

Postnatal growth of gut and muscle: competitors or collaborators

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Although growth and functional maturation are essentially continuous from conception to the attainment of sexual maturity, birth and weaning are particularly critical milestones in life. Birth is associated with a change in the route of nutrient delivery to the organism and weaning requires the attainment of full locomotor function as the organism is called upon to actively seek its own food. Weaning is associated also with major changes in the composition of the diet, changes which in their turn demand intestinal adaptation. Given this, the tissues responsible for the assimilation of nutrients and the tissues responsible for mobility must grow and develop rapidly during the immediate postnatal period. Table 1 summarizes information on the growth rates of the body, intestinal tract, liver, and the leg muscles of the infant rat. Although the rat, as an altricial species, represents one extreme of the interspecific spectrum of chemical and functional maturation at birth, the information illustrates two general points. First, that as a reflection of the chemical maturation of the body, the rate of accretion of body protein exceeds that of the body mass as a whole. Second, that gut and muscle grow during the sucking period with rate constants that are significantly greater than that of body protein as a whole. We have included values for the liver to show that organs that have been of major physiological significance to the fetus tend to grow during the suckling period at a slower rate than that of the body protein mass as a whole.

Table 1. Fractional rates of growth (%/d) of the whole body and of different components of the body of immature rats*

Age (d)	Body wt (%/d)	Protein deposition (%/d)			
		Body	Intestine	Muscle	Liver
4-10	13	14	17	18	10
10-16	9	11	8	14	7
16-28	6	10	17	11	14

* Values for muscle from Davis *et al.* (1991), for small intestine from Burrin *et al.* (1991) and for liver from Burrin *et al.* (1992a).

OVERALL METABOLIC ACTIVITY

We know that the overall level of metabolic activity in tissues of the gastrointestinal and skeletal muscular systems differ markedly between resting and active states. Thus, the values in Table 2 show that, despite a six–fourteenfold difference in their contributions to body mass, the contributions of the two tissues to overall energy expenditure in the quiescent state are essentially the same (Yen *et al.* 1989; Lobley, 1991). In ruminant

Table 2. *Estimated energy expenditure of the whole body, the portal-drained viscera (PDV) and the skeletal muscle of the quiescent pig and sheep*

	Body	PDV	Muscle
Pig*			
mol ATP/d	90	22	24
mol ATP/kg per d	2.81	18.1	1.6
% total expenditure		24	26
g/kg body wt		3.6	50
Sheep†			
mol ATP/d	58	20	19
mol ATP/kg per d	1.65	8.4	1.1
% total expenditure		34	32
g/kg body wt		6.9	40

* PDV (Yen *et al.* 1989); muscle estimated from hind-quarter metabolism (Reeds *et al.* 1985).

† Summarized from Lobley (1991).

Table 3. *Fractional rates of protein synthesis in tissues of immature rats**

Age (d)	Protein synthesis (%/d)			
	Leg muscles		Small intestine	Pancreas
	Phasic (Type II)	Tonic (Type I)		
5	31	34	50	100
10	23	25	60	150
16	23	30	60	150
21	21	28	95	230
28	16	20	110	300

* Values for muscle taken from Davis *et al.* (1991) and those for the visceral organs from Burrin *et al.* (1991).

species, the contribution of the metabolic activity of the gastrointestinal tract exceeds that of the quiescent skeletal musculature, possibly as a result of the nature of the diets that they commonly consume (Lobley, 1991). Thus, a number of studies (e.g. Koong *et al.* 1983; Ferrell & Koong, 1986; Burrin *et al.* 1990) have demonstrated that if large amounts of high-fibre diets are consumed, there is an increase in the contribution of the gastrointestinal tract to body mass and there are significant elevations in weight-specific rates of energy expenditure in the fasted state.

The same general comments apply to the respective contributions of gastrointestinal and skeletal muscle tissues to body protein mass and synthetic activity. Except during early postnatal life (Davis *et al.* 1989; Burrin *et al.* 1991; Table 3), the fractional rates of protein synthesis in the gastrointestinal and skeletal muscle mass differ by a factor of 5–10 (cf. McNurlan *et al.* 1979; Lobley *et al.* 1980; Simon *et al.* 1982; Garlick *et al.* 1983). Indeed, the difference is even greater if we include accessory tissues, such as the pancreas (Attaix *et al.* 1989; Burrin *et al.* 1991). It follows from these observations that the relative contributions of gastrointestinal and skeletal muscle to the growth of the

organism as a whole affect not only the relationship between weight and basal metabolism, but also might influence the efficiency with which dietary energy (carbon) and protein are utilized for body lipid and protein gain.

PROTEIN TURNOVER AND 'GROWTH'

After weaning, approximately 50% of the total protein synthesized by the skeletal musculature is deposited as new muscle tissue while only 10% of the total protein synthesized by the gastrointestinal tract is accumulated as new mass. This observation is misleading, however, because the nature of postnatal growth in the two systems differs. Although there is some interspecific variation (see Sarkar *et al.* 1977; DiMarco *et al.* 1987), the mature number of myofibres is established in the perinatal period. It is generally held that the subsequent growth of the muscle mass occurs largely by hypertrophy of an existing population of fibres. New cells are recruited into these myofibres but many are from a population of cells that had developed during late fetal and early neonatal life. Postnatal muscle growth, therefore, is associated with a substantial increase in the protein:DNA value. In contrast, the cells of the intestinal crypts of Lieberkühn's proliferate throughout life, migrate along the villi, and are lost to the intestinal lumen. In this sense alone, the gastrointestinal tract grows continuously throughout the postnatal life of the organism. In weaned rodents, sheep and pigs the daily rate of cell migration and loss is approximately 25% of the population of villus enterocytes (Dauncey *et al.* 1983; Southon *et al.* 1985; Attaix & Meslin, 1991), so that one-quarter of protein synthesis in the mucosa (and to some extent in the serosa; see Goldspink *et al.* 1984) is devoted to the production of new cells.

Another important functional difference between the two physiological systems is the high contribution of secretory activity to mucosal epithelial cell protein synthesis. These secretions take essentially three forms: first, the mucosa of the stomach and the exocrine pancreas secrete digestive enzymes continuously, especially during the suckling period when food is taken at frequent intervals. Second, throughout the gastrointestinal tract, significant quantities of mucus glycoproteins of variable carbohydrate and protein composition are secreted into the lumen and form a protective layer over the absorptive surface. Third, in the small intestine in particular, significant quantities of the enzymes responsible for the terminal stages of carbohydrate and protein digestion are synthesized in the endoplasmic reticulum and transported and inserted in the brush-border membrane of the villus enterocytes (Danielsen *et al.* 1984).

Only a small quantity of the extracellular digestive enzymes and mucins are stored in their cells of origin, so their fractional rates of synthesis can be exceedingly high (Table 3). For example, after weaning, the rat pancreas has an overall fractional rate of protein synthesis in excess of 300%/d (Burrin *et al.* 1991). Furthermore, the fractional rate of synthesis of the brush-border proteins is considerably higher than the fractional rate of synthesis of total mucosal protein (James *et al.* 1971), and the hydrolases of the brush-border membrane are synthesized at a particularly high rate (Dudley *et al.* 1992). In the case of the brush-border proteins, the high rate of turnover is probably driven, at least in part, by the fact that this surface is subject to attrition from extracellular proteases. Thus, at least 30% of the overall protein synthetic activity of the small intestinal mucosa appears to be devoted to the elaboration of proteins that are lost rapidly into the intestinal lumen (Table 4); if we include cell turnover, the rate of

Table 4. *Distribution of protein synthetic activity of the upper intestinal tract of growing pigs**

Protein synthesis		Secretory protein outflow†		
Total (g/d)	Fractional (%/d)	Total (g/d)	Percentage of protein pool	Percentage of protein synthesis
75	35	24	11	32

* Protein synthetic values are the sum of pancreas, stomach, and small intestine (Simon *et al.* 1982).

† Outflow values taken from de Lange *et al.* (1990).

Table 5. *Distribution of mucosal protein synthesis in fed adult rats**

	Total mucosa	Brush border	Cell loss	Cellular protein
Total (mg/d)	390	131	98	161
Rate (%/d)	125	420	25	40

* Values for mucosal protein mass from Goldspink *et al.* (1984), for protein synthesis from McNurlan *et al.* (1982), Goldspink *et al.* (1984) and Dudley *et al.* (1992) and for brush-border turnover from Dudley *et al.* (1992); cell turnover time is taken as 4 d.

synthesis of the constitutive proteins of the mucosal epithelium appear to be only 30–35%/d (Table 5). Thus, the term 'growth' as commonly applied, i.e. the accretion of new tissue, may well be inappropriate when we consider the gastrointestinal tract, and it could be argued that because of its secretory activity, a considerable proportion of mucosal protein synthetic activity is devoted to 'growth'. However, most of this protein synthesis is eventually lost to the intestinal lumen and represents a continual protein synthetic drain on the body. It has been argued (e.g. Reeds, 1990) that the failure to recapture intestinal secretions has a highly significant bearing on the magnitude of amino acid needs close to body protein equilibrium.

Although the skeletal musculature is not a secretory tissue, similar general comments apply with respect to the proportion of protein synthetic activity devoted to the elaboration of physiologically functional proteins. Approximately 50% of the total protein synthetic activity of mature skeletal muscle is devoted to the elaboration of myofibrillar proteins (Preedy & Sugden, 1989), i.e. those inherent in the physiological function of the tissue. The ratio of the fractional rates of myofibrillar and sarcoplasmic synthesis varies not only with age, but does so in proportion to the relative rates of accretion of these two protein fractions (Table 6).

NUTRITION AND THE GROWTH AND DEVELOPMENT OF GUT AND MUSCLE

Changes in dietary composition and intake undoubtedly have many highly significant effects on the growth and function of tissues of the gastrointestinal tract and skeletal muscle. However, the interactions between organic nutrient intake and intestinal growth and function are potentially complex. There may well be interactions between the stage of development and the relationship between nutritional status, growth and protein

Table 6. *Changes in skeletal muscle myofibrillar and sarcoplasmic protein synthesis with age*

(Mean values and standard deviations)

Age (d)	Protein synthesis (%/d)				Myofibrillar: sarcoplasmic
	Myofibrillar		Sarcoplasmic		
	Mean	SD	Mean	SD	
5	36	3	29	2	1.24
10	33	2	19	2	1.73
16	23	4	23	2	1.0
35	11	2	17	3	0.65

Values for suckling rats from M. L. Fiorotto, P. J. Reeds, D. G. Burrin and T. A. Davis (unpublished results) and those for 35-d-old rats from Preedy & Sugden (1989).

metabolic activity. For example, various authors have emphasized (e.g. Waterlow *et al.* 1978; McNurlan *et al.* 1979) that after an overnight fast there is a marked difference in the degree to which protein synthesis is reduced in the small intestinal mucosa and muscle, and mucosal protein synthesis is relatively insensitive to short-term changes in food intake. However, when neonatal rats and pigs are fasted, the change in the rate of protein synthesis in the small intestine is as great as that in skeletal muscle (Burrin *et al.* 1991, 1992a; Davis *et al.* 1991).

The first point at which the composition of the diet could have a significant effect on tissue growth and maturation is immediately after birth. There is a substantial literature that suggests that growth and, by implication, maturation of some tissues of the neonate are stimulated by the ingestion of species homologous milk and especially colostrum. Thus, the ingestion of colostrum during the first 24 h after birth appears to advance, at least temporarily, the growth of the gastrointestinal tract (Widdowson *et al.* 1976; Hall & Widdowson, 1979). This stimulatory effect is generally believed to be a response, at least in part, to the ingestion of trophic factors contained within mammary secretions (Klagsbrun, 1978; Heird *et al.* 1984; Berseth, 1987; Nichols *et al.* 1987; Francis *et al.* 1988). Although in some species, a significant proportion of early intestinal 'growth' after the consumption of colostrum represents the sequestration of milk proteins, especially IgG (Burrin *et al.* 1992b), the ingestion of colostrum acutely stimulates mucosal protein synthesis in both lambs (Patureau-Mirand *et al.* 1991) and pigs (Burrin *et al.* 1992b). Our recent work has demonstrated that the ingestion of colostrum during the first few hours after birth also stimulates protein synthesis in tissues other than those of the gastrointestinal tract, including skeletal muscle tissue (Burrin *et al.* 1992b; Table 7). Whether these effects on overall protein synthesis are also accompanied by an acceleration in maturation, as reflected in the expression of functionally important proteins, remains to be proven, but the possibility is exciting.

The interactions between changes in organic nutrient intake and growth beyond the immediate neonatal period are potentially more complex, especially in the gastrointestinal tract. Consideration of Table 1, for example, reveals that in the rat the postnatal growth of the small intestine is rapid immediately after birth, slows at approximately 16 d post partum, and then rises at weaning. This growth pattern

Table 7. Protein synthesis in the tissues of newborn piglets fed on water, mature sow's milk, and sow's colostrum†

(Mean values and standard deviations)

Feeding group . . .	Water		Milk		Colostrum	
	Mean	SD	Mean	SD	Mean	SD
	Intestinal tissue (μmol phenylalanine/kg per d)					
Jejunum	4.1	0.5	11.5	0.8	12.5	1.2
Ileum	2.9	0.2	8.6	0.8	11.4*	0.7
	Non-intestinal tissue (%/d)					
Liver	42	3	60	7	74*	4
Muscle	13	2	17	2	26*	2

Mean values were significantly higher than those for milk-fed animals: * $P < 0.05$.

† Values taken from Burrin *et al.* (1992b).

Table 8. Effects of preceding feed intake on contribution of gastrointestinal tissues to body weight (g/kg live weight)*

Intake . . .	Low	Medium	High
Rats	53.1	54.3	65.6
Pigs	34.6	39.8	48.1
Sheep: (a)	71.6	73.1	
(b)	57.2	66.6	67.3

* Values for rats taken from Ferrell & Koong (1986), those for pigs from Koong *et al.* (1983), and those for sheep from (a) Ferrell *et al.* (1986) and (b) Burrin *et al.* (1990).

illustrates the important influence of overall food (particularly solid matter) intake on the mass of the gastrointestinal tract. Evidence from studies of the relationship between early rodent growth and milk intake (Coward *et al.* 1982; Fiorotto *et al.* 1991) indicates that at approximately 16 d of postnatal age, milk intake becomes a significant limitation to the rate of overall weight gain; when expressed in terms of solid matter, the weight-specific feed intake at this age is probably as low as it will be until adulthood. As weaning is instituted, however, the high appetite of the very young animal, coupled with the ingestion of a diet containing substantial quantities of complex carbohydrates, leads to an increase in solid matter intake that is probably the highest that will be attained throughout the animal's life span. This time of maximum intake coincides with the time at which gut mass makes its largest contribution to body mass (Goldspink *et al.* 1984). The general relationships between intake and the mass of the intestine have been clearly demonstrated in a number of studies (Koong *et al.* 1983; Ferrell & Koong, 1986; Burrin *et al.* 1990; Table 8). These studies show clearly that high intakes are associated with a high contribution of gastrointestinal mass to body mass and, as we pointed out earlier, these events coincide with an increase in the weight-specific rate of fasting heat production.

Table 9. *Effect of combined protein and energy restriction on visceral and carcass protein deposition in immature pigs and rats*

	Rate of protein deposition (g protein/kg body-wt ^{0.75} per d)		
	Control	Restricted	Percentage change
Immature pigs (3.5–5 kg):			
70% restriction (Seve <i>et al.</i> 1986)			
Intestine	0.42	0.32	–23
Carcass	2.84	0.19	–93
40% restriction (S. Ebner and D. G. Burrin, unpublished results)			
Intestine	0.34	0.26	–23
Carcass	8.42	3.58	–57
Immature rats (11–15 g):			
25% restriction (M. L. Fiorotto, P. J. Reeds, D. G. Burrin and T. A. Davis, unpublished results)			
Intestine	0.22	0.18	–15
Carcass	6.71	5.16	–23

A number of studies of very young animals has established that gastrointestinal mass, at low levels of intake, particularly of protein, makes a disproportionately high contribution to body protein deposition as a whole (Table 9). In this case, however, the differences in the protein gain of the different tissues do not reflect the stimulation of gastrointestinal growth as had occurred in the experiments summarized in Table 8, but reflect the preservation of the intestine with either slow, or non-existent protein deposition in other components of the body, including the skeletal musculature. In fact, it appears that the preservation of protein deposition at the expense of lipid deposition in marginally nourished sucking animals (Fiorotto *et al.* 1991) extends to a hierarchy of tissue sensitivities; the gastrointestinal tract is relatively insensitive, the skeletal musculature shows some degree of sensitivity, and other tissues, particularly the skin and the liver, are especially sensitive to inadequate energy and protein intake.

During the immediate postnatal period, particularly in altricial mammals, substantial tissue maturation occurs in parallel with an increase in tissue mass. It is appropriate, therefore, to ask whether the nutritional regulation of the synthesis of proteins, whose function is to support the physiological demands of the body as a whole, is different from that of proteins whose prime function is the maintenance of the viability of cells in which they are synthesized. Present evidence poses a complex picture.

First of all, with respect to skeletal muscle protein turnover, evidence accumulated over the last decade suggests strongly that the sensitivity of the rates of degradation of myofibrillar and sarcoplasmic proteins to a variety of extracellular influences are not only quantitatively, but qualitatively different. The literature suggests that myofibrillar protein degradation is more sensitive to starvation (Lowell *et al.* 1986), protein intake (Goodman & Gomez, 1987), insulin (Smith *et al.* 1989) and glucocorticoids (Kayali *et al.* 1987) than is the degradation of sarcoplasmic proteins. In contrast, studies of the stimulatory effects of functional overload (Gregory *et al.* 1990) and the inhibitory effects of fasting (Preedy & Sugden, 1989) suggest that myofibrillar and sarcoplasmic protein synthesis are affected in similar proportions.

Our recent findings suggest that the differential sensitivity of the degradation of the two protein 'pools' of muscle applies to the nutritional regulation of myofibrillar and sarcoplasmic protein deposition during early life. In a partially completed study, we (M. L. Fiorotto and M. Perez, unpublished results) have found that although muscle protein deposition was reduced to only a small extent (-6%) in undernourished sucking rats, myofibrillar protein deposition was significantly (-15%) lower while the deposition of the sarcoplasmic proteins had not been affected by undernutrition. These differences in deposition were associated with equally low rates of synthesis of both muscle protein pools (-20%). The rate of sarcoplasmic protein degradation, however, was reduced by 50% , but that of myofibrillar protein was only 30% lower than the rate in well-nourished pups. Whether these early effects of undernutrition on the relative rates of accretion of contractile and non-contractile proteins of skeletal muscle are permanent remains to be investigated, but they have substantial implications for overall functional development of the skeletal musculature of undernourished infants.

A separate issue with respect to the interactions between early nutrition and functional development relates to the maturation process itself. The gastrointestinal tract of young mammals shows a characteristic development pattern of disaccharidase activity. This pattern is characterized by high levels of the enzyme lactase (*EC* 3.2.1.108) in early life followed by the subsequent acceleration of sucrase (*EC* 3.2.1.48) expression (Henning, 1986). Similarly, in the skeletal musculature of altricial mammals, different myosin isoforms are expressed as development proceeds (Whalen *et al.* 1979). In both cases, development involves the appearance of new enzymes accompanied by a progressive fall in the concentration of proteins characteristic of the immature state. Interestingly, recent studies of the impact of severe undernutrition on the intestinal tract of the young pig (M. A. Dudley and W. G. Pond, unpublished results) and of the changes in myosin isoform expression in the skeletal musculature of immature rats (M. L. Fiorotto and M. Perez, unpublished results) suggest that undernutrition does not substantially inhibit the appearance of proteins characteristic of the mature state, but does retard the disappearance of proteins characteristic of the immature animal. Thus, early undernutrition does not retard functional development in regard to when developmentally regulated proteins appear, but, perhaps by restricting protein degradation, undernutrition leads to the persistence of proteins associated with the newborn state.

CONCLUSION

The skeletal musculature and the gastrointestinal tract are not only of great significance to the physiological function of the young organism, but their relative masses affect the efficiency with which the animal utilizes organic macronutrients. The consumption of diets containing high levels of complex carbohydrate and the consumption of inadequate diets containing relatively low levels of protein appear to cause exaggerated growth of the gastrointestinal tract. Such growth conceivably affects both basal energy expenditure and the energetic efficiency with which dietary C is utilized for body protein and lipid accretion. It is possible that significant proportions of growth and functional regulation are intrinsic to the intestine, perhaps mediated by locally acting paracrine trophic factors elaborated by the lymphocytes and fibroblasts that are prominent within the mucosa, while postnatal muscle growth is regulated primarily by endocrine factors (such as insulin, corticosteroids and IGF-I) that circulate in the blood plasma. At the same time,

the growth of skeletal muscle and, as suggested by preliminary evidence, the accretion of the functional proteins of skeletal muscle appear to be specifically sensitive to the level of intake. Thus, it is possible that the consumption of inadequate diets at or around weaning may influence the mobility of the developing organism and, in the case of animals, their ability to forage for food.

These remarks imply that the gastrointestinal tract and the skeletal musculature are in effect competitors for the disposition of nutrients available over and above those needed to maintain metabolic and physiological viability. This conclusion, however, is too simplistic. It is important to remember that the gastrointestinal tract represents an important barrier that protects the organism from invasion by pathogenic bacteria and other parasites. Furthermore, unless some degree of gastrointestinal function is maintained during undernutrition, the subsequent assimilation of nutrients from more adequate diets may be compromised temporarily. Thus, the relative preservation of gut mass may serve an important adaptive function. At the same time, the skeletal muscle in effect functions as a protein store from which amino acids, such as glutamine and arginine, can be drawn in times of stress to preserve immune and perhaps gastrointestinal function. In other words, what could be seen as a 'competition' is in fact a regulated 'collaboration' in which the compromise of some functions ensures the maintenance of the organism as a whole.

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