Influence of nicotine on the core temperature response to a novel environment in pregnant rats

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Exposure of a male or nonpregnant female rat to a novel environment, such as a simulated open field, induces a transient increase in core temperature, which is often called stress-induced hyperthermia. Pregnancy alters this response such that the core temperature index increases significantly during exposure to a simulated open field on day 10 but not on days 15 and 20 of gestation in rats. The present experiments were carried out to determine whether chronic administration of nicotine, the primary pharmacological and addictive agent in tobacco, would alter the core temperature response to a novel environment during pregnancy in rats. The rationale for our experiments was based on the fact that chronic administration of nicotine has been shown to induce physiological changes that might alter the thermoregulatory response to perturbation. These changes include the following: 1) an increase norepinephrine turnover in brown adipose tissue of rats (16) and mice (34, 35), which is an indicator of sympathetic activity; 2) an increase guanosine diphosphate binding in brown adipose tissue of rats (16) and mice (35), which is an index of thermogenic activity; 3) an increase resting metabolic rate and oxygen consumption in brown adipose tissue in mice (35), and 4) an accentuation of the plasma corticosterone and epinephrine responses induced by immobilization stress in rabbits (19). Our experiments were carried out on chronically instrumented nonpregnant and pregnant rats that received nicotine for ~2 wk before they were exposed to a novel environment.

Methods

Experiments were carried out on 32 nonpregnant and 31 pregnant female Sprague-Dawley rats (aged 8–11 wk) undergoing their first pregnancy (Charles River Breeding Laboratories, St. Constant, Quebec, Canada). The rats were housed individually in Plexiglas cages at 22 ± 1°C in a 12:12-h light-dark cycle with lights on from 0700 to 1900 and were handled three or four times before an experiment to familiarize the animal with the investigator. All animals had continuous access to food (Lab Diet 5001, St. Louis, MO) and tap water.

Surgical preparation. For surgery, each nonpregnant and pregnant (day 7 or 8 of gestation) rat was anesthetized by inhalation of halothane (~2.0% for induction and maintenance) in oxygen. A paramedian laparotomy was done, and a free-floating battery-operated biotelemetry device (VM-FH, Mini-Mitter, Sunriver, OR) was inserted into the peritoneal cavity for later measurement of core temperature. In addition, an osmotic minipump (2ML4, ALZET, Palo Alto, CA) was inserted subcutaneously over the spine for continuous infusion of nicotine (hydrogen tartrate salt, Sigma Chemical, St. Louis, MO) dissolved in sterile water at doses of 0, 1, 2, 4, or 8 mg·kg⁻¹·24 h⁻¹ for 13–15 days.

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. Our laboratory contains two environmental chambers: a home environmental chamber in which the animals are housed on a day-to-day basis and an experimental environmental chamber that houses a simulated open field. The simulated open field consists of a 30-in. (width) × 60-in. (length) × 24-in. (height) white acrylic finish box that is illuminated by two hanging fluorescent lights.

Each pregnant and nonpregnant rat underwent two experiments: a home-cage experiment and an open-field experiment. Home-cage and open-field experiments were carried out in a random order in each animal in each of 10 groups of rats based on condition and dose of nicotine: nonpregnant (NP) 0 mg·kg⁻¹·24 h⁻¹, n = 8; NP 1 mg·kg⁻¹·24 h⁻¹, n = 6; NP 2 mg·kg⁻¹·24 h⁻¹, n = 6; NP 4 mg·kg⁻¹·24 h⁻¹, n = 6; NP 8 mg·kg⁻¹·24 h⁻¹, n = 6; pregnant (P) 0 mg·kg⁻¹·24 h⁻¹, n = 7; P 1 mg·kg⁻¹·24 h⁻¹, n = 5; P 2 mg·kg⁻¹·24 h⁻¹, n = 7; P 4 mg·kg⁻¹·24 h⁻¹, n = 6; P 8 mg·kg⁻¹·24 h⁻¹, n = 6. The nonpregnant rats were studied on 2 consecutive days, and the pregnant rats were studied on days 20 and 21 of gestation (term = 22 days). Nonpregnant and pregnant animals were exposed to nicotine for a similar duration before an experiment (i.e., 13–15 days). All experiments were carried out between 0800 and 1200 to avoid any possible circadian effects on the measured variables.

For a home-cage experiment, each rat was left in her cage in the home-environmental chamber for the duration of the experiment. For an open-field experiment, each rat was carried in her cage from the home-environmental chamber to the experimental environmental chamber. The cage was then placed on the floor, and she was picked up and placed in the center of the simulated open field.

For measurement of core temperature, both the animal cage in the home environmental chamber as well as the simulated open field in the experimental environmental chamber were placed on platform antennae (RLA1020 receiver, Data Sciences International, St. Paul, MN), which received the output frequency (Hz) from the biotelemetry device. The received output was then fed into a peripheral processor connected to an IBM computer for determination of core temperature (DataQuest III, Data Sciences International).

Experimental protocol. Core temperature was measured at 2-min intervals during a control period and at 10-min intervals for 3 h after the home-cage or open-field manipulation. A suitable control period was defined as one in which five consecutive measurements of core temperature did not vary by >0.1°C; a suitable control period was always obtained within 30 min. The reported control value for core temperature was the average of these five consecutive measurements of core temperature that did not vary by >0.1°C.

Statistical analysis. Statistical analysis was carried out by using a four-factor analysis of variance for repeated measures followed by a Newman-Keuls multiple-comparison test to determine whether time (control, 10 min, 20 min, 30 min, etc.), experiment (home cage or open field), gestation (nonpregnant or pregnant), or nicotine dose (0, 1, 2, 4, or 8 mg·kg⁻¹·24 h⁻¹) affected core temperature. In addition, a two-factor analysis of variance followed by a Newman-Keuls multiple-comparison test was used to determine whether gestation or dose of nicotine affected the core temperature index, expressed as area under the core temperature curve in degrees Celsius per hour (11). All results are presented as means ± SD. P < 0.05 was considered to be of statistical significance.

RESULTS

Chronic administration of nicotine did not significantly alter core temperature in either the nonpregnant or pregnant rats as measured during the control periods of both home-cage and simulated open-field experiments. As we have previously found (13), exposure to a simulated open field produced a significant increase in core temperature in nonpregnant but not in near-term pregnant rats (Fig. 1). Chronic nicotine administration, however, significantly altered the thermogenic response to a simulated open field in both nonpregnant and pregnant rats (Figs. 2 and 3). The core temperature index was influenced in an overall fashion by pregnancy (P < 0.001) and dose of nicotine (P < 0.001); there was not, however, an interaction between pregnancy and dose of nicotine on the core temperature index (P = 0.122). In nonpregnant rats, the core temperature index increased more during exposure to a
simulated open field after chronic administration of nicotine at all doses than after chronic administration of vehicle; the core temperature response was not dependent on the dose of nicotine. The increased core index resulted primarily from an increase in the duration of the core temperature response rather than from an increase in magnitude of the core temperature response (Figs. 1 and 3).

In pregnant rats, significant increases in the core temperature index occurred during exposure to a simulated open field after chronic administration of nicotine but only in doses of 2, 4, or 8 mg·kg⁻¹·24 h⁻¹; the core temperature response was dependent on the dose of nicotine. The increased core index resulted from an increase in the magnitude and duration of the core temperature response.

There were no significant effects of a home-cage experiment on core temperature in either nonpregnant or pregnant rats at any dose of nicotine.

**DISCUSSION**

Our experiments provide new information about the influence of nicotine on the thermoregulatory response of rats during exposure to a novel environment. A novel finding in our study was that although chronic administration of nicotine did not alter basal core temperature, it accentuated the core temperature response of both

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Fig. 3. Influence of pregnancy and nicotine on core temperature response to simulated open field. Data are means ± SD. Arrows, point of exposure to simulated open field. *P < 0.05 vs. C by ANOVA and Newman-Keuls test.
nicotine unmasks a maternal thermogenic response that is usually not present near term of pregnancy although it is during early gestation and in nonpregnant animals. From the standpoint of fetal oxygen supply and demand, it may be an advantage for the mother not to develop stress-induced hyperthermia for several reasons. One reason is that stress-induced hyperthermia may cause circulatory adjustments such that blood flow from internal body organs, including the uterus and placenta, shifts toward thermogenic organs (e.g., brown adipose tissue). A decrease in uteroplacental blood flow can compromise placental gas exchange, with a resulting decrease in fetal oxygen supply. Another reason is that during stress-induced hyperthermia, fetal core temperature, which is normally 0.4–0.8°C higher than maternal core temperature (1), would most likely increase in parallel (1) with the rise in maternal core temperature with a resulting increase in oxygen demand secondary to the temperature coefficient of metabolism (i.e., Q_10). Furthermore, in conditions in which fetal oxygen availability is severely limited (e.g., asphyxia during birth), an increase in fetal core temperature may exacerbate neuronal injury (9) and increase perinatal morbidity and mortality.

Previous experiments carried out on rodents have shown that administration of nicotine produces a decrease in core temperature but that the decrease is short lived (5, 22, 33). For example, Robinson et al. (22) showed that nicotine infusion (4 mg·kg$^{-1}$·h$^{-1}$) produced an abrupt decrease in core temperature in mice but that this effect was totally reversed within 12 h. Furthermore, Williams et al. (33) have shown that there is a circadian variation in the hypothermic effect of nicotine as well as in the development of tolerance to nicotine in rats, with both having peaks during the light phase of the light-dark cycle. Our experiments, which were carried out during the light phase of the light-dark cycle, did not show any effects of chronic administration of nicotine on basal core temperature in either nonpregnant or pregnant rats. Although our experiments were not designed to investigate the mechanism of the accentuated stress-induced hyperthermic response after chronic administration of nicotine, there are a number of possibilities. These include a heightened perception of the stimulus (2), an altered neuroendocrine response (19), and an altered thermoregulatory effector organ response (16, 34, 35). For example, Acri et al. (2) have shown that nicotine increases the amplitude of the acoustic startle reflex in rats, and this effect has been interpreted as evidence of attentional enhancement by nicotine. Furthermore, smoking has been shown to produce electroencephalogram arousal at low doses (6, 12) but may actually have an opposite effect at high doses (4).

The neuroendocrine responses to nicotine and stress have been well studied. Pertinent to the possible mechanisms of the accentuated stress-induced hyperthermia during exposure to a novel stimulus observed in our experiments are the data of Morse (19). He has shown that administration of nicotine or physical restraint increases plasma concentrations of corticosterone, epinephrine, norepinephrine, and glucose in chronically instrumented conscious rabbits. Furthermore, nicotine administration during restraint stress accentuated the increase in plasma corticosterone and epinephrine compared with the responses elicited by either factor alone. We have previously found that the corticosterone response of near-term pregnant rats is attenuated compared with nonpregnant rats when they are exposed to a simulated open field (26).

Last, it is possible that chronic administration of nicotine altered the thermoregulatory effector organ response in brown adipose tissue, which in turn accentuated stress-induced hyperthermia during exposure to a novel stimulus in both nonpregnant and pregnant animals. Previous experiments have shown that chronic exposure to nicotine increases norepinephrine turnover in brown adipose tissue, an indicator of sympathetic activity (16, 34, 35); increases guanosine diphosphate binding in brown adipose tissue, an index of thermogenic activity (16, 35); and increases resting metabolic rate and oxygen consumption in brown adipose tissue (35). All of these possible mechanisms of the accentuated stress-induced hyperthermic response after chronic administration of nicotine warrant investigation.

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