explained by the fact that fitness is not determined by an isolated organ or system. This hypothesis would predict that late Paleozoic radular teeth may be found as isolated microfossils (for example, in conodont concentrates) and in soft-bodied fossils. Radula-like structures are known from unskeletonized nonmollusks of Cambrian age (*25*). The naticid-like drillholes that we have described in Devonian brachiopods contribute to growing evidence (*26*) of a long prelude to the Mesozoic revolution in predation.

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29. The species are *R. penelope*, *R. vanuxemi*, and *R. leucosia*.

30. We thank R. Alexander, R. Bambach, J. Jablonski, J. Kitchell, V. Maes, R. Robertson, N. Sohl, G. Vermeij, and E. Yochelson for comments; T. Lutz for statistical analysis; D. Ricketts for micrographs; and Sigma Xi for a grant-in-aid to S.A.S.

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Corticotropin-Releasing Activity of Monokines

Abstract. *Hepatocyte-stimulating factor and interleukin-1 are proteins produced by monocytes in response to inflammatory challenge. Neither of these monokines had direct effects on steroid production by cultured adrenocortical cells. Both monokines stimulated pituitary cells (AtT-20) to release adrenocorticotropic hormone; interleukin-1 was equipotent with a combination of corticotropin-releasing factor and arginine vasopressin, and hepatocyte-stimulating factor was at least three times as effective. The synthetic glucocorticoid, dexamethasone, inhibited production of hepatocyte-stimulating factor by cultured monocytes. These results indicate an axis between monocytes and pituitary and adrenocortical cells which may play a role in regulating host defense.*

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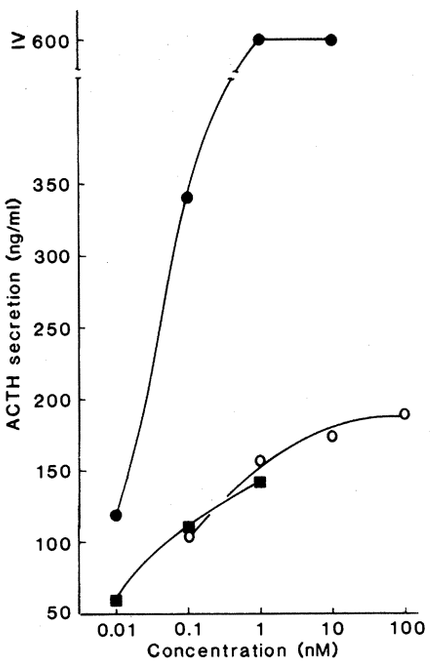
Recent findings suggest bidirectional communication between the immune and neuroendocrine systems (*1*). Of particular interest are molecules of the immune system that control neuroendocrine functions. Two major groups of immunologic mediators that are endogenous to the immune system have been identified—lymphokines and neuroendocrine peptide hormones (*1, 2*). The recent findings that interleukin-1 (Il-1) is present in the brain (*3*) and that it may function as an endogenous pyrogen (*4*) suggests that monocyte-derived factors (monokines) can also mediate control of certain neuroendocrine functions. Monokines also regulate the acute phase response that results from tissue damage. Since the pituitary-adrenal axis is activated during the acute phase response (*5*), we have investigated the potential role of monokines in the elevation of adrenocorticotropic hormone (ACTH) and glucocorticoid hormone concentrations. Specifically, we have studied the effects of Il-1 and a newly identified monokine, hepatocyte-stimulating factor (HSF) (*6–10*), on ACTH and glucocorticoid hormone concentrations in mouse pituitary (AtT-20) and adrenal (Y-1) cell lines, respectively.

To determine if monokines directly elicited an adrenal steroidogenic response, monocyte-conditioned medium (*11*) and purified preparations of HSF and Il-1 (*12*) were added to cultures of mouse adrenal tumor cells, and the culture supernatant fluids were assayed for steroid hormone production by radioimmunoassay (*13*). Neither the impure mixtures of monokines in monocyte-conditioned medium nor the purified Il-1 and HSF affected steroid hormone production by these cells. We next determined whether the elevated glucocorticoid concentrations seen during an acute phase response might indirectly result from the effect of monokines on ACTH release. Purified monokines were added to cultures of the AtT-20 pituitary tumor cells, and ACTH release was monitored. Both HSF and Il-1 were potent stimuli for ACTH release (Fig. 1). Interleukin-1 was equipotent with a combination of hypothalamic corticotropin-releasing factor (CRF) and arginine vasopressin. HSF was at least three times as effective at

eliciting ACTH release. The ACTH released in response to the monokines or CRF was biologically active, as evidenced by its ability to induce Y-1 adrenal cells to undergo morphologic rounding and steroidogenesis. This result suggests that the ACTH was processed and secreted by the pituitary cells rather than being released as a biologically inactive precursor (*14*). These observations also suggest that the extrahypothalamic CRF's reported by Brodish (*15*) after tissue injury may originate from monocytes. Thus, during an inflammatory challenge, HSF may represent a common regulator of both liver and pituitary cells. These molecules may also be responsible for the elevated glucocorticoid concentrations observed during the immune response and after injection of supernatant fluids from mitogen-activated spleen cells (*16*).



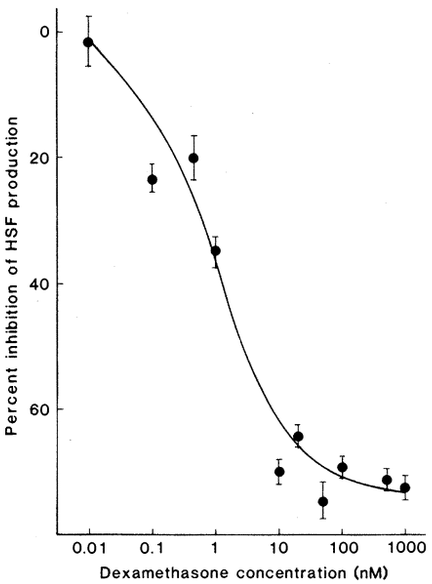


Fig. 1 (left). Effect of HSF and Il-1 on corticotropin production by pituitary cells. The CRF-responsive, ACTH-producing mouse pituitary tumor cells AtT-20 (*20*) were cultured at 2×10^7 cells per milliliter in Dulbecco's minimal essential medium supplemented with 0.1 percent bovine serum albumin in the presence of CRF and 100 ng of arginine vasopressin per milliliter (○), cloned murine Il-1 (■), or HSF (●) for 2 hours. Medium was harvested and assayed for ACTH concentration by a commercially available radioimmunoassay and by a bioassay (*20*). The bioassay consisted of incubating the AtT-20 cell culture fluids on Y-1 adrenal tumor cells and observing for morphologic rounding or measuring glucocorticoid release by radioimmunoassay (*21*). The bioassay results paralleled the radioimmunoassay results. Medium from untreated pituitary cell cultures and cultures treated with heat-inactivated Il-1 or HSF had 60 ng of ACTH per milliliter, and no statistically significant differences were observed between cultures. Results are the means of duplicates and represent 1 of 12 experiments giving similar results; variances were less than 2 percent of the means. Molar concentration of Il-1 was calculated on the basis of a molecular mass of 18 kD and a specific activity of 6×10^6 units of thymocyte proliferation activity per milligram of protein (*22*). The molar concentration of purified HSF was calculated on the basis of a molecular mass of 25 kD (*8, 9*). Fig. 2 (right). Effect of dexamethasone on production of HSF. Human peripheral blood monocytes were prepared (*8–11*) and cultured in McCoy's 5A medium with and without dexamethasone supplementation. After 24 hours of culture, conditioned medium was harvested, centrifuged to remove cells, sterile filtered, and 2 to 200 μl was added to primary cultures of rat hepatocytes to test HSF activity (*7–10*). Units of HSF activity were determined; one unit is that amount required to elicit half-maximal increases in fibrinogen production. Results are the means and standard deviations of 6 to 14 replicates and are expressed as percent inhibition compared with untreated controls.

Regulation of monokine production during an inflammatory challenge is complex (*8, 10, 17, 18*). For instance, glucocorticoids inhibit Il-1 production (*18*) as well as pituitary and leukocyte production of ACTH and endogenous opiates (*1, 2*). The synthetic glucocorticoid, dexamethasone, inhibited 75 percent of the HSF production by human peripheral blood monocytes (Fig. 2). In concentrations of 1 to 10 n*M*, dexamethasone inhibited 50 percent of the HSF production, which suggests that the effect was mediated through the glucocorticoid receptor, which has a dissociation constant of about 5 n*M* (*19*). These findings show that glucocorticoids inhibit HSF production and provide evidence for a feedback inhibitory loop.

Together, these data indicate a regulatory interaction between monocytes and the pituitary-adrenal axis (Fig. 3). Tissue injury or inflammation elicits monocyte HSF and Il-1 production, which in turn regulate the synthesis of the acute phase reactants and lymphocyte function, respectively. These monokines also activate the pituitary-adrenal axis and increase glucocorticoid concentrations. These steroid hormones may then act on hepatocytes to enhance plasma protein synthesis, on monocytes to block HSF and Il-1 synthesis, and on pituitary cells to inhibit ACTH release and subsequent glucocorticoid production. The potential ability of monocyte products to circumvent hypothalamic control of the pituitary-adrenal axis provides an explanation for endocrine activity during inflammation and tissue injury. The importance of this avenue of control is indicated by the fact that the monocyte-derived HSF is a more potent effector of pituitary cell release of ACTH than a combination of hypothalamic CRF and arginine vasopressin. Finally, a possible monocyte-pituitary axis is a part of a larger immune-neuroendocrine regulatory circuit, which seems to operate directly through innervated lymphoid organs and indirectly by virtue of ligands and receptors common to both systems (*1, 2*). An understanding of the interactions between the immune and neuroendocrine systems

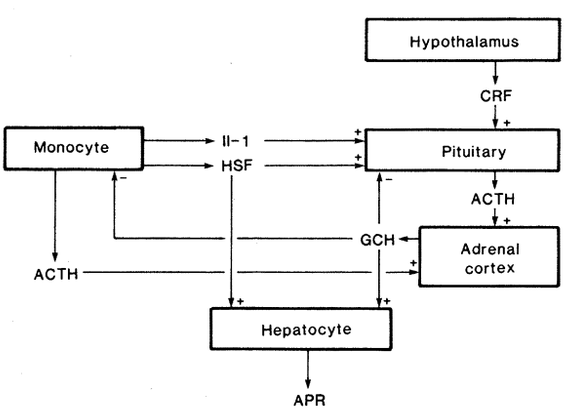


Fig. 3. Model for a monocyte-pituitary-adrenal axis. Stimulation of target tissue function is indicated by + and inhibition by −. Shown are CRF, HSF, and Il-1 stimulation of release of ACTH by pituitary corticotrophs; pituitary and monocyte ACTH stimulation of adrenal steroidogenesis; glucocorticoid hormones (GCH) inhibition of monokine and pituitary ACTH production. Also shown is the synergistic stimulation of hepatic acute phase reactant production (APR) by HSF and GCH.

should help explain the pathophysiology of diseases having immune and neuroendocrine components.

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12. For the preparation of HSF, the 25,000-dalton (25-kD) monokine was isolated by high-performance liquid chromatography through the use of a TSK-2000 SW gel permeation column (*8, 9*) from the fraction of human peripheral blood monocyte conditioned medium which eluted from a DE-53 ion exchange column (Whatman) between 40 m*M* and 60 m*M* sodium chloride in 20 m*M* tris, *p*H 7.2. The purified HSF had a specific activity of 3×10^5 units of activity per milligram of protein in the hepatocyte bioassay; no Il-1 was detected by the thymocyte proliferation assay of purified HSF. Crude and purified HSF preparations all elicited responses of hepatocyte fibrinogen and pituitary ACTH production; no differences between these target tissues were observed in the potencies of crude or purified HSF. Cloned murine Il-1 had no HSF activity as determined by the hepatocyte bioassay.
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Infanticide in Prairie Dogs: Lactating Females Kill Offspring of Close Kin

Abstract. *Infanticide, although common in a wide range of species including humans and other primates, is poorly understood. A 7-year study under natural conditions reveals that infanticide within colonies of black-tailed prairie dogs* (Cynomys ludovicianus) *is striking for three reasons. It is the major source of juvenile mortality, accounting for the total or partial demise of 51 percent of all litters born. The most common killers are resident lactating females. The most common victims are the offspring of close kin.*

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Infanticide, the killing of conspecific juveniles, has been observed in numerous species from diverse taxonomic groups including rotifers, insects, fish, amphibians, birds, and mammals (*1*). Infanticide has often been regarded as a pathological and maladaptive response to overcrowding (*2*), but evidence suggests that infanticide in some contexts may lead to increased reproductive success (*1, 3, 4*). Here I describe four different types of infanticide that occur in natural populations of black-tailed prairie dogs (*Cynomys ludovicianus*).

Black-tails are large, diurnal, colonial, harem-polygynous squirrels (Rodentia: Sciuridae). In Wind Cave National Park, South Dakota, they breed in February and March, and weaned or nearly weaned juveniles emerge from their burrows in May and June (*5–9*). Colony residents live in contiguous territorial groups called coteries (*7, 8*), where one adult (≥ 2 years) male, three or four adult females, and several yearling and juvenile offspring typically live. Since they usually remain in the natal coterie territory for life, females within a coterie are almost always genetically related (*9*). Males usually disperse as yearlings and attempt to enter another coterie (*9*). Estrous females usually mate with the adult male in the home coterie (*10*). Breeding within a coterie is synchronous (*7*), and inbreeding is rare (*9, 11*); with some exceptions, breeding in both sexes is deferred until individuals are 2 years old (*8, 10*). The study colony, inhabited for at least 35 years, is approximately 500 m by 130 m (6.6 hectares), and in late spring of each year (1976 through 1984) contains an average of 132.8 adults and yearlings [standard deviation (S.D.), ±8.9; range, 117 to 143], 84.1 juveniles (±20.2; range, 58 to 119), and 23.2 coteries (±2.3; range, 19 to 26). Through eartagging, observing, and electrophoretic analysis of blood samples, maternal, sibling, and putative paternal genetic relationships have been determined for all young weaned at the study colony since 1975 (761 young from 257 litters) (*9, 10, 12*). Since 1975, only 5 females and only 14 males have immigrated into the study colony and produced weaned offspring.

The average gestation period for black-tails is 34.8 days (S.D., ±0.7; range, 34 to 37 days; $n = 32$), and the average time between parturition and the first emergence of weaned or nearly weaned juveniles is 43.4 days (S.D., ±3.5; range, 38 to 50 days; $n = 17$). Infanticide occurs both before and after weaning and sometimes involves cannibalism. Infanticide before weaning usually occurs in the burrow, and detection requires watching burrows with young for possible marauders (*13*). Postweaning infanticide also frequently occurs underground and is detected by the abrupt, simultaneous disappearances of several marked juveniles or by finding maimed carcasses above ground (*14*). Because breeding is so seasonal, females that lose a litter to infanticide lose an entire breeding season. From 1978 through 1984, the study colony was observed for a total of more than 20,000 man-hours of observation; during this time field assistants and I detected 73 cases of infanticide.

Almost all adult females at the study colony mate each year (*10*), after which they typically build an underground nest. After parturition females usually defend their burrows from all conspecifics and sleep with the young at night (*8, 15*). Unguarded by the mother, unweaned offspring may be killed by another lactating female of the home coterie. Only 11 of 36 mothers (31 percent) whose burrows were marauded weaned a litter, compared to 57 of 97 (59 percent) whose burrows were not marauded [$P = 0.004$, χ^2 (1) = 8.36] (*16*).

Infanticide by females of the home coterie was the most common type: we detected 40 cases (three litters were marauded two times), 22 different killers, and 28 different victimized mothers (*17*). These infanticides accounted for the partial elimination of 11 percent (15 of 133)