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Impaired Thermal Regulation in Juvenile Rats Following Perinatal Methadone Exposure[1]

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THOMPSON, C I, I S ZAGON AND P J MCLAUGHLIN *Impaired thermal regulation in juvenile rats following perinatal methadone exposure* PHARMAC BIOCHEM BEHAV 10(4) 551–556, 1979 —Offspring of female rats injected daily with methadone (5 mg/kg) or saline were cross-fostered at birth to form groups exposed to methadone during gestation (G), lactation (L), or gestation and lactation (G-L), controls (C) were exposed only to saline Rectal temperature, body weight and food consumption were measured from postnatal Days 36–51 Ambient temperature was maintained at 21°C except for Days 42–45, when the temperature was 10°C Group G rats never differed from controls, but offspring in Groups L and G-L were hypothermic at room temperature, Group G-L rats exhibited a further temperature loss during the cold stress There were no group differences in food consumption after Day 39, and all groups increased food intake while in the cold Group differences in body weight were not reliable but Group G-L rats gained less weight than the rest during the experiment, whereas Group L rats gained more These results indicate that, depending upon treatment schedule, perinatal methadone exposure is associated with hypothermia during the postweaning period A prolonged withdrawal reaction from methadone may account for the impaired thermal regulation

Methadone Body temperature Rats Body weight Maternal narcotics Food consumption Progeny Ambient temperature

METHADONE is a narcotic analgesic that was first synthesized in 1945 as a substitute for morphine, and the pharmacological effects of the two opioids are qualitatively similar [20] In 1949 it was reported that methadone diminished the severity of the abstinence syndrome resulting from morphine withdrawal [12], and methadone was introduced in the United States as an alternative to heroin addiction in 1965 [8] Its role in this latter capacity is currently widespread, with both state and federal support.

It has been estimated that 80–85% of narcotic-addicted women are of childbearing age (i e , 14–40 years [13]), and methadone is widely used in maintenance programs for women who become pregnant [4] Recently, there has been a growing concern regarding the possible long-term effects of methadone exposure on the offspring Clinical evidence indicates that the symptoms of postnatal withdrawal from methadone may be severe and prolonged [1, 18, 19, 22]. Voracious appetite, hypertonicity and disturbed sleep sometimes occur and may persist for several weeks after birth [7]. It has been reported that infants of methadone-treated mothers are less likely than controls to be walking unaided at 1 year of age [22]. Hyperactivity has been observed for as long as 2 years, and decreased linear growth for at least 3 years has been associated with maternal dependence upon methadone [23]

The rat has been shown to be a useful model for human methadone addiction in many respects In line with human clinical data, the progeny of female rats given methadone during gestation and/or lactation exhibit retarded physical growth [6, 11, 15, 25, 27, 28, 30], delayed motor development [29,30], and hyperactivity [30]. Moreover, it has been demonstrated in our laboratory that these offspring evince serious deficiencies in brain development [25–28] and are impaired in adult learning ability [31] Experiments with rats thus support and extend the human clinical data and suggest that further evaluation of the sequelae of perinatal methadone exposure is needed.

One attribute that has not been systematically evaluated in the progeny of methadone-treated mothers is the regulation of body temperature Hyperthermia has been observed during the neonatal period in human infants of addicted mothers, in conjunction with the onset of other withdrawal symptoms including irritability and hyperactivity [19], but little is known regarding possible long-term alterations in thermal regulation

Depending on the schedule of drug administration, methadone may exert a considerable influence upon the body temperature of adult organisms Acute injections in rats cause a hypothermia that becomes increasingly evident when the ambient temperature is lowered Oka [16] reported that a methadone dose of 8 mg/kg caused a reduction in body temperature relative to control levels that persisted up to 2½ hr after the injection, and this reduction occurred regardless of whether the ambient temperature was 21° or 12°C, when the methadone dose was reduced to 4 mg/kg, however, hypothermia was produced only at the lower ambient tem-

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perature In humans, long-term changes in body temperature have been reported during methadone treatment and withdrawal Martin and his colleagues [14] reported that core body temperature was elevated throughout an entire 15-week period of methadone maintenance in a group of male federal prisoners, whereas withdrawal of the drug caused a persistent hypothermia that was still evident 3 months following the last treatment

The purpose of the present experiment was to determine whether any alterations in body temperature could be detected at 39–51 days of age in rats whose mothers had received methadone during gestation and/or lactation In view of the possibility that abnormalities in core temperature might depend upon ambient temperature, measures were taken both at room temperature and after 3 days in a cold environment Food intake characteristically increases when the ambient temperature is lowered [5,9] and, to further evaluate the ability of these offspring to respond to cold stress, measures of food intake and body weight also were taken before, during, and after the period of cold exposure

METHOD

Animals

Female (210–240 g) and male (250–300 g) Sprague-Dawley rats obtained from Charles River Labs (Wilmington, MA) were utilized in this study These adults were housed under controlled conditions [27], with water and Wayne Laboratory Chow available ad lib All animals were allowed 6 days to acclimate to their surroundings prior to initiation of the experimental procedures

Adult females were divided into two treatment groups One group received daily (0800 hr) intraperitoneal injections of 5 mg/kg dl-methadone hydrochloride (Dolophine, Eli Lilly Co , Indianapolis, IN) beginning 5 days prior to breeding and continuing until 21 days after parturition A second group of rats received an equal amount of physiologic saline throughout this period Rats were weighed every two days and appropriate dosage adjustments made Five days after initiating the injections 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 females were placed in solid-bottom cages to deliver their young

At parturition all offspring were cross-fostered to methadone- or saline-injected mothers in order to form four treatment groups (1) Group G-L was exposed to methadone during both gestation and lactation, (2) Group G was exposed to the drug during gestation only, (3) Group L was exposed to methadone during lactation only, and (4) Group C was a control group whose mothers received saline during both gestation and lactation Litters were culled to 8 pups per mother at birth, with 4 males and 4 females in each litter Pups were weaned on Day 21, and no further drug exposure occurred

Littermates remained together until Day 30, at which time they were housed individually in solid-bottom cages containing Easi-Litter (Westminster Scientific Co , Westminster, MD) Water and Wayne Laboratory Chow were continuously available throughout the experiment, and a 12 12 light-dark schedule (0700 to 1900 lights on) was maintained

A total of 37 offspring were studied from postnatal Days 36–51 Each of the four treatment groups contained either 4 or 5 animals of each sex, as follows (1) Group G-L, 5 males (M) and 5 females (F), (2) Group G, 5 M and 5 F, (3) Group L, 5 M and 4 F, and (4) Group C, 4 M and 4 F Group numbers reflected the number of naive animals available on Day 30, no fatalities occurred as a result of the procedures used in this experiment

Apparatus and Procedure

Core temperatures were determined using a Yellow Springs Telethermometer (Model 47) The thermister probe was inserted 6 cm into the rectum of hand-restrained animals and recordings were made after a period of one minute A preliminary measure was taken on Day 36 as a habituation procedure, and temperatures then were recorded every 3 days thereafter (at 1000 hr) until Day 51 At these times animals also were weighed and the amount of food consumed during the preceding 3-day interval was recorded

During the 3-day period extending from Days 42–45 rats were housed in a room with an ambient temperature of 10°C At all other times they were housed under standard conditions [27] in a colony room kept at 21°C with a humidity of 50%

Data Analysis

Body temperatures and weights were analyzed by a 3-factor analysis of variance, with the four Treatment Groups and Sex as between-group factors and the five Days (i e [39, 42, 45, 48, and 51]) as a within-group factor Food consumption and weight gains during the five 3-day periods (Days 36–51) were evaluated by a similar 3-factor analysis Feed efficiency ratios (g food eaten per g weight gained) were calculated for each animal over the 15-day experimental period and a 2-factor analysis of variance was used to evaluate the effects of Treatment Groups and Sex

Unweighted means analyses were used because of the unequal numbers of animals in each group Tests subsequent to significant F-ratios were made using the Newman-Keuls procedure [24]

RESULTS

Body Weight and Weight Gains

No Treatment Group differences in body weight were found in this experiment Males weighed more than females (overall mean=152 0 and 132 9 g, respectively), $F(1,29) = 12\ 40$, $p<0\ 01$, and the magnitude of this sex difference increased steadily with age, $F(4,116)=10\ 92$, $p<0\ 01$, males weighed an average of 12 4 g more than females on Day 36, and this difference increased to 30 5 g by Day 51.

Although the body weights of methadone-treated and control rats were comparable at given points in time, significant Treatment Group differences were observed in the amount of weight gained during the experiment, $F(3,29)=10\ 19$, $p<0\ 01$ Rats in the control group gained an average of 12 2 g during each 3-day period, whereas rats in Groups G, L, and G-L gained 11 0 g, 15 0 g, and 8 3 g, respectively Subsequent tests revealed that the weight gain of the Group G-L rats was significantly lower than that of animals in the other 3 groups, whereas Group L animals gained significantly more body weight than any of the other 3 groups (all 6 $ps<0\ 01$)

The mean increase in body weight for all groups combined varied during different 3-day periods, and this overall Days effect was significant $F(4,116)=41\ 60$, $p<0\ 01$ Aver-

age weight gains during the five successive 3-day periods between Days 36 and 51 were 9 5, 10 2, 2 5, 19.2 and 16 0 g, respectively From these data it can be seen that rats of all groups gained less weight while in the cold (Days 42–45, 2.5 g) than they did during any other 3-day period (all $ps<0$ 01) Immediately following the cold exposure, all groups of rats showed marked weight gains; this increase (Days 45–48, 19 2 g) was significantly greater than that of any other 3-day period (all $ps<0$ 05)

As might be expected, males of all groups exhibited greater 3-day weight gains than females (mean=13.4 g and 9 5 g, respectively) This overall sex effect was statistically reliable, $F(1,29)=19.87$, $p<0$ 01

Body Temperature

Animals in Groups L and G-L were hypothermic in this study, but those in Group G were not. The overall Treatment Groups effect was statistically reliable, $F(3,29)=21$ 08, $p<0.01$, as was the Treatment Groups × Days interaction, $F(12,116)=5$ 25, $p<0$ 01 Subsequent tests showed that the rectal temperatures of animals in Group L were significantly lower than control values ($p<0$ 01) on all days except Day 51. Similarly, the temperatures of animals in Group G-L were lower than control values on all days except Day 39 Rectal temperatures of rats in Group G never differed from those of controls Temperatures of the four treatment groups on each of the five measurement days are presented in Fig 1 No sex differences in body temperature were observed, and values for the two sexes have been combined in the figure

The hypothermia of rats in Group G-L was particularly evident following 3 days of exposure to an ambient temperature of 10°C As shown in Fig. 1, rectal temperatures in this group dropped by slightly more than 0 5°C between Days 42 and 45, the period of cold exposure ($p<0$ 05), an increase in body temperature of a similar magnitude occurred during the 3-day period immediately following the cold exposure ($p<0$ 05) In contrast, rats in Groups C, G, and L did not exhibit a variation in body temperature as a consequence of decreasing and then raising the ambient temperature, rectal temperatures of these animals at the end of 3 days in the cold room (Day 45) did not differ significantly from those recorded immediately preceding (Day 42) or 3 days after (Day 48) exposure to 10°C

Since rats in Group G-L were hypothermic prior to entering the cold room, the further decrease in body temperature during cold exposure resulted in a sizeable discrepancy from control values As can be seen in Fig. 1, the rectal temperatures of G-L animals on Days 42, 45 and 48 were lower than control values by 0 48°, 1 08° and 0 46°C, respectively

Food Consumption

Rats in Group L consumed less food than other animals during the first 3 days of the study, and the Treatment Groups × Days interaction was statistically reliable, $F(12,116)=3.44$, $p<0$ 01 The mean amounts of food consumed by rats in the four treatment groups during each 3-day period are presented in Table 1. From Days 36–39 the food consumption of rats in Group L was 66%, 73% and 71% of that observed in animals of Groups G, G-L and C, respectively (all $ps<0.01$) This hypophagia diminished as the study progressed Although Group L rats ate significantly less than Group G animals on Days 39–42, there were no reliable

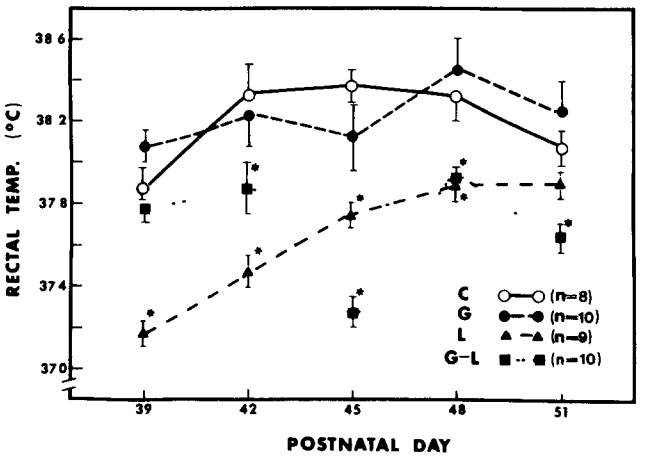

FIG 1 Mean rectal temperatures of juvenile rats following perinatal exposure to maternally-administered methadone Measurements on Day 45 were made at the end of a 3-day period of housing in an ambient temperature of 10°C, all other measurements were taken at an ambient temperature of 21°C Vertical bars represent standard errors of the means, and the symbol * indicates that the corresponding mean was significantly below the mean of the control group on that day ($p<0$ 01) Abbreviations C, control animals whose mothers were injected with saline, G, animals exposed to methadone only during gestation, L, animals exposed to methadone only during lactation (birth to 21 days), G-L, animals exposed to methadone during both gestation and lactation

Treatment Group differences in food consumption during, or subsequent to, the period of cold exposure (Days 42–51)

Rats in all groups ate more food while in the cold (Days 42–45) than they did during either of the two 3-day periods prior to cold exposure (see Table 1) With the exception of the nonsignificant increase in food intake between Days 39–42 and Days 42–45 for animals in Group G, these within-group differences were all statistically reliable

Males consumed more food than females (3-day means=57 2 and 50 3 g, respectively), and this overall Sex effect was statistically significant, $F(1,29)=9$ 19, $p<0$ 01 The Sex×Days interaction also was significant, $F(4,116)=2$ 91, $p<0$ 05, a reflection of increasing sex differences with age The amounts by which males consumed more food than females during the five successive 3-day periods from Days 36–51 were 2 9, 3 9, 7 6, 9 0 and 10 9 g, respectively, only the last 3 of these differences were statistically reliable (Days 42–51, $ps<0$ 01)

Feed Efficiency

A significant Treatment Group effect occurred in the feed efficiency analysis, $F(3,29)=10$ 82, $p<0.01$ The grams of food eaten per gram of body weight gained for each group during the 15-day experimental period was as follows Group C, 4 8; Group G, 5 5, Group L, 3.6 and Group G-L, 7.0 Subsequent tests indicated that rats in Group G-L required more food than animals in any other group to gain a gram of body weight, whereas rats in Group L required less food than animals in any other group (all $ps<0$ 05)

Male rats required less food than females to gain a gram of body weight between 36 and 51 days of age (mean=4 5 and 6 1 g, respectively) This overall Sex effect was statistically reliable, $F(1,29)=10$ 57, $p<0$ 01

TABLE 1

FOOD CONSUMPTION DURING SUCCESSIVE THREE-DAY PERIODS IN JUVENILE RATS PERINATALLY SUBJECTED TO METHADONE

Group*	Days 36–39	Days 39–42	Days 42–45†	Days 45–48	Days 48–51
C	46 9 ± 4 4‡§	47 6 ± 3 0§	58 8 ± 2 7	58 9 ± 3 9	60 8 ± 4 4
G	51 5 ± 3 1§	56 0 ± 3 0	61 0 ± 2 3	59 1 ± 2 6	58 5 ± 3 3
L	33 8 ± 2 3§¶	43 0 ± 2 4§	56 8 ± 2 0	57 1 ± 1 7	60 6 ± 1 4
G-L	46 5 ± 3 4§	46 4 ± 3 1§	56 6 ± 3 4	57 9 ± 3 5	58 5 ± 3 7

*Abbreviations C=saline controls, G=methadone exposure only during gestation, L=methadone exposure only during lactation, G-L=methadone exposure during both gestation and lactation

†Ambient temperature was maintained at 10° C, on all other days the ambient temperature was 21° C

‡Grams ± standard error of the mean

§Food intake lower than during Days 42–45 (at 10° C ambient temperature), $p<0$ 01

¶Food intake lower than that of Controls (or any other group), $p<0$ 01

DISCUSSION

Methadone has been shown to cross the placenta and enter the fetal circulation of humans [2,10] and rodents [11, 17, 21], and to enter the milk of lactating humans on methadone maintenance [3] Previous work in our laboratory [15, 25–30] has suggested that maternally-administered methadone causes numerous morphological and functional consequences for the offspring. The present experiment shows that such progeny also exhibit irregularities in temperature regulation

The major finding of this paper is that rat pups who nursed on mothers receiving methadone were hypothermic from two to four weeks after lactation had ended This hypothermia was evident when methadone exposure had occurred either during lactation only or during both gestation and lactation, but hypothermia was not found in animals exposed to methadone only during gestation This suggests that methadone exposure during the 21-day period following birth was critical for producing the temperature reductions observed in this study Nevertheless, exposure to methadone during both gestation and lactation may have had some cumulative effects, animals subjected to methadone only during lactation did not become increasingly hypothermic when the ambient temperature was lowered to 10°C, but hypothermia did become more evident in rats from Group G-L when the ambient temperature was lowered

Prenatal exposure to methadone did not always exacerbate the consequences of exposure during lactation, and sometimes even appeared to have an ameliorating effect Although the body temperatures of Group G-L animals were lower than those of any other group following the three days of cold stress (Day 45), rats in Group L were most hypothermic on Days 39 and 42 The explanation for these exceptionally low body temperatures at the beginning of the experiment for Group L animals is not clear, but it is noteworthy that Group L rats also consumed less food than animals in any other group from Days 36–39 Further work is needed to determine how these two findings might be related

Body weights did not differ among treatment groups in this experiment In previous studies we have found that rats in all three methadone-exposed groups typically weigh less than controls at 21 days of age [15, 27, 28], but by 60 days the earlier weight differences may completely disappear [27,28] It is not known whether the methadone-exposed animals in the present study were low in body weight at 21 days of age, but they clearly did not differ from controls by postnatal Day 39

Despite the fact that body weights did not differ on any given test day, there were reliable group differences in the amounts of weight gained during the 15-day experimental period, rats in Group G-L gained less weight than animals in any other group, whereas rats in Group L gained more than any other animals These differences in weight gain occurred in the absence of group differences in food intake, with the consequence that feed efficiency ratios also were altered, rats in Group G-L required more food than animals in any other group to gain a given amount of body weight, whereas rats in Group L required less food Since the weight gains and feed efficiency ratios of Groups G-L and L differed in opposite directions from control values, it would appear that these deviations are not related in any simple manner to the hypothermia that occurred in both of these groups

Homeotherms normally increase their food intake quite precisely in response to decreases in ambient temperature, thereby providing the fuel needed to maintain stable core temperatures [5,9] In the present study all groups increased their consumption of food during the period of cold stress (Days 42–45), and there were no between-group differences in food intake from Days 39–51 Thus, the decreased body temperature of animals in Group G-L during cold exposure cannot be attributed to failure to make an appropriate adjustment in food consumption

A prolonged withdrawal effect may be partially responsible for the hypothermia that was observed in this study It has been reported in humans that subnormal core temperatures occur during methadone withdrawal, and that hypothermia is still evident 110 days after termination of a 15-week treatment period [14] The fact that in the present study rats exposed to methadone only during the period of gestation did not exhibit hypothermia lends some support to this possibility, since these animals sustained a longer period of withdrawal prior to testing than did rats in Groups G-L and L (both of which were hypothermic)

If hypothermia reflects a withdrawal phenomenon, then

rats exposed to methadone during lactation should eventually become normothermic Based on the limited data available in the present study one might further predict that normothermia would be evident by 60 days of age Group G animals were not hypothermic when the study began, at which time they had been withdrawn from methadone for 39 days, and since rats in Groups L and G-L were removed from methadone exposure on postnatal Day 21 the 39th day of withdrawal for these animals would occur on Day 60.

We have some preliminary evidence supporting this prediction from a sample of rats whose rectal temperatures were taken only at 60 days of age (Thompson, Zagon and McLaughlin, unpublished observations). These animals received the same perinatal methadone or saline exposures as those of the present study, the sample sizes were all as large or larger (total n=59), and approximately equal numbers of males and females were used. The rectal temperatures of rats that had been perinatally exposed to methadone were slightly lower than control values at 60 days, but these differences were not statistically reliable (Group C, 38 1°C; Group G, 37 7°C; Group L, 37 7°C, Group G-L, 37 8°C) Moreover, animals in Groups L and G-L (but not Group G) exhibited a greater variability in their 60-day body temperatures than did animals in the control group ($p=0$ 034 and 0.067, respectively, 2-tailed). This variability at 60 days within Groups L and G-L also was greater than that observed in the present study at 51 days for animals in these groups ($ps<0$ 05, 2-tailed), whereas the variability within Groups G and C did not differ significantly at 51 and 60 days of age The increased variability within Groups L and G-L at 60 days suggests that recovery of normal body temperature may have occurred by this time in some, but not all, of the animals.

Whatever the mechanism involved, the present study indicates that rats exposed to methadone during lactation are hypothermic from two to four weeks after weaning, and rats exposed during both gestation and lactation have an additional difficulty in maintaining thermal stability when the ambient temperature is lowered Further investigation of possible short- and long-term consequences of these regulatory difficulties would be of interest, particularly in view of the widespread use of methadone in the treatment of heroin-addicted pregnant women

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