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Maternal Nutrient Storage and Efficiency in Production of Fetal Brain Tissue in Rats[1]

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Abstract. Maternal 'efficiencies' in production of fetal tissue, especially brain tissue, were studied in controls and in chronically (9 generations) undernourished rats. These 'efficiencies' were formulated as the ratio of a neonatal parameter (body weight, brain weight, DNA, or protein) to the food consumed during pregnancy. Mean or total values (for the entire litter) of the above parameters were used in computation of the above ratios. It was found that all these ratios were highly significantly lower for control animals than for undernourished. The gain in maternal body weight (postpartum versus day 0 of pregnancy), i.e., nutrient storage, was found to be significantly lower or even negative in the undernourished group, but increased through generations. We interpret these results as follows. Undernourished animals mobilize their nutrient reserves, avoid deamination of essential amino acids, and improve their intestinal absorption of nutrients; thus, they are more efficient than normal animals, even though the latter may produce more fetal tissue. These improvements suggest inducible enzymes. Individual mothers in each group vary considerably in their efficiency; the most efficient undernourished mothers may produce offspring that escape undernutrition, or, in the control group, offspring with outstanding values of brain and body parameters.

Introduction

In the previous work (16) we have studied the occurrence of rats with outstanding high values (more than 2 SD above the mean) of their neonatal parameters: body weight, brain weight, brain DNA and brain protein. Many of these newborns come from 'outstanding litters' (parameter values more than 2 SE above the mean). Some of the causes of such occurrences may reside in these individual fetuses themselves (their better genetic potential, better placental transfer, etc),.), but some must reside in their mothers (especially in cases of outstanding litters).

[1] A short abstract of this work has appeared (12).

Table I. Efficiency of offspring tissue production by pregnant rats: neonatal body and brain weights

Group	Maternal weight[1] (M), g	Food consumption[2]		Litter size	Offspring weight, g			
					mean		total (per litter)	
		per mother (F), g	per g maternal body weight (F/M)		body (Wm)	brain (BWm)	body (Wt)	brain (BWt)
Control	242.5 ± 26.0	305.8 ± 40.5	1.26 ± 0.14	9.40 ± 2.6	5.87 ± 0.45	0.167 ± 0.013	54.7 ± 14.6	1.57 ± 0.42
Undernourished	221.1 ± 23.3	217.5 ± 7.26	0.99 ± 0.10	9.73 ± 2.4	5.22 ± 0.59	0.150 ± 0.015	49.8 ± 11.3	1.46 ± 0.34
Difference[3], %	– 8.8	– 29	– 21	+ 3.5	– 11	– 10	– 9	– 7
p	<0.001	<0.001	<0.001	NS	<0.001	<0.001	NS	NS

Total number of mothers: control 53; undernourished (all generations together) 71.
Total number of offspring: control 498; undernourished 691.
1 Mean weight during pregnancy ± SD.
2 Total food consumption during pregnancy: mean ± SD.
3 Difference to control, in % of control.

The present work is concerned with the study of maternal 'efficiencies' in production of fetal tissue, in particular, fetal brain tissue. Maternal efficiencies may be expressed in many terms; in this work we studied the production of fetal tissues (neonatal body weight, brain weight, brain DNA and brain protein) in terms of food consumed during pregnancy. Mean values of the above parameters, as well as total values (for the entire litter) were used in computations of efficiencies. Appearance (or disappearance) of maternal nutrient reserves (which occurs during pregnancy) was determined, and we have also studied the production of fetal tissue in relation to changes in maternal body weight before and after pregnancy.

The above studies were conducted on rats normally nourished (controls) and on rats chronically undernourished (17) for 9 generations, in order to compare maternal efficiencies in these two groups. Finally, we also studied the variability in these efficiencies among individual mothers, with particular reference to cases of litters with outstanding values of brain and body parameters.

Materials and Methods

The animals and their nutrition regimes were as described in the previous work (17). The rats were Sprague-Dawley derived, and were bred in our closed colony for 42 generations. 3-month-old virgin females weighing 200–260 g were mated; the presence of a vaginal plug was considered day 0 of pregnancy. The control group C was fed *ad libitum* (mean 15.5 g/24 h) a pelleted diet (Wayne Mousebreeder Block, Allied

Efficiencies			
$\frac{Wm}{F} \times 10^2$	$\frac{BWm}{F} \times 10^4$	$\frac{Wt}{F} \times 10^2$	$\frac{BWt}{F} \times 10^4$
1.96 ± 0.32	5.56 ± 0.86	18.2 ± 5.2	52.2 ± 14.4
2.40 ± 0.26	6.90 ± 0.66	23.9 ± 4.6	67.2 ± 15.1
+ 22.4	+ 24	+ 31	+ 29
<0.001	<0.001	<0.001	<0.001

Mills, Chicago, Ill.) containing 20.5% protein. The experimental rats were fed 2/3 or 10 g/24 h of *ad libitum* diet, which is a rather mild protein/energy malnutrition. This feeding in the experimental group was started at the time of mating of F_0 generation, and continued throughout pregnancy and postweaning. In preliminary experiments we found that malnutrition of this kind during nursing may result in 100% mortality, and therefore the mothers and offspring were fed *ad libitum* during the period 0–60 days in F_1, and 0–15 days in all subsequent generations. The mothers were weighed at conception (time 0) and postpartum; the offspring were weighed at birth, and then decapitated; the brains were then immediately removed, weighed, frozen and subsequently used for analysis. The 'brain', as dissected, was cerebrum without cerebellum and olfactory lobes.

DNA was determined by a modification of the diphenylamine colorimetric method (14); protein was determined by a modification of the Lowry colorimetric method (6).

Results and Discussion

Maternal weight, maternal food consumption, litter size and offspring parameters are listed in tables I–III. In accordance with our previous study of chronic undernutrition (17), maternal body weights, *mean* individual offspring body weights, mean offspring brain DNA (cell number) and mean offspring brain protein significantly decreased in 9 generations of undernutrition. However, litter size, as well as *total* offspring weight per litter, total offspring brain DNA and total offspring brain protein were not significantly different from control. The parameters for the individual newborns were not significantly correlated ($r < 0.2$) with those for the total litter, either in control or in undernourished animals. Thus, mothers continue to produce essentially similar *total* mass of fetal tissue, despite maternal undernutrition.

Tables I–III also list the ratios of offspring's parameters (individual and total) to the total amounts of food consumed by the mother during the entire pregnancy. These ratios are highly significantly correlated ($r > 0.95$, $p < 0.001$) with the parameters themselves. Total food (rather than food per gram maternal body weight) was used here because this way the concept of efficiency (see below) will also include efficiency caused by low maternal weight (low basal metabolism needs); in addition, maternal weight is already included in neonatal parameters since these two are correlated (13).

The above ratios parameter/food may be considered the indices of maternal 'efficiency'. It can be seen that for each parameter (mean individual, or total offspring) the 'efficiencies' were highly significantly *higher in undernourished mothers*. Such results are unexpected; they will be further discussed below.

Table II. Efficiency of offspring tissue production by pregnant rats: neonatal brain DNA content

Group	Offspring brain DNA		$\frac{DNA_m}{F} \times 10^6$	$\frac{DNA_t}{F} \times 10^6$
	mean (DNA_m) $\times 10^6$, g	total (DNA_t) $\times 10^6$, g		
Control	570.5 ± 42.4	5,364 ± 1,556	1.90 ± 0.30	18.0 ± 5.5
Undernourished	508.9 ± 44.9	4,998 ± 1,083	2.34 ± 0.24	23.4 ± 4.9
Difference, %	−11	−7	+ 23	+ 30
p	< 0.001	NS	< 0.001	< 0.001

Other data as in table I.

Table IV lists maternal weight gain of the mother herself during pregnancy (after delivery, i.e., difference Δ between maternal body weight *postpartum* minus maternal body weight at day 0 of pregnancy). As expected, these differences are highly significantly lower in malnourished animals; in fact, in many animals they even have a negative value: the malnourished animal not only does not lay a normal deposit of nutrient reserves (for lactation), but even mobilizes her own nutrient reserves (18) for the nourishment of the fetuses, which in such cases are apparent 'parasites' (8).

Table V lists mean maternal weights, mean total litter weights and the above Δ values, through 9 generations of undernutrition. The values of Δ are not significantly correlated with mean maternal weights ($r < -0.4$) and with the total litter weights (or with other litter parameters) ($r < +0.05$). As can be seen from table V, the values of Δ increase with generations of undernutrition: they start with negative value (offspring generation F_1) but, with generations, they reach value (F_7) not much lower than the controls. Such results are unexpected. Since maternal body weights are not correlated with Δ, these increases in Δ cannot be attributed to any 'savings' on maternal basal metabolism that could be due to changes in body weights; rather, the outcome must be subject to a complex regulation of nutrient partition between the mother and her fetuses. Since the total litter weights are also not correlated with Δ, these increases in Δ cannot be attributed to any 'savings' on production of litter tissue (or to anticipated higher postnatal needs for lactation).

We interpret these results as follows. In the first generation (maternal F_0, offspring F_1), the pregnant animal, confronted with undernutri-

Table V. Maternal body weight gain in pregnancy (Δ), through generations of undernutrition

	Control
Mean maternal weight, g	242.5
Δ g	+ 39.88
Δ %	+ 16.92
Mean total litter weight, g	54.73

Other symbols and data as in table I.

Table III. Efficiency of offspring tissue production by pregnant rats: neonatal brain protein content

Group	Offspring brain protein		$\frac{Pm}{F} \times 10^5$	$\frac{Pt}{F} \times 10^5$
	mean (Pm) $\times 10^3$, g	total (Pt) $\times 10^3$, g		
Control	8.62 ± 1.26	79.95 ± 22.9	2.84 ± 0.52	26.46 ± 7.77
Undernourished	7.69 ± 1.03	75.09 ± 18.6	3.54 ± 0.50	34.18 ± 9.27
Difference, %	– 11	– 6	+ 25	+ 29
p	< 0.001	NS	< 0.001	< 0.001

Other data as in table I.

Table IV. Maternal body weight gains in pregnancy

Group	Maternal weight gain (Δ)[1]		Range	
	g	%	g	%
Control	39.9 ± 12.3	16.92 ± 5.595	+ 16 to + 70	+ 7.1 to + 26.7
Undernourished	6.18 ± 18.4	2.68 ± 8.5	– 34 to + 64	– 15 to + 31
Difference, %	– 85	– 84		
p	< 0.001	< 0.001		

Other data and symbols as in tables I–III.

[1] Gain in maternal body weight between mating (day 0 of pregnancy) and first day postpartum (g or % of mean weight).

Undernourished generation

Mother:	F_0	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Offspring:	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
	225.0	209.1	234.1	219.2	205.7	244.6	203.6	211.4	209.3
	– 9.82	– 1.43	+ 12.5	– 3.2	+ 18.4	+ 6	+ 12.5	+ 33.6	+ 25.3
	– 4.00	– 0.86	+ 5.65	– 1.07	+ 8.95	+ 2.35	+ 6.385	+ 16.07	+ 11.93
	56.55	48.8	52.5	42.75	34.32	44.53	49.7	46.54	49.78

tion for the first time, has to accomplish considerable mobilization of her nutrient reserves; undoubtedly involved here are corticosteroids (8) and growth hormones (pituitary and chorionic), which have been reported to be at higher levels during pregnancy and/or starvation (2, 3, 9, 18). As a result of this mobilization, the female loses weight (negative values of Δ, tables IV and V): her energy consumption is not sufficient for growing needs of fetal tissue and for her own basal metabolism. During subsequent generations she manages to end up with some small savings on her weight and on her litter weights, but these are not correlated with a substantial increase in her body weight gain (Δ) which almost reaches control value (table V): the continuously undernourished female must therefore become more efficient in food utilization. It has been reported that during malnutrition the organism reduces the catabolism of essential amino acids to urea, and increases activation of amino acids, thus favoring the incorporation of amino acids into proteins (reviews in 10, 11). Intestinal absorption of nutrients (for this reduced amount of food) also improves (14). These improvements may involve inducible enzymes. As a result, the efficiency of tissue production per gram food is considerably higher in undernourished animals (tables I–III).

It is of importance that, in both controls and undernourished animals, these efficiencies, as well as the values of Δ, show very high variabilities (efficiencies: standard deviation up to 30%; Δ range: −15% up to +31%). High efficiency in moderate undernutrition may be a composite of many maternal factors: efficient mobilization of maternal nutrient reserves (interplay between corticosteroids, growth hormones and insulin (1–3, 5, 7–9); high uteroplacental blood supply; the abovementioned lower destruction of essential amino acids and better intestinal absorption, etc. As a result, such mothers are more efficient producers of fetal tissue, including fetal brain tissue. In undernourished animals, such efficient mothers may produce offspring that escape undernutrition (15); in controls (normals), such efficient mothers may produce newborns with outstandingly high (OH) values of individual brain and body parameters (16). As to the entire litters (controls), those with highest total values of all parameters also came from highly efficient mothers who had 24–52% higher fetal tissue production per food consumed than in the average control. Thus, in summary, the occurrence of individual newborns or of entire litters with highest values of brain and body parameters necessitates not only high potential of fetuses themselves but also high maternal efficiency.

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