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Perinatal programming and functional teratogenesis: Impact on body weight regulation and obesity

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Abstract

It is increasingly accepted that alterations of the intrauterine and early postnatal nutritional, metabolic, and hormonal environment may cause predispositions for the development of diseases in later life. Studies in the offspring of diabetic mothers have decisively contributed to this perception. Alterations of the fetal and neonatal environment which offspring of diabetic mothers 'experience' seem to program a disposition to develop obesity, diabetes mellitus and Syndrome X-like alterations throughout later life. Underweight at birth is also suggested to lead to an increased risk of Syndrome X in later life ('Barker hypothesis'). Pathophysiological mechanisms are unclear. Hormones are important environment-dependent organizers of the developing neuro–endocrine–immune network, which finally regulates all fundamental processes of life. When present in non-physiological concentrations during 'critical periods' of perinatal life, induced by alterations in the intrauterine or neonatal environment, hormones can act as 'endogenous functional teratogens'. Perinatal hyperinsulinism is pathognomonic in the offspring of diabetic mothers. Early hyperinsulinism also occurs as a result of early postnatal overfeeding. In rats, endogenous hyperinsulinism, as well as peripheral or only intrahypothalamic insulin treatment during perinatal development, may lead to 'malprogramming' of neuroendocrine systems regulating body weight, food intake and metabolism. This results in an increased disposition to become obese and to develop diabetes throughout life. In conclusion, a complex malprogramming of the central regulation of body weight and metabolism may provide a general etiopathogenetic concept, explaining perinatally acquired dispositions, thereby opening a wide field of primary prevention.

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Keywords: Perinatal programming; Obesity; Gestational diabetes; Neonatal overnutrition; Prevention; Barker hypothesis

1. Introduction

The impact of the intrauterine and early postnatal environment on lasting determination of fundamental processes of life is more and more accepted. In particular, investigations and hypotheses by the groups of Hales and Barker led to the postulation of a so-called 'small-baby-syndrome' which was explained by a 'thrifty phenotype', acquired by 'poor fetal nutrition' [1,2]. This concept has largely contributed to worldwide attention to the phenomenon of early epigenetic conditioning, and terms like 'nutritional programming' or 'imprinting' have been proposed to describe it.

However, as illustrated in Fig. 1, these concepts and observations are not so new [3–16]. For instance, already in 1966 the concept of Biological Freudianism was introduced by Dubos [7], focussing on the long-term impact of the perinatal environment for later body weight. In 1979, Norbert Freinkel and Boyd Metzger described the concept of 'fuel-mediated teratogenesis'—lasting deleterious consequences resulting from fetal exposure to a diabetic intrauterine environment, which is altered both nutritionally and hormonally [12,13]. In the same year, Leona Aerts and Andre Van Assche provided fundamental experimental evidence for this assumption [17]. To the best of my knowledge, however, Günter Dörner was the first (1974) to postulate a general etiological concept of 'epigenetic', perinatal 'programming' of the lifetime functioning of fundamental regulatory systems and, thereby, the possibility of perinatal prophylaxis [8–10].

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2. Hormone-dependent ontogenesis and perinatal programming

By the early 1970s, a series of clinical as well as experimental studies had demonstrated that hormones are especially important environment-dependent organizers of the neuroendocrine system (Fig. 2), which ultimately regulates all fundamental processes of life. When present in non-physiological concentrations, induced by alterations of the intrauterine and/or early postnatal environment, hormones can therefore also act as 'endogenous functional teratogens' by malprogramming the neuro–endocrine–immune network, leading to developmental disorders and diseases throughout life. This means that the classical science of 'teratology' as the discipline of exogenously induced macroscopic malformations [4] should be supplemented by the science of 'functional teratology' as the discipline of perinatally acquired malfunctions [9]. Acting as critical endogenous effectors that transmit environmental information to the genome, hormones, neurotransmitters, and cytokines (as immune cell hormones) may play a decisive role in these processes. For instance, it has been well-known that early overstimulation of the hypothalamic–pituitary–adrenal axis (HPA), in particular when induced by stress or immune challenges in perinatal life, may lead to a lasting hyperactivity of the HPA, as demonstrated by Michael Meaney and colleagues in an impressive series of experimental studies [18,19]. Thus, one could say that hypercortisolism in early life may predispose to hypercortisolism throughout life. A similar impact of early sex steroid levels on reproductive functions has been observed [10].

History and Semantics

Lamarck, 1809:	**`Heredity of acquired conditions´**
Saint-Hilaire, 1837:	***`Teratology´*** **(structurally, i.e., terato*morpho*genesis)**
Lorenz, 1935:	**`Behavioural imprinting´**
Dubos, 1966:	**`Biological Freudianism´**
Dörner, 1974:	**Pre- and perinatal `Programming´** **`Functional Teratology´**
Freinkel & Metzger, 1979:	**`Fuel-mediated teratogenesis´**
Swaab, 1988:	**`Functional neuroteratology´**
Lucas, 1991:	**`Nutritional programming´**
Hales & Barker, 1992:	**`Fetal Programming´** (thrifty phenotype hypothesis)

Fig. 1. Historical milestones in the establishment of the concept of perinatal, environmental (epigenetic) 'programming' of ontogenesis, health, and disease.

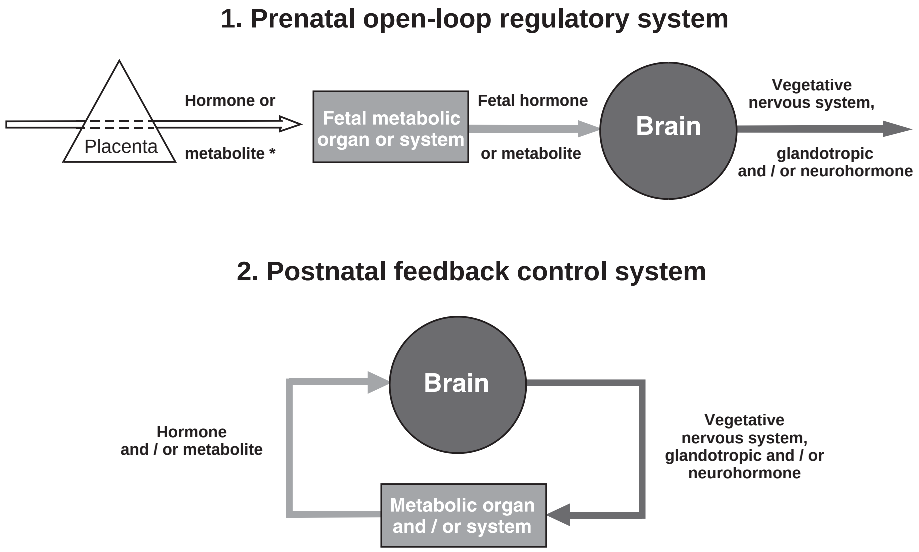
3. The diabetic pregnancy and perinatal malprogramming

Summarizing these observations on hormonal self-programming by steroid hormones, during critical phases of perinatal programming of the brain, primary linear, open-loop regulatory systems develop to secondarily closed, cybernetic feedback control systems. The functional ranges of central regulators, that means their set-points ('set-ranges'), are preprogrammed by the primary quantity of the respective hormones which are the secondarily regulated variables [8–11]. Hormones thereby act as 'ontogens', adjusting their own regulatory systems for the lifetime functions.

With regard to these rules of hormonal self-programming by steroid hormones, consider that pancreatic insulin secretion, along with food intake and body weight, are decisively regulated by central nervous structures, particularly in the hypothalamus, while circulating insulin is an essential satiety signal for the brain [20–23]. Brain-specific knockout of insulin signalling, as in terms of central insulin resistance, leads to hyperphagia and overweight in mice [24]. It is therefore particularly noteworthy that elevated insulin levels in fetal and perinatal life are pathognomonic in the children of mothers with diabetes during pregnancy (type 1 diabetes, type 2 diabetes, gestational diabetes), which affects at least one out of every ten pregnant woman in Germany [25]. Epidemiological and clinical evidence has been accumulating from a variety of authors, like Norbert Freinkel and Boyd Metzger, David Pettitt and Dana Dabelea, and Peter Weiss and colleagues [12,13,26–29], as well as from our group [11,30–36], showing that offspring exposed to maternal diabetes are at increased risk of becoming obese and developing overweight and diabetes themselves. Most interestingly, in these studies, it was clearly shown that this acquired disposition may occur irrespective of the genetic background and seems to depend, at least in part, on the perinatal insulin levels and perinatal hyperinsulinism [11,27,29,32–34].

Confirming clinical observations of a critical role of perinatal insulin levels for a lasting malprogramming, which we showed to occur independent of birth weight [34], experimental evidence has been accumulated showing that fetal and neonatal exposure to maternal diabetes may predispose to overweight and diabetes in later life. A series of epidemiological and clinical observations, in particular from the Kaulsdorf Cohort Study (KCS) in children of diabetic mothers [32–36], as well as experimental findings by our group, could continue to contribute to the development of knowledge in this field. Interestingly, in rats [11,31,42–45] and even in rhesus monkeys [46], a lasting deleterious impact of fetal or neonatal insulin exposure can be demonstrated on the later risk of becoming overweight and developing diabetes and alterations typical for the Metabolic Syndrome X.

With regard to hormones as dose-dependent self-organizers of their own neuroendocrine regulatory systems, we therefore hypothesize that insulin itself, when occurring in elevated


1. Prenatal open-loop regulatory system

2. Postnatal feedback control system

Fig. 2. General basic principle of 'biocybernetogenesis' of homeostatic regulatory systems of the organism (modified according to Dörner [8–10]). During critical phases of perinatal 'programming' of the brain and 'neuro–endocrine–immune network', primary linear, open-loop regulatory systems develop to secondarily closed, cybernetic feedback control systems (*transformation rule*). In these processes of 'self-organization', the functional ranges ('set-points') of central regulators are preprogrammed especially by the primary quantity of hormones (e.g., insulin) as the secondarily regulated variables, which thereby act as 'ontogens' adjusting their own regulatory systems for lifetime functions (*determination rule*).

concentrations during critical perinatal periods of development, may contribute to a lasting malprogramming of neuroendocrine systems regulating body weight and metabolism since insulin itself is an important modulator of central nervous development and growth. The *early experience* of elevated insulin concentrations during critical periods of neural coding might therefore lead to a malprogramming of central nervous regulators of body weight and metabolism. To experimentally investigate this working hypothesis, we used and created different models of perinatal hyperinsulinism, namely the offspring of diabetic mother rats, neonatally insulin-treated rats and neonatally overfed rats.

In the first model (streptozotocin treatment at the day of conception in outbred mother rats), the typical perinatal hyperinsulinemia occurred in the offspring of gestational diabetic mothers [11,31,37–39]. Crucial for our hypothesis was the observation that, indeed, hyperinsulinemia was accompanied by an elevation of insulin concentrations within the neonatal hypothalamus in perinatal life [37]. This is not self-evident since the blood–brain barrier is characterized by a saturable transport system for insulin. However, during fetal and early postnatal life, these mechanisms are not yet mature, thereby allowing increased insulin leakage from the circulation into the hypothalamus. During further life, lasting into adult ages, the offspring of gestational diabetic mother rats were characterized by hyperphagia, overweight, and impaired glucose tolerance [11,31,39]. All of these findings were accompanied by persisting basal hyperinsulinemia. That means that the experience of hyperinsulinism in early life may lead to hyperinsulinism throughout life.

In female F1 offspring, this perinatally acquired adipogenic and diabetogenic disposition resulted in *spontaneous* gestational diabetes during their own pregnancies, after mating with normal males. Consequently, the F2 offspring developed perinatal hyperinsulinism, accompanied again by basal hyperinsulinemia and impaired glucose tolerance in later life. The same occurred in the maternal-side F3 generation [11,31]. These observations strongly argue for an epigenetic mode of transmitting acquired materno-fetal malprogramming over successive generations, mediated intergeneratively by the intrauterine environment provided by maternal diabetes to the next generation in each case.

4. Insulin as ontogen and endogenous teratogen

All these findings were also observed in rats treated neonatally with subcutaneous insulin [11,31,45]. Therefore, we wondered whether there really exists a long-term adverse effect explicitly caused by exposure of the hypothalamus to elevated insulin levels during critical developmental periods. To investigate this, insulin was applied only and directly into the mediobasal hypothalamus of newborn rats. By means of stereotaxic operation, a long-acting insulin was applied, while in the control groups the same volume of the insulin-free, agar-vehicle was given [43,44]. In vitro studies revealed insulin release from the implants over a period of 4 days. Implants were topographically placed immediately adjacent to the ventromedial hypothalamic nucleus (VMN), which is well known to inhibit food intake as well as pancreatic insulin secretion, and to the lateral hypothalamic area (LHA), which stimulates food intake and insulin release [21,23].

When rats intrahypothalamically insulin-treated on their 2nd or 8th day of life were followed up into adult age, exciting data were obtained [43,44]. Beginning before the age of 3 weeks (i.e., at the end of the critical hypothalamic differentiation period), neonatally intrahypothalamically insulin-treated rats became obese, persisting throughout life. This overweight was accompanied by strongly impaired glucose tolerance, an increase in daily mean food intake, and lifelong persistent basal hyperinsulinemia.

These data indicate that temporary, intrahypothalamic elevation of insulin levels during critical windows of brain development may be a neuroendocrine teratogenetic risk factor. This epigenetic risk factor, when it occurs due to perinatal hyperinsulinemia in the offspring of gestational diabetic mothers, may cause a permanent, lifetime disposition to develop obesity and diabetes [11].

Thus, the question arises: which mechanisms underlie these phenomena of neuroendocrine malprogramming? As already mentioned, the VMN is well known to inhibit food intake and pancreatic insulin secretion [21]. We were therefore interested in characterizing this important hypothalamic nucleus in our experimental rat models. Computer-aided morphometric analyses revealed decreased numbers of neurons and decreased sizes of a variety of neuronal parameters in the VMN of neonatally intrahypothalamically insulin treated rats, while no morphometric alterations occurred in the LHA. Moreover, in neonatally subcutaneously insulin-treated rats and, most importantly, in the offspring of gestational diabetic mother rats, exactly the same alterations were observed, i.e., hypotrophy and hypoplasia of the VMN, and these were seen at weaning as well as in adult age [11,31,38,45]. Moreover and most importantly, however, all of this was shown to be preventable by adequate treatment of the maternal hyperglycemia [40].

In conclusion, these and other observations in different models of perinatal hyperinsulinism suggest that a perinatally acquired dysplasia and dysfunction of the VMN might contribute to the development of a disposition to hyperphagia, overweight and hyperinsulinemia throughout life. The persistent malorganization seems to be a consequence of elevated insulin levels during critical periods of early development. Interestingly, similar hypothalamic alterations were also observed in early postnatally overfed rats. At this point, we cannot but ask how all these findings might fit with the “Barker hypothesis” of a small-baby-syndrome and thrifty phenotypes [1,2].

5. Perinatal overfeeding and functional teratogenesis

It is important to consider that there is no doubt about the crucial etiogenetic role of overweight and obesity in the pathogenesis of the Metabolic Syndrome X. Interestingly enough, however, until now no study exists showing an independent inverse relation between birth weight and (over-)weight in later life. On the other hand, by mid 1970s, Ravelli and coworkers showed in their original study that early fetal undernutrition is associated with becoming obese later in life, whereas late fetal and early postnatal caloric restriction led to decreased rates of obesity in young adults [47]. These observations give rise to the suggestion that early fetal undernutrition and low birth weight as well as late fetal and early postnatal overfeeding, especially if occurring in underweight newborns, may lead to a lasting obesity disposition and consequent increased metabolic and atherogenic risk.

Rats reared in small litters have been proven appropriate models to study consequences of early postnatal overfeeding. While rats reared in small litters rapidly develop obesity, rats undernourished due to rearing in large litters become underweight until weaning [11,48,49]. In a variety of studies, overweight in small litter rats was observed to persist from early postnatal through juvenile into adult age, although standard diet was provided for all groups of rats after weaning. Interestingly, at least 30 years ago, Miller and Personage had demonstrated a strong inverse correlation between the body fat content in adult life and neonatally adjusted litter size in early life [50].

With regard to our main hypothesis, we first investigated whether both hyperinsulinemia and elevated hypothalamic insulin levels occur also in this animal model of early neonatal overfeeding. Indeed, similar to the offspring of gestational diabetic mother rats, early postnatally overfed, small litter rats displayed not only hyperinsulinemia but also an increase of intrahypothalamic insulin concentrations during early postnatal life [48]. In accordance with other investigators, during later life, persisting into adult ages, early postnatally overfed rats had hyperinsulinemia, as well as hyperphagia, overweight, impaired glucose tolerance, and an increase of systolic blood pressure [39]. Thus, a complex of symptoms characteristic for the Metabolic Syndrome X occurred in neonatally overfed rats. Interestingly, however, in rats underfed early postnatally due to nurturing in large litters, neither overweight nor hyperinsulinemia-impaired glucose tolerance or hypertension was observed in later life [11].

In this context recent epidemiological data of Nicolas Stettler are most noteworthy. In a series of impressive studies in different populations with thousands of participants, he clearly demonstrated that rapid weight gain in neonatal life is associated with increased risk of overweight and obesity in later life, independent of birth weight and weight at the age of 1 year [51]. These data strongly confirm and expand earlier observations of our group [11,52]. Rapid early weight gain, however, may mainly result from neonatal overfeeding. Thus, experimental and clinical data fit very well with a critical impact of early overfeeding and elevated weight gain and fat deposition in neonatal life as risk factors malprogramming the organism for persistent, long-term increase of obesity disposition. Most recently, this concept was strongly confirmed again by data on a particularly critical and independent role of the early neonatal period, i.e., the first week of life, for a nutritional malprogramming in normal as well as newborns of diabetic mothers, leading to long-term obesity disposition [35,36,53,54].

6. Malprogramming of hypothalamic neuropeptidergic systems

Looking for mechanisms possibly involved in neuroendocrine ‘malprogramming’, we were interested in additional hypothalamic systems involved in the regulation of food intake and body weight control. Neuropeptide Y (NPY) plays a key role in these regulatory processes, especially by acting in the orexigenic arcuate–paraventricular axis. This hypothalamic system consists of NPY-expressing neurons in the hypothalamic arcuate nucleus (ARC) which projects to the paraventricular nucleus (PVN). The expression and release of NPY within this axis is inhibited by circulating insulin and leptin, while fasting and a decrease of insulin and leptin lead to an activation of the NPY system, thereby stimulating food intake [22,23].

In our experiments [48,49], as expected, hyperinsulinemia and obesity in small litter rats were associated with a strong increase of leptin concentrations, while the hypoinsulinemic, underweight rats reared in large litters displayed decreased leptin levels. As further expected, hypoleptinemia, hypoinsulinemia and underweight in early underfed rats were accompanied by a physiological stimulation of the hypothalamic NPY system, indicated by an increased number of NPY neurons in the ARC and increased levels of NPY in the PVN. Most importantly, however, in the neonatally overnourished obese rats, characterized by elevated insulin and leptin levels, no decrease nor suppression of NPY was observed, and there were increases in both the number of NPY neurons in the ARC as well as in the NPY concentrations in the PVN [49]. In our opinion, these findings strongly indicate a malorganization and malprogramming of the hypothalamic NPY system, induced by overfeeding during the critical period of early postnatal life. An acquired hypothalamic resistance to the circulating satiety hormones leptin and insulin could be suggested [48,49].

If so, the most important question is whether this hypothalamic resistance to insulin and leptin may persist throughout later life. This would strongly indicate a neonatally acquired lasting malprogramming. Therefore, we investigated the electrophysiological responsiveness to leptin in arcuate neurons from hypothalamic brain slices of juvenile as well as adult rats reared in small litters compared to those reared in normal litters, and the following results were obtained [55]: Although all rats were fed a standard pellet diet after weaning on the 21st day of life, early postnatally overfed rats were hyperphagic and overweight throughout the study period. Interestingly, persisting hyperphagia and overweight in small litter rats were accompanied by nearly complete unresponsiveness of arcuate neurons to leptin. The number of neurons responding to leptin application with decreased firing rates was strongly reduced. Despite baseline activity similar to those in normal rats, arcuate neurons of small litter rats were not inhibited by leptin [55], and similar effects were observed with regard to insulin [56]. In our opinion, these data strongly indicate a neonatally acquired persisting hypothalamic hyporesponsiveness in terms of a relative resistance to leptin and insulin in early overfed rats (Fig. 3).

We consequently wondered whether a malorganization of the hypothalamic NPY system also occurs in the offspring of diabetic mothers. And, indeed, from weaning until adult ages, hyperphagia, overweight and persistent hyperinsulinemia in the offspring of gestationally diabetic mother rats were found to be associated with a persistently increased number of neurons expressing NPY in the ARC. Even positive correlations between the number of NPY neurons and the daily mean food intake as well as relative body weight were observed [39]. Most importantly, we could also demonstrate here that this perinatally acquired neuroendocrine malorganization is preventable by adequate treatment of maternal gestational hyperglycemia [41].

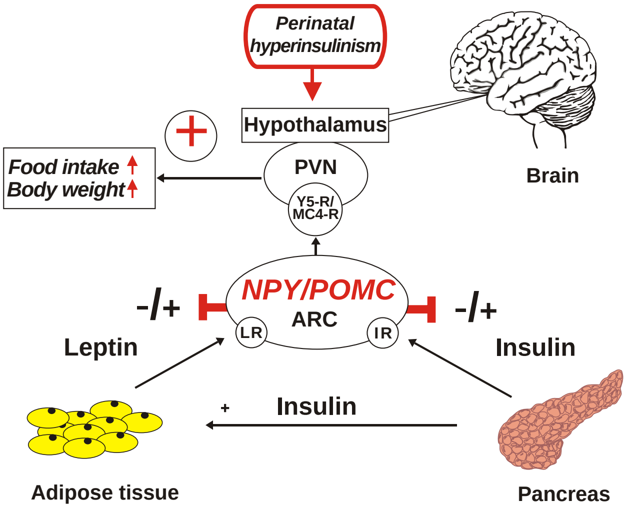


Fig. 3. Exemplary mechanism of perinatal neuroendocrine ‘malprogramming’. A temporary hyperinsulinism during critical periods of early development may result in a kind of persisting resistance (increased threshold) to the circulating satiety signals insulin and leptin in orexigenic as well as anorexigenic hypothalamic regulatory systems, leading to a perinatally acquired obesity disposition. NPY—neuropeptide Y; POMC—proopiomelanocortin.

Moreover, similar findings in terms of altered expression of, and/or response to, neuropeptides were observed, e.g., with regard to hypothalamic neurons expressing galanin, a neuropeptide which stimulates the ingestion of fat preferentially, and alterations confirming a kind of persisting resistance to circulating satiety signals and acquired functional imbalance favoring orexigenic as compared to anorexigenic circuits occurred also in further peptidergic systems (POMC/alpha-MSH, CCK-8S etc.) in the hypothalamus of these rats [57–60].

Taken together, these observations in different models of fetal and neonatal hyperinsulinism and hyperleptinism suggest that a perinatally acquired malorganization, malprogramming, and finally resistance of orexigenic as well as anorexigenic neurons in the ARC might contribute to the occurrence of hyperphagia, overweight, and hyperinsulinemia throughout later life (Fig. 3). These persistent alterations seem to be a consequence, at least in part, of elevated insulin and leptin levels during ‘critical periods’ of early development [11,23,27,29,32–46,48,49,61]. In our opinion, data accumulated and confirmed in a variety of models strongly indicate a perinatally acquired, persisting hypothalamic resistance, in terms of increased thresholds, to the circulating satiety signals insulin and leptin in perinatally hyperinsulinemic and hyperleptinemic rats. Considering the critical, decisive role of central nervous insulin signalling for the regulation of food intake and body weight [20,23,24], this kind of perinatally acquired, persisting hypothalamic insulin resistance may have long-term deleterious consequences for overweight disposition.

7. Summary and conclusions

In summary, maternal diabetes and early postnatal overfeeding may lead to a complex of Syndrome X-like alterations throughout life (Fig. 4). Since mechanisms of early programming of obesity and diabetes are unclear, a complex 'neuroendocrine malprogramming' of the regulation of body weight and metabolism may provide a general etiopathogenetic concept in this context. The association between elevated insulin concentrations during early development and acquired alterations in hypothalamic regulatory areas may indicate processes of disturbed hormone-dependent self-organization and programming of insulin-sensitive and insulin-regulating nuclei, integratively regulating food intake, body weight, and metabolism. Similarly, hyperleptinism and hypercortisolism may also lead to or contribute to such a kind of neuroendocrine malprogramming (Fig. 4). Moreover, a mod-

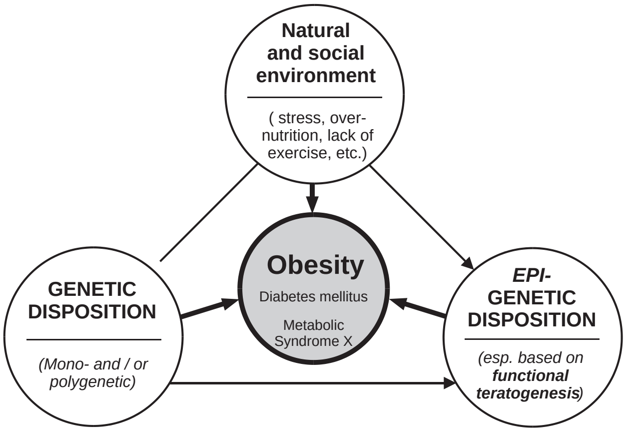


Fig. 5. Proposal of a fundamental extension of the etiopathology of obesity, in general.

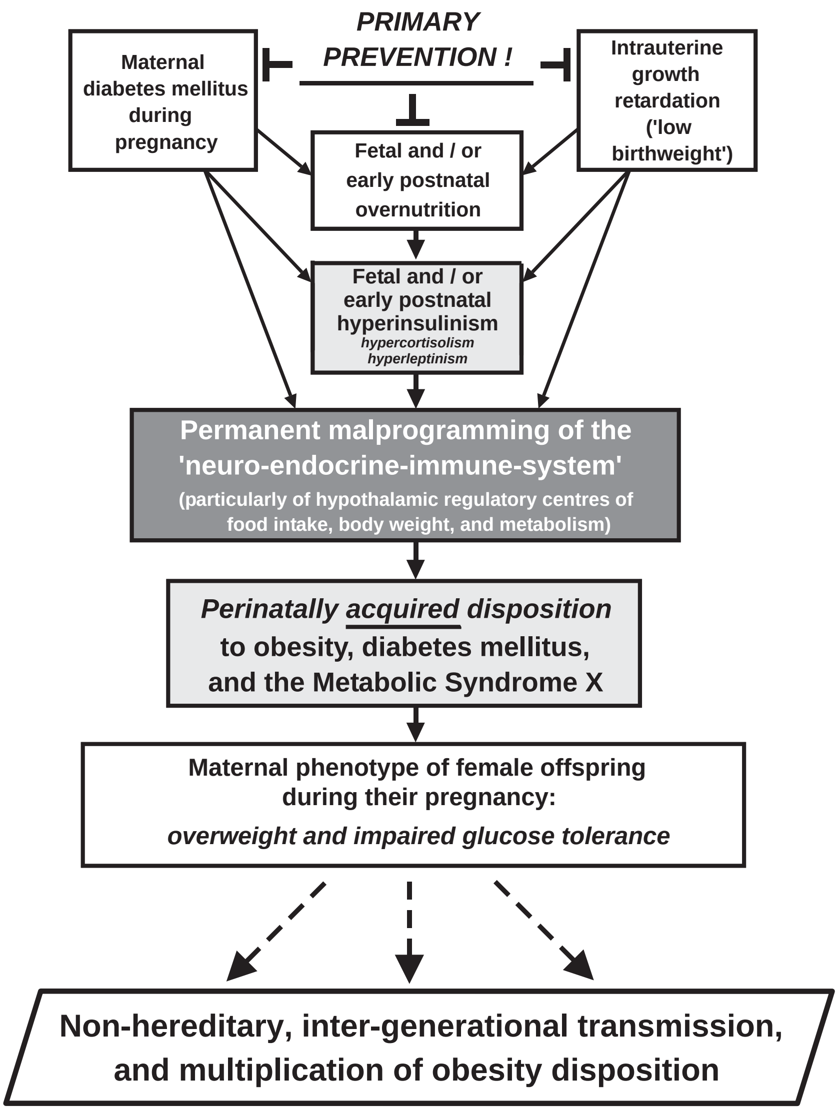


Fig. 4. General concept of 'functional teratogenesis' and possible primary prevention of materno-fetal transmission of perinatally acquired obesity disposition, which may pass on epigenetically to succeeding generations of the maternal descendents (*epigenetic transmission rule* [30]), leading to a snowball effect, intergenerative multiplication, and thereby considerable contribution to obesity epidemics.

ified neural coding perinatally acquired in this sense and the resultant disposition to obesity and diabetes may be passed on to succeeding generations in an epigenetic fashion, because of the resultant metabolic alterations resulting in the maternal intrauterine environment provided in each case by female offspring during their own gestation to the next generation, and so on (Fig. 4).

With regard to the widely discussed 'small-baby-syndrome' and 'thrifty-phenotype-hypothesis', we additionally would like to propose that early postnatal overfeeding of underweight newborns may substantially contribute to their long-term risk, a potential mechanism which has rarely been considered so far in interpretations on the 'Barker hypothesis'.

Most importantly, however, from a clinical point of view, all these observations point at the possibility of *primary prevention* of life-long increased disposition to obesity, diabetes, and consecutive risks by consequent screening for and treatment of maternal diabetes during pregnancy and lactation and by avoiding early postnatal overfeeding (Fig. 4).

8. A general perspective

Finally, in a more general view, all these observations, obtained by a variety of investigators, underline that *what we are is not only determined by our genes but also by the environmental conditions we experience during very early life*. In the great majority of cases obesity, diabetes, and critical cardiovascular endpoints are not due to a genetic defect per se, but rather to an interaction or imbalance between a genetic predisposition, probably in most cases from a polygenetic background, and unfavorable environmental conditions. Unfavorable environmental conditions, however, do not only refer to lifestyle but also to the nutritional, metabolic, and hormonal conditions 'experienced' by the fetus and newborn during decisive, circumscribed periods of early, pre- and perinatal development and programming of fundamental homeostatic systems and, therefore, lifetime functions and 'malfunctions', respectively, of the organism. On the other hand, this concept of epigenetic perinatal programming and 'functional teratogenesis' is, of course, not a concept of *para*genetic malprogramming. Especially with regard to the lasting consequences of deleterious epigenetic influences during 'critical periods' of early development, there is an important bridge between classical genetics and 'epigenetics' in this field [62,63]. In my opinion (Fig. 5), particular consideration in the future of gene–environment interactions during critical periods of early development may open a wide area of primary prevention, by integrative approaches considering genetic predispositions as well as perinatal epigenetic, environmental risk factors promoting a lasting malprogramming and functional teratogenesis which are, however, accessible to measures of primary prevention.

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