Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 4066–4071, March 1998
Psychology

Stress facilitates classical conditioning in males, but impairs classical conditioning in females through activational effects of ovarian hormones

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Communicated by Richard F. Thompson, University of Southern California, Los Angeles, CA, January 29, 1998 (received for review December 2, 1997)

ABSTRACT **Exposure to restraint and brief intermittent tailshocks facilitates associative learning of the classical conditioned eyeblink response in male rats. Based on evidence of sex differences in learning and responses to stressful events, we investigated sexually dimorphic effects of a stressor of restraint and intermittent tailshock on classical eyeblink conditioning 24 h after stressor cessation. Our results indicate that exposure to the acute stressor had diametrically opposed effects on the rate of acquisition of the conditioned response in male vs. female rats. Exposure to the stressor facilitated acquisition of the conditioned response in males, whereas exposure to the same stressful event dramatically impaired acquisition in females. We further demonstrate that the stress-induced impairment in female conditioning is dependent on the presence of ovarian hormones. Conditioning of stressed sham-ovariectomized females was significantly impaired relative to the unstressed controls, whereas conditioning in stressed ovariectomized females was not impaired. We present additional evidence that estrogen mediates the stress-induced impairment in female acquisition. Females administered sesame oil vehicle and then stressed were significantly impaired relative to their unstressed controls, whereas females administered the estrogen antagonist tamoxifen prior to stress were not impaired. In summary, these results indicate that exposure to the same aversive event can induce opposite behavioral responses in males vs. females. These effects underscore sex differences in associative learning and emotional responding, and implicate estrogen in the underlying neuronal mechanism.**

Prior exposure to an inescapable stressor of intermittent tailshock often impairs learning, and is referred to as "learned helplessness" (1–5). The impairment is typically observed during an operant conditioning task, in which an animal must perform an overt response to learn the operant contingency. Interestingly, the performance deficit in response to a stressful event is reported to be significantly reduced, if not absent, in females (6–9). In contrast to these effects on instrumental conditioning, exposure to a stressful event facilitates classical conditioning in males. The stress-induced facilitation of classical conditioning has been observed using several types of conditioning tasks including eyeblink (10–13), fear (14), and heart-rate conditioning (15). To our knowledge, the effects of stress on classical conditioning have not been examined in females.

It is well established that learning can be influenced by gender (7–9, 16–19). For example, females have been reported to learn faster than males in both instrumental (20) and classical conditioning tasks (21). In addition, behavioral responses to stressful experiences are influenced by sex (7–9, 16). Based on these differences in learning and the apparent lack of stress-induced helplessness symptomatology in females, we tested whether stress would enhance classical eyeblink conditioning in females, as it does in males (10–13). Our results indicate that exposure to a stressor of restraint and intermittent tailshocks facilitates acquisition of classical eyeblink conditioning in male rats, while significantly impairing acquisition in female rats.

Female sex hormones, estrogen and progesterone, are produced by the ovaries and influence learning and physiological responses to stress (22, 23). Estrogen is reported to enhance dendritic spine density and efficacy in the hippocampus and the amygdala (24–30), brain regions previously implicated in stress-induced effects on learning (31, 32). Here, we present evidence that the stress-induced impairment of classical eyeblink conditioning in females is dependent on the presence of ovarian hormones and the availability of estrogen receptors in the adult female brain.

MATERIALS AND METHODS

Effect of Sex and Stress on Acquisition of the Conditioned Response. Forty-four male and female Sprague–Dawley virgin rats (220–300 g) were obtained from the colony maintained at Princeton University in the Department of Psychology. Rats were housed in groups prior to surgery, and individually postoperatively to prevent damage to the headstage. Rats were given unlimited access to laboratory chow and water, and were maintained on a 12:12 light:dark cycle. Rats were anesthetized with pentobarbital (40–50 mg/kg), and four electrodes were implanted through the ridge of the eyelid. Two were used to deliver a periorbital shock to the eyelid, and two were used to detect eyeblinks by transmitting electromyographic activity from obicularis oculi. After surgery, 0.3 ml of penicillin (250,000 units/ml) (Apothecon, Princeton) was administered intramuscularly, and the rat was kept warm until recovery from anesthesia. Rats were provided with acetaminophen (IDE Interstate, Amityville, NY) diluted 1:100 in drinking water for 2 days.

Stressor Exposure. After 3–5 days of recovery, rats were exposed to the conditioning chamber and the spontaneous blink rate was recorded for 1 h without stimulus presentation. Stressed rats were taken into a different context, restrained in a Plexiglas tube, and exposed to 30 shocks to the tail (1 s, 1 mA, 60 Hz, 1 per min for 30 min). All rats were returned to the home cage for 24 h.

Conditioning Procedure. Twenty-four hours after stressor exposure, headstages were connected to a coiled cable allow-

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Abbreviations: CS, conditioned stimulus; CR, conditioned response; US, unconditioned stimulus; OVX, ovariectomized; TAM, tamoxifen; VEH, vehicle.

ing free movement within the conditioning chamber. Prior to conditioning, rats were exposed to 10 conditioned stimulus (CS) alone trials, each consisting of an 85-dB, 240-ms white noise burst. Male and female, stressed and unstressed rats were presented with paired ($n = 7$) or explicitly unpaired ($n = 4$) conditioning stimuli. A delay paradigm was used in which an 85-dB, 240-ms white noise CS with a 5-ms rise/fall time overlapped and coterminated with a 0.7-mA, 80-ms periorbital shock unconditioned stimulus (US). The intertrial interval was 20 ± 10 s. Each set of 10 trials consisted of a CS-alone, 4 paired trials, 1 US-alone, and 4 paired trials in sequence. Rats exposed to unpaired stimuli received an equal number of CS and US exposures, delivered in an explicitly unpaired manner with an intertrial interval of 20 ± 10 s. All rats were exposed to 300 trials a day for 2 days.

An eyelid electromyograph was filtered to pass 0.3–1.0 kHz and amplified (10,000×) with a differential ac amplifier, and passed to a 16 bit A/D card (Keithley–Metrabyte, Taunton, MA). The maximum value of a 240-ms pre-CS baseline response was added to 4 times its SD, and electromyographic responses greater than that were considered eyeblinks. Conditioned responses (CRs) occurred at least 80 ms *after* CS onset but prior to US onset on paired trials, or throughout the trial on CS alone trials. Eyeblinks that occurred within 80 ms of CS onset were considered sensitized responses.

Analgesic Responses. Immediately after training, analgesic responses were measured by a tailflick response. Rats were restrained by the torso, and the tail gently positioned in a starting notch on the restraining board. A photobeam of increasing intensity was stationed above the tail, and the time to elicit a tailflick response was recorded four times and averaged for each rat.

Reducing the Rate of Acquisition in Females. In a second experiment, adult female virgin rats were implanted with electrodes and later were exposed to the stressor ($n = 9$) or unstressed conditions ($n = 9$) as described. The same conditioning paradigm was implemented presenting only 300 trials, and the CS intensity was lowered from 85 to 80 dB.

Removal of Ovarian Hormones. In a third experiment, 37 adult female virgin rats (250–300 g), were anesthetized with pentobarbital (40 mg/kg) and bilaterally ovariectomized (OVX) (33) or subjected to a sham surgical procedure. Sham surgery included all aspects of the OVX procedure, except the fallopian tube and ovaries were left intact. Headstages and electrodes were implanted as described above. After 4–6 days of recovery from surgery, a group of OVX ($n = 9$) and sham-operated females ($n = 9$) were stressed and classically conditioned 24 h later. Performance was compared with that of unstressed OVX ($n = 10$) and sham-operated ($n = 9$) females.

Administration of the Estrogen Antagonist. In a fourth experiment, 41 adult female virgin rats (250–300 g), were anesthetized with pentobarbital (40 mg/kg), fitted with headstages and periorbital electrodes. Rats were randomly assigned to one of four groups: tamoxifen (TAM)/stress ($n = 11$), TAM/no stress ($n = 10$), vehicle (VEH)/stress ($n = 10$), VEH/no stress ($n = 10$). Rats received daily injections of either 0.5 ml of sesame oil VEH alone or sesame oil containing 1.5 mg of estrogen antagonist TAM [(*Z*)-1-(*p*-dimethylamino-ethoxyphenyl)-1,2-dipehenyl-1-butene] for 4 days. Stress rats were exposed to the stressor after the last injection, and all rats were trained 24 h later.

Vaginal Cytology. For the TAM study, vaginal cytology was obtained through daily vaginal smears (12:00 to 14:00). Sterile Q-tips were immersed in physiological saline and gently inserted into the vaginal tract, removing lose epithelial cells, then rolled onto a slide (34). Cells were dried, stained, and fixed in 95% EtOH, rinsed in distilled H_2O, stained in slightly alkaline 1% aqueous filtered toluidine blue, and rinsed in 70% and 90% EtOH, successively.

The stages of the estrous cycle are reflected in the vaginal cytology. Early proestrus is marked by pink staining epithelial cells, late proestrus and estrus by masses of dark blue staining cornified cells, and diestrus by dark staining leukocytes with scattered epithelial cells. We used a simplified three-stage classification scheme in which proestrus (early and mid proestrus), estrus (late proestrus and estrus), and diestrus (brief metestrus and diestrus combined) corresponded to basic differences in circulating hormone levels. Proestrus is associated with relatively high levels of circulating estrogen, estrus with intermediate levels, and diestrus with low levels of estrogen (35).

RESULTS

Effects of Sex and Stress on Acquisition of the CR. Exposure to the stressor had diametrically opposed effects on acquisition of the CR in males vs. females [$F(1, 36) = 14.28$; $P < 0.001$]. Post-hoc analysis using a Newman–Keuls comparison test indicated that exposure to the stressor facilitated acquisition of the CR in males ($P < 0.001$), whereas exposure to the same stressor impaired acquisition in females ($P < 0.001$), relative to their same-sex unstressed controls (Fig. 1). Females outperformed males under unstressed conditions ($P < 0.01$).

A significant interaction between stress, sex, and paired vs. unpaired training remained evident throughout 2 days of training (600 trials) [$F(1, 36) = 5.64$; $P < 0.02$)]. Females responded less to the CS after stressor exposure ($P < 0.05$), whereas males responded more to the CS after stressor

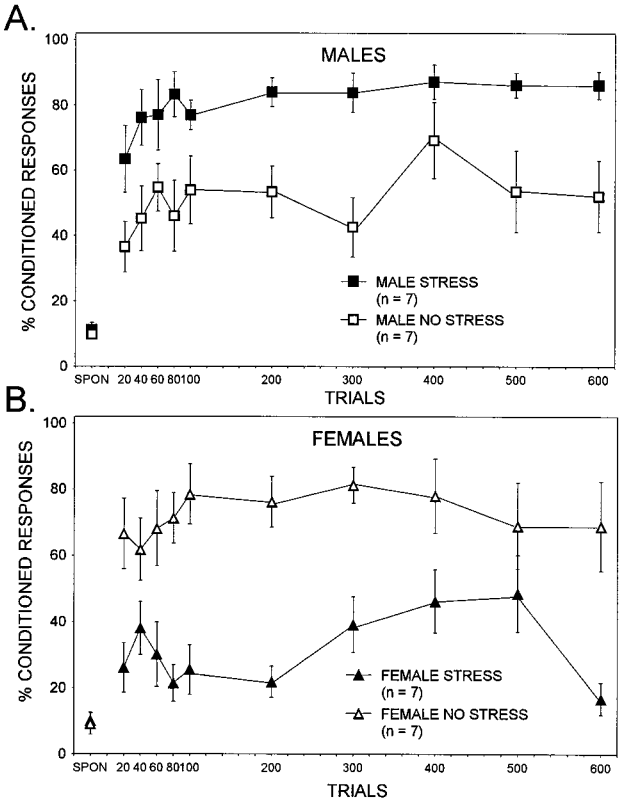

FIG. 1. Effects of sex and stress on acquisition of the conditioned eyeblink response. (*A*) In males, exposure to the stressor facilitated acquisition of the CR 24 h after stressor cessation. (*B*) In females, exposure to the same stressor impaired acquisition of the CR 24 h after stressor cessation. Unstressed females elicited more CRs than unstressed males during the first day of training (1–300 trials), but were not significantly different from each other by the second day of training (301–600 trials). Spontaneous (SPON) eyeblink activity was not affected by sex.

exposure ($P < 0.05$). However, the sex difference in the rate of acquisition in unstressed rats was not as long-lasting as the stress effect. During the last 100 trials, unstressed males were performing at a similar rate as unstressed females ($P = 0.26$). These results suggest that the differential performance between unstressed males and unstressed females can be overcome with continued training, while the dimorphic effects of stress on classical eyeblink conditioning are more persistent.

There were no sex differences in spontaneous blink rate prior to stressor exposure [$F(1, 40) = 0.00$; $P = 1.0$], eyeblink responses to the auditory stimulus prior to paired training [$F(1, 40) = 1.14$; $P = 0.29$] or responses to explicitly unpaired stimulus presentations [$F(1, 12) = 0.22$; $P = 0.65$] (Fig. 2). In addition, exposure to the stressor did not elicit responses to the CS on the first trial of training [Cochran Q test (3) = 0.82; $P = 0.85$], before any learning could have occurred. Therefore, the sexually opposed effects of stress on acquisition of the CR was not attributable to nonspecific effects of stressor exposure on spontaneous blinking, sensitization, or pseudoconditioning.

Despite previous reports of sex differences in analgesic responses (36), stressed males and stressed females did not differ in their tailflick response to a painful photobeam of increasing intensity [$F(1, 40) = 0.35$; $P = 0.55$] (Fig. 3). These results suggest that the diametrically opposed effects of stress on classical conditioning in males vs. females are not attributable to gross differences in analgesia induced by previous exposure to the tailshock stressor.

The Female Stress-Induced Impairment Remains Evident when the Initial Rate of Acquisition is Decreased. Acquisition during the first 20 trials was significantly higher in unstressed females (72% ± 11) than in unstressed males (37% ± 8%). Because unstressed females rapidly attain and sustain such a high level of responding, it is possible that their rate of learning cannot be further enhanced upon exposure to the stressor (a "ceiling effect"), and is impaired as a result (37). To evaluate this explanation for the sexually opposed effects of stress on classical conditioning, we reduced the initial rate of acquisition in the unstressed females by decreasing the intensity of the CS (38). During the first 20 trials of training, the rate of acquisition was 47% ± 7 in unstressed females, and similar to that observed in unstressed males in the first experiment (37% ± 8). After stressor exposure, however, females were still significantly impaired relative to the unstressed females [$F(1, 16) = 10.33$; $P < 0.005$] (Fig. 4). Thus, the stress-induced impairment of acquisition is not dependent on a high response rate early in training. Again, exposure to the stressor did not alter the spontaneous blink rate [$F(1, 16) = 0.021$; $P = 0.89$], or responses to the CS alone prior to training [$F(1, 16) = 0.09$; $P = 0.76$].

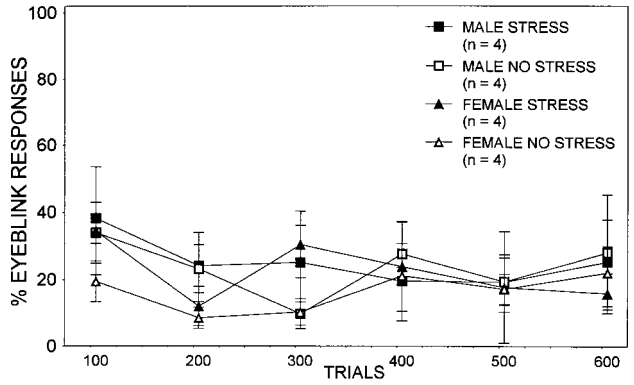

FIG. 2. Effects of sex and stress on pseudoconditioning. Exposure to the stressor or sex did not differentially affect responding to the white noise CS when it was presented in an explicitly unpaired manner with the periorbital eyeshock US.

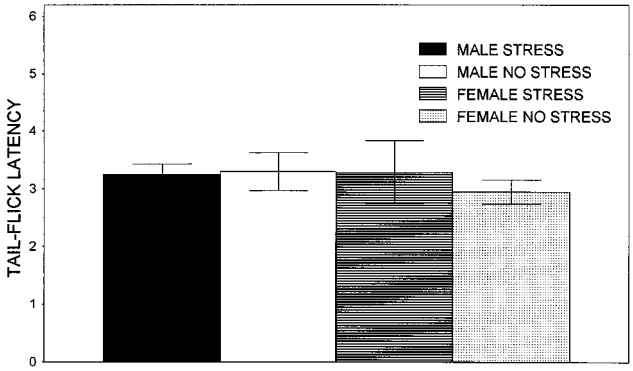

FIG. 3. The effects of sex and stress on analgesia. Sex and stress did not alter pain sensitivity measured as a tailflick response to a photobeam of light of increasing intensity.

The Stress-Induced Impairment of Classical Conditioning Is Dependent on the Presence of Ovarian Hormones. To determine whether the detrimental effect of stress on classical conditioning was dependent on the presence of ovarian hormones, we removed the ovaries and trained stressed and unstressed female rats. A significant interaction between exposure to ovariectomy and stress suggested that ovariectomy prevented the stress-induced impairment of classical conditioning [$F(1, 34) = 10.42$; $P < 0.005$] (Fig. 5). A post-hoc Newman–Keuls comparison test revealed that acquisition was impaired by stress in females with intact ovaries ($P < 0.01$), but not in females without ovaries ($P = 0.44$). In fact, during the last 100 trials, OVX females exposed to the stressor responded more than the unstressed OVX females [$F(2, 68) = 3.34$; $P = 0.04$], suggesting that the performance of OVX females can be facilitated in response to the stressor [as observed in males in experiment 1 (10–13)]. In contrast, removal of circulating ovarian hormones impaired performance during the last 100 trials of training ($P < 0.05$). These results implicate estrogen and/or progesterone in the enhanced performance of unstressed females, as well as the stress-induced impairment in the rate of acquisition.

Neither ovariectomy nor stressor exposure significantly altered the spontaneous blink rate [$F(1, 34) = 0.001$; $P = 0.97$]. Ovariectomy alone enhanced the number of sensitized responses from <1 of 10, to 2 of 10 responses to a white noise stimulus alone [$F(1, 34) = 5.96$; $P < 0.05$]. This minor increase in sensitized responses cannot account for the finding that OVX prevented the stress-induced impairment of CRs. Overall, these results indicate that the stress-induced impairment of

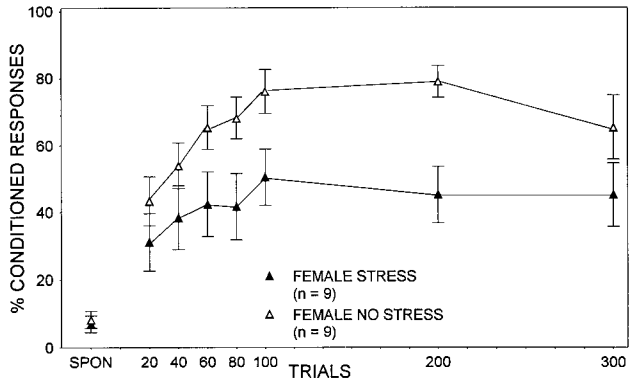

FIG. 4. Effect of stress on acquisition of the CR with a lower-intensity CS in females. A lower rate of acquisition was induced by reducing the CS intensity to 80 dB. Exposure to the stressor impaired acquisition of the CR in females 24 h after stressor cessation.

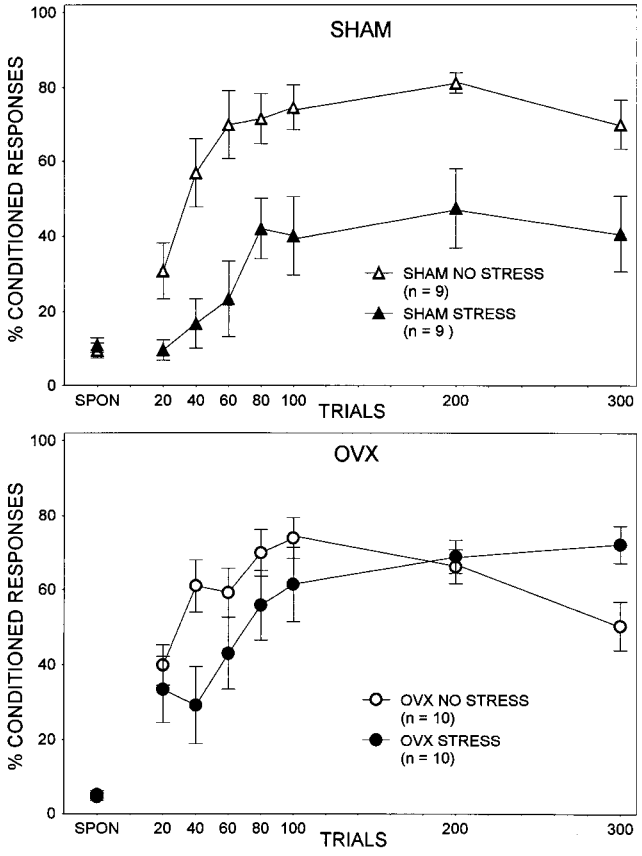

FIG. 5. Contribution of ovarian hormones to the stress-induced impairment of learning. (*A*) Females exposed to a sham surgery were impaired in their ability to acquire the conditioned eyeblink response 24 h after exposure to the stressor. (*B*) Removal of ovarian hormones prevented the stress-induced impairment of classical eyeblink conditioning in females.

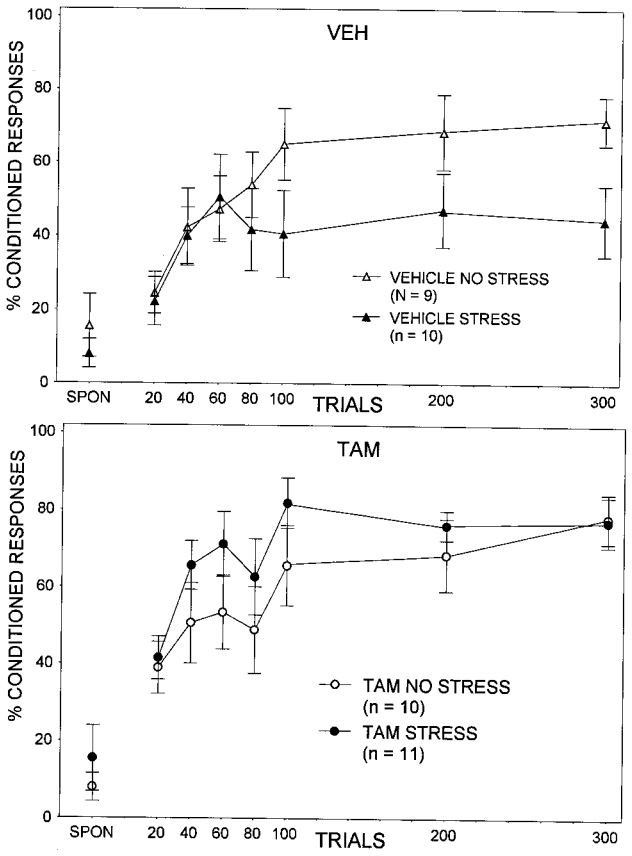

FIG. 6. Effect of the estrogen receptor antagonist on the stress-induced impairment of learning in females. (*A*) Stressed females receiving only VEH were impaired relative to the unstressed controls injected with VEH. (*B*) After receiving four injections of the estrogen antagonist TAM (0.0015 g/0.5 ml, 1 per day), females were not impaired by stressor exposure.

classical eyeblink conditioning in females is dependent on the activational effects of ovarian hormones.

The Stress-Induced Impairment of Classical Conditioning in Females Is Dependent on the Availability of Estrogen Receptors. To evaluate the potential role of estrogen in the stress-induced impairment of acquisition, estrogen receptors were blocked by using the antagonist TAM (39, 40, 45), and stress-effects on classical eyeblink conditioning were measured in adult female rats. Blocking estrogen receptors prevented the stress-induced impairment in the rate of acquisition [$F(1, 37) = 3.93$; $P = 0.05$] (Fig. 6). Post-hoc analysis using a Newman–Keuls comparison test revealed that exposure to the stressor impaired acquisition in the VEH ($P < 0.05$), but did not alter acquisition in females injected with the estrogen antagonist TAM ($P = 0.44$). The series of TAM or VEH injections, however, had no effect on acquisition alone ($P = 0.77$). Neither exposure to the stressor nor administration of the estrogen antagonist affected spontaneous blink rate [$F(1, 36) = 1.29$; $P = 0.26$] or responses to the CS-alone prior to training [$F(1, 37) = 0.09$; $P = 0.76$]. The vaginal smears of females administered TAM (20 of 21) contained leukocytes and scattered epithelial cells, a cytology indicative of diestrus and low levels of estrogen. In combination with the ovariectomy results, these data suggest that the stress-induced impairment of classical conditioning in females is dependent on the presence of estrogen and the availability of estrogen receptors.

DISCUSSION

Results from the present experiments indicate that exposure to a stressful event persistently facilitated classical eyeblink conditioning in males, while exposure to the very same stressor impaired classical conditioning in females (Fig. 1). Under unstressed conditions, however, females acquired the CR faster than males. The sexually opposed effect of the stressor on acquisition in males vs. females was not directly attributable to nonspecific effects of the stressor on performance. Sex and stressor exposure did not alter eyeblink responses to the conditioning stimuli when they were presented in an explicitly unpaired manner (Fig. 2), eyeblink responses to the auditory stimulus presented alone prior to training, nor analgesic responses measured by tailflick analgesia (Fig. 3). Moreover, exposure to the stressor did not elicit responses in males or females to the first trial of training, before any learning could have occurred. Further, exposure to the stressor impaired classical conditioning in females even after the initial rate of acquisition was lowered to a range similar to that of unstressed males (Fig. 4). These results suggest that exposure to the stressor of restraint and intermittent tailshock is not affecting conditioning by inducing pseudo-conditioning, sensitization, or hypoanalgesia. Instead, our results indicate that exposure to the same stressful environmental event can induce opposite effects on associative learning in males vs. females.

Evaluating the contribution of sex and stress to learning is complicated by the fact that both variables alter performance in learning tasks. For example, females tend to be more active than males (16), and are less activity impaired in response to shock (41). Consequently, females tend to outperform males on active avoidance tasks while performing poorly on passive avoidance tasks (7–9, 16, 42). The findings presented here do not appear to be attributable to basic differences in activity. In

a previous study, we reported that exposure to the stressor used here did not differentially affect motor activity 24 h later in males vs. females (43). Moreover, changes in gross motor activity should not alter the ability to acquire the conditioned eyeblink response, and all rats must elicit the unconditioned eyeblink response to eyelid stimulation as part of a reflex.

The present data indicate that the stress-induced impairment of classical eyeblink conditioning in females is dependent on the presence of the ovarian hormones, estrogen and progesterone. Removal of the ovaries prevented the stress-induced impairment, whereas exposure to a sham surgical procedure did not prevent its occurrence (Fig. 5). The loss of ovarian hormones also resulted in a learning impairment among unstressed females during late acquisition (last 100 out of 300 trials). Thus, the ovarian hormones, estrogen and progesterone, are implicated in both the stress-induced impairment of acquisition in females and the enhanced performance of unstressed females relative to unstressed males.

In the final experiment, our results specifically implicate estrogen in the stress-induced impairment of conditioning in females. Administration of the estrogen antagonist TAM prior to stressor exposure prevented the stress-induced impairment in acquisition of the CR (Fig. 6). TAM binds reversibly to the estrogen receptor (39), and inhibits binding of tritiated estradiol (44). Estrogen has at least two types of nuclear receptors (α and β receptors) (40), and TAM has binding affinity for both types of receptors to varying degrees (45). *In vivo*, TAM antagonizes estrogen-induced changes in uterine luminal fluid, prolactin, luteinizing hormone secretion, and lordosis behavior (46). Based on its antiestrogenic properties, TAM has been used as a tool to evaluate the role of estrogen in sexually dimorphic behaviors such as anxiety (47), agonistic behavior (e.g., ref. 48), and sexual receptivity (e.g., ref. 49). It is noted that acquisition of the CR was impaired in OVX females, but the learning rate of females administered TAM was not significantly altered. These results suggest that removal of estrogen hormone and blockade of its receptor do not necessarily have similar consequences on learning and may activate different cellular processes. Alternatively, the results may suggest a critical role for progesterone in the impaired performance associated with ovariectomy.

TAM administration resulted in the vaginal cytology of diestrus, a stage of the estrous cycle associated with low estrogen levels. These results raise the possibility that the effects of stress on acquisition of the CR are mediated by the stage of estrous and levels of circulating estrogen. Indeed, a study subsequent to those presented here established that the stress-induced impairment of classical conditioning in females occurs preferentially in proestrus, when estrogen levels are high (50).

The stress-induced impairment of learning in females may be mediated by a stress-induced disruption of ovarian hormones. Exposure to a relatively acute stressor can elevate ovarian steroids above their basal levels (51), and induce pseudopregnancy, a condition associated with elevated noncycling levels of ovarian hormones (52, 53). A disruption of estrogen and progesterone could be mediated by a rise in other stress-induced hormones, such as glucocorticoids. The activation of the hypothalamic-pituitary-adrenal axis is sexually dimorphic, with females exhibiting greater levels of glucocorticoids under both basal and stress-induced conditions (22, 23, 54). Like the effects of stress on learning reported here, these sex differences in the stress response are dependent on the presence of ovarian hormones (55).

Our data suggest that estrogen mediates the stress-induced impairment of associative learning, and adds to the growing body of evidence implicating a functional role for estrogen in effective memory formation. Recent clinical studies have reported that estrogen reduces the cognitive deficits and emotional outbursts associated with Alzheimer's, a disease marked by deterioration of hippocampal and amygdaloid neurons (56–58). Additionally, estrogen replacement has beneficial effects in women with reduced hormone levels (59, 60). The therapeutic effects of estrogen may be due in part to its growth-promoting and excitatory effects on neurons in limbic brain regions (24, 25, 27, 29, 61, 62). For example, estrogen treatment increases the density of dendritic spines in the hippocampus *in vivo* (27), and the increase is prevented by the estrogen antagonist TAM in cell culture (63), as well as *N*-methyl-D-aspartate (NMDA) receptor antagonists *in vivo* (64). Estrogen is also reported to inhibit calcium entry through L-type channels via effects on membrane receptors (65, 66). In males, the stress-induced facilitation of classical conditioning is dependent on NMDA receptor activation (11). Thus, changes in intracellular calcium via calcium channels or NMDA receptor activation are likely contributors to the effects of estrogen on synaptic density and efficacy, as well as the stress effects on learning reported here (12). In addition, estrogen modulates protein kinase C activity and growth-associated protein 43 (GAP-43/neuromodulin) mRNA (63, 67), both of which are implicated in neuronal mechanisms of learning and memory (68) and stress effects on learning (69). The behavioral phenomena described here could be a useful animal model for uncovering cellular processes that mediate the positive and negative consequences of estrogen therapy on cognitive processes.

In summary, our results suggest that exposure to a stressful event persistently facilitates classical eyeblink conditioning in males, but impairs conditioning in females. In addition, females outperform males under unstressed conditions. The impaired performance of females in response to stress is dependent on the presence of circulating ovarian hormones and the availability of estrogen receptors. These results implicate activational effects of estrogen in the sexually opposed effects of stress on associative learning and provide compelling evidence that sex differences in memory formation and emotional responding are, at least in part, determined by the presence of sex hormones.

This work was supported by grants to T.J.S. from the National Science Foundation (IBN-9511027), Whitehall Foundation, and the McDonnell-Pew Program in Cognitive Neuroscience.

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