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Possible Noradrenergic Involvement in Training Stimulus Intensity

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CROWE, S. F., K. T. NG AND M. E. GIBBS. *Possible noradrenergic involvement in training stimulus intensity.* PHARMACOL BIOCHEM BEHAV **39**(3) 717–722, 1991.—Day-old chicks trained on a single trial passive discrimination avoidance task using a concentrated chemical aversant, methyl anthranilate (MeA), have been shown to exhibit three stages of memory processing: short, intermediate and long term. A similar learning task with the aversant diluted to 20% in ethanol leads to short- and intermediate-term memory only, but not to long-term memory. The emergence of long-term memory has been shown to be associated with the production of a nonenergy-dependent phase of the intermediate memory stage. Subcutaneous administration of propranolol proved capable of inhibiting this nonenergy-dependent phase of memory under a number of training regimes: strongly reinforced training, and with weakly reinforced training presented twice or coupled with a selected dose of the stress-related hormone ACTH. This study supports the notion that there is a phase of memory that occurs prior to the protein synthesis-dependent phase of memory which is susceptible to interference by drugs affecting noradrenergic processes and which may be associated with the intensity of the training stimulus.

Day-old chicks Weakly reinforced training Propranolol Stress-related hormones Memory consolidation Intermediate memory

POSTTRAINING administration of acute stress hormones (18) has been shown to facilitate consolidation of memory following aversive training with a low-intensity training stimulus. Noradrenergic agonists such as noradrenaline (NA) and amphetamine (10), as well as hormones including arginine vasopressin (AVP) and adrenocorticotrophin (ACTH) (19), have also been shown to be effective in counteracting amnesia induced by agents such as ouabain and antibiotics (9).

The nature of the actions of the catecholamine agonists and the hormones is as yet unclear. Recent findings from Gibbs and Ng (13,14) are of interest here. Chicks trained on a single-trial passive discriminated avoidance learning task show a retention function consisting of three memory stages: short-term (STM), intermediate-term (ITM) and long-term memory (LTM), with the stages separated by transient deficits at 15 and 55 minutes postlearning (12,19). Gibbs and Ng (14) suggested that the ITM stage observed under these conditions consists of two phases: a phase A which is energy dependent and susceptible to blockade by the metabolic inhibitor 2,4 dinitrophenol (DNP), and a phase B, following from phase A, which is not susceptible to DNP inhibition. Gibbs and Ng (14) have suggested that consolidation of the learning experience into LTM may depend on a triggering mechanism operating in the transition of memory from phase A to phase B of ITM. NA, ACTH and AVP, at appropriate doses, have all been shown to extend phase A of ITM and to delay the cross-over from ITM to LTM by some 35 minutes, from 55 minutes to about 90 minutes postlearning (19). These authors suggested that the well-reported action of hormones in overcoming antibiotic inhibition of LTM (9) may be through their effect of extending phase A of ITM and thus delaying the triggering of LTM formation until after the inhibitory effects of the antibiotics have dissipated (14).

Day-old chicks trained on a passive avoidance task with reduced aversiveness of the training stimulus do not show consolidation of the experience into LTM (4–6). The evidence suggests that, within the Gibbs and Ng three-stage model of memory formation (12,19), the retention function under such training conditions consists of the short-term memory (STM) and the intermediate-term memory (ITM) stages, with no evidence of the LTM stage. Further, the intermediate stage of this function appears to consist entirely of Gibbs and Ng's ITM phase A, as determined by the reaction to DNP (4). Consolidation of this training experience into LTM was achieved with a second training trial with the weak training stimulus (5), or by the contingent application of the stress-related hormones NA, ACTH or vasopressin closely contiguous to the weak training experience (6). Furthermore, this occurred concomitantly with the appearance of phase B of ITM (4–6).

The posttrial injection of the noradrenergic neurotoxin DSP-4 has produced amnesia on active avoidance tasks (1,20), and the noradrenergic antagonists propranolol and alprenolol have produced amnesia in rats trained on passive avoidance tasks (3,15). DSP-4 has also been shown to interfere with imprinting in the day-old chick (8).

The β-adrenergic antagonist, sotalol, has also been shown to yield amnesia, sometime after 40 minutes postlearning, in chicks trained under a single-trial passive avoidance task (21).

The effect of sotalol on passive avoidance training was only

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observed when the drug was given between 10 and 25 minutes after training, and a similar effect was not obtained with two other β-antagonists, nadolol and timolol. With the latter two β-antagonists, memory loss was rapid, occurring within five minutes of administration independent of the time of administration relative to training. Furthermore, sotalol injected five minutes before training resulted in amnesia developing within 10 minutes posttraining.

These authors attributed the differences in action between the β-antagonists to possible differences in their effect on subtypes of β_2-receptors in chick brain, and/or the possibility that one type of β-antagonist might act predominantly centrally and one peripherally. Of particular concern to the present paper is the conclusion by these authors that the effect of sotalol administered sometime after training provided evidence of a sharp transition in memory processing at about 30 minutes after training. Indeed, they argued that sotalol given at these times prevents the establishment of long-term memory, possibly through some as yet unknown effect of sotalol on protein synthesis. This conclusion was based primarily on the earlier finding from our laboratories that antibiotics such as cycloheximide yielded amnesia sometime after 30 minutes posttraining if given immediately after or before training. When CXM was given five minutes or later after training, memory deficits did not appear until 60 minutes posttraining (12).

It is now clear that cycloheximide may have a dual action on memory formation (14) and that its inhibitory effect on memory between 30 and 60 minutes posttraining may be attributed to inhibition of Gibbs and Ng's DNP-insensitive phase B of intermediate memory. It would appear that the effect of sotalol obtained by Stephenson and Andrew (21) may also have been on phase B of intermediate-term memory.

Preliminary investigations in our laboratories suggest that another β-antagonist, propranolol, yields amnesia 180 minutes postlearning. In this paper, we report an attempt to replicate the observations of Stephenson and Andrew (21) using propranolol rather than sotalol. A comparison of the effects of the drug on strongly and weakly reinforced learning was carried out under arousal and repeated training manipulations, in the weakly reinforced training condition. Control chicks were treated with the α-adrenergic antagonist, yohimbine, or with saline.

METHOD

Animals

Day-old black Australorp white Leghorn chicks were obtained from a local hatchery on the morning of each experiment. Approximately 16 chicks were used for each data point, depending on the number successfully trained from an initial subject pool of 20 birds per data point.

Drugs

All drugs were made up in 154 mM NaCl. Yohimbine (4.0 mg/kg; Sigma), propranolol (4.0 mg/kg; Sigma), ACTH 1–24 (50 μg chick; Synthacen, Ciba Geigy) or saline was administered in a 100-μl dose subcutaneously in a ventral skin fold. All subcutaneous drugs were administered 10 minutes after training on the aversive red bead, except in the case of ACTH, which was injected immediately after the training trial. The drugs were injected blindly, and the codes were not broken until after the data had been scored.

Procedure

The experimental paradigm is essentially that described in Gibbs and Ng (12). Briefly, chicks were pretrained in pairs to peck at a red and a blue glass bead, dipped in water and presented in succession for 10 seconds each. Following pretraining, a red bead similar to the one used in pretraining was coated with an aversant solution (methyl anthranilate; Sigma) and presented to the chicks for a period of ten seconds. Previous studies have shown no differences in retention functions between chicks trained on the red bead and chicks trained on the blue bead (11). Chicks pecking at the bead typically show a disgust reaction which includes shaking their heads and wiping their beaks on the floor. The number of pecks in the 10-second period and the corresponding latencies to first peck for each bead for each chick were recorded by an on-line computer via a manual keyboard.

On retention trials, pairs of chicks were presented with a dry red and a dry blue bead in succession for 10 seconds each, and the number of pecks in each 10-second period for each bead and the corresponding latencies to first peck were recorded for each chick. The level of discrimination memory was indexed by a discrimination ratio, defined as the number of pecks at the blue bead on the test trial divided by the total number of pecks for each ten-second trial at both the red and the blue beads for all chicks pecking the blue bead on the test trial [cf. (4–6)]. Chicks avoiding the blue bead on the retention test were not included in the analysis of the ratios, since the resulting discrimination ratio for chicks avoiding both red and blue would be indeterminate. The small percentage of chicks in this category should not have substantially altered the findings.

RESULTS

Experiment 1: Relative Effectiveness of α- and β-Antagonists on Concentrated Methyl Anthranilate Training

Across a reasonable pharmacological range, α-adrenergic antagonists do not elicit amnesia compared with β-blockers (15,21). Stephenson and Andrew (21) found that the memory-impairing effect produced by β-adrenergic antagonists such as sotalol were not observed when similar doses of α-adrenergic antagonists were administered at similar times and in similar doses. In this experiment, a comparison was made between the effects of an α-adrenergic antagonist (yohimbine), a β-adrenergic antagonist (propranolol) and saline on chicks trained with strong aversant. The drugs were injected in a relatively high dose (4 mg/kg subcutaneously) and were administered at 10 minutes after the training trial, a time and dose which Stephenson and Andrew (21) found effective in their study with other β-blockers.

Results and discussion. The results of Experiment 1 are presented in Fig. 1. Using an unweighted means analysis of variance, there proved to be a significant overall difference, $F(2,49) = 3.69$, $p = 0.03$, between groups. A post hoc Newman-Keuls test revealed that the group treated with propranolol was significantly different at $\alpha = 0.05$ from either the saline- or yohimbine-treated groups.

This represents a replication of the Stephenson and Andrew (21) result that a β-blocker is, and an α-blocker is not, capable of inhibiting long-term memory formation. This finding warrants further investigation as to the time of effectiveness of the β-blocker on the strongly reinforced learning paradigm.

Experiment 2: Time of Effectiveness of Propranolol With Strong Training

In the Stephenson and Andrew (21) study, sotalol at various doses was effective in inducing amnesia at times up to 25 minutes after concentrated methyl anthranilate training but not at subsequent times. The emergence of the amnesia caused by so-

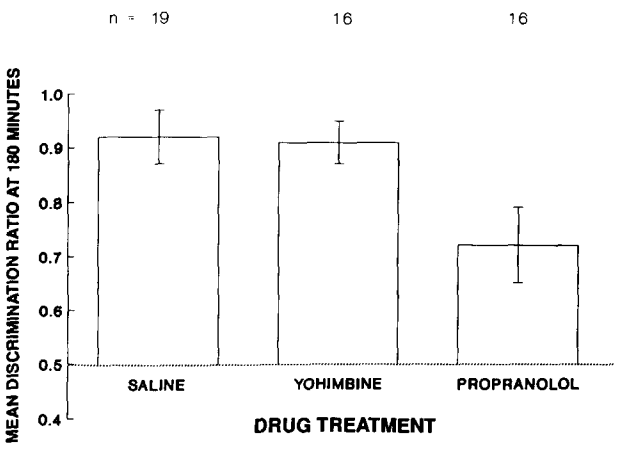

FIG. 1. Effect of subcutaneous administration of adrenergic blockers and saline ten minutes after learning on subjects trained with concentrated methyl anthranilate and tested at 180 minutes after training, as measured by mean discrimination ratio (±SEM).

talol was detectable from times after 30 minutes following training, a similar course of events to that observed with CXM injected immediately after or before training but not if administered after 5 minutes posttraining (14). In this study, a replication of the times of memory disruption using the β-blocker, propranolol, was investigated. Chicks were trained with concentrated methyl anthranilate and then received a subcutaneous injection of either saline or a 4-mg/kg dose of propranolol made up in saline ten minutes after initial training. Chicks were retention-tested at various times between 20 minutes and 50 minutes after initial training.

Results and discussion. The results of Experiment 2 are presented in Fig. 2. It can be seen from Fig. 2 that the avoidance time courses for saline and propranolol are consistent until the 30-minute posttraining retention test, where the two curves start to diverge. This observation is supported by both the 40- and

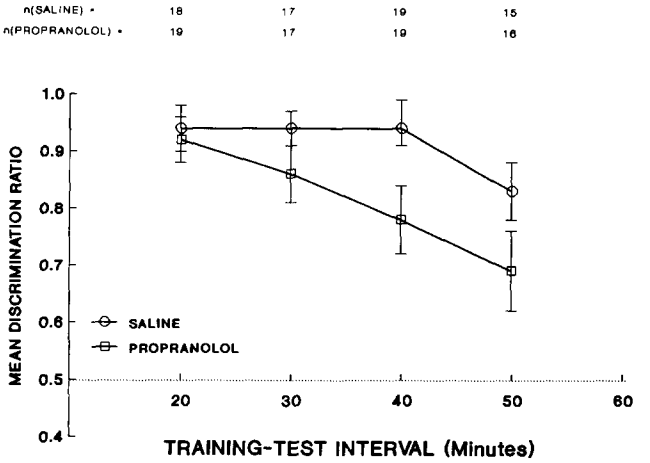

FIG. 2. Effect of propranolol or saline injected subcutaneously ten minutes after training on the time course of subjects trained with concentrated methyl anthranilate, as measured by mean discrimination ratio (±SEM).

50-minute posttraining time points, where a marked difference in levels of avoidance can be observed between the two treatments. The slope of both of the curves is gradual, however, and precise timing of the shift from phase A to phase B is made more difficult in the context of this finding.

Pairwise comparisons between mean discrimination ratios of propranolol- and saline-treated chicks revealed significant differences at the 40- and 50-minute retention tests [$F(1,132)=5.74$ and 6.42, respectively, $p=0.018$ and 0.012, respectively] but not at the other sampled times. This result again supports the findings of Stephenson and Andrew (21) using propranolol.

The results of Experiment 2 indicate that the β-blocker is effective in inhibiting the phase of memory between 30 and 50 minutes after concentrated methyl anthranilate training if injected 10 minutes after training.

It is interesting to compare this result with the effective time of administration of CXM (14). CXM produces a disruption of the ITM(B) phase if administered before or immediately after training but not if administered as early as 5 minutes after training. If the antibiotic is administered five minutes or later after training, it has no effect on the B phase but does result in the emergence of amnesia after 50 minutes following training. The latter effect has been interpreted as the effect of CXM on LTM exclusively (14). Clearly, there is a differential window of effectiveness of the two treatments. Both produce amnesia for the concentrated methyl anthranilate training at about 30 minutes after training, but propranolol and sotalol (21) are effective up to at least 10 minutes after training and, in the case of sotalol, up to 25 minutes after training. This result is interesting, but at this stage the reason for this differential time of effectiveness is unclear. It is possible that the effect of the β-antagonists is more direct in inhibiting phase B, but, other than the time of injection data, this remains speculative.

Experiment 3: The Effect of Propranolol on Weakly Reinforced Training

The results of Experiments 1 and 2 lend support to the notion that propranolol is able to disrupt memory for the strongly reinforced training experience at a time consistent with those observed by the appropriate application of CXM, the so-called ITM(B) phase. As previously observed (4), a single trial with the weakly reinforced training experience results in the nonappearance of LTM and of the ITM(B) phase. This experiment investigated whether propranolol applied at the same dose and at the same time as used in the concentrated methyl anthranilate case would have any effect on the processing of the weak training trial. The chicks were given a single training trial with a 20% v/v solution of methyl anthranilate in absolute ethanol. Ten minutes after training, chicks were given either a 100-μl subcutaneous injection of saline or a 4-mg/kg solution of propranolol made up in saline. The chicks were retention tested at 20, 30, 40 and 50 minutes after initial training.

Results and discussion. The results of Experiment 3 are presented in Fig. 3. The propranolol-treated group appears to be unaffected by the presence of the β-blocker. Pairwise comparisons between the mean discrimination ratios of saline- or propranolol-treated chicks yielded no significant differences ($\alpha=0.05$) between groups at any of the times sampled.

Experiment 3 supports the notion that the weakly reinforced training experience does not show evidence of the ITM(B) phase. It is interesting to speculate whether chicks given a second training trial with the 20% aversant solution (5) would feature a concomitant alteration in the susceptibility to drugs which

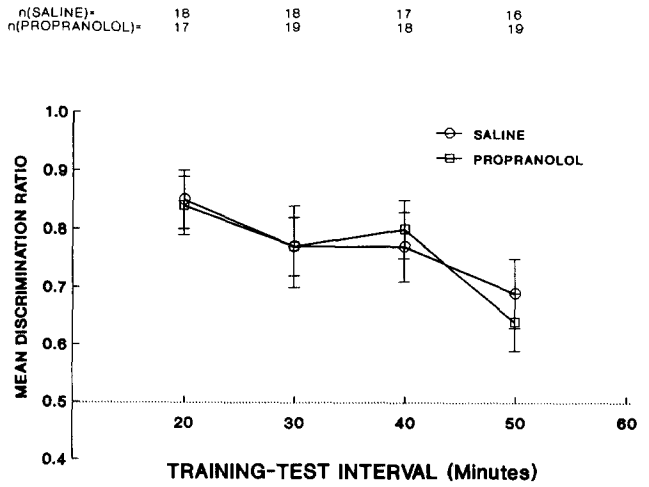

FIG. 3. Effect of propranolol or saline injected subcutaneously ten minutes after training on the time course of subjects trained with a 20% v/v methyl anthranilate solution, as measured by mean discrimination ratio (±SEM).

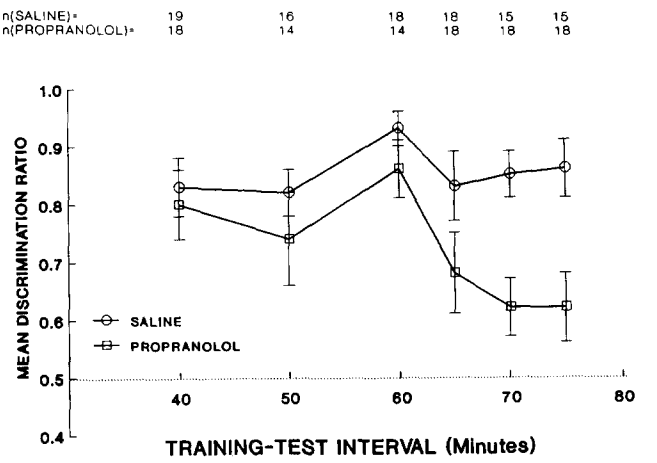

FIG. 4. Effect of propranolol or saline injected subcutaneously ten minutes after the second training exposure on the time course of subjects trained with two presentations of the 20% methyl anthranilate training stimulus at 15-minute intervals, as measured by mean discrimination ratio (±SEM).

alter the expression of the B phase, such as propranolol. This speculation is investigated in Experiment 4.

Experiment 4: The Effect of Propranolol on Chicks Given Two 20% Aversant Training Trials

The data emerging from Experiments 1, 2 and 3 indicate that propranolol is as effective as sotalol in inhibiting the memory stage observed between 30 and 50 minutes after concentrated methyl anthranilate training. Further, there is support for the observation that the weak training trial produced when chicks are trained with 20% methyl anthranilate does not produce evidence of a propranolol-sensitive memory phase or, in other words, does not produce a B phase. It is interesting to speculate what might happen to the status of the propranolol-sensitive memory phase in those subjects which were initially weakly trained and then received further input so as to result in a consolidation of the otherwise weak training (5,6). Previous research indicates that it is possible to produce this effect by two means: 1) by giving additional training trials with the same stimulus (5) or 2) by applying the biological consequences of strong reinforcement in chicks initially weakly trained (6). The next two experiments analyse the effect of propranolol on subjects given these manipulations in the attempt to produce long-term memory in initially weakly trained subjects.

The first manipulation to be investigated is the effect of retraining trials with the 20% aversant solution. Chicks were trained with a 20% v/v solution of methyl anthranilate in absolute ethanol. Fifteen minutes after the initial training trial, they were given a retraining trial, again using the 20% aversant solution. Ten minutes after the second presentation, chicks were given a 100-μl subcutaneous injection of either saline or a 4-mg/ml solution of propranolol made up in saline. Chicks were retention-tested at 40, 50, 60, 65, 70 and 75 minutes after initial training, that is, 25, 35, 45, 50, 55 and 60 minutes after the retraining trial.

Results and discussion. The results of Experiment 4 are presented in Fig. 4. With the saline-treated animals, the levels of avoidance are quite high throughout the ITM stage. This contrasts with the propranolol-treated chicks which feature high levels of avoidance until 60 minutes after the initial training trial and decline from there. It is interesting that the data for both groups seem to produce a peak level of avoidance at the 60-minute postlearning time point. At this stage, this observation has no obvious explanation. Pairwise comparisons between mean discrimination ratios yielded significant differences at 65, 70 and 75 minutes after initial training [$F(1,189)=3.98$, 9.49 and 9.86, respectively, $p=0.048$, 0.002, and 0.002, respectively].

The data correspond quite well with previous observations (5). With DNP, it was possible to establish that there was a significant difference between saline- and DNP-treated birds if they were retention tested at 30, 40, 50 and 55 minutes after initial training. The results of this experiment show that the retention time course was susceptible to inhibition by propranolol at 65, 70 and 75 minutes after training. The results are in accord with those observed with DNP using the same training regime, except in the case of the 60-minute training test interval, which suggests that there may be some variability from group to group with the transition from phase A to phase B of ITM.

The results of this experiment again provide support for the action of propranolol as an inhibitor of the ITM(B) phase, and show that, in those instances where an undertrained chick is given a retraining trial, there will be an alteration in the status of the ITM stage as compared to the unretrained controls. This difference is the emergence of the ITM(B) phase.

Experiment 5: The Effect of Propranolol on Weakly Reinforced Training in the Presence of ACTH 1–24

Previous research (6) has indicated that, if chicks initially trained with the 20% aversant solution were given an immediately posttraining subcutaneous injection of 150 μg/kg of noradrenaline, 50 μg ACTH 1–24 or 0.2 IU of AVP, this resulted in the chicks having discriminated memory of the weak training at 180 minutes. At this time, chicks which were untreated or were saline injected produced no evidence of discriminated memory. The emergence of discriminated memory was also associated with the alteration in the status of the ITM stage of memory. In chicks that were untreated or received an injection of saline, all of the observed memory between 20 and approxi-

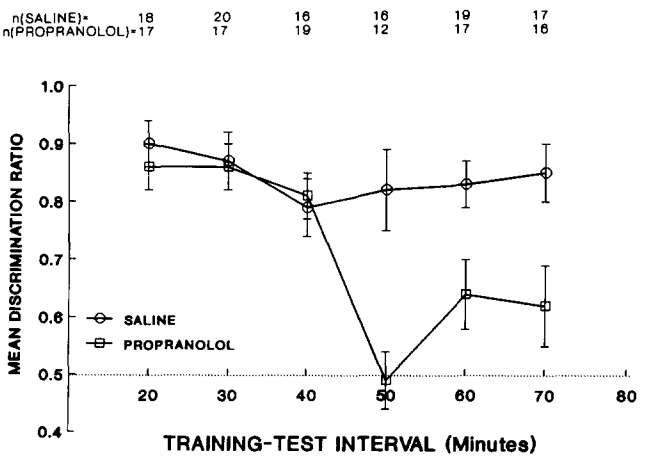

FIG. 5. Effect of propranolol or saline injected subcutaneously ten minutes after training on the time course of subjects trained with 20% methyl anthranilate and given an immediately posttraining dose of 50 μg ACTH subcutaneously, as measured by mean discrimination ratio (±SEM).

mately 40 minutes after training was susceptible to inhibition by DNP. In contrast, chicks trained with the 20% aversant and given NA, ACTH or AVP demonstrated LTM and showed a stage of ITM that was not susceptible to DNP inhibition. This evidence was interpreted as indicating that the modulated memory time course features the emergence of the ITM(B) phase, arising as a consequence of the modulatory treatment and emerging in association with LTM formation.

The aim of Experiment 5 was to investigate whether subjects trained with 20% aversant and given an immediately posttraining modulatory treatment would feature a similar alteration in the status of the propranolol-sensitive memory phase, as was observed in the concentrated aversant training experience (Experiment 2) or in the case of two presentations of the 20% aversant solution at 15-minute intervals (Experiment 4). Chicks were trained with a single aversant training trial with 20% v/v methyl anthranilate dissolved in absolute ethanol. Immediately after the training trial, all chicks were given a 100-μl subcutaneous injection of 50 μg ACTH 1–24 dissolved in saline. Ten minutes posttraining, each group was given a 100-μl injection of saline or a 4-mg/kg injection of solution of propranolol. Chicks were retention-tested at ten-minute intervals between 20 and 70 minutes after the training trial. All subjects received the ACTH, and the propranolol and saline were injected blindly.

Results and discussion. The results of Experiment 5 are presented in Fig. 5. It can be seen from this figure that the two time courses appear relatively consistent up to 40 minutes after initial training, at which time the saline-treated chicks retain good discriminated memory while the propranolol-treated chicks feature a return to untrained levels of avoidance.

Pairwise comparisons between the saline- and propranolol-treated groups yielded significant differences at 50, 60 and 70 minutes after initial training [$F(1,191)=13.31$, 6.79 and 8.59, respectively, $p=0.00$, 0.01 and 0.004, respectively]. The tests revealed no significant difference at the other times sampled.

The results of Experiment 5 yield support for the emergence of a propranolol-sensitive phase of memory between 50 and 70 minutes after initial weak training coupled with a posttraining injection of ACTH. This result also compares favourably with prior observations (6), in which it was possible to demonstrate that chicks trained under the same regime revealed memory susceptible to inhibition by DNP at 20, 30, and 40 minutes after training and not at times subsequent to this, corresponding to phase B of ITM. In this experiment, a reciprocal course of events is observed. Chicks were sensitive to inhibition by propranolol at 50, 60 and 70 minutes after initial training, during the postulated phase B of ITM.

The results of Experiment 5 also confirm that chicks trained with the 20% aversant solution and then given an immediately posttraining injection of ACTH demonstrate an alteration in the nature of the ITM stage of memory. Propranolol administered at 10 minutes after training and modulatory treatment results in disruption of the ITM(B) phase of memory. This result is supported by the earlier observation that chicks trained with the 20% solution and given ACTH are susceptible to inhibition of the ITM stage by DNP from 20 to 40 minutes after training and not at subsequent times. By divergent means, it has thus been possible to demonstrate the alteration in the status of the B phase of ITM in chicks weakly trained and given an immediate posttraining modulatory treatment.

DISCUSSION

The results of this series of experiments can be summarized as follows: 1) the effect of sotalol observed by Stephenson and Andrew (21) on chicks given concentrated methyl anthranilate training is mimicked by the action of propranolol if given in a similar dose and with similar times and routes of injection; 2) this effect is not produced by the α-adrenergic blocker yohimbine; and 3) weakly trained chicks do not feature a propranolol-sensitive phase of memory or LTM, while those treatments previously observed to produce LTM after weak training (i.e., two presentations or immediate posttraining hormone administration) yield evidence of the emergence of the ITM(B) phase.

The findings support the correlation between "optimal window" levels of central nervous system noradrenaline and ACTH and the consolidation of aversive information (6, 10, 13, 15, 16, 18), and it appears that propranolol can counteract the facilitatory effects of NA but only within narrow dose ranges for both drugs. The results are closely in accord with the observations made earlier regarding the presence and temporal characteristics of the ITM(B) phase, as determined by the application of DNP (4). By the convergence of the two inhibitory strategies, it seems reasonable to conclude that modulatory treatments act as a trigger to consolidate weakly reinforced learning experiences, and this triggering is invariably associated with the emergence of the ITM(B) phase of ITM before the expression of LTM. The present data suggest that noradrenaline may play a significant role in this triggering process, as originally suggested by Kety (16,17).

Some support for the speculation that NA-based triggering of LTM consolidation occurs sometime during the ITM phase comes from preliminary studies in our laboratory measuring levels of NA in whole forebrain after the various consolidated and non-consolidated training experiences. The results indicate a quite profound drop in NA levels at about 15 to 20 minutes after the aversant training. With strongly reinforced aversant or weak aversant presented twice or coupled with a 50-μg dose of ACTH directly after training, the level of NA in the samples reached a second peak at about 30 minutes after training. This change was observed, but not to the same extent in subjects trained with 20% aversant only. These findings are tentative, and further investigation is presently underway in our laboratory.

If the above speculation regarding the role of NA in memory formation is correct, then the controversy surrounding the basis of the inhibitory action of antibiotics on memory consolidation

(2) is resolved. Antibiotics such as CXM may prevent LTM consolidation either by blocking the triggering of the consolidation process through inhibition of catecholamine activity or by inhibiting the consolidation process per se through protein synthesis inhibition. Just what the neuronal process is that underlies the postulated triggering role of NA is not clear at present. A neurochemical pathway involving a NA-driven second messenger-activated hyperpolarization of neurons is a possibility, consistent with reports of cyclic AMP involvement in long-term facilitation of the gill withdrawal reflex in *Aplysia* (7).

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