

Review article

## 'Fetal programming' and 'functional teratogenesis': on epigenetic mechanisms and prevention of perinatally acquired lasting health risks\*

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### Abstract

Alterations of the intrauterine and early postnatal nutritional, metabolic, and hormonal environment may cause predispositions to the development of disorders and diseases in later life. Mechanisms responsible for this perinatally acquired 'malprogramming' still remain unclear. It has long been known, however, that hormones are environment-dependent organizers of the developing 'neuroendocrine-immune network', which regulates all fundamental processes of life. When present in non-physiological concentrations during critical ontogenetic periods, hormones can therefore also act as 'endogenous functional teratogens'.

Fetal and neonatal hyperinsulinism is a pathognomic feature in the offspring of diabetic mothers. Perinatal hyperinsulinism also occurs due to early postnatal overfeeding. Data obtained by our group indicate that elevated insulin concentrations during critical periods of perinatal life may induce a lasting 'malprogramming' of neuroendocrine systems regulating body weight, food intake, and metabolism. Similar characteristics may occur due to perinatal hyperleptinism, hypercortisolism etc. Since mechanisms of early 'programming' of obesity, diabetes, and the metabolic syndrome X are unclear, a complex 'neuroendocrine malprogramming' of the regulation of body weight and metabolism may provide a

\*This review is dedicated to Professor Günter Dörner, MD, inaugurator of 'Perinatal Hormonal Programming & Functional Teratology', on the occasion of his 75<sup>th</sup> birthday on 13<sup>th</sup> of July 2004. The lecture was held in part as an invited contribution at the 'Second World Congress on Fetal Origins of Adult Diseases', 7<sup>th</sup>–10<sup>th</sup> June 2003, Brighton, UK.

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general etiopathogenetic concept in this context, exemplarily revealing critical new implications for chances and challenges of perinatal preventive medicine in the future.

**Keywords:** Body weight regulation; diabetes mellitus; epigenesis; fundamental life functions; functional teratogenesis; metabolic syndrome X; neuroendocrine regulation; obesity; diabetes mellitus; perinatal preventive medicine; perinatal programming; self-organization.

### Introduction

During recent years, the role of the intrauterine and early postnatal environment in the lasting determination of fundamental processes of life has been more and more accepted. Especially, 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' [2, 17]. This concept has mainly contributed to worldwide attention to the phenomenon of early epigenetic conditioning, and terms like 'nutritional programming' or 'imprinting' were proposed to describe it.

However, as illustrated in Figure 1, these concepts and observations are not so new [1, 3, 6–9, 13, 15, 16, 22, 24, 25, 40, 45, 49]. For instance, as early as 1979 Norbert Freinkel and Boyd Metzger postulated the concept of 'fuel-mediated teratogenesis' of lasting deleterious consequences resulting from fetal exposure to a diabetic intrauterine environment [15, 16]. In the same year, Leona Aerts and Andre Van Assche from Belgium provided fundamental experimental evidence for this assumption [1]. To the best of my knowledge, however, it was Günter Dörner who was the first (1974) to postulate a general etiological concept on 'epigenetic', perinatal 'programming' of the lifetime function of fundamental regulatory systems and, thereby, also of possible disorders and diseases throughout later life [6–8].

In the early 1970s in a series of clinical as well as experimental studies he demonstrated that especially hormones are environment-dependent organizers of the neuroendocrine system (Figure 2), which finally regulates all fundamental processes of life. When present in non-physiological concentrations, induced by alterations of the intrauterine and/or early postnatal environment, hor-

<b>History and Semantics</b>	
Lamarck, 1809:	'Heredity of acquired conditions'
Saint-Hilaire, 1837:	<b>'Teratology'</b> (structurally, i.e., <i>teratomorphogenesis</i> )
Lorenz, 1935:	'Behavioural imprinting'
Werboff & Gottlieb, 1963:	'Behavioural teratology'
Dubos, 1966:	'Biological Freudianism'
Dörner, 1974:	<b>Pre- and perinatal 'Programming'</b> <b>'Functional Teratology'</b>
Freinkel & Metzger, 1979:	'Fuel-mediated teratogenesis'
Csaba, 1980:	'Hormonal imprinting'
Swaab, 1988:	'Functional neuroteratology'
Lucas, 1991:	'Nutritional programming'
Hales & Barker, 1992:	'Fetal Programming' (thrifty phenotype hypothesis)
Waterland & Garza, 1999:	'Metabolic imprinting'

**Figure 1** Historical summary of establishment and concept formation as well as of younger, partial reflections of the general developmental principle of perinatal, epigenetic 'programming' of ontogenesis.

mones 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 [40] should be supplemented by the science of 'Functional Teratology' as the discipline of perinatally acquired malfunctions [7]. Acting as critical endogenous effectors which 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 is well-known and long-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 lasting hyperactivity of the HPA, as it was shown especially by Michael Meaney and colleagues in an impressive series of experimental studies [14, 26]. Thus, one could say that hypercortisolism in early life may predispose to hypercortisolism throughout life. Similar observations were

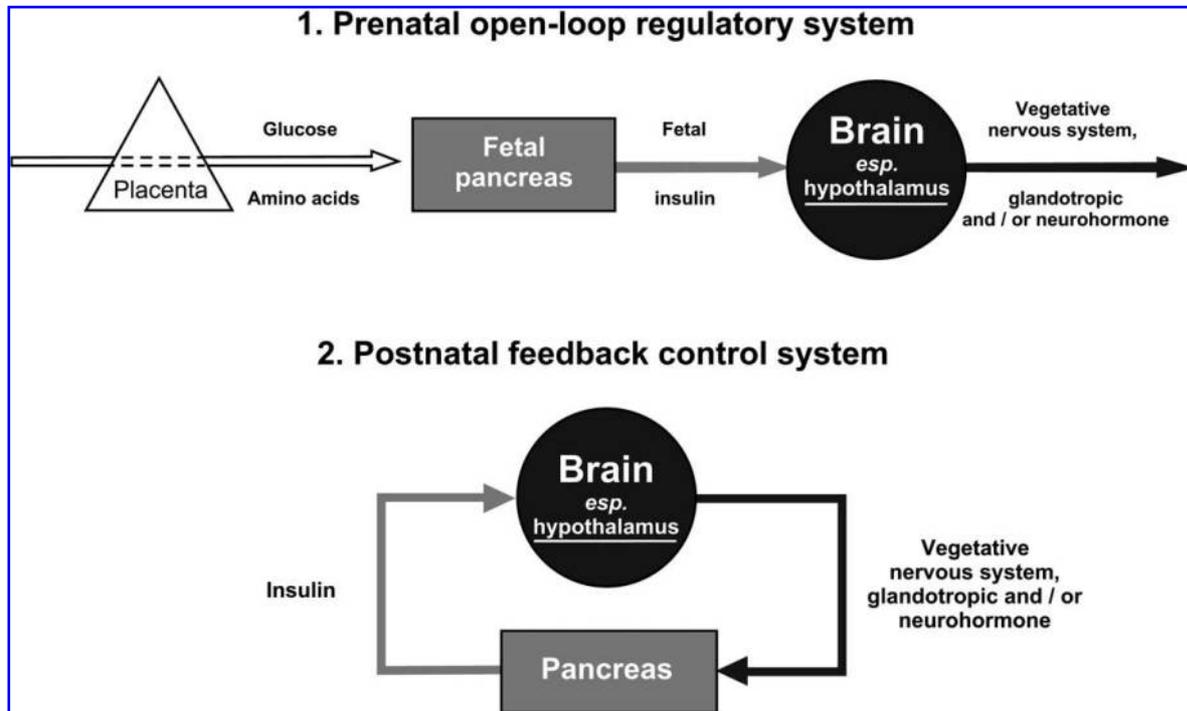
made for the impact of early sex steroid levels on reproductive functions.

### 'Perinatal programming' and 'functional teratogenesis' by maternal diabetes during pregnancy

With regard to these observations on hormonal 'self-programming' by steroid hormones it should be noted that also pancreatic insulin secretion as well as, e.g., food intake and body weight are decisively regulated by central nervous structures, particularly in the hypothalamus [20, 46]. It is noteworthy that, elevated insulin levels in fetal and perinatal life are pathognomic in children of mothers with diabetes during pregnancy (type 1 diabetes, type 2 diabetes, gestational diabetes), affecting, e.g., about every 10<sup>th</sup> pregnant woman in Germany [21]. Epidemiological and clinical evidence has been accumulate from a variety of authors, like Norbert Freinkel and Boyd Metzger, David Pettitt and Dana Dabelea, Peter Weiss and colleagues [4, 15, 16, 29, 42, 50] as well as from our own group [9, 11, 12, 19, 32, 33], showing that offspring exposed to maternal diabetes *in utero* are at increased risk of becoming obese and developing diabetes themselves. Most interestingly, in these studies it was clearly shown that this acquired disposition may occur even irrespective of the genetic background but seems to depend, at least in part, on the fetal insulin levels and perinatal hyperinsulinism [9, 19, 42, 50].

Confirming these clinical observations on the critical role of perinatal insulin levels for a lasting 'malprogramming', even independent of birth weight [19], experimental evidence accumulated showing that fetal and neonatal exposure to maternal diabetes may predispose to overweight and diabetes in later life. Interestingly, in rats [9, 12, 18, 28, 30, 31] and even in rhesus monkeys [44] a lasting deleterious impact of fetal or neonatal insulin treatment could 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 hypothesized that insulin itself, when occurring in elevated concentrations during critical perinatal periods of development, may contribute to a lasting 'malprogramming' of neuroendocrine systems regulating body weight and metabolism. In this respect note that insulin 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 offspring of diabetic



**Figure 2** General basic principle of 'biocybernetogenesis' of homeostatic regulatory systems of the organism, exemplified here by the 'hypothalamo-pancreatic' subsystem of metabolic regulation (adapted to Dörner [6, 8]). During critical phases of perinatal 'programming' of the brain and 'neuro-endocrine-immune network', primary linear, open-loop regulatory systems develop to secondary closed, cybernetic feedback control systems (transformation rule). In these processes of 'self-organization' the functional ranges ('set-points') of central regulators are preprogrammed 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 life-time functions (determination rule).

mother rats, neonatally insulin treated rats and neonatally overfed rats.

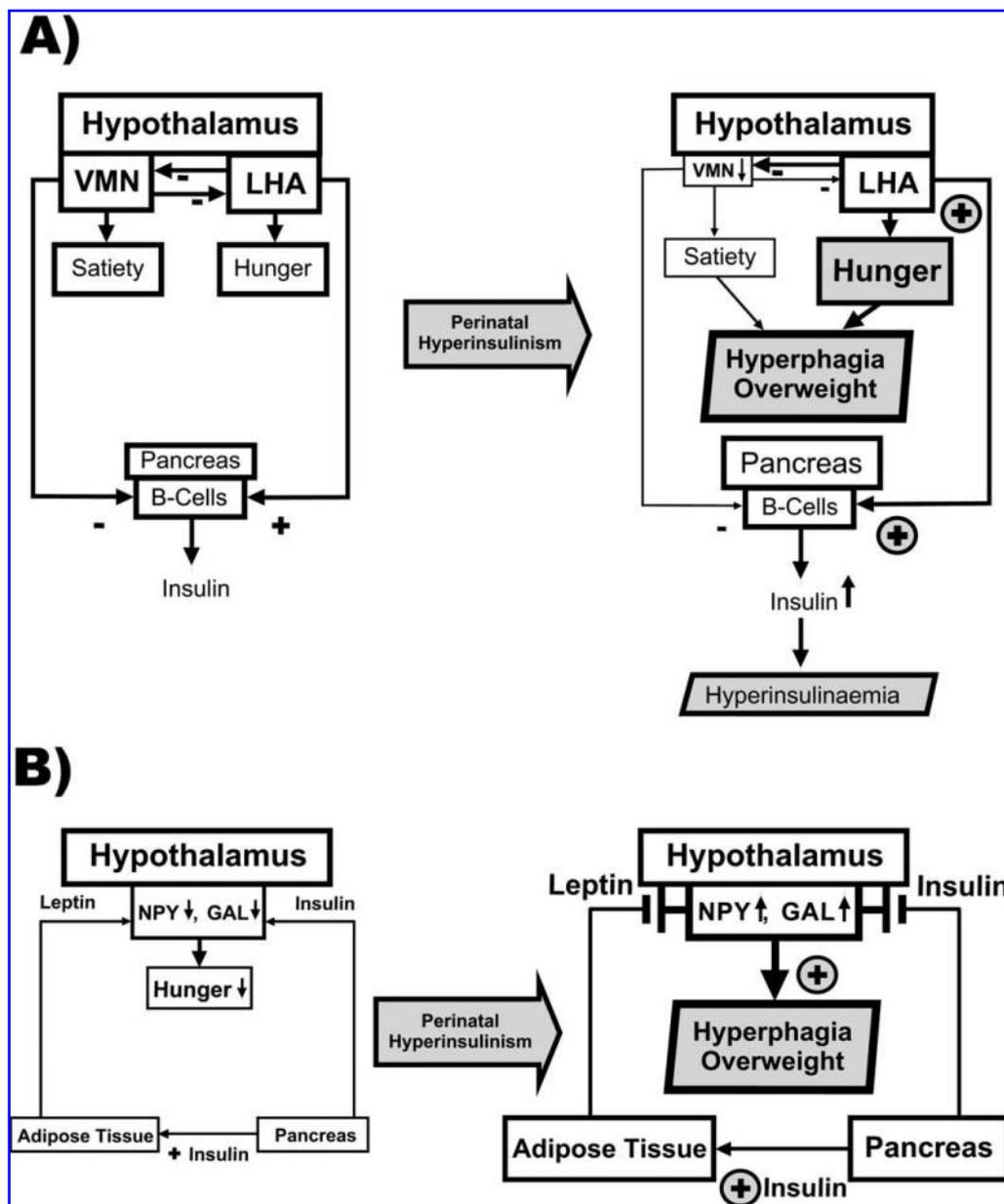
In the first model (streptozotocin-treatment on the day of conception in genetically indifferent mother rats), the typical perinatal hyperinsulinemia occurred in the offspring of gestational diabetic mothers [9, 12, 34–36]. Crucial for our hypothesis was the observation that, indeed, hyperinsulinemia was accompanied by an elevation of insulin concentrations within the hypothalamus in perinatal life [34]. 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 obviously allowing increased insulin leakage from the circulation into the hypothalamus. During further life, lasting into high adult age, the offspring of gestational diabetic mother rats were characterized by hyperphagia, overweight, and impaired glucose tolerance [9, 12, 36]. All of these findings were accompanied by persisting basal hyperinsulinemia. That means, that the 'experience' of hyperinsulinism in early life obviously led 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. Conse-

quently, 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 [9, 12]. These observations strongly suggest for an 'epigenetic' non-hereditary mode of transmitting acquired 'malprogramming' materno-fetally over successive generations, mediated intergeneratively by the intrauterine environment provided by maternal diabetes to the next generation in each case.

### 'Malprogramming' of the hypothalamus by perinatal hyperinsulinism

All these findings were also observed in neonatally subcutaneously insulin-treated rats [9, 12, 19]. Therefore, we wondered whether a long-term adverse effect explicitly caused by exposure of the hypothalamus to elevated insulin levels during critical developmental periods really exists. To investigate this, insulin was applied only and directly into the mediobasal hypothalamus of newborn rats. By means of stereotactic operation a long-acting insulin was applied, while in the control groups the same volume of the insulin-free, indifferent agar-vehicle was given [30, 31]. *In vitro* studies revealed insulin



**Figure 3** Exemplary mechanisms of perinatal neuroendocrine 'malprogramming'. An only temporary hyperinsulinism during critical periods of development may result in: **(A)** persisting dysplasia and impaired function of the hypothalamic ventromedial nucleus (VMN), a central nervous regulator and inhibitor of food intake and pancreatic insulin secretion (LHA – area lateralis hypothalami), as well as **(B)** persisting resistance to the peripheral, circulating satiety signals insulin and leptin in orexigenic hypothalamic regulatory systems which basically stimulate food intake (NPY – neuropeptide Y, GAL – galanin).

release from the implants over a period of four days. Implants were topographically placed immediately neighboring the ventromedial hypothalamic nucleus (VMN), which is well known to inhibit food intake as well as pancreatic insulin secretion, and the lateral hypothalamic area (LHA) which stimulates food intake and insulin release [46].

When these rats were followed up into adult age exciting data were obtained, in animals intrahypothalamically insulin-treated on their 2<sup>nd</sup> or 8<sup>th</sup> day of life [30, 31].

Beginning at the latest at 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. Overweight was accompanied by strongly impaired glucose tolerance, an increase in daily mean food intake, and lifelong persistent basal hyperinsulinemia.

These data clearly indicate that an only temporary, intrahypothalamic elevation of insulin levels during 'critical windows' of brain development may be a neuro-

endocrine teratogenic risk factor. This 'epigenetic' risk factor, as it occurs due to perinatal hyperinsulinemia in the offspring of gestational diabetic mothers, may cause a permanent, lifetime disposition to obesity and diabetes [9].

The question arises as to which mechanisms might underlie these phenomena of neuroendocrine 'malprogramming'. As already mentioned, the VMN is well-known to inhibit food intake and pancreatic insulin secretion. We therefore were interested in characterizing this important hypothalamic nucleus in our experimental rat models. Computer-aided morphometric analyses revealed decreased numbers and decreased sizes of neurons 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 at weaning as well as in adult age [9, 12, 18, 35].

In conclusion, these observations in three different models of perinatal hyperinsulinism suggest that a perinatally acquired dysplasia 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 (Figure 3).

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' on a 'small-baby-syndrome' and 'thrifty phenotype'.

### **'Malprogramming' by perinatal overfeeding**

In this context it is noteworthy that there is no doubt about the crucial etiogenetic role of overweight and obesity in the pathogenesis of the metabolic syndrome X. Interestingly enough, as early as the mid 1970s, in their original study Ravelli and coworkers showed that early fetal undernutrition is associated with becoming obese later in life, whereas late fetal and early postnatal caloric restriction, however, led to decreased rates of obesity in young adults [39]. These observations give rise to the suggestion that not (only) early fetal undernutrition but late fetal and early postnatal overfeeding may lead to a lasting obesity disposition and consecutive metabolic and atherogenic risks.

Rats reared in small litters have variously been proven to be an appropriate model 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

[9, 37, 38]. In a variety of studies, overweight in small litter rats was observed to persist from early postnatal through juvenile into adult age, although after weaning standard diet was provided for all groups of rats. Interestingly, already 30 years ago Miller and coworkers demonstrated a strong inverse correlation between the body fat content in adult life and the neonatally adjusted litter size in early life [27].

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 and, indeed, similarly 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 [37]. In accordance with other investigators, during further life, persisting into high adult age, in early postnatally overfed rats we observed hyperinsulinemia, as well as hyperphagia, overweight, an impaired glucose tolerance, and an increase of systolic blood pressure [37]. 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 were observed in later life [9].

In this context the recent epidemiological data of Nicolas Stettler are most noteworthy. In a series of impressive studies in different populations with thousands of participants he could clearly demonstrate that rapid weight gain in neonatal life is associated with increased risk of overweight and obesity in later life, even independent of birth weight and weight at the age of 1 year [43]. These data strongly confirm and expand earlier observations by Dörner et al. [10]. Rapid early weight gain, however, may mainly result from neonatal overfeeding.

### **Further mechanisms of 'neuroendocrine malprogramming'**

Looking for mechanisms possibly involved in neuroendocrine 'malprogramming' we were interested in further 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 project 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, particularly [20].

In our experiments [37, 38], 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 and suppression of NPY was observed, but increases in both the number of NPY neurons in the ARC as well as in the NPY concentrations in the PVN occurred [38]. 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 [37, 38].

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 [5]: Although all rats were fed a standard pellet diet after weaning on the 21<sup>st</sup> 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 [5]. In our opinion, these data strongly indicate a neonatally acquired persisting hypothalamic leptin resistance in early overfed rats.

Impressed by these observations, we consequently wondered whether a 'malorganization' of the hypothalamic NPY system also occurs in the offspring of diabetic mothers. And, indeed, from weaning until high adult age hyperphagia, overweight and persistent hyperinsulinemia in the offspring of gestational diabetic mother rats were found to be associated with a persistently increased number of neurons expressing NPY in the ARC. Positive correlations between the number of NPY neurons and the daily mean food intake as well as relative body weight were observed [36].

It is noteworthy, that similar findings were observed, e.g., with regard to hypothalamic neurons expressing

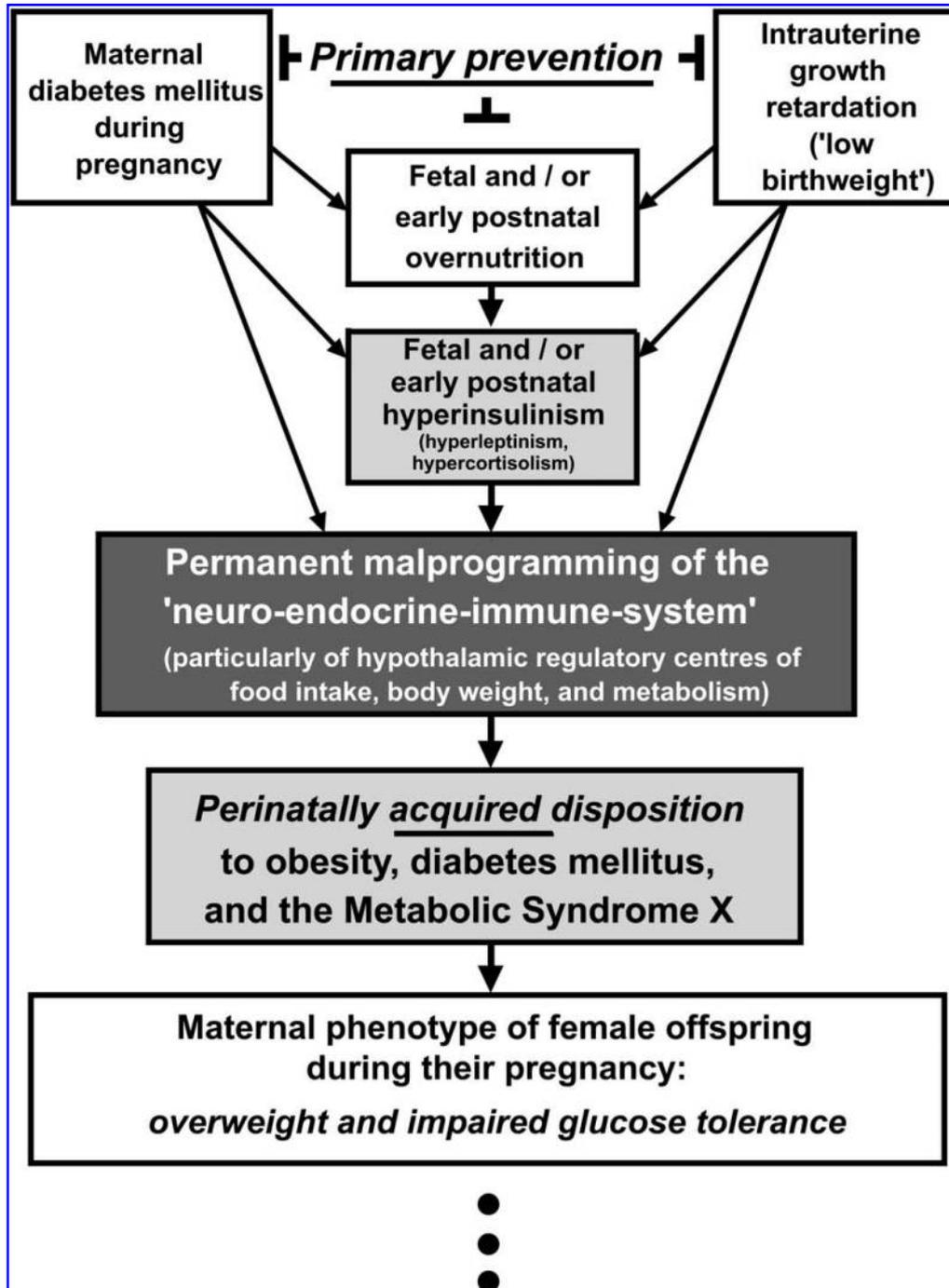
galanin, a neuropeptide which especially stimulates the ingestion of fat [34, 36, 37]. Taken together, these exemplary observations in different models of fetal and neonatal hyperinsulinism and hyperleptinism suggest that a perinatally acquired 'malorganization' of orexigenic neurons in the ARC might contribute to the occurrence of hyperphagia, overweight, and hyperinsulinemia etc. throughout later life. These persistent alterations seem to be a consequence, at least in part, of elevated insulin and leptin levels during 'critical periods' of early development. In our opinion, data strongly indicate a perinatally acquired, persisting hypothalamic resistance to insulin and leptin in perinatally hyperinsulinemic and hyperleptinemic rats (Figure 3).

## Summary and conclusions

In summary, maternal diabetes and early postnatal overfeeding may lead to a complex of syndrome X-like alterations throughout life (Figure 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, e.g., between elevated insulin concentrations during early development, and acquired alterations in hypothalamic regulatory areas might indicate processes of disturbed 'hormone-dependent self-organization' and 'programming' of these nuclei. Moreover, a modified neural coding and the resultant disposition to obesity and diabetes might be passed on to succeeding generations in a non-hereditary way, because of the resultant metabolic/'diabetic' 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 (Figure 4). With regard to the widely reflected '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 of the 'Barker-hypothesis'. Most importantly, from a clinical point of view all these observations point to the possibility of primary prevention of a life-long increased disposition to obesity, diabetes, and consecutive risks by consequent screening for and treatment of maternal diabetes during pregnancy and by avoiding early postnatal overfeeding (Figure 4).

Finally, taking 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 early life.

In the great majority of cases, e.g., obesity, diabetes, and critical cardiovascular endpoints are not due to a

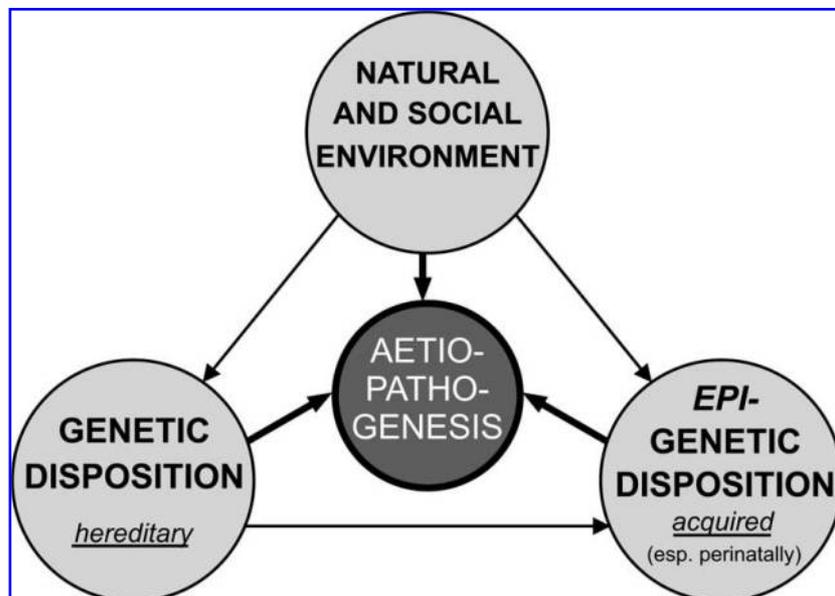


**Figure 4** Summarizing, general concept on 'functional teratogenesis' and possible primary prevention of a non-hereditary, materno-fetal transmission of increased dispositions to obesity, diabetes, and metabolic syndrome X, passed on epigenetically to succeeding generations of the maternal descendance (epigenetic transmission rule [11]).

genetic defect *per se* but to an interaction or imbalance between a genetic predisposition, mostly from a poly-genetic background, and unfavorable environmental conditions. Unfavorable environmental conditions, however, do not only refer to lifestyle but also to the hormonal and nutritional conditions 'experienced' by the fetus and newborn during decisive periods of early development

and 'programming' of fundamental homeostatic systems and, thereby, life-time 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 paragenetic 'malprogramming'. Especially with regard to the lasting consequences of



**Figure 5** Proposal of a fundamental extension of the 'etiopathology', in general.

deleterious epigenetic influences during 'critical periods' of early development there is an important bridge between classical genetics and 'epigenetics' in this field [23, 41]. In my opinion (Figure 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 on genetic predispositions and perinatal epigenetic risk factors promoting lasting 'malprogramming' and functional teratogenesis.

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## References

- [1] Aerts L, FA Van Assche: Is gestational diabetes an acquired condition? *J Dev Physiol* 1 (1979) 219
- [2] Barker DJP: In utero programming of chronic disease. *Clinical Science* 95 (1998) 115
- [3] Csaba G: The present state in the phylogeny and ontogeny of hormone receptors. *Horm Metabol Res* 16 (1984) 329
- [4] Dabelea D, RL Hanson, RS Lindsay, DJ Pettitt, G Imperatore, MM Gabir, J Roumain, PH Bennett, WC Knowler: Intra-uterine exposure to diabetes conveys risks for Type II diabetes and obesity: A study of discordant sibships. *Diabetes* 49 (2000) 2208
- [5] Davidowa H, A Plagemann: Decreased inhibition by leptin of hypothalamic arcuate neurons in neonatally overfed young rats. *NeuroReport* 11 (2000) 2795
- [6] Dörner G: Perinatal hormone levels and brain organization. *Anatomical Neuroendocrinology* 1 (1975) 245
- [7] Dörner G: Problems and terminology of functional teratology. *Acta biol med germ* 34 (1975) 1093
- [8] Dörner G: Hormones and brain differentiation. Elsevier, Amsterdam-Oxford-New York 1976
- [9] Dörner G, A Plagemann: Perinatal hyperinsulinism as possible predisposing factor for diabetes mellitus, obesity and enhanced cardiovascular risk in later life. *Horm Metab Res* 26 (1994) 213
- [10] Dörner G, H Grychtolik, M Julitz: Überernährung in den ersten drei Lebensmonaten als entscheidender Riskofaktor für die Entwicklung von Fettsucht und ihrer Folgeerkrankungen. *Dt Gesundheitswes* 32 (1977) 6
- [11] Dörner G, A Plagemann, H Reinagel: Familial diabetes aggregation in type I diabetics: gestational diabetes an apparent risk factor for increased diabetes susceptibility in the offspring. *Exp. Clin. Endocrinol.* 89 (1987) 84
- [12] Dörner G, A Plagemann, JC Rückert, F Götz, W Rohde, F Stahl, U Kürschner, J Gottschalk, A Mohnike, E Steindel: Teratogenetic maternofetal transmission and prevention of diabetes susceptibility. *Exp Clin Endocrinol* 91 (1988) 247

- [13] Dubos R, D Savage, R Schaedler: Biological Freudianism: Lasting effects of early environmental influences. *Pediatrics* 38 (1966) 789
- [14] Francis DD, MJ Meaney: Maternal care and the development of stress response. *Current Opinion in Neurobiology* 9 (1999) 128
- [15] Freinkel N: Of pregnancy and progeny. Banting lecture 1980. *Diabetes* 29 (1980) 1023
- [16] Freinkel N, BE Metzger: Pregnancy as a tissue culture experience: the critical implications of maternal metabolism for fetal development. In: *Pregnancy metabolism, diabetes, and the fetus*. Ciba Foundation Symposium 63, Amsterdam, Excerpta Medica 1979, pp 3
- [17] Hales CN, DJP Barker: Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 35 (1992) 595
- [18] Harder T, A Plagemann, W Rohde, G Dörner: Syndrome X-like alterations in adult female rats due to neonatal insulin treatment. *Metabolism* 47 (1998) 855
- [19] Harder T, R Kohlhoff, W Rohde, G Dörner, A Plagemann: Perinatal 'programming' of insulin resistance in later life: Critical impact of neonatal insulin and low birth weight in a risk population. *Diabetic Medicine* 18 (2001) 634
- [20] Kalra SP, PS Kalra: Nutritional infertility: the role of the interconnected hypothalamic neuropeptide Y-galanin-opioid network. *Front Neuroendocrinol* 17 (1996) 371
- [21] Kleinwechter H: The government sponsored model project Gestational diabetes (GDM) Schleswig-Holstein: Prevalence and foetal outcome in unselected women following the successful implementation of screening for GDM. *Diabetologia* 43 Suppl 1 (2000) A56
- [22] Lamarck JB: *Philosophie zoologiques*. Paris, 1809
- [23] Levin BE: The obesity epidemic: Metabolic imprinting on genetically susceptible neural circuits. *Obes Res* 8 (2000) 342
- [24] Lorenz K: Der Kumpan in der Umwelt des Vogels: Der Artgenosse als auslösendes Moment sozialer Verhaltensweisen. *Journal für Ornithologie* 83 (1935) 13
- [25] Lucas A: Programming by early nutrition in man. In: *The childhood environment and adult disease*. Ciba Foundation Symposium 156, Chichester, Wiley 1991, pp 38
- [26] Meaney MJ, J Diorio, D Francis, J Widdowson, P LaPlante, CH Caldji, S Sharma, JR Seckl, PM Plotsky: Early environmental regulation of forebrain glucocorticoid receptor gene expression: Implications for adrenocortical responses to stress. *Dev Neurosci* 18 (1996) 49
- [27] Miller DS, SR Personage: The effect of litter size on subsequent energy utilization. *Proc Nutr Soc* 31 (1971) 30
- [28] Ogata ES, JW Collins, S Finley: Insulin injection in the fetal rat: accelerated growth and altered fetal and neonatal glucose homeostasis. *Metabolism* 37 (1988) 649
- [29] Pettitt DJ, HR Baird, KA Aleck, PH Bennett, WC Knowler: Excessive obesity in offspring of pima indian women with diabetes during pregnancy. *NEJM* 308 (1983) 242
- [30] Plagemann A, I Heidrich, F Götz, W Rohde, G Dörner: Life-long enhanced diabetes susceptibility and obesity after temporary intrahypothalamic hyperinsulinism during brain organization. *Exp Clin Endocrinol* 99 (1992) 91
- [31] Plagemann A, I Heidrich, W Rohde, F Götz, G Dörner: Hyperinsulinism during differentiation of the hypothalamus is a diabetogenic and obesity risk factor in rats. *Neuroendocrinol Lett* 14 (1992) 373
- [32] Plagemann A, T Harder, R Kohlhoff, W Rohde, G Dörner: Overweight and obesity in infants of mothers with long-term insulin-dependent diabetes or gestational diabetes. *Int J Obesity* 21 (1997) 451
- [33] Plagemann A, T Harder, R Kohlhoff, W Rohde, G Dörner: Glucose tolerance and insulin secretion in infants of mothers with pregestational insulin-dependent diabetes mellitus or gestational diabetes. *Diabetologia* 40 (1997) 1094
- [34] Plagemann A, T Harder, A Rake, K Melchior, F Rittel, W Rohde, G Dörner: Hypothalamic insulin and neuropeptide Y in the offspring of gestational diabetic mother rats. *NeuroReport* 9 (1998) 4069
- [35] Plagemann A, T Harder, U Janert, A Rake, F Rittel, W Rohde, G Dörner: Malformations of hypothalamic nuclei in hyperinsulinaemic offspring of gestational diabetic mother rats. *Dev Neurosci* 21 (1999) 58
- [36] Plagemann A, T Harder, K Melchior, A Rake, W Rohde, G Dörner: Elevation of hypothalamic neuropeptide Y-neurons in adult offspring of diabetic mother rats. *NeuroReport* 10 (1999) 3211
- [37] Plagemann A, T Harder, A Rake, M Voits, H Fink, W Rohde, G Dörner: Perinatal elevation of hypothalamic insulin, acquired malformation of hypothalamic galanergic neurons, and syndrome X-like alterations in adulthood of neonatally overfed rats. *Brain Res* 836 (1999) 146
- [38] Plagemann A, T Harder, A Rake, T Waas, K Melchior, T Ziska, W Rohde, G Dörner: Observations on the orexigenic hypothalamic neuropeptide Y-system in neonatally overfed weanling rats. *J Neuroendocrinol* 11 (1999) 541
- [39] Ravelli GP, ZA Stein, MW Susser: Obesity in young men after famine exposure in utero and early infancy. *NEJM* 295 (1976) 349
- [40] Saint-Hilaire EG: *Histoire générale et particulière des anomalies de l'organisation chez l'homme et les animaux ou traité de teratologie*. Bruxelles, 1837
- [41] Schmidt I, C Schoelch, T Ziska, D Schneider, E Simon, A Plagemann: Interaction of genetic and environmental programming of the leptin system and of obesity disposition. *Am J Physiol Physiol Genomics* 23 (2000) 113
- [42] Silverman BL, BE Metzger, NH Cho, CA Loeb: Impaired glucose tolerance in adolescent offspring of diabetic mothers. *Diabetes Care* 18 (1995) 611
- [43] Stettler NS, BS Zemel, S Kumanyika, VA Stallings: Infant weight gain in a multicenter, cohort study. *Pediatrics* 109 (2002) 194
- [44] Susa JB, JM Boylan, P Sehgal, R Schwartz: Impaired insulin secretion after intravenous glucose in neonatal rhesus monkeys that had been chronically hyperinsulinemic in utero. *Proc Soc Exp Biol Med* 199 (1992) 327
- [45] Swaab DF, GJ Boer, MGP Feenstra: Concept of functional neuroteratology and the importance of neurochemistry. *Progress in Brain Research* 73 (1988) 3
- [46] Szabo AJ: *CNS regulation of carbohydrate metabolism*. Academic Press, New York 1983
- [47] Ugrumov MV, IP Ivanova, MS Mitskevich: Permeability of the blood-brain barrier in the median eminence during the perinatal period in rats. *Cell Tissue Res* 230 (1983) 649
- [48] Waterland RA, C Garza: Potential mechanisms of metabolic imprinting that lead to chronic disease. *Am J Clin Nutr* 69 (1999) 79
- [49] Werboff J, JS Gottlieb: *Drugs in pregnancy: behavioral teratology*. *Obstet Gynecol Surv* 18 (1963) 420
- [50] Weiss PAM, HS Scholz, J Haas, KF Tamussino, J Seissler, MH Borkenstein: Long-term follow-up of infants of mothers with Type I Diabetes. *Diabetes Care* 23 (2000) 905