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Stimulatory vs. Inhibitory Effects of Acute Stress on Plasma LH: Differential Effects of Pretreatment with Dexamethasone or the Steroid Receptor Antagonist, RU 486

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BRISKI, K. P. *Stimulatory vs. inhibitory effects of acute stress on plasma LH: Differential effects of pretreatment with dexamethasone or the steroid receptor antagonist, RU 486.* PHARMACOL BIOCHEM BEHAV **55**(1) 19–26, 1996.—Acute stress elicits variable patterns of pituitary LH release in intact rats. While the pituitary–adrenal axis is capable of discrimination between stressors of graded intensity, the effects of variable glucocorticoid output on the direction and magnitude of LH release during stress remain unclear. The present studies compared the effects of a psychological stress and two different physical stressors on peripheral corticosterone (CORT) and LH concentrations. Plasma CORT levels were elevated during each stress, but this increase in hormone release was significantly greater in response to physical stress. This differential CORT sensitivity to psychological vs. physical stress was correlated with divergent patterns of pituitary LH release; novel environment (NE) stress resulted in a transient increase in plasma LH, whereas both physical stressors ultimately caused a reduction in circulating hormone levels. Pretreatment with the glucocorticoid receptor (GR) antagonist, RU 486, reversed physical stress-induced decreases in LH release, but did not further facilitate circulating LH during NE stress. Other studies showed that stimulation of GRs prior to stress with the potent ligand, dexamethasone (DEX), blunted the stimulatory effects of NE stress on circulating LH. Additional experiments investigated whether prolonged exposure to elevated glucocorticoid levels elicits adaptive responses from the hypothalamic–pituitary LH axis to acute stress. Chronic DEX administration resulted in a significant attenuation of the inhibitory LH response to acute immobilization, but had no impact upon the facilatory effects of NE stress on LH release. The current studies confirm previous reports of variation in the magnitude of CORT secretion elicited by stressors of different intensity, and provide new evidence that inhibitory patterns of pituitary LH release may be correlated with a high degree of activation of the pituitary–adrenal axis. Attenuation of the facilatory effects of novel environment stress on LH release by pretreatment with the GR agonist, DEX, suggests that GR-induced inhibition of LH requires occupation of GRs beyond that which occurs during this mild stressor. The present findings that stress-induced decreases in plasma LH are blunted by chronic glucocorticoid exposure support a role for glucocorticoid-dependent mechanisms in adaptation of GR-mediated inhibitory responses to stress.

Luteinizing hormone Glucocorticoids Dexamethasone Stress RU 486

STRESS is thought to influence pituitary luteinizing hormone (LH) secretion indirectly through central neural pathways that regulate hypothalamic gonadotropin-releasing hormone (GnRH) release (6), as well as by direct effects of circulating adrenal glucocorticoid hormones on pituitary gonadotropes (11,19). Recent reports that adrenalectomy (ADX) (38) or glucocorticoid receptor (GR) blockade (15) prevent stress-induced decreases in plasma LH support a role for glucocorticoids in suppression of the hypothalamic–pituitary LH neuroendocrine axis by stress. Glucocorticoids apparently inhibit LH, in part, via receptor-mediated mechanisms because the administration of the selective receptor agonist, RU 362, results in decreased circulating LH (7), whereas pharmacological antagonism of GRs elevates basal plasma hormone levels (13). Glucocorticoids may act through central as well as pituitary GRs to suppress LH during stress, because intracerebroventricular (ICV) administration of the GR antagonist, RU 486, was found to attenuate inhibitory patterns of LH release during stress (15).

Intact rats of both sexes exhibit a reduction in pituitary LH secretion following chronic imposition of stress (26,45). Acute stress, on the other hand, elicits variable patterns of

LH release in these animals, as indicated by reports that circulating LH levels are increased (1,2,8–10,24,33,43), decreased (5,15,23,40), or unaltered (16,23,37) following a single stress exposure. Acute psychological stress (handling, visual, audiogenic, novel environment) consistently results in elevated plasma LH levels (1,2,9,10,24,33,43) whereas the effects of physical stressors (forced exercise, cold, restraint, swim, foot shock) are more variable, in that these stressors have been shown to inhibit LH (5,16,40), in some cases following a transient increase in circulating LH (8,12,23), or alternatively, to have no effect on hormone release (16,23,37). It is not clear if these diverse hormonal responses reflect disparate effects of different stressors on neuroendocrine regulatory pathways and/or on adrenal glucocorticoid secretion. Recent studies indicate that the magnitude of stress-induced increases in circulating corticosterone (CORT), the predominant adrenal glucocorticoid in rats, is proportional to stressor intensity (3,29,31), and that physical stress elicits a greater elevation in plasma CORT concentrations than psychological stress (3). Inhibition of basal circulating LH by systemic injection of exogenous CORT is dose dependent (7), suggesting that the level or duration of adrenal glucocorticoid output may influence the direction and/or magnitude of the pituitary LH response to acute stress. In the present studies, we investigated whether acute stress-induced elevation vs. suppression of circulating LH is correlated with differences in endogenous CORT secretion. The current studies also examined whether the direction and/or magnitude of LH hormonal responses could be modified by prior activation of GRs by the potent ligand, dexamethasone (DEX).

Stress is a ubiquitous, often unpredictable feature of daily life. Because stress is typically experienced as a series of episodes rather than as a single, isolated event, it is necessary to consider the influence of prior glucocorticoid exposure on the responsiveness of the hypothalamic–pituitary LH axis to stress. Several groups have shown that habituation of stimulatory as well as inhibitory patterns of LH release occurs as a consequence of chronic stress exposure (18,42,43,46), but the role of persistent elevations in plasma glucocorticoids in these adaptations in endocrine function remains unclear. Whereas intact rats exhibit an attenuation of daily restraint stress-induced decreases in plasma LH between 6–15 days of repetitive stress, this inhibitory response continues unabated in repetitively stressed, adrenalectomized rats (47), suggesting that stress-induced increases in glucocorticoid secretion may be necessary for adaptive alterations in LH responses during stress. The following studies describe the effects of daily DEX administration on the responsiveness of the hypothalamic–pituitary LH axis to acute stimulatory vs. inhibitory stress.

METHOD

Animals

Adult male Sprague–Dawley rats were purchased from Simonsen Laboratories (200–240 g Gilroy, CA), and housed in groups of threee to four per cage for at least 10 days after arrival. The animals were maintained under a 14 L:10 D schedule (lights on at 0500 h), fed and watered ad lib, and handled daily. Intravenous (IV) cardiac cannulas were implanted under ketamine:xylazine anesthesia (0.2 ml IP, 100 mg ketamine:10 mg xylazine/ml; Henry Schein, Inc., Port Washington, NY) and exteriorized at the base of the skull, 48 h prior to experimentation, and the animals were subsequently transferred to individual cages within the original animal room. Test subjects were prepared for blood sampling at 0900 h by attachment of a silastic leader to the free end of each IV cannula, and allowed to acclimate between 1.5 and 2.0 h before drug administration and/or blood sampling.

Experimental Design

Experiment 1. This study evaluated the effects of psychological vs. physical stressors on circulating LH and CORT levels in intact male rats. Groups of rats were exposed to either (a) NE stress, which involved transfer of animals to another room in their home cages (120 min, $n = 12$); (b) restraint (REST) stress, or confinement within a plastic restraint tube (180 min, $n = 12$); or (c) immobilization (IM) stress, or enwrapment within a paper cocoon (180 min, $n = 14$); (d) nonstressed controls remained undisturbed in their home cages in the original animal room ($n = 12$). At −15 min, half of the animals in each group were pretreated by subcutaneous (SC) injection of the GR antagonist, RU 486, at a dose of 2.5 mg/kg (15), or with the vehicle, propylene glycol (PG). Blood samples (0.4 ml) from individual test subjects were collected prior to stress and at serial time points during stress exposure, into a heparinized syringe attached via a silastic leader to the free ends of the IV cannula. Sampling was carried out during REST and IM without disruption of stress. Samples were rapidly centrifuged to separate blood cells from plasma, which was collected and stored at −20°C until assay for LH and CORT. After each sample, the blood cells were resuspended in sterile lactated Ringer's solution and returned to the donor animal.

Experiment 2. This study compared the effects of exogenous glucocorticoid administration on patterns of LH release evoked by stressors exerting either a solely stimulatory or inhibitory influence on hormone release. At −45 min, three groups of rats ($n = 12$ per group) were injected IV with 50 (group 1) or 500 μg dexamethasone sodium phosphate (DEX; Merck Sharpe and Dohme, West Point, PA)/rat (group 2), or vehicle alone (lactated Ringer's solution, group 3). Beginning at time zero, half of the animals in each group were exposed to NE (120 min) or IM stress (180 min). Blood samples were obtained immediately prior to initiation of stress, and at serial time points during stress exposure. The plasma was saved for LH RIA.

Experiment 3. In this study, the effects of chronic glucocorticoid pretreatment on LH responses to stimulatory vs. inhibitory stress were investigated. Groups of rats ($n = 12$ per group) received daily IV injections of either 5.0 mg DEX/kg (group 1) or vehicle (group 2), for 14 days. Twenty four hours after the last injection, half of the animals in each group were exposed to either NE (120 min) or IM stress (180 min). Blood samples were collected prior to as well as during stress.

Radioimmunoassays

LH. Plasma LH was measured using reagents kindly provided by the National Hormone and Pituitary Agency, and expressed in terms of LH-RP-2. In this nonequilibrium assay, 50% displacement of tracer is achieved with 156 pg unlabeled hormone, while the sensitivity is approximately 19 pg LH/tube. Intra- and interassay coefficients of variation for this assay are 8 and 12%, respectively.

CORT. Circulating CORT was assayed with kit reagents (prod. no. TKR-C1) purchased from Diagnostic Products Corp., Los Angeles, CA. The sensitivity of this assay is approximately 6 ng CORT/ml; 50% displacement of tracer is achieved by incubation with 150 ng CORT/mL. The intraassay coefficient of variation for this assay is 7%. All samples from a given experiment were analyzed simultaneously in the same assay.

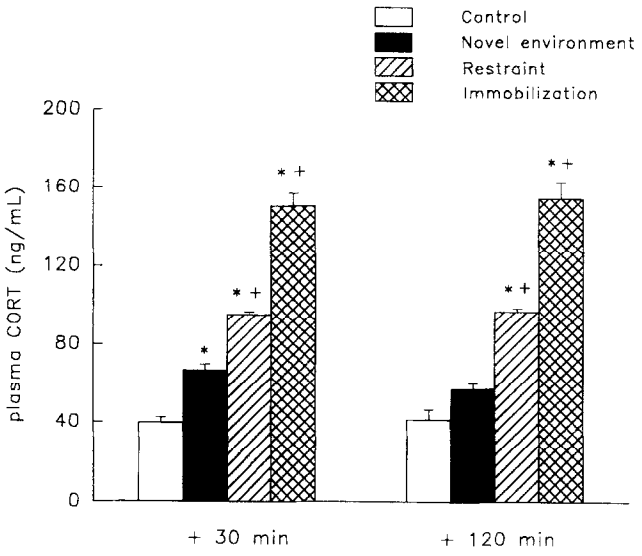

FIG. 1. Differential effects of psychological vs. physical stress on plasma CORT. Circulating CORT was measured at +30 and +120 min after initiation of NE (filled bars), restraint (diagonal bars), or immobilization stress (crosshatched bars); plasma hormone levels were also determined in nonstressed controls (open bars) at the same time points. *$p < 0.05$, compared to the nonstress control group. $^{+}p < 0.05$, compared to the NE stress group.

Statistics

Group means were evaluated by two-way analysis of variance, followed by Duncan's multiple range test. Differences were considered significant if $p < 0.05$.

RESULTS

Acute NE, REST, and IM stress each elicited an increase in circulating CORT, compared to the nonstressed control group (Fig. 1). At both +30, $F_{0.95}(3, 21) = 12.13$, $p < 0.001$, and +120 min, $F_{0.95}(3,21) = 25.85$, $p < 0.001$, plasma CORT levels were significantly different between the groups exposed to physical stress vs. animals subjected to NE stress. Each stressor exerted differential effects on pituitary LH release. As shown in Fig. 2b, NE stress elicited a transient elevation in circulating LH, $F_{0.95}(7, 39) = 16.71$, $p < 0.001$; at +30 and +60 min after onset of stress, hormone levels were significantly increased relative to prestress basal levels, but were restored to this baseline at +120 min. REST stress (Fig. 2c), $F_{0.95}(9, 49) = 8.26$, $p < 0.001$, resulted in a biphasic pattern of LH release, characterized by an increase in plasma LH that was detected at +30 and +60 min, as well as a secondary decline in circulating hormone levels that reached significance at +180 min. In contrast, IM stress had no effect on plasma LH concentrations between time zero and +60 min after initiation of stress; however, LH release was subsequently inhibited at +120 and +180 min (Fig. 2d), $F_{0.95}(9, 57) = 19.70$, $p < 0.001$.

Administration of the GR antagonist, RU 486, to nonstressed rats stimulated basal LH release (Fig. 2a), $F_{0.95}(9, 49) = 14.55$, $p < 0.001$. Although pretreatment of NE-stressed rats with RU 486 did not enhance LH release above levels detected in stressed animals injected with vehicle alone before stress (Fig. 2b), plasma LH levels were still elevated compared to baseline at +120 min. Animals injected with RU 486 prior to REST stress exhibited an increase in LH release over baseline between +30 and +120 min; plasma LH levels detected at +120 and +180 min were significantly higher than those in stressed rats injected with vehicle alone. As shown in Fig. 2d, the administration of RU 486 before the onset of IM stress resulted in significantly elevated plasma LH levels, compared to the vehicle-treated, immobilized group, at both +120 and +180 min of stress.

Intact nonstressed rats injected IV with DEX exhibited a dose-proportionate reduction in plasma LH (Fig. 3a), $F_{0.95}(11, 59) = 10.35$, $p < 0.001$. The effects of pretreatment with DEX on NE or IM stress-induced patterns of LH release are shown in Fig. 3b and c, respectively. Animals injected with the higher dose of DEX (500 μg) showed a reduction in the facilatory effects of NE stress on LH release, compared to rats pretreated with only vehicle, $F_{0.95}(11, 68) = 21.29$, $p < 0.001$; in this group, plasma LH levels were increased over baseline at only one time point (i.e., +30 min) after initiation of stress. In contrast, circulating LH was elevated to a similar extent during NE stress in groups of rats pretreated with either 50 μg DEX or vehicle. Figure 3c shows that DEX also elicited dose-dependent effects on patterns of LH release during IM stress, $F_{0.95}(13, 71) = 8.41$, $p < 0.001$. Whereas a significant reduction in plasma LH was detected in animals pretreated with either vehicle or 50 μg DEX at +180 min, other rats pretreated with 500 μg DEX showed significant decreases in circulating LH at +120 as well as +180 min after onset of stress.

Groups of animals given chronic daily injections of vehicle or DEX exhibited a transient increase in circulating LH during exposure to NE stress (Fig. 4a), $F_{0.95}(7, 47) = 13.83$, $p < 0.001$. Patterns of pituitary LH release during acute NE stress were not different between animals previously given daily injections of vehicle or DEX However, the inhibitory LH response to IM stress was modified as a consequence of prior chronic exposure to DEX (Fig. 4b); mean plasma LH levels were significantly different between the steroid- vs. vehicle-treated groups between +60 and +180 min of stress, $F_{0.95}(9, 47) = 11.42$, $p < 0.001$.

DISCUSSION

The current findings confirm previous reports of variation in the magnitude of endogenous CORT secretion elicited by different stressors, and provide new evidence that stimulation vs. inhibition of pituitary LH release during acute stress may be correlated with the magnitude of adrenal glucocorticoid secretion. In the current studies, the mean increase in plasma CORT levels in animals transferred to novel surroundings was significantly less than that evoked by either physical stressor, for example, REST or IM. These results reflect the capability of the hypothalamic–pituitary–adrenal (HPA) axis for discriminative responses to specific stress stimuli, particularly emotional stressors vs. others characterized by both physical and emotive components. We report here that differential sensitivity of the HPA axis to psychological vs. physical stress is correlated with divergent patterns of pituitary LH release, because NE stress had a solely facilatory effect upon circulating LH levels, whereas physical stress elicited either a biphasic pattern of hormone release (REST) or a decline in plasma LH (IM).

A role for GRs in mechanisms underlying suppressive effects of both REST and IM stress on pituitary LH release is supported by present findings that pretreatment with the steroid receptor antagonist, RU 486, effectively blunted decreases in plasma LH caused by both physical stressors. Drug administration had no effect on hormone release, however,

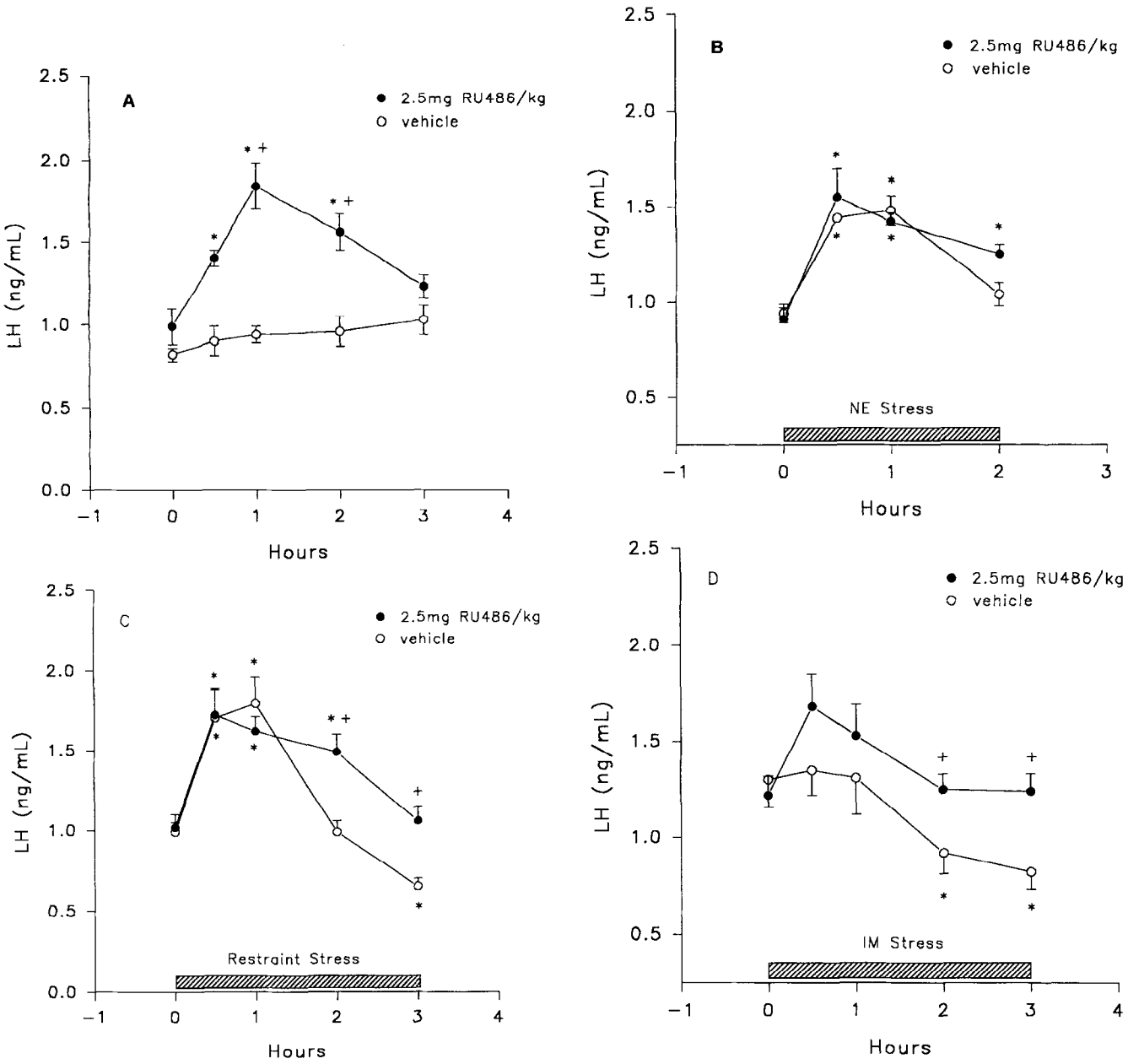

FIG. 2. Effects of pretreatment with the GR antagonist, RU 486, on patterns of pituitary LH release during psychological vs. physical stress. At −15 min, groups of rats were injected sc with vehicle (open circles) or 2.5 mg RU 486/kg (filled circles) before initiation, at time zero, of novel enviroment stress (panel B), restraint stress (panel C), or immobilization stress (panel D), or return to their home cages (panel A). Data point represent mean plasma LH levels ± SEM for five to seven rats. *$p < 0.05$, compared to time zero. +$p < 0.05$, compared to the vehicle-treated group at the same time point.

in other animals exposed to stress of an unfamiliar environment. The inability of RU 486 to further elevate plasma LH levels during NE stress may indicate, on one hand, that the inhibitory impact of GRs on the GnRH-pituitary LH axis may be minimal under these specific stress conditions. Alternatively, this neuroendocrine axis may be incapable of responding to pharmacological blockade of GR-mediated inhibitiory signals because secretory output during NE stress is already maximal. At present, it is not known if total GR occupancy differs in response to psychological vs. physical stress.

It has been shown that in addition to its affinity for GR, RU 486 also exhibits antiprogestin as well as weak antiandrogenic activity. It is possible, therefore, that observed drug effects on patterns of LH release during stress may reflect antagonistism by RU 486 of multiple types of steroid receptors. Because plasma progesterone and testosterone concentrations were not measured in the present studies, we do not know the extent, if any, to which secretion of these steroid hormones was altered under the experimental stress conditions described here. Pharmacological blockade of androgen receptors proba-

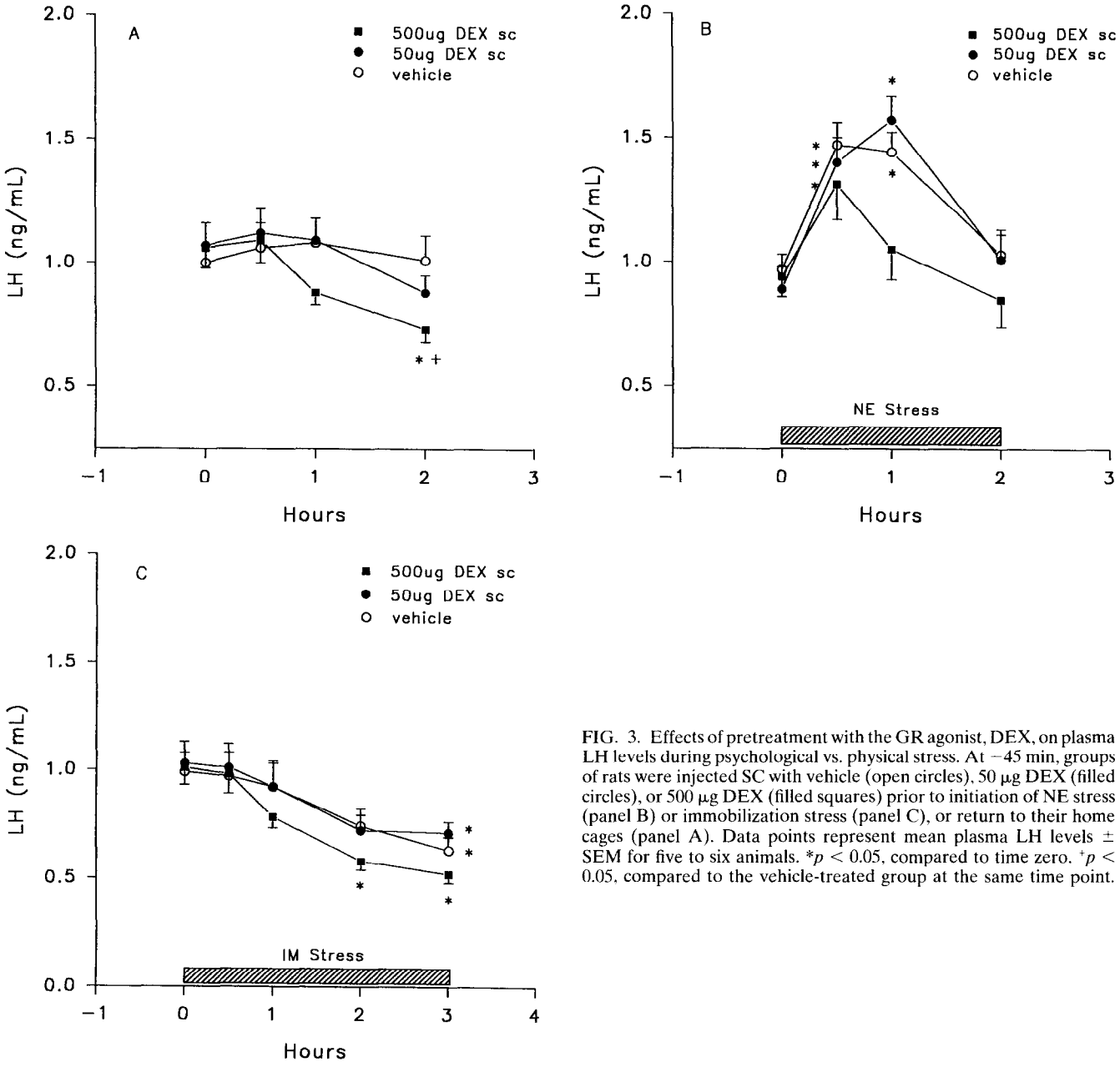

FIG. 3. Effects of pretreatment with the GR agonist, DEX, on plasma LH levels during psychological vs. physical stress. At −45 min, groups of rats were injected SC with vehicle (open circles), 50 μg DEX (filled circles), or 500 μg DEX (filled squares) prior to initiation of NE stress (panel B) or immobilization stress (panel C), or return to their home cages (panel A). Data points represent mean plasma LH levels ± SEM for five to six animals. *$p < 0.05$, compared to time zero. $^{+}p < 0.05$, compared to the vehicle-treated group at the same time point.

bly has only a minimal facilatory effect upon LH release during physical stress, because circulating testesterone levels are reportedly diminished in parallel with stress-associated decreases in LH (16). Although secretion of both LH and testosterone are increased in response to acute psychological stress (34,43), the present findings show that RU 486 treatment has no significant impact on patterns of LH release under such stress conditions. There is some evidence that adrenal progesterone secretion is increased during stress (20), but the physiological role of progesterone in the regulation of the hypothalamic GnRH-pituitary LH in the male is not well characterized (27).

In light of evidence that elevated circulating LH levels during acute stress reflect an increase in hypothalamic GnRH release (35), transient facilation of LH release during the first hour of exposure to NE or REST stress may be indicative of early activation of central stimulatory pathways. The present findings that DEX pretreatment can significantly attenuate NE stress-induced increases in plasma LH suggest that the responsiveness of the GnRH-pituitary LH axis to stimulatory neural signals may be diminished in the presence of high circulating glucocorticoid levels.

The potential influence of GRs on both pituitary and neuroendocrine mechanisms governing LH release during stress is supported by various lines of experimental evidence. GR exist in high concentration in the anterior pituitary (21). Exogenous glucocorticoids have been reported to diminish GnRH- stimulated LH release during perfusion of anterior pituitary tissue fragments in vitro (11,19); localization of GRs within gonadotropes (32) indicate that glucocorticoids may exert direct effects on LH secretion. Exogenous glucocorticoid administra-

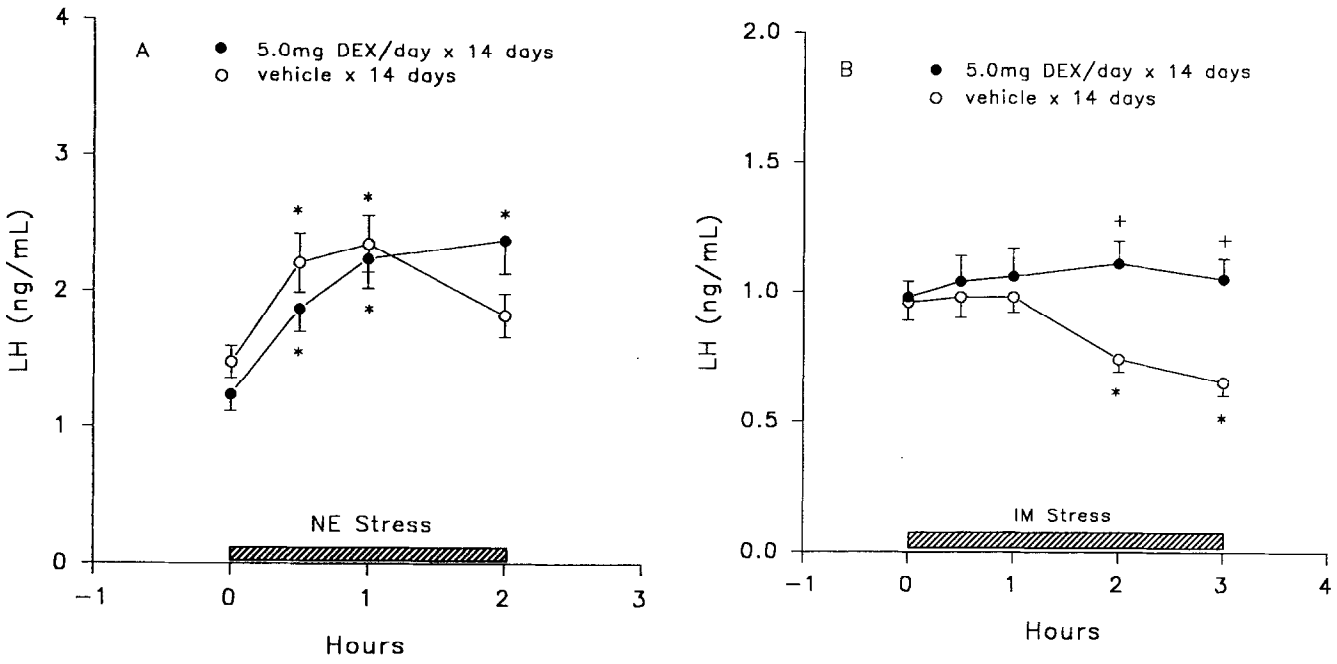

FIG. 4. Effects of chronic daily administration of DEX on subsequent release of LH during psychological vs. physical stress. Groups of rats were injected for 14 consecutive days with either 5.0 mg DEX/kg (filled circles) or vehicle (open circles). Twenty-five hours after the final injection, the animals were exposed to NE stress (panel A) or immobilization stress (panel B). Data points indicate mean plasma LH levels ± SEM for five to six animals. *$p < 0.05$, compared to time zero. $^{\dagger}p < 0.05$, compared to vehicle-treated controls at the same time point.

tion has been reported to suppress plasma LH levels in vivo, without altering pituitary GnRH receptors and/or LH responsiveness to GnRH challenge (4,22,36,41). GRs have been identified within several brain sites that participate in the regulation of reproductive hormone secretion, including the medial preoptic area (MPOA), paraventricular nucleus (PVN), and arcuate nucleus (ARC) (25). Chronic intracerebral glucocorticoid implants suppress normal development of the reproductive tract (44) and inhibit ovulation (28), whereas administration of exogenous glucocorticoids via an intracerebroventricular (ICV) route (7,11) or into the ARC (14) results in diminished circulating LH. Recent observations that ICV pretreatment with RU 486 effectively blunts IM stress-induced decreases in plasma homone levels (15) suggest that glucocorticoids secreted during stress act, in part, through neuroendocrine mechanisms to inhibit pituitary LH release.

In the ARC, GRs have been colocalized with neuropeptide Y (NPY) and proopiomelanocortin (POMC)-related peptides (17,30); β-endorphin, which is cleaved from POMC, may mediate local steroid effects on pathways regulating LH because opiate receptor antagonism can attenuate decreases in plasma LH observed after intra-ARC administration of exogenous glucocortiocids (14). ARC POMC-synthesizing neurons may constitute an important center for the integration of neural and hormonal signals elicited by stress, in light of evidence that well-documented inhibitory effects of corticotropin-releasing factor (CRF) on LH release are also apparently mediated by β-endorphin (37). Further studies are needed to evaluate the functional relationship between ARC GR and stress-sensitive neuroendocrine pathways that have been characterized as pertinent to the regulation of LH release during stress.

The present studies also show that chronic daily treatment with DEX results in attenuation of the inhibitory LH response to IM stress. These results indicate that prolonged glucocorticoid excess promotes habituation of the hypothalamic-pituitary LH axis to suppressive effects of stress on circulating LH, suggesting that stimulation of endogenous glucocorticoid secretion plays a role in adaptive hormonal responses to chronic stress. In contrast, daily administration of DEX did not blunt the facilatory effects of NE stress on hormone release. In light of reports that repeated exposure to acute psychological stress causes an eventual attenuation of the stimulatory LH response (1,10), the current findings that NE stress-induced increases in plasma LH are not altered in chronic glucocorticoid-treated rats suggest that nonsteroidal mechanisms may underlie adaptation of the facilatory effects of stress on LH release. At present, it is not clear how prolonged exposure to glucocorticoids acts to attenuate inhibitory LH responses to stress. Downregulation of anterior pituitary and/or central GRs pertinent to neuroendocrine control of LH may occur, although in one study, hypothalamic GRs were not diminished following chronic stress exposure (42). However, further studies are needed to determine if local receptor populations in specific neuroendocrine sites, for example, within the medial preoptic area, arcuate nucleus, paraventricular nucleus, and median eminence, are altered in terms of number or affinity by glucocorticoid excess.

In summary, the present studies show that stimulatory vs. inhibitory patterns of pituitary LH release are correlated with differential activation of adrenal CORT secretion, and implicate GRs in mechanisms mediating inhibitory effects of physical stress on circulating LH. Although Lastly, attenuation of acute stress-induced inhibition of circulating LH by prior chronic exposure to glucocorticoids suggests that habituation of this inhibitory hormonal response requires glucocorticoid-dependent mechanisms.

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