Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition

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Vickers, M. H., B. H. Breier, D. McCarthy, and P. D. Gluckman. Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition. Am J Physiol Regul Integr Comp Physiol 285: R271–R273, 2003; 10.1152/ajpregu.00051.2003.—The discovery of a link between in utero experience and later metabolic and cardiovascular disease is one of the most important advances in epidemiology research of recent years. There is now increasing evidence that alterations in the fetal environment have long-term consequences on metabolic and endocrine pathophysiology in adult life. This process has been termed “fetal programming,” and we have shown that undernutrition of the mother during gestation leads to obesity, hypertension, hyperphagia, hyperinsulinemia, and hyperleptinemia in offspring. Using this model of maternal undernutrition throughout pregnancy, we investigated whether prenatal influences may lead to alterations in postnatal locomotor behavior, independent of postnatal nutrition. Virgin Wistar rats were time mated and randomly assigned to receive food either ad libitum (ad libitum group) or at 30% of ad libitum intake (undernourished group). Offspring from UN mothers were significantly less active than AD offspring. At weaning, offspring were assigned to one of two diets [control or hypercaloric (30% fat)]. At ages of 35 days, 145 days, and 420 days, voluntary locomotor activity was assessed. At all ages studied, offspring from undernourished mothers were significantly less active than offspring born of normal birth weight for all parameters measured, independent of postnatal nutrition. Sedentary behavior in programmed offspring was exacerbated by postnatal hypercaloric nutrition. This work is the first to clearly separate prenatal from postnatal effects and shows that lifestyle choices themselves may have a prenatal origin. We have shown that predispositions to obesity, altered eating behavior, and sedentary activity are linked and occur independently of postnatal hypercaloric nutrition. Moreover, the prenatal influence may be permanent as offspring of undernourished mothers were still significantly less active compared with normal offspring at an advanced adult age, even in the presence of a healthy diet throughout postnatal life.

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Fig. 1. Locomotor behavior in Wistar rats as a consequence of a normal or adverse fetal environment (n = 6–8/group). A: locomotor activity at 35 days of age in males and females; P < 0.0001 for effect of fetal programming and gender. B: locomotor activity at day 145 in females; P < 0.001 for effect of fetal programming; P < 0.05 for effect of hypercaloric diet. Data analyzed by factorial ANOVA, and data are shown as means ± SE.

Fig. 2. Locomotor behavior and food intake in Wistar rats as a consequence of a normal or adverse fetal environment (n = 6–8/group). A: food intake (kcal·g body wt$^{-1}$·day$^{-1}$ over a 5-day period) in females at day 145; P < 0.005 for effect of fetal programming, P < 0.05 for postnatal hypercaloric diet. B: locomotor activity at 14 mo in males and females; P < 0.005 for effect of fetal programing and gender. Data analyzed by factorial ANOVA, and data are shown as means ± SE.

MATERIALS AND METHODS

We have developed an animal model of fetal programming using maternal undernutrition (9). Virgin Wistar rats (age 100 ± 5 days) were time mated using a rat estrous cycle monitor to assess the stage of estrous of the animals before introducing the male. After confirmation of mating, rats were housed individually in standard rat cages containing wood shavings as bedding and free access to water. All rats were kept in the same room with a constant temperature maintained at 25°C and a 12:12-h light-dark cycle. Animals were assigned to one of two nutritional groups (n = 15 per group): (1) undernutrition (30% of ad libitum) of a standard diet throughout gestation (undernourished group), or (2) standard diet ad libitum throughout gestation (ad libitum-fed group). Food intake and maternal weights were recorded daily until birth. After birth, pups were weighed, and litter size was recorded. Pups from undernourished mothers were cross-fostered onto dams that received ad libitum feeding throughout pregnancy. Litter size was adjusted to eight pups/litter to ensure adequate and standardized nutrition until weaning. After weaning, male offspring from ad libitum-fed and undernourished mothers were divided into two balanced postnatal groups to be fed either a standard diet (protein 19.9%, fat 5%, digestible energy 3,504 kcal/kg, protein energy/total energy 22.7%) or a hypercaloric diet (protein 28.5%, fat 30%, digestible energy 4,922 kcal/kg, protein energy/total energy 22.7%). The mineral and vitamin content in the two diets was identical and in accordance with the requirements for standard rat diets.

Two separate studies were undertaken. In the first study, voluntary locomotor activity was assessed in the offspring (n = 6 per group of each gender) during the peripubertal period (35 days) and in adulthood (145 days). This was done after three habituation trials using Optimax behavioral testing apparatus (Columbus Instruments). During trials of 15-min duration, animals were examined on distance traveled, stereotyped movement, ambulatory time, time spent resting, and bursts of stereotypic movement. Food intake was also measured over a 5-day period from day 140 to day 145. In a second study an identical manipulation was used prenatally, but all rats (8 per group of each gender) were maintained on a normal diet after weaning, and their behavior was studied at 14 mo of age. The Animal Ethics Committee of the University of Auckland approved all animal work.

RESULTS

In the first study, offspring that were undernourished in utero were significantly more sedentary in postnatal life than those born of ad libitum-fed mothers for all parameters measured, and this was independent of postnatal diet (Fig. 1, A and B). Analysis of ingestive behavior revealed hyperphagia in mature offspring that had been exposed to maternal undernutrition. This was independent of postnatal diet, although sedentary behavior was exacerbated by hypercaloric nutrition (Fig. 2A). Importantly, in the animals tested at a peripubertal age, diminished locomotor activity was already present before the development of maturity-
onset obesity and was significantly reduced in males compared with females.

In the second trial, offspring of undernourished mothers at 14 mo of age were shown to be significantly less active than offspring of normally fed mothers (Fig. 2B). A gender effect was observed, with males significantly less active than females, but the prenatal effect was significant in each gender. This second study confirms that the sedentary effect is persistent through life, is solely related to prenatal maternal diet, and occurs in both genders.

**DISCUSSION**

These results suggest that an adverse prenatal environment can lead to the development of both abnormal eating and exercise behaviors, and we have previously shown that it leads to physiological features of the metabolic syndrome (9). The present study raises the intriguing possibility that some behaviors and lifestyle choices that exacerbate the metabolic syndrome in humans are an inherent part of the syndrome and may have a prenatal origin. The implications of this hypothesis are profound, because if sedentary behavior and overeating are determined during prenatal development, this may explain why public health attempts to improve exercise and to reduce food intake in adults with hypertension, insulin resistance, and hyperlipidemia are often ineffective.

Further studies are necessary to define the neurobiology of these altered behaviors. Other behaviors have been shown to have a perinatal environmental origin, at least in rodents. For example, Meaney (6) showed that the environmental demand on the mother during the neonatal period leads to adaptive responses in neurotransmitter and neuroendocrine pathways that are reflected in the quality of maternal care to her offspring. This, in turn, programs stress reactivity and associated behavior patterns of the offspring and influences the relationship between mother and offspring in the next generation.

Until now, evidence that the fetal or early neonatal environment may lead to obesity and inactivity has been rather weak because lifestyle influences obscure the linkage between metabolic predisposition and maturity-onset obesity. This report is the first to clearly separate prenatal from postnatal effects and shows that the lifestyle choices themselves may have a prenatal origin. We have shown that predispositions to obesity, altered eating behavior, and sedentary activity are linked and occur independently of postnatal hypercaloric nutrition. Moreover, the prenatal influence seems permanent as offspring of undernourished mothers were still significantly more inactive and obese compared with normal offspring at an advanced adult age, even in the presence of a healthy diet throughout postnatal life.

These studies suggest that the “couch potato” syndrome may have its origins during prenatal development. This has major implications for public health policy; health care funding may be better spent on improving pregnancy care rather than waiting until metabolic and cardiovascular disorders manifest in offspring years or decades later.

**REFERENCES**