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Effect of nutrition on plasma C-type natriuretic peptide forms in adult sheep: evidence for enhanced C-type natriuretic peptide degradation during caloric restriction

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Abstract

Previous studies in lambs and children show that the plasma concentration of amino terminal pro–C-type natriuretic peptide (NTproCNP), a stable product of proCNP, is strongly correlated with skeletal growth and markers of bone formation. Consistent with these findings, CNP expression is sensitive to nutritional status and is reduced by caloric restriction (CR) in both the fetus and the postnatal lamb. However, the effect of nutritional status on CNP in the adult, once linear growth is complete, is unknown. Hypothesizing that reduced CNP synthesis during CR is contingent on the presence of active growth plates, we studied the effect of CR (25% of maintenance) or loading (CL, 200% of maintenance) on CNP forms and alkaline phosphatase (ALP) in adult ewes and compared the findings to responses in a control group (C) fed a maintenance diet of 10.6 MJ of metabolizable energy. Live body weight was reduced (17%) in the CR group and increased (10%) in the CL group after 16 days of intervention. Plasma CNP concentration and ALP both fell in CR sheep and were significantly lower than C ($P < .05$ for both), returning toward basal levels 1 week after refeeding. In contrast, plasma NTproCNP did not differ (CR vs C). There were no significant changes in CNP forms and ALP in CL sheep compared with C. Fall in plasma CNP but not in NTproCNP in CR adult sheep suggests that CNP degradation (not synthesis) is altered, and contrasts with previous findings in growing lambs where CR reduces both CNP forms.

1. Introduction

C-type natriuretic peptide (CNP), along with the cardiac peptides atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), belongs to a family of structurally related hormones with important actions within cardiovascular and skeletal tissues [1]. Secreted by the heart, ANP and BNP circulate in plasma to regulate blood pressure and intravascular volume, whereas CNP, sourced from a variety of tissues [2-4], is barely detectable in plasma (at least in healthy adults) and appears to act locally in keeping with a largely paracrine role. All 3 hormones have antiproliferative actions within the heart and vasculature, whereas cell proliferation and hypertrophy characterize responses in skeletal tissues [5,6]. Recent studies in rodents [7-9] and humans [10] clearly show that CNP has a crucial role in endochondral bone growth. C-type natriuretic peptide strongly stimulates chondrocyte growth and expansion of growth plate tissues, and genetic modifications at several loci within the CNP signaling pathway strongly impact on postnatal growth in rodents [7,9,11-13]. Consistent with these findings, the plasma concentration of amino terminal proCNP (NTproCNP, the first 50 amino acid residues of the prohormone), a stable product of proCNP synthesis and readily detectable in blood, is strongly correlated with skeletal growth and markers of bone formation in children, as well as during normal growth and during interventions affecting growth velocity in lambs [14,15]. Although the source of these changes in proCNP products (NTproCNP and CNP) in plasma remains to be fully clarified, their

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presence in growth plate tissue extracts at higher concentrations than plasma [14] suggests that these tissues contribute to circulating concentrations in juveniles.

In the course of previous studies of CNP regulation in growing lambs, we found that the plasma concentrations of both CNP and NTproCNP were acutely sensitive to changes in nutrition. Thus, in both the fetus [16] and postnatal lambs [15], caloric restriction (CR) rapidly and reversibly reduced circulating plasma CNP and NTproCNP. In 4-week-old rapidly growing lambs, these changes were also associated with a fall in plasma alkaline phosphatase (ALP) and downward trends in skeletal growth [15]. These findings presumably reflect reduced proCNP synthesis within the growth plate or closely related tissues in response to acute changes in energy balance; but the role of other organs, or change in metabolism of CNP forms, could not be excluded. Hypothesizing that reduced CNP synthesis (fall in both CNP and NTproCNP) during CR is contingent on the presence of active growth plates—and that circulating CNP forms will be unaffected by CR once skeletal linear growth has ceased—we have now studied the response of plasma CNP forms in adult ewes to a 16-day period of CR (25% of normal maintenance) and compared the changes with those in adult ewes fed a normal diet (control) or challenged by caloric loading (200% of maintenance).

2. Materials and Methods

2.1. Animal studies

Twenty-four adult (>3 years of age) healthy Coopworth ewes were housed in individual pens and fed a maintenance diet (80% pellets, 20% chaff) containing 10.6 MJ of metabolizable energy (MJME). After a 14-day run-in period (day −8 animals were shorn), the sheep were randomized into 3 groups (n = 8) to receive (*a*) a maintenance diet comprising 10.6 MJME (control group [C]), (*b*) a calorie-restricted diet comprising 25% of maintenance (CR), or (*c*) a calorie-loaded diet comprising 200% of maintenance (CL) for a period of 16 days. After the intervention, ewes received a normal maintenance diet for a further period of 14 days. Animals were fed twice daily, at 8:00 AM and 4:00 PM. Caloric intake per day in each sheep was calculated by measuring the weight of pellets and chaff consumed. Live weight was measured at intervals of 2 to 4 days throughout the study. Jugular venous blood was drawn before morning feeding for measurement of plasma concentrations of glucose, urea, CNP forms (NTproCNP and CNP), insulin-like growth factor–1 (IGF-1), and ALP. All animal studies were approved by the Lincoln University Animal Ethics Committee.

2.2. Plasma assays

Blood samples were collected in chilled standard blood collection tubes containing EDTA (7.5 mg/mL, Vacutainer; Becton-Dickinson, Plymouth, UK) or lithium heparin (Vacuette; Greiner Bio-One, Kremsmuenster, Austria) and centrifuged at 4°C; the plasma was stored at −20°C before analysis for CNP, NTproCNP, IGF-I (EDTA plasma) or urea, and ALP (heparin plasma, Aerosetc8000 analyzer; Abbott Laboratories). Insulin-like growth factor–I was measured by radioimmunoassay (RIA) after acid ethanol extraction and cryoprecipitation [17] using an antiserum B-71 provided by Dr BH Breier (Liggins Institute, University of Auckland, New Zealand). All plasma samples from individual sheep were measured in duplicate in the one assay.

2.3. RIA for NTproCNP

Amino terminal proCNP was assayed as previously described [18], except that a more sensitive primary rabbit antiserum (J39) raised against NTproCNP(1-15) was used (100 μL 1:6000 diluted antiserum/assay tube). Peptide standards were made from synthetic human proCNP(1-19), taking into account the purity data supplied (Chiron Technologies, Victoria, Australia).Within- and between-assay coefficients of variation were 4.9% and 6.4%, respectively, at 22 pmol/L.

2.4. RIA for CNP

C-type natriuretic peptide was assayed as previously described [19] using a commercial antiserum (catalog no. RAB-014-03; Phoenix Pharmaceuticals, Belmont, CA). The rabbit antiserum raised against proCNP-(82-103) shows 100% cross-reactivity with CNP-22 and human CNP-53 (Phoenix Pharmaceuticals data sheet). Within- and between-assay coefficients of variation were 3.6% and 8.3%, respectively, at 7.5 pmol/L. Cross-reactivity with the natriuretic peptides hANP, hBNP32, and ovine BNP26 was less than 0.004%, 2.3%, and 1.4%, respectively.

2.5. Statistical methods

Data are presented as means ± SEM where appropriate. Analysis of variance with repeated measures was used to assess changes in biochemical measurements using time and interventions as the independent variables. Where significant changes were observed with analysis of variance, Bonferroni post hoc analysis was used to detect differences from baseline values and control time-matched data as appropriate. Statistical significance was assumed when $P < .05$.

3. Results

Mean caloric intake and change in live weight are shown in Fig. 1. Before the intervention, mean live weight was similar in each group. As expected from changes in caloric intake, live weight was stable in the control group, fell 17% in CR, and rose 10% in CL by day 16. Live weight returned to basal values within 2 weeks of completing the intervention. Plasma urea concentration fell significantly in

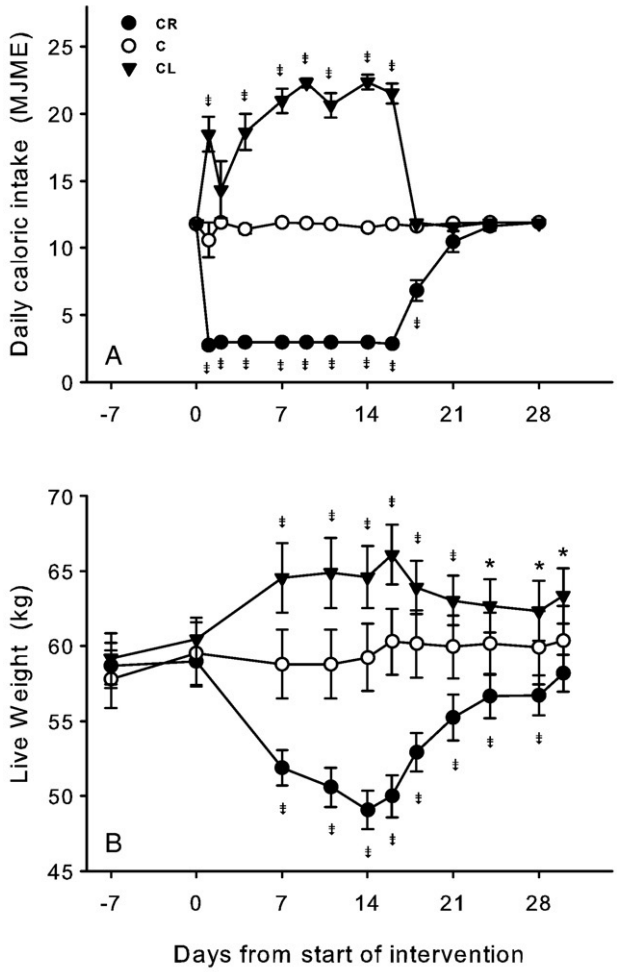

Fig. 1. (A) Mean caloric intake (n = 8 per group) of sheep fed a maintenance diet containing 10.6 MJME (control, open circles), calorie-restricted diet (25% maintenance, CR, filled circles), or calorie-loaded diet (200% maintenance, CL, filled triangles) for 16 days (days 0-16). (B) Effect of the dietary interventions on mean live weight (n = 8). Vertical bars represent ±SEM. Significant differences from control time-matched data are indicated by *$P < .05$ and ‡$P < .001$.

the CR group across the intervention period, returning to basal values within 2 weeks of completing the intervention (F = 3.4, $P < .001$), but did not change in C or CL groups (Table 1). No significant changes occurred in plasma glucose or IGF-1 concentrations in any of the 3 groups during interventions (Table 1).

Changes in plasma concentrations of CNP forms and ALP during CR and CL, relative to those in C, are shown in Figs. 2 and 3, respectively. Values for NTproCNP, CNP, and ALP concentrations at the start of the intervention were similar in all 3 groups. During CR, plasma concentrations of CNP and ALP both fell and were significantly lower than those in the control group (F = 3.2, $P < .05$ and F = 5.9, $P < .001$, respectively), returning toward basal levels at 1 week after refeeding. In contrast, the concentration of NTproCNP, higher than control values during CR, was not significantly affected (Fig. 2). As shown in Fig. 3, although the mean plasma concentrations of NTproCNP and CNP were higher than those in the C group during CL, these changes were not significant.

Fall in plasma CNP concentration but not in NTproCNP during CR prompted analysis of the molar ratio of NTproCNP to CNP (NTproCNP/CNP ratio) in all 3 groups before, during, and after interventions. Compared with the ratios in C and CL groups, there was a highly significant rise during CR (F = 2.7, $P < .001$), returning to basal values after refeeding (Fig. 4).

4. Discussion

The present findings from adult ewes—fall in plasma CNP concentration during CR without change in NTproCNP concentration—contrast with previous observations in growing lambs [15] where both CNP forms were similarly reduced. Taken together, the findings support the hypothesis that falls in CNP synthesis (ie, decline in both plasma CNP and NTproCNP concentrations) during CR are contingent on the presence of active growth plates. In addition, the current study reveals unexpected findings consistent with increases in CNP degradation during CR in adults.

As expected, adult basal values of NTproCNP (16.9 ± 0.5 pmol/L), CNP (0.6 ± 0.1 pmol/L), and ALP (57 ± 4 U/L) were all lower than found in 4-week-old lambs (39 ± 1 pmol/L, 3.1 ± 0.3 pmol/L, and 423 ± 28 U/L, respectively [15]), in keeping with their skeletal maturity. Percentage decrements in body weight after CR appeared to be greater in adults (17% after 16 days vs 10% after 6 days in lambs [15]). Although the duration of CR was different in the 2 studies (6 days in lambs, 16 days in adult ewes), these observations suggest that in the current study the catabolic insult should have been sufficient to reduce CNP synthesis in any nutrient-sensitive tissues. Failure to find such

Table 1
Effect of CR or CL on plasma urea, glucose, and IGF-1 concentration

	Day −7	Day 0	Day 7	Day 14	Day 21	Day 28
Urea (mmol/L)						
C	6.5 ± 0.4	7.5 ± 0.6	7.9 ± 0.3	7.6 ± 0.4	8.4 ± 0.4	8.5 ± 0.5
CR	7.0 ± 0.3	6.5 ± 0.4	5.6 ± 0.3*	6.3 ± 0.2	6.4 ± 0.4	8.0 ± 0.6
CL	6.3 ± 0.5	8.1 ± 0.5	8.4 ± 0.4	8.8 ± 0.3	7.6 ± 0.3	8.6 ± 0.3
Glucose (mmol/L)						
C	4.8 ± 0.7	4.5 ± 0.1	4.0 ± 0.1	3.9 ± 0.1	3.6 ± 0.1	3.5 ± 0.1
CR	5.1 ± 0.6	4.4 ± 0.1	4.1 ± 0.1	3.6 ± 0.1	4.1 ± 0.1	3.6 ± 0.1
CL	4.4 ± 0.1	3.9 ± 0.2	4.3 ± 0.1	3.9 ± 0.1	3.7 ± 0.1	3.3 ± 0.2
IGF-1 (pmol/L)						
C	145 ± 18	194 ± 16	182 ± 15	172 ± 12	159 ± 18	176 ± 13
CR	139 ± 12	225 ± 21	197 ± 10	186 ± 13	170 ± 20	188 ± 21
CL	134 ± 19	202 ± 31	187 ± 18	177 ± 23	193 ± 26	183 ± 34

Results are expressed as means ± SEM (n = 8). Significant differences from time-matched control data (Bonferroni post hoc analysis) are indicated by asterisks.

* $P < .05$.

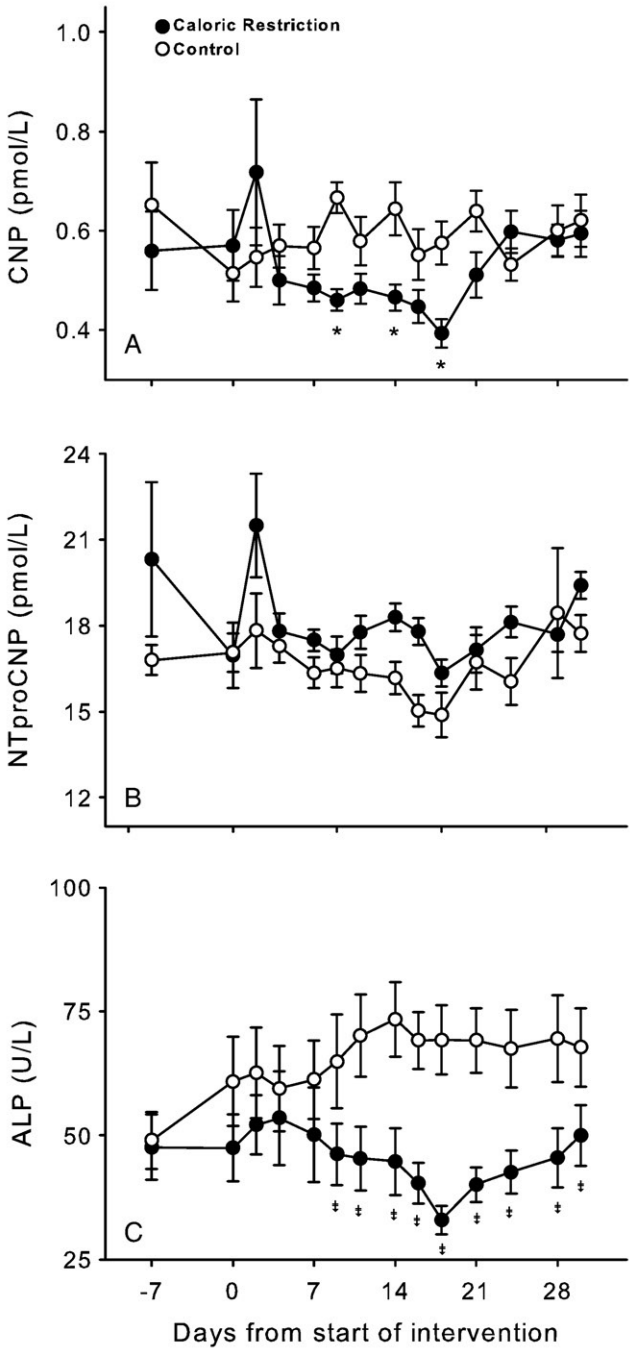

Fig. 2. Effect of CR (filled circles, n = 8) on mean plasma CNP (A), NTproCNP (B), and ALP (C) concentration. The control sheep (open circles, n = 8) received a maintenance diet. Vertical bars represent ±SEM. Significant differences from control time-matched data are indicated by $^{*}P < .05$ and $^{‡}P < .001$.

evidence suggests that, unlike juveniles, CNP synthesis itself is not nutrient sensitive in adults. No significant changes in concentration of either CNP form were seen during CL.

The significant fall in plasma CNP concentration alone and the prompt return to basal levels after cessation of CR were unexpected findings. This selective response of the bioactive CNP form is highlighted when changes in the NTproCNP/CNP ratio are viewed across interventions in all 3 groups. Assuming that CNP and NTproCNP, after intracellular production, are cosecreted in equimolar amounts [20], the steady-state concentration of the 2 forms in the circulation is likely to differ because of differences in

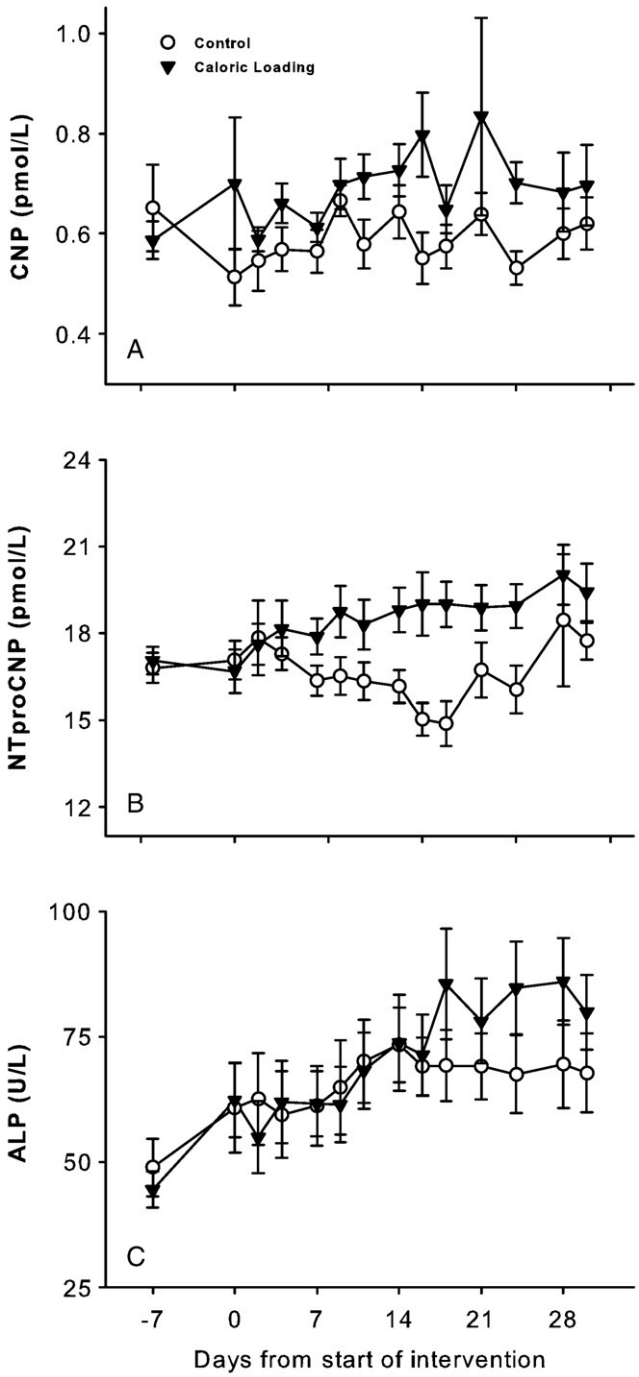

Fig. 3. Effect of CL (filled triangles, n = 8) on mean plasma CNP (A), NTproCNP (B), and ALP (C) concentration. The control sheep (open circles, n = 8) received a maintenance diet. Vertical bars represent ±SEM.

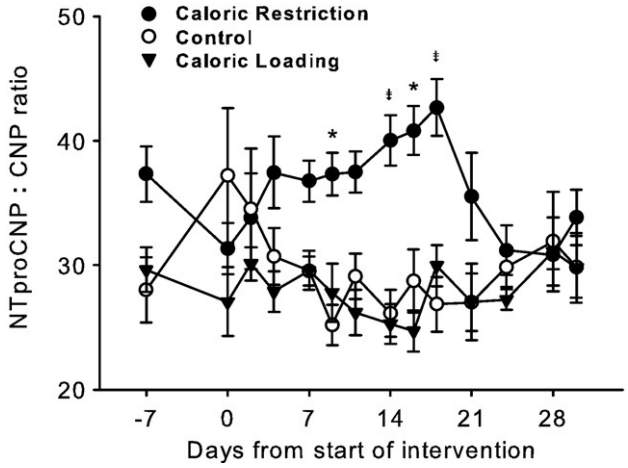

Fig. 4. Effect of CR (filled circles, n = 8) or CL (filled triangles, n = 8) on the mean molar plasma NTproCNP/CNP ratio. The control sheep (open circles, n = 8) received a maintenance diet. Vertical bars represent ±SEM. Significant differences from control time-matched data are indicated by $^{*}P < .05$ and $^{‡}P < .001$.

degradation rates, distributional volume, and renal clearance. In contrast to NTproCNP, CNP is highly vulnerable to enzyme hydrolysis by neprilysin [21] and binds with high affinity to the natriuretic peptide clearance receptor (NPR-C) [22]. Together, these presumably account for the high NTproCNP/CNP ratio normally present in plasma. Increase (or decrease) in concentration of both CNP forms is likely to reflect increase (or decrease) in CNP synthesis within tissues. Decrease in CNP without change in NTproCNP could be due to increased enzyme hydrolysis or enhanced activity of NRP-C. To our knowledge, there are no reports suggesting that neprilysin activity is affected by CR. In contrast, the abundant expression of NPR-C in adipose tissue [23] is reduced by fasting in rodents [24]. Such changes would be expected to increase the concentration of CNP, not reduce it as found here. A fall in the concentration of other circulating natriuretic peptides (ANP, BNP) during CR has the potential to reduce CNP concentrations by increasing available binding sites on NPR-C [25-27]. However, the effect of CR on the cardiac hormones ANP and BNP is unclear, with evidence supporting no change [28,29], fall [30,31], or increase in their activity [32,33]. A further possibility accounting for the differences is reduced CNP synthesis associated with a concomitant and selective decrease in renal clearance of NTproCNP. Although unlikely, this cannot be excluded.

A more attractive alternative to the above is provided by the recent discovery of osteocrin [34], a natural (endogenous) NPR-C–specific ligand synthesized by cells of osteoblast lineage [35] and at sites of bone remodeling in the mature skeleton [36]. The same protein (termed *musclin*) has been identified in skeletal muscle [37]. Osteocrin binds strongly to NPR-C and, when overexpressed in rodents [35], induces a syndrome of bone overgrowth, similar to that observed in the NPR-C knockout mouse [12]. Because osteocrin synthesis is highly sensitive to energy balance [37], gene expression reducing as insulin falls during fasting or CR, a selective reduction in CNP without change in NTproCNP would be anticipated. Clearly, future studies of CNP and osteocrin gene expression, together with changes in the tissue protein level themselves, are needed to clarify these issues. In particular, the specific tissues contributing to the changes we observe in the circulation need examination. In this context, it is notable that the change in NTproCNP/CNP ratio is closely associated with highly significant falls in plasma ALP concentration, raising the possibility that the local (adaptive) changes in osteoblastogenesis, occurring in response to CR [38], are linked to the fall in CNP and ALP concentration observed here. A similar trend for the ratio to rise during CR also occurs in lambs [15] (basal ratio 13.2 ± 1.6 vs 15 ± 1.4 on day 6 of CR). However, change in the ratio is likely to be less obvious in lambs where much larger (picomolar) reductions in both CNP forms occur during acute CR, presumably in response to diminishing numbers of proliferating growth plate chondrocytes [39]. Taken together, the findings suggest that, whereas tissue responses to CR (fall in plasma CNP and ALP concentration) are similar in immature and mature sheep, the underlying mechanisms (reduced CNP synthesis in the former, enhanced degradation in the latter) are likely to differ.

The changes in plasma CNP concentration we observed were small (maximum mean fall during CR, 0.2 pmol/L) and unlikely to affect systemic pressure [40] or fat metabolism [41]. Nevertheless, the results illustrate the power of serial sampling in controlled studies using sensitive analytical tools in detecting subtle changes in hormone synthesis and metabolism. By measuring both circulating forms of CNP in the appropriate context, these tools have the potential to reveal more of CNP's paracrine physiology in vivo.

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