AVP mediates the attenuated febrile response to administration of PGE$_1$ in rats near term of pregnancy

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Eliason, Heather L., and James E. Fewell. AVP mediates the attenuated febrile response to administration of PGE$_1$ in rats near term of pregnancy. Am. J. Physiol. 275 (Regulatory Integrative Comp. Physiol. 44): R691–R696, 1998.—Rats have an attenuated febrile response to intracerebroventricular injection of PGE$_1$ near the term of pregnancy, the mechanism of which is unknown. The present experiments were carried out to test the hypothesis that arginine vasopressin (AVP), functioning as an endogenous antipyretic substance in the central nervous system, mediates this attenuated febrile response. The febrile response to intracerebroventricular injection of 0.2 µg PGE$_1$ was determined in pregnant and nonpregnant rats after an intracerebroventricular injection of either vehicle or a vasopressin V$_1$-receptor antagonist. After intracerebroventricular administration of vehicle, intracerebroventricular administration of 0.2 µg PGE$_1$ produced significant increases in core temperature in both nonpregnant and pregnant animals. The increase in core temperature, however, was attenuated both in magnitude and duration in pregnant compared with nonpregnant animals. After intracerebroventricular administration of a vasopressin V$_1$-receptor antagonist, intracerebroventricular administration of 0.2 µg PGE$_1$ produced significant increases in core temperature that were similar in nonpregnant and pregnant animals. Our data support the hypothesis that a pregnancy-related activation of AVP as an endogenous antipyretic substance in the central nervous system attenuates the febrile response to intracerebroventricular administration of PGE$_1$ near term of pregnancy in rats.

arginine vasopressin; endogenous antipyretic; prostaglandin

NUMEROUS PHYSIOLOGICAL changes occur during the maternal adaptation to pregnancy. In rats, these changes include reversible alterations in thermostatic control. For example, baseline core temperature decreases as gestation advances and then increases around the time of parturition (11, 17). Furthermore, there are different thermostatic responses to cold (9, 14), to psychological stress (12), and to pyrogens such as bacterial endotoxin (21), interleukin-1β (30), and PGE$_1$ (10, 34) in near-term pregnant rats compared with those observed in nonpregnant rats. The mechanism of these pregnancy-induced changes in thermostatic control is presently unknown.

We have previously shown that the febrile response to intracerebroventricular administration of PGE$_1$ (34) is attenuated in pregnant rats compared with nonpregnant rats when the experiments are carried out at an ambient temperature below thermoneutrality. Given that nonshivering thermogenesis in brown adipose tissue, which is an important autonomic thermostatic effector for heat production during the development of fever in rats (13), is impaired near term of pregnancy in rodents (1, 35), we then postulated that the attenuated febrile response was forced by an impairment of this autonomic thermostatic effector response such that core temperature did not increase to reach the new central nervous system thermostatic “set point” following PGE$_1$ administration. If this were true, we would expect near-term pregnant rats to develop a “normal” fever following PGE$_1$ administration when placed in a thermocline where behavioral as well as autonomic thermostatic effectors could be used to increase core temperature. Additional experiments have provided evidence that this does not occur, despite activation of both behavioral and autonomic thermostatic effectors following intracerebroventricular injection of PGE$_1$ (10). Although we observed an activation of both behavioral and autonomic thermostatic effectors following intracerebroventricular injection of PGE$_1$, the duration of activation was abbreviated in pregnant compared with nonpregnant rats; this appeared to limit the magnitude of the febrile response.

It is possible that the abbreviated thermostatic effector response observed in rats near the term of pregnancy resulted from activation of an endogenous antipyretic system. Arginine vasopressin (AVP), which functions as an endogenous antipyretic substance in the central nervous system (15), is elevated in a number of hypothalamic nuclei in rats near term of pregnancy (5, 19). Furthermore, Ruwe et al. (29) have shown that administration of AVP into the ventral septal area of the rat limits the increase in core temperature evoked by intracerebroventricular injection of PGE$_2$. Thus it is possible that a pregnancy-related activation of AVP as an endogenous antipyretic substance limits the febrile response to intracerebroventricular injection of PGE$_1$. Our present experiments were carried out to test this hypothesis.

METHODS

Experiments were carried out on 58 nonpregnant and 63 pregnant Sprague-Dawley rats undergoing their first pregnancy and weighing 237 ± 9 and 267 ± 14 g, respectively, at the time of surgery and 245 ± 8 and 303 ± 13 g, respectively, at the time of experiment (Charles River Laboratories). The rats were housed individually in Plexiglas cages at 22 ± 1°C in a 12:12-h light-dark cycle (lights on at 0700) and were handled several times before an experiment to familiarize the animal with the investigator. All animals had continuous access to food (Lab Diet 5001) and tap water.

Surgical Preparation

No less than 5 days before an experiment, each rat was anesthetized by an intraperitoneal injection of pentobarbital...
sodium (50 mg/kg). A paramedian laparotomy was performed, and a free-floating battery-operated biotelemetry device (VM-FH, Mini-Mitter) was inserted into the peritoneal cavity for later measurement of core temperature. The skin was then sutured to close the incision.

The animal's head was then 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 cerebral 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 (26). J eweler's screws and dental acrylic were used to fix the guide cannula to the skull. The skin was then sutured to close the incision. A 25-gauge stainless steel styllet was placed into the guide cannula between surgery and an 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**

For an experiment, each animal was placed into a metabolic chamber, which consisted of a 60-cm double-walled Perspex cylinder with an internal diameter of 10 cm and a perforated plastic platform along the bottom. Ambient temperature within the chamber was maintained at 25 ± 1°C by circulating water from a temperature-controlled bath (Endocal Refrigerated Circulating Bath RTE-8DD) between the walls of the cylinder. The metabolic chamber was placed over a series of platform antennas (PhysioTel CTR 86, Data Sciences International), which received the output frequency (Hz) from the biotelemetry device and interfaced with a peripheral processor (Dataquest III, Data Sciences International) for determination of core temperature. Room air flowed into the chamber at a rate of 2.07 l/min.

**Experimental Protocol**

Two series of experiments were carried out. The first series of experiments was designed to define the relationship between intracerebroventricular injection of PGE1 and the core temperature responses of both pregnant and nonpregnant rats. The second series of experiments was designed to test the hypothesis that AVP mediates the attenuated febrile response to intracerebroventricular administration of PGE1 near the term of pregnancy in rats.

Experimental series 1. Twenty-eight nonpregnant and 31 pregnant rats were randomly divided into six groups based on injectate, and each animal was studied only once. The rats were given an intracerebroventricular injection of either vehicle or PGE1 on the day of an experiment, the animal was brought into the laboratory, weighed, and placed in the metabolic chamber for 1 h. At the end of this hour, control measurements were made. A period of five consecutive measurements at 2-min intervals in which core temperature was stable (±0.2°C) was considered to be a suitable control period. The rat was then removed from the metabolic chamber and given an intracerebroventricular injection of either vehicle or 1.0 nmol vasopressin (V1-receptor antagonist) in 10 µl aCSF. The rat was then returned to the chamber for 30 min, during which core temperature was recorded at 6-min intervals. A second intracerebroventricular injection of either vehicle or 0.2 µg PGE1 in 10 µl of aCSF was then administered, and core temperature was recorded at 6-min intervals for 2 h. After an experiment, the animal was removed from the metabolic chamber and correct cannula placement was verified as previously described.

**Prostaglandin**

PGE1 was purchased as Prostin from Upjohn (ampule of 500 µg/ml). aCSF [in mM: 128 NaCl, 2.5 KCl, 1.3 CaCl2, 1.0 MgCl2, 135 Cl− (19)] was added to make working solutions of 40, 200, or 400 µg/ml of PGE1. These solutions were divided into 0.25 ml portions and stored in sterile plastic vials at −70°C. At the time of injection, the desired solution was removed from the freezer, and the injection cannula was filled with the appropriate volume of PGE1.

**Vasopressin V1a-Receptor Antagonist**

A selective vasopressin V1a-receptor antagonist (Pmp1, O-Me-Tyr2-[Arg8]-vasopressin) was purchased as powder form from Peninsula Laboratories. The powder was dissolved in aCSF to make a working solution of 0.2 nmol/µl. This solution was divided into 0.25-ml aliquots and stored in sterile plastic vials at −20°C. Injections were made in the same manner as the prostaglandin injections, with a total injected volume of 10 µl.

**Statistical Analysis**

Statistical analysis was carried out using a three-factor ANOVA for repeated measures followed by a Newman-Keuls multiple-comparison test to determine whether state (nonpregnant or pregnant), injectate (vehicle or vasopressin V1a-receptor antagonist), or time influenced the core temperature response to PGE1. An ANOVA followed by a Newman-Keuls multiple-comparison test was used to determine whether drug or state influenced fever indexes. Fever indexes for the 2-h period following the second intracerebroventricular injection were expressed as area under the core temperature curve.
in degrees Celsius per hour. All data are presented as means ± SD, and P < 0.05 was considered to be of statistical significance.

RESULTS

Experimental Series 1

Intracerebroventricular administration of 0.2 µg PGE₁ produced an approximate half-maximal core temperature response in both nonpregnant and pregnant animals. This dose was therefore used in subsequent experiments to test the hypothesis that a pregnancy-related activation of AVP as an endogenous antipyretic substance limits the febrile response to intracerebroventricular injection of PGE₁.

Experimental Series 2

After intracerebroventricular administration of vehicle, intracerebroventricular administration of 0.2 µg PGE₁ produced significant increases in core temperature in both nonpregnant and pregnant animals (Fig. 1). The core temperature response, however, was significantly attenuated in pregnant compared with nonpregnant animals (Fig. 2). There were no significant effects on core temperature of intracerebroventricular administration of vehicle following intracerebroventricular administration of a vasopressin V₁-receptor antagonist.

After intracerebroventricular administration of V₁-receptor antagonist, intracerebroventricular administration of 0.2 µg PGE₁ again produced significant increases in core temperature in both nonpregnant and pregnant animals (Fig. 3). This time, however, the core temperature responses to PGE₁ were similar in pregnant and nonpregnant animals whether they were expressed as change in core temperature (Fig. 4) or as fever index (Fig. 5). There were no significant effects on core temperature of intracerebroventricular administration of vehicle following intracerebroventricular administration of a vasopressin V₁-receptor antagonist.

DISCUSSION

Our experiments provide new information about pregnancy and fever in rats. Novel findings in our study were that 1) intracerebroventricular injection of 0.2 µg PGE₁ following an intracerebroventricular injection of vehicle produced a significant increase in core temperature in both nonpregnant and pregnant animals, the magnitude and duration of which, however, were significantly greater in nonpregnant compared with pregnant rats, and 2) intracerebroventricular injection of 0.2 µg PGE₁ following an intracerebroventricular injection of a vasopressin V₁-receptor antagonist produced a signifi-
cant increase in core temperature that was similar in nonpregnant and pregnant animals. Thus our data support the hypothesis that a pregnancy-related activation of AVP as an endogenous antipyretic substance in the central nervous system attenuates the febrile response to intracerebroventricular administration of PGE₁ near the term of pregnancy in rats.

Fever, which is defined as a regulated increase in core temperature (32), is achieved by activation of heat-conserving and heat-producing mechanisms, the relative contributions of which depend on the pyrogen dose and type, the ambient temperature, and the age and size of the host (3). Considerable evidence has accumulated that prostaglandins of the E series play a role in mediating the febrile response to exogenous and endogenous pyrogens (33). More than twenty years ago, Milton and Wendlandt (22) showed that intracerebroventricular administration of PGE produced a dose-dependent increase in deep body temperature in cats. Similar observations have been made in other species, including rabbits (23) and rats (20, 28), and numerous studies have shown that prostaglandins are released into the cerebrospinal fluid during pyrogen-induced fevers (2, 6, 27). Furthermore, Komaki et al. (18) have shown that an intravenous injection of interleukin-1β causes release of PGE₂ into the interstitial fluid of the organum vasculosum laminae terminalis and the medial preoptic area of the hypothalamus in rats. Although it is generally acknowledged that PGE₂ is likely to be the “natural” prostaglandin mediator of fever, there is no evidence that PGE₁, as used in our experiments, acts in any way differently from PGE₂ (24).

That fever is suppressed at term of pregnancy was first shown to occur in sheep by Kasting et al. (16) in 1978. From these early experiments, they suggested that fever was suppressed around the time of parturition by some endogenously produced substance to...
which they gave the term endogenous antipyretic. Subsequent experiments provided evidence that AVP functions as an endogenous antipyretic substance and that its site of action is not peripheral but rather in the ventral septal region of the brain rostral to the anterior commissure and close to the diagonal band of Broca (7). Following these experiments, it was suggested that "arginine vasopressin may be involved in a form of natural antipyresis occurring around the time of parturition in the ewe and in the newborn lamb" (7). The site of action is not species specific because it has been shown that injection or perfusion of AVP into the ventral septal area has an antipyretic effect in sheep (7), rabbits (25), guinea pigs (38), and rats (29). AVP has been shown to exert its antipyretic effect through the vasopressin V1 receptor rather than through the vasopressin V2 receptor (8). In the rat, the antipyretic action of AVP is evident when the peptide is infused into the cerebroventricular system (36, 37) as well as when it is injected into the ventral septal area (29). This apparent exception to site specificity may result from the fact that the rat brain is small enough to allow cerebroventricular AVP to reach the ventral septal area in sufficient concentration to promote antipyresis. Similarly, this may explain why a cerebroventricular injection of a vasopressin V1-receptor antagonist was successful in restoring the febrile response to PGE1 in rats during late gestation in our experiments.

In summary, our data support the hypothesis that a pregnancy-related activation of AVP as an endogenous antipyretic substance limits the febrile response to intracerebroventricular injection of PGE1. Although prostaglandins of the E series play a role in mediating the febrile response to exogenous and endogenous pyrogens (33) as well as to psychological stress (4, 31), whether or not the pregnancy-related alteration of the thermoregulatory responses to these stimuli is mediated solely by AVP functioning as an endogenous antipyretic substance in the central nervous system remains to be determined.

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