Brain Mast Cells Act As an Immune Gate to the Hypothalamic-Pituitary-Adrenal Axis in Dogs

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Abstract

Mast cells perform a significant role in the host defense against parasitic and some bacterial infections. Here we show that in the dog, degranulation of brain mast cells evokes hypothalamic-pituitary-adrenal responses via histamine release. A large number of mast cells were found in a circumscribed ventral region of the hypothalamus, including the pars tuberalis and median eminence. When these intracranial mast cells were passively sensitized with immunoglobulin E via either the intracerebroventricular or intravenous route, there was a marked increase in the adrenal cortisol secretion elicited by a subsequent antigenic challenge (whether this was delivered via the central or peripheral route). Comp.48/80, a mast cell secretagogue, also increased cortisol secretion when administered intracerebroventricularly. Pretreatment (intracerebroventricularly) with anti-corticotropin–releasing factor antibodies or a histamine H_1 blocker, but not an H_2 blocker, attenuated the evoked increases in cortisol. These data show that in the dog, degranulation of brain mast cells evokes hypothalamic-pituitary-adrenal responses via centrally released histamine and corticotrophin-releasing factor. On the basis of these data, we suggest that intracranial mast cells may act as an allergen sensor, and that the activated adrenocortical response may represent a life-saving host defense reaction to a type I allergy.

Key words: hypersensitivity • immunoglobulin E • histamine • corticotropin-releasing factor • adrenal cortisol secretion

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Introduction

Although they represent a line of host defense against acute bacterial peritonitis (1, 2), mast cells, key cells in triggering immediate hypersensitive reactions, have long been thought to play a life-threatening role in IgE-dependent allergic reactions (3, 4). Connective tissue-type mast cells are abundant in the circumventricular organs in a variety of mammalian brains (5–9). Mast cells interact functionally with neurons in the peripheral or central nervous systems (8–10), and degranulate in response to physical or psychological stress (6, 7, 11, 12). Interestingly, in the median eminence (ME),* but not in the leptomeninges, numerous mast cells are found close to corticotropin-releasing factor (CRF)-positive nerve processes (12). Furthermore, anaphylactic shock and administration of histamine, a chemical mediator preformed in mast cells, both evoke a hypothalamic-pituitary-adrenal (HPA) response (13–18). To us, these findings suggested the speculative notion that brain mast cells may act to increase adrenocortical secretion when immediate hypersensitivity occurs. However, the physiological role of brain parenchymal mast cells, especially those located in the ME, is poorly understood. In dogs passively sensitized with IgE, we studied whether, and how, degranulation of the brain mast cells in response to an antigenic challenge might lead to activation of the HPA axis.

Materials and Methods

IgE Preparations. To obtain dog anti-OVA IgE antibodies, a previously described method for immunization that induces production of IgE (19) was employed, as follows. 50 μg of OVA dissolved in 1.0 ml saline with 12 mg $Al_2(OH)_3$ was intraperitoneally administered to newborn mongrel dogs within 24 h after their birth, and boosters were given at 1-mo intervals. The titer of IgE antibodies against OVA was measured by the passive cutaneous anaphylaxis (PCA) method at least 2 d after a passive sensi-

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**Abbreviations used in this paper:* ACSF, artificial cerebrospinal fluid; ACTH, adrenocorticotropic hormone; AH, adenohypophysis; BBB, blood-brain barrier; BP, blood pressure; CRF, corticotropin-releasing factor; EAML, external auditory meatus line; HPA, hypothalamic-pituitary-adrenal; HR, heart rate; icv, intracerebroventricular; ME, median eminence; PCA, passive cutaneous anaphylaxis; PT, pars tuberalis; V_{III}, cerebral third ventricle.

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tization in immune naive dogs (19). The IgE (titer between 600 and 800 times) produced by three dogs was used in this study. To determine whether the adrenal responses were induced by IgE antibodies or IgG1 antibodies, denatured serum for immunization was prepared by heating at 56°C for 2 h (20, 21).

Animals. Adult male mongrel dogs weighing from 10.2 to 12.3 kg were used in the experiments designed to investigate the IgE-dependent HPA response. The protocols conformed with guidelines on the conduct of animal experiments issued by the Animal Care and Use Committee of Nagasaki University. All animal experiments were performed under sodium pentobarbital anesthesia (25 mg/kg, intravenously). For passive sensitization via the intracerebroventricular (icv) route, 2.0 ml immunized serum was ultrafiltrated using a diaflow membrane filter (CF50; Amicon; substances below 50,000 mol wt are filtered out) for 2 h at 800 *g*. Once made up to 1.0 ml with artificial cerebrospinal fluid (ACSF), the ultrafiltrated serum was infused through a 27-gauge needle held within a cerebral guide cannula (22-gauge stainless steel) stereotaxically implanted into the cerebral third ventricle (V_{III}). This infusion was given for 4 h at a rate of 4.2 μl/min some 24 h before an antigenic challenge. For passive sensitization via the intravenous (iv) route, 2.0 ml immunized serum was infused into the saphenous vein over a 4-h period. To collect adrenal venous blood, a glass cannula was placed into the left lumboadrenal vein through a retroperitoneal lumbar approach (22). The antigenic challenge was delivered by infusing OVA dissolved in ACSF at a rate of 16 μl/min for 5 min via the icv or iv routes. Adrenal blood samples were collected in graduated tubes at 10 min before, and at 20, 30, and 60 min after an antigenic or pharmacologic challenge. These samples were centrifuged immediately after collection. The cortisol in the adrenal venous plasma was determined by the fluorometric method, the adrenal cortisol secretion rate being calculated in μg/kg body weight/min (13). Blood pressure (BP) and heart rate (HR) were monitored from the femoral artery before and after an antigenic challenge. Lyophilized anti-CRF antiserum (equivalent to 12.5 μl rabbit antiserum against human CRF; Sigma-Aldrich) was dissolved in 500 μl ACSF and infused into the V_{III} at a rate of 16 μl/min for 30 min (ending 5 min before the onset of an antigenic or pharmacologic challenge). Pyrilamine maleate (2.0 μg/kg; Sigma-Aldrich) or metiamide (200 μg/kg; SKF-Japan) was dissolved in ACSF and infused into the V_{III} at a rate of 16 μl/min for 30 min (ending 5 min before the onset of the above challenges).

Histology. For the histological study, seven dogs of either sex weighing between 4.5 and 12.3 kg that had received no experimental treatment were given an overdose of pentobarbital sodium. The brain was perfused transcardially with saline containing 0.1 M phosphate buffer, pH 7.4 (immediately after the heart stopped beating) followed by perfusion with 4% paraformaldehyde in 0.1 M phosphate buffer. After removing and trimming the brain, serial coronal sections were cut on a microslicer (DTK-1000; Dosaka EM) without freezing. Each serial section (100 μm in thickness) was soaked in 0.1% aqueous toluidine blue (dissolved in phosphate buffer, pH 7.4). The following brain region (shaded in Fig. 1 A, inset) was surveyed: longitudinal axis, from 14 mm rostral (posterior margin of the mammillary body) to 27 mm rostral (anterior margin of the optic chiasma) to the external auditory meatus line (EAML; R_0 in Fig. 1 A); vertical axis, from 2 mm above (basal part of the hypophysis) to 23 mm above (top margin of the anterior commissure) the EAML; transverse axis, from the midline to 3 mm either side. Each serial coronal section was divided into several areas with the aid of a graduated eyepiece fitted to a light microscope. In each of these areas, every mast cell stained metachromatically was counted (panfocusing the mast cells). Counting operations were performed in order from the most rostral serial coronal section to the most caudal, and then repeated in the reverse order. The numbers given for the mast cells in each coronal section were obtained by taking the average of these two values.

Statistics. Statistics were performed using a repeated one-way or two-way analysis of variance (ANOVA) with a post hoc test (Fisher's Protected Least Significant Difference [PLSD]) for multiple comparisons.

Results

Numerous Mast Cells Are Found in a Lower Region of the Hypothalamus. In coronal serial sections of the dog brain, large numbers of mast cells were found in the region between 18 and 20 mm (R_{20}) rostral to the EAML (Fig. 1 A and inset). They were largely found in the bottom of the V_{III} (Fig. 1 B) and in a zone within 2 mm of the midline on either side containing the ME (Fig. 1 C), the pars tuberalis (PT; Fig. 1 D), and the infundibular stalk. Most of the mast cells located in the ME were found in close association with capillaries (solid arrow in Fig. 1, C and E, and white arrow in Fig. 1 D). Large numbers of mast cells were arranged side by side in the border region of the ventral ME where neuronal tissues contact the basal part of the adenohypophysis (AH) via the epithelium extending from the PT (white arrowhead in Fig. 1 C). Mast cells were also seen around the circumference of arteries or veins running through the parenchyma of the brain areas surveyed; however, the number of such mast cells did not exceed five in a given serial coronal section. Although numerous mast cells were seen within the anterior or posterior pituitary gland or in the leptomeninges around the areas surveyed, these were not included in the representation of the sagittal distribution of cell numbers shown in Fig. 1 A.

An Antigen Challenge Evokes HPA Response via Histamine in Sensitized Animals. The protocols of the various experiments carried out to study IgE-dependent adrenocortical activation are summarized in Table I. The timing of the peak secretion of adrenal cortisol in response to an antigenic challenge depended on whether the icv or iv route was used to deliver the challenge. An antigen challenge (1.6 μg/kg OVA) delivered via the icv route markedly increased the adrenal cortisol secretion rate in dogs passively sensitized with IgE via the icv route (Sicv/Cicv experiment, Fig. 2 A). Plasma immunoreactive adrenocorticotropic hormone (ACTH) was significantly increased at 20 min (data not shown) and the maximal cortisol secretion rate (5 times the basal rate) was detected at 60 min after the antigen challenge. These responses occurred without any significant changes in arterial BP or HR (data not shown). Pretreatment with anti-CRF antiserum (icv) significantly attenuated the evoked increase in cortisol (Fig. 2 A). Furthermore, pretreatment with pyrilamine maleate (2.0 μg/kg), an H_1-histaminergic antagonist, also suppressed the increase completely when administered intracerebroventricularly (Fig. 2 A), but not when the same dose was given via the iv route (data not shown). By contrast, even a large

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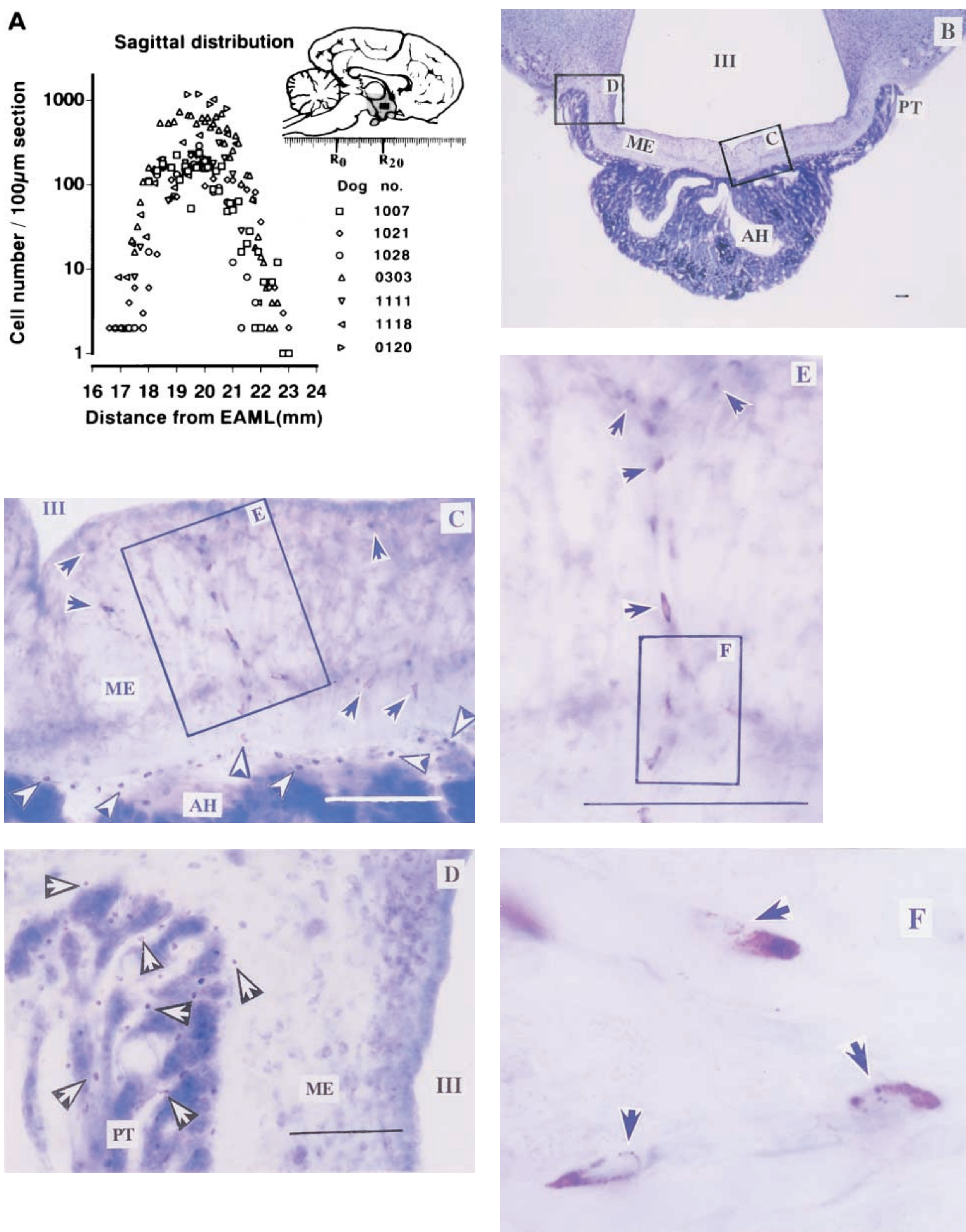

Figure 1. Mast cells in the dog brain. (A) Sagittal distribution of mast cells in the ventral hypothalamic region in serial coronal sections from 17 to 23 mm rostral to EAML (R_0) in seven dogs. Inset: drawing of midline sagittal section of the brain. Shaded area was surveyed for mast cells. (B) Representative photomicrograph of a coronal section at 19.5 mm rostral to EAML in dog no. 0120. The section includes the bottom of the third ventricle (III), the PT, the ME, and the AH, and it was stained with toluidine blue. Areas indicated by rectangles are depicted at high magnification in other photomicrographs, as described below. (C) Photomicrograph of rectangular area C (see B). (D) Photomicrograph of rectangular area D (see B). (E) Photomicrograph of area E (see C). Vertical bars, 100 μm. (F) Photomicrograph of rectangular area F (see E). Arrows show numerous metachromatic red-purple granules stained with toluidine blue in each mast cell. Original magnification: ×1,000.

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Table I. *Summary of Experimental Protocols*

	Sensitization (S) with IgE	
	icv	iv
Challenge (C) with antigen		
icv	Sicv/Cicv (Fig. 2 A)	Siv/Cicv (Fig. 3 A)
iv	Sicv/Civ (Fig. 2 B)	Siv/Civ (Fig. 3 B)

dose of metiamide (~200 μg/kg, icv), an H_2-histaminergic antagonist, did not significantly alter the increase (Fig. 2 A).

An Antigen Challenge Delivered Peripherally Can Reach Intracranial Mast Cells Sensitized via the Central Route. In the Sicv/Civ experiment, too, an antigen challenge (iv) increased adrenal cortisol secretion, the secretion this time peaking at 20 min after the challenge (Fig. 2 B). A significant increase in cortisol was observed after a 4.8 μg/kg antigen challenge (three times larger than that seen after an icv antigen challenge), but not after a 1.6 μg/kg antigen challenge (same dose as that used for the icv challenge). BP and HR did not change significantly after the 4.8 μg/kg OVA challenge (data not shown). Pretreatment (icv) with an H_1 blocker, but not with anti-CRF antiserum, significantly suppressed the increase in cortisol (Fig. 2 B).

IgE Given Peripherally Can Sensitize Mast Cells Located in the Intracranial Region. In dogs sensitized with IgE via the iv route, a marked increase in cortisol secretion rate (to 4.4 times the basal level) was evoked when a 1.6 μg/kg OVA challenge was delivered via the icv route (Siv/Cicv experiment, Fig. 3 A), but not when it was delivered via the iv route (Siv/Civ experiment; Fig. 3 B). Pretreatment (icv) with either an H_1 antagonist or anti-CRF antiserum reduced the increase in cortisol by 61 and 51%, respectively, of the peak response seen in dogs not given either of these pretreatments (Fig. 3 A). In the Siv/Civ experiment, an antigenic challenge significantly increased the cortisol secretion rate when 8.0 μg/kg OVA (five times larger than the dose used in the Sicv/Cicv experiment) was given, but not when the dose used was 1.6 or 4.8 μg/kg OVA (Fig. 3 B). Neither IgE denatured by heating nor immune naive sera ever induced significant changes in adrenal cortisol secretion, BP, or HR, nor did they induce a PCA reaction.

Pharmacologic Challenge also Activates HPA Response via Histamine and CRF Release. To confirm whether degranulation of brain mast cells does or does not activate adrenocortical secretion, Comp.48/80, a specific mast cell secretagogue, was employed. An icv administration of Comp.48/80 significantly increased the cortisol secretion rate at 30 min after the pharmacologic challenge (Fig. 4) with a concomitant increase in plasma immunoreactive ACTH (data not shown). Neither the plasma histamine level nor BP or HR changed significantly as a result of the pharmacologic challenge (data not shown). The Comp.48/80-evoked in-

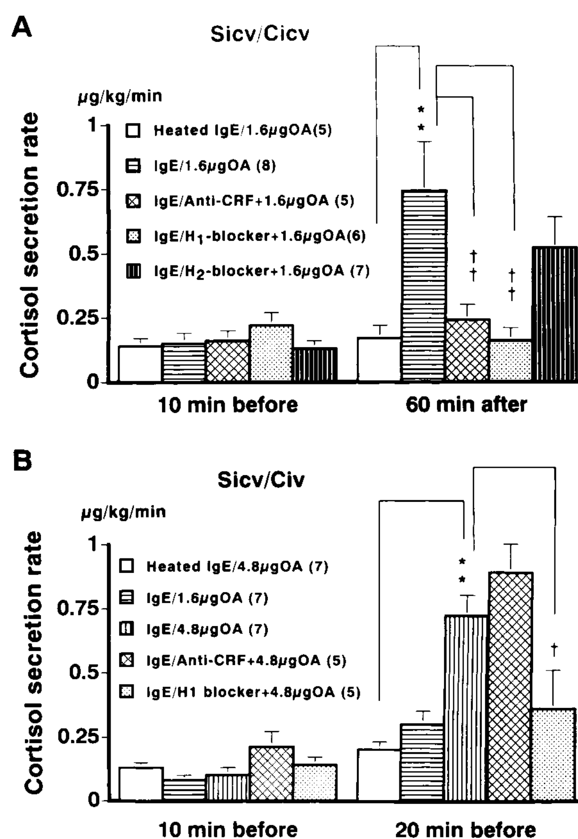

Figure 2. Effect of an antigenic challenge (C) delivered via the icv (A) or iv (B) route on adrenal cortisol secretion rate in dogs sensitized (S) with IgE via the icv route. (A) In the Sicv/Cicv experiment, cortisol secretion increased dramatically after a 1.6 μg/kg OVA challenge in dogs sensitized with IgE (but not in those given denatured IgE). The increase was attenuated by pretreatment with anti-CRF antiserum or an H_1 blocker, but not by pretreatment with an H_2 blocker. (B) In the Sicv/Civ experiment, cortisol secretion increased markedly in response to a 4.8 μg/kg OVA challenge via the iv route, but this did not occur with a 1.6 μg/kg OVA challenge via the same route. An H_1 blocker significantly attenuated the increase, but anti-CRF antiserum did not. Numbers in parenthesis indicate number of animals. All data are means ± SE. $^{**}P < 0.01$ versus animals sensitized with heat-inactivated IgE. $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$ versus animals without pretreatment.

crease in cortisol was completely suppressed by pretreatment (icv) with anti-CRF antiserum or an H_1-histaminergic blocker, but not by pretreatment with an H_2 blocker. These findings were similar to those obtained in experiments in which activation of the HPA response was evoked by IgE-dependent degranulation (Figs. 2 A and 3 A).

Discussion

The reaginic hypersensitivity of the sera used in these experiments to OVA antigen, which induced the observed adrenal responses and PCA reactions, was completely abolished by heating the sera at 56°C for 2 h. The reaginic activity was detectable by the presence of homogenous PCA reactions within 3 d after passive sensitization of the skin. This shows that the central role in the activation of the HPA axis is played by the IgE antibodies, rather than IgG1

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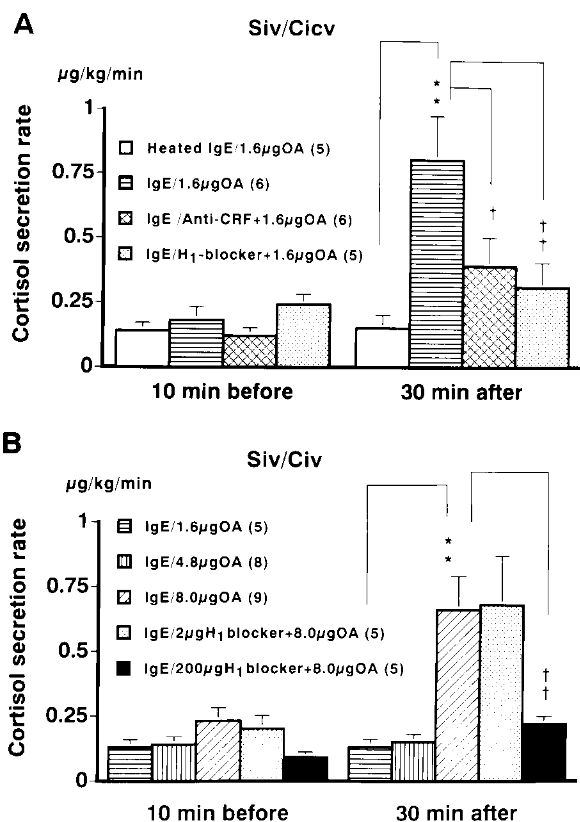

Figure 3. Effect of an antigen challenge (C) delivered via the icv (A) or iv (B) route on adrenal cortisol secretion rate in dogs sensitized (S) with IgE via the iv route. (A) In the Siv/Cicv experiment, a 1.6 μg/kg OVA challenge markedly increased cortisol secretion in dogs sensitized with IgE (but not in those given denatured IgE). The increase was attenuated by pretreatment with anti-CRF antiserum or an H_1 blocker. (B) In the Siv/Civ experiment, an 8.0 μg/kg OVA challenge increased cortisol secretion significantly, but a 1.6 or 4.8 μg/kg OVA challenge did not. The increase after the 8.0 μg/kg OVA challenge was markedly attenuated by pretreatment with 200 μg/kg of an H_1 blocker (but not by 2 μg/kg). Numbers in parenthesis indicate number of animals. All data are means ± SE. $^{**}P < 0.01$ versus animals sensitized with heat-inactivated IgE. $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$ versus animals without pretreatment.

antibodies, present in the actively immunized sera employed in our experiments (8, 20, 21).

In our first set of experiments, in dogs sensitized with IgE via the icv route, an antigenic challenge delivered via either the icv or iv route evoked an increased HPA response (in the Sicv/Cicv and Sicv/Civ experiments; Fig. 2). The adrenal cortisol secretion rate increased markedly in response to a 1.6 μg/kg antigen challenge in the Sicv/Cicv experiment. In the Sicv/Civ experiment, a 4.8 μg/kg antigenic challenge also evoked an HPA response, but a 1.6 μg/kg antigen challenge did not. These evoked adrenal responses were (a) significantly reduced by pretreatment with an H_1 antagonist via the icv route, but not by such pretreatment via the iv route, and (b) unchanged after pretreatment with an H_2 antagonist. In addition, a significant attenuation of the HPA response evoked by an antigenic challenge given via the icv route was observed when animals were pretreated with an anti-CRF antiserum via the icv route. It

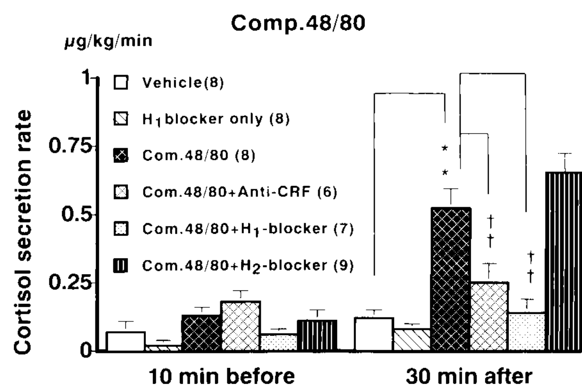

Figure 4. Effect of Comp.48/80 on adrenal cortisol secretion rate in dogs. Comp.48/80 (Sigma-Aldrich) was given into V_{III} at a rate of 7.5 μg/kg/min for 5 min with or without antagonists. In response to Comp.48/80, cortisol secretion increased to four times the basal level. Pretreatment with anti-CRF antiserum or an H_1 blocker significantly attenuated the increase (but an H_2 blocker did not). Numbers in parenthesis indicate number of animals. All data are means ± SE. $^{**}P < 0.01$ versus vehicle control. $^{\dagger\dagger}P < 0.01$ versus animals without pretreatment.

is well documented that an administration of histamine via either the iv or icv route produces an HPA response (13–18), and that the HPA activation induced by histamine seems to be caused indirectly via activation of hypothalamic neurons or release of neurotransmitters, including CRF, arginin-vasopressin, and oxytocin (18, 23). Furthermore, there is evidence that the histamine-induced ACTH secretion is mediated by H_1-histaminergic receptors (17, 18, 23–26), although the sites of action are not well defined (16, 17). Following on from these studies, our data showed that an antigenic challenge triggers degranulation of sensitized brain mast cells, followed by liberation of histamine in an intracranial region, and that the liberated histamine subsequently evokes a release of CRF (a neuropeptide that activates ACTH secretion from the pituitary gland) via H_1 receptors located within the brain. Furthermore, our data suggest that intracranial mast cells sensitized with IgE via the icv route degranulate and liberate histamine even when the antigen challenge is delivered via the iv route. In the Sicv/Civ experiment, however, pretreatment with anti-CRF had no significant effect on the evoked adrenal response. This ineffectiveness of pretreatment with anti-CRF antibodies against the increase in cortisol evoked by an iv antigenic challenge may suggest that the mast cells that liberate histamine in response to such a challenge are located in intracranial regions other than the ME, probably in the AH and/or PT. Another possibility is that hypothalamic neurotransmitters or hormones, such as catecholamines, vasopressin, or oxytocin, may contribute to the activation of the pituitary-adrenal response (17, 18, 23).

In the second set of experiments, involving dogs sensitized with IgE via the iv route, antigenic challenge via either the icv or iv route evoked significant increases in adrenal cortisol secretion (experiments Siv/Cicv and Siv/Civ; Fig. 3). In the Siv/Cicv experiment, our results suggest that a 1.6 μg/kg antigen challenge again evoked an adrenal re-

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sponse via liberated histamine and subsequent release of CRF. To evoke an adrenal response, the dose used for antigenic challenge needed a larger dose (8.0 μg/kg antigen) in the Siv/Civ experiment than that needed in the Sicv/Cicv (1.6 μg/kg) or Sicv/Civ (4.8 μg/kg) experiments. These data indicate that intracranial mast cells can be sensitized passively with IgE not only via the central route, but also via the peripheral route. The above results also suggest that mast cells located outside the blood-brain barrier (BBB) in the intracranial region can be sensitized with IgE, and show that an icv antigenic challenge can also trigger degranulation of mast cells sensitized via the peripheral route. This degranulation, too, may activate the HPA axis via histamine and CRF released within the brain.

It has been well documented that there is a high density of mast cells in the ME (12, 27–29) in various mammals. In our study, numerous mast cells were identified morphologically in the ventral part of the hypothalamus (PT and ME) in close association with the capillaries of the so-called primary plexus of the hypophyseal portal system. Previously, the distribution and densities of H_1 receptors in the brain have been investigated using [^{3}H]mepyramine in rats (30, 31) or [^{131}I]iodobolpyramine in guinea pigs (32). These studies showed that H_1 receptors are widely distributed within the brain. However, in the part of the hypothalamus containing the ME, there are differences in the pharmacology, density, and distribution of H_1 receptors among the rat, mouse, guinea pig, rabbit, and human brains (31–34). At present, it is unclear whether H_1 receptors are present in the dog ME, and if they are, how many H_1 receptors are concentrated there. In our previous study, however, the bulk of the histamine-induced increase in adrenal cortisol secretion was abolished by lesions in the anterior or posterior ME (13). Therefore, it seems likely that at least some of the mast cells that degranulate in response to an antigenic or pharmacologic challenge are located in the ME and PT, and that histamine liberated from these mast cells may act on CRF-containing neuronal terminals in the ME in a paracrine fashion (17).

Furthermore, the ME, which lacks the BBB, is a major integrative link between neuronal terminals projecting from the hypothalamic nuclei and the AH. This integration is mediated not just by neurotransmitters and neuropeptides, but also by immune-mediated inflammatory substances (35). Thus, to judge from our data, the hypothalamic mast cells would seem to be located in an ideal position to detect and respond to exogenous agents as well as to endogenous stimuli (2). However, we have no data to help us decide whether exogenous antigens can gain access to intracranial mast cells from the external world after crossing the barriers in the respiratory or gastrointestinal tracts. A degranulation of mast cells leads to an increased permeability of blood vessels, so small and local, but repeated, activation of mast cells located in the airways or peritoneal cavity might permit penetration of the antigen into the circulatory system. However, this issue remains to be resolved. A further point of interest is that CRF secreted from sympathetic nerve terminals during stress can apparently induce degranulation of mast cells located in the thalamus, leptomeninges, or peritoneal tissue (11, 12, 36). Moreover, brain mast cells can be activated by direct stimulation of sensory nerves (37) or by neuropeptides, such as substance P (7, 37). Thus, on the basis of these data, brain mast cells, some of which are located in the ME, may cross-talk with CRF-containing neurons.

Mast cells have long been regarded as an appendix of the human immune system, at least in the developed world, because of their involvement in tissue-damaging processes as well as in allergic and anaphylactic reactions. Indeed, IgE-dependent immediate hypersensitivity reactions are frequently associated with dysfunctions of the cardiovascular or respiratory systems, which can have life-threatening consequences for allergic individuals (3, 4). However, both pharmacologic glucocorticoids and physiologic adrenal corticosteroids can ameliorate the severity of these dysfunctions and suppress the subsequent immune-mediated inflammation (6, 35, 38–41). Thus, an activation of cortisol secretion after degranulation of intracranial mast cells could conceivably evoke a life-saving host defense response against severe systemic anaphylaxis or respiratory disorders when a type I allergic reaction is triggered by peripheral mast cells. It may, indeed, provide a negative feedback mechanism acting to modulate subsequently evoked peripheral inflammatory responses.

A very recent study indicated that mast cells may play a major role in many immune-mediated diseases of the central nervous system, such as experimental allergic encephalomyelitis (42), as well as in alterations in the BBB (6). In future, the experimental system employed in this study (sensitization with IgE followed by antigenic challenge) might be a useful experimental model for studying the induction and/or progress of intracranial mast cell–related neuroinflammatory conditions in vivo or for investigating mast cell–dependent alterations in the properties of the BBB.

This study suggests that we need to enlarge our concept of the role of intracranial mast cells; in fact, we need to add a protective role in type I allergy to their previously reported protective role during bacterial infections (1, 2). Intracranial mast cells located in the ME can be sensitized with IgE, as can mast cells situated in the periphery. Intracranial mast cells activated by a complex containing IgE bound to FcεR1 and then antigen challenged are able to evoke an HPA response, suggesting a link between intracranial mast cells and neuroendocrine networks. Consequently, the mast cells located in the ME and PT could be seen as an immune gate to the HPA axis: upon receiving antigenic information, intracranial mast cells would in effect communicate with neural and endocrine networks as well as with other brain immune cells, such as microglia and astrocytes (6, 7, 43, 44).

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