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Intracerebroventricular infusion of interleukin 1 rapidly decreases peripheral cellular immune responses

(T cell/natural killer cell/interleukin 2/immunosuppression/corticosteroids)

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ABSTRACT **Low doses (50–200 pg or 3.1–12.4 fmol) of interleukin 1 (IL-1) infused into the brain of rats produced rapid suppression of various cellular immune responses in peripheral lymphocytes of rats. Fifteen minutes after infusion of purified IL-1β into the lateral ventricle, natural killer cell activity, response to phytohemagglutinin stimulation, and interleukin 2 production were markedly suppressed in lymphocytes isolated from blood and spleen. These effects were due to infusion of IL-1 into brain since they did not occur when IL-1 was infused into the cisterna magna (essentially posterior to brain) or was injected intraperitoneally. Effects of IL-1 in brain could be blocked by simultaneous infusion of α-melanocyte-stimulating hormone, which is known to block the biological actions of IL-1. To stimulate release of endogenous IL-1 in brain, lipopolysaccharide was infused; this produced similar effects as IL-1, and these effects also were blocked by α-melanocyte-stimulating hormone. At longer intervals after infusion of IL-1 and lipopolysaccharide (3, 6, and 24 hr), immune responses returned to baseline or remained suppressed; i.e., "rebound" immunopotentiation did not occur. Finally, IL-1 infusion suppressed cellular immune responses in adrenalectomized animals, thereby showing that the effects of central IL-1 on peripheral cellular immune responses were, at least in part, independent of the stimulatory effect of IL-1 on secretion of adrenal hormones. These results indicate a link from brain to peripheral immune responses by means of action of a cytokine acting in the brain.**

Interleukin 1 (IL-1), a cytokine originally detected in macrophages, now has been shown to have biological effects when introduced into the brain as well as peripherally. Infusion of IL-1 into the brain induces fever (1) and slow wave sleep (2, 3) and activates the hypothalamic–pituitary axis by increasing the secretion of corticotropin-releasing factor and adrenocorticotrophic hormone (4–7). IL-1 is produced *in vitro* by cells found in brain, such as astrocytes and microglia (8, 9), and IL-1 has been detected in brain following brain injury (10–12). Recently, it has been reported that IL-1 is distributed in the brain in such a manner as to suggest that it functions as a neuromodulator or neurotransmitter (13, 14). Since IL-1 initially was determined to play a crucial role in immunological responses, we investigated whether centrally administered IL-1 would affect immune responses.

MATERIALS AND METHODS

Subjects. Male Sprague–Dawley rats weighing 200–300 g were housed two per cage on bedding for at least 2 weeks after receipt from the shipper. Animals in the colony were kept in enclosed, laminar-flow racks designed by Riley *et al.* (15) in which animals on any given shelf do not come in contact with the odors or noises of other animals in the colony.

Infusion Procedure. Animals were infused through a cannula stereotaxically implanted in the lateral ventricle 4–6 days prior to infusion [for details of cannula construction, surgery, and infusion, see Weiss *et al.* (16)]. For all infusions, the solution was introduced slowly over 8 min. The infusion volume was 20 μl except for the initial dose–response study in which different volumes were used to give different doses of IL-1 (2.5, 5.0, 10.0, and 20.0 μl for 25, 50, 100, and 200 pg, respectively). Following infusion, animals were anesthetized for immunological measurements after an interval of 15 min except in these instances: when lipopolysaccharide (LPS) was infused, a 90-min interval was used to allow for stimulation of IL-1 release; in the time-course experiment, intervals were 3, 6, and 24 hr as indicated; and in the study utilizing adrenalectomized animals, the interval was 1 hr. Rectal body temperatures were taken by telethermometer immediately prior to infusion and again just prior to anesthesia.

Immunological Assays. After blood collection by cardiac puncture and removal of spleens under sterile conditions, mononuclear cells were separated on Ficoll/Hypaque density gradients. Viable lymphocytes were counted by trypan blue dye exclusion. Natural killer (NK) cell activity was determined by the method of Reynolds *et al.* (17). To determine lymphocyte response to a mitogen, 0.1-ml aliquots of lymphocyte suspension [2×10^6 cells per ml in RPMI 1640 medium containing 10% (vol/vol) heat-inactivated fetal calf serum] were mixed with phytohemagglutinin (PHA) at 10 μg/ml. After 3 days, 1 μCi (1 Ci = 37 GBq) of [^{3}H]thymidine was added for 4 hr, cells were then harvested, and the amount of incorporated [^{3}H]thymidine was determined. To determine IL-2 production and IL-2 receptor expression, the methods of Gillis *et al.* (18) and Kuribayashi *et al.* (19) were used. Plasma corticosterone was measured as described by Naylor *et al.* (20).

Statistical Analysis. Each measure was analyzed by analysis of variance. Where a significant overall F score was obtained, comparisons of individual groups were carried out by protected t tests (21). The number of subjects in each of the experiments was as follows: for each group in experiments 1, 3, and 4 (i.e., shown in figures), $n = 4$; for all other experiments, $n = 3$.

RESULTS

Dose-Related Suppression of Peripheral Cellular Immune Responses by Intraventricular IL-1. The results of infusing increasing doses of recombinant IL-1β (Genzyme) into the lateral ventricle are shown in Table 1. For ease of visualization, the results for one of the measures (NK cell activity) are

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Abbreviations: IL-*n*, interleukin *n*; LPS, lipopolysaccharide; NK, natural killer; PHA, phytohemagglutinin; α-MSH, α-melanocyte-stimulating hormone.

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shown in Fig. 1. Fifteen minutes after completion of infusion into the brain, IL-1 markedly decreased, in a dose-dependent manner, the ability of the lymphocytes from blood and spleen to (*i*) lyse ^{51}Cr-labeled targets, (*ii*) respond to PHA, and (*iii*) produce IL-2 upon stimulation. This inhibition was seen relative to responses of lymphocytes from three control groups: (*i*) unoperated animals simply removed from their home cages for measurement (home cage control), (*ii*) cannulated animals handled as were infused animals but receiving no infusion (surgery control), and (*iii*) cannulated animals infused with IL-1 inactivated by heating of the solution for 10 min at 100°C (inactive IL-1). Inhibition of cellular immunological responses was evident in splenocytes of animals infused with 50 pg of IL-1; inhibition of these responses in peripheral blood lymphocytes required the next higher dose. Expression of IL-2 receptors in these cells did not differ significantly from that seen in cells from control animals. Also, no differences were found in the absolute number of lymphocytes counted in blood and spleen.

To determine whether any effects of IL-1 might be due to the vehicle solution that contained 0.1% bovine serum albumin (ultrapure) as a stabilizing protein, an additional experiment was conducted with three groups of animals: home cage controls, animals infused with 20 μl of vehicle, and animals infused with IL-1 (200 pg in 20 μl). Vehicle-infused animals did not differ from cage controls in the measures examined (PHA stimulation of blood lymphocytes and NK cell activity in blood and splenic lymphocytes), while animals infused with IL-1 showed reduced responses as indicated for similarly infused animals in Table 1. Thus, vehicle was not responsible for the effects seen.

Infused IL-1 Acted in Brain. Although it was unlikely that the low doses of IL-1 that affected cellular immune responses when infused into the brain (i.e., 3.1–12.5 fmol, which corresponds to 50–200 pg) exerted these effects by diffusing out of the brain, this possibility was tested directly. The results are shown in Table 2. Infusion of 200 picograms of IL-1 into the lateral ventricle produced the same suppression of cellular immune responses as shown in Table 1. In contrast, infusion of this quantity of IL-1 into the cisterna magna or intraperitoneal injection of IL-1 did not alter peripheral immune responses. Thus, the site(s) that mediates the effects of IL-1 described here is reached by infusion of the peptide into the lateral ventricle and is not reached by injection of peptide into the periphery or infusion posterior to the cerebellum.

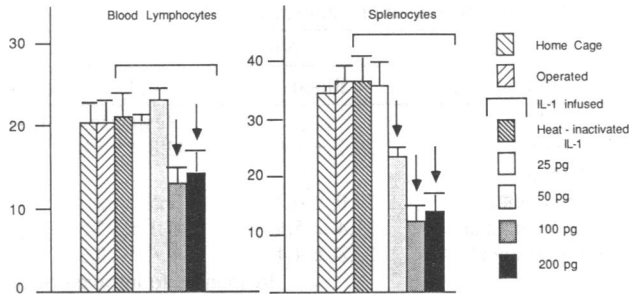

FIG. 1. NK cell activity in groups infused intracerebroventricularly with different amounts of IL-1. Means and SEM are shown; the values given are the percent of target cells lysed. Effector:target cell ratio was 50:1. Lymphocytes were taken 15 min after infusion. ↓, Group differs significantly (at least $P < 0.05$) from each of the three control groups (home cage, operated, and infused with heat-inactivated IL-1).

Blockage of Effects with α-Melanocyte-Stimulating Hormone (α-MSH). The results of infusion of IL-1 (100 pg), α-MSH (10 ng), which has been found to inhibit biological actions of IL-1 (22–25), or both are shown in Table 2. For one measure (NK cell activity), the findings are also shown graphically in Fig. 2. As had been found, IL-1 decreased NK cell activity, lymphocyte stimulation by PHA, and IL-2 production. Animals that received simultaneous administration of α-MSH and IL-1 exhibited immune responses comparable to those seen in control animals; thus, central administration of α-MSH blocked the immunosuppressive effects of IL-1. Infusion of α-MSH alone was without effect.

Intraventricular LPS Depresses Cellular Immune Responses, and This Effect Is Blocked by α-MSH. The results of infusion of 10 ng of LPS, a substance known to stimulate IL-1 release (26, 27), α-MSH (10 ng), or both are shown in Table 2 and Fig. 3. Animals infused with LPS showed significant inhibition of cellular immune responses in spleen and blood taken 90 min after the infusion. α-MSH, which blocks the action of IL-1 without affecting the production of IL-1 (25), eliminated the ability of LPS to suppress peripheral cellular immune responses when simultaneously administered with LPS.

Table 1. Cellular immune response following intracerebroventricular infusion of various doses of IL-1

Condition	NK cell activity*		PHA response†		IL-2 production‡	IL-2 receptor expression§	Steroid concentration¶	Body temp. increase,‖ °C
	Blood	Spleen	Blood	Spleen				
Cage control	21.3 ± 3.2	33.9 ± 1.0	49.0 ± 3.2	31.6 ± 5.0	4.4 ± 0.3	1.17 ± 0.06	13.1 ± 0.9	0.3 ± 0.1
Surgical control	21.2 ± 3.2	35.8 ± 2.8	44.5 ± 3.6	28.3 ± 3.1	3.7 ± 0.2	1.01 ± 0.09	13.1 ± 1.0	0.6 ± 0.2
Inactive IL-1	21.0 ± 2.6	36.0 ± 4.6	46.8 ± 5.3	30.0 ± 3.9	4.6 ± 0.3	1.00 ± 0.13	13.1 ± 2.0	0.9 ± 0.1
IL-1 (pg)								
25	21.2 ± 0.4	35.6 ± 4.7	45.3 ± 2.9	31.7 ± 4.0	4.0 ± 0.2	0.95 ± 0.09	14.3 ± 1.0	0.2 ± 0.1
50	22.9 ± 1.8	22.9 ± 1.6**	41.4 ± 2.6	19.6 ± 1.8**	3.1 ± 0.5††	0.99 ± 0.09	20.4 ± 0.6**	0.7 ± 0.2
100	13.0 ± 1.7**	12.6 ± 3.9**	29.1 ± 3.0**	12.0 ± 3.0**	2.4 ± 0.3**	1.02 ± 0.09	24.5 ± 3.3**	0.7 ± 0.3
200	13.4 ± 2.4**	13.6 ± 2.6**	26.8 ± 2.2**	11.4 ± 2.6**	2.5 ± 0.2**	1.16 ± 0.05	23.0 ± 7.9**	1.0 ± 0.3

Measures of NK cell activity, response to PHA, IL-2 production, and IL-2 receptor expression are the response of an equivalent number of cells from each condition. Values are the means ± SEM.

*Blood and spleen indicate the source of lymphocytes. Values are the percentage of target cells lysed. The effector:target cell ratio was 50:1.

†Blood and spleen indicate the source of lymphocytes. Values are the cpm × 10^{-3} of incorporated [^{3}H]thymidine.

‡Values are cpm × 10^{-2} of incorporated [^{3}H]thymidine. IL-2 production is the response of PHA-stimulated (48 hr, 10 μg/ml) lymphocytes; IL-2 in the supernatant was measured by incorporation of [^{3}H]thymidine into IL-2-dependent CTLL cells for which the supernatant is the sole source of IL-2. IL-2 production was assessed in splenic lymphocytes.

§Units of IL-2 adsorbed by PHA-stimulated lymphocytes during incubation at 0°C with 2.0 units of IL-2. IL-2 receptor expression was assessed in splenic lymphocytes.

¶The concentration is the number of micrograms of steroid per 100 ml of plasma.

‖Change in body temperature (temp.) from the initial temperature before infusion to the temperature just prior to anesthesia.

**Group mean differs significantly (at least $P < 0.05$) from each of the three control conditions (cage control, surgically cannulated control, and cannulated animals infused with heat-inactivated IL-1).

††Group mean differs significantly from cage controls and animals infused with heat-inactivated IL-1.

Table 2. Cellular immune responses to IL-1

Condition	NK cell activity		PHA response		IL-2 production	Body temp. increase
	Blood	Spleen	Blood	Spleen		
Responses to IL-1 given in different locations						
Cage control	29.1 ± 3.6	42.8 ± 5.8	28.8 ± 5.2	53.2 ± 7.7	7.3 ± 0.9	
IL-1 (200 pg)						
Lateral ventricle	10.0 ± 0.7*	15.5 ± 2.7*	15.0 ± 1.9*	8.7 ± 2.4*	3.0 ± 0.7*	
Cisterna magna	31.4 ± 5.6	48.1 ± 5.5	34.8 ± 7.3	45.1 ± 6.8	6.4 ± 0.8	
Intraperitoneal	22.8 ± 4.4	44.6 ± 8.3	26.2 ± 5.4	66.2 ± 4.0	7.7 ± 0.7	
Responses to intraventricular IL-1 and an IL-1 inhibitor (α-MSH)						
Cage control	29.0 ± 4.8	39.4 ± 1.0	42.9 ± 3.3	26.8 ± 3.6	3.1 ± 0.3	0.3 ± 0.1
IL-1 (100 pg)	16.6 ± 3.4*	10.8 ± 2.9*	15.5 ± 1.5*	9.2 ± 1.1*	2.0 ± 0.2*	0.6 ± 0.4
α-MSH (10 ng)	30.4 ± 3.4	39.6 ± 0.8	45.3 ± 2.7	24.5 ± 4.8	3.6 ± 0.3	0.3 ± 0.3
IL-1 + α-MSH	30.8 ± 2.4	37.0 ± 2.2	38.5 ± 4.2	20.9 ± 4.0	3.0 ± 0.3	0.6 ± 0.3
Responses to intraventricular LPS and an IL-1 inhibitor (α-MSH)						
Cage control	31.4 ± 2.8	49.8 ± 10.6	NT	23.8 ± 1.8	2.7 ± 0.2	−0.3 ± 0.3
LPS (10 ng)	16.3 ± 3.8*	16.8 ± 2.3*	NT	12.4 ± 1.3*	1.6 ± 0.1*	−1.0 ± 0.2*
α-MSH (10 ng)	34.5 ± 1.4	43.2 ± 10.9	NT	20.0 ± 2.1	2.9 ± 0.2	0.4 ± 0.2
LPS + α-MSH	33.8 ± 2.5	48.0 ± 5.2	NT	19.3 ± 2.2	2.4 ± 0.1	0.4 ± 0.2

NK cell activity, PHA response, IL-2 production, and body temperature increase were determined as described in Table 1. NT, not tested. *Group mean differs significantly from each of the other three groups in the study.

Effects of IL-1 and LPS at Longer Intervals After Infusion. The results of infusion of IL-1 (200 pg), LPS (10 ng), or vehicle on cellular immune responses at 3, 6, and 24 hr after infusion are shown in Fig. 4. After IL-1 infusion, suppressed responses were present 3 hr later as they were after 15 min in earlier experiments. IL-1-induced suppression for most measures was not seen 6 or 24 hr after infusion. The only exception was NK cell activity, for which the response of splenic lymphocytes was still suppressed 6 hr after infusion, whereas blood lymphocytes showed a small but statistically significant elevation above vehicle-injected animals at 6 hr. The elevation in NK cell activity seen in blood lymphocytes 6 hr after IL-1 infusion was the only instance where an infusion produced a response elevated above vehicle-injected animals; however, the size of this effect and the absence of such elevation at 24 hr suggest that this change is not of importance. LPS infusion produced suppression of cellular immune responses that generally persisted across all time points measured after infusion, through 24 hr. It is unclear why suppression of NK cell activity in LPS-infused animals failed to reach statistical significance in blood lymphocytes 3 hr postinfusion; this would appear to be an anomaly in this particular experiment.

Effect of IL-1 Infused into Adrenalectomized Animals. Plasma steroid concentrations at the time of sacrifice following infusion of different doses of IL-1 are shown in Table 1. The results show that IL-1 in excess of 25 pg stimulated steroid secretion above the levels seen in control groups. However, these values in the control groups were all much higher (approximately 13.0 μg/dl) than values normally obtained for untreated animals in our laboratory. The elevated steroid levels of control groups probably resulted from the anesthesia procedure; ≈5 min elapsed after animals were injected with pentobarbital before they completely lost consciousness to enable the blood sample to be drawn. Consequently, four additional animals were infused with 200 pg of IL-1 and three control animals were infused with vehicle; these animals were sacrificed rapidly by decapitation (instead of pentobarbital) 15 min after infusion. In vehicle-injected control animals sacrificed in this way, the mean (± SEM) steroid concentration was 1.06 ± 0.16 μg/dl while the value for each of the four IL-1-infused animals exceeded the peak value of 20 μg/dl that could be measured in the steroid assay used. These results therefore show that control conditions did not elevate steroids prior to anesthesia, whereas steroid concentrations were elevated markedly by IL-1 infusion.

To determine whether elevated plasma steroids resulting from IL-1 infusion played a role in the suppression of cellular immune responses seen in earlier experiments, IL-1 (100 pg) was infused into adrenalectomized animals (adrenalectomy performed at time of cannula implantation) and normal (sham-operated) animals. The results are shown in Fig. 5. Suppression of immune responses following IL-1 was less pronounced in adrenalectomized than in sham-operated animals. However, IL-1 infusion into adrenalectomized animals nevertheless produced statistically significant suppression of all cellular immune responses suppressed in normal animals. Thus, adrenalectomy did not eliminate suppression of cellular immune responses produced by IL-1 in brain.

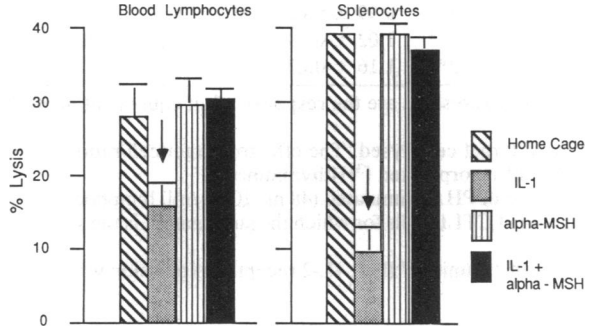

FIG. 2. NK cell activity in groups infused with IL-1 (100 pg), α-MSH (10 ng), or both. Other details are as given in Fig. 1. ↓, Differs significantly from each of the other groups.

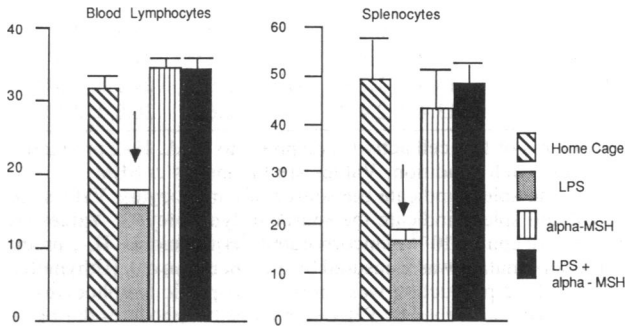

FIG. 3. NK cell activity in groups infused with LPS (10 ng), α-MSH (10 ng), or both. Lymphocytes were taken 90 min after infusion. Values are percent of target cells lysed. ↓, Differs significantly from each of the other groups. Other details are as given in Fig. 1.

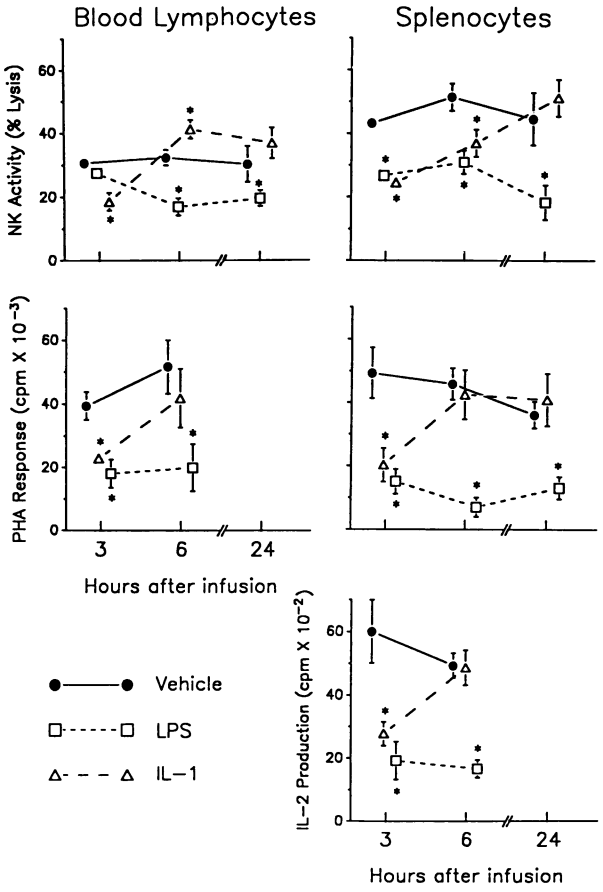

FIG. 4. NK cell activity, response to PHA, and IL-2 production in groups infused with IL-1 (200 pg), LPS (10 ng), or vehicle, with lymphocytes taken 3, 6, and 24 hr after infusion. Means ± SEM are shown. $n = 3$ for each group at each time point. Measures were not made of PHA response in blood lymphocytes or IL-2 production in splenocytes at 24 hr. *, Differs significantly from vehicle-infused animals at the same time point.

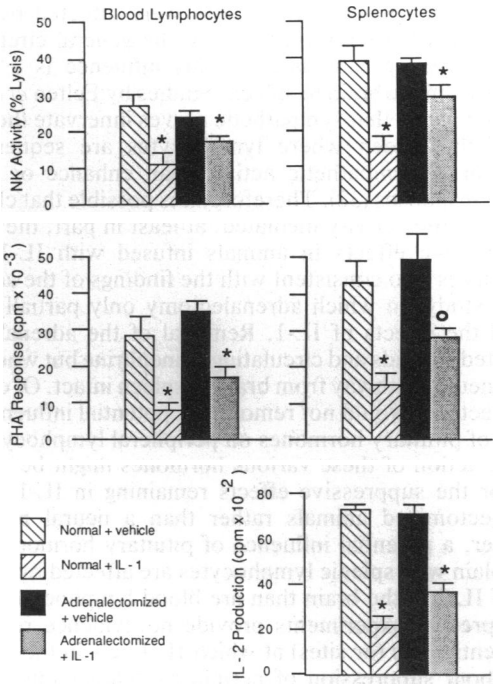

FIG. 5. NK cell activity, response to PHA stimulation, and IL-2 production of lymphocytes from normal animals and adrenalectomized animals infused with either vehicle or IL-1 (100 pg). Means and SEM are shown. Steroid values measured at sacrifice were (in μg/dl) normal + vehicle, 30.8 ± 1.6; normal + IL-1, 41.0 ± 3.9; adrenalectomized + vehicle, 0.6 ± 0.1; adrenalectomized + IL-1 = 0.6 ± 0.1. The first two groups differ significantly from one another, and the last two groups differ from each of the first two. No differences in IL-2 receptor expression were found between the groups. Statistical significance is designated as follows: *, Differs significantly from normal + vehicle and adrenalectomized + vehicle; ○, differs significantly from normal + vehicle, adrenalectomized + vehicle, and normal + IL-1.

DISCUSSION

Femtomole concentrations of IL-1 infused into the lateral ventricles result in suppression of cellular immune responses. Effects were present 15 min after the conclusion of an 8-min infusion of IL-1. The time course of these effects reveals that suppressed responses of lymphocytes from blood and spleen persist for hours after infusion of either IL-1 or LPS and that the rapid suppression of cellular immune responses to IL-1 in the brain is not a transient precursor to subsequent "rebound" enhancement of immune responses.

LPS injected into the brain also suppressed peripheral immune responses. As noted earlier, LPS is known to stimulate release of endogenous IL-1 (26, 27), and LPS was infused to determine whether release of endogenous IL-1 in brain would suppress peripheral immune responses. However, LPS is a bacterial endotoxin and might have acted by means of some nonspecific toxic action rather than by means of release of IL-1. Infusion of α-MSH blocked the suppression of immune responses produced by LPS infusion into the brain, suggesting that LPS acted through endogenously released IL-1. At the least, any other mediator of the LPS effect also would have to be blocked by α-MSH in brain.

The mechanism by which intracerebroventricular IL-1 leads to suppression of the cellular immune responses appears not to depend upon a pyrogenic action of IL-1. As shown in Table 1, no pyrogenic effect was evident 15 min after infusion of doses used in the present study; at this time, only a small temperature increase was seen in the infused groups, and similar increases were seen in control infused animals, apparently as a result of handling and other procedures involved in the infusion. Moreover, suppression of immune parameters was evident in animals infused with LPS; these animals showed a *decrease* in body temperature, an effect that has been observed previously (28).

A likely mechanism by which IL-1 introduced into brain might suppress peripheral immune responses is by raising the circulating level of glucocorticoids (29, 30). As noted earlier, IL-1 stimulates secretion of glucocorticoids (4–7), and this was observed in the present study even with the very low doses of IL-1 infused (see Table 1). IL-1 was infused into adrenalectomized animals to test directly whether suppressed immune responses following IL-1 infusion into brain depended on elevation of plasma glucocorticoids. Approximately 50% of the suppression of immune responses produced by intraventricular IL-1 infusion in normal animals was seen in adrenalectomized animals despite the absence of adrenal hormones. Thus, circulating glucocorticoids may well contribute to the suppression of cellular immune responses produced by IL-1 infusion but do not account for the entire effect.

The results described in the previous paragraph, as well as other observations, point to the likelihood that a neural pathway is involved in mediating the suppression of peripheral immune responses seen in these studies. Perhaps the strongest suggestion of this comes from the initial dose–response study, which revealed that splenic lymphocytes were suppressed by the 50-pg dose of IL-1 that had no effect on blood lymphocytes; not until the next higher dose of 100 pg did blood lymphocytes show suppressed responses. This

indicates that splenic lymphocytes were affected by some influence apart from any present in the general circulatory system. A likely candidate for this influence is a neural pathway from the brain to spleen. Studies by Felten *et al.* (31) have established that sympathetic nerves innervate the white pulp of the spleen where lymphocytes are sequestered. Alteration of sympathetic activity can enhance or inhibit immune responses (32). Therefore, it is possible that changes in sympathetic activity mediated, at least in part, the immunosuppressive effects in animals infused with IL-1. This possibility is also consistent with the findings of the adrenalectomy study, in which adrenalectomy only partially ameliorated the effects of IL-1. Removal of the adrenal gland eliminated steroids and circulating epinephrine but would still leave a neural pathway from brain to spleen intact. Of course, adrenalectomy would not remove the potential influence of a variety of pituitary hormones on peripheral lymphocytes, so that the action of these various hormones might be responsible for the suppressive effects remaining in IL-1-infused adrenalectomized animals rather than a neural pathway. However, a potential influence of pituitary hormones does not explain why splenic lymphocytes are affected by a lower dose of IL-1 in the brain than are blood lymphocytes.

The present experiments provide no evidence regarding the potential site (or sites) at which IL-1 acts in the brain to bring about suppression of peripheral cellular immune responses. Several authors have suggested that IL-1 may act through one of the circumventricular organs, the organum vasculosum lamina terminalis (33–35). IL-1 introduced into the lateral ventricle clearly would have ready access to this structure because it lies in the ventricular system just posterior to the lateral ventricle. LPS, which had similar immunological effects in the present experiments as did IL-1, might also have induced release of IL-1 into the ventricular system and thereby operated through the same site. However, the present study provides no evidence as to where in the brain IL-1 was released as a consequence of intraventricular LPS, so it is also possible that LPS caused IL-1 to be released at some other site to produce the immunological changes measured. Although there is presently no evidence that IL-1 in peripheral circulation can enter the brain, the concentrations infused in the present experiment that effectively suppressed immune responses were sufficiently low that some crossover of IL-1 from peripheral circulation might be sufficient to produce these responses. It should be noted that fragments of IL-1 appear to possess biological activity (36); whether such fragments of IL-1 might ever gain access to the brain from the peripheral circulation remains to be demonstrated.

As a final observation, the fact that α-MSH blocked suppression of cellular immune responses produced by both exogenous IL-1 and endogenous IL-1 stimulated by LPS is noteworthy. Recent evidence (37) indicates that IL-1 activates the gene for proopiomelanocortin, a product of which is α-MSH. Consistent with this is the observation that during fever, a response most commonly mediated by IL-1, α-MSH is elevated (38, 39). Thus, whereas IL-1 in the brain is capable of suppressing various cellular immune responses (present data), this effect is inhibited by α-MSH, which IL-1 appears to stimulate. This suggests that suppression of cellular immune responses by IL-1 in brain is of sufficient biological significance to be subject to negative feedback. In this regard, historically IL-1 has been associated with promotion of peripheral cellular immune responses as an important element in the elaboration of the overall immune response (e.g., ref. 1). Injection of large doses of IL-1 into the periphery indeed has been shown to promote immune responses (40). The relationship between rapidly mobilized suppression of cellular immune responses mediated by IL-1 in brain and the promotion of immune responses by IL-1 in the periphery remains to be determined.

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