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Reduced linoleic acid intake in early postnatal life improves metabolic outcomes in adult rodents following a Western-style diet challenge

Annemarie Oosting[a,*], *Diane Kegler*[a], *Bert J.M. van de Heijning*[a], *Henkjan J. Verkade*[b], *Eline M. van der Beek*[c]

[a] *Nutricia Research, Uppsalalaan 12, 3584, CT, Utrecht, the Netherlands*
[b] *Department of Pediatric Gastroenterology and Hepatology, Beatrix Children's Hospital–University Medical Center Groningen, University of Groningen, Post Office Box 30.001, 9700 RB, Groningen, the Netherlands*
[c] *Nutricia Research, Matrix Building #05-01B, Singapore 138671, Singapore*

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ABSTRACT

The global increase in dietary *n*-6 polyunsaturated fatty acid (PUFA) intake has been suggested to contribute to the rise in obesity incidence. We hypothesized that reduced *n*-6 PUFA intake during early postnatal life improves adult body composition and metabolic phenotype upon a Western diet challenge. Male offspring of C57Bl/6j mice and Wistar rats were subjected to a control diet (CTRL; 3.16 En% linoleic acid [LA]) or a low *n*-6 PUFA diet (low LA; 1.36 En% LA) from postnatal days (PNs) 2 to 42. Subsequently, all animals were switched to a Western-style diet (2.54 En% LA) until PN98. We monitored body composition by dual-energy x-ray absorptiometry and glucose homeostasis by an intravenous glucose and insulin tolerance test in rats and by the homeostasis model assessment of insulin resistance (HOMA-IR) in mice. At PN98, plasma lipids, glucose, insulin, and adipokines were measured and adipocyte number and size were analyzed. In mice, the postnatal low-LA diet decreased fat accumulation during the adult Western-style diet challenge (–27% compared with CTRL, $P < .001$). Simultaneously, it reduced fasting triglyceride levels and lowered fasting resistin and leptin levels. In rats, the low-LA diet did not affect adult body composition, but decreased the number of retroperitoneal adipocytes and increased the number of large adipocytes. In conclusion, lowering dietary *n*-6 PUFA intake in early life protected against detrimental effects of an obesogenic diet in adulthood on metabolic homeostasis and fat mass accumulation.

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1. Introduction

Incidence of obesity and its comorbidities has increased rapidly during the last decades [1,2]. This profound increase cannot solely be explained by contemporary lifestyle factors such as an unbalanced diet or reduced physical activity [3]. Accumulating evidence shows that dietary factors in critical developmental periods, including fetal life, infancy, and early

Abbreviations: BW, body weight; FM, fat mass; IMF, infant milk formula; LBM, lean body mass; PN, postnatal day; TC, total cholesterol; WAT, white adipose tissue; WSD, Western-style diet.

* *Corresponding author*. Tel.: +31 30 2095000; fax: +31 30 2100436.
E-mail address: annemarie.oosting@danone.com (A. Oosting).

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childhood, are associated with obesity risk later in life [4–8]. Both overnutrition and undernutrition during pregnancy and infancy resulted in higher susceptibility to obesity and in poor metabolic health in adult life [9–12]. Apart from nutrient quantity, also nutrient quality, specifically fatty acid (FA) composition, is suggested to be a factor in nutritional programming of metabolic phenotype in adult life.

Dietary *n*-3 and *n*-6 polyunsaturated FAs (PUFAs) are pivotal for healthy growth and development [13,14]. It is widely acknowledged that the balance between *n*-3 and *n*-6 PUFAs is important in lifelong metabolic health and disease risk [15,16]. However, complex interactions between *n*-3 and *n*-6 PUFAs, both the essential FAs linoleic acid (LA; 18:2*n*-6) and α-linolenic acid (ALA; 18:3*n*-3) and their respective long-chain metabolites arachidonic acid (ARA; 20:4*n*-6) and docosahexaenoic acid (22:6*n*-3), have resulted in controversy on their health effects. Absolute amounts of *n*-6 and *n*-3, *n*-6/*n*-3 ratio, but also total amount of dietary fat and macronutrient composition are known to modulate PUFA effects [17–25].

Dietary *n*-3 PUFAs during pregnancy and/or lactation have been reported to program toward reduced fat mass (FM) in animal [26,27] and human subjects [28–30]. However, systemic reviews on animal [31] and human [32] studies have shown contradictory results.

N-6 PUFAs, both ARA and its precursor LA, have been associated with enhanced adipogenesis, lipogenesis, and inflammation in humans and rodents [33–35]. These findings support the hypothesis that the global shift toward excess dietary *n*-6 intake and insufficient *n*-3 intake in the past decades [36,37] plays a role in the worldwide increased incidence of obesity and its comorbidities [15,19]. Exposure to a high *n*-6 PUFA diet in early postnatal development may amplify detrimental effects on metabolic health [38]. Only very few experimental rodent studies investigated sustained effects of *n*-6 PUFA on metabolic health [17,25,39]; however, data concerning the role of *n*-6 PUFA in a diet with normal lipid content, specifically during early postnatal life, are lacking.

White adipose tissue (WAT) development is driven by both proliferation and differentiation of preadipocytes to mature adipocytes, for example, adipogenesis, as well as the lipid storage capacity of these mature adipocytes [40,41]. In humans, adipocyte number is established during childhood and adolescence, whereas adipocyte size can increase throughout life. Although adipogenesis in WAT is crucial to prevent ectopic fat deposition and lipotoxicity [42], both increase in cell number and size are positively correlated with FM [43]. In rodents, total adipocyte number is set between 9 and 18 weeks of age [40,44,45], whereas adipocyte size can increase until senescence in rodents [46]. Experimental data from in vitro and in vivo studies in rodents suggest that *n*-3 and *n*-6 PUFAs differentially modulate proliferation and differentiation of preadipocytes via several mechanisms including gene transcription, messenger RNA processing and posttranscriptional processes [19,21]. Linoleic acid can be converted to ARA (20:4*n*-6). Arachidonic acid and its eicosanoid metabolites have the capacity to stimulate adipogenesis through direct activation of peroxisome proliferator–activated receptors δ and γ [19]. In addition, *n*-3 and *n*-6 PUFAs are known to have differential effects on transcription factors involved in WAT lipogenesis with *n*-3 inhibiting and *n*-6 PUFA stimulating expression of lipogenic transcription factors in rats [21]. These findings led us to speculate that dietary *n*-6 PUFA during gestation and lactation modulates adipose tissue development, thereby affecting susceptibility to obesity later in life.

We hypothesized that reduction of LA exposure in early postnatal life would reduce susceptibility to obesity and prevent an adverse metabolic phenotype later in life. If dietary LA content in early postnatal life would be able to influence early-life growth of WAT, this could result in ways to beneficially modify fat accumulation and metabolic state in a mild obesogenic adult environment.

To test our hypothesis, we used C57Bl/6 mice and Wistar rats, both commonly used models to study metabolic programming [47–52]. The experimental design with exposure to reduced LA exclusively during lactation and early postweaning enables us to selectively investigate the importance of early dietary FA composition during a critical developmental period for WAT development [40,44,45]. The early diet was discontinued before the onset of puberty because this is considered a separate critical window of development [53,54], which was not in scope of our research objective. In the present study, the mouse model was used to gain insight on programming effects on body composition over time. To investigate programming effects on adult metabolic phenotype in more detail, we performed functional tests on insulin sensitivity and analyze WAT morphology number in a subcutaneous and visceral WAT depot in Wistar rats.

2. Methods and materials

2.1. Animals

All experimental procedures were approved by the Animal Experimental Committee DEC-Consult, Bilthoven, the Netherlands, and complied with the principles of laboratory animal care. Mice and rats were housed at Wageningen University and Research Centre (CKP, WUR, Wageningen, the Netherlands) on a 12:12-hour light/dark cycle (light on 0600 hours = Zeitgeber time 0 hours) in a temperature- and humidity-controlled room (21 ± 2°C and 50% ± 5%, respectively). Food and water were available ad libitum during the entire experimental protocol, except before blood sampling when animals were fasted for at least 4 hours during the light phase (from 7:30 AM; Zeitgeber time = 1.5 hours onward). Food intake was measured per cage twice a week by weighing remaining diet on the food hopper. Body weight (BW) was measured per litter before weaning and individually after weaning twice a week.

2.2. Experimental diets

All diets (Table 5) were semisynthetic, consisted of AIN93-G ingredients (Research Diet Services, Wijk bij Duurstede, the Netherlands) and contained 21 En% fat, 17 En% protein, and 62 En% carbohydrates. The composition of mineral and vitamin mix was according to the American Institute of Nutrition formulation of AIN93G purified diets for laboratory rodents [55].

Mice and rats were assigned to either a postnatal control (CTRL) diet that contained a mixture of vegetable oils with an FA composition similar to infant milk formula (IMF) or a diet that contained an oil blend with ~50% less LA (Table 5). Diets were thus different in FA composition but had similar total FA

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