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Neuromodulative Actions of Cytokines

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Interleukin 1, interferon α_2, and tumor necrosis factor α are cytokines that centrally mediate various reactions typical of the host defense responses to infection. The preoptic-anterior hypothalamus is an important, but not exclusive, integrative and controlling region for several of these effects. Although these cytokines display some common functional activities (e.g., pyrogenicity, somnogenicity), the characteristics of the responses they induce are different. Their effects, moreover, can be evoked or suppressed selectively, indicating that the neuronal substrates and/or neuromodulators used are distinct, each possessing discrete but partially overlapping sensory combinations. Nevertheless, it is not yet obvious how these systems are organized and integrated in host defense. It is also unclear whether these cytokines are elaborated peripherally and gain access to the brain or whether they are induced centrally. The available data suggest that circulating cytokines probably do not penetrate the brain but may activate elements in the organum vasculosum laminae terminalis. This site appears to be critically important for the production of the centrally mediated effects of blood-borne cytokines; it is speculated that the cytokines evoke there local signals that transduce their message; serotonin may be linked to these signals.

Fever is the most manifest and best known sign of infection [1]. Infected animals of many species characteristically exhibit an array of other signs as well, however, including increases (e.g., acute-phase proteins, copper) or decreases (e.g., albumin, iron) in the concentrations of various plasma constituents, neutrophilic leukocytosis, increased sleepiness, reduced appetite, hyperinsulinemia and hyperglucagonemia with consequent alterations in blood glucose levels, changes in the circulating levels of certain pituitary peptides (e.g., adrenocorticotropic hormone), and enhancement of certain immune functions [2–4]. It is well known that fever is a centrally regulated response, induced by the action, predominantly in the preoptic area of the anterior hypothalamus (POA), of endogenous substances liberated primarily by activated mononuclear phagocytes, but also by many other cell types. Originally, these substances were thought to be but one, and it was called leukocytic pyrogen (LP) [5]. Today, we know that LP was a mixture of factors belonging to a class now termed cytokines, produced by cells of the immune system. Indeed, several cytokines have been shown to be pyrogenic: interleukin 1 (IL-1), tumor necrosis factor α (TNF), interferon

Abbreviations: ACTH: adrenocorticotropic stimulating hormone AV3V: anteroventral third ventricle CNS: central nervous system CRF: corticotropin releasing hormone CSF: cerebrospinal fluid hr: human recombinant 5HT: serotonin icv: intracerebroventricular(ly) IFN: interferon-α_2 IL: interleukin ip: intraperitoneal(ly) iPO: intrapreoptic(ally) iv: intravenous(ly) LP: leukocytic pyrogen LPS: lipopolysaccharide (endotoxin) MO: medulla oblongata OVLT: organum vasculosum laminae terminalis PG: prostaglandin POA: preoptic area of the anterior hypothalamus TNF: tumor necrosis factor α VMH: ventromedial hypothalamus

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α_2 (IFN), interleukin 6 (IL-6), and macrophage inflammatory protein 1 [6–9]; IL-1 exists in two biochemically distinct forms, α and β, which share many, but not all, of each other's bioactivities [2]. We now know, in addition, that these cytokines also mediate various other systemic responses typical of infection, and lately it has become apparent that several of these, too, are mediated centrally. Indeed, that the central nervous system (CNS) plays a major role in the modulation of host defense responses against infection is no longer in doubt [10].

The purpose of this paper is to review briefly what is currently known regarding the sites and modes of actions in the brain of these cytokines/endogenous pyrogens in prompting their multiple responses. IL-6 and macrophage inflammatory protein 1, however, will not be considered in this context, as they have as yet been insufficiently studied.

IMMUNE SIGNAL TRANSDUCTION BY THE BRAIN

Since endogenous pyrogens are thought to be produced peripherally and since, moreover, their intravenous (iv) injection induces fever, a centrally regulated thermoregulatory response, after a relatively short latency, it has generally been assumed that the effective cytokines are released systemically and transported to the brain by the blood. It has not yet been possible, however, to demonstrate that endogenous pyrogens cross the blood-brain barrier and localize in any brain site. Indeed, being water-soluble peptides, cytokines would not be expected to cross the blood-brain barrier readily without specific carrier systems, of which, so far, none have been identified. But the cytokines might pass into the brain through the circumventricular organs, which have no blood-brain barrier [11]; to wit, the organum vasculosum laminae terminalis (OVLT) and the area postrema are located close to cytokine-sensitive, fever-producing sites in the medial preoptic area and the medulla oblongata (MO), respectively (see below). Indeed, we showed [12,13] in guinea pigs and sheep that ablation of the vascular plexus of the OVLT, in the anteroventral third ventricular wall (AV3V), results in the suppression of the fever and acute-phase proteinemia evoked by intraperitoneally (ip) administered lipopolysaccharide (LPS). But in rats and rabbits, on the other hand, Stitt [14] found that small lesions of the ventrorostral OVLT transiently enhance the febrile responsiveness to semipurified IL-1 given iv. Very recently, however, we found again [15] that AV3V lesions attenuate the fevers caused in guinea pigs not only by ip injected LPS, but also by iv injected LPS, IL-1β, IFN, and TNF. Destruction of the AV3V did not affect the pyrogenic sensitivity to intrapreoptically (iPO) injected IL-1 [12] or the normal thermoregulation of these animals [16]. Thus, these data indicate that the integrity of the vascular plexus of the OVLT is critically important for the induction of centrally mediated responses to systemically elaborated or injected cytokines. One might then presume that the lack of a blood-brain barrier at this site would allow circulating endogenous pyrogens to pass through the fenestrated endothelium and perivascular spaces into the clefts of the OVLT. It is not clear, however, how these substances would penetrate deeper into the neuropil since tight junctions surround the OVLT interstitium, preventing free diffusion into the POA or adjacent third ventricle. Indeed, no IL-1 has as yet been detected in the hypothalamus of rabbits [17] or in the ventricular cerebrospinal fluid (CSF) of cats [18] at any stage of their febrile course after iv administered pyrogens. We, too [19], have been unable to find any trace of human recombinant (hr) ^{125}I-IL-1α anywhere within the brains of guinea pigs 5 to 60 minutes after injection of pyrogenic doses of this compound into an

internal carotid. Thus, circulating cytokines may not actually pass into the neuropil, but rather may activate certain critical elements contained within the OVLT that, in turn, may evoke secondary signals that transduce their message. It has been proposed that prostaglandin (PG) E, which is pyrogenic when applied locally into the POA, may be such a second mediator [20]. A possible target of circulating IL-1 could be certain mesenchymally derived phagocytic cells reportedly extant within the perivascular space of the OVLT, which presumably are capable of releasing PGE [14]. Since this lipophilic molecule is able to diffuse across the blood-brain barrier [21], an alternative target of IL-1 could be the endothelial cells of the OVLT; endothelial cells release prostanoids in response to fentomolar concentrations of IL-1 within seconds after exposure. interestingly without demonstrable IL-1-specific receptor binding [22]. Whatever the source of the PGE, a difficulty with the concept is that the diffusion time of PGE from the OVLT to the POA is longer than the latency of the febrile response to IL-1 given iv; however, PGE could act initially and directly on neurons in the OVLT. Indeed, Stitt [20] has reported that the OVLT region of rats is markedly more sensitive to the pyrogenic action of PGE than is the POA. On the other hand, we found in guinea pigs [23] that PGE and IL-1 in doses that are pyrogenic when administered into the POA are ineffective when microinjected into the OVLT. Although this discrepancy could be accounted for simply by species differences, it is noteworthy that IL-1-induced phospholipase A_2 appears later *in vitro* in fibroblasts of rats [24] than the onset of fever following IL-1 *in vivo* in guinea pigs [23]. Since all the biological effects of the cytokines are not modulated by PGE (see below), an alternative possibility could be that the cytokines are somehow detected by sensory elements in the OVLT and transduced into neuronal signals that are transmitted to the POA. In support, we recently found [25] that certain OVLT neurons in brain slice preparations from guinea pigs were excited by hrTNF; these units also were excited by serotonin (5HT). 5HT terminals are abundant in the OVLT and may, therefore, have a role in transmitting these signals. It is conceivable that blood-borne cytokines could by this means induce the release of glial [26–30; Bakouche and Lachman, this issue] and/or neuronal [31–33] second messengers. If so, secondarily brain-synthesized rather than originally evoked peripheral endogenous factors might be the ultimate central mediators of host defense mechanisms. Since the induction of new cytokines is slow, these factors could be different, locally stored neuromodulators; however, this and other possibilities remain speculative at present.

LOCALIZATION OF CYTOKINE ACTIONS IN THE BRAIN: THE PREOPTIC AREA

Fever

Evidence that discrete brain sites activate febrigenic responses was derived primarily from studies in which cytokines were microinjected into various brain regions initially selected on the basis of their demonstrated involvement in temperature regulation (reviewed in [34]). Thus, such studies have established that IL-1, TNF, and IFN elicit the most rapidly developing and most intense febrile responses when delivered into the POA. Interestingly, however, the courses of the fevers each cytokine evokes are distinct [35]. Thus, the fevers produced by IL-1 are generally quick in onset, unimodal, and relatively brief. Those induced by TNF, by contrast, are bimodal and somewhat prolonged, while those caused by IFN, although unimodal, are more protracted and

develop after longer latencies than those provoked by IL-1. The bases for these differential patterns are not yet known, but they could be related to the involvement in these responses of distinct second messengers and/or neuronal substrates (see below).

Acute-Phase Proteinemia

Many studies have established that perfused livers and primary cultures of hepatocytes incubated with IL-1 secrete acute-phase proteins into the medium [36], and it has been shown that IL-1 specifically modulates the pre-translational expression of the genes for several proteins in human and rat hepatocytes [37]. In additon to this direct effect, however, IL-1 may also modulate acute-phase protein hepatic synthesis indirectly through an action on the CNS. This possibility was originally suggested by observations that intracerebroventricular (icv) injections of IL-1 induce, in addition to fever, several of the blood chemical changes typical of IL-1's effects following its systemic administration [38,39]. We have shown that the locus of this central mediation is also the POA [40]. Injections of IL-1 into this site augment the plasma levels of copper (hence ceruloplasmin, to which virtually all plasma copper is bound) and of protein-bound N-acetylneuraminic acid (the terminal residue of most plasma glycoproteins) similar to the responses induced by ip injection, although the iPO dose was one order of magnitude smaller than the ip dose; such a small dose does not induce either fever or hyperproteinemia when injected systemically. TNF and IFN do not, however, share this activity with IL-1 when given centrally [41–43], although TNF reportedly induces elevations of acute-phase protein plasma levels, both when given peripherally and *in vitro* [44,45]. It was recently reported that the POA also mediates the IL-1-induced leukocytosis of rats [46].

Other Host Defense Responses

Further evidence of POA involvement in cytokine-mediated host defense responses is provided by other demonstrations that the central administration of microquantities of cytokines enhances slow-wave sleep in rabbits [Krueger et al., this issue]; a hypnogenic controller has been identified in, among other loci, the POA [47]. The iPO administration of IL-1 also induces a prompt hyperinsulinemia in anesthetized, fasted rats [48], similar to its effect when given iv at ten times the dose, indicating that, in addition to its direct modulating influence on pancreatic islets [49], it also induces a signal in the hypothalamus for pancreatic insulin secretion. It has not yet been reported whether the latter effect is also inducible centrally by TNF and IFN, and whether thus evoked sleepiness and hyperinsulinemia survive OVLT lesions.

Extra-POA Sites: Persistence of IL-1 Effects After POA Lesions

Although the POA is the preeminent site driving the febrigenic and other responses to IL-1, TNF, and IFN, these responses remain relatively unimpaired when the POA is disconnected from the brain by various means (reviewed in [34,50,51–52]). These results indicate, therefore, that additional sites exist outside the POA that are also capable of mediating these effects. Indeed, sites in which microinjections of IL-1 evoke fever have variously been localized in the lateral hypothalamus, midbrain reticular formation, pons, and MO of guinea pigs and rabbits [23,53,54]; MO temperature-sensitive units have also been shown to respond appropriately to locally applied crude IL-1 [55,56]. The heights and durations of the febrile responses elicited from these extra-POA loci progressively diminish, however, as their distance from the POA

increases. Moreover, by microcutting each reactive site from its connections upstream or downstream, then microinjecting IL-1 above or below the cuts, we showed [57] that the lateral hypothalamus and pons are not independent pyrogenic controllers because IL-1 injected locally into these sites did not induce fever when they were disconnected from the POA above while connected to the thermoeffectors below. Only the MO appeared capable of autonomous control, as microinjection of IL-1 into this site when it was separated from the rest of the brain above still elicited fever [57]. The precise boundaries of these various controllers and their functional interconnections are as yet unclear. It is also not yet known whether any of these extra-POA fever-producing sites are similarly capable of driving other acute-phase actions of the cytokines. Although IL-1 receptors are widely distributed throughout the brain [58], the injection of this cytokine into the cerebellum or cortex does not produce pyrogenic effects (reviewed in [34]); other possible effects have not yet been measured.

OTHER CENTRAL ACTIONS OF CYTOKINES

Food Intake

IL-1 and TNF have also been implicated in cachexia. Their systemic administration induces anorexia and weight loss [59–61], as occurs in infectious disease [62,63]. It was recently reported [64] that icv injections of hrIL-1β and hrTNF suppress nighttime feeding and prandial drinking in rats. Glucose-sensitive neurons in the lateral hypothalamic area thought to be involved in the regulation of food intake are depressed by the electrophoretic application of these cytokines, consistent with the functional data and suggestive of the participation of hypothalamic feeding-associated sites in the suppression of feeding by these factors. To what extent the decrease in food intake may also be attributable to, for example, IL-1-induced hyperinsulinemia and sleepiness, or to other immunomodulators that may be elaborated and provide regulatory signals to feeding cannot, however, be evaluated at present [65,66].

Neuroimmunoendocrine Responses

Recent evidence indicates that IL-1 and TNF, but not IFN, modulate the secretion of various pituitary peptides, including prolactin, growth hormone, thyrotropin-releasing hormone, adrenocorticotropic hormone (ACTH), and luteinizing hormone-releasing hormone [67–69]. It is currently under debate whether IL-1 or TNF acts directly on the pituitary cells or on the hypothalamic sites of their releasing factors to produce these effects [70–72]. Their importance lies in that these peptides provide one of the means by which the central nervous and immune systems may communicate [73,74]. The precise brain loci of their actions are not yet known, but some recent evidence suggests that the POA may be the site wherein IL-1 and TNF initiate the secretion of corticotropin-releasing factor (CRF) and that the OVLT may be involved in this process [75,76; Saphier et al., this issue]. The neurons involved in this response have not yet been characterized, but it has long been known that exogenous pyrogens and thermal stimulation of the POA evoke elevations of plasma glucocorticoids, thereby implicating thermosensitive units in this effect [77,78]. Furthermore, there is evidence in rabbits that cortisone, $ACTH_{1-24}$, and CRF may participate in antipyresis [79], while in rats, by contrast, IL-1β-induced fever may require CRF [80]. The antipyretic activity of ACTH may, in fact, be due to a fragment of $ACTH_{1-24}$, α-melanocyte-stimulating hormone or $ACTH_{1-13}$, which not only blocks the fever, but

also the acute-phase hyperproteinemia [81; Lipton, this issue], somnogenesis [81], and certain inflammatory and immune effects of IL-1 [87].

NEURAL BASIS OF CYTOKINE ACTIONS

Neural Connections Involved in IL-1 Actions

There is some evidence that the ventromedial hypothalamus (VMH) may contain fibers of passage that modulate IL-1 effects, as horizontal separation of the POA from the VMH attenuates the fevers produced by systemic injections of exogenous pyrogens [83]; PGE and IL-1 microinjected into the VMH, however, do not evoke thermal responses [23]. The posterior hypothalamus also seems necessary for fever production, since its destruction abolishes the febrile response to systemic pyrogens [84]; however, direct injection of IL-1 into the posterior hypothalamus does not elicit a febrile response [53,85,86].

Neuronal Correlates of the Functional Effects of the Cytokines

The POA and MO, among other brain regions, contain neurons that are sensitive to small changes in their local temperatures [87]. Two types have been identified: warm-sensitive neurons, the firing rates of which increase with local warming and decrease with local cooling, and cold-sensitive neurons, the firing rates of which, conversely, increase with local cooling and decrease with local warming. The directions of the changes in the electrical activities of these neurons are well correlated with the thermoeffector responses induced by the relevant stimuli; i.e., excitation of warm-sensitive neurons is associated with heat loss responses, while that of cold-sensitive neurons is associated with heat production responses. Consistent with the diminished heat loss and enhanced heat production that underlie the development of fever [88], the febrile rise induced by each of the three cytokines under review is associated with decreased activity of warm-sensitive and increased activity of cold-sensitive neurons in the POA and MO [89; Shibata, this issue]. It is not yet clear, however, whether these units are the direct targets of the cytokines. Thus, although localized cooling of the POA induces thermoregulatory responses typical of fever, this effect cannot be construed as evidence that the cytokines act specifically on the warm or cold population of thermosensitive units. Indeed, a significant proportion of thermo*in*sensitive units is also affected by these cytokines [Shibata, this issue]. Interestingly, few individual neurons exposed *in vitro* to all three cytokines or to PGE respond identically to all, or even to any two, of these substances [35,90; Shibata, this issue]. The thermosensitive neurons in the POA do not appear to be involved, however, in the control of the acute-phase protein response to IL-1; *viz.*, POA cooling or heating does not induce any change in the plasma levels of acute-phase reactants [91]. These results suggest, therefore, that the central actions of IL-1 intiating these *non*febrile acute-phase effects do not involve the thermosensitive neurons in the POA. Hence, the units postulated to be driving the febrile and these nonthermal responses to IL-1 are distinct. Thermosensitive units may, however, be implicated in the IL-1- and TNF-induced neuroendocrine response; *viz.*, it has long been known that hypothalamic heating or cooling, as well as the administration of pyrogens increases the secretions of, among others, ACTH and glucocorticoids [77,78]. Some evidence also exists showing that preoptic thermosensitive neurons may be involved in immunostimulation: both heating and cooling of the POA cause elevated antibody titers [92,93]. These responses occur independently of

the direction of body temperature changes [94], however, and only the primary humoral immune response is affected [95]. Similarly, both localized preoptic heating and stimulation with capsaicin (which specifically excites warm-sensitive neurons [96]) induce slow-wave sleep-like electroencephalographic synchronization in rats [47,97,98]; these results are consistent with the sleepiness often experienced in moderately warm environments. But the neurons facilitated in this instance, i.e., warm-sensitive neurons, are generally inhibited by the cytokines, albeit these factors are somnogenic. This paradox further illustrates the variety and distinctiveness of neurons sensitive to these cytokines.

Lately, preoptic thermosensitive neurons have also been found to be osmo-, reproductive hormone-, and glucose-sensitive [99,100]. It is thus possible that the integration of host defense responses is accomplished through the activation of a neuronal circuit that permits interactions among these multivariate functions.

PUTATIVE MEDIATORS OF THE CENTRAL ACTIONS OF CYTOKINES

Various neurochemical substances that influence, in particular, the febrile response to cytokines have been identified [101,102]. Little is known about the central mediators of the other responses. In general, both facilitatory and inhibitory factors operate in the overall modulation of their effects, but their precise modes of involvement, singly or in concert, have not yet been ascertained.

Eicosanoids

Several lines of evidence suggest that PGE may mediate the febrigenic action of cytokines on POA thermosensitive units [20,77,103–105]. For instance, PGE microinjected icv or iPO *in vivo* is febrigenic and generally depresses the firing rates of warm-sensitive and augments those of cold-sensitive neurons, analogous to the actions of the cytokines. Moreover, all three cytokines stimulate PGE synthesis by hypothalamic tissue *in vivo* [105] and *in vitro* [106–108]; however, these effects could be artifactual [109]. Difficult to reconcile also are findings that PGE applied iontophoretically *in vivo* [110] or added to slice preparations *in vitro* [90,111] facilitates the electrical activities of most neurons, regardless of their thermal specificity, and that PGE and IL-1 also often produce disparate responses in the same neuron [90]. These results would seem inconsistent with the hypothesis that cytokines affect fever-producing neuronal activity through the mediation of PGE. On the other hand, the antipyretic activity of PGE synthetase inhibitors, e.g., aspirin and indomethacin, is well documented, albeit their central administration does not consistently block fever [112]. It should be noted in this regard that although PGE is undoubtedly released by POA slices incubated with cytokines, it is also produced in response to various other agents, the reported *in vivo* thermoregulatory effects of which are not consistently hyperthermogenic, e.g., norepinephrine, 5HT, acetylcholine, angiotensin II, and histamine [113,114]. Furthermore, posterior hypothalamus and cortical slices also yield PGE in response to these agents, although their injections into these brain regions do not evoke thermal responses. Thus, the release of PGE from the POA may be a nonspecific response to a variety of stimuli, and its role in fever production remains ambiguous.

It has been suggested that other prostanoids may mediate cytokine-induced fever [115,116]. Indeed, PGD_2, $F_{2\alpha}$, and I_2 and thromboxane A_2 are all secreted by POA slices incubated with IL-1 in parallel with PGE [117]. The core temperature rises

provoked by their iPO administration are not, however, similar in latency, height, duration, or course to those produced by IL-1, thereby seemingly precluding their direct participation in the response to IL-1 [23], although they might have a role in the response to TNF or IFN. The latter has not yet been examined.

The leukotrienes B_4, C_4, D_4, and E_4, similarly, do not appear to participate in the brain events initiating fever, as their intrapreoptic injection does not evoke fever-like body temperature rises [118,119].

Neither the PGs nor the leukotrienes are involved in the central mediation of acute-phase proteinemia, whether induced by the systemic [120,121] or central [40,119,122] administration of IL-1.

Other central effects induced by IL-1 and TNF, e.g., somnogenesis and anorexia, are also activated without the intermediation of PGE [61,123]. Similarly, conflicting results have been reported regarding the role of PGE in the enhanced pancreatic secretion of insulin evoked by the central administration of IL-1 [48,124] and the releases of hypothalamic CRF and pituitary ACTH [125,126].

It would seem, therefore, that the diverse actions of these cytokines are not universally mediated by PGE. Hence, separate central mechanisms may operate in regulating their individual effects.

Opioid Peptides

Studies on a possible role of the endogenous opioids in fever production have been prompted by findings that β-endorphin and various other opioid peptides are pyrogenic when microinjected in low doses into the POA [127], and that increases in CSF and hypothalamic tissue levels of β-endorphin occur during endotoxin- and IL-1-induced fevers in rabbits and sheep [128,129]. But, on the other hand, it has been reported that low doses of naloxone injected iv or into the third ventricle do not alter the subsequent febrile responses to iv IL-1 in cats and rabbits [130,131] or to iv LPS and icv arachidonic acid, PGE, and PGI_2 in rabbits and guinea pigs [132,133]. Since naloxone at low doses, however, is primarily a μ-receptor antagonist, we [134] investigated whether δ and/or κ receptors might be involved in fever production. Although the δ-agonist D-(ala^2)-met-enkephalinamide and the κ-agonist dynorphin A injected directly into the POA of conscious guinea pigs produced, like the μ-agonist morphine, rises in body temperature, the courses of these responses differed from those produced by iPO injections of IL-1; but viewed in retrospect, the courses resembled those produced by TNF and IFN. Indeed, it was recently reported [135] that naloxone blocks the IFN-induced activity of preoptic thermosensitive neurons, suggesting that IFN may exert its febrigenic action partly through opiate receptors. In support, we found [136] that naloxone administered subcutaneously in high doses, such that its opiate receptor blocking effect is more generalized, inhibited the unimodal fever produced by iv hrIFN, prevented the first body temperature rise of the bimodal febrile response to hrTNF and reduced the second, and attenuated the first and suppressed the second of the two-peaked response to LPS; the effect of naloxone on hrIL-1-induced fever was not tested in these experiments. These results suggest, therefore, that two processes may mediate the pyrogenic effects of these cytokines, *viz.*, an endogenous opioid- and a PGE-dependent mechanism, but it remains to be established where these mechanisms operate and how they interact.

Interestingly, natural human purified IL-1β and IFN also reduce the specific binding of opioid agonists to their receptors in various brain regions [137,138]. The

significance of these findings is still obscure, but opioids have been implicated in the central modulation of, in addition to body temperature, sleep, appetite, and immune function, all of which are altered during infection. By contrast, the opioids do not appear to have a role in IL-1-induced acute-phase proteinemia [134].

CONCLUSIONS

It is apparent that cytokines play an important intermediary role in the neuromodulation of diverse host defense responses against infection, and that the POA is an important integrative and controlling region of several cytokine-produced effects; however, the origin of these cytokines—are they induced peripherally or centrally?—remains enigmatic. Cytokines do not share all of each other's biological activities, and those activities they do have in common often display distinctive characteristics, suggesting differences in the modes of action of these cytokines. The various functions that they mediate, moreover, are separable, evidently using distinct neuronal substrates and neuromodulators. It would appear, therefore, that neurons sensitive to cytokines may consist of different sets, with discrete, although partially overlapping, sensitivities and effectors. The location and boundaries of specific neural controllers, the organizaton of their interconnections, and the mechanisms of their activation in integrating the individual components of multivariate, complex host defense responses can, however, as yet only be tentatively described. Hence, much work remains in order to establish in what ways these cytokines interact in the central control of host defense responses to infectious pathogens.

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