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Different receptor mechanisms mediate the pyrogenic and behavioral effects of interleukin 1

(interleukin 1 receptor antagonist/sickness/food-motivated behavior/social behavior/fever)

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ABSTRACT **Interleukin 1 (IL-1) is a cytokine released during immune activation that mediates the host's response to infection and inflammation. Peripheral and central injections of IL-1 induce fever and sickness behavior, including decreased food motivation and reduced interest in social activities. To determine the receptor mechanisms responsible for these effects, rats were injected with IL-1 receptor antagonist (IL-1ra), an endogenous cytokine that acts as a pure antagonist of IL-1 receptors. IL-1ra blocked the increased body temperature and oxygen consumption induced by injection of recombinant human IL-1 only when both cytokines were administered i.p. In contrast, i.p. or intracerebroventricular administration of IL-1ra blocked the depressive effect of IL-1β on food-motivated behavior and social exploration when this cytokine was administered by the same route as the antagonist. In addition, intracerebroventricular IL-1ra blocked the reduction in social exploration produced by i.p. IL-1β but had only partial antagonist effects on the decrease in food-motivated behavior induced by i.p. IL-1β. In each case, the dose of IL-1ra was 100- to 1000-fold in excess of the biologically active dose of IL-1. These results suggest that the receptor mechanisms that mediate the behavioral and pyrogenic effects of IL-1 are heterogeneous.**

Interleukin 1 (IL-1) is an endogenous pyrogen that is synthesized and released by activated macrophages and mediates many of the local and systemic responses to infection and inflammation (1). Peripheral and central injections of this cytokine activate the pituitary–adrenal axis (2, 3) and cause fever (4) and enhanced thermogenesis (5). IL-1 also induces hypersomnia (6), anorexia, adipsia, and loss of interest in usual activities, including social interactions (7). These latter effects are reminiscent of the profound behavioral alterations characteristic of febrile states (8).

Whether IL-1 acts at central or peripheral sites, or both, to cause these physiological and behavioral changes is unclear. It is generally accepted that IL-1 enters the brain at the level of the organum vasculosum of the lamina terminalis (9). This circumventricular organ lies in the anteroventral wall of the third ventricle and is devoid of a blood–brain barrier. It is hypothesized that IL-1 induces the synthesis and release of prostaglandins of the PGE_2 series, which then diffuse freely to target brain areas (10, 11). However, IL-1 is also present in the brain as shown by immunocytochemistry (12, 13) and *in situ* hybridization (14). IL-1 receptors have been identified in the mouse brain and are located mainly in the adenohypophysis and the dentate gyrus of the hippocampus (15, 16). There is some evidence for communication between the central and peripheral IL-1 compartments. Peripheral injections of IL-1 or endotoxin, a potent activator of macrophages, increase IL-1 levels in murine brain extracts (17); however, negative findings have been reported in cerebrospinal fluid extracted from the third ventricle of cats (18).

The effects of IL-1 on its cellular targets are mediated by two high-affinity receptors representing separate gene products (19): one type of receptor predominates on T cells and fibroblasts (type I), and the other one predominates on B cells and macrophages (type II). The nature of the receptors that mediate the thermogenic and behavioral effects of IL-1 has not yet been elucidated. Binding characteristics of brain IL-1 receptors resemble those seen on murine immune T cells (15, 16), suggesting that type I receptors are also present in the brain.

Recently, a natural human IL-1 receptor antagonist (IL-1ra) has been characterized and cloned (20, 21). IL-1ra binds to both human and murine type I receptors with an affinity similar to that of IL-1 (20–24). Furthermore, IL-1ra blocks most inflammatory and immune effects of IL-1 that are mediated by type I receptors (21, 24, 25). In contrast, the ability of IL-1ra to act as an antagonist of type II receptors appears to be species and cell-type specific. Although IL-1ra binds to human type II receptors with approximately the same affinity as IL-1, it binds very poorly, if at all, to murine type II receptors (21–24). However, this binding may depend on cell type because IL-1ra binds to receptors on mature immune and hematopoietic cell types but not on their bone-marrow precursors (22, 24). In spite of these limitations, this antagonist provides a useful tool to assess the nature and localization of the IL-1 receptors that mediate the pyrogenic and behavioral effects of this monokine.

We report here that pretreatment with IL-1ra blocks the thermogenic, anorexic, and behavioral effects of recombinant human IL-1β when both molecules are administered peripherally. However, central injection of IL-1ra does not inhibit the thermogenic effects of centrally injected IL-1β, in spite of its ability to fully block the behavioral effects of this cytokine. In addition, central administration of IL-1ra blocks the effects of peripherally injected IL-1β on social exploration but has only limited antagonistic activity on the reduction in food-motivated behavior induced by peripheral injection of IL-1β. These results suggest that different receptor mechanisms mediate the neural effects of IL-1β.

MATERIALS AND METHODS

Subjects. Male Sprague–Dawley or Wistar rats weighing 250–350 g at the beginning of the experiment were housed

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Abbreviations: IL-1, interleukin 1; IL-1ra, IL-1 receptor antagonist; i.c.v., intracerebroventricular(ly); V_{O_2}, resting oxygen consumption.

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individually or in pairs in a room maintained at 24 ± 2°C and on a 12 hr:12 hr light–dark cycle. Rats had free access to food and water.

Surgery. Animals were anesthetized with sodium pentobarbital (60 mg/kg i.p.) or a mixture of ketamine and xylazine (61 and 9 mg/kg i.p., respectively), and indwelling guide cannulae were stereotaxically implanted into the third ventricle for those rats used in the thermogenesis experiments or above the right or left lateral ventricle for those rats used for behavioral experiments. Surgery occurred at least 5 days before the initiation of all experiments.

Thermogenesis. Resting oxygen consumption (V_{O_2}) was measured in conscious animals between 0800 and 1800 hr for periods of 2–3 hr before and 2 hr after treatments in closed-circuit indirect calorimeters maintained at 24°C, as described (26). All rats were habituated to the calorimeters on several occasions before they were injected. V_{O_2} was continuously measured, and resting values (lowest 5-min values) were recorded during each 30-min period (27). Colonic temperatures were measured immediately before and 2 hr after treatments by insertion of a plastic-coated thermocouple 5 cm beyond the rectum.

Food-Motivated Behavior. Rats were food-deprived for 2 days before being trained to press a bar for a 45-mg food pellet in a standard Skinner box on a fixed-ratio 10 (FR-10) schedule (i.e., one food pellet for every 10 lever presses). Thereafter, rats were maintained at 80–85% of their free-feeding body weight. FR-10 performance was measured by the number of bar presses during 5-min test sessions at various intervals after treatment (28).

Social Exploration. Rats submitted to a reverse dark–light cycle (lights on from 1600 to 0400 hr) were tested in their home cage during the dark phase with 1-mo-old juveniles as social stimuli (29). Each test consisted of a 5-min exposure to a juvenile. The amount of time the adult spent investigating the juvenile (mainly, anogenital sniffing) was determined to the nearest 0.1 sec by an observer blind to the treatment administered to the adult animal.

Experimental Design. In all three experiments, rats were tested in one of three conditions: (*i*) i.p. injections of both IL-1ra and IL-1; (*ii*) intracerebroventricular (i.c.v.) injections of both IL-1ra and IL-1β; or (*iii*) i.c.v. injection of IL-1ra followed by i.p. injection of IL-1β. Different groups of animals were used for each condition. In each condition, rats were injected with IL-1ra or saline, followed 5 min (thermogenesis) or 15 min (food-motivated behavior and social exploration) later by IL-1β or saline, according to a 2 × 2 factorial design. A minimum of 3 days separated each series of injections. The order of treatment was randomized—each rat receiving all the combinations of treatments according to a counterbalanced design. For clarity, only the maximum effects (i.e., 1 or 2 hr post-IL-1β values) are reported for each treatment condition.

Cytokines. Recombinant human IL-1β (specific activity of 2.5×10^7 units per mg) was from Glaxo (IMB, Geneva). IL-1β was injected at doses found to induce significant changes in colonic temperature (4), V_{O_2} (5), food-motivated behavior (28), and social exploration (29). The human IL-1ra was supplied by Synergen (Boulder, CO) and was injected at doses 500–2000 times higher than IL-1β. Apyrogenic 0.9% saline was used as a vehicle for both i.p. and i.c.v. injections. All injections were administered to conscious, lightly restrained animals.

Statistics. For each dependent variable, results were analyzed by using 2-way ANOVA (route of injection × treatment) with repeated measurements on the treatment factor.

RESULTS

Thermogenesis and Body Temperature. Pretreatment values for colonic temperature (37.2–37.7°C) and V_{O_2} (14.2–15.3 ml of O_2/min per $kg^{0.75}$) were stable and comparable for all animals. Injection of either IL-1ra or vehicle caused small, nonsignificant changes in colonic temperature (−0.1 ± 0.1°C) and V_{O_2} (2.6 ± 1.2%). Peripheral (1 μg) or central (5 ng) administration of IL-1β elicited significant increases in V_{O_2} (18–20%, Fig. 1), which were maximal 60–90 min after injection and remained elevated for at least 120 min. Colonic temperature measured 2 hr after administration of IL-1β (i.p. or i.c.v.) was elevated by 1.4–1.6°C (Fig. 1). Peripheral injection of 10 μg of IL-1ra before IL-1β (1 μg i.p.) caused slight but nonsignificant reductions in V_{O_2} and colonic temperature compared with the effect of IL-1β alone (16.4 ± 1.6% increase in V_{O_2}, 1.3 ± 0.2°C increase in temperature). Injection of 100 or 500 μg of IL-1ra (i.p.) significantly attenuated the effects of IL-1β on V_{O_2} and colonic temperature by 74 and 87%, respectively, so that responses did not differ significantly from those elicited by IL-1ra alone. In contrast, central injection of 1, 5, or 10 μg of IL-1ra did not significantly alter the thermogenic or pyrogenic effects of either centrally or peripherally administered IL-1β (Fig. 1).

Food-Motivated Behavior. Pretreatment rates of lever pressing for food varied between, but not within, animals. A large reduction in the response for food occurred 1 hr after i.p. and 2 hr after i.c.v. injections of IL-1β. These decreases persisted, at least, until 4 hr after IL-1β but generally returned to near baseline by 8 hr after IL-1β. Control injections of IL-1ra or saline had no effect (data not shown).

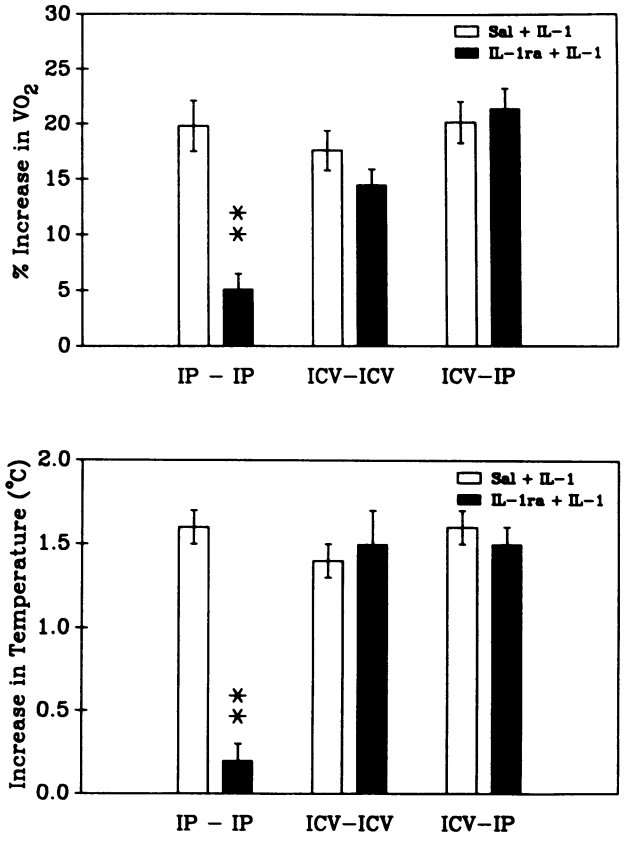

FIG. 1. Effects of blockade of IL-1 receptors by IL-1ra on increases in V_{O_2} and colonic temperature induced by IL-1β in Sprague–Dawley rats. IL-1ra [500 μg i.p. (IP), 10 μg i.c.v. (ICV)] or 0.9% saline (Sal) was injected 5 min before IL-1β (1 μg i.p. or 5 ng i.c.v.). IP-IP, experimental condition *i*; ICV-ICV, experimental condition *ii*; ICV-IP, experimental condition *iii* (see text). (*Upper*) Maximum percent increases in V_{O_2} above preinjection values over the 2-hr recording period. (*Lower*) Difference from preinjection values of colonic temperature measured 2 hr after injection. Vertical bars represent SEM (**, $P < 0.01$ compared with IL-1β).

Fig. 2 presents the results of only the maximal effect of IL-1β (1 or 2 hr after injection i.p. or i.c.v., respectively). IL-1ra completely blocked the effects of IL-1β on food-motivated behavior when administered by the same route. This blockade was effective throughout the entire observation period. One hour after i.p. injection of IL-1β (4 μg), response rate decreased to 3 ± 2% of baseline compared with 113 ± 12% for rats pretreated with IL-1ra (2.4 mg per rat; $P < 0.001$; Fig. 2). A similar blockade was also seen 2 hr after i.c.v. injections (24 μg of IL-1ra; 40 ng of IL-1β; 13 ± 13% versus 102 ± 3%; $P < 0.001$; Fig. 2). In contrast, i.c.v. injection of IL-1ra (24 μg) only partially blocked the effect of i.p. IL-1β (4 μg) 1 hr after injection (61 ± 15% versus 14 ± 9%; $P < 0.001$ both between treatments and compared with controls; data not shown). Increasing the dose of IL-1ra ≈10 times (211 μg) did not significantly augment the partial blockade (77 ± 16% versus 5 ± 5%; $P < 0.05$ and 0.001 compared with control, $P < 0.001$ between treatments, Fig. 2). Moreover, this partial blockade was seen only in the first hour after IL-1β; after this time there were few differences between rats treated with IL-1ra or saline.

Social Exploration. Pretreatment values for social exploration were stable and similar for all animals. IL-1β, injected either i.p. or i.c.v., induced a profound reduction in social investigation of juveniles by adult animals. This decrease persisted for 4 hr, and recovery was complete by 24 hr. Injection of IL-1ra or saline did not significantly affect social exploration (data not shown).

Fig. 3 presents the effects measured 2 hr after IL-1β. Peripheral (4 μg) or central (30 ng) administration of IL-1β elicited profound decreases in social exploration (Fig. 3, $P < 0.01$). Injection of IL-1ra by the same route (3 mg and 60 μg, respectively) completely blocked this effect. In the same manner, central injection of the IL-1ra (4 μg) antagonized the effects of peripherally injected IL-1β (4 μg) on social exploration ($P < 0.001$).

DISCUSSION

Cytokines, such as IL-1, that are released from macrophages after exposure to pathogens are now known to coordinate the host's local and systemic responses to infection and inflammation (1). However, the type and location of receptors that

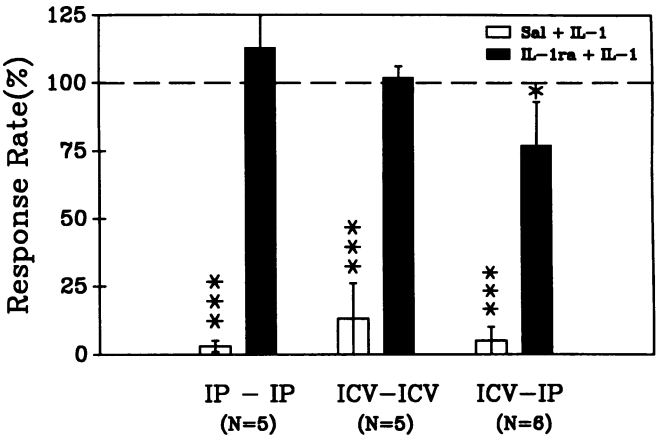

FIG. 2. Effects of blockade of IL-1 receptors by IL-1ra on decrease in food-motivated behavior induced by IL-1 in Wistar rats. IL-1ra (2.4 mg i.p., 24 or 211 μg i.c.v.) or 0.9% saline was injected 15 min before IL-1 (4 μg i.p. or 40 ng i.c.v.). Injections were given immediately after the first test session. Data collected 1 hr [IP-IP (experimental condition *i*) and ICV-IP (experimental condition *iii*)] or 2 hr [ICV-ICV (experimental condition *ii*)] after the injections are expressed as percentage of preinjection values (*, $P < 0.05$; ***, $P < 0.001$ compared with saline-injected controls). Preinjection values were, respectively, 278, 210, and 191 lever presses per 5 min.

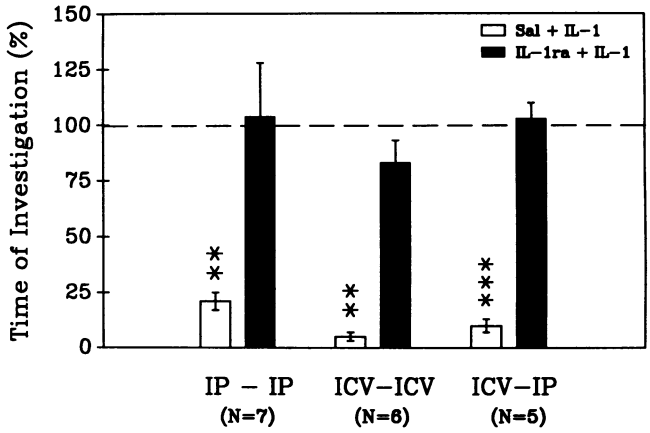

FIG. 3. Effects of blockade of IL-1 receptors by IL-1ra on decrease in social exploration induced by IL-1 in Wistar rats. IL-1ra (3 mg i.p., 60 or 4 μg i.c.v.) or 0.9% saline was injected 15 min before IL-1 (4 μg i.p. or 30 ng i.c.v.). Injections were given immediately after the first test session. Data collected 2 hr after the injections are expressed as percentage of preinjection values (**, $P < 0.01$; ***, $P < 0.001$ with comparison to saline-injected controls). Preinjection values were, respectively, 93, 106, and 80 sec. IP-IP, experimental condition *i*; ICV-ICV, experimental condition *ii*; ICV-IP, experimental condition *iii*.

mediate these changes on nonimmune targets are currently unknown. The present results show that (*i*) pretreatment with a specific antagonist of IL-1 receptors completely prevents the thermogenic and behavioral effects of IL-1β when both molecules are administered peripherally, (*ii*) central administration of this antagonist also inhibits the behavioral effects of centrally administered IL-1β but has no effect on the enhanced thermogenesis induced by this route of administration, and (*iii*) central injection of IL-1ra prevents the reduction in social behavior induced by peripherally administered IL-1β but only partially attenuates the reduction in food-motivated behavior induced by the same treatment.

Although these results were obtained in different experimental conditions, with different doses and time courses depending on the variable under study, the observed differences are unlikely to be artifactual. In all three experiments, the sources of IL-1β and IL-1ra were the same, and the results concerning the effects of IL-1β agree with published findings (28–31). In addition, other data point to the existence of different mechanisms for the central effects of IL-1β on thermogenesis and behavior in the rat. In particular, corticotropin-releasing factor antagonists have been found to block thermogenic, but not behavioral, effects of IL-1β (28, 30). Therefore, the present findings can be interpreted to suggest that different receptor subtypes mediate the behavioral and pyrogenic activity of IL-1β.

On immune cells, there are at least two classes of IL-1 receptors—namely, IL-1RtI or type I, an 80-kDa single-chain protein found mainly in T cells and fibroblasts, and IL-1RtII or type II, a 68-kDa protein expressed in B cells and macrophages (19). IL-1ra has a similar affinity for these two types of receptors in human cells. Its affinity is similar to that of IL-1α but slightly lower than IL-1β (22). Despite this difference, IL-1ra can completely block the binding of both forms of interleukin 1 to both interleukin 1 receptors in human tissue (21–24). The evidence is less clear in murine cells and is nonexistent in rat cells. In mature immune and hematopoietic murine cells, IL-1ra blocks the binding of IL-1 to type I receptors but does not appear to effectively bind to type II receptors (21–24). If the target nerve cells for the effects of IL-1 on fever and thermogenesis contain type II receptors, the differences in the inability of IL-1ra to block fever induced by

central injections of IL-1 would be explained. Preliminary results with antibodies to the type II receptor suggest that this might be the case because central injections of these antibodies block the pyrogenic effects of centrally administered IL-1 (N.J.R., unpublished observations).

There are alternative interpretations to the existence of different subtypes of IL-1 receptors. (*i*) It is known that the response of a given cell to IL-1 depends not only on the type of IL-1 receptor on the cell surface but also on the number of receptors (32). It is, therefore, possible that the fever response is not blocked by IL-1ra injected i.c.v. because the receptor number is very high on those nerve cells responsive to IL-1, and very few of these receptors need to be occupied by IL-1 to elicit a response. It is also known that cells vary in the number of occupied receptors needed to elicit a response (32).

Supporting this possibility is the fact that inhibition of the biological effects of IL-1 has been shown to require doses of IL-1ra that are 100- to 1000-fold in excess of the amount of IL-1 administered (21, 25, 33, 34). In addition, Opp and Krueger (35) recently reported that i.c.v. injection of a 10,000-fold excess of IL-1ra was needed to block slow-wave sleep and fever induced in rabbits by 10 ng of IL-1 administered by the same route. However, the amount of IL-1ra needed i.c.v. in the present experiments for blocking the effects of centrally injected IL-1β on social exploration and food-motivated behavior was in the usual range—i.e., 500- to 2000-fold the dose of IL-1β, and increasing further the dosage of IL-1ra had no effect on the thermogenic activity of centrally injected IL-1β.

The ability of IL-1ra to block the behavioral effects of IL-1β at its central sites of action provides a means to investigate whether the effects of peripherally administered IL-1β are mediated by central IL-1 receptors. This situation proved valid for social behavior. However, food-motivated behavior appears to be mediated by both central and peripheral IL-1 receptors. These latter results agree with previous suggestions of a prostaglandin-dependent peripheral mechanism for the decrease in feeding induced by peripherally injected IL-1 (36–38). A possible site of action for these effects is the gastrointestinal tract (39, 40). When IL-1 is injected centrally rather than peripherally, the cytokine could actually produce its effects by acting on central IL-1 receptors that then would induce gastrointestinal effects (39, 40) responsible for the observed alterations in food-motivated behavior.

Our data provide evidence for the existence of different IL-1 receptors mediating the pyrogenic and behavioral effects of IL-1β. In addition, these data can be interpreted as suggesting that decreases in social investigation are mediated centrally, whereas changes in food-motivated behavior are mediated both peripherally and centrally.

Existence of multiple receptor subtypes for IL-1 in the brain has important potential implications because this existence suggests that pharmacological intervention may allow differential modulation of IL-1 actions *in vivo*.

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