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LPS induced hypothermia in pregnant rats: A regulated thermoregulatory response

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Abstract

Intraperitoneal administration of *E. coli* LPS in doses that elicit half-maximal (EC_{50} – 20 ug/kg) and maximal (EC_{100} – 160 ug/kg) febrile responses in nonpregnant rats produce hypothermia in near-term pregnant rats. The present experiments have been carried out to determine if the hypothermia results from a "regulated" or "forced" thermoregulatory response. Chronically-instrumented pregnant rats were allocated to one of two experimental groups depending upon whether they were studied in an experimental apparatus configured as a metabolic chamber with a uniform ambient temperature of 25 °C or configured as a thermocline with a linear temperature gradient ranging from 10 °C to 40 °C. The pregnant rats developed hypothermia following intraperitoneal administration of 160 ug/kg of *E. coli* LPS when they were studied in the thermal gradient as well as when they were studied in the uniform thermoneutral environment. They did not attempt to prevent the hypothermia following administration of bacterial pyrogen by moving to a warmer region of the thermocline. Thus, our data provide evidence that the hypothermia which occurs following intraperitoneal administration of an EC_{100} dose of *E. coli* LPS results from a regulated rather than a forced thermoregulatory response. The mechanism and consequences of this pregnancy-induced thermoregulatory response to bacterial pyrogen are unknown.

Keywords: Fever; Pregnancy; Rat

1. Introduction

Numerous physiological changes occur during the maternal adaptation to pregnancy including reversible changes in thermoregulatory control. In rats, these include a "regulated" decrease in core temperature near the term of pregnancy and a "forced" increase in core temperature shortly after parturition and during lactation [1,2]. In addition to alterations in basal thermoregulatory control, pregnancy also influences the thermoregulatory response to cold, psychological stress and bacterial pyrogen [3–5]. For example, we have recently shown that intraperitoneal administration of *E. coli* LPS in doses that elicit half-maximal (EC_{50}) and maximal (EC_{100}) febrile responses in nonpregnant rats produce a gestation- and dose-dependent hypothermia in pregnant rats [5]. At present, we do not know the mechanism or consequences of this pregnancy-induced thermoregulatory response to bacterial pyrogen.

Does the hypothermia result from a forced thermoregulatory response such that core temperature falls below the central nervous system thermoregulatory set-point and represent pathophysiology secondary to decreased metabolic heat production, hypotension and uncontrolled heat loss, and perhaps the early stages of a septic-shock-like state? Alternatively, does the hypothermia result from a regulated thermoregulatory response such that core temperature follows a decrease in the central nervous system thermoregulatory set-point and represent a unique but normal physiological component of the maternal adaptation to pregnancy [6–9]? If the hypothermia is forced and results from decreased metabolic heat production, hypotension and uncontrolled heat loss, one would expect near-term pregnant rats to maintain their core temperature or perhaps to mount a febrile response if studied in a thermal gradient (i.e., a thermocline) where they could minimize heat loss and/or facilitate heat gain by moving to an ambient temperature near or above their core temperature. Accordingly, the present experiments have been carried out to investigate the core temperature response of near-term pregnant rats to bacterial pyrogen when they were studied in

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a thermocline with a linear thermal gradient of 10 °C to 40 °C as well as when they were studied in a metabolic chamber regulated to 25 °C (i.e., the selected ambient temperature and thermoneutral temperature of nonpregnant and pregnant rats [2]). We hypothesized that near-term pregnant rats would maintain their core temperature following administration of bacterial pyrogen when they were studied in a thermocline and thus allowed to utilize behavioral as well as autonomic thermoregulatory effectors to regulate core temperature.

2. Methods

Experiments were carried out on 19 time-mated pregnant Sprague Dawley rats (Charles River Laboratories) undergoing their first pregnancy; the day of mating was considered to be day 0 of gestation. The rats were housed individually in Plexiglas cages kept in a humidity- (30–40%) and temperature- (25 ± 1 °C, the selected ambient temperature and thermoneutral temperature of nonpregnant and pregnant rats [2]) controlled environmental chamber on a 12:12 h light–dark cycle with lights on from 0700 h. The rats were handled and draped to simulate the injection protocol before being placed in the apparatus of study — metabolic chamber or thermocline — for 1 h on the 3 consecutive days before an experiment to familiarize the animals with the investigator and experimental procedures. All animals had continuous access to food (Lab Diet 5001) and tap water.

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.

2.1. Experimental protocol

The pregnant rats were allocated to one of two experimental groups depending upon whether the experimental apparatus in which they were studied was configured as a metabolic chamber with a uniform ambient temperature of 25 °C or configured as a thermocline with a linear temperature gradient ranging from 10 °C to 40 °C. On the day prior to an experiment, each rat was removed from its cage and weighed. On the day of an experiment, each rat was placed in the experimental apparatus and after at least 1 h had passed and following an acceptable control period — defined as five, two-minute measurements of core temperature that did not vary by more than ±0.2 °C — was removed from the experimental apparatus and given an intraperitoneal injection of 160 ug/kg *E. coli* LPS. The rat was then returned to the experimental apparatus and core temperature as well as position in the experimental apparatus was measured at two-minute intervals for a period of 6 h. All experiments were carried out during the light cycle and began at ~1000 h to avoid circadian variations in basal core and the core temperature response to perturbation.

2.2. Surgical preparation

Five days before an experiment, each animal was placed in a cylindrical anesthesia chamber (Kent Scientific Corporation) and anesthesia was rapidly induced with 2% halothane in oxygen.

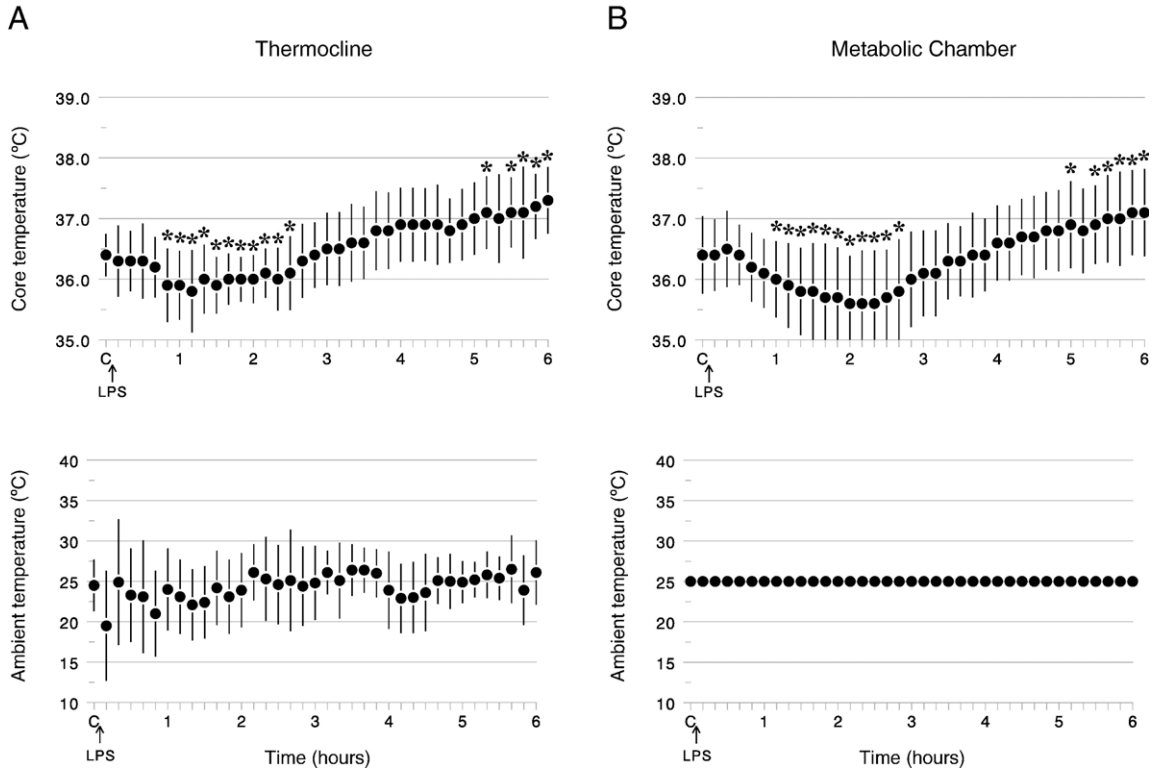

Fig. 1. Core temperature and ambient temperature measured before and after intraperitoneal administration of 160 μg/kg *E. coli* LPS (arrow) in pregnant rats studied in a thermocline (A) or metabolic chamber (B) on day 20 of gestation. Data are presented as means ± standard deviation. *$p < 0.05$ versus C by ANOVA and Newman–Keuls.