Differential Effects of Adrenergic and Corticosteroid Hormonal Systems on Human Short- and Long-Term Declarative Memory for Emotionally Arousing Material

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The effects of adrenergic and corticosteroid hormonal systems on emotional memory were measured in 64 young men. Placebo, propranolol (40 or 80 mg; beta blocker), or metyrapone (corticosteroid synthesis inhibitor) was administered before the viewing of a story composed of emotional and neutral segments. Short- and long-term declarative memory for the story was assessed. Propranolol 40 mg had no effects on declarative memory. Propranolol 80 mg impaired short- and long-term declarative memory for emotionally arousing material. Metyrapone did not impair short-term declarative memory but impaired long-term declarative memory for emotionally arousing and neutral material. Results demonstrate that adrenergic and corticosteroid hormonal systems differentially affect declarative memory for emotionally arousing and neutral material, and suggest that interactions between adrenal hormonal systems modulate emotionally arousing declarative memory in humans.

Previous data obtained in both animal and human studies have shown that adrenal hormones secreted during a stressful or emotionally arousing experience can produce a retrograde enhancement of memory for that experience (Buchanan & Lovallo, 2001; McGaugh, 2000; Roozendaal, 2002). This enhancement of declarative memory for stimuli inducing stressful or emotional responses may be essential for species’ survival (see Hamann, 2001).

Two major types of adrenal hormones, adrenergic and corticosteroid hormones, are involved in the memory-enhancing effects of emotionally arousing stimuli. In rodents, postlearning stimulation of the noradrenergic system enhances long-term declarative memory of an inhibitory avoidance task, whereas postlearning blockade of the central noradrenergic system inhibits it (McGaugh, 1990, 2000). In humans, prelearning blockade of central beta-adrenergic receptors inhibits long-term declarative memory for emotionally arousing material (Cahill, Prins, Weber, & McGaugh, 1994; Van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998), whereas prelearning or postlearning stimulation of the noradrenergic system enhances it (Cahill & Alkire, 2003; O’Carroll, Drysdale, Cahill, Shajahan, & Ebsmeier, 1999; Southwick et al., 2002).

In the same vein, posttraining injections of moderate doses of synthetic corticosteroids enhance, and pretraining corticosterone synthesis inhibition impairs, long-term expression of conditioned fear and inhibitory avoidance in animals (Cordero, Kruyt, Merino, & Sandi, 2002; Liu, Tsuji, Takeda, Takada, & Matsumiya, 1999; Roozendaal, 2002; Roozendaal, Bohus, & McGaugh, 1996; Sandi, 1998). These results concord with recent human findings showing that administration of synthetic corticosteroids has a specific enhancing effect on declarative memory for highly arousing material (Buchanan & Lovallo, 2001). However, they stand in contrast to other published results showing enhancing effects of synthetic corticosteroids on declarative memory for both emotional and neutral information (Abercrombie, Kalin, Thuro, Rosenkranz, & Davidson, 2003).

Adrenal hormones may facilitate memory consolidation for emotional information through their interactions with noradrenergic and corticosteroid receptors located in the amygdala (Roozendaal, 2002), in turn modulating hippocampal activity and enhancing consolidation for emotionally arousing material (Abe, 2001; Roozendaal, 2002). New evidence suggests that the influence of the amygdala on declarative memory varies according to the delay at which the recall of the learned material occurs (Bianchini, Souza, Medina, & Izquierdo, 1999). Memory performance tested shortly after learning (i.e., short-term declarative memory) generally refers to consolidation processes occurring within the first 3 hr after learning (i.e., early phase), whereas memory performance tested after an extensive delay (i.e., long-term declarative memory) generally refers to the consolidation processes taking
place 3 hr postlearning (i.e., late phase) that persist for at least a day and involve gene transcription and protein synthesis (Kandel, 2001). Some neuropsychological studies have reported that emotionally arousing material enhances declarative memory when assessed 1 week later (long-term memory recall) but has no effect on declarative memory when assessed within 1 hr after learning (short-term declarative memory; Kleinsmith & Kaplan, 1963; Quevedo et al., 2003). In most of the previous studies examining the effects of adrenergic or corticosteroid hormones on declarative memory for emotionally arousing material, short-term declarative memory has not been assessed (with the exception of Abercrombie et al., 2003), thus leaving open the question as to whether these adrenal hormones can affect the early processes of consolidation. The addition of a condition measuring short-term declarative memory in protocols assessing the effects of adrenal hormones on declarative memory for emotionally arousing material is thus necessary to specify the modulating effects of these hormones on consolidation processes of emotional material.

Accordingly, the goal of this study was to assess short- and long-term declarative memory of emotionally arousing and neutral material in humans after pharmacological manipulation of adrenergic or corticosteroid systems. Young men were administered either a blocker of beta-adrenergic receptors (propranolol) or an inhibitor of corticosteroid synthesis (metyrapone), and short-term (5 min after learning) and long-term (1 week after learning) declarative memory for emotionally arousing and neutral material was compared with short- and long-term declarative memory measured under a placebo condition.

Method

Participants

Sixty-four healthy English- and French-speaking men participated in this study. The study was approved by the Douglas Hospital Research Ethics Board, and informed consent was obtained from all participants, who were compensated for taking part in the study. Participants were recruited in the community and underwent psychological and physical examinations, as well as routine blood and urine laboratory tests. To be included in the study, individuals were required to be exempt of any significant abnormalities on clinical examination. Twenty-eight men, between the ages of 19 and 36 years, participated in Experiment 1 and were randomly assigned to one of three experimental conditions: placebo (n = 14) or propranolol 80 mg (n = 14). All 28 participants were nonsmokers. Education level and body mass index were not different between groups (ps > .53).

Declarative Memory Task

In both experiments, participants viewed a narrated series of 11 colored pictures presenting a story composed of emotionally arousing and neutral segments. The story presented was designed according to the method used by Cahill et al. (1994), except that the theme of the story was different. Specifically, a young girl engaged in a woodworking activity with her grandfather was injured and subsequently rushed to the hospital. The series of pictures was separated into three phases: Phase 1 (Pictures 1 to 4) presented neutral information, Phase 2 (Pictures 5–8) presented emotionally negative information, and Phase 3 (Pictures 9–11) presented neutral information. Narratives accompanying Phases 1 and 3 were neutral, whereas narratives accompanying Phase 2 were emotionally negative.

Given the incidental nature of the declarative memory task (i.e., participants were not aware of the later memory evaluation; see Cahill et al., 1994), participants were told that we were interested in their physiological reactions (i.e., pulse, blood pressure, and hormone levels) to the stimuli and were asked to relax and simply watch the story presented as if they were at the movies. Free recall of the story was assessed at two time points, namely, 5 min after viewing (i.e., during the first experimental session) and 1 week later (i.e., during the second experimental session; see Neuroendocrine Protocols section). At the end of the first session, participants were asked to return to the laboratory 1 week later to provide a blood sample for baseline physiological measures. On their arrival, participants were informed that no physiological measures would be taken, and they were instead asked to recall as much information as possible about the story viewed a week earlier (long-term declarative memory condition). At the end of the meeting, the experimenter asked the participants whether they anticipated the declarative memory tests; all reported that the declarative memory tests were unexpected, for both the short- and long-term free recall. All participants were debriefed with respect to the real goal of the study at the end of the second session.

For the short- and long-term recall conditions, participants were encouraged to remember as much as they could about the main story line, as well as any details that came to mind. Free recalls were tape-recorded to be analyzed later. The experimenter scoring the results was unaware of drug conditions. Participants were credited with the recall of a picture (for a total of 1 point per picture) if they remembered elements that could only have been seen in that particular picture and not in any other picture or mentioned in the narration. Because the number of pictures per phase varied, the total scores per story phase were calculated as percentages of correct responses. French and English versions of the story were used, and there were no differences in short- and long-term free recall with regard to the language in which the story was presented (p > .10).

Neuroendocrine Protocols

In Experiment 1, participants were tested individually on two separate occasions. Participants, who abstained from smoking for the entire protocol, arrived at the laboratory at 5:45 a.m., and smokers were asked to refrain from smoking for the entire protocol. At 6 a.m., a catheter was inserted in the participant’s arm, and baseline blood samples and pulse and blood pressure measures were taken at 6:20 a.m. and 6:40 a.m. Cardiac activity was

ADRENAL HORMONAL SYSTEMS AND EMOTIONAL MEMORY 421

propranolol had no effects on the sympathoadrenal system (see Results section), we designed a second experiment in which 80 mg propranolol were administered. A higher drug dosage could indeed be more efficient in blocking peripheral and central beta-adrenergic receptors so as to modulate declarative memory for emotionally arousing material. Twenty-eight men, between the ages of 20 and 34 years, participated in Experiment 2 and were randomly assigned to one of two experimental conditions: placebo (n = 14) or propranolol 80 mg (n = 14). All 28 participants were nonsmokers. Education level and body mass index were not different between groups (ps > .53).

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measured with the Welch Allyn Atlas Vital Signs Monitor (Skaneateles Falls, NY). At 6:45 a.m., a first dose of metyrapone 750 mg p.o. was administered, while the placebo group received placebo pills. At 8 a.m., a light snack (yogurt and fruit) was given to participants. At 9:45 a.m., pulse and blood pressure were measured and the placebo group received a placebo, while the medication groups received their respective drugs (propranolol 40 mg or second dose of metyrapone 750 mg p.o.). These specific drug doses (40 mg propranolol, 2 × 750 mg p.o. metyrapone) were selected because they had proven efficient in blocking beta-adrenergic receptors (Cahill et al., 1994; Van Stegeren et al., 1998) and inhibiting corticosteroid secretion (Lupien, Wilkinson, Briè, Ménard, et al., 2002; Lupien, Wilkinson, Briè, Ng Ying Kin, et al., 2002; Wilkinson, Peskind, & Raskind, 1997; Wilkinson et al., 2001) in humans. As well, time of drug administration was carefully selected to ensure peak plasma propranolol and metyrapone levels at the time declarative memory was evaluated (Cahill et al., 1994; Wilkinson et al., 1997, 2001).

At 10 a.m., participants had a light breakfast. At 10:20 a.m., a blood sample and pulse and blood pressure measures were taken. Sixty-five minutes after drug treatment (i.e., at 10:50 a.m.), participants viewed the emotional story, and a final set of physiological measures was taken at 10:55 a.m. Immediately after viewing the story, participants rated how emotional they thought the story was on an 11-point scale ranging from not emotional (0) to very emotional (10), and they were submitted to the surprise free recall 5 min later (11 a.m.). Participants left the laboratory at 11:30 a.m. after being examined by the medical supervisors of the study (Ridha Joober and Serge Beaulieu). The second experimental session occurred a week later, at which time participants came back to the laboratory for the supposed physiological measures and were asked instead to recall the story (see earlier declarative memory task description).

The neuroendocrine protocol for Experiment 2 was similar to the one used for Experiment 1, except that we modified the dose of propranolol administered (80 mg instead of 40 mg as in Experiment 1) as well as the time that elapsed between drug administration and declarative memory testing (90 min instead of 65 min as in Experiment 1) to make sure that drug peak levels would be reached during declarative memory testing (American Hospital Formulary Service, 1999). Finally, the effects of propranolol 80 mg on circulating levels of corticosteroids were measured in saliva samples (Experiment 1 involved the use of blood samples), because this methodology is less invasive and provided us with a measure of the free, and thus active, portion of the steroid. The increase in the time that elapsed between drug administration and declarative memory testing explains the additional three saliva samples taken in Experiment 2 (see Figure 1b), allowing us to reliably assess drug effects on cortisol levels. In both experiments, the participants and experimenter were unaware of drug conditions. No side effects (e.g., nausea, dizziness, or fatigue) due to either propranolol (40 or 80 mg) or metyrapone (2 × 750 mg p.o.) were reported by participants.

Cortisol Assays

Blood samples (10 ml) were collected in Vacutainer tubes containing the anticoagulant EDTA and immediately centrifuged at 900 g at 4 °C. Plasma samples were stored at −80 °C in polystyrene tubes until assayed. Cortisol levels were measured with the ICN Immuchem coated tube radioimmunoassay kit (Medicorp, Montreal, Quebec, Canada). In this kit, the antibodies are raised in rabbit and are covalently bound to the inner surface of polystyrene tubes. The tracer reagent buffer contains a chemical agent that will release cortisol from corticosteroid binding globulin in the plasma sample. The free cortisol competes with the 1251 cortisol for the coated antibodies. The intra-assay and interassay coefficients of variation were 7.0% and 7.9% for mean concentrations of 4.4 μg/dl and 4.8 μg/dl, respectively. The sensitivity of the assay was 0.15 μg/dl.

Salivary cortisol samples were collected with the Sarstedt Salivette device (Sarstedt, Nümbrecht, Germany) and stored at −20 °C until assayed. Samples were thawed and spun at 3,000 rpm and 4 °C for 20 min, and cortisol concentrations were determined by radioimmunoassay with a kit from Diagnostic Systems Laboratories (Webster, TX). Salivary samples of cortisol were mixed with 500 μl 125I-labeled cortisol reagent and 500 μl cortisol antiserum complex reagent. Total binding and nonspecific binding typically ranged from 47%–63% and 0.5%–1.5%, respectively. Bound antigens were separated through a preracted double antibody system. When this technique is used, cross-reactivity of the antigen is less than 4% with 11-deoxycortisol and less than 1% with any other naturally occurring steroids. The intra-assay and interassay coefficients of variation were 4.6% and 5%, respectively. The limit of detection of the assay was 0.01 μg/dl. All samples were assayed in duplicates.

Data Analysis

In Experiment 1, because of data lost for cardiac activity measures, one measure of pulse and systolic and diastolic blood pressure was estimated for 3 different participants according to the formula used by Cochran and Cox (1957). In Experiment 2, 1 participant in the placebo group was withdrawn from all analyses (physiological and cognitive analyses) because of cortisol data loss (n = 27, 13 in the placebo group and 14 in the propranolol group). In the case of both experiments, data were verified for assumptions of normality and sphericity, and logarithmic transformations
or Greenhouse–Geisser (1959) corrections were applied when normality or sphericity was not met. Consequently, although the cortisol data were logged in both experiments, to allow the proper statistical analysis, cortisol results are presented as untransformed results in µg/dl units for the sake of comparison between studies.

We conducted mixed analyses of variance (ANOVIAs) using treatment (placebo vs. propranolol vs. metyrapone) as the between-subjects factor and cortisol samples, pulse measures, and systolic and diastolic blood pressure measures as the within-subject factors to evaluate the effects of treatment on physiological measures. We conducted a mixed ANOVA using treatment as the between-subjects factor (placebo vs. propranolol vs. metyrapone), along with time of recall (short- vs. long-term free recall) and story phase (1 vs. 2 vs. 3) as within-subject factors, to measure the effects of treatment on mean percentages of recall of emotionally arousing and neutral material. Preliminary analyses revealed that, in both experiments, there was no interaction between treatment and Neutral Story Phases 1 and 3 (ps > .25). As a result, recall scores on Phases 1 and 3 were averaged, and the factor of valence (emotional vs. neutral) was entered in the mixed ANOVA assessing drug effects on declarative memory. Simple effects and, when appropriate, Tukey’s honestly significant difference analyses were conducted on all significant physiological and cognitive findings.

Results

Physiological Measures

Comparison of plasma cortisol levels between groups in Experiment 1 showed that cortisol levels were significantly decreased after metyrapone treatment, whereas propranolol 40 mg and placebo had no effects on cortisol levels (significant interaction between treatment and cortisol samples), F(2, 39) = 9.20, p < .01 (see Figure 1a). There was no effect of treatment on measures of pulse (p > .05), systolic blood pressure (p > .32), or diastolic blood pressure (p > .10; see Table 1). Because propranolol 40 mg has been reported to diminish cardiac activity 1 hr after its admin-

<table>
<thead>
<tr>
<th>Measure</th>
<th>Time of measurement: Experiment 1</th>
<th>Time of measurement: Experiment 2</th>
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<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
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<tr>
<td>Placebo</td>
<td>113.08 ± 7.52</td>
<td>112.85 ± 7.85</td>
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<tr>
<td>Propranolol 40 mg</td>
<td>116.00 ± 8.72</td>
<td>115.91 ± 9.53</td>
</tr>
<tr>
<td>Metyrapone 2 × 750 mg p.o.</td>
<td>115.17 ± 10.67</td>
<td>115.50 ± 12.09</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td></td>
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<tr>
<td>Placebo</td>
<td>67.62 ± 5.94</td>
<td>66.69 ± 5.92</td>
</tr>
<tr>
<td>Propranolol 40 mg</td>
<td>72.27 ± 5.69</td>
<td>71.36 ± 7.08</td>
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<tr>
<td>Metyrapone 2 × 750 mg p.o.</td>
<td>69.92 ± 7.27</td>
<td>69.08 ± 7.35</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>64.62 ± 7.75</td>
<td>65.23 ± 8.46</td>
</tr>
<tr>
<td>Placebo</td>
<td>72.55 ± 7.44</td>
<td>71.64 ± 6.74</td>
</tr>
<tr>
<td>Propranolol 40 mg</td>
<td></td>
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<tr>
<td>Metyrapone 2 × 750 mg p.o.</td>
<td>66.25 ± 8.31</td>
<td>66.08 ± 7.98</td>
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Note. All times of measurement are morning hours. bpm = beats per minute.
*p < .05, significantly different from placebo.
istration (Cahill et al., 1994), we compared pulse and systolic and diastolic blood pressure at 9:45 a.m. (the time of propranolol administration) and 10:45 a.m.; we found no group differences (all ps > .25).

Comparison of salivary cortisol levels between groups in Experiment 2 showed that propranolol 80 mg significantly enhanced free cortisol levels approximately 1.5 hr after its administration (significant interaction between treatment and cortisol samples), F(2, 58) = 3.86, p < .03 (see Figure 1b). As shown in Table 1, group differences in cardiac activity measures showed that propranolol 80 mg significantly reduced pulse for the 11:05 a.m. measure (significant interaction between treatment and pulse measures), F(4, 99) = 5.70, p < .01, and significantly reduced systolic blood pressure at 11:15 a.m. and 11:25 a.m. (significant interaction between treatment and systolic blood pressure measures), F(5, 122) = 3.95, p < .01; however, it had no impact on diastolic blood pressure (p > .33).

Cognitive Measures

When comparing the effects of placebo, propranolol 40 mg, and metyrapone on short- and long-term declarative memory for emotionally arousing and neutral material (Experiment 1), we found a significant interaction between treatment and time of recall, F(2, 33) = 6.04, p < .01. Short-term declarative memory was not affected by either drug (p > .56), whereas long-term declarative memory for emotionally arousing and neutral material was significantly impaired after metyrapone treatment (p < .05; see Figure 2a). There was no effect of treatment on subjective emotional rating of the stories (p > .85; see Table 2).

When comparing the effects of placebo and propranolol 80 mg on short- and long-term declarative memory for emotionally arousing and neutral material, we found a significant interaction between treatment and valence, F(1, 25) = 5.46, p < .03. Both short- and long-term declarative memory of emotionally arousing material was significantly impaired after propranolol 80 mg treatment (p < .02), whereas short- and long-term declarative memory for neutral material was not (p > .51; see Figure 2b). There were no significant-between-groups differences in subjective emotional ratings of the stories (p > .40; see Table 2).

Discussion

The results of this study have three major implications with regard to the effects of adrenergic and corticosteroid hormonal systems on declarative memory for emotionally arousing material. First, they stand in contrast with previous published studies showing that the administration of 40 mg propranolol abolishes the memory-enhancing effect of emotionally arousing material in humans (Cahill et al., 1994; Van Stegeren et al., 1998). Here, in a population of young male controls, we did not find any significant effects of propranolol 40 mg on declarative memory for emotionally arousing material. Second, they extend previous studies assessing the effects of propranolol on declarative memory for emotionally arousing material (Cahill et al., 1994; O’Carroll et al., 1999; Van Stegeren et al., 1998) by showing that both short-term and long-term declarative memory for emotionally arousing material is impaired after blockade of the noradrenergic system with 80 mg propranolol. Finally, they extend previous studies assessing the effects of metyrapone on declarative memory for neutral material (Lupien, Wilkinson, Briere, Menard, et al., 2002) by showing that inhibition of corticosteroid synthesis before exposure to emotionally arousing and neutral material impairs long-term retention of both types of material. Altogether, these findings suggest a somewhat differential effect of both types of adrenal hormones on short- and long-term declarative memory for emotionally arousing information.

Effects of Propranolol 40 mg on Declarative Memory for Emotionally Arousing and Neutral Material

Previous human studies (Cahill et al., 1994; Van Stegeren et al., 1998) have observed impaired long-term declarative memory for emotionally arousing material after noradrenergic blockade with a dose of 40 mg propranolol; in the present study, however, physiological and cognitive measures were not affected with this dose. Two major factors could explain this discrepancy. First, given that nicotine has been linked to increased renal clearance of beta blockers in everyday smokers (Miller, 1990; Zevin & Benowitz, 1999), the presence of a smoker in the propranolol 40 mg group could explain the lack of effect of this dose. However, removing this participant from the analyses did not modify the results obtained.

Alternatively, the differences observed might be related to the absence of women in our sample. In all of the previous published reports on the effect of 40 mg propranolol on memory for emotionally arousing material, the samples were composed of more women than men (Cahill et al., 1994; Van Stegeren et al., 1998). Kendall, Jack, Quaterman, Smith, and Zaman (1984) demonstrated that propranolol blood concentrations are increased by the use of contraceptive pills, thus optimizing the pharmacological actions of beta blockers. Moreover, estrogen has been shown to enhance noradrenaline secretion and noradrenergic receptor sensitization (Herbison, Simonian, Thanky, & Bicknell, 2000). Thus, it is possible that, in the studies performed by the Cahill and Van Stegeren groups, women in the high estrogen phase of their menstrual cycle or those using contraceptive pills contributed significantly to the observed propranolol-induced inhibition of retrograde enhancement of long-term declarative memory for emotionally arousing material. Because we were able to confirm the research of Cahill and Van Stegeren’s groups using a dose of 80 mg propranolol in men, further studies should pay careful attention to the dose of propranolol used when testing populations of either men or women. Implications of the inclusion of men or women in studies assessing the effects of emotionally arousing experiences on declarative memory in humans have recently been discussed (see Cahill, 2003; Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001).

Effects of Propranolol 80 mg on Declarative Memory for Emotionally Arousing and Neutral Material

The results obtained with administration of 80 mg propranolol were consistent with previous research showing impaired long-term retention of emotionally arousing material after noradrenergic blockade in both animals (McGaugh, 1990, 2000) and humans (Cahill et al., 1994; Van Stegeren et al., 1998). However, in addition to what has previously been reported with regard to the
specific effects of emotionally arousing material on long-term declarative memory (Kleinsmith & Kaplan, 1963; Quevedo et al., 2003), here we showed that short-term declarative memory for emotional material can be modulated by pharmacological manipulations of the adrenergic hormonal system.

Inclusion of a short-term recall condition in this study allowed us to show that propranolol 80 mg impaired both short-term and long-term declarative memory of emotionally arousing material while having no impact on short- and long-term declarative memory of neutral material. These results confirm the specific role of adrenergic hormones in declarative memory for emotionally arousing material (Cahill et al., 1994; Van Stegeren et al., 1998), and they further extend the effects of these hormones to short-term declarative memory function. These data can be interpreted as
showing an effect of propranolol on arousal at encoding (see Cahill & Alkire, 2003; Hamann, 2001) or as showing an effect of propranolol on the neurobiochemical mechanisms involved in both short- and long-term declarative memory. Some studies have reported that beta blockers induce side effects such as sedation and attention-concentration deficits (McAinsh & Cruickshank, 1992). However, in this study, propranolol 80 mg selectively attenuated declarative memory for emotionally arousing material, whereas it did not affect declarative memory for neutral events, a finding difficult to reconcile with an encoding arousal explanation. Moreover, memory performance in the propranolol 80 mg group cannot be attributed to reduced emotional responsiveness, because subjective emotional reactions to the arousing story were the same for the placebo and propranolol groups.

Alternatively, the effects of propranolol on the neurobiochemical mechanisms involved in short- and long-term memory formation could best explain our findings. Previous animal studies demonstrated that activation of beta-noradrenergic receptors is necessary to induce both the early (short-term) and late (long-term) phases of long-term potentiation in the hippocampus (Hopkins & Johnston, 1988; Huang & Kandel, 1996). Long-term potentiation is a form of neuronal plasticity that has been shown to sustain the hyperstriatum ventrale of chicks 5 min after training on an avoidance learning task result in memory loss 30 min posttraining and impaired long-term declarative memory loss (Gibbs & Summers, 2002). Similarly, intracerebral injections of propranolol into the hyperstriatum ventrale of chicks 5 min after training on an avoidance learning task result in memory loss 30 min posttraining and impaired long-term memory consolidation (Gibbs & Summers, 2002). Combined, these findings suggest that blockade of adrenergic receptors has a significant impact on both short- and long-term declarative memory. Our results showing impairing effects of propranolol 80 mg on both short- and long-term declarative memory go along with this suggestion.

**Effects of Metyrapone on Declarative Memory for Emotionally Arousing and Neutral Material**

In contrast to the results we obtained with administration of propranolol 80 mg, we found that inhibition of corticosteroid synthesis by administration of metyrapone did not impair short-term declarative memory of emotionally arousing and neutral material, although 1 week later, when corticosteroid synthesis was no longer inhibited, long-term declarative memory of both types of material was significantly impaired. These data are in line with animal studies showing impaired long-term consolidation for avoidance learning paradigms after corticosteroid depletion due to metyrapone or adrenalectomy (Liu et al., 1999; Roozendaal, 2002; Sandi, 1998) and with human research acknowledging a necessary role for optimal levels of corticosteroids in long-term declarative memory for both emotionally arousing (Abercrombie et al., 2003; Buchanan & Lovullo, 2001) and neutral (Abercrombie et al., 2003) material.

A possible explanation for the effects of metyrapone on long-term declarative memory of emotionally arousing and neutral information resides in the differential involvement of the two corticosteroid receptors, mineralocorticoid (MRs) and glucocorticoid (GRs) receptors, in memory formation (for a complete review, see de Kloet, Otzl, & Joëls, 1999). MRs have a 6- to 10-fold higher affinity for corticosteroids than GRs (Reul & de Kloet, 1985). A wealth of evidence now demonstrates that activation of MRs is mandatory for successful acquisition of environmental cues necessary to encode information, whereas activation of GRs is necessary for long-term memory consolidation of this information (de Kloet et al., 1999; Sandi, 1998).

A closer look at the findings depicted in Figure 1a shows that metyrapone treatment induced a significant decrease in circulating corticosteroid levels, although there were some steroids still in circulation (which was predicted on the basis of the morning administration of the drug; see Lupien, Wilkinson, Brière, Ménard, et al., 2002). These low concentrations of corticosteroids after metyrapone administration might have induced a selective occupation of MRs, thus permitting the acquisition of information to be remembered and allowing short-term recall of this information. In contrast, the absence of occupancy of GRs due to the low levels of circulating corticosteroids might have prevented long-term consolidation of the information, thus leading to impaired long-term declarative memory of both neutral and emotionally arousing material. Corticosteroids have been shown to modulate memory consolidation by strengthening long-term memory storage through glycoprotein synthesis, for example neural cell adhesion molecules (NCAMs; Merino, Cordero, & Sandi, 2000; Sandi, 1998; Sandi, Rose, Mileusnic, & Lancashire, 1995). Lowered corticosteroid levels after metyrapone administration might have interfered with the glycoprotein synthesis process (Loscertales, Rose, & Sandi, 1997; Sandi, 1998), thus leading to the pattern of results observed in the present study.

Differential occupation of MRs and GRs under different metyrapone treatments could also explain the apparent discrepancy between the short-term declarative memory results of our study and those of Lupien, Wilkinson, Brière, Ménard, et al. (2002), who reported impaired short-term declarative memory of neutral information after administration of a similar dose of metyrapone (2 × 750 mg p.o.). In our study metyrapone was administered at 6:45 a.m. and 9:45 a.m., whereas in Lupien et al.’s study metyrapone was administered at 6 a.m. and 9 a.m., times of higher corticosteroid levels due to the circadian rhythm of this hormone. This difference in the time of administration of the drug led to a difference in the extent of inhibition of corticosteroids by metyrap-
one. In our study, the mean corticosteroid level after metyrapone treatment was 7.70 µg/dl at the time of short-term memory recall; in Lupien et al.’s study, the corresponding mean corticosteroid level was 5.13 µg/dl. These circulating levels of corticosteroids at the time of memory testing in Lupien et al.’s study might have been too low to substantially occupy MRs, thus provoking the short-term declarative memory deficits reported by these authors. Clearly, a study assessing the effects of different doses of metyrapone on declarative memory for emotionally arousing or neutral material should yield valuable data with regard to the potential role of activation of MRs in declarative memory for such material.

**Interactions Between the Adrenergic and Corticosteroid Hormonal Systems in Modulation of Declarative Memory**

One must keep in mind, however, that the influence of both adrenergic and corticosteroid hormones on declarative memory may be due to their interactive effects in the regulation of consolidation (Borrell, de Kloet, & Bohus, 1984; Borrell, de Kloet, Versteeg, & Bohus, 1983; Roozendaal, 2000; Roozendaal et al., 1996). Even though we did not specifically assess the interactive properties of these two hormonal systems for declarative memory of emotionally arousing material, some interesting findings emerged from our study that allow us to speculate about such interactions.

In Experiment 2, propranolol 80 mg induced a significant increase in salivary corticosteroid levels, representing the free portion of the steroid that easily crosses the blood–brain barrier. This finding, also observed in previous animal (Lewis, Groom, Barber, & Henderson, 1981) and human (Kizildere, Glück, Zietz, Schölmerich, & Straub, 2003) studies, raises the intriguing possibility that the impairing effects of propranolol 80 mg on short- and long-term declarative memory may be due, at least in part, to propranolol-induced increases in corticosteroid levels.

This could be possible given that the amygdala expresses GRs (Honkanieniemi et al., 1992) and studies by Roozendaal and collaborators (for a complete review, see Roozendaal, 2002) have demonstrated an important interplay between adrenergic and corticosteroid activity for consolidation of emotionally arousing material within this structure. For example, pretraining administration of a GR antagonist (e.g., RU-38486; Roozendaal, Quirarte, & McGaugh, 2002) has been shown to block the enhanced retention performance typically associated with posttraining basolateral amygdala infusions of beta-adrenergic receptor agonists in inhibitory avoidance tasks. Therefore, one could suggest that propranolol, by blocking beta-adrenergic receptors, and metyrapone, by inhibiting corticosteroid synthesis, interfered with the necessary interaction of adrenergic and corticosteroid hormones in the amygdala, thus preventing any enhancing effects of these hormones on declarative memory for emotionally arousing and neutral material.

Given the complex neuroendocrine interactions involved between adrenergic and corticosteroid hormones, future studies measuring circulating levels of both adrenergic and corticosteroid hormones, as well as studies involving specific agonists and antagonists of adrenergic and corticosteroid receptors, will be necessary to clarify the potential interactions of these two adrenal hormones in memory consolidation for emotionally arousing material.
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