Declarative Memory after Stress in Humans: Differential Involvement of the β-Adrenergic and Corticosteroid Systems

Françoise S. Maheu, Ridha Joober, and Sonia J. Lupien

Laboratory of Human Stress Research (F.S.M., R.J., S.J.L.), Douglas Hospital Research Centre, Montréal, Québec, Canada H4H 1R3; Department of Psychology (F.S.M.), University of Montréal, Montréal, Québec, Canada H3C 3J7; and Department of Psychiatry (R.J., S.J.L.), McGill University, Montréal, Québec, Canada H3A 1A1

To determine the role played by the β-adrenergic and corticosteroid systems in the modulatory effects of stress on declarative memory function, 42 young men were administered a placebo, propranolol (β-adrenergic blocker), or metyrapone (corticosteroid synthesis inhibitor) before being submitted to a psychological stress protocol. Immediately after stress, subjects viewed a neutral story, unrelated to the stressor. Short-term (5 min post learning) and long-term (1 wk post learning) recall of the story was assessed. Placebo and propranolol groups showed significant stress-related increases in corticosteroid levels, whereas metyrapone prevented corticosteroid reactivity to the stressor. Stress triggered significant elevations in cardiac activity (heart rate, systolic and diastolic blood pressure levels) in all three groups, with the metyrapone group showing the strongest elevation in heart rate levels in response to stress. Compared with placebo, propranolol had no effect on short- and long-term recall of the story learned after stress, whereas metyrapone impaired short-term recall of the story, with no further effects on long-term declarative memory. These results suggest that, contrary to the β-adrenergic system, the corticosteroid system is implicated in declarative memory function after stress in humans. (J Clin Endocrinol Metab 90: 1697–1704, 2005)

The physiological response of an organism to acute stress enables it to cope efficiently with the threat. During this process, animals (1–3) and humans (4, 5) develop vivid memories of the stressful and emotionally arousing situation. Interestingly, stressful and emotionally arousing experiences have also been shown to modulate subsequent declarative memory for material unrelated to the source of the stressor (e.g. Refs. 6–11; for a review, see Refs. 12–14). Declarative memory refers to the conscious or voluntary recollection of previously learned information (15). The effects of stress on subsequent declarative memory for material unrelated to the stressor can have important implications in everyday life, given the presence and reoccurrence of various sources of stress in the modern environment. The β-adrenergic and corticosteroid systems have been studied in relation to the memory-modulating effects of stressful and emotionally arousing experiences. The rationale for studying the impact of these hormonal systems is that both systems, when activated during stressful and emotionally arousing events, modulate activity in the frontal lobes, hippocampus, and amygdala, three brain structures involved in declarative memory processes (1, 2, 12–14, 16, 17).

In humans, the activation of the corticosteroid system has been shown to modulate poststress memory performance. Studies that have assessed the effects of stress on subsequent memory processing of material unrelated to the stressor reported that stress sometimes enhances (6), has no effect (18, 19), or sometimes impairs memory performance (9–11, 14, 20). The β-adrenergic system has also been associated with the memory-modulating effects of stress in humans. So far, all of the studies performed have shown that this system is particularly involved in the enhancement of memory for events that triggered the stressful experience in the first place. Indeed, pre- or postlearning stimulation of the β-adrenergic system enhances memory for the events that triggered the stressful experience (21–23), whereas blockade of β-adrenergic receptors before learning inhibits declarative memory for these stressful events (22, 24–26).

Although the studies summarized above suggest an important role of the β-adrenergic and corticosteroid systems in modulating human memory function in a stressful context, there are still discrepancies in the potential implication of these systems that necessitate further investigation. First, in contrast to the well-described effects of the β-adrenergic system in modulating memory for events that induced a stressful experience, it is unclear at this point whether this system is also implicated in the modulation of human memory for events that are memorized after stress and are consequently not related to the stressful event itself. Second, in most of the human studies measuring the effects of stress on subsequent memory processing [with the exception of Cahill et al. (6), and Wolf et al. (18)], memory performance is tested only shortly after learning (9–11, 19; for a review, see Refs. 14, 20). Declarative memory formation, however, is a time-dependent process in which both short-term memory (STM) and long-term memory (LTM) processes are initiated after learning to consolidate new memories. The STM trace (i.e.
memory performance tested within the first 3 h after learning) grows rapidly and then decays within hours, whereas the LTM trace (i.e., memory performance tested at least 3 h after learning) grows more slowly and is relatively permanent (1, 27). Both the β-adrenergic and corticosteroid systems have been shown to modulate short- (e.g., Refs. 24 and 28) and long-term (e.g., Refs. 21–26, 28; see Ref. 5) memory consolidation of the stressful events themselves. However, the role played by these two systems in modulating the effects of a stressful experience on short- and long-term consolidation of material unrelated to the stressor is to be further defined.

Accordingly, the goal of this study was to disentangle and specify the role played by the β-adrenergic and corticosteroid hormonal systems in modulating short- and long-term declarative memory of neutral material learned after stress in humans. Young men were administered either a blocker of peripheral and central β-adrenergic receptors (propranolol) or an inhibitor of corticosteroid synthesis (metyrapone) before being exposed to a psychological stress task. Poststress short-term (5-min delayed recall) and long-term (1-wk delayed recall) declarative memory was compared with poststress short- and long-term declarative memory measured under a placebo condition.

Subjects and Methods

Experimental subjects

Forty-two healthy English- and French-speaking men participated in this experiment. The study was conducted according to human research guidelines and was approved by the Douglas Hospital Research Ethics Board. Informed consent was obtained from all subjects, who were compensated for taking part in the study. Subjects, aged between 18 and 34 yr, were randomly assigned to one of three experimental conditions: oral (p.o.) placebo (n = 14); propranolol 80 mg p.o., a blocker of peripheral and central β-adrenergic receptors (n = 14); or metyrapone, an inhibitor of corticosteroid synthesis (two doses, 750 mg p.o. each; n = 14). Age, body mass index, and education level were not different among groups (P > 0.27). All subjects were nonsmokers. Subjects were recruited in the community and underwent psychological and physical examinations as well as blood and urine laboratory routine tests. To be included in the study, individuals were required to be exempt of a present or lifetime history of psychiatric disorders (axis I and II disorders) as evaluated with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV (29). Participants were also required to be medication free and exempt of current medical problems, clinically significant electrocardiogram abnormalities, and any significant abnormalities on laboratory tests. Individuals working night shifts were excluded from the study. Care was also taken not to evaluate subjects during stressful periods (such as exam periods), and individuals who had undergone major life changes (e.g., death of a close family member in the past year) were not included in the study. Women were excluded from the study to avoid any confounding effects of the menstrual cycle and contraceptive pill on declarative memory (30), total basal corticosteroid levels (31), and β-blocker catabolism (32).

Declarative memory task

Subjects viewed a 5-min narrated series of 11 color pictures presenting a neutral story. Specifically, a young girl engaged in a safely organized woodworking activity with her grandfather before going, later on, to an optometrist appointment with her grandmother. Narratives accompanying each picture were neutral and matched with regard to the comprehensibility, complexity, syntax, and grammatical structure.

Given the incidental nature of the declarative memory task (i.e., subjects were not aware of the later memory evaluation; Ref. 33), subjects were told that they would be viewing pleasant, unpleasant, and neutral pictures and that we were interested in their physiological reactions (i.e., heart rate levels, blood pressure levels, and hormone levels) to these pictures. Participants 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 wk later (i.e., during the second experimental session; see Psychoneuroendocrine protocol). At the end of the first session, participants were given a phone call meeting, to occur 1 wk later, to complete a questionnaire on emotions. When called back, subjects were informed that no questionnaire needed to be completed and were instead asked to recall as much information as possible about the story viewed 1 wk earlier (long-term declarative memory condition). At the end of the phone call meeting, the experimenter asked the subjects whether they anticipated the declarative memory tests; all reported that the declarative memory tests were unsuspected, for both the short- and long-term free recall. All subjects 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 would come to mind. Free recall was tape recorded to be analyzed later. The experimenter scoring the results was unaware of drug conditions. Subjects were credit-rated with the recall of a picture (for a total of one 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. The total declarative memory task procedure, including the viewing of the story and the 5-min delayed recall, took 15 min to be completed. 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 > 0.10).

Psychological stress protocol

Subjects were submitted to a psychological stress task, the Trier Social Stress Test (TSST), developed by Kirschbaum et al. (34). This laboratory stressor consists of a free speech and a mental arithmetic task performed in front of an audience. The total procedure, including preliminary instructions and a preparation period, takes 20 min. A wealth of findings demonstrated the efficacy of the TSST in substantially increasing free salivary cortisol levels and cardiac activity (e.g., Refs. 9–11, 18, 34, 35).

Psychoneuroendocrine protocol

Subjects were tested individually on two separate occasions. For the first experimental session, participants were asked to have a light breakfast at no later than 0700 h, during which they were asked not to have any citrus products, coffee, tea, and sweets. They were also asked to avoid exercising the morning of the initial session and were asked not to eat and drink anything but water 1 h before the start of the experiment. Subjects arrived at the laboratory at 1130 h, and baseline free salivary cortisol samples, heart rate, and blood pressure measures were taken at 1150 and 1200 h. Cardiac activity was measured with the Welch Allyn Atlas vital signs monitor (Skaneateles Falls, NY). At 1205 h, a first dose of metyrapone 750 mg p.o. was administered, whereas the placebo and propranolol groups were given placebo pills. A light lunch was given at 1245 h, and additional saliva samples, heart rate, and blood pressure measures were taken at 1225, 1315, 1340, and 1420 h.

At 1450 h, heart rate and blood pressure measures were taken and then, at 1452 h, the placebo group received a placebo, whereas the propranolol groups were given placebo pills. A light lunch was given at 1245 h, and additional saliva samples, heart rate, and blood pressure measures were taken at 1225, 1315, 1340, and 1420 h.

At 1450 h, heart rate and blood pressure measures were taken and then, at 1452 h, the placebo group received a placebo, whereas the medication groups received their respective drugs (propranolol 80 mg p.o. or second dose of metyrapone 750 mg p.o.). These specific drug doses (80 mg propranolol, 2 × 750 mg metyrapone) were selected because they had proven efficient in blocking peripheral and central β-adrenergic receptors (24, 36) and inhibiting corticosteroid secretion (24, 37–40) in humans. No side effects (nausea, dizziness, fatigue, sedation, etc.) due to either propranolol (80 mg) or metyrapone (2 × 750 mg) were reported by subjects. The times of drug administration were also carefully selected to ensure peak plasma propranolol and metyrapone effects at the time of declarative memory evaluation (24, 37–41). The subjects and experimenter were unaware of drug conditions.

Saliva samples, heart rate, and blood pressure measures were taken at 1520 and 1550 h, and subjects were submitted to the TSST at 1555 h. Additional saliva samples, heart rate, and blood pressure measures were then taken every 10 min from 1605 to 1705 h. Five minutes after the
psychological stress task ended (i.e. at 1620 h), subjects viewed the neutral story and were submitted to a surprise free recall 5 min later (i.e. at 1630 h). Subjects left the laboratory at 1715 h, after being examined by the medical supervisor of the study (R.J.). The second experimental session occurred 1 wk later, at which time participants were called over the phone and asked to recall the story (see earlier Declarative memory task description).

Salivary cortisol assays

Free salivary cortisol samples were collected with the Sarstedt salivette device (Sarstedt, Germany) and stored at −20 C until assayed. Samples were thawed and spun at 3000 rpm and 4 C for 20 min, and cortisol concentrations were determined by RIA with a kit from Diagnostic Systems Laboratories (Webster, TX). Salivary samples of cortisol were mixed with 500 μl 125I-labeled corticosterone reagent and 500 μl cortisol antiserum complex reagent. Total binding and nonspecific binding typically ranged from 47 to 63 and 0.5 to 1.5%, respectively. Bound cortisol antiserum complex reagent. Total binding and nonspecific binding were separated through a prereacted 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- and interassay coefficients of variation were verified for assumptions of normality and sphericity, and logarithmic transformations or Greenhouse-Geiser corrections were applied when normality or sphericity was not met. Although the salivary cortisol data were logged to allow proper statistical analyses, salivary cortisol results are presented as untransformed results in micrograms per deciliter units for the sake of comparison between studies.

Mixed ANOVAs using treatment (placebo vs. propranolol vs. metyrapone) as the between-subjects factor and salivary cortisol samples, heart rate, and systolic and diastolic blood pressure measures as the within-subjects factors were performed to evaluate the effects of treatment on physiological measures. A mixed ANOVA using treatment as the between-subjects factor (placebo vs. propranolol vs. metyrapone) and time of recall (short- and long-term free recall) as the within-subjects factor was performed to measure the effects of treatment on the mean percentage recall of material. Simple effects and, when appropriate, Student Newman-Keuls post hoc tests, were conducted on all significant physiological and cognitive findings.

Results

Effects of treatment on salivary cortisol measures

The ANOVA measuring the effects of treatment on salivary cortisol samples revealed that there was a significant two-way interaction between treatment and salivary cortisol samples [F (12, 224) = 5.25, P < 0.01]. For free salivary cortisol measures taken before the TSST, post hoc comparisons between groups demonstrated group differences at 1340 h (Fig. 1). At that time, the placebo and propranolol groups were under the influence of placebo pills (because propranolol 80 mg was only administered after cardiac parameters were measured, at 1452 h; see Subjects and Methods), whereas the metyrapone group was under the influence of the first dose of metyrapone (750 mg p.o.; see Subjects and Methods). Results showed that salivary cortisol levels in the placebo and propranolol groups were significantly increased, compared with those in the metyrapone group (P < 0.01). These results are attributable to the fact that metyrapone had already started to decrease salivary cortisol levels in the metyrapone group at 1340 h, whereas salivary cortisol levels were enhanced in the placebo and propranolol groups at that time due to the administration of a light lunch at 1245 h (37, 44, 45).

For free salivary cortisol measures taken during and after the TSST, post hoc comparisons between groups showed that the placebo and propranolol groups presented significant stress-induced elevations in salivary cortisol levels, whereas cortisol reactivity to the stressor was significantly suppressed by the metyrapone treatment (P < 0.005; Fig. 1). Finally, post hoc analyses revealed that salivary cortisol levels in the propranolol group remained significantly elevated at the end of the study (the 1705-h sample), compared with salivary cortisol levels in the placebo and the metyrapone groups (P < 0.03; Fig. 1). Salivary cortisol levels in the propranolol group, therefore, were returning to baseline levels more slowly than salivary cortisol levels in the placebo group. This result is consistent with previous human findings showing increased cortisol levels after propranolol administration (24, 46–49).
Effects of treatment on cardiac activity measures

When comparing the effects of treatment on heart rate measures, we found a significant two-way interaction between treatment and heart rate measures [F (12, 235) = 5.39, P < 0.01]. For heart rate measures taken before the TSST, post hoc comparisons between groups showed that, compared with heart rate levels in the placebo group, heart rate levels in the propranolol group were significantly elevated at 1420 and 1450 h (P < 0.03; Fig. 2A). Importantly, at both these time points, the placebo and propranolol groups were under the influence of placebo pills (see Subjects and Methods). This increase in heart rate levels in the propranolol group, which was observed before propranolol administration but after ingestion of a light lunch, could possibly be due to the effects of slow food digestion in some of the participants (50–52), who could have been more heavily distributed in the pro-

![Fig. 2. Mean (±SEM) cardiovascular measures in the placebo, propranolol, and metyrapone groups. A, Heart rate measures: *, propranolol and metyrapone groups present significantly higher heart rate levels than placebo group (P < 0.03); **, metyrapone group presents significantly higher heart rate levels than placebo group (P < 0.04); and ***, higher heart rate levels than the placebo and propranolol groups (P < 0.05). B, Systolic blood pressure measures. *, propranolol group presents lower systolic blood pressure than placebo and metyrapone groups (P < 0.03), and **, lower systolic blood pressure levels than placebo group (P < 0.03). C, Diastolic blood pressure measures. †, Diastolic blood pressure level was significantly elevated at 1315 h, compared with 1450 h, in all three groups (main effect of diastolic blood pressure measure; P < 0.01). † †, Diastolic blood pressure measures were significantly elevated in all three groups during the stress task until 20 min after the end of the stressor (main effect of diastolic blood pressure measure; P < 0.01).
propranolol group. Post hoc analyses further reported that, compared with heart rate levels in the placebo group, metyrapone treatment significantly elevated heart rate levels at 1420 and 1450 h (as in the propranolol group) as well as at 1520 h ($P < 0.04$; Fig. 2A).

For heart rate measures taken during and after the TSST, post hoc comparisons among groups showed that metyrapone treatment significantly increased heart rate levels at 1605 and 1615 h as well as from 1645 to 1705 h ($P < 0.05$), compared with heart rate levels measured in both the placebo and propranolol groups (Fig. 2A). Therefore, metyrapone treatment elevated heart rate levels 1.5 h before the start of the TSST (i.e. at 1420 h) and maintained heart rate levels elevated for most of the rest of the study (Fig. 2A).

When comparing the effects of treatment on systolic blood pressure measures, we found a significant two-way interaction between treatment and systolic blood pressure measures [$F (13, 255) = 1.94, P < 0.03$]. Post hoc analyses revealed that there was no impact of treatment on systolic blood pressure measures taken before the TSST ($P > 0.1$). For systolic blood pressure levels measured during and after the TSST, post hoc comparisons among groups showed that propranolol treatment significantly reduced systolic blood pressure levels at 1625 h, compared with the placebo and metyrapone treatment ($P < 0.03$), and at 1655 h, compared with the placebo group only ($P < 0.03$; Fig. 2B).

Finally, the ANOVA measuring the effects of treatment on diastolic blood pressure measures revealed that there was a significant two-way interaction between treatment and diastolic blood pressure measures [$F (15, 284) = 1.83, P < 0.04$]. However, the simple effects analyses and Student Newman-Keuls post hoc tests revealed no significant differences between groups ($P > 0.1$). The ANOVA measuring the effects of treatment on diastolic blood pressure measures also revealed a main effect of diastolic blood pressure measures [$F (7, 284) = 55.82, P < 0.01$] but no main effect of treatment ($P > 0.1$). Post hoc analyses performed on the main effect of diastolic blood pressure measures revealed that, for diastolic blood pressure measures taken before the TSST, the diastolic blood pressure level measured at 1315 h was significantly higher than the diastolic blood pressure level measured at 1450 h, in all three groups ($P < 0.01$; Fig. 2C). This could be due to the administration of a light lunch at 1245 h (50–52). For diastolic blood pressure measures taken during and after the TSST, post hoc analyses revealed that there was a significant elevation in diastolic blood pressure levels in all three groups during the TSST, until 20 min after the end of the TSST ($P < 0.01$; Fig. 2C).

Effects of treatment on memory performance

When comparing the effects of placebo, propranolol, and metyrapone on STM and LTM for the neutral story, we found a significant two-way interaction between treatment and time of recall [$F (2, 39) = 3.74, P < 0.033$]. Post hoc comparisons between groups revealed that, when compared with the placebo group, subjects in the metyrapone group showed impaired STM performance ($P < 0.05$), whereas subjects in the propranolol group presented a STM performance similar to that of the placebo group ($P > 0.47$). There were no group differences for LTM performance ($P > 0.25$; Fig. 3).

Discussion

The results of this study provide additional evidence that the corticosteroid system modulates declarative memory processes after stress in young human subjects. In recent studies, it was shown that when participants were exposed to a psychological stress task, i.e. a public speaking task, the stressor usually impaired declarative memory for neutral material learned after stress (9–11, 14, 20; but see Refs. 18 and 19). The public speaking tasks, in most of these studies, were found to be stressors of moderate to high intensity and to produce a greater and more robust cortisol stress reactivity, compared with other psychological stress tasks (e.g. Stroop task; see Ref. 53). In the present study, we demonstrated that inhibition of corticosteroid synthesis before exposure to stress also impairs memory performance because impaired short-term declarative memory recall for information not related to the source of the stressor was observed after metyrapone administration. These findings further strengthen animal and human research acknowledging that optimal levels of corticosteroids enhance poststress declarative memory function, whereas extremely low or elevated levels of corticosteroids impair poststress memory performance (e.g. Refs. 6, 7, 9–11, 54, 55; see Refs. 2, 3, 12–14, 20, 56). In contrast, the $\beta$-adrenergic system does not seem to be implicated in the effects of stress on subsequent declarative memory function in humans because blockade of peripheral and central $\beta$-adrenergic receptors before the stressor did not influence poststress declarative STM and LTM processes.

The STM deficits observed in the metyrapone group can be explained by the differential involvement of the two corticosteroid receptors, the mineralocorticoid receptors (MRs) and the glucocorticoid receptors (GRs), in declarative memory processes as well as by the time of day at which metyrapone was administered. MRs have a 6 to 10 times higher affinity for corticosteroids than GRs (57; for a complete review, see Ref. 56). 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 LTM consolidation of this information (3, 56).

In this study, metyrapone was administered in the afternoon (PM), at a time when circulating levels of corticosteroids are already low. Indeed, in humans, endogenous corticosteroid levels follow a circadian rhythm, with higher levels in the morning (AM) phase, and lower levels in the PM phase. These endogenous variations in corticosteroid levels thus lead to a differential activation of MRs and GRs in the AM vs. PM phase. During the circadian peak of corticosteroid secretion, in the AM phase, MRs are saturated and there is a 67–74% occupation of GRs. In the PM phase, however, endogenous levels of corticosteroid occupy 90% of MRs and 10% of GRs only (56). When submitted to a stressor, practically all of the MRs are activated, whereas around 75% of the GRs are occupied (56, 57). In the present study, however, the administration of metyrapone treatment in the PM phase, well before the stress task, suppressed the corticosteroid system’s reactivity to stress and most probably prevented any important occupation of both the MRs and GRs. Because stress-induced activation of the corticosteroid system has been shown to modulate declarative memory for material unrelated to the stressor according to an inverted U-shaped function (3, 12–14, 20, 56), the low level of activity in the corticosteroid system (extreme left end of the inverted U-shaped function) after metyrapone administration may have prevented the learning and consolidation of the neutral story.

Group differences observed for STM recall were lost for LTM performance. Such findings could be explained by a normal significant decrease, from the STM to the LTM condition, of recall performance in the placebo and propranolol groups to the level of the LTM performance observed in the metyrapone group. In humans, behavioral data report such a decrease, from STM to LTM recall, of declarative memory for neutral, low-arousing material (58, 59). Concomitantly, the absence of further decrease in declarative memory performance over time in the metyrapone group, possibly due to a floor effect, could explain the absence of group differences for the LTM recall.

Decreased activity in the corticosteroid system, leading to learning and consolidation impairments, offers an interesting explanation for the STM deficits observed in the metyrapone group. Some of the findings emerging from this study, however, permit us to offer a second explanation for the STM deficits observed in the metyrapone group. Specifically, our data bring us to suggest the possibility that the STM impairments observed here may not be attributable to the effects of the metyrapone treatment on the corticosteroid system solely but also to the dissociation in the activation of the cardiovascular and corticosteroid systems induced by the administration of metyrapone before exposure to stress. Indeed, although both the placebo and propranolol groups showed an increase in heart rate levels in response to the stressor, it is the metyrapone group that displayed the strongest heart rate elevation in response to the stressor. The presence of an increased cardiovascular tone in states of low levels of circulating corticosteroids is not surprising because the cardiovascular system is sustained by the catecholaminergic system, and many animal studies have reported enhancements in catecholaminergic responses under basal or stress conditions after adrenalectomy (60; for a review, see Ref. 61) and metyrapone administration (62). Suppressing the adrenal glands’ function does in fact prevent the protective inhibitory effects of corticosteroids on the catecholaminergic system (61). The metyrapone group, which presented the strongest increase in heart rate levels accompanied by the lowest corticosteroid system activity, was also the only group demonstrating impairments in short-term declarative memory performance. Interestingly, important stress-induced increases in heart rate activity have been linked to deficits in concentration and attention (63) and impairments in performance on motor tasks (64) and declarative memory tasks (63, 65) in previous human studies.

It could therefore be suggested that the impairing effects of stress on human declarative memory processes could be due to the complex interactions that exist among the different systems activated during the first (e.g., cardiovascular, peripheral and central noradrenergic systems activation) and second (corticosteroid system activation) waves of the stress response, more than to the unique effects of one of these systems. Intriguingly, in humans, most of the studies assessing the effects of the cardiovascular, peripheral/central noradrenergic, and corticosteroid systems on declarative memory after stress usually concentrate on only one of these systems (9–11, 18, 19, 63, 65). Recently, however, a human study performed by Cahill et al. (6) measured both stress-induced elevations in salivary cortisol and heart rate levels, but unfortunately, these authors reported only the effects of the stress-induced cortisol increases on declarative memory function. To this day, only one study measured and reported the effects of peripheral/central noradrenergic and corticosteroid responses to stress and their subsequent effects on cognitive function in humans. Skosnik et al. (66) showed that stress impaired selective attention (i.e., the ability to filter out irrelevant information). In their study, the stressor induced a significant increase in noradrenaline activity as assessed by α-amylase levels (correlate of noradrenaline), whereas it did not induce an increase in salivary cortisol levels.

Hence, in both the study by Skosnik et al. (66) and our study, cognitive impairments were observed when exposure to stress led to a significant increase in noradrenergic-related systems, such as the cardiovascular system and the peripheral/central noradrenergic system, with no increase in salivary cortisol levels. Such results allude to recent work (67, 68) suggesting that the two components of the stress response do not necessarily always display the unidirectional activity increases that are thought to occur in response to stress but rather can present some dissociation in their response to stressful events. Such dissociations could thus be, in part, responsible for some of the impairing effects of stress on declarative memory performance reported in humans.

In this study, the effects of 80 mg propranolol on cardiac parameters yielded mixed results. We were expecting, as reported in previous human studies (46, 47, 69, 70), to observe a decrease in cardiac reactivity to stress after administration of propranolol. However, a close look at Fig. 2 shows that stress increased heart rate and systolic and diastolic blood pressure measures in the propranolol group, despite β-receptors blockade. The only impact 80 mg propranolol had on cardiac activity after stress was to decrease systolic blood pressure activity at two time points, i.e. at 1625
and 1655 h. Furthermore, in contrast to the results obtained with metyrapone treatment, propranolol treatment had no influence on short- and long-term declarative memory performance measured after stress. Altogether, these results demonstrate that propranolol 80 mg did not have its expected impact on the cardiac parameters measured, and also suggest that the human β-adrenergic system is not implicated in the modulating effects of stress on subsequent declarative memory for material unrelated to the stressor.

The lack of effects of 80 mg propranolol on cardiac parameters could be explained by the time at which the stress task occurred after the administration of 80 mg propranolol. In a previous study using the same dose of propranolol (80 mg) in young male participants that were not exposed to a stressor, we found that propranolol started decreasing cardiac activity (heart rate and systolic blood pressure measures) 105 min after drug administration (24). In the present study, we did not allow a period of 105 min after drug administration before stressing the subjects (the stress protocol started 60 min after drug administration). Waiting 105 min before applying the stress task could have permitted us to observe the decreased cardiac activity due to the drug alone and the subsequent effects of stress on cardiac reactivity in the propranolol group. We chose not to use such a design because the main goal of this study was to assess the role played by the β-adrenergic and corticosteroid hormonal systems in modulating memory performance after stress, and this procedure (waiting 105 min before starting the stress protocol) increases the time that elapses between drug administration and the testing of memory. Indeed, if we had allowed a period of 105 min before stressing the subjects (with the stressor lasting 20 min) and tested memory 5 min later, then memory would have been tested 130 min after drug administration, at a time when propranolol would have started to be importantly cleared out of the circulation (41). Any memory effects observed in such a protocol would have been difficult to interpret in line with a drug effect. Consequently, the lack of effects of propranolol on cardiac activity in the present study could be due to the administration of the stress task before 80 mg propranolol had time to reach peak plasma levels. Therefore, subjects were stressed before 80 mg propranolol could efficiently reduce cardiac activity, resulting in an elevation of heart rate and systolic and diastolic blood pressure levels after the TSST in the propranolol group.

Finally, in this study, the lack of effects of propranolol treatment on memory performance could be attributed to the dose of propranolol (i.e., 80 mg) used in conjunction with a stress paradigm (i.e., the TSST). Indeed, in our previous study measuring the effects of 80 mg propranolol on declarative memory in young individuals not exposed to a stressor (24), we demonstrated that propranolol impaired short- (5 min post learning) and long-term (1 wk post learning) recall of emotionally arousing material, whereas it had no impact on short- and long-term recall of neutral material. Here, when young individuals were stressed after treatment with propranolol, we report that 80 mg of the β-blocker had no impact on STM and LTM for neutral material. Therefore, these results seem to suggest that the β-adrenergic system is not implicated in the modulating effects of stress on subsequent declarative memory for neutral material unrelated to the stressor in humans and rather suggest that β-adrenergic activity is specifically implicated in modulating declarative memory for emotionally arousing material only. Still, it could be argued that a dose of 80 mg propranolol, which has a significant impact on memory when given without a stressor, is not high enough to impact this variable when it is administered in interaction with a stressor.

Altogether the results of this study suggest that, in humans, the corticosteroid system modulates the effects of stress on subsequent declarative memory function, whereas the β-adrenergic system, when blocked with doses of propranolol that usually inhibit recall of emotional information, does not have any effect on recall of neutral information learned after stress. Furthermore, findings from this experiment suggest that a dissociation between the activity of the cardiovascular system and the corticosteroid system may be implicated in the memory-modulating effects of stress on subsequent declarative memory function. Because stress triggers the activation of many different systems (71), future studies could gain new insights by measuring the simultaneous and differential effects of these different stress systems on learning and memory in human populations, rather than concentrating on only one stress system when assessing the impact of a stressor on human memory.

Acknowledgments

The authors thank the anonymous reviewers for their helpful comments on revision of this manuscript.

Received January 6, 2004. Accepted November 23, 2004.

Address all correspondence and requests for reprints to: Sonia J. Lupien, Laboratory of Human Stress Research, Douglas Hospital Research Centre, Frank B. Common Building, 6875 LaSalle Boulevard, Verdun, Quebec H4H 1R3, Canada. E-mail: sonia.lupien@mcgill.ca.

This work was supported by Grant 15000 from the Canadian Institutes of Health Research (CIHR) (to S.J.L.). F.S.M. was supported by a doctoral fellowship from CIHR, and S.J.L.’s work is supported by an Investigator Award from CIHR Institute of Aging.

References

17. Sara SJ 2000 Retrieval and reconsolidation: toward a neurobiology of remembering. Learn Mem 7:73–84
18. Wolf OT, Schönholzer NC, Hoffelner DH, Reischies FM, Kirschbaum C 2002 Moderate psychosocial stress appears not to impair recall of words learned 4 weeks prior to stress exposure. Stress 5:59–64
43. de Kloet ER, Oitzl MS, Vreugdenhil G 1999 Stress and cognition: are corticosteroids good or bad guys? Trends Neurosci 22:422–426
50. Mandler G 1984 Mind and body, the psychology of emotion and stress. New York: W.W. Norton and Co.; 320

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.