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Interleukin-1α Injection Into Ventromedial Hypothalamic Nucleus of Normal Rats Depresses Food Intake and Increases Release of Dopamine and Serotonin

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YANG, Z.-J., V. BLAHA, M. M. MEGUID, A. LAVIANO, A. OLER, AND Z. ZADAK. *Interleukin-1α injection into ventromedial hypothalamic nucleus of normal rats depresses food intake and increases release of dopamine and serotonin.* PHARMACOL BIOCHEM BEHAV **62**(1) 61–65, 1999.—A microdialysis injector probe administered IL-1α into ventromedial hypothalamus (VMN) and concurrently measured release of dopamine (DA), DOPAC, 5-HT, and 5-HIAA. After baseline dialyses, six rats received 2-ng IL-1α and six rats received vehicle (1 μl saline) into VMN. Sixty minutes later, food was provided for 40 min while VMN monoamines were measured every 20 min. Vehicle had no significant effect on monoamines, their metabolites, or food intake. Food intake was significantly lower in IL-1α rats vs. controls ($p < 0.01$). Baseline levels of VMN monoamines (pg/10 μl dialysate) in IL-1α and vehicle groups were similar. DA and 5-HT rose immediately on injecting IL-1α and remained higher ($p < 0.05$) than basal during the first 60 min and 40 min sampling period, respectively. Levels of 5-HIAA also increased ($p < 0.01$). Eating decreased VMN DA in controls, and decreased VMN DOPAC in IL-1α–treated rats. During eating, VMN 5-HT in control rats significantly increased while increasing VMN 5-HIAA occurred in IL-1α rats. Findings show that an IL-1α pathophysiological dose injected into the VMN was associated with anorexia and significantly increased dopaminergic and serotonergic activities and suggest that enhanced VMN DA and 5-HT activities may be part of an IL-1α–initiated cascade involved in IL-1α–associated anorexia. © 1998 Elsevier Science Inc.

IL-1α VMN Microdialysis 5-HT Food intake Anorexia Cytokine Feeding

INTERLEUKIN-1 is one of the cytokines produced by macrophages and lymphocytes during acute and chronic pathological processes (19). In addition to its activity in the immune system, one of the remarkable effects of IL-1 is to induce anorexia (15,20). The mechanisms underlying the anorectic effect of IL-1α are not fully understood, but a direct central action has been postulated, based on (a) circulating IL-1 crossing the blood–brain barrier (2); (b) IL-1 is known to be synthesized in the brain by astrocytes and microglia (7); (c) IL-1 receptors and immunoreactive fibers have been identified in the brain, including the hypothalamus (10); (d) IL-1β–induced food intake suppression could be blocked by intracerebroventricular administration of a specific IL-1 receptor antagonist (20); (e) detec-tion of IL-1α in the cerebrospinal fluid (CSF) of anorectic tumor-bearing rats, with the concentrations of IL-1α correlating with the magnitude of anorexia (16); and (f) a pathophysiological dose (2 ng) of IL-1 induces anorexia when administered centrally, but, when administered peripherally, a pharmacological dose (microgram) is needed to induce anorexia (21).

The involvement of hypothalamic monoamines in food intake control suggests that IL-1 may exert its anorectic effect

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by activating and/or modulating hypothalamic monoaminergic systems. The central serotoninergic systems have been implicated in satiety, and the major inhibitory effect of serotonin (5-HT) on feeding activity has been proposed as mediated by medial hypothalamic nuclei, including the nucleus of ventromedial hypothalamus (VMN) (8,11). Recent observations that IL-1 activated general hypothalamic catecholamine and 5-HT turnover (5,6) and augmented release of dopamine (DA) and 5-HT in hypothalamus of rats (14,27) also suggest possible involvement of VMN monoaminergic activity in IL-1-induced anorexia. To examine a possible linkage between IL-1α–induced anorexia and VMN monoamines, a specially designed microdialysis probe (to which a microinjection needle is attached) was used to allow direct administration of IL-1α into the VMN while concomitantly measuring the release of 5-HT, DA, and their intermediate metabolites, 5-HIAA and DOPAC, in the same region. We report changes in 5-HT, DA, and their metabolites specifically in the VMN after direct injection of a pathophysiological dose of IL-1α.

METHOD

Subjects

Twelve male Fishcher-344 rats (Taconic Farm Co., Germantown, NY) weighing 275–290 g were housed in holding cages for 1 week after purchasing to acclimate them to the constant study environmental conditions: 12L:12D (lights on at 0600), 26 ± 1°C room temperature, and 45% relative humidity. Tap water and standard rat chow (diet 5008, Ralston Purina, St. Louis, MO) were available ad lib. Animal care was in accordance with NIH guidelines. The experimental protocols were approved by the Institutional Animal Care and Use Committee.

Surgery

After acclimatization, rats were anesthetized with a mixture of Ketamine, Xylazine and Acepromazine (150:30:5 mg/ml) at 0.6 ml/kg body weight intramuscularly. The rat was placed in the stereotaxic instrument and the skull was exposed at the site of an incision on top of the head. An intracerebral cannula guide was implanted into the VMN. The stereotaxic coordinates from the bregma were: medialateral, 1.0 mm from the middle line; and dorsalventral, 8.2 mm ventral from the surface of the dura (18). The cannula guide was fixed to the skull with acrylic dental cement. After operation, rats were kept individually in plastic metabolic cages (Nalgene Company, Rochester, NY) and were allowed to recover for 10 days.

Microdialysis Design

Ten days after surgery, the rat was placed into a bowl-like cage (CMA/120 Awake Animal System, BAS, West Lafayette, IN) at 1700 h, and food was removed but water was freely available. Next day at 0700 h, a microdialysis probe was inserted into the cannula guide under light Fentrane® inhalation anesthesia. The schedule of the experiment is depicted in Fig. 1.

Microdialysis Probe

The microdialysis probe (Eicom, Kyoto, Japan) had three stainless steel tubes. Two tubes were inserted inside the lumen of the cellulose dialysis membrane (2-mm long, 200 μm o.d.), one as an inlet and the other as an outlet. The tip of the microdialysis membrane extended 2 mm below the cannula guide into the VMN. A parallel microinjection needle (75 mm o.d.) was attached to the microdialysis tubes outside the microdialysis membrane, and its tip extended 1 mm into the VMN below the cannula guide. According to our in vitro calibration test, a relative recovery rate was about 10–12% for DA and 6–8% for 5-HT at a flow rate of 1 μl/min.

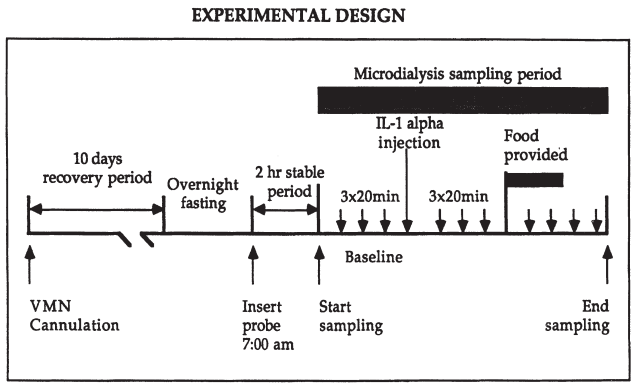

FIG. 1. Schema of experimental design. For details, see the Method section.

Microdialysis

A Ringer-type solution containing 147.0 mM N^{a+}, 2.4 mM Ca^{++}, 4.0 mM K^{+} and 155.8 mM Cl− was perfused through the microdialysis membrane. The flow rate of 1 μl/min allowed the collection of 20-μl samples every 20 min. After the probe had been perfused for 60 min to allow equilibration, sequential 20 min samples were collected into microvials containing 2 μl of 0.1 N HCl. After three baseline fractions had been collected, a dose of 2 ng human recombinant IL-1α (Hoffmann–LaRoche) dissolved in 1 μl of saline was injected through the microinjection tube into the VMN over a 2-min period in six rats. Sampling was continued for 60 min. As a control, the same volume of vehicle was injected into six other rats at the same velocity. Then, food pellets were provided ad lib, and the VMN dialysate were continuously collected every 20 min for a further 2 h. Simultaneously, the feeding activity of the rats was monitored by the investigator.

Monoamines Measurement

All samples were measured immediately after collection. Monoamines were detected using a reverse-phase liquid chromatography with ESA Model 5014 High Sensitivity Analytical Cell and ESA MD-150 column (3 × 150 × 3 mm i.d.). The mobile phase consisted of 75 mM $NaH_2PO_4 \cdot H_2O$, 1.4 mM OSA, 10 mM EDTA, and 10% acetonitrile. Buffer pH was adjusted to 3.1 with H_3PO_4. The concentration of monoamines was determined by comparison with peak areas of standards run with each experiment.

Histology

After microdialysis, all rats were anesthetized and perfused with normal saline and 10% formalin. The brain was removed and fixed. One of us (A.O.) cut serial coronal sections

that were mounted and stained. The location of each dialysis probe in the VMN of each rat was verified and compared to locations using the stereotaxic atlas of Pellegrino et al. (18).

Data Analysis

The baseline concentrations of 5-HT, 5-HIAA, DA, and DOPAC are expressed as pg per 10 μl dialysate. It is important to indicate that these values are not the actual extracellular 5-HT, 5-HIAA, DA, and DOPAC concentrations in the VMN because in vitro recovery procedures do not take into account diffusion kinetics in brain tissue. The baseline 5-HT, 5-HIAA, DA, and DOPAC levels were determined by using a mean value of three consecutive samples prior to IL-1α or vehicle microinjection. The changes in 5-HT, 5-HIAA, DA, and DOPAC are expressed as percent variations from the mean baseline.

All data are expressed as mean ± SE. ANOVA was used to analyze the time-course data within the groups while the two-tailed Student's *t*-test was used to compare IL-1α and vehicle-treated rats.

RESULTS

Food Intake

Daily food intake prior to microdialysis was similar in both groups of rats (16.9 ± 0.7 g in IL-1α and 16.4 ± 1.1 g in vehicle-treated rats). After overnight food deprivation, food intake during the feeding period, 60 min after either VMN IL-1α or vehicle injection, was significantly ($p < 0.01$) lower in the IL-1α group (1.3 ± 0.3 g) vs. the vehicle-treated rats (3.5 ± 0.2 g).

Baseline VMN Monoamine Levels

Baseline levels (pg/10 μl) of VMN monoamines in the two groups of rats, IL-1α and vehicle-treated, were similar: 5-HT was 5.5 ± 0.4 and 5.8 ± 1.1, respectively; 5-HIAA was 159 ± 18 and 208 ± 46; DA was 17.9 ± 0.8 and 19.2 ± 0.4; and DOPAC was 41 ± 6 and 45 ± 4, respectively. These data are depicted in Figs. 2 and 3, in which baseline is expressed as 100%.

IL-1α–Associated VMN Monoamine Changes

IL-1α administration was associated with an increased release of 5-HT, its intermediate metabolite 5-HIAA, and DA. Vehicle administration exerted no effect on the monoamine or their metabolites. Increased DA levels were noted immediately after the administration of IL-1α and remained 1.5–1.2 times higher than the basal levels. On the other hand, approximately 1.5–2 times elevations of 5-HT level appeared relatively briefly during the first 40-min sampling period. The levels of 5-HIAA also increased by 1.2–1.5 times. These data are shown in Figs 2 and 3, expressed as percent change from baseline.

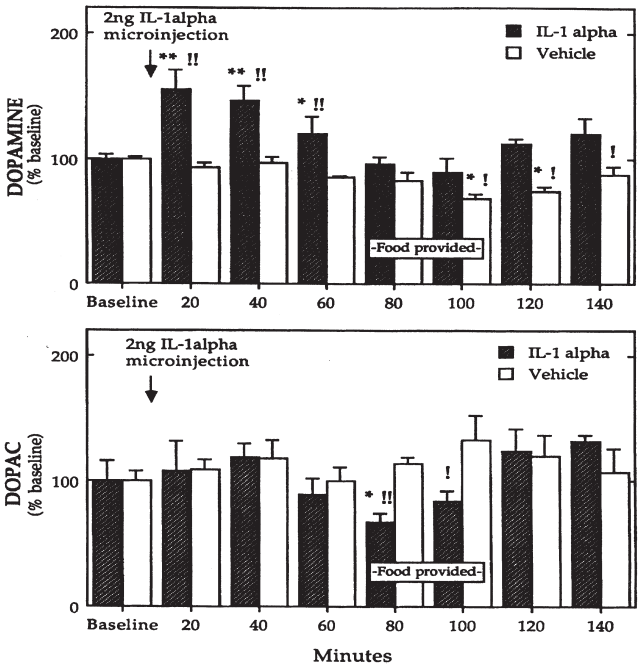

FIG. 2. The changes of VMN-DA (top) and DOPAC (bottom) levels before (baseline), during and after intra-VMN IL-1α or normal saline injection; and during and after refeeding. IL-1α injection significantly increased DA levels for 60 min. Eating induced a significantly lower DA level and higher DOPAC level. Open bar: normal saline injection rats; shaded bar: IL-1α injection rats. *$p < 0.05$; **$p < 0.01$ vs. preinjection; ! $p < 0.05$; !! $p < 0.01$ between two groups

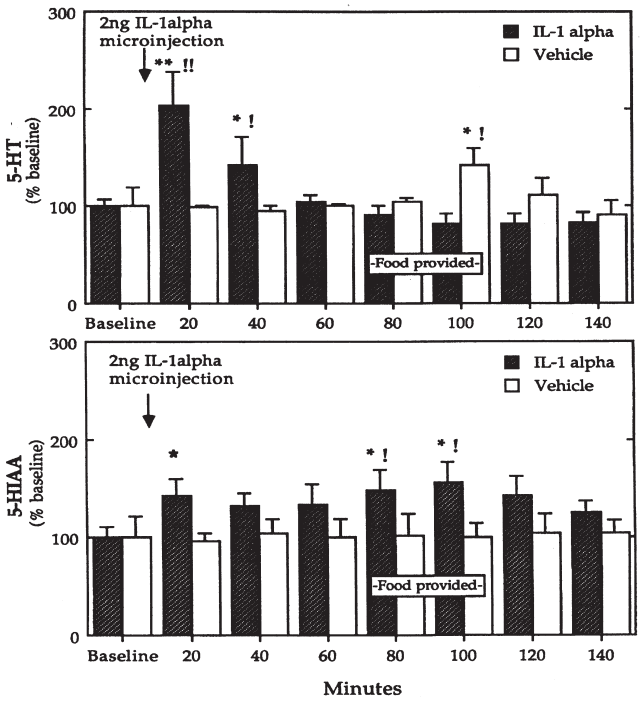

FIG. 3. The changes of VMN-5-HT (top) and -5-HIAA (bottom) levels before (baseline), during and after intra-VMN IL-1α or normal saline injection; and during and after refeeding. IL-1α injection induced a transient increase in 5-HT levels (for 40 min); and modest increase in 5-HIAA levels. Eating induced the significantly higher 5-HT and 5-HIAA levels. Open bar: normal saline injection rats; shaded bar: IL-1α injection rats. *$p < 0.05$; **$p < 0.01$ vs. preinjection; ! $p < 0.05$; !! $p < 0.01$ between two groups.

Eating-Associated VMN Monoamine Changes

The relative changes in VMN 5-HT, 5-HIAA, DA, and DOPAC are shown in Figs. 2 and 3. Eating was associated with a decrease in VMN DA levels in vehicle-treated rats when compared to baseline. Eating was also associated with a decrease in VMN DOPAC level in IL-1α–treated rats. During feeding period, there was a significant increase in VMN 5-HT level in vehicle-treated rats, while 5-HIAA increased in IL-1α rats.

DISCUSSION

The main findings of this study are: 1) injection of 2 ng of IL-1α into the VMN induced profound anorexia in the overnight food-deprived (but not water-deprived) rat; 2) IL-1α was associated with an immediate increase in the release of VMN DA, 5-HT, and 5-HIAA; 3) the duration of the increased release lasted longer for VMN DA than for VMN 5-HT; and 4) 60 min after IL-1α injection, VMN 5-HT had returned to preinjection (and control) levels. In contrast, 5) VMN-DA was still above preinjection (and control rat) levels 60 min after IL-1α injection; and 6) eating increased VMN 5-HIAA release, whereas it decreased VMN DOPAC release in IL-1α–treated rats.

In studies of mechanisms underlying cytokine-induced anorexia, it was recently suggested that the cytokine administration should be at doses that produce estimated pathophysiological concentrations to emulate situations in which disease processes induce anorexia (21,26). The present study provides supportive data in showing that a pathophysiological dose (2 ng) of IL-1α is capable of inducing profound anorexia when it is directly injected into the VMN, a feeding-regulating area. In our observations, anorexia induced by IL-1α is mainly due to early development of satiety, because the rats start eating immediately when food is provided but stop eating after ingesting only a small amount of food. Such early satiety has long been linked to enhanced serotonergic activity.

Our findings demonstrate that an interaction exists between IL-1α and VMN monoamine activity. The magnitudes and the time courses of the responses of VMN dopaminergic and serotonergic systems to IL-1α are different. The different response of DA and 5-HT to the same stimulus was also observed in one of our other studies in which the administration of nicotine (a known anorectic agent) into the LHA induced a long-lasting increase in DA release but a shorter increase in 5-HT release (29). In the present study, IL-1α injection also induced a longer lasting increase in DA release than in 5-HT release. It is yet unclear whether this different response if due to: 1) a quantitatively different number of cell bodies of DA and 5-HT systems in these areas; 2) selective activation of IL-1α on DA and 5-HT systems; or 3) different kinetics of DA and 5-HT release or reuptake. The increased levels of 5-HT associated with increased levels of its metabolite 5-HIAA suggest that the increased levels of VMN 5-HT are probably due to an increase in the release of 5-HT, whereas the reason for increased levels of VMN DA accompanied by unchanged levels of its metabolite DOPAC is currently uncertain. A nonlinear change between DA and DOPAC has been observed by others and explained on the basis that, after DA has been released, part of it is transformed into 3-MT in the synaptic cleft, while only part of it is metabolized into DOPAC. Some of DOPAC is also converted into HVA after its exit into the extracellular space (17); thus, caution is warranted when the ratio of DOPAC to DA is used to interpret dopaminergic activity.

Whereas we previously were unable to demonstrate an increase in LHA dopamine activity via microdialysis during a continuous systemic IL-1α infusion (30) and the hepatic vagus does not appear to mediate IL-1α–induced anorexia (9), there are elegant data demonstrating the relationship between cytokine and neurotransmitter interaction in the hypothalamus (22). Both intravenous and intraperitoneal IL-1β activated the hypothalamic– pituitary–adrenocortical axis leading to an increase in plasma ACTH and corticosterone while simultaneously increasing hypothalamic norepinephrine (25). Furthermore, this cytokine–neurotransmitter interaction was more clearly shown, when an immobile–stress stimulus induced increase in the rat's hypothalamic Il-1, norepinephrin, dopamine, serotonin, and their metabolites, as well as plasma ACTH, could be inhibited with IL-1Ra pretreatment. The time course of the hypothalamic changes suggested that the stress stimulus augmented the effects of preexisting Il-1 in the hypothalamus that led to elevation of monoamine release in the hypothalamus and activation of the hypothalamus–pituitary–adrenal axis (24).

The present study also confirms our previous observations that eating induces a long-lasting decrease in VMN-DA levels (12,31), although the function of VMN DA in food intake control still needs to be further defined. Mapping studies revealed that DA injection-induced suppression of food intake is a site-specific phenomenon. The area of the greatest sensitivity is at the perifornical region of the lateral hypothalamus. Within the hypothalamus, all medial sites extending from the PVN caudal to the posterior hypothalamus were found to be totally unresponsive to DA injection (10). It could thus be argued that the function of the dopaminergic system in the VMN may not be associated with an inhibitory role in food intake. Hence, the increased VMN DA level might not be directly responsible for IL-1α injection-induced anorexia, but its action may be via modulating other neuromodulator's activity, for example, stimulating the release of corticotropin-releasing hormones (CRH) (14,27). It has been proposed that food intake suppression by IL-1 may be CRH dependent, because CRH is known to inhibit food intake when administered centrally (1,4,28).

Brain 5-HT has an inhibitory influence on food intake in both animals and in humans, and its major satiety effect has been proposed to be in the PVN-MH (13). In one of our previously reported studies, the activity of VMN 5-HT significantly increased when anorexia occurred during tumor growth; VMN 5-HT activity returned to the control level and food intake normalized after removal of the tumor (3). We also observed that the IL-1α concentration in the cerebrospinal fluid increased in tumor-induced anorectic rats, and that the magnitude of the anorexia was proportional to the degree of the increased concentration of the IL-1α (16). Our current study provides interesting data that an association exists among either IL-1α, increased 5-HT activity and anorexia, or that the VMN serotoninergic system may be involved in IL-1α–induced anorexia. This is supported by the other studies (22,24,25). During the current reported study, food was provided 60 min after the IL-1α injection, when (theoretically) the bioavailability of IL-1α had disappeared because of its short half-life, and when the VMN 5-HT level had returned to the preinjection and control level. This phenomenon suggests that a pathophysiological dose of IL-1α may initially induce a cascade reaction involving the hypothalamus–pituitary–adrenocortical axis (22). The messengers it carries may thus be amplified via stimulation of DA and 5-HT release to carry out the effector response.

In summary, this study demonstrates that injection of a pathophysiological dose of IL-1α into the VMN was associated with a considerable degree of anorexia and a significantly associated increase in dopaminergic and serotonergic activities, suggesting that the enhanced VMN DA and 5-HT activities may be a part of IL-1α initiated cascade, and thus involved in IL-1α–induced anorexia.

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