Effects of Controlled Compensatory Growth on Mammary Gland Development and Lactation in Rats

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ABSTRACT : The objective of this study was to examine the effect of compensatory growth nutritional regimen on mammary gland growth and lactation. One hundred twenty-two Sprague Dawley female rats (35 days of age) were randomly assigned to either a control or a stair-step compensatory nutrition (SSCN) feeding regimen or an alternating 2-2-3-3-week schedule beginning with 40% energy restriction for 2 weeks followed by re-alimentation (control diet) for 2 weeks. Pup weight gain and milk yield were improved 8% and 8 to 15%, respectively, by the SSCN regimen. The gene expression of ß-casein was 2.3-fold greater in the SSCN group than in the control group during early lactation, but they were greater at all stages of the second lactation. The gene expression of insulin-like growth factor-I was 40% lower in the SSCN group than in the control group during early lactation of the second lactation, but during late lactation it was 80% greater than in the control group. The concentration of serum corticosterone tended to be higher in the SSCN group during the late stage of the first lactation. These results suggest that the stair-step compensatory nutrition regimen improves lactation performance and persistency by modulation of cell differentiation and apoptotic cell death. ***(Asian-Aust. J. Anim. Sci. 2002. Vol 15, No. 9 : 1364-1370)***

Key Words : Compensatory Growth, Mammary Gland, Lactation, Cell Differentiation, Rats

INTRODUCTION

Mammary growth is a main determinant of milk yield capacity and longevity of lactation (Knight and Peaker, 1984; Park and Jacobson, 1993). Growth and differentiation of mammary gland are regulated by various hormones, growth and nutritional factors including the plane of nutrition (Borellini and Oka, 1989). Nutritional status is critical to mammary development, especially during hormone-senistive developmental stages, including pre-pubertal through early lactation (Park et al., 1988; Broster and Broster, 1984). Milk production is a complex and dynamic process. In essence, it is related to cell hyperplasia during gestation, hypertrophy during early lactation, and cell death during declining lactation. Lactation performance is function of two interrelated factors, peak yield and lactation persistency, defined as the change of yield with time in mid-lactation (Forsyth, 1996). Compensatory growth, referred to as catch-up growth, may be defined as the acceleration in growth that occurs when a period of growth restriction ends and favorable conditions are restored (Ashworth and Millward, 1986). The compensatory growth nutrition regimen is a combination of both energy restriction and re-alimentation that allows minimal development of mammary tissues during an energy restriction phase, whereas a compensatory growth phase immediately after energy restriction stimulates rapid and fuller development of the mammary gland. Our studies (Kim et al., 1998; Moon and Park, 1999; Ford and Park, 2001) as well as those of others (Barash et al., 1994; Choi et al., 1997 and 1998) have shown that a controlled compensatory nutrition regimen imposed during hormone-sensitive growth stages before first parturition can significantly affect mammary development and lactation performance. There are many other ways to improve the milk production including the supplement of nutrients (El Hag et al., 2002; Alshaikh et al., 2002), the genetic selection by breeding (Pongpiachan et al., 2000), and the improvement of the quality of feed (Chen et al., 2002). Those methods and the compensatory nutrition regimen can be additive effects on the improvement of mammary growth and lactation potential of animals. However, the cellular mechanisms responsible for the effects of nutritionally induced compensatory growth on mammary gland development and subsequent lactation are not well defined, despite the potentially beneficial role of a controlled nutrition regimen in improving lactation. Therefore, our objective was to investigate the biological mechanisms on the influence of a compensatory nutrition regimen on mammary development and lactation in rats.

MATERIALS AND METHODS

Animals and experimental design

One hundred twenty-two female Sprague Dawley rats (28 days of age) were housed individually in metal wire mesh bottom cages and acclimated to the experimental environment: 25°C and 50% relative humidity with 12 h light:dark cycle for one week. At 5 weeks of age, rats were

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randomly assigned to either control or stair-step compensatory nutrition (SSCN) regimen groups. The control group was offered free access to a control diet (a modified AIN-93 G diet) throughout the trial period (Table 1). The SSCN group was subjected to an alternating 2-2-3-3-week schedule beginning with an energy restriction diet (40% energy restriction) for 2 weeks followed by a control diet, ad libitum, for 2 weeks. This step was repeated with 3 weeks intervals. The SSCN rats were fed to ensure 60% energy level of the control group during energy restriction periods: for example, if the control group consumed 10 g/day, the amount of feed offered to the SSCN group was 6 g/day. During the re-alimentation period, the SSCN rats were offered a control diet. Therefore, the SSCN rats received an overall 20% energy restriction (average from all stair-step periods) compared with the conventionally fed control group. The energy restriction diet was formulated to contain the same isonutrient intake of protein, vitamins, and minerals as the control diet except for energy content. Upon completion of stair-step nutrition regimen (ca. 15 weeks of age), rats were maintained on a control diet with free access for the remaining experimental period. Rats were bred during the second week of the second re-alimentation period. One week after weaning, dams were mated for the second cycle of lactation. Feed intake was recorded twice per week up to the time of mating. Feed records were discontinued at this time due to the complexity of polygamous breeding. All rats were weighed weekly until parturition and every 3 days during the lactation period.

Table 1. Compositions and chemical analysis of the experimental diet

	Control	SSCN[1]
Ingredients, %		
Casein	20.0	33.4
Sucrose	10.0	8.0
Cornstarch	52.9	29.9
Fiber	5.0	7.5
Soybean oil	7.0	13.0
L-Cystine	0.3	0.5
Mineral mix[2]	3.5	5.83
Vitamin mix[3]	1.0	1.67
Choline bitartrate	0.25	0.42
Tert-Butylhydroquinone	0.0014	0.002
Chemical analysis		
Crude protein	17.3	28.9
Gross energy, kcal/kg[4]	3,838	3,834

[1] SSCN=Stair-step compensatory nutrition

[2] Consists of calcium carbonate (357 g), potassium phosphate (196 g), potassium citrate (70.78 g), sodium chloride (74 g), magnesium oxide (24 g), potassium sulfate (46.6 g), manganous carbonate (0.63 g), ferric citrate (6.06 g), zinc carbonate (1.65 g), cupric carbonate (0.3 g), sodium selenite (0.01 g), potassium iodate (0.01g), and chromium potassium sulfate (0.275 g) per kg of mixture and sucrose to make 1 kg (American Institute of Nutrition, 1993).

[3] Consists of thiamineúHCl (600 mg), riboflavin (600 mg), pyridoxineúHCl (700 mg), nicotinic acid (3 g), calcium pantothenate (1.6 g), folic acid (200 mg), D-biotin (20 mg), cyanocobalamin (2.5 g), vitamin A 500,000 IU/g (800 mg), vitamin E 500 IU/g (15 g), vitamin D3 (250 mg), and vitamin K (75 mg) per kilogram of mixture and sucrose to make 1 kg (American Institute of Nutrition, 1993).

[4] The gross energy was based on the standard physiological fuel values for protein, fat, and carbohydrate of 4, 9, and 4, respectively.

Lactation performance

Rats were checked daily at 9 a.m. for litters. The day on which a litter was found was designated as day 1 of lactation. Litter size in both groups was adjusted to 8 pups per dam on day 3 of lactation. If the litter size was less than 8 pups per dam during the trial, those results were eliminated from the data pool. Litters and dams were weighed on days 3, 6, 9, 12, 15, 18, and 21 of lactation to evaluate lactation performance. Pup weight gain indicated lactation performance. On day 14 of lactation, for indirect estimate of milk yield, pups were removed from their mothers for 6 h and kept without food and water in plastic cages with wood shavings. After 6 h, pups were weighed and returned to their mothers to suckle. After 1 h, pups were weighed again, and net weight gain was an index of milk yield per 6 h. This is a modified weigh-suckle-weigh procedure (Morag, 1970; Reddy and Donker, 1965).

Mammary tissue and blood sampling

Six to seven rats per treatment group were killed by CO_2 gas for mammary tissue collection during different physiological stages: early lactation (EL, d2), mid-lactation (ML, d12), and late lactation (LL, d19). Fresh mammary tissue was extracted for total RNA for Northern blot analysis. Blood was collected by cardiac puncture and centrifuged at 3,000×g for 20 min at 4°C. The serum was stored at -20°C until assayed for corticosterone by radioimmunoassay (CAC rat corticosterone, Diagnostics Products Corporation, Los Angeles, CA).

RNA extraction and northern blot analysis

Total RNA was extracted from fresh mammary tissues using guanidine thiocyanate and phenol extraction method (Chomczynski and Sacchi, 1987). Total RNA (20 μg/lane) was fractionated by electrophoresis on 1.0% agarose gels containing 2.2 M formaldehyde and transferred to nylon membranes. The membranes were baked for 1 h in a vacuum oven at 80°C and then hybridized with cDNA probes: rat β-casein (donated by Dr. J. Rosen, Baylor College of Medicine, Houston, TX) and human insulin-like growth factor-I (American Type Culture Collection, Rockville, MD). The denatured cDNA probes (specific activity, 1×10^7 cpm) were labeled with [^{32}P]dATP by random priming method (Multiprime DNA Labeling Systems, Amersham Life Science, Arlington Heights, IL).

Prehybridization and hybridization solutions consisted of 50% formamide, 5×SSPE, 5×Denhardt's solution, 0.5% SDS, and 100 μg/ml denatured salmon sperm DNA. The membranes were prehybridized for 3 h at 42°C. Hybridization was performed for 18 h at 42°C. The membranes were washed twice at room temperature in a solution containing 5×SSPE and 0.5% SDS, followed by washing twice at 37°C in a solution containing 1×SSPE and 0.5% SDS. The membranes were exposed to X-ray film (Kodak, Rochester, NY) with an intensifying screen at -70°C. The signals on Northern blots were quantitated with the Personal Densitometer SI system (Molecular Dynamics, Sunnyvale, CA).

Statistical analysis

Data were analyzed by the general linear model procedures with Statistical Analysis System (SAS, 1988). Hypotheses were tested with exact significance levels.

RESULTS AND DISCUSSION

Growth performance

The 2-2-3-3-week stair-step nutrition model was designed to induce compensatory growth during peripuberty and gestation. Growth performance averaged by treatment groups for the dietary trial period is summarized in Table 2. Rats reared on the SSCN regimen gained (p=0.0209) less (1.76 vs 2.10 g/day) and consumed less diet (p=0.0001). The feed efficiency did not differ between the two groups. Although the weight of the SSCN group was less than the weight of the control group during the dietary treatment stage (197.09 g vs 216.28 g), the dam body weight of the SSCN group was similar to the control group weight during lactation (data not shown). Through modulation of endocrine status, energy restriction redirects energy flow to energy conserving activities, mainly maintenance and repair functions, for optimum cellular economy by down-regulating genes involved in cell proliferation (Walford and Crew, 1989). Also, energy restriction reduces certain energy wasteful substrate metabolic systems, e.g., futile pathway which may not be important metabolically for growth and maintenance (Newsholme, 1980). In our SSCN model, the re-alimentation phase following energy restriction is synchronous with one or more critical hormonal stages of development (peripuberty through late gestation). This phase induces compensatory growth. We expected that the body weight of the SSCN group would catch up to the weight of the control group by week 9 and week 15 of age. These points were the end of the first and second re-alimentation phases, respectively. Although the weight of the SSCN group did not catch up at these points, the SSCN group weight was nearly the same as that of the control during the lactation period. The delayed weight catch-up may have been due to an insufficient energy content in the control diet fed during the re-alimentation period. The physical gut size of an animal limits the amount of nutrients it can consume. Therefore, it may be necessary to increase the energy content (e.g., 120% or 130% energy level of control) of the diet instead of increasing the amount of feed during the re-alimentation period to induce maximum growth.

Table 2. Effects of compensatory nutrition regimen on growth performance and feed efficiency of rats

Treatment	Control	SSCN[1]	SEM[2]	P[3]
Body weight (g)				
Initial	98.75	98.58	1.18	0.8985
Final[4]	216.28	197.09	1.99	0.0001
Daily gain (g/day)	2.10	1.76	0.05	0.0209
Feed intake (g/day)	13.70	11.68	0.11	0.0001
Feed efficiency (intake/gain)	6.52	6.64	1.50	0.7851

[1] SSCN=Stair-step compensatory nutrition.
[2] Standard error of the mean, where n=61.
[3] Probability is the significance level of F-test for equality of two study groups.
[4] Data used were from the first week of the second re-alimentation phase.

Lactation performance

The daily pup weight gains and estimated milk yield during the first lactation period are summarized in Table 3. The daily weight gains did not differ between the two groups until mid-lactation. The daily pup gain was greater in the SSCN group during mid-lactation (day 9 to day 12)

Table 3. Effects of compensatory nutrition regimen on daily pup gains and estimated milk yield

	Control	SSCN[1]	SEM[2]	P[3]
Lactation		Pup gains (g/day)		
day 3-6	1.24	1.32	0.06	0.5832
day 6-9	1.88	1.95	0.08	0.6257
day 9-12	2.43	2.76	0.09	0.0179
day 12-15	2.92	3.09	0.11	0.2351
day 15-18	2.74	2.92	0.09	0.1895
day 18-21	3.02	3.36	0.13	0.0150
Overall	2.37	2.56	0.04	0.0011
Lactation		Milk yield (g/d/dam)[4]		
day 6	14.75	15.65	0.55	0.5377
day 9	21.92	23.64	0.76	0.2402
day 12	29.90	32.43	0.69	0.0838
day 15	37.29	40.42	0.87	0.0328
day 18	40.86	46.94	1.92	0.0001
Overall	28.94	31.81	0.56	0.0008

[1] SSCN=Stair-step compensatory nutrition.
[2] Standard error of the mean, where n=30.
[3] Probability is the significance level of F-test for equality of two study groups.
[4] Milk yield was estimated by multiple regression equation (Sampson and Jansen, 1984) as follows:

$$Yield=[0.0322-(0.0667\times weight)+(0.877\times gain)]\times 8$$

where Yield=Total milk yield per litter (g); weight=Average pup weight (g); gain=Average rate of pup weight gain (g/day) and 8=Litter size.

than in the control group (p=0.0179). After mid-lactation, the degree of improvement decreased, but the daily gain was higher in the SSCN group during late lactation than in the control group (p=0.0150). Therefore, the overall daily gain was improved in the SSCN group (p=0.0011). Litter or pup weight gain is commonly used as an index of lactation performance in the rodent. Pup weight gain during mid- and late lactation showed the expected effects of the SSCN regimen on lactation performance. Mammary tissues of animals on the compensatory nutrition regimen exhibit hyperplasia and hypertrophy as demonstrated by increased nucleic acids and cellular protein, and mammary tissues that have undergone compensatory growth have increased total mammary parenchyma and significantly decreased fat deposition (Park et al., 1988, 1989, 1994). In present study, the SSCN regimen increased peak milk yield and improved lactation persistency after the peak of lactation. These results suggest that the SSCN regimen had a significant beneficial effect on lactation performance.

Milk yield estimates were calculated by the multiple regression analysis for prediction of milk yield from pup body weight and net daily weight gain (Sampson and Jansen, 1984). The milk yield did not differ until day 9 of lactation between the two groups. However, the estimated daily milk yield was significantly improved in the SSCN group after day 12 of lactation. The estimated milk yield of the SSCN group was 8%, 8%, and 15% greater, respectively, on days 12, 15 and 18 of lactation than that of the control group.

The increased milk yield after mid-lactation in the SSCN group may reflect the improved lactation performance and persistency. This lactation performance is a function of two factors: peak milk yield and lactation persistency. These two factors can be affected by the number of secretory epithelial cells (cell proliferation), cellular differentiation, and the maintenance of cellular activity (Knight and Wilde, 1993), but cell loss after the peak of lactation is largely responsible for the decline in lactation.

Milk yield was estimated indirectly by the weigh-suckle-weigh technique on day 14 of lactation during two lactation cycles (Table 4). Although not significant, the estimated milk yields were 10% (first lactation) to 12.6% (second lactation) higher in the SSCN group than in the control group. The daily energy allowance of the growing animal is a major determinant of the subsequent ability to express her inherited capacity for milk production (Johnsson, 1988; Tucker, 1987). In the present study, the improved lactation performance during the first lactation stage was continued onto the second lactation cycle. Therefore, we can postulate that a controlled dietary restriction regimen during the growing period may influence the genetic potential to produce milk and that this phenomenon carries over to the succeeding lactation cycles.

Table 4. Effects of compensatory nutrition regimen on milk yield on day 14 of lactation during two lactation cycles by weigh-suckle-weigh procedure

Treatment	Control	SSCN[1]	SEM[2]	P[3]
Lactation cycle	Milk yield (g/dam/6 h)[4]			
First lactation	14.21 (29)[5]	15.59 (38)	0.64	0.1457
Second lactation	15.15 (6)	17.06 (7)	1.03	0.2174

[1] SSCN=Sair-step compensatory nutrition.
[2] Standard error of the mean.
[3] Probability is the significance level of F-test for equality of two study groups.
[4] Milk yield was estimated by weigh-suckle-weigh procedure for 6 h.
[5] Parenthesis represents the number of dams.

Evaluation of cell differentiation and cell death

β-casein gene expression : The gene expression of ß-casein was determined in mammary tissue from different stages of lactation by Northern blot analysis (Table 5). The level of β-casein mRNA was 2.3-fold greater in the SSCN group than in the control group during early lactation. However, it did not differ between the two groups during the mid- and late lactation stages. Epithelial cell differentiation in mammary gland has been assessed by measuring the expression, at the protein or mRNA level, of milk protein genes. In mice, induction of β-casein mRNA indicates that differentiation begins in mid-pregnancy and increases progressively until parturition, at which time the mammary gland already contains 60% of the casein mRNA concentration found at peak lactation (Harris et al., 1991). In the present study, differentiation of epithelial cells was greater during mid-lactation than during late-lactation. The increased expression of milk protein mRNA in the SSCN group during early lactation may reflect the occurrence of earlier cell differentiation in the SSCN group than in the control group. The gene expressions of β-casein in the SSCN group during the second lactation cycle were generally higher than those in the control group during all stages of lactation (Table 5). Asynchronous induction of individual milk production genes (β-casein, acetyl-CoA carboxylase, and whey acidic protein) indicates that differentiation is a sequential process rather than a discrete event in each cell (Burgoyne and Wilde, 1994). We do not know the reason why mammary cell differentiation was greater in the SSCN rats, but we believe that it may be due to increased lactogenic hormonal stimuli (Bohnet et al., 1977). At this point, it appears that the increased cell differentiation (β-casein gene expression) seen in the SSCN rats carries over to the second lactation cycle.

IGF-I gene expression : The gene expression of IGF-I was about 40% lower in mammary tissues from the SSCN group than in those of the control group during early lactation (Table 5). It was not different during mid-lactation; but during late lactation, the level of the IGF-I

Table 5. The relative mRNA expressions of ß-casein and IGF-I in mammary tissues during early, mid, and late lactation of the first and second lactation cycles of rats fed a control diet or subjected to a compensatory nutrition regimen[1]

	Lactation stages					
	EL[2]		ML[3]		LL[4]	
	Control	SSCN[5]	Control	SSCN	Control	SSCN
β-casein						
First lactation	1.00	2.32	2.49	2.57	1.65	1.74
Second lactation	1.00	1.48	1.98	3.10	1.50	2.83
IGF-I						
First lactation[6]	-	-	-	-	-	-
Second lactation	1.00	0.75	1.26	1.43	1.21	1.79

[1] Relative mRNA is expressed as an arbitrary unit; the gene expression of the control rats during early lactation was set to a value of one. The pooled (n=6) total RNA (20 μg per lane) was fractionated on a 1% agarose, 2.2 M formaldehyde gel, transferred to a nylon membrane, and hybridized with ß-casein or IGF-I cDNA.
[2] EL=Early lactation (day2).
[3] ML=Mid-lactation (day12).
[4] LL=Late lactation (day19).
[5] SSCN=Stair-step compensatory nutrition group.
[6] Data were not available.

gene was 80% greater in the SSCN group than in the control group. The IGF-I is believed to mediate the galactopoetic action of growth hormone in cows (Davis et al., 1987). The concentration of IGF is higher in the rat at day 7 of pregnancy compared with virgin or lactating rats (Collier et al., 1989). IGF-I exerts its mitotic effect during pregnancy, but it suppresses lactation in rats (Flint et al., 1994). The expression of IGF-I during early lactation may be a possible negative factor for milk production in rats, but the exact role of IGF-I in fully differentiated mammary tissue is not clear. The viability of most cells depends on the presence of growth factors. IGF-I supports the viability of nonproliferating cells in culture (Bozyczko-Coyne et al., 1993; Svrzic and Schubert, 1990). IGF-I directly promotes cell cycle progression. IGF-I receptor activation may inhibit apoptosis. Therefore, we hypothesize that the elevation of the IGF-I gene during late lactation may have depressed apoptosis in the mammary cells of the SSCN group.

Corticosterone : The concentrations of serum corticosterone did not differ between the two groups during early and mid-lactation, but tended to increase in the SSCN group during late lactation (p=0.0750) (Table 6). Continuous milk production during lactation depends on a complex interplay of lactogenic hormones and the suckling stimulus exerted by the young. Cell death during mammary involution is regulated by apoptosis (Strange et al., 1992; Walker et al., 1989) and is characterized by a drop in lactogenic hormones (hydrocortisone, insulin, and prolactin); glucocorticoid hormones have been shown to prevent involution (Ossowski et al., 1979) and apoptosis (Feng et al., 1995). Corticosterone is the most abundant circulating steroid in the rat and the major glucocorticoid secreted by the rat adrenal cortex. We suggested that the maintenance of high levels of corticosterone during late lactation in the SSCN group may suppress gradual involution or apoptosis. However, two issues concerning the interpretation of this data deserve attention: the relatively small sample sizes and the large variations between individual values. Corticosterone release follows a diurnal rhythm and is sensitive to stress. Nonetheless, we may still be able to relate the relatively high concentration of corticosterone with low apoptotic cell death in the SSCN group during late lactation. The concentrations of serum corticosterone did not differ between the two groups during all stages of the second lactation cycle (Table 6). The basal secretion of glucocorticoids does not change during lactation in the cow (Koprowski and Tucker, 1973). However, in rats, basal and suckling-induced increases in glucocorticoids decrease with advancing lactation and declining milk yields (Larson, 1985). The overall trend in corticosterone levels was similar between the lactation stages in the control group. In the SSCN group, however,

Table 6. Effect of compensatory nutrition regimen on serum corticosterone during various stages of the first and second lactation cycles in rats

	Control	SSCN[1]	SEM[2]	P[3]
	Corticosterone (ng/ml)			
First lactation				
Early lactation	227.6 (4)[4]	220.8 (4)	93.3	0.9592
Mid-lactation	425.2 (5)	335.0 (4)	84.7	0.4627
Late lactation	409.1 (5)	657.0 (4)	93.3	0.0750
Second lactation				
Early lactation	357.9 (4)	235.7 (3)	103.7	0.4164
Mid-lactation	315.9 (3)	378.8 (5)	98.7	0.6597
Late lactation	278.1 (5)	437.4 (5)	86.2	0.2067

[1] SSCN=stair-step compensatory nutrition.
[2] Standard error of the mean.
[3] Probability is the significance of F-test for equality of two study groups.
[4] Parenthesis represents the number of rats.

levels tended to increase during the later stages. Active milk synthesis may be coupled with increased availability of corticosterone.

The evaluation of cell death using IGF-I gene expression or corticosterone was not strongly supported the decreased cell death in SSCN group. However, the direct detection of apoptosis in situ by end-labeling as we reported (Moon and Park, 1999) previously, confirmed that mammary tissue from the compensatory nutrition group had fewer apoptotic cells than tissue from the control group during late lactation. Taken together, cell differentiation and cell death was responsible to increase lactation performance and persistency.

CONCLUSION

A controlled compensatory nutrition regimen during hormone-sensitive developmental stages stimulates mammary development and differentiation and significantly enhances subsequent lactation performance. In the present study, the stair-step compensatory nutrition regimen improved lactation performance and persistency by modulation of cell differentiation. The improved overall mammary growth and lactation potential of rats reared on the compensatory nutrition regimen have led us to hypothesize that compensatory nutrition-directed mammary hyperplasia and hypertrophy together with elevated metabolic activities are permanently maintained. This galactopoiesis, in turn, brings about the suppression of mammary cell loss (apoptosis), thereby enhancing persistency of lactation. We believe that mammary growth during the late gestation period offers a great opportunity for lactation enhancement. A working model of our stair-step compensatory nutrition regimen could be designed to enhance mammary development and lactation performance. In evaluating a suitable nutrition regimen, four important factors must be considered: (a) type of model (e.g., number of stair-steps), (b) nature (e.g., energy versus total feed restriction), (c) intensity of compensatory growth (e.g., length and degree of restriction and re-alimentation), and (d) placement of stair-step in relation to the developmental stages.

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