Cross-Fostering to Diabetic Rat Dams Affects Early Development of Mediobasal Hypothalamic Nuclei Regulating Food Intake, Body Weight, and Metabolism

Sonja Fahrenkrog, Thomas Harder, Elke Stolaczyk, Kerstin Melchior, Kerstin Franke, Joachim W. Dudenhausen, and Andreas Plagemann

Clinic of Obstetrics, Division of Experimental Obstetrics, Charité—University Medicine Berlin, Campus Virchow-Klinikum, Berlin, Germany

ABSTRACT Exposure to maternal gestational diabetes (GD) “programs” offspring for obesity in childhood and later life. Recent clinical data suggest that neonatal ingestion of breast milk from diabetic mothers might be crucially involved. Mediobasal hypothalamic nuclei such as the ventromedial nucleus (VMN), the paraventricular nucleus (PVN) and the arcuate nucleus (ARC) play a key role in the central nervous system regulation of food intake and body weight. In the ARC, orexigenic neuropeptides such as neurotensin Y (NPY), galanin (GAL), and agouti-related peptide (AGRP) and anorexigenic neuropeptides such as proopiomelanocortin (POMC) and alpha-melanocyte-stimulating hormone (MSH) are expressed. We investigated the effects of neonatal exposure to milk from GD rat dams on the development of hypothalamic nuclei in weanling rats. Offspring of control (CO) rat dams cross-fostered to GD rat dams (CO-GD) developed early postnatal growth delay. On d 21 of life, CO-GD rats showed structural and functional hypothalamic “malprogramming.” The ARC of CO-GD rats showed increased immunopositivity of both NPY and AGRP under basal conditions, despite normal levels of glucose, leptin, and insulin. Conversely, CO-GD rats showed decreased immunopositivity of both POMC and MSH and decreased density of immunopositive neurons, compared with offspring of control rat dams cross-fostered to control rat dams. No morphometric alterations were found in the VMN, whereas CO-GD rats showed an increased total number of neurons in the PVN. In summary, neonatal exposure to maternal diabetes through the intake of dam’s milk in rats leads to a complex malprogramming of hypothalamic orexigenic and anorexigenic circuits that are critically involved in the lifelong regulation of food intake, body weight, and metabolism. J. Nutr. 134: 648–654, 2004.

KEY WORDS: gestational diabetes • breastfeeding • nutritional programming • hypothalamus • regulation of food intake and body weight

Experimental and clinical investigations have shown that offspring of mothers with diabetes during pregnancy are at increased risk of developing obesity and diabetogenic disturbances in later life (1–8). Offspring of streptozotocin-diabetic rat dams, a well-established model for gestational diabetes (GD),3 display hyperphagia and become overweight in later life (6,7). This is associated with malformations of the ventromedial hypothalamic nucleus (VMN) (9), a key regulator of food intake, body weight, and metabolism (10). Moreover, juvenile and adult offspring of GD rat dams show persisting malorganization of the hypothalamic neurons that express orexigenic neuropeptides in the arcuate hypothalamic nucleus (ARC) (6,7). We hypothesised that these hypothalamic alterations could be responsible for the lasting alterations in food intake, body weight, and metabolism observed in the offspring of GD dams.

Within the mediobasal hypothalamus, a network of orexigenic and anorexigenic neuropeptides is critically involved in the complex regulation of food intake, body weight, and metabolism [for review, see Kalra et al. (11)]. Neuropeptide Y (NPY) and galanin (GAL) are probably the most intensively investigated neuropeptides that stimulate food intake and consequently weight (11,12). Proopiomelanocortin (POMC) and its splice-product α-melanocyte-stimulating hormone (MSH) are the main functional antagonists, which decrease food intake and consequently weight (13). Within the anorexigenic POMC-MSH system, agouti-related peptide (AGRP) acts as a physiological antagonist at the melanocortin-4 (MC-4) receptor, thereby exerting orexigenic effects (14).

Physiologically, insulin and leptin act as peripheral satiety

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2 To whom correspondence should be addressed.
E-mail: andreas.plagemann@charite.de.
3 Abbreviations used: ABC, avidin-biotin-peroxidase complex; AGRP, agouti-related peptide; ARC, arcuate hypothalamic nucleus; BVI, brain volume index; CO, control group; CO-CO, offspring of control rat dams cross-fostered to control rat dams; CO-GD, offspring of control rat dams cross-fostered to diabetic rat dams; GAL, galanin; GD, gestational diabetes; MO-4, melanocortin-4; MF, microscopic field; MSH, α-melanocyte-stimulating hormone; NPY, neuropeptide Y; POMC, proopiomelanocortin; PVN, paraventricular hypothalamic nucleus; STZ, streptozotocin; VMN, ventromedial hypothalamic nucleus.

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signals by regulating the expression and release of both orexigenic and anorexigenic neuropeptides within the ARC, the major site of expression: Increased concentration of both hormones causes downregulation of expression and release of the orexigenic neuropeptides NPY, GAL, and AGRP and simultaneous upregulation of the anorexigenic peptides POMC and MSH (11,12).

We recently showed that neonatal exposure to breast milk from diabetic mothers might be coresponsible for an increased risk of developing obesity and consequent diabetogenic disturbances in the offspring of mothers that were diabetic during pregnancy (15). Reifsnnyder et al. (16) demonstrated that New Zealand obese mouse pups (a genetic animal model for obesity and type 2 diabetes) suckled by diabetic mothers became more obese and had higher insulin and leptin levels in adulthood than did those reared by control dams, independent of their genetic background. Against this background, we hypothesized that the functional and hypothalamic alterations in the offspring of diabetic rats described above might be at least partly a direct consequence of exposure to milk from diabetic dams. The possible role of maternal milk in the development of short- and long-term alterations in the offspring of diabetic rat dams has rarely been investigated. Therefore, we investigated whether exposing rat pups to milk from diabetic mothers affects the development of the neurons involved in lifelong hypothalamic regulation of food intake, body weight, and metabolism.

**MATERIALS AND METHODS**

**Animals.** Female virgin Wistar rats [CRL: (WI)/BR; Charles River] were time-mated with normal males. On the day of conception (d 1 of gestation), GD was induced in female rats by injection of a single dose of streptozotocin (STZ; 40 mg/kg body wt i.p.; Sigma). The control females (CO group) were injected with the solvent only (citrate buffer, Merck, pH 4.5). Rats were kept under standard conditions with a 12:12-h dark-light cycle and had free access to tap water and a standard pellet diet (Altromin 1314; Altromin). All procedures were carried out in accordance with European Communities Council Directive 86/609/EEC and were approved by the local animal welfare committee.

**Cross-fostering schedule.** Immediately after birth (d 1 of life), offspring of CO rat dams were randomly cross-fostered either to CO rat dams (CO-CO group; n = 6 litters) or to GD rat dams (CO-GD group; n = 4 litters). Pups born to GD mothers were not studied further in this experiment. Litter sizes were adjusted to 10–12 pups per nest. Pups were reared in these nests until weaning (d 21 of life). Maternal blood samples for determination of whole blood glucose concentration (glucoseoxidase-peroxidase method; Dr. Lange) were taken during lactation, on d 16 of the suckling period. Leptin concentration was measured using a commercial radioimmunoassay (rat leptin RIA kit, Linco). Recombinant rat leptin (Linco) served as the standard preparation. The intraassay variation was 2.0 to 4.6% in a concentration range of 1.6 to 11.6 µg/L (n = 20).

**Conventional and immunocytochemical staining.** Neuronomorphological investigations were performed as previously described (6,7,9,17). In brief, 5-µm-thick serial coronal sections were cut through the hypothalamus at planes 24 to 32 (18). Alternate slides were stained with cresyl violet (Nissl+) or immunostained for NPY, POMC, MSH, and GAL, using the avidin-biotin-peroxidase complex (ABC) method (Vectastain Kit; Vector Laboratories). Samples were incubated with a rabbit antibody to rat NPY (1:6000; Peninsula), POMC (1:5000; Phoenix), MSH (1:1500; DPC Biermann), AGRP (1:1300; Phoenix), or GAL (1:5000; Peninsula) for 48 h in a humid chamber at 4°C. After washing, slides were treated with biotinylated antimouse IgG (2.00 µg/mL; Vector), then incubated with ABC for 2 h. Sections were exposed to a 0.05% solution of 3,3’-diaminobenzidine tetrahydrochloride (Sigma) for 20 min. Specificity of the labeling procedure was verified by the absence of immunocytochemical reaction in sections in which the primary antibody was omitted or was replaced with normal serum.

**Neuronomorphometric analysis.** Morphometrical analyses of the VMN, PVN, and ARC were performed using an image analyzing system (KS 400 V.3.0; Zeiss) connected to a light microscope (Axioscop; Zeiss) by a video camera (DWC-9300P; Sony). The BVI, a measure of whole-brain volume (19), was calculated from images at the level of the mediobasal hypothalamus (17). The areas of the VMN and PVN were calculated by interactive tracing using their boundaries in all Nissl-stained serial sections at a final magnification of 90X. The volume of each hypothalamic nucleus was calculated from these values using the Simpson rule (21). The relative volumes of the VMN and the PVN were calculated by dividing the volume of the nucleus by the BVI (20).

In all successive sections showing these nuclei, neurons were identified by a distinct nucleus and soma appearance (22). They were counted in the VMN and the PVN at a final magnification of 2000X. Localization of measurement was chosen as described previously (17). At planes 24 to 28 (18), 4 microscopic fields (MF) in the anterior part of the VMN and 3 MF in the magnocellular and parvocellular parts of the PVN, respectively, were counted in both hemispheres of the brain in each section (Fig. 1). At planes 30 to 31, 4 MF were counted bilaterally in each part of the VMN (central, ventrolateral, and dorsomedial), and 3 MF were counted bilaterally in the PVN. From these measurements, the total number of neurons in the VMN and PVN were calculated as previously described (23).

Using successive serial sections, the Nissl-, NPY-, POMC-, MSH-, AGRP-, and GAL-positive neurons in the ARC were counted in both hemispheres of the brain at a final magnification of 1700X. This was carried out by one investigator who had no knowledge of the experimental group. Only those neurons with a distinct nucleus and soma appearance were included in the measurement (6,7,22). In addition, the area within the ARC that was immunopositive for the respective neuropeptide was quantified by the image analyzing system (23). Using control sections, the detection threshold was calibrated for each neuropeptide before every series of measurement (25,26). The area within the ARC that was immunopositive for each neuropeptide was expressed as a percentage of the area of the measurement field (27). For each rat, the mean of all investigated sections was calculated for each morphometric variable. These means were used in the calculation of each group mean (CO-CO, CO-GD).

**Statistical analysis.** Data are presented as means ± SEM. One-way ANOVA analyses followed by unpaired t tests were used to evaluate differences between the groups. Relations between variables were analyzed using Spearman’s rank correlation tests. Values of P < 0.05 were considered significant. All evaluations were performed using SPSS for Windows 10.0 (SPSS).

**RESULTS**

Administration of STZ to pregnant rats resulted in marked hyperglycemia that was still detectable during lactation, on d
16 postpartum (CO: 8.4 ± 1.0 mmol/L, n = 6 vs. GD: 16 ± 3.3 mmol/L, n = 4; P < 0.01). Until weaning (d 21), the groups did not differ in neonatal mortality (CO-CO: 0/50 vs. CO-GD: 2/47). Offspring reared by GD dams (CO-GD) developed a symmetric growth delay in body weight as well as in body length until d 21 of life (Fig. 2A, B). However, on d 21 of life, blood glucose, plasma insulin, and plasma leptin concentrations did not differ between CO-CO and CO-GD rats (Fig. 3A–C).

Rats reared by diabetic dams (CO-GD) had a smaller brain volume, as measured by BVI. Neither absolute volume nor relative volume of the VMN differed between groups. In contrast, the relative volume of the PVN was markedly greater in CO-GD than in CO-CO rats (Table 1).

The overall numerical density of neurons (Nissl+) did not differ between groups in any of the hypothalamic nuclei analyzed (Table 2). However, the PVN contained a larger total number of neurons in CO-GD rats, whereas the VMN did not differ between groups in this variable (Table 2).

We then investigated the numerical density of neurons in the ARC expressing the orexigenic neuropeptides NPY, GAL, and AGRP, and those expressing the anorexigenic peptides POMC and MSH. In addition, we measured the areas within the ARC that were immunopositive for these neuropeptides. Although the absolute and relative numerical density of NPY-positive neurons did not differ between groups, the area within the ARC that was immunopositive for NPY was markedly larger in CO-GD rats (Fig. 4A). Immunopositivity for NPY in the ARC was positively correlated with maternal blood glucose on d 16 of lactation (r = 0.71; P < 0.005; n = 14).

However, the absolute and relative numerical density of POMC-positive neurons was markedly lower in CO-GD rats, compared with CO-CO rats. The POMC-immunopositive area within the ARC was also smaller in CO-GD rats (Fig. 4B). Maternal blood glucose on d 16 of lactation was negatively correlated with the absolute (r = −0.73; P < 0.005) and relative (r = −0.70; P < 0.005) numerical density of POMC-positive neurons and the POMC-immunopositive area (r = −0.60; P < 0.05; all n = 14). Concurrently, the absolute and relative numerical density of

**TABLE 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>CO-CO</th>
<th>CO-GD</th>
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<tbody>
<tr>
<td>BVI, mm³</td>
<td>95 ± 1.6</td>
<td>87 ± 2.2*</td>
</tr>
<tr>
<td>VMN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute volume, mm³ × 10⁻³</td>
<td>188 ± 11</td>
<td>171 ± 4.9</td>
</tr>
<tr>
<td>Relative volume²</td>
<td>198 ± 13</td>
<td>197 ± 4.9</td>
</tr>
<tr>
<td>PVN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute volume, mm³ × 10⁻³</td>
<td>38 ± 1.3</td>
<td>39 ± 1.4</td>
</tr>
<tr>
<td>Relative volume²</td>
<td>40 ± 1.5</td>
<td>44 ± 1.1†</td>
</tr>
</tbody>
</table>

1 Values are means ± SEM. * P < 0.01; † P < 0.05; different from the CO-CO group.

2 Relative volume = (absolute volume/BVI) × 10⁻⁵.
TABLE 2

Numerical density of Nissl+ neurons within the VMN, PVN, and ARC, and total number of neurons in the VMN and PVN on d 21 of life in rats nourished by CO-CO and CO-GD

<table>
<thead>
<tr>
<th>Hypothalamic area</th>
<th>CO-CO (n = 6)</th>
<th>CO-GD (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neuronal density, n/mm²</td>
<td></td>
</tr>
<tr>
<td>VMNtot</td>
<td>2,768 ± 93</td>
<td>2,940 ± 125</td>
</tr>
<tr>
<td>VMNa</td>
<td>2,923 ± 66</td>
<td>2,985 ± 69</td>
</tr>
<tr>
<td>VMNd</td>
<td>3,247 ± 106</td>
<td>3,371 ± 139</td>
</tr>
<tr>
<td>VMNc</td>
<td>1,966 ± 273</td>
<td>2,350 ± 254</td>
</tr>
<tr>
<td>VMNv</td>
<td>2,935 ± 126</td>
<td>3,055 ± 114</td>
</tr>
<tr>
<td>PVNtot</td>
<td>2,281 ± 70</td>
<td>2,545 ± 131</td>
</tr>
<tr>
<td>PVNm</td>
<td>2,216 ± 64</td>
<td>2,509 ± 146</td>
</tr>
<tr>
<td>PVNp</td>
<td>2,313 ± 75</td>
<td>2,569 ± 129</td>
</tr>
<tr>
<td>ARC</td>
<td>2,182 ± 53</td>
<td>2,385 ± 93</td>
</tr>
<tr>
<td>Total number of neurons, n</td>
<td>104,338 ± 7,002</td>
<td>101,410 ± 6,311</td>
</tr>
<tr>
<td>VMN</td>
<td>17,315 ± 573</td>
<td>19,558 ± 693*</td>
</tr>
<tr>
<td>PVN</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Values are means ± SEM. * Different from the CO-CO group, P < 0.05.

2 Abbreviations: PVNm, paraventricular hypothalamic nucleus, magnocellular part; PVNp, paraventricular hypothalamic nucleus, parvocellular part; PVNtot, paraventricular hypothalamic nucleus, total; VMNa, ventromedial hypothalamic nucleus, anterior part; VMNd, ventromedial hypothalamic nucleus, central part; VMNd, ventromedial hypothalamic nucleus, dorsal part; VMNv, ventromedial hypothalamic nucleus, ventrolateral part; VMNtot, ventromedial hypothalamic nucleus, total.

...development of the hypothalamic neurons that express orexigenic and anorexigenic neuropeptides. This may indicate a pathogenic effect of breast milk from diabetic mothers.

We observed a progressive delay in growth during neonatal life in the rats reared by diabetic dams, which has rarely been taken into account in this model. In humans, neonatal ingestion of breast milk from diabetic mothers may dose-dependently increase the risk of obesity in early childhood (15). Breast milk from diabetic mothers is characterized by increased levels of glucose and insulin, which both diffuse from maternal circulation into milk [(28); for review, see Neubauer (29)]. In nontreated diabetic rat dams, this is combined with a marked decrease in milk synthesis and milk ejection (30), which apparently led to quantitative undernutrition in the offspring in our experiment. However, factors other than maternal milk that are altered in this model may contribute to the outcome to a certain degree. For example, alterations in maternal behavior caused by maternal diabetes might affect neurodevelopment in the offspring.

In previous studies, we observed a decreased numerical density and a decreased total number of neurons in the VMN in offspring of GD rat dams, which persisted from weaning (d21 of life) into adulthood (2,4,9). These general neuronal alterations were restricted to the VMN, whereas other hypothalamic nuclei such as the PVN were not affected (9,23). Moreover, we showed that these alterations could be prevented by treatment of maternal gestational hyperglycemia (23,31). Because the VMN inhibits food intake, body weight gain, and insulin secretion (10), we concluded that the decreased numerical density and number of neurons might lead to impaired function of this nucleus. Impaired function of the VMN may contribute to the development of hyperphagia, obesity, and diabetogenic disturbances in the offspring of GD rat dams [(2,9); for review, see Dörner and Plagemann (4)].

Remarkably, there were no general morphometric alterations in the VMN in the current experiment. In rats, the critical differentiation period for the VMN begins in the second half of gestation, and continues until the end of wk 3 of neonatal life (32). Unlike our previous studies, exposure to maternal diabetes was restricted to the suckling period in the present experiment. Therefore, we conclude that exposure to a diabetic intrauterine milieu is crucial for the development of a general malorganization of the VMN in the offspring of diabetic rat dams, whereas exposure to altered lactation and milk alone is not sufficient.

...development of the hypothalamic neurons that express orexigenic and anorexigenic neuropeptides. This may indicate a pathogenic effect of breast milk from diabetic mothers.

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GD mothers. This supports previous studies with the offspring of GD rat dams (6,7). Notably, because blood glucose and, especially, plasma leptin and insulin concentrations did not differ between groups under basal conditions, the nonstimulated basal upregulation of NPY in CO-GD rats strongly suggests that exposure to milk from diabetic mothers alone may be sufficient to cause “malprogramming” of the NPY-ergic system, regardless of the intrauterine period. This malprogramming indicates a kind of uncoupling or resistance of this important orexigenic neuropeptidergic system to the physiological effects of leptin and insulin, obviously caused by the altered neonatal nutrition. The expression of NPY in the diencephalon begins ~14 d postconception in rats (37). During the neonatal period, NPY expression in the ARC is strongly enhanced in rats, indicating a particular critical period in the development of this neuropeptidergic system (38). Notably, a causal relation between the ingestion of glucose-enriched milk from diabetic mothers and the hypothalamic NPY expression in the weaning offspring is further supported by the positive correlation between maternal blood glucose during lactation and NPY immunopositivity in the offspring.

However, the numerical density of NPY neurons did not change, as it did in previous studies with offspring of GD rat dams (6,7). The severity of maternal diabetes might explain this phenomenon, as it obviously leads to a growth delay during neonatal development, which is probably caused by reduced maternal lactational performance (30). Therefore, we conclude that intrauterine as well as neonatal exposure are crucial for functional and structural malorganization of NPY-ergic neurons in this animal model. This interpretation is supported by animal-model studies of perinatal undernutrition, in which the number of NPY-expressing neurons did not differ between groups (39). Rather, one study even reported decreased numerical densities of NPY-positive neurons (17). Therefore, in newborn rats exposed to milk from diabetic mothers, the effects of neonatal undernutrition (i.e., reduced milk intake) might have interacted with the effects of neonatal ingestion of milk enriched with glucose and insulin.

FIGURE 4 Numerical density, percentage of neurons, and area of immunopositivity of neurons expressing NPY+ (A), POMC+ (B), MSH+ (C), AGRP+ (D), and GAL+ (E) in the arcuate hypothalamic nucleus in 21-d-old rats nourished by control CO-CO (n = 6) and CO-GD (n = 8). Data are percentages of CO-CO group values. *P < 0.05; **P < 0.01; ***P < 0.005; ****P < 0.001: different from the CO-CO group.
There was a similar phenomenon regarding the GAL-expressing neurons in the ARC. Rats in the CO-GD group had a lower numerical density of GAL-positive neurons and a smaller GAL-immunopositive area, indicating both structural and functional inhibition or hypoactivity of this neuropeptidic system. In addition to acting as an orexigenic neuropeptide, GAL plays an important role in the regulation of growth, by stimulating growth hormone secretion (40,41). On one hand, early neonatal overnutrition stimulates GAL in the ARC (42). On the other hand, studies report a reduced numerical density of GAL-immunopositive neurons in animal models of perinatal growth retardation, such as the offspring of rat dams fed a low-protein diet (17,43) or rats raised in large litters (44). The expression of GAL in the ARC begins during late neonatal life, ~11 d after birth (45), corresponding to the period of exposure to milk from diabetic dams in our model. Despite increased concentrations of glucose and insulin (46), milk from diabetic rat dams can induce a growth delay in the newborn offspring, probably due to decreased milk volume and decreased amino acid concentrations (33), which interact crucially with the growth hormone–somatostatin–GAL network during development (47). Consequently, GAL expression was positively correlated to body weight and inversely correlated to maternal blood glucose concentration during lactation in our model.

Both POMC and its splice product MSH showed structural disorganization and functional downregulation in CO-GD rats. This supression occurred despite normal plasma leptin and insulin concentrations. Together with the inverse correlation between maternal blood glucose during midlactation and MSH expression, this might indicate that exposure to milk from diabetic mothers causes malprogramming of the POMC/MSH-ergic hypothalamic system. The point at which MSH-ergic neurons appear in the ARC, around d 16 of postnatal life (48), might provide an anatomical and physiological basis for such a malprogramming, due to the kind of neonatal nutrition used in the present study. In addition, we attempted to characterize neurons expressing the neuropeptide AGRP, which acts as a physiological antagonist at the MC-4 receptor within the melanocortinergic system. Again, as in the case of NPY, there was an upregulation of this orexigenic neuropeptide in the ARC of weaning CO-GD rats. The expression of AGRP increases markedly during neonatal life, beginning on d 2 (38). In principle, it is possible that the increased expression of AGRP in the present study was induced by increased expression of NPY or vice versa, because these neuropeptides stimulate each other and are coexpressed to a high degree (49). However, the differing extent of hyperactivity and the positive correlation between maternal blood glucose during lactation and AGRP immunopositivity in the offspring seem to indicate an independent malprogramming of this orexigenic neuropeptidic system due to ingestion of milk from diabetic mothers.

In summary, this study indicates that neonatal exposure to maternal diabetes, especially exposure to milk from diabetic mothers, causes a complex malorganization and malprogramming of hypothalamic orexigenic and anorexigenic neuropeptidic systems in the offspring. This could contribute to the development of hyperphagia, obesity, and diabeticogenic disturbances in infancy and in later life. Notably, even subtle alterations in these neuropeptidergic circuits might initiate a vicious circle, as similarly suggested by Lustig (50). Hypothalamic malprogramming due to altered organization of neuropeptidergic regulatory systems may initially lead to more or less discrete functional consequences, such as moderate hyperphagia, hyperglycemia, hyperinsulinemia and hyperleptinemia, and insulin and leptin resistance. However, this may result in further (e.g., age-accelerated) dysfunction or even damage to hypothalamic neurons due to, e.g., glucotoxicity and/or a progressive induction of hypothalamic resistance to insulin and leptin, which further augments functional consequences, and so on.

Therefore, the data seem to support clinical observations showing a crucial role of neonatal exposure to breast milk from diabetic mothers in the pathogenesis of later obesity (15). Further research on the possible long-term effects of breast feeding on the offspring of diabetic mothers is obviously needed.

LITERATURE CITED


