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Implications of intrauterine protein malnutrition on prostate growth, maturation and aging

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ABSTRACT

Aims: Maternal malnutrition by low protein diet is associated with an increased incidence of metabolic disorders and decreased male fertility in adult life. This study aimed to assess the impact of maternal protein malnutrition (MPM) on prostate growth, tissue organization and lesion incidence with aging.
Main methods: Wistar rat dams were distributed into two groups, which were control (NP; fed a normal diet containing 17% protein) or a restricted protein diet (RP, fed a diet containing 6% protein) during gestation. After delivery all mothers and offspring received a normal diet. Biometrical parameters, hormonal levels and prostates were harvested at post-natal days (PND) 30, 120 and 360.
Key findings: MPM promoted low birth weight, decreased ano-genital distance (AGD) and reduced androgen plasma levels of male pups. Prostatic lobes from RP groups presented reduced glandular weight, epithelial cell height and alveolar diameter. The epithelial cell proliferation and collagen deposition were increased in RP group. Incidences of epithelial dysplasia and prostatitis were higher in the RP offspring than in the NP offspring at PND360.
Significance: Our findings show that MPM delays prostate development, growth and maturation until adulthood, probably as a result of low testosterone stimuli. The higher incidence of cellular dysplasia and prostatitis suggests that MPM increases prostate susceptibility to diseases with aging.

Introduction

Epidemiological studies have linked malnutrition in pregnancy with many chronic diseases (Langley-Evans et al., 2012). Malnutrition is a medical condition caused by an improper or insufficient diet. It is technically a category of diseases that includes the following: undernutrition, obesity and overweight, and micronutrient deficiency among others. However, it is frequently used to mean just undernutrition from either inadequate calories or inadequate specific dietary components, such as protein (Dimosthenopoulos, 2010).

During gestation, the female rat needs at least 12% of the diet to be protein (Benevenga et al., 1995). Maternal protein malnutrition (MPM) during gestation impairs overall growth and development (Wu et al., 2012). The "Barker hypothesis" (Barker, 1997) proposes that suboptimal intrauterine environment induces compensatory responses in the fetus that may permanently affect the adult phenotype and disease susceptibility (Bateson et al., 2004; Nijland et al., 2008). Rodent models have shown that MPM by low protein diet during pregnancy or during early postnatal life can lead to metabolic and physiological changes in the offspring, even when the animals have free access to a normal diet after weaning (Zambrano et al., 2005, 2006).

Table 1
Composition of the two isocaloric diets.

Ingredients (g/kg)	Control diet 17% of protein	Low protein diet 6% of protein[a]
Cornstarch	397	480
Casein (84%)	202	71.5
Dextrin (90–94%)	130.5	159
Sucrose	100	121
Soybean oil	70	70
Fiber	50	50
Mineral mix (AIN 93%)[b]	35	35[c]
Vitamin mix (AIN 93)[b]	10	10
L-Cystine	3	1
Choline bitartrate	2.5	2.5
Total energy (Kcal g^{-1})	3.76	3.76

[a] The low protein diet was prepared by PragSoluções (PragSoluções, SP, Brazil). Diets were supplemented with L-Cystine as sulfur amino acid.
[b] Vitamin and mineral mixtures were formulated to meet the American Institute of Nutrition AIN-93G recommendation for rodent diets (Reeves et al., 1993).
[c] Potassium phosphate, monobasic, was added to the salt mix of this diet to maintain phosphorus at the levels found in the control casein diet (3 g/kg of diet) and the calcium: phosphorus ratio has been kept at 1.3 in both diets.

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Table 2
Effects of maternal protein malnutrition on the biometric parameters from dams and litter.

Parameters	Experimental groups	
	NP	RP
Data of pregnant rat (n = 12 each group)		
Body weight (g) — GD1	234.21 ± 14.83	236.32 ± 12.35
Body weight (g) — GD21	358.42 ± 11.61	328.53 ± 11.91[a]
Body weight gain (g) — GD21-GD1	124.24 ± 12.25	93.25 ± 13.12[a]
Maternal food intake (g day^{-1}) at GD2	20.26 ± 2.01	19.95 ± 2.33
Maternal food intake (g day^{-1}) at GD20	22.17 ± 2.32	22.85 ± 3.13
Data of litter (n = 96 each group) at PND1		
Litter male birth weight (g)	6.68 ± 0.38	4.46 ± 0.39[a]
Litter male ano-genital distance (mm)	3.33 ± 0.34	2.68 ± 0.22[a]
Litter male ano-genital distance/birth weight (mm g^{-1})	0.21 ± 0.01	0.16 ± 0.01[a]

NP, normal-protein diet group; RP, restrict-protein diet group; GD, gestational day; PND, post-natal day. Values are expressed as mean ± SD.
[a] Indicates that RP group is significantly different from NP group with $p<0.05$.

MPM could promote structural change in different organs, such as an altered cell number, an imbalanced distribution of different cell types within an organ, and an altered blood supply and receptor numbers (Vicente et al., 2004; Lins et al., 2005). In addition, these changes can modify hormone production and the capacity of cells to respond to hormone signals (Bertram and Hanson, 2001; Langley-Evans and McMullen, 2010; Qasem et al., 2012).

A few reports in sheep and rats indicate that male sexual development and the normal ontogeny of gonadal development and function can be disrupted by maternal malnutrition (Rae et al., 2002; McMillen et al., 2008; Gardner et al., 2009). Zambrano et al. (2005) have shown that intrauterine maternal protein malnutrition alone was sufficient to reduce sperm count and influence their ability to impregnate female rats. MPM also reduces the serum concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone. In these studies, the weights of the testis, epididymis and prostate were reported to be decreased (Fernandez-Twinn et al., 2003, 2007; Santos et al., 2004; Zambrano et al., 2005, 2006; Guzman et al., 2006; Ramos et al., 2010). However, no previous studies investigated the effects of MPM during pregnancy on the prostate development. The prostate gland plays a fundamental role in reproductive biology. The prostate gland secretes different nutrients that partly compose seminal fluid, which is essential for sperm motility and nutrition (Untergasser et al., 2005). Moreover, early changes in prostate development may permanently alter the prostate morphology and function and influence the onset of late-life diseases, such as prostatitis, benign prostatic hyperplasia and prostate cancer (Risbridger et al., 2005; Prins et al., 2006; Cowin et al., 2008).

Therefore, the aim of the present study is to evaluate the effects of MPM on the prostate gland morphology of rats at three important phases: growth, maturation and aging.

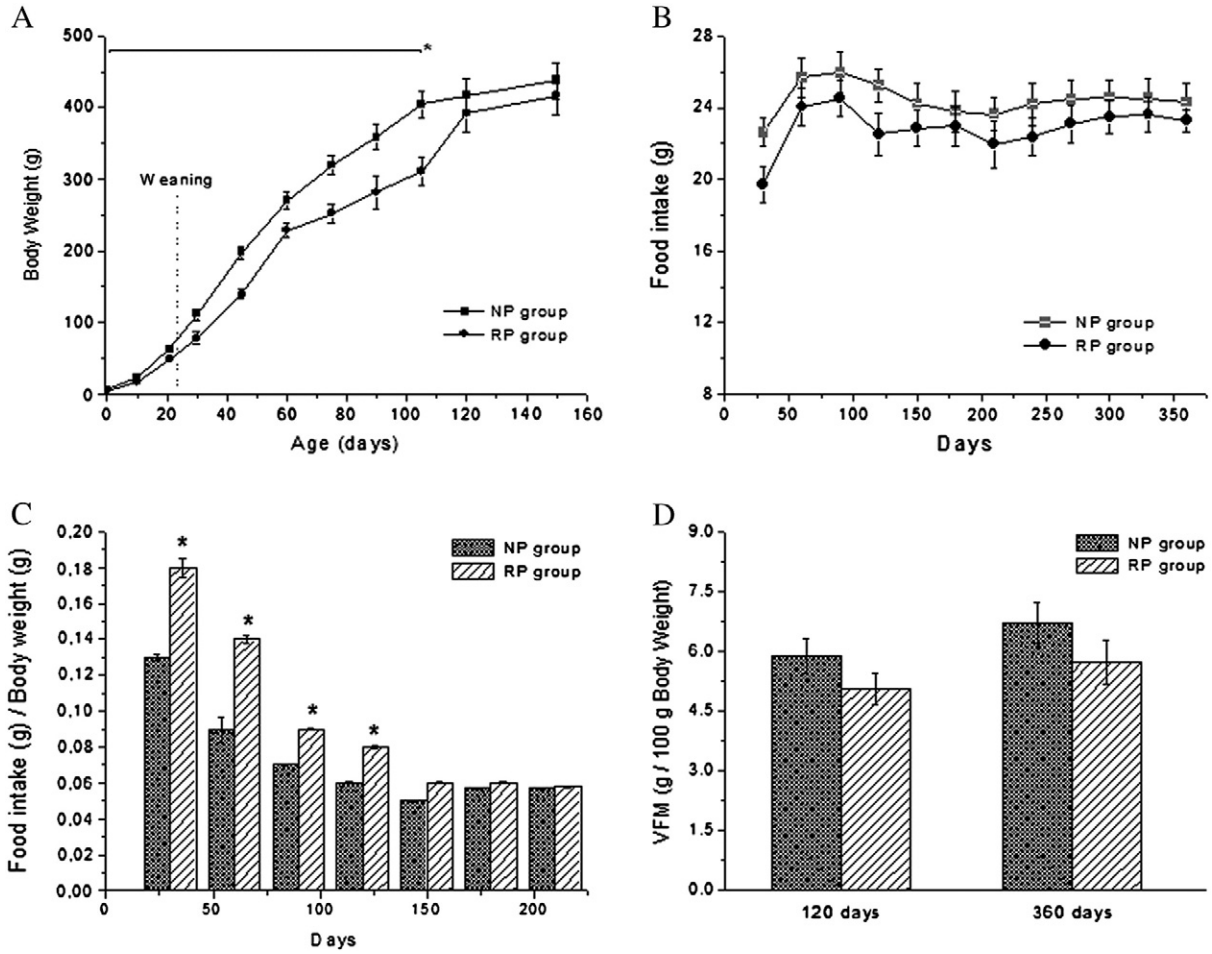

Fig. 1. Data from body weight and food intake measurements. A) Mean body weight of pups whose mothers were fed a control (NP) or low protein diet (RP) during gestation from day 1 until post-natal day (PDN) 150. B) Food intake of NP and RP pups after weaning until PDN 360. C) Post-weaning body weight normalized food intake in NP and RP offspring. D) Body composition: visceral fat mass (VFM) (g/100 g body weight). Values are means for at least twelve animals per group with standard deviation represented by vertical bars. * indicates that RP group is significantly different from NP group with $p<0.05$.