Arginine vasopressin does not mediate the attenuated febrile response to intravenous IL-1β in pregnant rats

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Eliason, Heather L., and James E. Fewell. Arginine vasopressin does not mediate the attenuated febrile response to intravenous IL-1β in pregnant rats. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R450–R454, 1999.—Rats have an attenuated febrile response to intravenous endogenous pyrogen [e.g., interleukin-1β (IL-1β)] near the term of pregnancy. The present experiments were carried out on 25 nonpregnant and 32 pregnant rats to test the hypothesis that arginine vasopressin functioning as an endogenous antipyretic substance in the central nervous system mediates this attenuated febrile response. An intravenous injection of recombinant rat IL-1β (rrIL-1β) after intracerebroventricular vehicle produced a significant increase in core temperature in both nonpregnant and pregnant animals, the magnitude and duration of which was greater in the nonpregnant rats. In nonpregnant rats, intravenous rrIL-1β after intracerebroventricular vasopressin V1-receptor antagonist accentuated the core temperature response compared with that observed with intravenous rrIL-1β after intracerebroventricular vehicle. In pregnant animals, however, intravenous rrIL-1β after intracerebroventricular vasopressin V1-receptor antagonist produced a decrease in core temperature rather than an increase in core temperature, which was observed with intravenous rrIL-1β after intracerebroventricular vehicle. Thus our data do not support the hypothesis that a pregnancy-related activation of arginine vasopressin as an endogenous antipyretic substance in the central nervous system attenuates the febrile response to intravenous rrIL-1β near the term of pregnancy in rats.
The animal's head was placed in a stereotaxic frame, and the skull was exposed by means of a midline scalp incision. A stainless steel guide cannula (1.5-cm long, 20-gauge thin-walled tubing; Small Parts) was placed 1 mm above the left lateral ventricle using the coordinates anterior-posterior –0.6 mm, lateral 2.0 mm in relation to the bregma, and 2.0 mm below the surface of the brain (28). jeweler's screws and dental acrylic were used to fix the guide cannula to the skull. A 25-gauge stainless steel stylet was placed into the guide cannula between surgery and experiment.

All surgical and experimental procedures were carried out in accordance with the Guide to the Care and Use of Experimental Animals provided by the Canadian Council on Animal Care, and with the approval of the Animal Care Committee of the University of Calgary.

Conditions of observations. During the experiment, each animal was studied in its home cage in an environmental chamber. Ambient temperature within the chamber was maintained at 22 ± 1°C. Each cage was placed over a platform antenna (PhysioTel CTR 86, Data Sciences International) that received the output frequency from the biotelemetry device and interfaced with a peripheral processor (Daqstat IV, Data Sciences International) for determination of core temperature.

Experimental protocol. Twenty-five nonpregnant and thirty-two pregnant rats were randomly allocated to four experimental groups based on the combination of injectate (V1-receptor antagonist) and injectate (intracerebroventricular vehicle or vasopressin V1-receptor antagonist) and each animal was studied only once. Pregnant animals were studied on day 19, 20, or 21 of gestation (term ~22 days). On the day before each experiment, the animal was removed from its cage, weighed, and then returned to its cage in the environmental chamber. On the day of the experiment, after a suitable control period, the rat was removed from its cage and given an intracerebroventricular injection of either 10 µl vehicle (artificial cerebrospinal fluid (aCSF)) or 1.0 nmol vasopressin V1-receptor antagonist dissolved in 10 µl aCSF. A suitable control period was defined as one in which five consecutive 2-min measurements of core temperature did not vary by >0.2°C. The rat was returned to its cage for 30 min, during which core temperature was recorded at 10-min intervals. Then the animal was removed from its cage and intravenously injected with either 0.2 ml vehicle (phosphate-buffered saline containing 1% bovine serum albumin) or 0.2 µg/kg rrIL-1β dissolved in 0.2 ml of vehicle. The catheter was flushed with 0.2 ml of sterile normal saline, making the total injected volume 0.4 ml in all rats. The animal was then returned to its home cage, and core temperature was recorded at 10-min intervals for 6 h.

After each experiment the rat was anesthetized with pentobarbital sodium. The injection cannula was reinserted into the guide cannula, and 10 µl of black ink was injected into the ventricle via gravity flow. The chest was then opened and the vascular system was perfused through the heart with normal saline, followed by 10% buffered Formalin to fix the brain tissue. The brain was then removed and sectioned. The presence of ink in the cerebroventricular system verified correct placement of the injection cannula.

RESULTS

After intracerebroventricular administration of vehicle, intravenous administration of rrIL-1β produced significant increases in core temperature in both nonpregnant and pregnant animals (Fig. 1). The core temperature response, however, was significantly delayed and attenuated in both magnitude and duration in pregnant compared with nonpregnant animals. The average change in core temperature from control expressed as degrees Celsius per hour for the 6-h period after injection 2. All data are presented as means ± SD, and P < 0.05 was considered to be of statistical significance.

After intracerebroventricular administration of vasopressin V1-receptor antagonist, intravenous administration of rrIL-1β produces a significant increase in core temperature in nonpregnant rats and a short-lived but significant decrease in core temperature in pregnant rats (Fig. 3). Furthermore, the average change in core temperature was significantly greater in nonpregnant rats after vasopressin V1-receptor antagonist/rrIL-1β than after vehicle/rrIL-1β (Fig. 2). In contrast, the average change in core temperature was lower in pregnant rats after vasopressin V1-receptor antagonist/
rrIL-1β than after vehicle/rrIL-1β. There were no significant effects of intravenous administration of vehicle after intracerebroventricular administration of a vasopressin V1-receptor antagonist on core temperature in either nonpregnant or pregnant rats.

**DISCUSSION**

Our experiments provide new information about pregnancy and fever in rats. Novel findings of the study were as follows. 1) Intravenous injection of rrIL-1β after an intracerebroventricular injection of vehicle produced a significant increase in core temperature in both nonpregnant and pregnant animals, but the magnitude and duration of this increase were significantly greater in nonpregnant compared with pregnant rats. 2) In nonpregnant animals, intravenous injection of rrIL-1β after an intracerebroventricular injection of a vasopressin V1-receptor antagonist produced an increase in core temperature that was significantly greater in magnitude and duration than that observed with an intravenous injection of rrIL-1β after an intracerebroventricular injection of vehicle. 3) In pregnant animals, intravenous injection of rrIL-1β after an intracerebroventricular injection of a vasopressin V1-receptor antagonist produced a decrease in core temperature rather than an increase in core temperature, which was observed with an intravenous injection of rrIL-1β after an intracerebroventricular injection of vehicle. Thus our data do not support the hypothesis that a pregnancy-related activation of arginine vasopressin as an endogenous antipyretic substance in the central nervous system attenuates the febrile response to rrIL-1β near the term of pregnancy in rats.

Beeson (1) identified endogenous pyrogen in 1948 as a substance produced and released by circulating leukocytes and fixed macrophages in response to exogenous pyrogens (i.e., bacterial endotoxin, lipopolysaccharide), and which produces an increase in body temperature. This substance was later renamed IL-1 and its release, as well as the release of other endogenous pyrogens such as IL-6, tumor necrosis factor, and interferons-α and -γ, constitute an essential step in the genesis of fever after exposure to exogenous pyrogens (10). Because IL-1β fails to accumulate in the brain in significant quantities after peripheral injection (4), it has been postulated that endogenous pyrogens induce fever through production of one or more end mediators such as prostaglandins of the E series (2, 7, 18, 24). These end mediators act directly or indirectly in the central nervous system to activate heat-conserving and heat-producing mechanisms, the relative contributions of
which depend on the pyrogen type and dose, ambient and core temperature, and the age and size of the host (3). Therefore, fever is a complex process involving multiple steps, each of which could be influenced by the programmed rheostatic (25) changes in physiology that accompany the maternal adaptation to pregnancy.

Simrose and Fewell (30) were the first to show that pregnancy alters the febrile response to endogenous pyrogen in rats. In their experiments, the intravenous administration of a half-maximal effective dose (ED50) of recombinant human IL-1β (i.e., 0.1 μg/kg as determined in nonpregnant Sprague-Dawley rats) produced an increase in core temperature on day 13 of gestation but produced a decrease in core temperature on days 17 and 21 of gestation. In the present study, rats that were given an intracerebroventricular injection of vehicle before an intravenous ED50 of rrIL-1β developed a small but significant fever on days 19, 20, and 21 of gestation. These differences most likely result from the pyrogenic effects of recombinant human vs. rat IL-1β given to the latter species.

In nonpregnant rats, intravenous injection of rrIL-1β after an intracerebroventricular injection of a vasopressin V1-receptor antagonist produced an increase in core temperature that was significantly greater in magnitude and duration than that observed with an intravenous injection of rrIL-1β after an intracerebroventricular injection of vehicle. The increased magnitude and duration of the febrile response of nonpregnant rats are consistent with the V1-receptor antagonist preventing the endogenous antipyretic effect of arginine vasopressin and are consistent with previous experiments carried out on rats (9, 26, 27). More difficult to explain are the results obtained in the pregnant rats, that is, an intravenous injection of rrIL-1β after an intracerebroventricular injection of a vasopressin V1-receptor antagonist produced a decrease in core temperature rather than an increase in core temperature, which was observed with an intravenous injection of rrIL-1β after an intracerebroventricular injection of vehicle. This hypothermic response, however, appears to be due to an interaction between the V1-receptor antagonist and rrIL-1β because the V1-receptor antagonist had no effect on core temperature in either nonpregnant or pregnant rats when it was followed by vehicle. Regardless of the mechanism, our data do not support the hypothesis that a pregnancy-related activation of arginine vasopressin as an endogenous antipyretic substance in the central nervous system attenuates the febrile response to rrIL-1β near the term of pregnancy in rats.

Fever is a highly regulated process involving the synthesis and release of both pyrogens and antipyretics. Endogenous antipyretics are produced and released by the body during the course of the febrile response and effectively limit the magnitude and duration of the core temperature response. Among the substances that have been identified as endogenous antipyretics are arginine vasopressin (8, 9), α-melanocyte-stimulating hormone (21, 22), IL-1 receptor antagonist (32), and IL-10 (20). Our current experiments provide evidence that arginine vasopressin does not mediate the attenuated febrile response to intravenous injection as it does to intracerebroventricular injection of PGE1 (13) near the term of pregnancy in rats. Perhaps intravenous administration of rrIL-1β does not elicit a normal end mediator response (i.e., a normal prostaglandin E response) in pregnant animals as it does in nonpregnant animals because there is an alteration in the number or properties of cytokine receptors near the term of pregnancy, or, alternatively, there may be increases in the circulating levels of IL-1 receptor antagonist in rats as there is in humans near the term of pregnancy (29). Alternatively, plasma levels of α-melanocyte stimulating hormone increase near term of pregnancy in humans. These possibilities warrant further investigation.

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