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Long-Term Thermoregulatory Changes Following Perinatal Methadone Exposure in Rats[1]

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THOMPSON, C. I. AND I. S. ZAGON. *Long-term thermoregulatory changes following perinatal methadone exposure in rats*. PHARMAC. BIOCHEM. BEHAV. **14**(5) 653–659, 1981.—Offspring of female rats injected daily with methadone (5 mg/kg, IP) or saline were cross-fostered at birth to form drug groups exposed during gestation (G), lactation (L), or both gestation and lactation (G-L); controls were exposed only to saline. Rectal temperatures were taken on postnatal Days 20, 43, 57 and 75, and at 3-day intervals from Days 128–140 and 157–169. Ambient temperature was 21°C except from Days 131–134 (10°C) and 160–163 (33°C). Methadone-exposed rats tended to have lower rectal temperatures than controls at 21°C; this was significant on Days 57 and 160 for Group G, on Days 43 and 160 for Group L, and on Days 43, 57, 128, 160 and 166 for Group G-L. Relative to controls, Groups G and G-L became hypothermic during cold stress and hyperthermic during heat stress. Thermal deviations were unrelated to changes in food intake and body weight. These results indicate that perinatal methadone exposure in rats produces thermoregulatory changes that persist into adulthood.

Methadone Maternal narcotics Behavioral teratology Body temperature Ambient temperature Body weight Food intake Defecation Rats

METHADONE, like other opiate agonists, can induce substantial changes in body temperature [1,24]. The magnitude and direction of these changes depend upon several factors, including drug dosage and ambient temperature. In adult rodents, for example, acute injections of methadone have been reported to cause a dose-dependent hypothermia that increases in magnitude as the ambient temperature is reduced below 21°C [20,24], whereas a dose-dependent hyperthermia occurs at an ambient temperature of 30° [24].

Immature organisms are particularly sensitive to the effects of methadone upon body temperature. Shah and Donald [25] reported that 8-day-old rats injected with 5 mg/kg methadone (and tested at an ambient temperature of 24.5°C) exhibited an 8°C drop in rectal temperature when compared with saline-injected controls, whereas at 20 days the same acute dose reduced rectal temperature by only 4°. Using a different exposure paradigm, we demonstrated that the maternal use of methadone, either during gestation and lactation or during lactation only, caused rat offspring to have an abnormally low rectal temperature at 39–51 days of age [31]. Average core temperatures ranged from 0.5° to 1.0°C below control values at an ambient temperature of 21°C, and rats exposed during both gestation and lactation exhibited an additional drop of 0.5° below control values after three days at an ambient temperature of 10°C.

The purpose of the present study was to further investigate the short-term and long-term implications of perinatal methadone exposure for thermal regulation. From 20 to 169 days of age, rectal temperatures of rats maternally exposed to methadone during gestation and/or lactation were periodically compared, at normal room temperature (21°C), with those of control animals whose mothers received saline. In addition, temperatures of adult offspring were measured in response to 3-day periods of cold stress (10°C) and heat stress (33°C). Food intake, body weight, and incidence of defecation during weighing also were recorded, in order to investigate any possible association between these variables and alterations in core temperature.

METHOD

Animals and Treatment Groups

Sprague-Dawley male (250–300 g) and primiparous female (210–240 g) rats, obtained from Charles River Labs (Wilmington, MA), parented the offspring tested in this study. These adults were housed under standard laboratory conditions, described in detail elsewhere [34], and were allowed 6 days to acclimate to their surroundings prior to the initiation of experimental procedures.

Adult female rats were divided into two treatment groups.

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One group received daily (0800 hr) IP injections of 5 mg/kg *dl*-methadone hydrochloride (Dolophine; Eli Lilly Co., Indianapolis, IN) beginning 5 days prior to mating and continuing until 21 days after parturition. A second group received an equivalent volume of physiologic saline throughout this period. Female rats were weighed every two days and appropriate dosage adjustments made. Five days after initiating the drug treatment females were housed with a single male, and vaginal smears were taken daily until the presence of sperm indicated that mating had occurred. Three days prior to parturition, pregnant females were housed in solid-bottom cages containing Easi-Litter (Westminster Scientific Co., Westminster, MD) to deliver their young.

Within 4 hr of birth all offspring were cross-fostered to methadone- or saline-injected mothers in order to establish four treatment groups: (1) Group G-L was exposed to methadone during both gestation and lactation; (2) Group G was exposed to methadone during gestation only; (3) Group L was exposed to methadone during lactation only; and (4) Group C was an injection-control group whose biological and foster mothers both were injected with saline. Litters were culled to 10 pups per foster mother on postnatal Day 4, with 5 males and 5 females in each litter.

At weaning (postnatal Day 21), rat pups were removed from their mothers and the 5 like-sexed offspring from each foster litter were housed together in wire-bottom cages with a 2700 cm^2 floor area. This housing arrangement was maintained until termination of the study, except that any deaths reduced the number of animals within a cage to less than 5. Offspring received no drug or saline treatments after weaning. Water and Wayne Laboratory Chow were available ad lib throughout all phases of the experiment.

A total of 120 rats were tested. At the beginning of the study there were 60 control animals and 60 methadone-exposed animals, with 20 rats each in Groups G, L, and G-L. Males and females were equally represented in all groups. By the end of the study (Day 169), subject attrition had reduced group sizes to the following: Group C, 27 males and 29 females; Group G, 9 males and 7 females; Group L, 5 males and 9 females; and Group G-L, 9 males and 10 females.

Apparatus and Environmental Rooms

Rectal temperatures were determined using a Yellow Springs Telethermometer (Model 47). Increases in body size necessitated the use of a small probe for animals 43 days of age and younger, and a larger probe thereafter; both were calibrated against one another in a water bath. Measurements were taken with the probe inserted to a constant depth that increased with age (e.g., 4 cm at 20 days and 8 cm at 154 days and older). Rats were placed in plastic restrainers of appropriate size for the 60 sec required to obtain a stable reading.

Rats normally were housed at an ambient temperature of 21 ± 0.5°C and a humidity of 50 ± 10%. The only exceptions were two 3-day periods when rats were maintained at 10°C (Days 131–134) or at 33°C (Days 160–163). A 12:12 light-dark cycle was maintained at all times, with lights on at 0700 hr.

Procedure

Core temperature and body weight were recorded on postnatal days 20, 43, 57 and 75, at an ambient temperature of 21°C. Rats were evaluated in a randomized sequence between 0830 and 1130 hr, with body weights taken immediately prior to core temperatures.

The effects of cold stress upon core temperature, food intake, body weight, and defecation during the weighing procedure were assessed using measurements taken at 3-day intervals from Days 125 to 140. Immediately following the measurements on Day 131, all rats were removed from the usual 21°C environment and were placed for 3 days in a room maintained at 10°C. Measurements were recorded in the cold room on Day 134, following which all animals were returned to the 21° environment for the remainder of this series. Food intake was calculated as the average 3-day consumption per animal for all rats within a given home cage. Incidence of defecation during weighing was recorded as the number of boluses deposited in the weighing basket during the interval required to determine body weight.

Effects of heat stress were evaluated by a series of measurements taken at 3-day intervals from Days 154 to 169. Test procedures and dependent variables were identical to those used during the cold stress series. Immediately following the measurements on Day 160, all animals were transferred from their usual 21°C environment to a room maintained at 33°, where they remained until after measurements were recorded on Day 163; they then were returned to the 21° environment for the remainder of the study.

Data Analysis

Data were analyzed by analysis of variance (ANOVA), using an unweighted means procedure to correct for the unequal numbers of cases in each cell [33]. The four Drug Treatments (Groups G, L, G-L, and C) and Sex were treated as between-group variables; Days was a repeated variable whenever the analysis included measures taken on more than one day. The conservative adjustment of Greenhouse and Geisser [10], which reduces the df of both numerator and denominator prior to entering the table of critical F values, was made on all tests involving a repeated variable; the reduced dfs are identified hereafter as "corrected" values. Tests subsequent to ANOVA were made using the Neuman-Keuls procedure [33].

Data were analyzed under three headings: (1) development, Days 20–75; (2) cold stress, Days 128–140; and (3) heat stress, Days 157–169. In the ANOVAs related to development, body temperatures were analyzed in a single analysis, with Days as a repeated measure; body weights were analyzed separately at each age. In the cold stress ANOVAs, rectal temperatures on Days 128, 131, 134, 137 and 140 were repeated measures, with temperatures on Day 134 obtained at 10°C. Body weights, defecations during weighing, and 3-day food intakes were analyzed using analyses similar to that used for temperature, with the following exceptions: (1) defecation scores were analyzed for six days (including Day 125), rather than five, because of a relatively high frequency of defecation at the beginning of the series; and (2) the unit of analysis for food intake was average consumption of all animals within a home cage (containing rats from a single drug treatment and sex combination), rather than a score for each animal. The heat stress ANOVAs analyzed the same variables as those analyzed for the cold stress group. The form of each heat stress ANOVA was identical to that described for the cold stress analyses.

RESULTS

Development

Rectal temperature. Mean rectal temperatures for each

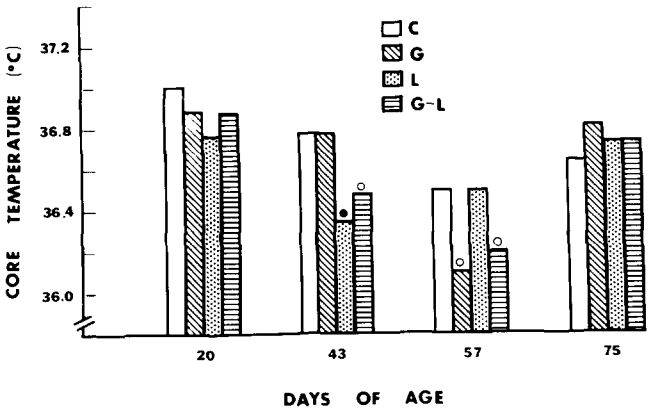

FIG. 1. Rectal temperatures of developing male and female rats following perinatal exposure to maternally-administered methadone. All measures were taken at an ambient temperature of 21°C. The within-group error estimate ($\sqrt{\text{MS error}/n}$, harmonic $\bar{x}$) is 0.09°C. Abbreviations: C, control rats whose mothers received saline (29 male, 29 female); G, rats exposed to methadone only during gestation (10 male, 10 female); L, rats exposed to methadone only during lactation (birth to 21 days, 6 male, 6 female); G-L, rats exposed to methadone during both gestation and lactation (10 male, 10 female). ○Significantly lower than controls, $p<0.05$. ●Significantly lower than controls, $p<0.01$.

TABLE 1

BODY WEIGHT OF RAT OFFSPRING PERINATALLY EXPOSED TO METHADONE

		Drug Treatment*			
Age	Error†	C	G	L	G-L
20	± 0.3	45.8‡	35.8§¶	38.2§	37.6§
43	± 3.4	127.5	129.6	109.6§	118.9
57	± 5.5	182.0	189.4	170.7	181.9
75	±11.9	260.5	254.5	241.8	260.1
128–140	± 2.9	383.2	365.6§	352.4§¶	387.4
157–169	± 3.3	405.5	382.3§	363.8§¶	406.6

*Abbreviations: C, control rats whose mothers received saline; G, rats exposed to methadone during gestation; L, rats exposed to methadone during lactation; G-L rats exposed to methadone during both gestation and lactation.

†Within-group error estimate($\sqrt{\text{MS error}/n}$, harmonic $\bar{x}$). Presented for average weight on Days 128–140 and 157–169 (1/5 the error estimate for 5 combined weights).

‡Unweighted means (males and females), in g. Presented as average weight (1/5 or 5 combined weights taken at 3-day intervals) for Days 128–140 and 157–169.

§Significantly less than controls, $p<0.01$.

¶Significantly less than all other groups, $p<0.01$.

drug group on Days 20, 43, 57 and 75 are shown in Fig. 1; there were no sex differences at these ages, and data from males and females are combined. The Drug Treatment×Age interaction was statistically significant, F(3,106 corrected)=4.14, $p<0.01$. Subsequent tests revealed that: (1) methadone-exposed rats tended to have lower temperatures than controls on Days 43 and 57 (significant for Groups L and G-L on Day 43, and for Groups G and G-L on Day 57); (2) there were no between-group differences in rectal temperatures on Days 20 or 75; and (3) all four treatment groups exhibited significantly lower rectal temperatures on Day 57 than they did on Days 20 or 75 (all ps<0.05).

Body weight. Body weights are shown in Table 1 for rats in Groups C, G, L, and G-L. Overall group differences (males and females combined) were statistically significant on Day 20, F(3,112)=153.38, $p<0.01$, and on Day 43, F(3,112)=7.50, $p<0.01$, but not on Days 57 or 75. Subsequent tests revealed that on Day 20 rats from all three methadone-exposed groups weighed significantly less than the control animals, with the percentage less ranging from 16.6% (Group L) to 21.8% (Group G). On Day 43, only rats in Group L weighed significantly less (14.0%) than the control animals.

Sex differences in body weight were significant at all four ages (all ps<0.01). Mean weights for males vs females were as follows: Day 20, 39.8 vs 38.9 g; Day 43, 129.8 vs 112.6 g; Day 57, 200.7 vs 161.2 g; and Day 75, 297.9 vs 210.5 g.

Cold Stress

Rectal temperature. Mean rectal temperatures during the cold stress series are shown in Fig. 2. The Drug Treatment×Day interaction was statistically significant, F(3,103 corrected)=4.05, $p<0.01$, reflecting the fact that differences between the methadone-exposed and control rats were greater at an ambient temperature of 10°C than they were at 21°C. Methadone-exposed animals usually exhibited no temperature abnormality when the ambient temperature was 21°C; the only exception occurred for rats in Groups G-L, whose rectal temperatures were below control values on Day 128. When the ambient temperature was 10°C, however, rectal temperatures were significantly below control levels for rats in groups G and G-L; this reduction was greatest for rats in Group G-L, whose rectal temperatures were significantly lower even than those of the animals in Group G.

Analysis of within-group changes across days in the cold stress series (Fig. 2) revealed that the rectal temperatures of rats from all three methadone-treated groups were significantly lower during cold stress (Day 134) than they had been immediately prior to entering the cold room (Day 131, all ps<0.05), whereas control rats exhibited no significant drop in body temperature. Three days after termination of the cold stress (Day 137), however, body temperatures of rats from all four groups, including the controls, were significantly higher than they had been on Day 134 (all ps<0.05).

Core temperatures of female rats were higher than those of males across Days 128–140, and the overall Sex factor was statistically significant, F(1,103)=29.15, $p<0.01$. Average rectal temperature on the five combined test days was 37.93°C for female rats, and 37.51°C for males. There was no interaction between Sex and Drug Treatment: that is, any effects of a particular methadone treatment upon core temperature were similar for males and females.

Food intake. Rats from the four treatment groups consumed different total amounts of food on Days 125–140, and the overall Drug Treatment effect was significant,

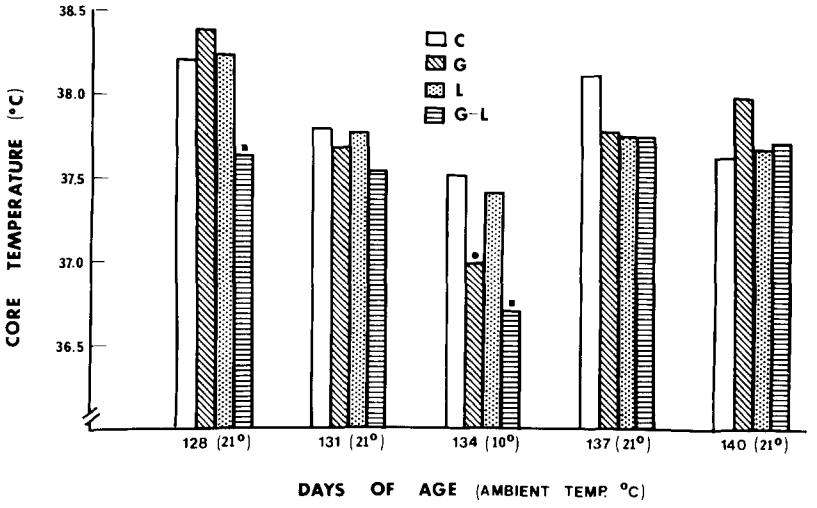

FIG. 2. Rectal temperatures before, during, and after a 3-day period of cold stress in adult male and female rats perinatally exposed to methadone. The within-group error estimate ($\sqrt{\text{MS error}/n}$, harmonic $\bar{x}$) is 0.11. Abbreviations: See Fig. 1. ●Significantly lower than controls, $p<0.01$. ■Significantly lower than controls and all other methadone groups, $p<0.01$.

$F(3,16)=3.90$, $p<0.05$. Mean 15-day intakes, for males and females combined, are shown in Table 2. Rats in Group G ate 8.1% more food than control animals, rats in Group L ate 10.6% less than controls, and rats in Group G-L did not differ from controls in food consumption. There were no interactions between Drug Treatments and Days or Sex, indicating that the effects of perinatal methadone upon food intake were equivalent for male and female offspring and were not dependent upon ambient temperature.

Food intake for all animals was greatest at 10°C, and the overall Days effect was significant, $F(1,16$ corrected$)=67.88$, $p<0.01$. Average food consumption for males and females of all groups was 102.3 g during the 3 days at 10°C, compared to an average intake that ranged from 82.5 g to 87.1 g during the four 3-day periods that ambient temperature was 21°C.

Body weight. Average body weights for each drug group (male and female combined) on the five measurements taken from Days 128–140 are shown in Table 1. The overall Drug Treatment effect was significant, $F(3,103)=6.26$, $p<0.01$. Rats in Group G-L exhibited no abnormality in body weight, but rats in Groups G and L weighed significantly less than the controls (4.6% and 8.0% less, respectively). Low weights were most evident in Group L, where the rats weighed significantly less even than those in Group G.

Male rats from all groups gained more weight than females during Days 128–140, and the Day×Sex Interaction was significant, $F(1,103$ corrected$)=6.76$, $p<0.05$. Mean body weights for all males on Days 128, 131, 134, 137 and 140 were 455.2, 466.8, 458.3, 465.8 and 473.2 g, respectively, and the corresponding means for females were 277.3, 282.3, 276.0, 283.1 and 283.3 g.

Defecation during weighing. Total defecation scores, recorded during the six weighing sessions on Days 125–140, were significantly higher for rats in the control group (mean=9.6) than for animals in Groups G, L or G-L (means=5.2, 6.6 and 5.0, respectively), $F(3,103)=3.13$, $p<0.05$. The Sex factor was significant, $F(1,103)=8.13$, $p<0.01$, with male rats defecating more often than females (mean=8.3 vs 4.9). The Days factor also was significant, $F(1,103$ corrected$)=12.71$, $p<0.01$, with rats defecating more often on the first day of the series (Day 125, mean=2.3) than on any of the remaining five days (range of means=1.0 to 1.3).

TABLE 2

FOOD INTAKE OF ADULT RATS PERINATALLY EXPOSED TO METHADONE

		Drug Treatment* (Number of Cages)†			
Days‡	Error§	C (12)	G (4)	L (4)	G-L (4)
125–140	±9.0	442.8¶	478.8#	395.7**	450.7
154–169	±5.4	385.4	388.4	329.7**	380.6

*Abbreviations: See Table 1.

†Unit of analysis is mean intake for all animals within a cage; equal numbers of male and female cages in each drug treatment.

‡Ambient temperature 10°C on Days 131–134, 33° on Days 160–163, and 21 on all other days.

§Within-group error estimate($\sqrt{\text{MS error}/n}$, harmonic $\bar{x}$).

¶Mean 15-day intake (g) per animal; males and females combined.

#Significantly greater than controls, $p<0.05$.

**Significantly less than controls, $p<0.01$.

Heat Stress

Rectal temperature. Mean rectal temperatures during the heat stress series are shown in Fig. 3. The Drug Treatment×Day interaction was statistically significant, $F(3,97$

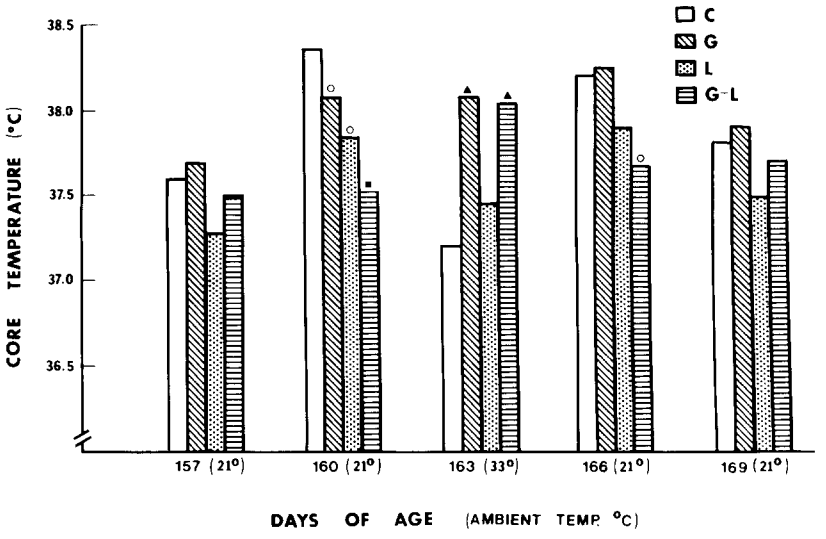

FIG. 3. Rectal temperatures before, during, and after a 3-day period of heat stress in adult male and female rats perinatally exposed to methadone. The within-group error estimate ($\sqrt{\text{MS error}/n}$, harmonic $\bar{x}$) is 0.11. Abbreviations: See Fig. 1. ○Significantly lower than controls, $p<0.05$. ■Significantly lower than controls and all other methadone groups, $p<0.01$. ▲Significantly higher than controls, $p<0.01$.

corrected)=6.53, $p<0.01$, reflecting a tendency for the body temperatures of methadone-exposed rats to be equal to or lower than control values at an ambient temperature of 21°C, but higher than control values at an ambient temperature of 33°C. Subnormal rectal temperatures at 21°C were most apparent on Day 160, at which time temperatures for all three methadone-exposed groups were significantly below control values, with Group G-L temperatures the lowest of all. In contrast, heat stress (Day 163) resulted in an abnormal elevation of body temperature in Groups G and G-L; these two groups were the same ones that had been hypothermic relative to controls during cold stress.

Analysis of within-group changes across days in the heat stress series (Fig. 3) revealed that the rectal temperatures of control rats *decreased* after three days at 33°C; that is, body temperatures were significantly lower on Day 163 than they had been either immediately before entry into the hot room (Day 160) or three days after reentry into the 21°C environment (Day 166). Rats in Group L, who maintained their rectal temperatures at control levels during heat stress, also exhibited a significantly lower temperature on Day 163 than they did on Days 160 and 166. In contrast, rats in Group G, who were hyperthermic relative to controls on Day 163, exhibited no significant changes in body temperature across Days 160–166; thus, their relative hyperthermia on Day 163 resulted from a failure to lower their rectal temperature normally in response to heat stress. Rats in Group G-L, who also were hyperthermic on Day 163, had a significantly higher core temperature on Day 163 than on any other day; their hyperthermia during heat stress thus reflected an actual elevation of body temperature.

Core temperatures of female rats were higher than those of males, and the overall Sex factor was significant, $F(1,97)=48.66$, $p<0.01$. Average rectal temperature on Days 157–169 was 38.08°C for female rats, and 37.51°C for males. The effects of methadone upon rectal temperature were similar for males and females (i.e., no interaction between Drug Treatment and Sex).

Food intake. Mean food intake from Days 154 to 169, for males and females combined, is shown in Table 2. The overall Drug Treatment effect was significant, $F(3,16)=5.21$, $p<0.05$. Rats in Group L ate 14.5% less food than controls, whereas the food intake of rats in Groups G and G-L did not differ from control levels. These differences are similar to those that occurred on Days 125–140, except that Group G consumed more food than controls during the earlier 15-day period.

Male rats from all groups consistently consumed more food than females, but during the three days of heat stress this difference (18.3 g) was less than that observed during the remaining 3-day periods (range=25.0 to 32.1 g), resulting in a significant Day×Sex interaction, $F(1,16$ corrected)=5.59, $p<0.05$. Rats of both sexes consumed significantly less food during heat stress (males 64.7 g, females 46.4 g) than they did during any other 3-day period (range=86.1 to 101.7 g for males, 61.1 to 70.0 g for females).

Body weight. Average body weights on Days 157–169 for rats in each drug treatment group (male and female combined) are shown in Table 1. The overall Drug Treatment effect was significant, $F(3,97)=7.38$, $p<0.01$. Body weights of rats in Groups G and L were significantly below control levels (5.7% and 10.3%, respectively), with rats in Group L weighing significantly less even than those in Group G; in contrast, rats in Group G-L did not differ from the controls. This pattern of weight differences is identical to that observed earlier, on Days 128–140.

Male rats from all groups consistently weighed more than females, but after three days of heat stress the average magnitude of this difference was less than on any of the other four measurement days, resulting in a significant Day×Sex

interaction, $F(1,97 \text{ corrected}) = 15.99$, $p < 0.01$. Mean body weights for males on Days 157, 160, 163, 166 and 169 were 499.0, 504.8, 479.7, 501.1 and 503.9 g, respectively, and the corresponding means for females were 294.0, 297.4, 293.0, 296.1 and 300.1 g.

Defecation during weighing. Overall group differences in incidence of defecation, measured during the six weighing sessions on Days 154–169, were only marginally significant, $F(3,97) = 2.61$, $p < 0.10$. However, specific comparisons using the Neuman-Keuls procedure suggested that rats in Group G-L defecated less frequently (mean=2.7) than did rats in Groups G, L and C (means=6.1, 6.6 and 6.7, respectively; all $ps < 0.01$). Overall, male rats defecated more often than females (mean=8.3 vs 3.5), $F(1,97) = 17.61$, $p < 0.01$.

DISCUSSION

The maternal use of methadone during pregnancy or lactation directly exposes the infant to this opioid. Methadone has been shown to cross the placenta and enter the fetal circulation of humans [2,13], and rodents [15, 23, 26], and to enter the milk of lactating humans on methadone maintenance [3].

In an earlier paper [31], we reported that some schedules of perinatal methadone exposure (L or G-L) caused rats to be hypothermic relative to controls at 39–51 days of age, at ambient temperatures of either 21°C or 10°C. The present study shows that: (1) changes in body temperature can persist considerably longer than 51 days; (2) these changes can take the form of either an increase or a decrease, depending on the ambient temperature; and (3) the extent of the abnormality depends upon the schedule of methadone exposure.

This study provided no evidence for abnormal rectal temperatures in any methadone-exposed group at 20 days of age, suggesting that temperature deviations may not be expressed until sometime after weaning. At 43 days, rats from Groups L and G-L were hypothermic relative to controls; this age falls within the 39–51 day age range tested in our earlier study [31], and the deviant groups are the same as those reported previously. At 57 days and beyond, none of the drug groups was consistently hypothermic at an ambient temperature of 21°C. Nevertheless, all three groups exhibited abnormally low temperatures upon occasion; this occurred twice for Group G (Days 57 and 160), once for Group L (Day 160), and four times for Group G-L (Days 57, 128, 160, and 166).

When adult animals were subjected to cold stress or heat stress, the thermal responses of rats that had been exposed to methadone *in utero* differed significantly from those of controls. Moreover, the direction of these group differences depended upon the environmental temperature. Thus, rats from Groups G and G-L became hypothermic relative to controls when the ambient temperature was lowered to 10°C, and these same animals became hyperthermic when the ambient temperature was raised to 33°C. These data suggest that perinatal methadone exposure does not simply raise or lower a "set point" about which body temperature is otherwise defended normally; rather, it appears to allow a passive, uncompensated, hypothermia or hyperthermia, depending upon the ambient temperature (see [5]).

In contrast to the rats exposed to methadone *in utero*, rats exposed to methadone only through the maternal milk (Group L) appeared to thermoregulate normally in response to cold stress and heat stress. Suckling on methadone-treated females did exacerbate the effect of prenatal exposure, however, because the deficits of rats from Groups G-L were greater than those of animals from Group G. Thus, after three days of cold stress the rectal temperatures of G-L rats fell significantly below those of Group G animals, and after three days of heat stress the temperatures of G-L rats rose significantly above those of Group G animals. These differences are similar to those found at 21°C, where G-L rats exhibited abnormally low temperatures somewhat more frequently than did animals from Group G (or Group L).

Body weights were subnormal for all methadone groups at 20 days. However, only Group L was subnormal at 43 days, and all drug groups were within normal weight limits on Days 57 and 75. These data support those of other investigators, who have reported that methadone-exposed rat pups are low in body weight until weaning but that this deficit tends to diminish or disappear within a few weeks [16, 19, 27, 34, 36]. When the present rats were retested between Days 128 and 169, however, animals in Groups G and L again weighed less than controls. This suggests that perinatal methadone exposure can produce both a short-term and a long-term decrement in body weight, although weight may be normal during an intermediate period encompassing adolescence.

The ability to adjust food intake in response to changes in ambient temperature was not disrupted by perinatal exposure to methadone. In accord with numerous other studies showing that mammals eat more in a cool environment than in a warm one (e.g., [4, 12, 17]), the food consumption of all treatment groups increased when ambient temperature was lowered to 10°C and decreased when ambient temperature was raised to 33°C. Total food intake, however, was significantly altered in two methadone groups, and the direction of this alteration depended upon the schedule of perinatal exposure; thus, Group G animals consumed more food than controls (Days 125–140) and Group L animals consumed less (Days 125–140 and 154–169). The increased intake of rats from Group G is particularly interesting in view of the subnormal body weight of these animals; together, these findings suggest a possible long-term reduction in the efficiency of food utilization following fetal exposure to methadone. A subnormal body weight also occurred in Group L animals, but this may have been due to their diminished food intake rather than to any change in feed efficiency.

It seems unlikely that alterations in food intake and body weight are directly related to the thermoregulatory changes that were observed in the present adult offspring. Food intake and body weight appeared completely normal for rats from Group G-L, but these animals exhibited the greatest deviations in body temperature. On the other hand, rats from Group L were subnormal in both food intake and body weight, and these animals exhibited the fewest long-term changes in thermoregulation.

Rats that had been perinatally exposed to methadone defecated less often than controls while being weighed. This reduction was apparent for all three methadone groups at 125–140 days, and for rats from Group G-L at 154–169 days. Since defecation levels often are taken as behavioral index of emotionality, the present data suggest that perinatal methadone exposure may reduce adult emotionality in rats.

Previous laboratory and clinical evidence has demonstrated that the offspring of methadone-using mothers may suffer numerous difficulties, including severe and prolonged withdrawal [3, 6, 13, 30], brain abnormalities [7, 9, 18, 28, 35, 36], growth retardation [8, 15, 16, 19, 27, 32, 34], delayed behavioral development [30,37], altered activity levels [11,

14, 22, 29, 32, 38], and impaired learning ability [21, 22, 39]. The present findings suggest that this list should be extended to include long-term alterations in food intake, body weight, emotionality, and thermoregulation.

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