Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 57 (Suppl 2) (2008) S22 – S26
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Prenatal imprinting of postnatal specific appetites and feeding behavior

Stylianos Nicolaïdis*,[1]
84 Bd du maréchal Joffre, 92340 Bourg La Reine, France

Abstract

Epigenetic influences on the fetus's genotype have been shown to occur during intrauterine life. Experimentally imposed extracellular dehydration in pregnant rats (a model for human hyponatremia caused by gravidic vomiting) brings about a dramatic enhancement of salt appetite not only in the dam, but also in offspring when they reach adulthood. This phenomenon has been verified in human newborn infants and adults whose mothers experienced nausea and/or vomiting during pregnancy. Alcohol consumption during pregnancy enhances its palatability for the offspring. Ingestion of olfactory test substances like anise or carrot by the mother during pregnancy gives rise to a preference for the same testants in the offspring. Under- or overnutrition in the pregnant mother appears to play a role in reprogramming the postnatal regulation of both feeding and fat reserves in offspring. Both maternal under- and overnutrition during pregnancy predispose the offspring to later development of obesity and type 2 diabetes mellitus. A careful examination of the systems concerned with the regulation of food intake, and the neurosubstances involved in such regulation, reveals some of the mechanisms by which maternal nutritional status can affect the offspring and their food-related behaviors.

1. Introduction

Epigenetic influences imported from the maternal "universe" during fetal life superimpose changes in the genetic templates of the offspring—changes that affect their subsequent feeding behavior, specific appetites, and metabolism. Indeed, a number of studies, both in humans and laboratory animals, demonstrate that such prenatal changes can be considered to have been "imprinted" or "programmed." By modifying brain properties and organ structure, such imprinting can bring about permanent alterations in the regulatory mechanisms of the offspring.

This article is concerned with the prenatal imprinting that affects specific appetites and/or feeding in general during the later life of the offspring.

2. Specific appetites

2.1. Salt appetite

The most important and best understood of specific appetites is sodium chloride (NaCl) or salt appetite, also referred to as *salt hunger* or *natriophilia*. Salt appetite leads to a strong drive to seek and consume salt from a variety of sources and allows herbivores and omnivores to offset both their usual and unusual losses of NaCl via the urine, feces, and skin [1]. Sodium appetite increases in response to hypovolemic and hypoosmotic deficits. When these deficits recur, excessive salt hunger (hypernatriophilia) develops, as if each experience of sodium deficit were leaving behind a sort of memory (hormonally induced by angiotensin II and aldosterone) that, over time, increases the readiness and strength of the ingestive response. The problem is that, besides demonstrating physiologically appropriate natriophilia, the subject also develops a need-independent (excessive) sodium intake, a classic cause of hypertension. Importantly, an intensified sodium appetite and the related propensity to prefer and consume salty foods are unequally distributed between and within subpopulations of humans and also in rats. The question is why differences in natriophilia exist within populations. Is there something in an individual's history that accounts for the subsequent

STATEMENT OF CONFLICT OF INTEREST: The author is a member of the Scientific Committee of the Collège International de Recherche Servier (CIRS).

* Tel.: +33 1 46 60 47 60.
E-mail address: snicolaidis@laposte.net.
[1] Formerly at: Centre National de Recherche Scientifique (CNRS) of the Collège de France, Paris 5, France.

0026-0495/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2008.07.004

neuroendocrine resetting and, as a result, for a greater or lesser degree of natriophilia? Does an individual's history of salt craving start in utero? Is it possible that vomiting and nausea, often observed during pregnancy, bring about hyponatremia and extracellular dehydration and, thereby, a permanent natriophilic trait in offspring?

Because hypernatriophilic responses can be induced, even in the suckling rat [2], we tested the hypothesis that extracellular dehydration imposed on a pregnant rat could bring about hypernatriophilia in its offspring when they reach adulthood [3].

Pregnant rats were treated with a subcutaneous injection of a colloid solution of polyethylene glycol (PEG), which absorbs and sequesters under the skin a large volume of isotonic fluid and thus produces extracellular dehydration, which, in turn, induces thirst and exaggerates salt appetite. The control dams received a subcutaneous injection of the vehicle. Eighty days after birth, the adult offspring of these treated pregnant rats were tested; and their salt-motivated behavior was compared with that of the offspring of control dams. We measured the offspring's basic preference for a 3% NaCl solution vs plain water. As expected, the offspring of the PEG-treated dams showed a dramatic increase in salt appetite as compared with the offspring of the untreated, control dams. The increased salt appetite was observed both under basal conditions and, to an even greater extent, after the offspring themselves were dehydrated with PEG.

These results demonstrate that extracellular dehydration during pregnancy can enhance the natriophilic propensity in offspring of both sexes. As the design of this experiment was conceived to provide a model for human extracellular dehydration due to gravidic vomiting or nausea, these results suggested that at least 1 type of ordinary observed hypernatriophilia, together with its implications for the epidemiology of hypertension, could be attributed to gravidic dehydration [3].

This hypothesis was successfully verified by Crystal and Bernstein [4] in a series of human investigations. First, in a cohort of 169 students, they found that those who reported higher salt use were precisely the ones whose mothers had experienced vomiting during pregnancy. Afterward, they tested students for their tendency to like and consume more of the saltier snacks. Again, they found that natriophilia was concentrated among subjects whose mothers had experienced nausea and vomiting during pregnancy [4]. In a subsequent study, these authors tested 16-week–old infants whose mothers had (or had not) experienced vomiting during pregnancy for their responses to water or salty solutions. Pleasantness was measured by observations of their facial, oral-motor expression and their consumption of the test solution. Again, infants whose mothers had reported gravidic vomiting showed the strongest preference for saltiness [5].

Kochli and coworkers [6] showed that maternal nausea and vomiting during pregnancy correlated with increased salt appetite in offspring. They also found an enhanced salt preference in infants that had experienced mineralofluid loss in their early life or in utero [7].

Finally, Curtis and associates [8] have shown in the rat that manipulations of dietary NaCl levels during gestation and the early postnatal period lead to persistent changes both in "need-free" and stimulated NaCl intake by adult rats.

2.2. Mechanism of salt appetite

The ingestive (like the renal) response to osmovolemic deficits involves activation of the renin-angiotensin system, which acts synergistically with the mineralocorticoid hormone aldosterone. These 2 hormones produce their natriophilic effect by acting directly at the central level [9]. The brain area responsible for the effect of angiotensin II through the AT1 receptors [10] is the anterior wall of the third ventricle, between 2 circumventricular vascular organs: the subfornical organ and the organum vasculosum laminae terminalis. Aldosterone's area of action is located in the central and medial amygdala [11].

Both hormones cross the placental barrier and act directly on the fetal brain. When angiotensin II and aldosterone are injected into a pregnant rat (instead of inducing extracellular dehydration), we still observe hypernatriophilia in the offspring.

It was also shown that the process of sensitization vis-à-vis salt consumption represents a form of long-term plasticity that differs from associative learning, but shares the common mechanisms of motivation and reward [10]. Roitman et al [12] showed that enhancement of salt appetite is accompanied by alterations in neurons of the nucleus accumbens. The neurons in question had significantly more dendritic branches and spines than controls—a picture consistent with synaptic reorganization. Thus, neuronal alterations common to salt and drug sensitization may represent a more general mechanism underlying enhanced behavioral responses to subsequent exposures to such challenges.

2.3. Water intake

Surprisingly few investigations have addressed one of the most fundamental of the ingestive behaviors—water intake. In this regard, a detailed examination of the mechanism by which hydration is regulated in the fetus may advance our understanding of both normal and pathologic states of hydration that occur later. For example, it has been shown that fetal swallowing activity—which contributes to the regulation of amniotic fluid volume—is influenced by fetal maturation and affected by the presence of neurologic pathology [13].

It has been shown that some dipsogenic mechanisms in the near-term ovine fetus (osmolality, angiotensin II) are mature. Furthermore, Ross and Desai [14] have reported that phenotypic predisposition of osmoregulatory and cardiovascular (blood pressure) regulation may be programmed in utero. These authors were interested in the developmental consequences of drought-induced water deprivation during pregnancy—a condition associated with dehydration-

induced anorexia and concomitant undernutrition. Maternal dehydration results in low–birth-weight offspring who later develop plasma hypernatremic hypertonicity and arterial hypertension. Interestingly, if permitted rapid catch-up growth by nutrient availability during lactation, these offspring exhibit increased body weight, body fat, and leptin resistance as adults. Conversely, if the catch-up growth is delayed by postnatal nutrition restriction (often observed after a drought), the offspring exhibit normal body weight, body fat, and plasma leptin levels as adults—a sad consolation for populations suffering from drought [15].

2.4. Other specific appetites

The fetus experiences flavors imported from the maternal diet early in its development. Recent advances in the technology of recording fetal activity by ultrasonography have permitted investigators to visualize in real time movements of the mouth such as mouth opening, suckling, or tongue protrusion [13]. Flavors from the mother's diet reach the amniotic fluid, are swallowed by the fetus, and come in contact with the olfactogustatory apparatus that is functional in fetuses. In addition, some of these same flavors will be experienced again later in breast milk, a liquid that, like amniotic fluid, contains flavors generated by the foods, spices, and beverages consumed by the mother. In these ways, prenatal and perinatal imprinting of appetites for specific flavors can arise from early exposure to flavors originally derived from the maternal diet [15].

2.5. Olfactory testants

We know that one of the earliest and most persistent of memories is olfactory memory. Our memories are capable of browsing the world of fragrances in our early history. But how early? Today, it is established that strong olfactory memory is restricted not only to earliest infancy but extends back into intrauterine life. Le Magnen first postulated in his lessons in 1970 this kind of intrauterine olfactory memory. Since then, its actual existence has been demonstrated in various mammals such as rats, rabbits, and sheep. The introduction of odorants into amniotic fluid, either by direct infusion or via maternal ingestion, has been shown to induce a preference for the same olfactory testants in the offspring—a preference manifested in both their early and late postnatal development [16].

These animal findings were confirmed in human studies. In 1 human study, the olfactory responsiveness to anise was assessed in neonates born to mothers who had, or had not, consumed anise flavor during pregnancy. Neonates born to anise-consuming mothers displayed a persistent preference for anise odor, whereas those born to non–anise-consuming mothers showed aversion or neutral responses [16]. The foregoing studies contribute to our understanding of the basis of the large variety of food preferences observed among individuals and, particularly, among infants.

In another study from the Monell Chemical Senses Center, one population of pregnant women was exposed to carrot flavor, whereas another population was not so exposed. Studies of their offspring disclosed that, in contrast to control infants whose mother remained unexposed to carrot during pregnancy and lactation, the infants exposed prenatally to carrot flavor exhibited fewer negative facial expressions while being fed a carrot-flavored cereal. Moreover, the infants who were exposed to carrots prenatally were perceived by their mothers as preferring the carrot-flavored cereal to a plain cereal. Thus, prenatal exposure to a flavor can enhance infants' enjoyment of that flavor in solid foods during weaning [17].

Observations of this kind in humans extend and confirm evidence from animal studies and suggest that prenatal programming has survival value, for example, allowing the newborn to locate the source of maternal milk just by smell. These studies also show that the diets consumed by mothers influence the hedonic choices of their offspring and may help explain the large variety of food preferences among individuals and the transmission of taste preferences from one generation to the next—providing the basis for cultural and ethnic differences in cuisine.

2.6. Alcohol

Given the fact that many pregnant women still consume alcohol in varying amounts, it is extremely important to pay attention to the numerous adverse effects in the offspring of such maternal behavior. In the present review, however, we address only the effects of maternal alcohol consumption on later alcohol intake by the offspring.

In the rat, the effects of an acute prenatal alcohol experience (occurring during gestational day 21 [the last day of pregnancy]) were assessed in the offspring [18]. Their short prenatal experience was sufficient to significantly increase both their ethanol odor preference and (when given the opportunity) their alcohol intake [19]. The authors wrote, "From a clinical perspective, an enhanced preference for ethanol odor may be an important contributor to the risk for an enhanced postnatal avidity for the drug."

Observations similar to those described above have been reported recently in humans. They confirm the findings in rats concerning the effects of maternal alcohol consumption during pregnancy on alcohol-related behavior in the offspring. These studies strongly suggest that maternal alcohol consumption is an important factor that contributes to the perpetuation of the vicious cycle of abuse arising from fetal exposure to adult alcohol abuse [19].

2.7. Effect on feeding

Apart from their effect on specific appetites, changes in prenatal nutrition via the placenta (and later during breast feeding) help reprogram development of the regulation of both feeding and fat reserves in adult life. Evidence from epidemiologic studies and animal models

indicates that the origins of obesity and related metabolic disorders lie not only in the interaction between genes and postnatal risk factors, but also in the interaction between genes and the embryonic, fetal, and early postnatal environment.

When maternal nutrition in the rat is restricted to 30% of control intake throughout the whole of gestation, offspring are smaller; but the relative mass of the retroperitoneal fat pad is increased at 100 days of age. Food intake in the offspring of the undernourished rats (cross-fostered to ad libitum–fed mothers) is increased early in postnatal life, increased with advancing age, and amplified by postnatal hypercaloric nutrition [20].

A number of human studies have found a correlation between birth weight and subsequent body mass index in both childhood and adult life [21].

Studies in humans suggest that low birth weight significantly enhances the risk of developing both adult obesity and the accompanying metabolic syndrome, an observation that appears to be in conflict with evidence that an elevated birth weight also increases risk of childhood and adult obesity. Taylor and Poston [22] have published a detailed review of the permanent programming effect on appetite and the body's energy balance of the maternal nutritional and hormonal environments. In their review, they also consider the mechanisms that contribute to the perpetuation of a perturbed energy economy (eg, chronic obesity) or one that functions normally (eg, maintenance of desirable weight).

From a teleological point of view, when the fetal environment is unsatisfactory, there is an adaptive response, which optimizes the growth of the most indispensable bodily organs at the expense of others that are less essential. All these lead to an altered postnatal metabolism designed to improve postnatal survival under conditions of intermittent or prolonged semistarvation. Ironically, these adaptations only become disadvantageous when food is abundant in the postnatal environment.

This article will not review the research on the mechanisms of prenatal programming that affect postnatal feeding, metabolism, and body weight in response to maternal over- or underfeeding, and pathologies like diabetes. Most of the relevant neurosubstances and their hypothalamic circuitries are under active investigation [23].

3. Conclusion

From the evolutionary standpoint, we can see a clear biological framework that allows us to understand the important role played by the prenatal environment in promoting both successful reproduction and the health of subsequent populations. However, we have to distinguish among the many fetal adaptations that occur in response to environmental changes so that we can identify those that (*a*) confer an immediate adaptive benefit but have no functional consequences in the postnatal period beyond fetal survival, (*b*) confer an immediate adaptive benefit but restrict the spectrum of adaptive responses in the face of a mismatched postnatal environment, or (*c*) confer no immediate adaptive benefit but prepare the new individual to adapt more effectively in the future. For example, prenatally imprinted diet preferences are useful for the future infant in the sense that they favor easier neophilia and less neophobia. By taking advantage of their mother's experience, offspring gain a larger spectrum of food choices—a state of affairs that gives them a better chance of survival in nature.

From a public health standpoint, an improved knowledge of the prenatal and early postnatal factors that program subsequent obesity should permit formulation of a targeted attack upon these factors, thereby ensuring a more effective campaign against the ever-growing epidemic of obesity—a disorder easier to prevent than cure. For example, when gestational diabetes, hyperinsulinemia, insulin resistance, and hyperleptinemia occur during pregnancy, prompt intervention is critically important if long-term complications affecting both the mother and her child are to be avoided or minimized.

Acknowledgment

The author thanks Theodore B VanItallie, MD, for his helpful editorial comments.

References

[1] Richter CP. Salt appetite of mammals: its dependence on instinct and metabolism. In: Autuori M, editor. L'Instinct dans le comportement des animaux et de l'homme. Paris: Masson; 1956. p. 577.
[2] Leshem M. The ontogeny of salt hunger in the rat. Neurosci Biobehav Rev 1999;23:649-59.
[3] Nicolaidis S, Galaverna O, Metzler CH. Extracellular dehydration during pregnancy increases salt appetite of offspring. Am J Physiol 1990;258(Regulatory Integrative Comp Physiol 27):R281-3.
[4] Crystal SR, Bernstein IL. Morning sickness: impact on offspring salt preference. Appetite 1995;25:231-40.
[5] Crystal SR, Bernstein IL. Infant salt preference and mother's morning sickness. Appetite 1998;30:297-307.
[6] Kochli A, Tenenbaum-Rakover Y, Leshem M. Increased salt appetite in patients with congenital adrenal hyperplasia 21-hydroxylase deficiency. Am J Physiol Regul Integr Comp Physiol 2005;288: R1673-81.
[7] Leshem M. Salt preference in adolescence is predicted by common prenatal and infantile mineralofluid loss. Physiol Behav 1998;63: 699-704.
[8] Curtis KS, Krause EG, Wong DL, Contreras RJ. Gestational and early postnatal dietary NaCl levels affect NaCl intake, but not stimulated water intake, by adult rats. J Physiol Regul Integr Comp Physiol 2004; 286:R1043-50.
[9] Sakai RR, Nicolaidis S, Epstein AN. Salt appetite is suppressed by interference with angiotensin II and aldosterone. Am J Physiol 1986; 251:R762-8.
[10] Thornton SN, Nicolaïdis S. Long-term mineralocorticoid-induced changes in rat neuron properties plus interaction of aldosterone and ANG II. Am J Physiol 1994;266(2 Pt 2):R564-71.

[11] Galaverna O, De Luca Jr LA, Schulkin J, Yao SZ, Epstein AN. Deficits in NaCl ingestion after damage to the central nucleus of the amygdala in the rat. Brain Res Bull 1991;28:89-98.
[12] Roitman MF, Na E, Anderson G, Jones TA, Bernstein IL. Induction of a salt appetite alters dendritic morphology in nucleus accumbens and sensitizes rats to amphetamine. J Neurosci 2002;22:RC225.
[13] van Woerden EE, van Geijn HP, Caron FJM, et al. Fetal mouth movements during behavioural states 1F and 2F. Eur J Obstet Gynecol Reprod Biol 1988;29:97-105.
[14] Ross MG, Desai M. Gestational programming: population survival effects of drought and famine during pregnancy. Am J Physiol Regul Integr Comp Physiol 2005;288:R25-33.
[15] Ross MG, Nijland MJM. Development of ingestive behaviour. Am J Physiol Regul Integr Comp Physiol 1998;274:R879-93.
[16] Schaal B, Marlier L, Soussignan R. Neonatal responsiveness to the odour of amniotic fluid. Biol Neonat 1995;67:397-406.
[17] Mennella JA, Jagnow CP, Beauchamp GK. Prenatal and postnatal flavor learning by human infants. Pediatrics 2001;107:e88.
[18] Chotro MG, Molina JC. Acute ethanol contamination of the amniotic fluid during gestational day 21: postnatal changes in alcohol responsiveness in rats. Dev Psychobiol 1990;6:535-47.
[19] Youngentob SL, Molina JC, Spear NE, Youngentob LM. The effect of gestational ethanol exposure on voluntary ethanol intake in early postnatal and adult rats. Behav Neurosci 2007;121: 1306-15.
[20] Vickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman PD. Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. Am J Physiol Endocrinol Metab 2000;279:E83-7.
[21] Lenfant C. Low birth weight and blood pressure. Metabolism [this issue]
[22] Taylor PD, Poston L. Developmental programming of obesity in mammals. Exp Physiol 2007;92:287-98.
[23] Mcmillen I, Robinson C, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. Physiol Rev 2005;85:571-633.