

Epinephrine enhancement of human memory consolidation: Interaction with arousal at encoding

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Abstract

Abundant evidence indicates that endogenous stress hormones like epinephrine and cortisol modulate memory consolidation in animals. Despite this evidence, there has been no demonstration that endogenous stress hormones modulate memory consolidation in humans. In the present study, healthy subjects viewed a series of 21 slides, and immediately after received an intravenous infusion of either saline or epinephrine (40 or 80 ng/kg/min). Memory for the first three (primacy) and last three (recency) slides viewed was assessed with an incidental free recall test one week later. Epinephrine dose-dependently increased memory for the primacy slides, but did not affect memory of the recency slides. A subsequent experiment involving new subjects revealed significantly higher electrodermal responses to the primacy compared with recency slides. These findings support the view (Gold & McGaugh, 1975) that endogenous stress hormones modulate memory consolidation for experiences that induce their release. Additionally, they suggest that in humans these hormones may interact with the degree of arousal at initial encoding of information to modulate memory consolidation processes for that information.

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1. Introduction

Considerable evidence suggests that adrenergic hormones modulate the consolidation of long-term memory for experiences that induce their release. For example, post-training injection of adrenergic drugs or hormones enhances memory consolidation in many species (Cahill & McGaugh, 1998; Cahill, Prins, Weber, & McGaugh, 1994; Gold & Van Buskirk, 1975; McGaugh, 2000; McGaugh, Cahill, & Roozendaal, 1996; Soetens, Cas-aer, D'Hooge, & Hueting, 1995). Despite this evidence, no demonstrations exist of enhanced memory consolidation in humans produced by adrenergic hormones, although enhanced consolidation in humans has been reported with post-learning administration of amphetamine (Soetens et al., 1995) glucose (Manning, Parsons, & Gold, 1992), and yohimbine (Southwick et al., 2002). The hypothesis that endogenous adrenergic hormones compose a necessary part of an endogenous memory-

modulating system for emotionally arousing events in humans (Cahill & McGaugh, 1998) requires that, in appropriate conditions, these hormones be shown to enhance human long-term memory consolidation.

In this study, healthy humans received an intravenous infusion of epinephrine (EPI) after viewing a series of standardized slides. On the basis of a straightforward 'time dependency' view of memory consolidation (McGaugh, 1966), we predicted that EPI would most likely enhance memory for the slides viewed most recently before the infusion (recency effect). Other evidence suggests that drug-induced memory enhancement in humans can be restricted to the primacy portion of a series of items (Crow, 1979; Messier, Pierre, Desrochers, & Gravel, 1998). Therefore, we also examined the influence of EPI on retention of the initial slides viewed (primacy effect).

2. Materials and methods

Healthy volunteers (mean age (\pm SEM) = 21.9 \pm 0.7 years, 22 male, 20 female) viewed a series of 21 stan-

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standardized slides (Lang, Bradley, & Cuthbert, 1999) while seated comfortably before a viewing screen. Prior to slide viewing, each subject received an intravenous line in their left arm, and electrodes for continuous monitoring of heart rate (MP100 recording system, Biopac Instruments, Santa Barbara, CA) and pressure cuff on their right arm for blood pressure monitoring. The time between insertion of the i.v. line and the start of the slide viewing was typically 10–15 min. Subjects were instructed that they might find some of the slides to be pleasant, some unpleasant, and some neutral. Each slide was presented for 20 s, during which time the subjects (a) identified the object or event depicted in the slide and (b) rated their personal emotional reaction to viewing the slide on a scale of 0–10. These responses were typically completed within 10 s of slide onset. Slides were chosen for their neutral-to-low arousal quality as previously determined by standardized ratings (Lang et al., 1999), and were shown in random order for each subject with the exception of the first slide (a light bulb), which was the same for all subjects. The average standardized rating (see Lang et al., 1999) of arousal for the slides was 4.64 ± 0.31 , and the average valence rating was 5.15 ± 0.45 .

Immediately after slide viewing, each subject received an infusion of either epinephrine (40 or 80 ng/kg/min, 3 min) or saline. Both the subjects and the investigator responsible for the memory testing (L.C.) were blind to the experimental group, although subjects in the epinephrine groups often reported feeling the effects of the infusions on their heart rate. The change in heart rate in response to the infusion for each subject was determined by subtracting the heart rate at the end of presentation of the last slide (baseline) from the heart rate 1, 2, and 3 min after the start of the infusion.

One week later subjects returned to the laboratory and received an unexpected memory test. Subjects freely recalled as many slides as they could from the previous week, with no time limitations. All subjects finished this recall procedure within 15 min. Because animal research demonstrates that drug enhancement of memory cannot be detected when overall performance is too high or too low, 4 subjects with exceptionally high (>2 SD from the mean, $n = 2$) or low (<2 SD from the mean, $n = 2$) total recall of slides were eliminated prior to the analysis. We defined the “primacy” portion as the first three slides viewed both to be consistent with the general approach of previous studies (Crow, 1979; Messier et al., 1998), and because informal observations suggested that electrodermal responses to slides presented in our conditions typically were substantial only for approximately the first 3 slides. “Recency” was defined as the last three slides to parallel the primacy definition. All subjects indicated that they were unaware that their memory would be tested. The number of subjects/group was as follows: Saline = 17; EPI 40 = 10; EPI 80 = 15.

At the time of Experiment 1, we did not have a formal capability for recording electrodermal skin responses (EDR). To test the hypothesis that the effect of EPI on primacy but not recency slides observed in Experiment 1 was related to a differential arousal response to the primacy compared with recency slides, in Experiment 2 we examined in new subjects the EDR's to the same slides viewed by subjects in Experiment 1. Eight subjects (19.8 ± 0.49 years, 5 female, 3 male) sat passively during slide viewing to minimize disturbance to EDR recording. Slides were presented for 20 s each. EDRs were recorded with a standardized system (MP100, Biopac Instruments, Santa Barbara, CA) for the measurement of skin conductance. Recording electrodes were attached via velcro strips to the index and middle fingers of the left hand after subjects washed their hands. Skin conductance electrode paste (BioPac systems) was applied to insure appropriate contact. Subjects were requested to keep their left hand as still as possible to avoid movement artifacts in the recordings. The EDR for each subject to each slide was determined by subtracting the baseline conductance level (immediately before a slide was presented) from the peak change from baseline that occurred not less than 1 s and not more than 10 s after the slide was presented. The responses of each subject to the primacy and recency slides they viewed were averaged. This average was then used for primary group comparisons.

All subjects in Experiment 1 received monetary compensation for their participation in the study. Those in Experiment 2 received course credit. All experiments were approved by the University Institutional Review Board.

3. Results

Post-learning epinephrine administration significantly enhanced memory for the primacy slides (Fig. 1). A one-factor ANOVA of recall scores revealed a significant effect of drug condition [$F(2, 39) = 3.74, p < .05$]. Post-hoc *t* tests comparisons revealed a significant difference that subjects in the EPI 80 group recalled significantly more of the primacy slides than did subjects in the saline group [$t(30) = -2.78, p = .009$]. ANOVA of recall scores for the recency portion revealed no significant difference between the groups ($p > .10$).

Fig. 2 shows the average change in heart rate for each group for each one-minute interval of the infusion period. A one-factor (drug condition) repeated measures ANOVA revealed a highly significant effect of drug condition [$F(2, 39) = 23.3, p < .0001$]. Post-hoc *t* test comparisons revealed that the heart rate of both subjects in the EPI 40 and EPI 80 groups were significantly higher than that of subjects in the saline group at each time interval. Interestingly, in many subjects receiving

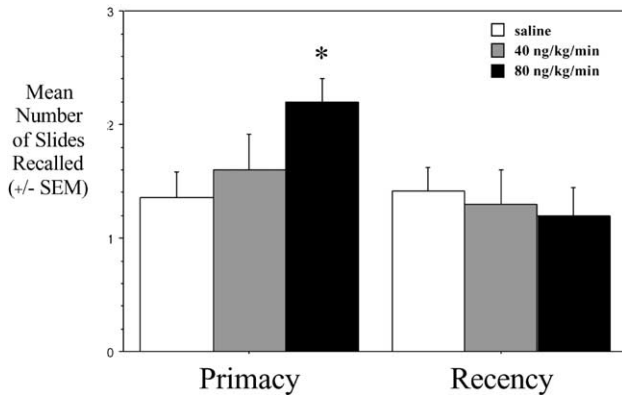


Fig. 1. Mean recall of the first three (primacy) and last three (recency) slides viewed in each experimental group. Post-learning epinephrine administration (80 ng/kg/min) significantly enhanced recall of the primacy slides, but did not affect recall of the recency slides.

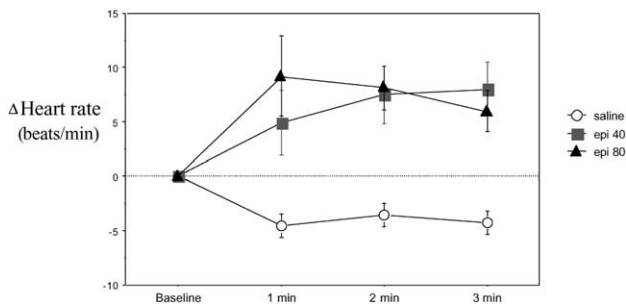


Fig. 2. Mean (\pm SEM) change in heart rate from baseline during the epinephrine infusions. Infusion duration was 3 min.

epinephrine heart rate returned to baseline levels (that recorded at the end of the slide presentation) prior to the end of the epinephrine infusion, an effect perhaps due to compensatory action of the baroreceptor reflex (Obrist et al., 1978). Immediately before the start of the slide presentation, the average (\pm SEM) heart rate for all subjects was $74.7 (\pm 1.8)$ beats/minute, the average systolic blood pressure was $114.9 (\pm 1.9)$ mmHg, and the average diastolic blood pressure was $63.5 (\pm 1.8)$ mmHg. These same values at the end of the slide show (immediately before the infusions) were $72.8 (\pm 1.9)$ beats/min, $114.8 (\pm 1.9)$ mmHg, and $64.8 (\pm 1.4)$ mmHg, respectively. There were no significant differences in any of these measures before versus after the slide presentation.

We also compared the average change in heart rate (HR) to the primacy and recency slides, determined by subtracting the HR at the moment when a slide was first presented from the greatest deviation from that value (positive or negative) while the slide was being viewed. The average change for each of the three primacy slides and for each of the three recency slides was determined for each subject, and these averages were then combined to create a group average. This analysis revealed an

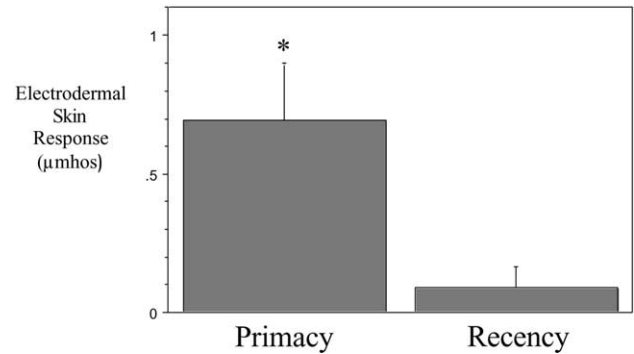


Fig. 3. Mean (\pm SEM) electrodermal skin response to the slides. The EDR response was significantly higher to the primacy slides than it was to the recency slides ($p < .001$).

increased HR to the primacy slides (7.6 ± 0.52) that was significantly higher than that to the recency slides (4.7 ± 0.48) ($p < .001$, two-tailed paired t test). The average subjective rating of arousal in response to the primacy slides was $3.48 (\pm 0.22)$ and for the recency slides was $3.93 (\pm 0.23)$, the somewhat lower values to the primacy slides being due primarily to the fact that one very neutral slide (slide 1) was included in each case in the primacy condition.

Fig. 3 shows the average EDRs from Experiment 2 to the slides used in Experiment 1. The results reveal that the average response of subjects in our conditions to the primacy slides is significantly higher than that to the recency slides [$t(23) = 2.66, p < .02$], for which essentially no skin response was observed.

4. Discussion

These findings support two primary conclusions. First, consistent with prior animal research, adrenergic hormones can produce retrograde enhancement of long-term memory in humans. Because epinephrine was administered *after* learning, its enhancing effect on memory cannot be attributed to actions on attentional, emotional, perceptual, or encoding processes during slide presentation. The findings thus provide new support for the hypothesis that adrenergic hormones, released by emotionally stressful events, modulate memory consolidation of the events (McGaugh et al., 1996), and support the view that endogenous stress hormones are an essential component of an endogenous memory modulating system for emotionally arousing events that helps insure memory strength that is, in general, proportional to memory importance (Cahill & McGaugh, 1998). More generally, these findings add to the presently limited number of studies demonstrating modulation of human memory consolidation with post-training manipulations (e.g., Colrain, Mangan, Pellett, & Bates, 1992; Manning et al., 1992; Scholey, Moss, &

Wesnes, 1998; Soetens et al., 1995; Southwick et al., 2002; Weingartner & Parker, 1984).

It should be noted that findings of two studies from our laboratory performed after the present study suggest substantial sex-related influences on neural mechanisms of memory for emotional events (Cahill et al., 2001; Cahill & van Stegeren, in press). The present study involved too few male and female subjects to allow substantial conclusions about potential sex-related influences to be drawn. Thus the question of whether sex may influence the effects of post-learning stress hormones on memory consolidation in humans remains open, but seems to us to merit attention in future studies.

The second, but at present more speculative, conclusion from this study is that post-learning adrenergic hormone activity *interacts* with the degree of arousal associated with initial encoding to influence consolidation of recently acquired information. This interaction is suggested by the very different EDRs to slides whose retention was modulated by epinephrine (although these EDRs were determined in different subjects than those who received the epinephrine infusions), and by the significantly higher HR acceleration in response to the primacy compared with recency slides in the subjects who received infusions. Prior research established in rats that exogenously administered epinephrine interacts with epinephrine released during a learning event to influence consolidation (Gold & van Buskirk, 1978). The basic concept of an interaction between exogenous and endogenous hormone levels derived from animal research is in principle consistent with the interaction between post-learning hormones and arousal at initial encoding proposed here.

Other evidence consistent with this proposal comes from studies of human subjects. For example, selective actions of both glucose (Messier et al., 1998) and the cholinergic antagonist scopolamine (Crow, 1979) on memory for the primacy portion of word lists have been reported. However in both of these studies, in contrast to the present study, drug administration occurred pre-training. Buchanan and Lovallo (2001) reported that pre-learning cortisol administration selectively enhanced long term memory of arousing pictures. Conversely, de Quervain, Roozendaal, Nitsch, McGaugh, and Hock (2000) reported no effect of post-training corticosterone administration on consolidation of memory for non-arousing material. Finally Nielson et al. (1996) reported that post-learning muscle tension arousal enhanced memory for words only when ‘priming’ tension was administered before learning, and raise the possibility that a ‘priming’ arousal in the present experiment (perhaps associated with insertion of the i.v line) may also have influenced the results. Collectively, each of the above findings is consistent with the possibility that hormone effects on memory may depend in some manner on the degree of arousal associated with the initial

learning, although this issue has not, to our knowledge, been systematically explored in either infra-human or human subject work.

An alternative interpretation of the present findings is that enhanced attention, rather than arousal, is the critical variable with which post-learning hormones interact to modulate memory. While this possibility cannot be completely ruled out from the present data, we make two observations about it. First, subjects in this study were required to name and rate (and thus attend to) all slides in the series. Second, enhanced attention typically associated with an orienting response has been tightly linked to heart rate deceleration (e.g., Lacey & Lacey, 1974). In the present study, memory enhancement with epinephrine was associated with slides that accelerated heart rate, consistent with the possibility that these slides (the primacy slides) were encoded with heightened arousal.

In summary, the present findings provide the first demonstration of enhanced human long-term memory consolidation produced with a naturally occurring stress hormone (epinephrine). With the additional evidence suggesting that epinephrine selectively enhances memory consolidation for relatively arousing information, future studies can begin to better characterize the hypothesized interaction between post-learning hormone activation and arousal at initial encoding in human memory consolidation.

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