(*17*); this difference, however, is only apparent at limiting protein concentrations (*17, 22*). It is possible that transformation by p21(Ile^{116}) represents an in vitro anomaly; that is, this form of the protein may be unable to transform cells by the criterion of malignancy. There is some support for this: substitutions at certain positions (for example, 59 and 63) can be activating by in vitro criteria, but have yet to be found as activating lesions in vivo (*23*). Alternatively, there is compelling evidence that activating lesions promoted by the action of carcinogens occur in a profoundly nonrandom fashion. For example, in 36 animals harboring tumors with position 12–activated H-*ras* genes induced by the action of *N*-nitroso-*N*-methylurea, the same mutation (a G → A transition in the second nucleotide of the 12th codon) accounted for each activation (*24*). As such, it is possible that the majority of "spontaneous" mutations are similarly nonrandom; if so, perhaps nucleotides comprising codon-116 are relatively resistant to the action of those carcinogens to which humans are most typically exposed.

Note added in proof: After submission of this manuscript Sigal *et al.* (*25*) reported that p21^{ras} substituted at position 119 displays reduced affinity toward guanine nucleotides and increased morphological transformation potential.

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Immunoregulatory Feedback Between Interleukin-1 and Glucocorticoid Hormones

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The production and action of immunoregulatory cytokines, including interleukin-1 (IL-1), are inhibited by glucocorticoid hormones in vivo and in vitro. Conversely, glucocorticoid blood levels were increased by factors released by human leukocytes exposed to Newcastle disease virus preparations. This activity was neutralized by an antibody to IL-1. Therefore the capacity of IL-1 to stimulate the pituitary-adrenal axis was tested. Administration of subpyrogenic doses of homogeneous human monocyte–derived IL-1 or the *p*I 7 form of human recombinant IL-1 to mice and rats increased blood levels of adrenocorticotropic hormone (ACTH) and glucocorticoids. Another monokine, tumor necrosis factor, and the lymphokines IL-2 and γ-interferon had no such effects when administered in doses equivalent to or higher than those of IL-1. The stimulatory effect of IL-1 on the pituitary-adrenal axis seemed not to be mediated by the secondary release of products from mature T lymphocytes since IL-1 was endocrinologically active when injected into athymic nude mice. These results strongly support the existence of an immunoregulatory feedback circuit in which IL-1 acts as an afferent and glucocorticoid as an efferent hormonal signal.

INTERLEUKIN-1 (IL-1), A PROTEIN produced predominantly by stimulated macrophages and monocytes, exerts several biological actions. Among the immunological effects of IL-1 are the control of differentiation and activation of lymphocytes and the stimulation of lymphokine production (*1*). IL-1 has also several nonimmunological functions. It acts as an endogenous pyrogen, stimulates hepatocytes to elaborate acute-phase proteins, augments granulocyte superoxide production, and alters fibroblast growth and collagenase and prostaglandin production (*2*). In humans and animals, the production and action of IL-1, of several lymphokines, and of other mediators of inflammation are inhibited by glucocorticoids (*3, 4*). These properties of glucocorticoids explain at least in part their effects on immune and inflammatory responses. The existence of a physiological interaction between adrenocortical and immune cell functions is reflected by the fact that animals undergoing immunological responses to various antigens show, at the same time, increased glucocorticoid blood levels in proportion to the magnitude of the immune response (*5*). Furthermore, incompletely characterized agents derived from activated lymphoid cells have been shown to increase blood levels of glucocorticoids (*6,*

While studying neuroendocrine effects following the inoculation of Newcastle disease virus (NDV) into mice, we observed a marked increase in the blood levels of adrenocorticotropic hormone (ACTH) and corticosterone. This increase was also observed when animals were injected with supernatants derived from cocultures of NDV preparations and either human peripheral blood leukocytes (HPBL) or mouse spleen cells (*8*). Since the injection of appropriate control supernatants had no effect, the increase in ACTH and corticosterone appeared to be induced by a product released from stimulated leukocytes (*9*). Supernatants from cultures of leukocytes exposed to natural infective agents or their products are expected to contain IL-1 (*10*). We therefore treated the human leukocyte–derived, endocrinologically active supernatants with an

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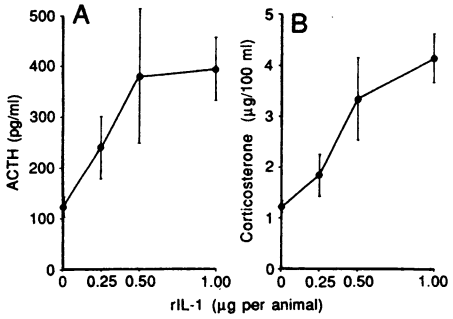

Fig. 1. Changes in ACTH and corticosterone blood levels in C3H/HeJ mice after injection of different doses of rIL-1. The rIL-1 was obtained as described in the legend to Table 2. C3H/HeJ mice were given different dilutions of rIL-1 injected intraperitoneally. Two hours later, the animals were killed and (A) ACTH and (B) corticosterone serum levels were determined by radioimmunoassay. Each point in the curves represents the mean ± SEM of hormone determinations from seven or eight animals.

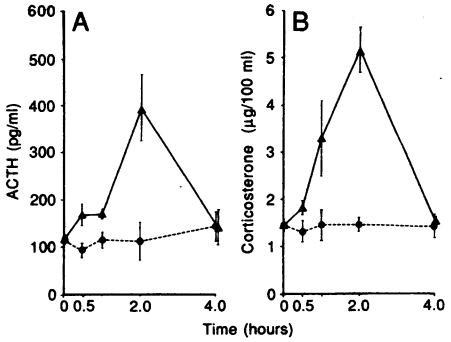

Fig. 2. Time course of increase in ACTH and corticosterone after rIL-1 administration to C3H/HeJ mice. The mice received 1 μg of rIL-1 in 0.5 ml of control medium (—) or 0.5 ml of control medium (---) injected intraperitoneally. At the time indicated, animals were killed, and (A) ACTH and (B) corticosterone serum levels were determined by radioimmunoassay. Each point in the curves represents the mean ± SEM of hormone determinations from seven or eight animals.

antibody to human IL-1. This antibody completely neutralized the capacity of these supernatants to increase corticosterone blood levels in rats (Table 1). The injection of control supernatants similarly treated with the antibody had no effect in these animals. This experiment provided a first indication that IL-1 could affect the pituitary-adrenal axis.

We next tested highly purified human IL-1 and recombinant human IL-1 (rIL-1) for their ability to increase ACTH and corticosterone levels. Mice were chosen as recipients because of the scarcity of homogeneous natural IL-1; the C3H/HeJ strain was used because of its resistance to endotoxin. Both the natural and recombinant forms of IL-1 increased by severalfold the levels of ACTH and corticosterone (Table 2). A dose-response curve (Fig. 1) revealed that small amounts of IL-1 (0.5 to 1 μg) are sufficient to increase ACTH and corticosterone blood levels in C3H/HeJ mice. Similar results were obtained upon injection of 0.5 μg of rIL-1 into Wistar albino rats. An indication of the potency of IL-1 is the estimate that 4×10^6 macrophages can produce 1 μg of IL-1 in 24 hours (*11*). Figure 2 represents the time kinetics of the increase in ACTH and corticosterone after 1 μg of rIL-1 is injected into C3H/HeJ mice. The peak response was detected 2 hours after injection.

In other experiments, we observed that neither of the two preparations of IL-1 at the injected doses induced temperature increases in C3H/HeJ mice. This is probably because temperature increases in mice in response to IL-1 requires prewarming (*12*). Thus the ACTH and glucocorticoid increase is not secondary to pyrogenic effects of IL-1 in these animals.

IL-1 could act either directly or through the secondary induction of another messenger. The latter possibility needs consideration since IL-1 may stimulate activated T

Table 1. Anti–IL-1 treatment of supernatants from human peripheral blood leukocytes cocultured with Newcastle disease virus neutralized the capacity of the supernatants to increase corticosterone blood levels. Newcastle disease virus (kindly provided by K. Bienz, Basel), at 100 hemagglutination units per milliliter, was added to HPBL (10^7 cells per milliliter), in RPMI 1640 supplemented with 25 m*M* Hepes buffer, L-glutamine, antibiotics, and 1% heat-inactivated pooled human serum. After incubation of the mixture in flasks for 18 hours at 37°C, the supernatants were collected and ultracentrifuged for 2 hours at 160,000*g* to deplete them of the virus (HPBL + NDV supernatant). The control supernatant was incubated in culture medium for the same time period and ultracentrifuged as above. [Supernatants from cultures of HPBL to which NDV was added at the end of the culture period and further treated in a similar way did not show glucocorticoid increasing activity. Therefore culture medium alone was used as control in further experiments (*8*).] One portion of each type of supernatant was incubated with 2% (by volume) rabbit antibody to human IL-1 (gamma globulin preparation) for 20 hours at 4°C (HPBL + NDV + anti–IL-1 and control + anti–IL-1). The antibody was prepared and purified as described (*20*), with the exception that the antigen used for immunization was highly purified human monocyte–derived IL-1. This antibody, which had been shown earlier to neutralize IL-1 activities in several assays, was the same as used to clone IL-1 (*21*) and does not recognize TNF (*15*) nor α- or γ-interferon (*22*). The other portion of the supernatants received the same treatment but without addition of anti–IL-1. Female Wistar albino rats (2 to 3 months old) were caged individually for 7 days before the experiments were started and kept isolated throughout. Animals received intraperitoneal injections (0.5 ml) of the different supernatants. Two hours after the injection, rats were exposed to ether for 20 seconds and killed by decapitation between 10 and 11 a.m. Plasma corticosterone was determined by radioimmunoassay as described (*7*). Results are presented as the means ± SEM. Data were analyzed by one- and two-way analyses of variance. Corticosterone levels for rats injected with HPBL + NDV supernatant were significantly ($P < 0.01$, with Bonferroni correction) different from those for rats injected with HPBL + NDV + anti–IL-1 supernatant and those injected with control supernatants. There was no statistically significant difference between animals injected with control supernatants and control + anti–IL-1 supernatant nor with control + anti–IL-1 and HPBL + NDV + anti–IL-1 supernatants.

Supernatant	*n*	Plasma corticosterone (μg/100 ml)
Control	9	12.50 ± 3.16
Control + anti–IL-1	12	12.51 ± 2.82
HPBL + NDV	11	52.99 ± 4.23
HPBL + NDV + anti–IL-1	13	14.47 ± 3.78

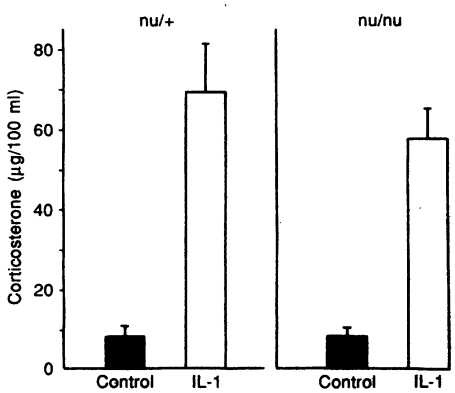

Fig. 3. Changes in corticosterone blood levels in athymic nude mice after administration of rIL-1. The rIL-1 was obtained as described in the legend to Table 2, but 41 amino acids of the precursor peptide were removed by enzymatic digestion and contained amino acids 112 to 269 (molecular size 17,500). The low endotoxin content of this preparation has no effect in vivo (0.06 pg per microgram of IL-1 protein) (*24*). One-month-old athymic nude BALB/c mice (*nu/nu*) and thymus-bearing littermates (*nu/+*) received either 1 μg of rIL-1 in 0.5 ml of control medium (□) or 0.5 ml of control medium (■) injected intraperitoneally. Animals were killed 2 hours later, and corticosterone serum levels were determined by radioimmunoassay. Each column with a vertical bar represents the mean plus SEM of six (*nu/nu*) or four determinations (*nu/+*). Corticosterone values of mice injected with rIL-1 were significantly ($P < 0.01$ with Bonferroni correction) different from those of mice injected with control medium. There was no statistically significant difference between *nu/+* and *nu/nu* animals injected with control medium, nor between *nu/+* and *nu/nu* mice injected with rIL-1.

Table 2. IL-1 increases serum levels of corticosterone and ACTH in mice. Natural IL-1 was purified from human monocytes stimulated with heat-killed *Staphylococcus albus*. IL-1 was separated from these supernatants by sequential immunoabsorption, gel-filtration, and chromatofocusing on 17.5% sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE). The purified IL-1 appeared as a single band with a molecular size of 17.5 kD (*23*). This IL-1 had an isoelectric point of 7.1 and was active in lymphocyte and fever assays. This material was negative in the *Limulus* test and 5 ml produced a monophasic fever when injected intravenously into rabbits (*13*). Purified human rIL-1 (*p*I 7 form or β form) was expressed in *Escherichia coli* as described (*24*) and contained amino acids 71 to 269 (molecular size 24,500). The preparation was 99.5% pure as assessed by SDS-PAGE and NH_2-terminal amino acid sequence analysis. It contained 20 to 40 pg of endotoxin per microgram of IL-1 protein. Two-month-old, endotoxin-resistant, male C3H/HeJ mice obtained from Bomholtgard, Ry, Denmark, were caged individually for 7 days before the experiments were started and kept isolated throughout. Animals received intraperitoneally 0.5 ml of control medium or 1 μg of rIL-1 in 0.5 ml of control medium or 0.5 ml of purified IL-1 (about 2000 IL-1 units per milliliter). Mice were killed 2 hours later and serum levels of corticosterone and ACTH were determined by radioimmunoassay as described (*7*). Similar results were obtained when 0.5 ml of purified natural human IL-1 was injected intraperitoneally into albino male mice or Wistar albino male rats. Corticosterone and ACTH values of rats injected with IL-1 were significantly different (corticosterone: $P < 0.005$; ACTH: $P < 0.01$) from those of rats injected with control medium. There was no statistically significant difference ($P > 0.1$) between animals injected with rIL-1 and purified IL-1.

Preparation	*n*	Corticosterone (μg/100 ml)	ACTH (pg/ml)
Control	10	1.49 ± 0.16	123.50 ± 17.47
rIL-1	10	5.03 ± 0.77	428.40 ± 84.97
Purified IL-1	7	6.15 ± 1.29	607.30 ± 139.10

cells present in conventionally reared animals and thus the lymphomonokine cascade. Evidence against this possibility was obtained from experiments in which IL-1 was injected into athymic nude mice. These animals are unable to produce T cell–derived lymphokines, for example IL-2 (*13*). Administration of rIL-1 to nude mice caused an increase in glucocorticoid levels of the same magnitude as the effect observed in heterozygous thymus-bearing littermates (Fig. 3). We concluded that the stimulatory effect of IL-1 on the pituitary-adrenal axis is not mediated by lymphokines or other mediators released by mature T cells after stimulation with IL-1. This conclusion is supported by experiments in which we administered natural or recombinant IL-2 or recombinant γ-interferon in various doses and detected no increase in corticosterone levels. The described endocrine effect of IL-1 seems not to be shared by all monokines. Tumor necrosis factor (TNF), for example, when administered to mice and rats in doses equivalent to or higher than those used for IL-1, did not increase corticosterone blood levels, even though TNF is a monokine with several biological properties in common with IL-1 (*14*), particularly the ability to stimulate the anterior hypothalamus to induce fever (*15*). The increase in ACTH levels after IL-1 is injected indicates that the pituitary is involved. Whether IL-1 acts on ACTH-producing cells in the pituitary or rather via release of corticotropin-releasing factor from the hypothalamus warrants further study (*16*).

Glucocorticoids are anti-inflammatory and block the production and action of several lymphokines (*3*) such as IL-2 and γ-interferon, as well as the production of prostaglandins (*17*). In addition they can block IL-1 production by macrophages and also inhibit the induction of Ia antigens necessary for antigen presentation (*4*). Thus, increased levels of glucocorticoid can interfere with several essential steps in the immune response. It is therefore conceivable that when IL-1 concentrations reach a certain level in the circulation during infection or during inflammatory or immune responses, the pituitary-adrenal axis becomes activated and glucocorticoid blood levels increase. As a consequence, immune cell functions and production of monokines and lymphokines such as IL-1, IL-2, and others will be affected. In fact, increased glucocorticoid concentrations have been detected during the course of immune responses (*5*) and infectious diseases (*18*). This evidence suggests that an IL-1–mediated glucocorticoid increase constitutes part of a normal host response to environmental antigenic stimuli. This endocrine response reflects, in our view, the existence of a feedback circuit involving products of immunocompetent cells such as IL-1 and the pituitary-adrenal axis. Such glucocorticoid-associated immunoregulatory mechanisms may exert a continuous surveillance of immunological cells and activity (*19*). Overstimulation of the pituitary-adrenal axis by messengers derived from the immune system may contribute to pathological states. For example, a massive and sustained release of IL-1, causing increased glucocorticoid blood levels, may be one of the factors mediating the immunosuppression observed during the acute phase of several infectious diseases, thus favoring superinfection.

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