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Late Effects of Early Nutritional Manipulations

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Summary

Effects of early neonatal interventions on metabolic parameters later in life (s.c. late effects) were studied in rats using two models; namely, (a) the effects of premature weaning and (b) the effects of "dietary" manipulations during the suckling period (s.c. small vs. large litters). (a) Premature weaning of rats caused an earlier degeneration of spermiogenesis and elevated plasma cholesterol levels in adult animals when compared to levels found in animals weaned 12 days later (on day 30 after birth). In adult rats, radioiodine uptake in thyroid glands was lower in the group weaned prematurely. Premature weaning was followed by a decrease of corticosterone production in adrenal glands in adult animals; in female adult prematurely weaned rats, an elevated response of adrenal cortex to stressors was observed. Several other studies explored the "immediate" effects of early, premature weaning. (b) Early exposure to high fat diet evoked a hypercholesterolaemic response in adulthood following brief exposure to HF diet. Rats from litters reduced to 3 or 4 pups per mother on postnatal day 3 exhibited 2 days later plasma levels of cholesterol higher than in rats raised in large litters of 8 or 14. The difference between small and large litters was preserved for the whole lifespan of the animals. In adulthood, rats from small litters were fatter and had higher levels of plasma cholesterol and insulin. Other studies suggester that early dietary experience may regulate the pattern of drug metabolism in adult life. An inhibition of diurnal plasma corticosterone variation was found in rats overfed during the neonatal period and an increased stimulation of lipolysis by norepinephrine and lipogenesis by insulin was demonstrated in neonatally underfed rats. Interesting studies were reported in longitudinally studies in children: at the age of 9–12 year brest-fed children (for more than 6 months) had the highest cholesterol levels; on the other hand significantly increased levels of APO B, Apo A1, ATH index and Apo/B Apo A1 quotient ($p<0.05$) were found in the nonbreast-fed group (27 references).

Key words

Spermiogenesis – Cholesterol – Corticosterone production – Gluconeogenesis – Lipogenesis – Glucagon – Insulin – Thyroid stimulating hormone – Drug metabolism – Studies in children

Effects of early neonatal interventions on metabolic parameters later in life (so called late effects as defined by Křeček 1962, 1971) were studied in rats using two models – the effects of premature weaning and the effects of "dietary" manipulations during the suckling period (small vs. large litters). It is clear that both models represent not only simple dietary interventions, but complex situations involving various stressor effects, including maternal deprivation.

The effects of premature weaning

Kubát *et al.* (1961, 1962) showed that premature weaning of rats (day 18 after birth) to a standard, high-carbohydrate laboratory diet caused earlier degeneration of spermiogenesis and elevated plasma cholesterol levels in adult animals when compared to animals weaned 12 days later (on day 30 after birth). These observations were then extended. Rats were weaned on day 18 after birth to a high-fat or high-carbohydrate diet and received the usual Purina Chow diet from day 30 to day 42 after birth. The rats were then offered a high-fat diet for 2 days before being sacrificed. Plasma cholesterol levels were elevated in rats fed the high-carbohydrate diet from day 18 to day 30 (Hahn 1977). Other experiments, in which rats were weaned on day 15 after birth and fed a high-fat or high-carbohydrate diet for 15 days, while control animals remained with the mother up to the postnatal day 30, confirmed that plasma cholesterol levels in adult male animals depend on their early nutritional history. Levels were lowest in normally weaned rats and highest in prematurely weaned rats and in those rats fed a high-carbohydrate diet between postnatal days 15 and 30 (Hahn and Kirby 1973, Hahn and Koldovský 1969, 1976, 1979).

Other studies investigated the role of dietary fat alone without cholesterol by feeding experimental diets containing either high fat (corn oil), low sucrose (HF) or low fat, high sucrose (HS) to pregnant rats (from day 18 of gestation). After birth, mothers and pups were fed the diets until weaning (30 days) when serum cholesterol levels were the same in both groups. Animals were fed a stock diet until the age of 7 months. At that time, half the animals from each original group (HF or HS) were challenged with HF diet for 3 days; the other half were fed stock diet. There was no significant difference in serum cholesterol between HF and HS animals fed the stock diet. Animals originally fed HF diet had significantly raised serum cholesterol in response to the late HF challenge; the original HS group did not. Early exposure to HF diet, even without cholesterol, could thus evoke a hypercholesterolaemic response in adulthood following the challenge by brief exposure to the HF diet (Coates *et al.* 1983).

In adult rats, radioiodine uptake in thyroid glands was lower in the group weaned prematurely. Premature weaning was followed by a decrease of corticosterone production in adrenal glands in adult animals (Kraus *et al.* 1967). In female adult prematurely weaned rats, an elevated response of adrenal cortex to stressors was observed (Macho 1979).

Other studies explored the "immediate" effects of early premature weaning. Plasma levels of cholesterol were rapidly decreased by weaning to the high-carbohydrate diet (Hahn 1986). Interestingly, fasting for 24 hours caused a much less pronounced fall in plasma cholesterol levels, indicating the specific effect of dietary carbohydrate on cholesterol metabolism.

To some extent, feeding a HF diet to prematurely weaned animals maintained the preweaning metabolic state, even though there was a gradual decrease in gluconeogenesis and fatty acid oxidation, as evidenced by the blood level of ketones. Feeding the same HF diet to 18- and 40-day-old rats indicated that the 18-day-old group was more sensitive to the dietary change; plasma level of cholesterol rose to much higher values in the younger animals (Hahn *et al.* 1977).

Macho (1979) summarized data showing that rats weaned on postnatal day 18 exhibited decreased plasma thyroxine levels during the first two days. At a later postweaning period, an increase of iodine uptake and the thyroid hormone synthesis was noted in the thyroid gland. In the experiments mentioned above, Hahn (1977) found that in both brown and white adipose tissues the rates of gluconeogenesis, as judged from the activity of phosphoenolpyruvate carboxykinase (PEPK), and of fatty acid synthesis, as indicated by the activities of fatty acid synthetase (FAS), malic enzyme, and the citric cleavage enzyme were both significantly greater in animals previously fed the high-carbohydrate diet than in those that had consumed a HF diet (Hahn 1977). Interestingly, the diet fed between postnatal days 18 and 30 had no effect on enzyme activities in the liver. However, Palkovič *et al.* (1976) demonstrated a rapid increase of the activity of enzymes involved in lipogenesis (malic enzyme and ATP-citrate lyase) in the liver of early weaned rats.

Premature weaning caused an early fall in plasma glucagon levels, the extent of the decrease depending on the diet to which the animals had been weaned. Thus, the insulin: glucagon ratio was highest for the high-carbohydrate diet and lowest for the high-fat and Purina Chow diets. Changes in enzyme activities in both liver and brown fat occurred in dependence on the diet composition – a high-carbohydrate diet resulting in a rapid fall of gluconeogenesis and fatty acid oxidation and a rise of glycolysis and fatty acid synthesis (Hahn *et al.* 1978).

The effects of "dietary" manipulations during the suckling period

Rats from litters reduced to 3 or 4 pups per mother on postnatal day 3 exhibited two days later plasma levels of cholesterol higher than rats raised in large litters of 8 or 14 pup. In the larger litters, plasma insulin levels were also elevated. The difference between small and large litters was preserved for the whole lifespan of the animals. In adulthood, rats from small litters were fatter and had higher levels of plasma cholesterol and insulin (Hahn 1986).

Other studies suggested that early dietary experience may regulate the pattern of drug metabolism in adult life. Pregnant rats were fed high-fat HF, 35 calories) or low-fat (LF, 5 calories) diet from 18 days of gestation to the end of the suckling period. Thereafter, male progeny were fed the stock diet for 6 months, then sacrificed or challenged for 3 days with the HF diet. At the age of 7 months, cytochrome P-450 was lower in LF-fed than in HF-fed animals. The high fat challenge reduced aminopyrine

N-demethylase in LF animals and benzopyrene hydroxylase in HF animals (Sonawane *et al.* 1983).

An inhibition of diurnal plasma corticosterone variation was found in neonatally overfed rats during the neonatal period (Macho *et al.* 1982). An increase of plasma corticosterone levels and adrenal steroid production was demonstrated in suckling and adult rats underfed during the neonatal period. Enhanced radioiodine uptake and TSH plasma levels were observed in rats underfed during the neonatal period (Macho 1979).

Increased stimulation of lipolysis by norepinephrine or ACTH, and lipogenesis by insulin was demonstrated in neonatally underfed rats during the neonatal period (Macho 1979). The smaller adipocytes from underfed rats showed higher binding affinity and increased concentrations of insulin surface receptors (Ficková and Macho 1981). Differences in neonatal nutrition were followed by changes in the response of insulin receptors of adipocytes to starvation (Macho *et al.* 1985). Neonatal undernutrition in rats was associated with increased hepatocyte glucagon receptors and higher sensitivity of cAMP production to hormone stimulation (Ficková and Macho 1988).

Studies in children

The influence of neonatal nutrition on the homeostasis of lipids and lipoproteins in later life was studied in a group of 82 healthy children. They were followed longitudinally from birth up to prepuberty (9–10 years of age) (Hromadová *et al.* 1985, 1989, Michaličková *et al.* 1987), and early pubertal stage, (11–15 years of age) (Štrbák *et al.* 1991, 1993), and were divided into 4 groups according to the duration of the period of breast feeding (i. e., nonbreast-fed or breast-fed for 3, 6 or more than 6 months). The results showed that the children breast-fed for more than 6 months had the highest cholesterol levels in both periods, which was similar as in the same children of pre-school age (6–7 years of age) (Hromadová *et al.* 1991). In addition, significantly increased levels of Apo B, Apo A1, ATH index and Apo B/Apo A1 quotient were found at the early pubertal age in those children who were included in the first group (i. e. nonbreast-fed). No differences were found between sexes in the above parameters. It can thus be concluded that the age at weaning may be important for the later development of children.

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Reprint Requests

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