a period of three min, during which time it was able to retest that shock was still associated with the dark box. Step through latency, the time from placement in the light box until the delivery of shock, was recorded for all animals. If the step through latency exceeded five min during the training trial, the animal was eliminated from the experiment.

Retention testing was carried out 24 hr after training. Each rat was, in turn, placed in the light box and step through latency was measured. If a rat did not step through within three min, a score of 180 (sec) was recorded and the animal was considered to have displayed perfect memory.

*Results and Discussion*

It appeared that some CXM-treated animals were behaviourally depressed at the time of training; however, no significant differences between the step-through latencies for control and experimental groups were observed at any of the selected time points. The mean step through latency at the time of training was 29.8 ± 5.6 sec for control rats and 32.4 ± 6.1 sec for CXM-treated rats.

As can be seen from the results displayed in Fig. 3, the control rats generally exhibited perfect memory, with all animals trained at 3 hr or longer after the operation having step through latencies of 180 sec on the retention test. The control rats trained at one hr after the operation had a significantly lower step through latency then all other controls ($U = 0$, $p<0.05$), for which ether may have been responsible.

Experimental groups had significantly lower step through latencies on the retention test than the corresponding control groups which were trained at 1, 3, 5, 7 and 9 hr ($U = 0$, $p<0.05$) but not those trained at 11 or 17 hr ($U = 12$ and 18, respectively, $p>0.05$) after the operation.

Since both the control group and the CXM-treated group exhibited amnesia when trained one hr after the operation, the amnesia displayed in the latter group cannot be attributed solely to the effects of cycloheximide. Rather, the amnesia may be due to an ether effect associated with the technique of drug administration.

However, when training is given at 3, 5, 7, or 9 hr after CXM, the amnesia can be ascribed to the drug itself. Moreover, since the amnesia time course (Fig. 3) does not exactly correspond to the time course for CXM effects on locomotor activity (Fig. 1) or operant responding (Fig. 2), it is possible that the amnesic effects of CXM are separable from its behavioural debilitating effects, as other workers

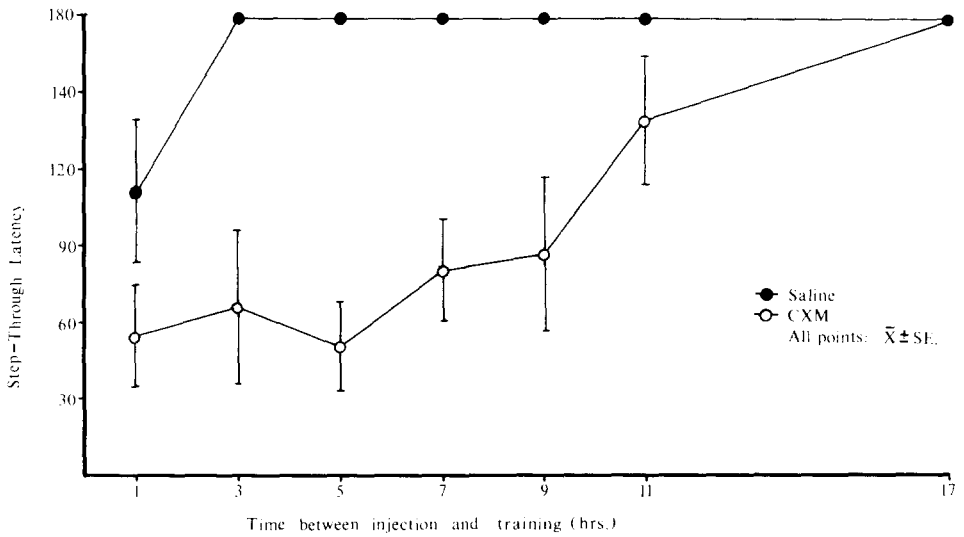


FIG. 3. Time course of amnesia for a passive avoidance response produced by central administration of CXM. Animals were trained at times indicated after intraventricular injection of CXM or isotonic saline and tested for memory of the task 24 hr later by measuring their step through latencies. Each point is the mean ± SE for 6 rats.

have suggested [17,30]. In particular, it should be emphasized that CXM-treated rats displayed a reasonably good memory when trained at 11 hr after the injection, (Fig. 3) even though behavioural depression was still marked at 12 hr (Fig. 1 and 2).

It is important to note that the time course for CXM-induced amnesia reported here is different from that reported by Tucker and Gibbs [36] for the taste aversion task: they did not observe any amnesia when animals were trained at 1 and 3 hr after CXM injection, while the present findings did (Fig. 3). One interpretation of these differing findings is that the amnesic effects of CXM are task specific, a phenomenon not previously reported in the literature on this topic. Clearly, if the time course of CXM-induced amnesia varies for different tasks, more than one biochemical effect of CXM must be involved.

## EFFECTS OF CYCLOHEXIMIDE ON PROTEIN SYNTHESIS

Tucker and Gibbs [36] reported that amnesia for taste aversion could only be produced in rats if training took place 5–9 hr after the central administration of CXM. It was claimed, in effect, that this supported the hypothesis that the synthesis of specific protein is required for the formation of stable long-term memory, as Barondes and Cohen [3] had shown that maximal inhibition of protein synthesis occurs 5–8 hr after the central administration of CXM to mice. There has been no report in the literature of the time course of inhibition of cerebral protein synthesis after the central administration of CXM to rats; therefore this claim has not, until now, been refutable.

It has now been shown that the time course of amnesia for a passive avoidance response differs from that for taste aversion. Clearly, the inhibition of protein synthesis by centrally administered CXM cannot correspond to both of these time courses. Therefore, the argument put forward by Tucker and Gibbs [36] and a number of other workers [4,34] cannot be supported. That this is the case can be confirmed by the actual determination of the time course of protein synthesis inhibition, the objective of the present experiment.

### *Method*

*Animals.* The animals were 60 male rats, weighing 250–400 g and 120–180 days old at the time of the experiment. These animals were randomly divided into two groups of 28 and one group of four. The first group of 28 received an intraventricular injection of 400 μg of CXM as previously described. The second group received an intraventricular injection of isotonic saline. Cerebral rates of protein synthesis were determined either 1, 2, 4, 6, 8, 12, or 24 hr after treatment, four rats being allocated to each time point. The single group of four animals received no treatment prior to the determination of their rates of cerebral protein synthesis.

*Procedure.* Biochemical procedures were based upon those described by other workers [9,12]. L-(4,5-$^3$H) leucine (1 Ci/mmol) was injected intraperitoneally (70 μCi/kg, 140 μCi/ml) 15 min prior to the time point being investigated. Animals were sacrificed 30 min later, thereby giving an indication of the rate of amino acid incorporation, and thus the rate of protein synthesis, ranging from 15 min prior to the desired time point to 15 min after. Animals were sacrificed by means of decapitation. The brain was rapidly removed, rinsed in ice water, and homogenized in 15 ml of 0.1 M NaOH containing 0.1 mg/ml DL-leucine. The homogenate was then allowed to stand in ice for one hr. A 10 ml aliquot of the homogenate was then removed and protein precipitated by the addition of 30 ml of ice-cold 12% TCA. This was allowed to stand in ice for at least 30 min. After centrifugation, the supernatant was removed, measured and a 0.5 ml aliquot placed in 18 ml of scintillation fluid. The precipitate was twice more suspended in 12% TCA and centrifuged, and then once in diethyl ether. Finally, the precipitate was washed with water and filtered by suction to dryness on glass-fibre filter paper. After further drying, the sample was weighed and 70 mg oxidized. The tritiated water given off upon oxidization was collected in 18 ml of scintillation fluid.

Scintillation fluid was prepared by dissolving 6 g of PPO and 0.4 g of Bis MSB in 500 ml of triton and 1500 ml of xylene. Radioactivity was measured with a Packard Tri-Carb liquid scintillation counter for 10 min. Appropriate corrections for counting efficiencies were made. Knowing the total volume of the TCA-supernatant and the total weight of the TCA-precipitate, accurate estimates could be made of the counts per min of the whole supernatant and the whole precipitate. The degree of incorporaion of labelled amino acid into cerebral protein, which is regarded as a measure of the rate of protein synthesis, was calculated for each animal as the ratio of counts per min in the precipitate to the total activity of tritiated leucine in the sample;

$$\text{i.e., \% Incorporation} = \frac{\text{Precipitate cpm}}{\text{Precipate cpm + supernatant cpm}}$$

Protein synthesis inhibition could be calculated as follows:

$$\text{\% Inhibition} = 100 \times \left(1 - \frac{\text{Experimental Incorporation}}{\text{Mean Control Incorporation}}\right)$$

### *Results and Discussion*

The effects of centrally administered CXM upon cerebral protein synthesis are summarized in Fig. 4. A significant variation occurred in the degree of incorporation exhibited by the control animals over the 24-hr period $H(6) = 12.68$, $p<0.05$, but only the 2-hr group was found to be significantly different from the unoperated control group ($U = 0$, $p<0.05$). All experimental groups except the 24-hr group displayed significantly lower levels of incorporation than the corresponding controls ($U = 0$ at all points, $p<0.05$). The 24-hr experimental group showed a significantly greater degree of incorporation than the 24-hr control group ($U = 1$, $p<0.05$).

Calculations of protein synthesis inhibition, derived from the incorporation values presented in Fig. 4, indicates that the maximal degree of protein synthesis inhibition occurs during the first 2-hr (80%) after central administration of CXM, with less but still significant inhibition being observed at 4 (70%), 6 (60%), 8 (60%), and 12 hr (40%), and a slight elevation at 24 hr (20%). These data, then, correlate reasonably well with the time course of the amnesic effects of CXM on the passive avoidance response (cf. Figs. 3 and 4). However, they do not correlate with the time course of the amnesic effects of CXM on taste aversion [36]: no amnesia was observed at a time (1 hr) when protein synthesis inhibition was maximal. Clearly then, the amnesic effects of CXM in the taste aversion paradigm

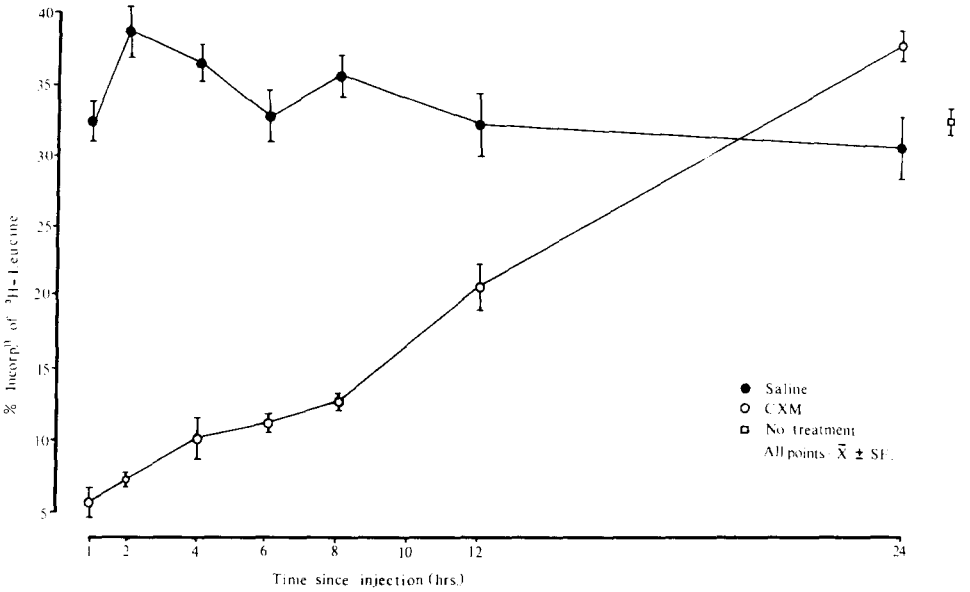


FIG. 4. Effects of centrally administered CXM or isotonic saline upon amino acid incorporation into cerebral protein. Animals were injected with radioactive leucine 15 min before the times indicated on the abscissa and sacrificed by decapitation 30 min after this injection. Each point is the mean ± SE for 4 rats.

cannot be ascribed to the protein inhibition produced by CXM.

### REVERSAL OF CYCLOHEXIMIDE'S AMNESIC EFFECTS

Since the amnesic effects of CXM in some tasks do not correlate with the time course of protein synthesis inhibition, it is possible that the apparent correlation observed in these studies may not reflect a causal relationship; both may be related to a third variable, e.g., biogenic amine levels. Recent reports support the suggestions that biogenic amines may be involved in memory storage processes [1, 7, 20, 28, 35] and that the amnesic effects of CXM may be mediated by its influence on biogenic amines [10, 11, 14]. Thus, the objective of the final experiment in this series was to assess whether the amnesic effects of CXM on a passive avoidance response might be mediated by the biogenic amines, noradrenaline, dopamine, and/or serotonin.

*Method*

The animals were 36 male rats, weighing 200–300 g and 100–120 days old at the time of the experiment. Animals were randomly divided into six groups, all receiving an intraventricular injection of 400 $\mu$g of CXM five hr prior to training, as this time appeared to give the maximum degree of amnesia (See Fig. 2). Immediately after training each group received one of the following drug treatments in an attempt to reverse the amnesia produced by CXM: (1) 1 ml/kg isotonic saline (2) 5 mg/kg d-amphetamine sulfate, (3) 5 mg/kg imipramine hydrochloride, (4) 100 mg/kg l-tryptophan, (5) 5 mg/kg corticosterone, (6) 5 mg/kg hydrocortisone. The latter two drugs were injected subcutaneously; the former four, intraperitoneally. Amphetamine and imipramine were dissolved in isotonic saline; tryptophan was made up in 1% carboxy-methyl-cellulose, as suspending agent; corticosterone and hydrocortisone were first dissolved in one part ethanol and then diluted with nine parts of isotonic saline. All drugs were administered in a volume of 1 ml/kg except tryptophan, which was administered in a volume of 2 ml/kg. These drugs by themselves had no effect on retention when injected after training. Retention was tested 24 hr after the training session.

*Results and Discussion*

The results of step through latencies on the retention test are summarized in Fig. 5. There was a tendency for each of the drugs administered after training to produce some reversal of the amnesic effects of CXM; however, only those groups treated with l-tryptophan and corticosterone had significantly longer step through latencies than the control group which received isotonic saline immediately after training ($U = 3$ and 5, respectively, $p<0.05$).

The drugs used in this reversal experiment were selected on the basis of evidence that they may selectively alter the levels of the biogenic amines. d-Amphetamine, for example, is a well-known stimulator of the release of noradrenaline and dopamine, while l-tryptophan is a metabolic precursor of serotonin which has been shown to triple the levels of serotonin in rodents when used in the same dose as employed in this study [18]. Both corticosterone [23] and hydrocortisone [26] have been shown to modulate the central levels of serotonin but appear to do so by somewhat different mechanisms. Finally, imipramine increases the functional levels of both noradrenaline and serotonin by blocking their reuptake into presynaptic terminals [22].

The fact that only l-tryptophan and corticosterone produced a significant reversal of CXM-induced amnesia suggests that serotonin may be an important mediator of memory for a passive avoidance response. However, since there was a tendency for d-amphetamine and imipramine to reverse the amnesia and since only single doses of these agents were used, it would be unwise to conclude that noradrenaline and dopamine were not mediators of the

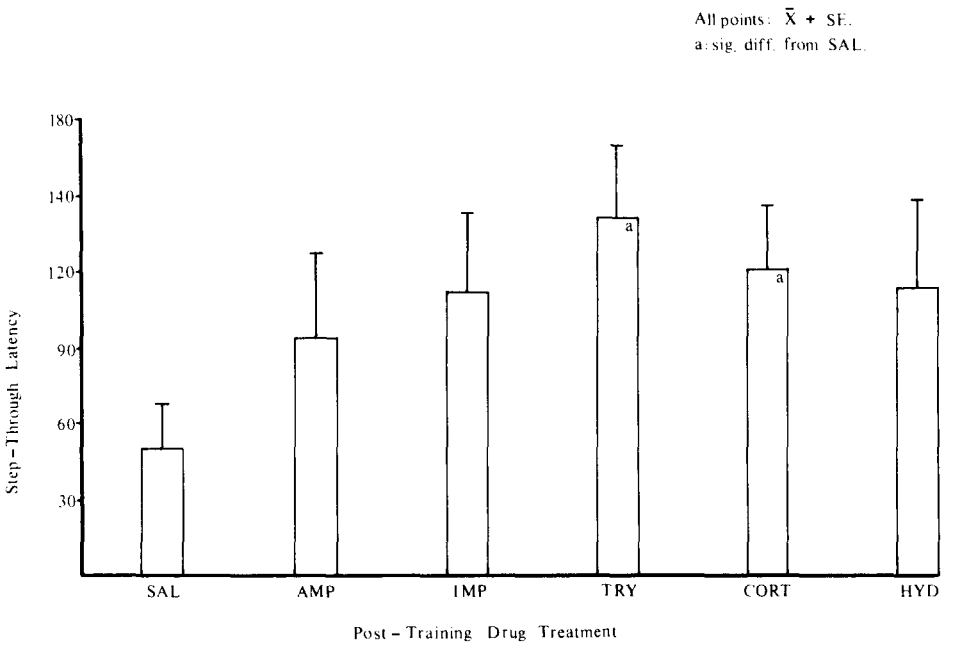


FIG. 5. Reversal of effects of centrally administered CXM by posttraining injections of drugs interacting with biogenic amines. CXM (400 μg) was administered intraventricularly 5 hr before the training session. Isotonic saline (SAL), 5 mg/kg d-amphetamine (AMP), 5 mg/kg imipramine (IMP), 100 mg/kg l-tryptophan (TRY), 5 mg/kg Corticosterone (CORT), or 5 mg/kg hydrocortisone (HYD) were administered immediately after training. N = 6 for each treatment.

CXM-induced amnesia of the passive avoidance response. Work with additional doses of these agents is required. Nevertheless, it should be pointed out that if both catecholamines and serotonin were involved in memory consolidation of a passive avoidance response, it would be expected that imipramine would have reversed amnesia to the greatest extent. Thus, the present results favour serotonin as playing a major role in the CXM-induced amnesia of a passive avoidance response.

## GENERAL DISCUSSION

It may be concluded that CXM is more likely to be affecting consolidation of memory rather than acquisition because of the following two observations: (1) Relatively little amnesia was observed when CXM was given 11 hr before the training session (Fig. 3), while there was still a very significant behavioural depression 12 hr after CXM administration (Figs. 1 and 2). (2) The administration of l-tryptophan and corticosterone, which produced significant reversal of the CXM-induced amnesia (Fig. 5), was after the training trial and could therefore only affect those biochemical processes that were taking place after acquisition had occurred.

The results of the present studies have contributed further information to the growing body of evidence which has questioned the specificity of the relationship between protein synthesis inhibition induced by CXM and its amnesic effects (e.g., [5, 10, 11, 14, 25]). Lajtha [21] originally proposed that inhibitors of protein synthesis may cause amnesia by preventing the replacement of constitutive brain protein, rather than by blocking cerebral protein synthesis specifically required for long-term memory. This possibility has recently been reexamined [32] in the case of administration via the periphery and it was concluded that it did not account for the observed amnesia. This possibility has not been directly investigated in the case of central administration of CXM. The findings of the present studies, however, do allow certain tentative conclusions to be drawn. The most obvious consequence of this hypothesis is that the longer the period of protein synthesis inhibition, the greater the expected probability of amnesia due to a greater depletion of constitutive protein. The findings of the present study contradict this. Amnesia was observed if training was given after only one hr of inhibition of cerebral protein synthesis, but did not occur to a significant extent if training was given after 9 hr of continuous inhibition (See Fig. 3).

In their recent study utilizing the same procedure as reported in these experiments Tucker and Gibbs [36] called attention to the similarity between their amnesia time course and that reported by Barondes and Cohen [3] for inhibition of cerebral protein synthesis following central administration of CXM in mice. The present study, however, has shown that the time course of protein synthesis inhibition by centrally administered CXM in rats does not correlate with the amnesia time course reported by Tucker and Gibbs [36]. Therefore, if one is to maintain the notion of the relationship between memory disruption and inhibition of a memory-specific protein by CXM, the hypothesis must be modified. It could be postulated, for example, that CXM may produce different amnesia time courses in different tasks by affecting the rate of synthesis of specific proteins, which may be important for the specific tasks, in a different manner.

An alternative, and perhaps more parsimonious, hypothesis is that the task-specific time courses for CXM-induced amnesia may be related to the differential effects of this drug on the levels of biogenic amines. Based upon

the reversal study reported here, one would predict that a decreased level of serotonin induced by CXM would correlate closely with the amnesia time course for passive avoidance response. On the other hand, the amnesia time course for the taste aversion task [36] may be closely, although not necessarily, correlated with the levels of other biogenic amines. Only further studies with the paradigm reported in the present paper will permit a firm conclusion on this point.

An important implication of the present work is that CXM may produce differing time courses of amnesia depending on the task. This finding may be taken as evidence that different mechanisms must be involved in the consolidation of memory for these tasks. Other work also suggests that different mechanisms may underlie the memories for passive avoidance and taste aversion [6,24]. One example of this work is the finding that scopolamine, which has been frequently reported to produce amnesia for a passive avoidance response [2,16] does not do so for taste aversion [13]. Other workers have proposed that biogenic amines may be differentially involved in the consolidation of memory for active and passive avoidance tasks [1,7].

The present results are consistent with other literature [1, 7, 20, 28, 35] suggesting that biogenic amines may play an important role in memory storage processes and that the amnesic effects of CXM may be mediated by its influence on biogenic amines [10, 11, 14]. Further studies with the approach reported in the present experiments may help to clarify the relationship between biogenic amines and memory consolidation.

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