It was widely believed that psychological factors could alter the development and prognosis of various diseases including cancer, as well as injury. It was reported that soldiers injured during a battle in the victorious army could recover from their wounds and survive, whereas the soldiers suffered the similar injury in the defeated army could not recover and died. The fact that the survival period of a husband or wife who has been bereft is extremely short, suggesting that some emotional factors, such as loneliness, anxiety, depression, and frustration caused by the death of his or her beloved may have affected the well-being of the person. The influence of the mind on the immune function was also demonstrated by the ability to use classic Pavlovian conditioning to suppress antibody production\(^1\) and to enhance natural killer cell activity\(^2\). More direct evidence for a central and peripheral nervous system origin of immunoregulation comes from observations of both positive and negative effects of electrolytic and chemical lesions of the nervous system on immunologic functions and leukocyte number\(^3\).

The immune system is usually considered to be the most important natural defence against microbial infection and non-self substances. Cancerous cells in the body also act as non-self cells which will be recognized and destroyed by the immune cells. Tissue damage caused by injury also triggers a cascade of immune reaction which aids the body in repairing the damaged tissues. There is a great deal of evidence that immune mechanisms particularly cytotoxic T cells and "natural killer" cells can destroy cancer cells in vitro or in experimental cancer of rodents. Although there is little evidence for a crucial role of the immune system in natural cancer of humans or animals, it is probable that the immune system does play a part in controlling human cancer, and it is relevant to consider the impact of the mind on this system. Stressors such as loud noises, vibration, and handling tend to depress immune reactivity in rodents. Stress can diminish antibody formation, delayed hypersensitivity, and skin allograft rejection in experimental animals. Enhancement by stress has also been recorded and the complexity of its effects is well shown in the study by Monjan and Collector (1974) in which chronic auditory stress diminished lymphocyte functions for the first 3 weeks and enhanced them for the following 3 weeks\(^2\). One of the most impressive finding was the demonstration by Bartrop, et al (1977) that the response of peripheral blood lymphocytes was suppressed 8 weeks after bereavement\(^2\); this result was independently confirmed by Schleifer et al (1983). Kiecolt-Glaser et al (1983) have shown that psychiatric inpatients scoring high on a loneliness scale had increased blood cortisol levels and relatively low natural-killer cell and lymphocyte stimulation levels\(^3\).
Possible effects of neuroendocrines and other hormones on immunological cells have recently attracted much attention. One of the mechanisms is stress-induced corticosteroid release that alters the distribution and reactivity of lymphocytes and may depress immune responses. Other hormonal mechanisms include the tendency of androgens, estrogens, and progesterone to diminish immune responses, while growth hormone, thyroxin, and insulin may elevate them. In addition, prolactin, TSH, vasopressin, oxytocin, somatostatin, substance P, VIP, hCG have been reported to modulate immunefunction. Demonstrated that the stress-induced suppression of mitogen-induced lymphocyte proliferation could be reversed by adrenalectomy; the observation that the reversal was not complete implied that the stress was also acting through pathways other than adrenal hormone. Lymphocytes indeed have surface receptors for a variety of neuropeptides. Among neuropeptides, opioid peptides are the most studied peptides in the modulatory effects on the immune system. Those representative actions are shown in Table 1.

Table 1: Modulatory effects of opioid peptides on the immune function.

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Actions</th>
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<tbody>
<tr>
<td>Leu- or Met-Enkephalin</td>
<td>Suppression of Ig synthesis</td>
</tr>
<tr>
<td></td>
<td>Enhancement of IFN-γ synthesis</td>
</tr>
<tr>
<td></td>
<td>Enhancement of NK cell activity</td>
</tr>
<tr>
<td></td>
<td>Chemotactic for monocytes</td>
</tr>
<tr>
<td>α-Endorphin</td>
<td>Suppression of Ig synthesis and secretion</td>
</tr>
<tr>
<td></td>
<td>Suppression of antigen-specific T-cell helper factor</td>
</tr>
<tr>
<td>β-Endorphin</td>
<td>Enhancement of Ig and INF-γ synthesis</td>
</tr>
<tr>
<td></td>
<td>Modulation of T-cell proliferation</td>
</tr>
<tr>
<td></td>
<td>Enhancement of T-cell generation</td>
</tr>
<tr>
<td></td>
<td>Enhancement of NK cell activity</td>
</tr>
<tr>
<td></td>
<td>Chemotactic for monocytes and neutrophils</td>
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</tbody>
</table>

The most important advance in neuroimmunology is the observation that communication between the neuroendocrine and immune systems is not unidirectional but is bidirectional. Various neuropeptides are indeed produced by leukocytes. The best-studied neuropeptides that are produced by leukocytes are those peptides derived from proopiomelanocortin (POMC). Human peripheral blood lymphocytes and mouse spleen cells were initially observed to express immunoreactive ACTH and endorphins simultaneously following virus infection or interaction with transformed cells or bacterial lipopolysaccharide. Although synthesis of ACTH and endorphins by most lymphocytes are induced
by these factors, a subpopulation of mouse splenic macrophages, as well as rat lymphocytes in the tunica propria, produced these peptides in a constitutive fashion 25), 10). These peptides were identified by its antigenicity to a monospecific antibody, retention time on RPHPLC, molecular weight and the biological activity. In addition to POMC-driven neuropeptides, the immune system also synthesizes other neuropeptides and hormones, including chorionic gonadotropin, TSH, prolactin, growth hormone, VIP, arginine vasopressin, oxytocin, neurophysin, and somatostatin.

As in pituitary corticotrophs, processing of leukocyte-derived ACTH and β-endorphin appears to be regulated by corticotropin-releasing factor (CRF) or hormone (CRH). As demonstrated on the pituitary, the synthesis of CRH-stimulated POMC-related peptides is blocked by dexamethasone. In addition to producing neuropeptides, the immune cells also possess receptors for many neuropeptides and hormones. Mouse spleen mononuclear cells have both high-affinity and low-affinity receptors for ACTH18). Human peripheral blood mononuclear leukocytes are not particularly unlike mouse splenocytes in that they also have both similar high-affinity and low-affinity receptors for ACTH.

These findings of the similarities and interactions of the immune and neuroendocrine systems provide a rationale for using leukocytes as models of neuroendocrine tissues. It has been shown that ACTH binds specifically to mouse splenocytes and inhibits the production of antibodies and interferon18), 19). The finding has a clinical implication. In the clinical practice, the inaccessibility of many tissues makes routine investigation for receptor defects impossible. ACTH insensitivity syndrome is an example of this problem. Defects in adrenal ACTH receptors have been postulated because of high circulating ACTH levels and the ability of the adrenal-cortex cells to achieve steroidogenesis through an elevation of cyclic AMP. In the majority of cases, the clinical presentation includes hyperpigmentation, hypoglycemia, and extremely low glucocorticoid levels with normal mineralocorticoid concentrations. Smith et al. (1987) studied leukocyte-ACTH binding in a child known to have isolated glucocorticoid deficiency due to ACTH insensitivity and found that high-affinity ACTH binding did not occur in this patient.

The interaction between the immune and neuroendocrine systems is not limited to the regulation of immune cells by neuroendocrine peptide hormones, but also the products of the immune system affect the neuroendocrine function by their direct action on the endocrine organs or through their action on the central neuroendocrine system. We have shown that interleukin 1 (IL-1) suppressed FSH-induced progesterone section and 125I-labeled hCG binding (a measurement of LH receptors) in cultured rat granulosa cells13). IL-1 produced a dose-dependent inhibition of LH receptors in FSH-stimulated rat granulosa cells, without changing the affinity. A minimum of 12–24 hr of exposure to IL-1 is necessary to significantly inhibit FSH-induced LH receptor formation14). The finding may have clinical implication, because it is known that patients with endometriosis often develop infertility. Endometriosis is known to be associated with infiltration of monocytes in the peritoneum, resulting increased production of IL-1 by these monocytes which may affects
the ovarian function.

It has been well established that ACTH release by the pituitary gland is regulated by hypothalamic CRH which is triggered by stress. However, when the stress is extremely severe, such as extensive destruction of tissues, a substance produced by the tissue appears to directly stimulate ACTH release. This substance was named as tissue CRF\(^6\). Although three decades have passed since the concept of tissue CRF was presented, tissue CRF has never been isolated or chemically identified. Therefore, we have recently started re-examining various tissues for the presence of a substance with CRF activity which is determined by the release of ACTH by the test material in the rat pituitary cell cultures. It was recently reported that murine IL-1 stimulated ACTH release from mouse ACTH-secreting pituitary tumor cells (AtT-20), suggesting that IL-1 may be a tissue CRF\(^3\). In our hand, however, neither human IL-1\(_\alpha\) nor IL-1\(_\beta\) stimulated the ACTH release from normal pituitary cells in concentrations ranging from 0.01 to 10 nM. IL-1\(_\beta\) caused a slight, but significant, increase in ACTH release at a concentration of 100 nM, while IL-1\(_\alpha\) did not, even at the highest dose tested. IL-1\(_\beta\) exhibited a synergistic action with synthetic rat CRH in ACTH secretion at 10 and 100 nM of CRH, but the interaction was not striking. Both of the monokines failed to cause any change in the secretions of growth hormone, prolactin, FSH and LH throughout concentrations ranging from 0.01 to 100 nM. The effects of possible sex-related differences and prolonged preincubation of cultured pituitary cells in serum-free medium prior to assay incubation were also tested, providing no significantly different findings\(^3^6\). These results suggest that the physiological significance of IL-1 as a tissue CRF is indeed questionable and should be further clarified.

IL-1 administered intravenously (iv), however, consistently elicited a striking ACTH release in conscious unrestrained rats. This ACTH response to IL-1 was completely abolished by preinjection of 0.5ml rabbit antiserum generated against rat CRH, but not by normal rabbit serum. The IL-1-induced ACTH release did not seem to be caused by a general stress effect of IL-1 because plasma prolactin (PRL) levels, another indicator of a stress response, were not altered by the injection of IL-1\(^3\). These results suggest that IL-1 acts centrally in the brain to stimulate the secretion of CRH, thereby eliciting ACTH release, and that a direct action of IL-1 on the pituitary gland is unlikely.

March et al. (1985) recently described the cloning and expression of two human IL-1 complementary DNAs, termed IL-1\(_\alpha\) and IL-1\(_\beta\). Although the primary translation products of these genes are 271 and 269 amino acids long, respectively, expression in E.coli of the carboxy-terminal 159 and 153 amino acids produce IL-1 biological activities. Since the discovery of the two forms of IL-1, investigation has been underway to determine whether IL-1\(_\alpha\) and IL-1\(_\beta\) share all the biological activities previously attributed to IL-1. To date, it has been shown that IL-1\(_\alpha\) and IL-1\(_\beta\) exert similar immunological responses and bind the identical cell surface receptors on immune cells, in spite of distant homology in their respective amino acid sequences which are only 26% homologous in the full molecules. Recently, a direct expression strategy was used to clone the receptor for IL-1 from mouse
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T cells. The product of the cloned complementary DNA bind both IL-1α and IL-1β in a manner indistinguishable from that of the native T cell IL-1 receptor. The extracellular, IL-1 binding portion of the receptor is 319 amino acids in length and is composed of three immunoglobulin-like domains. The cytoplasmic portion of the receptor is 217 amino acids long31). Despite similar biological activities between IL-1α and IL-1β in the immune system, the effects of these two forms of IL-1 on the hypothalamic-pituitary-adrenal axis are different. In freely moving, conscious rats, iv injection of human recombinant IL-1 significantly increased the plasma levels of ACTH in a dose-related manner, whereas IL-1α did not35), 36), 37).

We have then examined the specific binding sites for IL-1 in the rat brain and pituitary. A single type of high-affinity binding sites for IL-1β was identified in the rat hypothalamic membrane preparation (Kd = 1.0 ± 0.2nM) and cerebral cortex (Kd = 1.3 ± 0.2nM), but not in the pituitary. The maximum binding capacity (Bmax) in the hypothalamus (Bmax = 75.4 ± 10.8 fmol/mg protein) was 4 times greater than in the cerebral cortex (Bmax = 17.2 ± 1.5 fmol/mg protein). Neither various neuropeptides nor IL-2 appeared to influence the binding of [125I] IL-1β to the hypothalamic membrane preparations. The potency of unlabeled IL-1α to replace the binding of [125I] IL-1β to the hypothalamic membrane preparations was considerably less than that of unlabeled IL-1β (about 100 times). These findings indicate that IL-1β receptors are heterogeneously distributed in the central nervous system and that IL-1α does not bind with IL-1β receptors in the brain to the same extent21). The finding suggests the presence of subpopulation of IL-1 receptors in the central nervous system.

In order to confirm that the primary site of action of IL-1β in stimulation of ACTH release is the brain, the ACTH responses to IL-1β administered iv and intracerebroventricularly (icv) in conscious rats were compared. A dose as small as 3 ng of IL-1β injected icv induced a significant rise in plasma ACTH levels, whereas 100 ng/100 g was needed for a significant response when injected iv. ICV injection of 0.3 ng IL-1α tended to increase plasma ACTH levels, but not significantly. IV injection of 1000 ng/100 g IL-1α induced a maximal response with a pronounced elevation of plasma ACTH levels at 10 and 30 min after injection, but plasma ACTH levels fell at 60 min post injection. On the other hand, icv injection of 30 ng IL-1β raised plasma ACTH levels at 10 min, reaching peak values between 30 and 60 min post injection, and plasma ACTH levels remained elevated for 2–3 h after injection. As demonstrated for pyrogen-induced febrile reaction, pretreatment with indomethacin completely prevented the ACTH response induced by either iv or icv injection of IL-1β. Administration of indomethacin did not alter the elevation of plasma ACTH levels induced by immobilization stress, however. On the other hand, vagotomy did not alter the ACTH response to iv administered IL-1β. Neither iv or icv injection of IL-1β in a dose which induced a maximal ACTH response altered plasma PRL levels. These findings strongly suggest that the brain is the primary site of action of IL-1β, and that IL-1β transmits the message of the immune system to the brain and, possibly, CRH neurons. It is also suggested
that prostaglandins may be involved in this central action of IL-1β\(^{21}\).

The next question is how blood-borne IL-1 with a mw of 17,500 reaches the brain tissue crossing the blood-brain-barrier (BBB). It has been suggested that IL-1 induces fever through its central action and that the primary site in the brain for the febrile reaction to blood-borne pyrogen is the preoptic area (POA)\(^{8}\). Other reports indicated that placement of lesions in the anteroventral area of the third ventricle and the organum vasculosum of the lamina terminalis (OVLT) altered febrile response to systemic injection of pyrogen\(^{34}\). It was suggested that the circulating IL-1 or pyrogen may reach the brain tissues through a region where the BBB is absent, such as the circumventricular organs. Studies of the ultrastructures of the OVLT and subfornical organ (SFO) of the circumventricular organs suggested that they have both sensory and neurosecretory functions\(^{38}\). The OVLT and SFO were also reported to be the most sensitive areas for the “drinking response” induced by systemic angiotensin II\(^{28}\). Electrical stimulation of neurons in the POA which is adjacent to both OVLT and SFO has been demonstrated to increase firing rates of neurons in the paraventricular nucleus (PVN) and plasma corticosterone levels in rats\(^{30}\). Bearing these reports in mind, we examined the effects of iv injection of IL-1 on ACTH release in conscious rats bearing lesion in the OVLT, SFO, or POA in order to determine whether these areas might be involved or were essential to the mechanism by which blood-borne IL-1β triggers ACTH release (Katsuura et al, in press). In addition, the purported involvement of PGs in IL-1β-induced ACTH response was also investigated. The lesion in the specific area of the rat brain was made either by radiofrequency current (RL) or microinjection (1μl) of kainic acid (KL), a neurotoxin, by the aid of a stereotaxic instrument. Microinjection of the material in the conscious rats was made through the guide cannula implanted on the skull.

The effect of RL and KL of the OVLT on ACTH response to iv injection of IL-1β (1μg/100 g BW) was examined 1 week post-operatively. IL-1β iv in sham-operated rats induced a significant elevation of plasma ACTH levels at 10 and 30 min postinjection, with peak levels occurring at 10 min to a similar extent as the ACTH response in the intact rats in our previous experiments. Insertion of the electrode for RL into the OVLT without passing a current (sham operation) did not alter basal ACTH levels or the ACTH response to IL-1β one week after the operation. On the other hand, the ACTH response to IL-1β was markedly enhanced in rats with RL of the OVLT, as compared with that of sham-operated animals. ACTH levels in OVLT-lesioned rats were 1.8-fold higher than in sham-operated rats 10 min postinjection of IL-1β. ACTH levels at 60 min postinjection were still higher than the corresponding values. Similarly, an enhanced ACTH response to IL-1β was demonstrated in rats with OVLT lesion induced by 0.3μg kainic acid. ACTH levels 30 and 60 min after IL-1β injection were 2.0 and 3.1 times higher than corresponding values in the sham-operated control rats which received 1μl 0.9% saline. A similar result was obtained in the rats with OVLT lesion induced by 3μg of kainic acid. ACTH levels 10, 30 and 60 min after IL-1β injection iv were 1.9, 2.3 and 5.8 times higher than corresponding values in the sham-operated rats. At 120 min after IL-1β injection, ACTH levels returned to basal levels.
The effect of OVLT lesion on ACTH response to iv injection of IL-1β was also examined 3 weeks post-operatively. The ACTH response in rats with RL and sham-operated control rats was similar. However, in rats with KL the ACTH response remained augmented. The effect of RL of the SFO on ACTH response to IL-1β iv was also examined 1 week post-operatively. RL of the SFO altered neither basal ACTH levels nor ACTH response to IL-1β iv significantly, suggesting that SFO is not the essential area in the pathway through which IL-1 triggers ACTH release.

As mentioned before, iv administration of indomethacin (Idm) (1 mg/100 g BW) completely blocked ACTH response to IL-1β iv in rats. The findings described above suggests that the OVLT may be a site where transduction of blood-borne immune signals carried by IL-1β into neuronal signals may take place; and that non-neuronal elements, not destroyed by RL or KL, in and near the OVLT, such as astrocytes, are involved in ACTH secretion. Studies by others have shown that astrocytes were proliferated by RL or KL and it has also been reported that astrocytes release PGs and microinjection of Idm (10 μg/1 μl saline) into the OVLT 5 min prior to IL-1β iv indeed significantly suppressed the ACTH response. At 10, 30 and 60 min after IL-1β injection, ACTH levels in Idm-pretreated rats were significantly lower than the corresponding values in the control animals. Injection of Idm into the OVLT itself did not alter plasma ACTH levels.

ACTH response to IL-1β was also examined in rats bearing bilateral RL or KL in POA. Control rats were either sham-operated or injected with 1 μl 0.9% saline in the POA one week prior to the experiments with IL-1β iv which resulted in significant elevation of plasma ACTH levels at 10 and 30 min postinjection in these control rats to the same extent as demonstrated in intact animals. On the other hand, in animals with RL in POA, plasma ACTH levels at 10 and 30 min postinjection were reduced to 45 and 60% of levels of sham-operated control rats, respectively. ACTH levels at 10 and 30 min after IL-1β injection in the animals with KL in POA were also reduced to 70 and 65% of the corresponding values of rats which received microinjection of saline in the POA 7 days before the experiment. Neither RL or KL of POA altered basal plasma ACTH levels. It is possible that POA lesion may suppress ACTH release by affecting a common pathway for CRH-ACTH stimulation. Therefore, an experiment was conducted to examine whether RL in the POA would also suppress ACTH release induced by immobilization stress. The increase in plasma ACTH levels resulting from immobilization stress was not diminished by RL in the POA, suggesting the suppression of IL-1β-induced ACTH response by POA lesion is specific.

In other experiment, PGE antagonist (SC-19220) was microinjected into the POA bilaterally (1 μl/1 μl saline) in each side 5 min before injection of IL-1β iv. This treatment completely blocked the ACTH response to IL-1β iv. Microinjection of 1 μl 0.9% saline into the POA did not alter basal ACTH levels or ACTH response to IL-1β iv. On the other hand, microinjection of PGE₂ (1 μg/1 μl saline) into the POA resulted in considerable elevation of plasma ACTH levels over a 2 h period after injection. PGE₁ (1 μg/1 μl saline) also induced significant increase in plasma ACTH levels at 10 min after microinjection, but
to a lesser extent. Microinjection of PGD$_2$ (1 $\mu$g/1 $\mu$l saline) into the POA did not increase plasma ACTH levels. Plasma ACTH levels were also increased at 10, 30 and 60 min after microinjection of PGE$_2$ (2 $\mu$g/1 $\mu$l saline) into the OVLT. However, the ACTH response appeared to be smaller than that resulting from microinjection of PGE$_2$ into the POA. The result suggest that the POA is the primary site of action of PGE$_2$ with regard to the stimulation of ACTH release.

It is interesting that RL and KL of the OVLT resulted in a considerably enhanced ACTH response to IL-1$\beta$ iv one week post-operatively. The magnitude of the response, however, returned to a normal level 3 weeks after placement of RL but still remained enhanced after KL. The pattern observed after RL appears to be similar to the change in febrile response induced by systemic injection of pyrogen that was enhanced 6 days after placement of electrolytic lesion in OVLT in rabbits and rats, and returned to the control level 19 days after the operation. Since physical damage of the brain tissues temporarily increased permeability of the local blood vessels at the site of injury (Klatzo et al, 1958), it is possible that RL also increases permeability of the local blood vessels in the lesioned area. This state of increased vascular permeability persists for 19 days and then returns to normal (Klatzo et al, 1985). It is, therefore, possible that blood-borne IL-1$\beta$ has better access to the brain tissue through the lesioned OVLT 1 week postoperatively, than at 3 weeks postoperatively when vascular permeability has returned to normal. Therefore, the enhanced ACTH response to IL-1$\beta$ iv 1 week after RL in the OVLT might be partly explained by the temporal increase in the vascular permeability resulting from RL. This view, however, is not likely to explain the mechanism of an enhanced ACTH response to IL-1$\beta$ in rats bearing KL of the OVLT which does not damage the vascular structure. An increased ACTH response to IL-1$\beta$ iv persisted 3 weeks after microinjection of kainic acid in the OVLT. Morphological and biochemical studies showed that one of the effects of kainic acid in the brain is increased proliferation of astrocytes for 27 days (Nicklas et al, 1979), which is comparable with our result that ACTH response to IL-1$\beta$ in rats with KL of the OVLT was enhanced for 3 weeks. Mechanical injury of brain tissue, including RL, is also known to stimulate proliferation of astrocytes which produce nerve growth factor for repair of the damaged neuronal tissue. Neuronal cell structures, both cell bodies and fibers, in the OVLT may not be required for IL-1-induced ACTH response, because although RL destroyed these neuronal structures, the ACTH response remained augmented one week after placement of lesion. Therefore, these findings support our postulation that IL-1$\beta$ acts on non-neuronal components, most likely astrocytes in the OVLT. Astrocytes proliferated by lesion or kainic acid may release a larger amount of a mediator which induced the enhancement of ACTH response in response to IL-1$\beta$. Lesion induced by either RL or KL in the POA resulted in an entirely opposite effect on the IL-1$\beta$-induced ACTH response. In this area, lesion suppressed the response. Lesion in the SFO had no effect on the response. Decreased response following POA lesion suggests that the neuronal elements essential for the ACTH response to IL-1$\beta$ were interfered with. In other words, the neuronal structures,
especially kainic acid-sensitive cell bodies, in the POA may play an important role in the transmission of the immune signal to CRH neurons.

Our recent study demonstrated that IL-1β stimulated the release of PGE2 from rat astrocyte cultures, but not from neuron cultures\(^\text{22}\). The present experiment showed that Idm microinjected into the OVLT suppressed IL-1β-induced ACTH release. This finding supports the view that PGs synthesized and released from astrocytes in the OVLT, following entry of blood-borne IL-1β into these tissues, may represent a transduced form for the signal carried by IL-1β to which the neurons respond. Since the POA is located in close proximity to the OVLT, it is possible that PGs diffuse to the POA from the OVLT. The wide spaces, not found elsewhere in the brain, which surround the capillaries in the OVLT and other circumventricular organs may be specialized “pools” for the mixing and rapid interstitial distribution of chemical substances such as PGs. While ion concentrations in the brain cell microenvironment of interstitial fluid (ISF) may be viewed as stable over long periods of time, neuronal function is associated with short-term variations in ISF composition\(^\text{27}\). There are also changes in the concentrations of other chemical components, including classical transmitters, peptides, PGs etc.\(^\text{27}\). Evidence is now accumulating that these dynamic variations are not “noise”, but that they represent “meaningful signals” to neighboring neurons and glial cells\(^\text{27}\). According to this concept, signals may be carried to neighboring cells, or even over longer distances, by neuroactive substances circulating within the isolated milieu of the brain behind the blood-brain barrier.

Neurons in the POA may play an important role in transmitting the immune signal to CRH neurons in PVN. It is possible that these neurons in the POA respond directly to PGs, or indirectly via classical neurotransmitter interneurons. The present study showed that PGE2 microinjected into the POA induced a greater response than injection into the OVLT. Complete abolishment of the ACTH response to IL-1β iv after microinjection of PGE2 antagonist into the POA may substantiate that the target cells for PGE2 involved in the IL-1-induced ACTH response mechanism are present in the POA.

Moreover, IL-1 appears to be synthesized in neurons and astrocytes\(^\text{5, 11}\). IL-1 may also be considered as a growth factor which is involved in repair of damaged neuronal tissues (Neito-Sampedra, Berman, 1988). Whether endogenous IL-1 in the brain is also involved in the ACTH response to blood-borne IL-1 is unclear. Although experimental manipulation such as insertion of an electrode or cannula into the OVLT or POA might stimulate release of endogenous IL-1, the failure to increase plasma ACTH levels in sham-operated animals indicates that involvement of endogenous IL-1 in the acute ACTH response to IL-1 iv is negligible.

It is likely that the neurons in the POA activated by PGE2 transmit the signal to the CRH neurons in the PVN. A recent electrophysiological study by others demonstrated that microapplication of arachidonate in the POA altered the firing rate of some neurons in that area\(^\text{16}\), and that stimulation of the POA by high frequency current resulted in an increased firing of neurons in the PVN and increased plasma corticosterone levels\(^\text{30}\). Moreover, histo-
chemical studies using transport of horseradish peroxidase in the neuronal fibers demonstrated a direct connection between the neurons in the POA and those in the PVN\(^7\).

Based on the present result as well as other studies, we propose the following hypothesis regarding the central mechanism of ACTH release induced by blood-borne IL-1\\beta. Blood-borne IL-1\\beta penetrates the fenestrated endothelium of the OVLT and enters into the perivascular region where it activates the astrocytes abundantly present in this area. These astrocytes then release PGE\(_2\) into interstitial spaces and PGE\(_2\) diffuses, or is transported within the isolated milieu behind the BBB toward its target neurons in the POA. PGE\(_2\) binds its specific neuronal receptors and then activates the neuronal activity which is transmitted to CRH neurons in PVN in the ordinary fashion of neuronal transmission. The activation of CRH neurons in the PVN stimulates the release of CRH from the nerve terminals in the median eminence into the hypophysial portal circulation, thereby stimulating the pituitary corticotrophs. It is well-established that the median eminence is the site where neuronal signals are transduced to humoral signals. In contrast, the OVLT may serve as the gate where the blood-borne-humoral signals enter into the brain tissue and are transduced into neuronal signals, and it may be there that PGE\(_2\) acts as a second messenger for IL-1\\beta-induced ACTH secretion.

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