0013-7227/03/$15.00/0
Printed in U.S.A.

Endocrinology 144(10):4453–4458

doi: 10.1210/en.2003-0338

The Role of Endogenous Interleukin-1 in Stress-Induced Adrenal Activation and Adrenalectomy-Induced Adrenocorticotropic Hormone Hypersecretion

I. GOSHEN, R. YIRMIYA, K. IVERFELDT, AND J. WEIDENFELD

Department of Psychology (I.G., R.Y.), The Hebrew University of Jerusalem, Jerusalem 91905, Israel; Department of Neurochemistry and Neurotoxicology (K.I.), Stockholm University, SE-106 91 Stockholm, Sweden; and Department of Neurology (J.W.), the Agnes Ginges Center for Human Neurogenetics, Hadassah University Hospital, Jerusalem 91120, Israel

To examine the role of IL-1 in the regulation of the hypothalamo-pituitary-adrenal (HPA) axis, mice with knockout of the IL-1 receptor type I (IL-1rKO) were exposed to psychological and metabolic stressors. When exposed to mild stressors (auditory stress or a low dose of 2-deoxyglucose), IL-1rKO mice displayed a significantly diminished corticosterone secretion, compared with wild-type (WT) controls. In response to more severe stressors (60-min restraint or a high dose of 2-deoxyglucose), both groups exhibited a similar increase in corticosterone secretion. To examine the role of IL-1 in HPA axis feedback regulation, serum ACTH levels were measured after adrenalectomy (ADX) in IL-1rKO mice and in mice with transgenic overexpression of IL-1 receptor antagonist within the brain (IL-1raTG). As expected, WT controls exhibited ADX-induced ACTH hypersecretion, whereas IL-1rKO and IL-1raTG mice showed no increase in ACTH levels, suggesting that brain IL-1 has a critical role in ADX-associated ACTH hypersecretion. Similarly, WT mice that were chronically exposed to IL-1ra *in utero* displayed a diminished ADX-induced ACTH hypersecretion, compared with vehicle-treated controls, suggesting a developmental role of IL-1 in HPA axis regulation. In conclusion, our results suggest that endogenous IL-1 plays a critical role in HPA axis activation after stress and ADX. (*Endocrinology* 144: 4453–4458, 2003)

A VARIETY OF stressful physiological and psychological conditions induce the activation of the hypothalamo-pituitary-adrenal (HPA) axis. The response of the HPA axis to stressful stimuli depends on several neural inputs, mediated mainly by norepinephrine (NE) and serotonine (5-HT), which project from discrete brain stem nuclei to neuroendocrine cells located in the paraventricular nucleus (PVN) of the hypothalamus (1). In response to stressful stimuli, these PVN neurons secrete CRH, the major ACTH secretagogue, into the anterior pituitary; and subsequently, ACTH induces the secretion of glucocorticoids (GC) from the adrenal cortex (2). The responses of the HPA axis are also regulated by an efficient negative feedback system, exerted by GC via corticosteroid receptors, located mainly in the hippocampus, PVN, and pituitary (3, 4). One notable example for the action of this system is the marked increase in ACTH levels after adrenalectomy (ADX) (5).

Other factors that were implicated in the activation of the HPA axis are proinflammatory cytokines, particularly IL-1 (6–7), which is produced by many types of cells, including immune cells in the periphery as well as glia and neurons within the brain (8). IL-1 is expressed throughout the components of the HPA axis (6–7) and influences all of its levels: IL-1 induces the secretion of CRH from the hypothalamus (9, 10) and ACTH from the pituitary (11), via the IL-1 type I receptors in these regions (6, 7). Additionally, IL-1 stimulates GC secretion from the adrenal, although no known IL-1 receptors were found in this gland (6, 7). IL-1 may be also involved in the GC negative feedback mechanism by altering the levels of brain CG receptors in the hippocampus (12, 13).

In addition to its role in immunoregulation of inflammatory processes, IL-1 plays a major role in the modulation of neuroendocrine systems during illness (14). Immune challenges, such as local inflammation, viral infection, and endotoxin exposure, induce the production and secretion of brain IL-1, followed by HPA axis activation (6, 7). It was shown, by us and by others, that IL-1 blockade using IL-1 receptor antagonist (IL-1ra) during these conditions prevents the increase in GC (7, 15). Endogenous IL-1 activates the HPA axis not only during sickness, but also in various stressful situations. IL-1 gene expression, protein levels, and biological activity are increased after exposure to several types of stress, such as restraint (16, 17) and inescapable shock (18). Furthermore, impairments in IL-1 signaling, caused by either IL-1ra administration or genetically induced IL-1 deficiency, diminish the increase in GC secretion following stress (16, 19).

The interaction between IL-1 and the HPA axis is bidirectional. On the one hand, IL-1 activates the HPA axis, as detailed above; and on the other hand, GC suppress the production of IL-1, mainly by decreasing IL-1 mRNA levels, both by inhibiting its transcription and by destabilizing it (20). Accordingly, it has been shown that removal of endogenous GC augments IL-1 secretion, *e.g.* the increase in IL-1 protein levels, after stress, is more distinct in adrenalectomized rats (18, 21). Recently, we demonstrated an increase in IL-1 gene expression in rats after ADX. Furthermore, we found that IL-1 gene expression in astrocyte cultures can be

Abbreviations: ADX, Adrenalectomy; CNS, central nervous system; CS, corticosterone; 2DG, 2-deoxyglucose; GC, glucocorticoids; HPA, hypothalamo-pituitary-adrenal; 5-HT, serotonine; IL-1rKO, knockout of the IL-1 receptor type I; IL-1raTG, transgenic overexpression of IL-1 receptor antagonist; NE, norepinephrine; PVN, paraventricular nucleus; WT, wild-type.

detected only when cortisol is removed from the culture medium (22). Therefore, we hypothesized that, in addition to its putative role in the stress response, brain IL-1 may be involved in ADX-induced hypersecretion of ACTH.

In the present study, we further assessed the role of IL-1 in the regulation of adrenocortical activation after exposure to various stressors, using IL-1 receptor type I-deficient mice (IL-1rKO). Furthermore, we tested, for the first time, the role of IL-1 in HPA axis regulation after ADX, using IL-1rKO mice, as well as mice with transgenic overexpression of IL-1 receptor antagonist within the central nervous system (CNS) (IL-1raTG). To assess whether the results found using the genetically engineered mice can be ascribed to developmental influences of the IL-1 deficiency, we also tested ADX-induced ACTH hypersecretion in mice that were prenatally treated with IL-1ra.

Materials and Methods

Subjects

Subjects were male IL-1rKO mice and their 129/Sv X C57BL/6 wild-type (WT) controls (23) (Jackson Laboratories, Bar Harbor, ME) and IL-1raTG mice and their B6CBA WT controls (24) (Stockholm University). Both IL-1rKO and IL-1raTG mice demonstrate a defective response to IL-1 (23–24). No differences in vitality were found between these strains and their respective controls. Subjects were 2–4 months old. Animals were housed in an air-conditioned room (22 ± 1 C), with food and water *ad libitum*. All the experiments were performed during the first 2 h of the light phase of a reversed 12-h light, 12-h dark cycle (lights off at 0700 h). The experiments were approved by the Hebrew University Committee on Animal Care and Use.

Stressful stimuli

Twenty-four hours before the experiment, mice were divided into separate cages. At the experiment day, control nonstressed mice were taken from their new home-cages and killed by decapitation immediately, alternately with stressed mice. Mice subjected to acoustic stress were exposed to a ringing bell (109 decibels) for 4 min and were killed by decapitation 10 min after stress initiation. Mice subjected to restraint stress were placed in a perforated cylinder (3 cm in diameter; 10 cm in length) for 60 min and were killed immediately upon removal from the cylinder. To induce metabolic stress (cytoglucopenia), mice were ip injected with either 250 or 500 mg/kg 2-deoxyglucose (2DG, dissolved in 0.2 ml; Sigma, Rehovot, Israel) or saline (same volume) and were killed by decapitation 1 h after the injection. Administration of 2DG, which inhibits intracellular glucose use, is commonly used as a model of metabolic stress, influencing the HPA axis via central mechanisms (25).

ADX

Mice were anesthetized with pentobarbital (60 mg/kg, ip), and the adrenal glands were bilaterally removed. Sham operations were similar in all aspects apart from the removal of the glands. After operation, mice were provided with 0.45% NaCl as their drinking solution instead of water. Eight days after operation, mice were killed by rapid decapitation, and trunk blood was collected. Blood was centrifuged for 20 min at 2000 rmp, and serum was collected for ACTH analysis. The complete removal of the adrenal glands was confirmed by measuring corticosterone (CS) levels, which were found to be below the detection limit of the kit in all the ADX-operated mice.

Determination of ACTH and CS levels

CS was determined by RIA, as previously described (26). The sensitivity limit of the assay was 0.5 μg/100 ml, and the intra- and interassay coefficients of variation were 6.4% and 7.2%, respectively. The percent of cross-reactivity of the antiserum with various steroids was: cortisol, 4.5; estradiol, less than 0.1; progesterone, 15.7; and testosterone, 7.9.

ACTH concentrations were determined by RIA kit (Nichols Institute Diagnostics, San Juan Capistrano, CA). The sensitivity limit of the assay was 10 pg/ml. There was no cross-reactivity of the antiserum with α-MSH, β-MSH, β-lipotrophic hormone, or β-endorphin.

Prenatal IL-1ra exposure

Pregnancy was determined by the presence of vaginal plugs, and dams were sc implanted, on d 7 of gestation, with Alzet osmotic micropumps secreting human IL-1ra (20 mg/kg·d for 14 d; Amgen, Thousand Oaks, CA). Using ELISA, we found that exogenous human IL-1ra crossed both the placenta and the blood brain barrier and reached the fetal CNS (34.22 ± 7.8 and 10.74 ± 3.08 pg/mg brain tissue in IL-1ra and vehicle-treated fetuses, respectively) on d 15 of gestation. Two control groups were used in this experiment: The first group was implanted with vehicle-secreting micropumps, and the second group received no treatment. Within 24 h of birth, pups from all groups were transferred to untreated nursing dams. To minimize the influence of inherent familial effects, only one pup from each litter was assigned for each experimental group. ACTH levels after ADX were tested, as described above, at the age of 4 months.

Statistical analysis

The results were analyzed by a two-way ANOVA, followed by the Tukey *post hoc* analysis.

Results

Effects of impaired IL-1 signaling on CS levels in response to different stress modalities and intensities

In response to auditory stress, WT control mice exhibited a significant increase in CS levels ($P < 0.01$), whereas the levels of CS in IL-1rKO mice remained unchanged (Fig. 1A). This finding was reflected by a significant strain by treatment interaction ($F_{1,36} = 6.818$, $P < 0.02$). In response to 60-min restraint stress, both groups exhibited a marked increase in CS secretion ($F_{1,20} = 585.16$, $P < 0.001$), and there was no difference between IL-1rKO and control mice ($P > 0.2$).

Exposure to a mild metabolic stress (250 mg/kg 2DG injection) resulted in a significant increase in CS levels in WT mice ($P < 0.05$), whereas the levels of CS in IL-1rKO mice remained unchanged (Fig. 1B). This finding was reflected by a significant strain by treatment interaction ($F_{1,31} = 4.498$, $P < 0.05$). In contrast, exposure to the more severe metabolic stress (500 mg/kg 2DG injection) resulted in a significant increase in CS levels in both strains ($F_{1,27} = 59.11$, $P < 0.0001$), and no difference was found between IL-1rKO and control mice ($P > 0.2$).

Effects of impaired IL-1 signaling on ADX-induced ACTH hypersecretion

Eight days after ADX, the levels of ACTH were markedly increased in C57BL/6x129/Sv WT mice ($P < 0.05$), whereas the levels of ACTH in IL-1rKO mice remained unchanged (Fig. 2A). This finding was reflected by a significant strain by treatment interaction ($F_{1,22}$=4.78, $P < 0.05$). Similarly, 8 d after ADX ACTH, levels were significantly increased in C57BL/6xCBA WT mice ($P < 0.01$), whereas the levels of ACTH in IL-1raTG mice remained unchanged (Fig. 2B). This finding was reflected by a significant strain by treatment interaction ($F_{1,25} = 12.4$, $P < 0.005$).

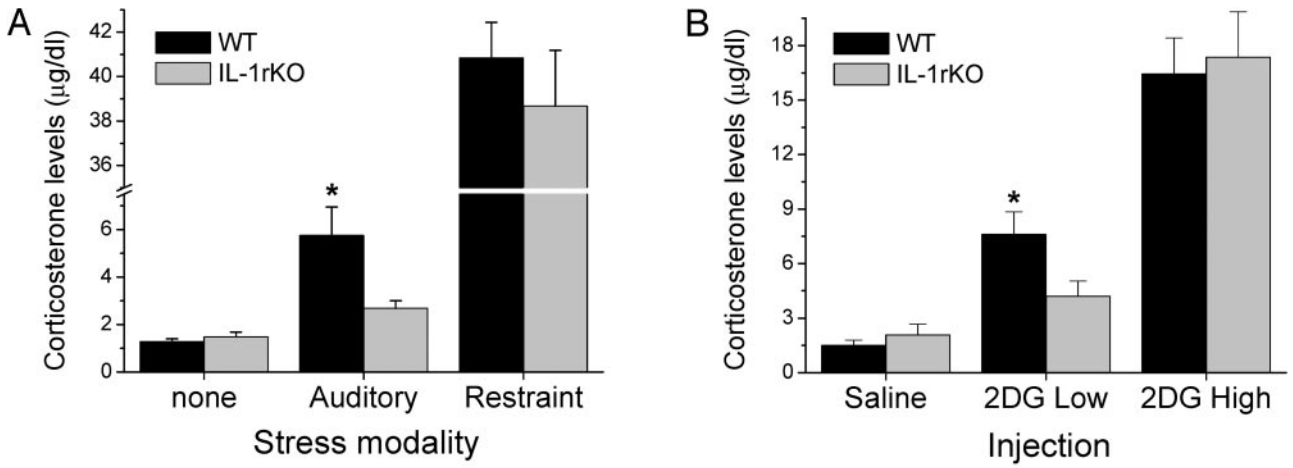

FIG. 1. Effects of impaired IL-1 signaling on CS levels in response to different stress modalities and intensities. A, WT mice (n = 10) and IL-1rKO mice (n = 10) displayed similar basal CS levels. IL-1rKO mice (n = 10) displayed decreased CS secretion, compared with WT controls (n = 10), in response to auditory stress but not in response to 60 min of restraint (n = 7 and 6, respectively). *, $P < 0.01$, compared with nonstressed WT and auditory-stressed IL-1rKO. B, WT mice (n = 5) and IL-1rKO mice (n = 10) displayed similar CS levels after saline injection. IL-1rKO mice (n = 12) exhibited no elevation in CS secretion in response to a low-dose 2DG (250 mg/kg) injection, compared with WT controls (n = 5), but a normal elevation in CS secretion in response to a high-dose (500 mg/kg) 2DG injection (n = 10 and 6, respectively). *, $P < 0.05$, compared with WT mice injected with saline and IL-1rKO mice injected with a low dose of 2DG. Data are presented as mean ± SEM.

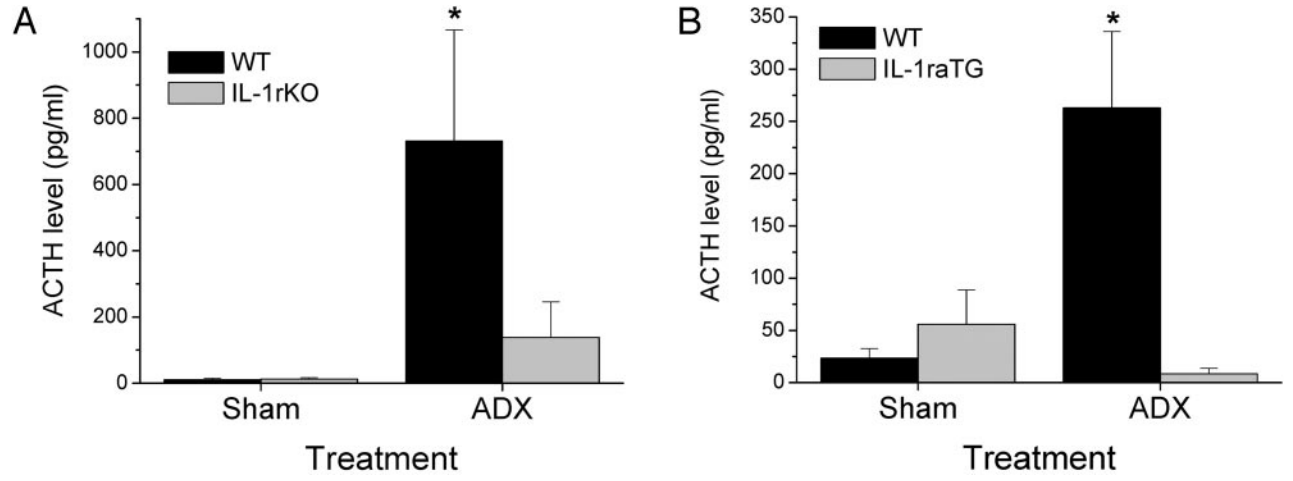

FIG. 2. Effects of impaired IL-1 signaling on ADX-induced ACTH hypersecretion. A, Sham-operated WT mice (n = 7) and IL-1rKO mice (n = 9) displayed similar basal ACTH levels. After ADX, WT controls (n = 5) exhibited a marked ACTH hypersecretion, whereas IL-1rKO mice (n = 5) showed no increase in ACTH levels. *, $P < 0.05$, compared with sham-operated WT mice and ADX IL-1rKO mice. B, Sham-operated WT mice (n = 8) and IL-1raTG mice, which over-express IL-1ra within the brain (n = 8), displayed similar basal ACTH levels. After ADX, WT controls (n = 7) demonstrated a marked ACTH hypersecretion, whereas IL-1raTG mice (n = 6) displayed no change in ACTH secretion. *, $P < 0.0001$, compared with sham-operated WT mice and ADX IL-1raTG mice. Data are presented as mean ± SEM.

Effects of impaired IL-1 signaling during brain development on ADX-induced ACTH hypersecretion

Vehicle-treated and nontreated C57BL/6xCBA control mice exhibited a similar pattern of ACTH secretion; hence, data from these groups was merged. Eight days after ADX, there was a significant overall increase in ACTH levels [$F_{(1,43)} = 6.46$, $P < 0.05$]. However, *post hoc* tests showed that this increase was significant in the control mice ($P < 0.05$) but not in mice that were prenatally treated with IL-1ra ($P > 0.5$) (Fig. 3).

Discussion

The present study demonstrates that IL-1rKO mice displayed impaired adrenocortical activation after mild psychological and metabolic stressors. However, after exposure to severe stressors, these mice demonstrated normal CS secretion. IL-1rKO and IL-1raTG mice also exhibited an almost-complete abolishment of ACTH hypersecretion after ADX. IL-1rKO mice are shown to have no expression of IL-1 receptor type I, which seems to mediate all of the known biological functions of IL-1, and are reported to have a defective response to IL-1α and IL-1β (23). IL-1raTG mice have astrocyte-directed overexpression of the human IL-1ra gene under the control of the murine glial fibrillary acidic protein promoter and are insensitive to the administration of exogenous IL-1 (24). The deficits in ADX-induced HPA axis activation that accompany the impairments in IL-1 signaling cannot be attributed to any peripheral influences, because IL-1raTG mice overexpress IL-1ra only within the CNS (24).

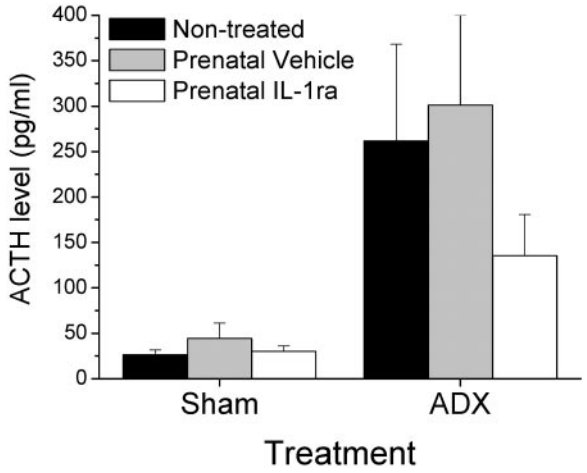

FIG. 3. Effects of prenatal IL-1ra treatment on ADX-induced ACTH hypersecretion in adult offspring: Sham-operated mice that were prenatally treated with IL-1ra during the last 2 wk of gestation (n = 8), vehicle-treated mice (n = 7), and nontreated mice (n = 5) displayed similar basal ACTH levels. After ADX, control mice [vehicle-treated (n = 10) and nontreated (n = 11)], but not prenatal IL-1ra-treated mice (n = 9), displayed a significant ACTH hypersecretion.

Our results regarding the role of IL-1 in stress response are in accordance with previous studies showing that IL-1 levels are increased after exposure to various stressors, such as restraint (16, 17) and inescapable shock (18), and that IL-1 receptor type I gene expression in the pituitary is also enhanced after stress or CRH injection (27, 28). IL-1 by itself can activate the HPA axis, and either pharmacological or genetic disruption of IL-1 signaling, using IL-1ra administration or IL-1 knockout mice, diminishes stress-induced increase in CS secretion (6, 7, 19). In the present study, a diminished increase in CS levels was found in IL-1rKO mice only in response to relatively mild stressors, such as bell ringing and cytoglucopenia induced by 250 mg/kg 2DG injection, suggesting that IL-1 signaling via its type I receptor is important for adrenocortical activation after moderate stress. However, in response to more severe stressors, such as 60 min of restraint or 500 mg/kg 2DG injection, no difference was found between IL-1rKO and WT controls. This finding is consistent with the findings of a previous study reporting that, 2 h after turpentine injection, IL-1-deficient mice demonstrate normal HPA axis activation; whereas at 8 h after injection, their response was abolished (19). In contrast with our findings, treatment with IL-1ra before (but not during) exposure to restraint stress significantly inhibited ACTH secretion in rats (16). Differences between species and methodologies may account for this inconsistency. For example, in the pharmacological study (16), young rats were subjected to stress in relatively large restrainers; whereas in the present study, adult mice were entered into much tighter restraining tubes. Thus, it is possible that the stress induced in the pharmacological study was milder than the one induced in the present study and, therefore, its effects were attenuated by blockade of IL-1 receptors.

It is possible that the response to robust stressors may also involve other mediators, which may compensate for the absence of IL-1 signaling. One of these mediators may be the cytokine TNF-α, which often works in synergism with IL-1 (8, 29). Indeed, in a preliminary study, we found that TNF p55 receptor-deficient mice demonstrated normal CS secretion after exposure to auditory stress but decreased CS secretion after 60 min of restraint stress. It should be noted that the finding that mild stress-induced CS secretion in IL-1rKO mice is blunted during a single time point (which coincides with maximal activation in normal animals) (16, 25) cannot exclude the possibility that the strain differences are attributable to changes in the kinetics, rather than the amplitude, of CS secretion from the adrenal. Thus, the possibility that the CS response to the auditory stress and the low dose of 2DG are slower to develop in the IL-1rKO mice should be further explored.

Feedback regulation of the HPA axis is considered to involve inhibitory actions of GC via GC receptors. Several studies (*e.g.* Ref. 3) suggest that the primary target for GC feedback inhibition is not only the hypothalamic CRH neurons but also other hypothalamic and extrahypothalamic (*e.g.* hippocampus, pituitary) systems that regulate CRH expression and release (3, 4). The action of this system is exemplified by the marked increase in ACTH levels after ADX (5). In addition to ACTH hypersecretion, ADX is also associated with enhanced expression of IL-1 gene in the hypothalamus, pituitary, and brain stem, as well as increased production of IL-1 protein in the pituitary (22, 30). These findings suggest that GC may have a tonic inhibitory effect on brain IL-1. In the present study, after removal of this inhibitory effect by ADX, ACTH levels were markedly elevated in WT controls but did not increase in IL-1rKO or IL-1raTG mice, suggesting that brain IL-1 may have an important role in ADX-induced ACTH hypersecretion. Together, these findings suggest that the removal of the direct inhibitory signal exerted by GC is not sufficient for ADX-associated ACTH hypersecretion. Rather, this hypersecretion is critically dependent on an excitatory signal, provided by the elevated levels of IL-1, which is a potent HPA axis activator (6, 7).

The exact mechanism by which endogenous IL-1 is involved in the regulation of the HPA axis is not clear. Among the possible mediators of its actions are NE and 5-HT, which are known to play an important role in regulating HPA axis responses to various stressful stimuli (1, 31–33). Furthermore, it has been shown that IL-1 has a facilitatory role on noradrenergic and serotonergic systems; for example, either peripheral or intrahypothalamic IL-1 administration stimulates NE secretion in the hypothalamus *in vivo* (16, 34, 35), and intrahypothalamic or intrahippocampal IL-1 administration induces the secretion of 5-HT in these regions (35, 36). IL-1ra can block the increase in NE and 5-HT after stress, as well as the increase in ACTH plasma levels (16). Additionally, neurotoxic lesions that produce depletion of hypothalamic NE inhibit the increase in plasma ACTH and CS levels in response to IL-1 (37, 38). NE may be also involved in the effects of IL-1 on ACTH hypersecretion after ADX, because it was shown that hypothalamic NE depletion by 6-OHDA injection does not affect basal ACTH levels but reduces the increase in ACTH hypersecretion after ADX (39). Together, these findings suggest that the influence of IL-1 signaling on HPA axis regulation after stress or ADX may be, at least partly, mediated by NE and/or 5-HT systems.

The impairment in ADX-induced ACTH hypersecretion in

IL-1rKO and IL-1raTG mice may result from the lack of IL-1 signaling, either acutely or during brain development. To assess the latter possibility, we tested the effect of IL-1 blockade during the last 2 wk of gestation, mimicking the effect of excess IL-1ra during the same developmental period in IL-1raTG mice. IL-1 influences brain development both directly by inducing neuronal differentiation (*e.g.* Ref. 40), as well as indirectly by the enhancement of trophic factors, *e.g.* NGF and CNTF (41, 42). Similar to the results found in the two IL-1 signaling-deficient mice strains, IL-1ra prenatally treated mice exhibited no ACTH hypersecretion after ADX. This result suggests that during fetal development, IL-1 may have a role in the maturition of brain systems that regulate the HPA axis. It should be noted that this developmental effect does not rule out the possibility that IL-1 is also involved in activation of the HPA axis after various stimuli, as suggested by previous studies using IL-1ra in adult animals (7, 15, 16). Further research will be needed to fully understand the developmental and acute influences of IL-1, or their combination, on the HPA axis.

In conclusion, the results of the present study demonstrate that, in addition to its role in mediating illness-associated neuroendocrine response, IL-1 has an important role in the activation of CS secretion after exposure to different modalities of mild, but not severe, stress. Furthermore, our study demonstrates a novel modulatory role for IL-1 in ADX-induced ACTH hypersecretion. Thus, alterations in IL-1 levels during noninflammatory conditions play a role in HPA axis activation and its regulation by GC-associated feedback control mechanisms.

Acknowledgments

The authors would like to thank Anna Itzik for her excellent help in running the experiments.

Received March 18, 2003. Accepted June 30, 2003.

Address all correspondence and requests for reprints to: Raz Yirmiya, Ph.D., Department of Psychology, The Hebrew University of Jerusalem, Mount Scopus, Jerusalem 91905, Israel. E-mail: razyirmiya@huji.ac.il.

R.Y. is a member of the Eric Roland Center for Neurodegenerative Diseases at the Hebrew University of Jerusalem.

References

1. **Plotsky PM, Cunningham ET, Widmaier EP** 1989 Catecholaminergic modulation of corticotropin-releasing factor and adrenocorticotropin secretion. Endocr Rev 10:437–358
2. **Antoni FA** 1986 Hypothalamic control of adrenocorticotropin secretion: advances since the discovery of 41-residue corticotropin-releasing factor. Endocr Rev 7:351–378
3. **Keller-Wood ME, Dallman MF** 1984 Corticosteroid inhibition of ACTH secretion. Endocr Rev 5:1–24
4. **Jacobson L, Sapolsky R** 1991 The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. Endocr Rev 12: 118–134
5. **Dallman MF, Jones MT, Vernikos-Danellis J, Ganong WF** 1972 Corticosteroid feedback control of ACTH secretion: rapid effects of bilateral adrenalectomy on plasma ACTH in the rat. Endocrinology 91:961–968
6. **Besedovsky HO, del-Rey A** 1996 Immune-neuro-endocrine interactions: facts and hypotheses. Endocr Rev 17:64–102
7. **Turnbull AV, Rivier CL** 1999 Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. Physiol Rev 79:1–71
8. **Dinarello CA** 1996 Biologic basis for interleukin-1 in disease. Blood 87:2095–2147
9. **Berkenbosch F, van Oers J, del Rey A, Tilders F, Besedovsky H** 1987 Corticotropin-releasing factor-producing neurons in the rat activated by interleukin-1. Science 238:524–526
10. **Sapolsky R, Rivier C, Yamamoto G, Plotsky P, Vale W** 1987 Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. Science 238:522–524
11. **Bernton EW, Beach JE, Holaday JW, Smallridge RC, Fein HG** 1987 Release of multiple hormones by a direct action of interleukin-1 on pituitary cells. Science 238:519–521
12. **Weidenfeld J, Abramsky O, Ovadia H** 1898 Effect of interleukin-1 on ACTH and corticosterone secretion in dexamethasone and adrenalectomized pretreated male rats. Neuroendocrinology 50:650–654
13. **Miller AH, Pariante CM, Pearce BD** 1999 Effects of cytokines on glucocorticoid receptor expression and function. Glucocorticoid resistance and relevance to depression. Adv Exp Med Biol 461:107–116
14. **Rothwell NJ, Luheshi GN** 2000 Interleukin 1 in the brain: biology, pathology and therapeutic target. Trends Neurosci 23:618–625
15. **Ben-Hur T, Cialic R, Itzik A, Yirmiya R, Weidenfeld J** 2001 Acute effects of purified and UV-inactivated Herpes simplex virus type 1 on the hypothalamo-pituitary-adrenocortical axis. Neuroendocrinology 74:160–166
16. **Shintani F, Nakaki T, Kanba S, Sato K, Yagi G, Shiozawa M, Aiso S, Kato R, Asai M** 1995 Involvement of interleukin-1 in immobilization stress-induced increase in plasma adrenocorticotropic hormone and in release of hypothalamic monoamines in the rat. J Neurosci 15:1961–1970
17. **Suzuki E, Shintani F, Kanba S, Asai M, Nakaki T** 1997 Immobilization stress increases mRNA levels of interleukin-1 receptor antagonist in various rat brain regions. Cell Mol Neurobiol 17:557–561
18. **Nguyen KT, Deak T, Owens SM, Kohno T, Fleshner M, Watkins LR, Maier SF** 1998 Exposure to acute stress induces brain interleukin-1b protein in the rat. J Neurosci 18:2239–2246
19. **Horai R, Asano M, Sudo K, Kanuka H, Suzuki M, Nishihara M, Takahashi M, Iwakura Y** 1998 Production of mice deficient in genes interleukin (IL)-1α, IL-1β, IL-1α/β, and IL-1 receptor antagonist shows that IL-1β is crucial in turpentine-induced fever development and glucocorticoid secretion. J Exp Med 187:1463–1475
20. **Lee SW, Tsou AP, Chan H, Thomas J, Petrie K, Eugui EM, Allison AC** 1988 Glucocorticoids selectively inhibit the transcription of the Interleukin-1β gene and decrease the stability of Interleukin 1β mRNA. Proc Natl Acad Sci USA 85:1204–1208
21. **Nguyen KT, Deak T, Will MJ, Hansen MK, Hunsaker BN, Fleshner M, Watkins LR, Maier SF** 2000 Timecourse and corticosterone sensitivity of the brain, pituitary, and serum interleukin-1 protein response to acute stress. Brain Res 859:193–201
22. **Ben-Hur T, Cialic R, Itzik A, Barak O, Yirmiya R, Weidenfeld J** 2001 A novel permissive role for glucocorticoids in induction of febrile and behavioral signs of experimental herpes simplex virus encephalitis. Neuroscience 108:119–127
23. **Labow M, Shuster D, Zetterstorm M, Nunes P, Terry R, Cullinan EB, Bartfei T, Solorzano C, Moldawer LL, Chizzonite R, McIntyre KW** 1997 Absence of IL-1 signaling and reduced inflammatory response in IL-1 type I receptor deficient mice. J Immunol 159:2452–2461
24. **Lundkvist J, Sundgren-Andersson AK, Tingsborg S, Ostlund P, Engfors C, Alheim K, Bartfai T, Iverfeldt K, Schultzberg M** 1999 Acute-phase response in transgenic mice with CNS overexpression of IL-1 receptor antagonist. Am J Physiol 276:644–651
25. **Weidenfeld J, Corcos AP, Wohlman A, Feldman S** 1994 Characterization of the 2-deoxyglucose effect on the adrenocortical axis. Endocrinology 134:1924–1931
26. **Weidenfeld J, Yirmiya R** 1996 Effects of bacterial endotoxin on the glucocorticoid feedback regulation of adrenocortical response to stress. Neuroimmunomodulation 3:352–357
27. **Takao T, Hashimoto K, De Souza EB** 1995 Modulation of interleukin-1 receptors in the brain-endocrine-immune axis by stress and infection. Brain Behav Immun 9:276–291
28. **Pournajafi-Nazarloo HP, Takao T, Nanamiya W, Asaba K, De-Souza EB, Hashimoto K** 2001 Effect of non-peptide corticotropin-releasing factor receptor type 1 antagonist on adrenocorticotropic hormone release and interleukin-1 receptors followed by stress. Brain Res 902:119–126
29. **Yirmiya R, Weidenfeld J, Barak O, Avitsur R, Pollak Y, Gallily R, Wohlman A, Ovadia H, Ben-Hur T** 1999 The role of brain cytokines in mediating the behavioral and neuroendocrine effects of intracerebral mycoplasma fermentans. Brain Res 829:28–38
30. **Goujon E, Parnet P, Laye S, Combe C, Dantzer R** 1996 Adrenalectomy enhances pro-inflammatory cytokines gene expression, in the spleen, pituitary, and brain of mice in response to lipopolysaccharide. Mol Brain Res 36:53–62
31. **Szafarczyk A, Guillaume V, Conte-Devolx B, Alonso G, Malaval F, Pares-Herbute N, Oliver C, Assenmacher I** 1988 Central catecholaminergic system stimulates secretion of CRH at different sites. Am J Physiol 255:463–468
32. **Fuller RW** 1992 The involvement of serotonine in regulation of pituitary-adrenocortical function. Front Neuroendocrinol 13:150–170
33. **Feldman S, Conforti N, Weidenfeld J** 1995 Limbic pathways and hypothalamic neurotransmitters mediating adrenocortical response to neural stimuli. Neurosci Biobehav Rev 19:235–240
34. **Dunn AJ** 1988 Systemic interleukin-1 administration stimulates hypothalamic

norepinephrine metabolism paralleling the increased plasma corticosterone. Life Sci 43:429–435
35. **Shintani F, Kanba S, Nakaki T, Nibuya M, Kinoshita N, Suzuki E, Yagi G, Kato R, Asai M** 1993 Interleukin-1β augments release of norepinephrine, dopamine, and serotonin in the rat anterior hypothalamus. J Neurosci 13: 3574–3581
36. **Linthorst AC, Flachskamm C, Muller-Preuss P, Holsboer F, Reul JM** 1995 Effect of bacterial endotoxin and interleukin-1β on hippocampal serotonergic neurotransmission, behavioral activity, and free corticosterone levels: an *in vivo* microdialysis study. J Neurosci 15:2920–2934
37. **Weidenfeld J, Abramsky O, Ovadia H** 1989 Evidence for the involvement of the central nervous adrenergic system in interleukin-1-induced adrenocortical response. Neuropharmacology 28:1411–1414
38. **Chuluyan HE, Saphier D, Rohn WM, Dunn AJ** 1992 Noradrenergic innervation of the hypothalamus participates in adrenocortical responses to Interleukin-1. Neuroendocrinology 56:106–111
39. **Weidenfeld J, Feldman S** 1991 Effects of norepinephrine depletion on median eminence CRF-41 content and serum ACTH in control and adrenalectomized rats. Brain Res 542:201–204
40. **Potter ED, Ling ZD, Carvey PM** 1999 Cytokine-induced conversion of mesencephalic-derived progenitor cells into dopamine neurons. Cell Tissue Res 296:235–246
41. **Gadient RA, Cron KC, Otten U** 1990 Interleukin-1β and tumor necrosis factor-α synergistically stimulate nerve growth factor (NGF) release from cultured rat astrodytes. Neurosci Lett 117:335–340
42. **Kamiguchi H, Yoshida K, Sasaki H, Inaba M, Wakamoto H, Otani M, Toya S** 1995 Release of ciliary neurotrophic factor from cultured astrocytes and its modulation by cytokines. Neurochem Res 20:1187–1193