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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.

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].

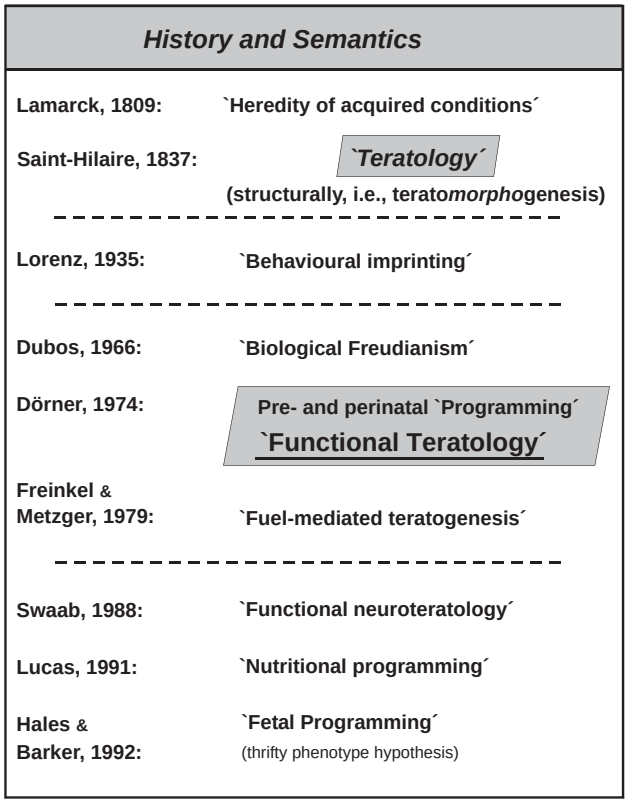

Fig. 1. Historical milestones in the establishment of the concept of perinatal, environmental (epigenetic) 'programming' of ontogenesis, health, and disease.

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