

## References

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*Energy partitioning between body storage of protein and fat during starvation and refeeding: sources of intra-individual variation of P-ratios – Reply by Henry et al.*

We read with great interest the comments made by Dulloo (1998) in response to our paper (Henry *et al.* 1997). We are entirely in agreement that the partitioning of stored energy between lean and fat tissue compartments is an individual characteristic. This characteristic is probably genetically determined and serves, as Dulloo *et al.* (1996) have described, as a metabolic ‘memory’ for a preferred set of body tissue proportions.

However, we beg to differ with the inferences Dulloo has drawn from a comparison between the results from our experiments and those of his own. We suspect that divergence of views is as much the result of semantic problems as of any fundamental conceptual conflict. We, therefore, will try once more to express our position as carefully as possible.

1. In the computer model of adult body weight regulation, Payne & Dugdale (1977) made three assumptions. One of those was that for a given individual there would always be close equality between the proportion of energy withdrawn from tissues in the form of protein ( $P_{\text{fast}}$ ), during negative energy balance and the corresponding proportion deposited during positive balance ( $P_{\text{refed}}$ ). It is important to recognize that the long-term stability of the model depends on this condition being applied to the calculation of day-to-day changes in energy balance. These changes are then summed over time, and then used to predict longer-term weight variations. The key assumption, therefore, is the short-term equality of  $P_{\text{fast}}$  and  $P_{\text{refed}}$ . For practical reasons, however, actual measurements of P-ratios usually have to be made over time periods substantially longer than one day.

2. It is likely that changes in the absolute values of  $P_{\text{fast}}$  and  $P_{\text{refed}}$  will occur in response to changes of energetic efficiency and body composition throughout growth, reproductive activity and senescence. Indeed, Dugdale & Payne (1975) had already pointed out that the partitioning of stored energy in individual human infants swings rapidly and repeatedly over a manifold range, during the first months of life. Needless to say that other environmental and metabolic insults are also likely to bring changes in the absolute values of  $P_{\text{fast}}$  and  $P_{\text{refed}}$ .
3. The objectives of our recent work have therefore been: (i) to quantify some of the changes in P-ratios throughout growth and development; (ii) to assess the degree to which  $P_{\text{fast}}$  and  $P_{\text{refed}}$  remained equal despite those changes (by measuring them sequentially in the same individuals, using periods of time kept as short as possible); (iii) to test the hypothesis that despite changes in the average ratios of groups of individuals intra-individual differences are still maintained. We reported only partial success: P-ratios measured during fasting in older but still slowly-growing rats were not significantly different from those measured during subsequent refeeding. Intra-individual differences were sustained throughout the measurements, in both weanling and the older animals. However, we found a major inequality between  $P_{\text{fast}}$  and  $P_{\text{refed}}$  in the weanling animals. The average ratio measured during a 3 d fast at the mid-point-age of 31 d was followed by a value three-fold higher, during subsequent refeeding, at a mid-point-age of 41 d. This effect is the reverse of the differences shown in Dulloo’s Table 1 (p. 108). There the values for  $P_{\text{refed}}$  derived from cross-sectional measurements on

older but still growing rats are lower after a period of semi-starvation, than those for *ad libitum*-fed controls. Dulloo *et al.* (1996) interpreted this as the result of compensatory adaptation to the period of depletion.

It is useful to be able to draw upon Dulloo's comments and the figures provided in Table 1, to throw some light on what is clearly a complex situation. At mid-point age of 72 d the rats studied by Dulloo & Girardier (1990) were at a stage of life intermediate between our weanling and adult (136 d) females. Both the magnitudes of the P-ratios and the effects of underfeeding differ from ours. We can identify some possibilities for the discrepancies.

First, a part (all-be-it small) results from the method of calculation. In the 1990 paper the results are not expressed as P-ratios, but as separate estimates of incremental changes in stored protein and fat, expressed as gross energy (9.22 kcal/g for fat and 5.42 kcal/g for protein). It appears that for the 1996 paper these were used directly to compute P-ratios. However, Payne & Dugdale (1977) chose to define P-ratios in terms of metabolizable energy (using the conventional factors 9.0 and 4.0, or their SI equivalents). We have adhered to that convention, which results in a significant difference, particularly at lower values of the ratio. Recalculation suggests that to put the figures in Table 1 on a comparable basis, those for refeeding should be 0.25, for weight-matched controls 0.38, and for age-matched controls 0.43.

Second, differences in experimental design are likely to be of greater significance. Dulloo & Girardier (1990) did not make any measurements during the fasting period, regarding this as a means of 'pre-conditioning' the animals. Thus, their results cannot contribute to our interest in the question of the short-term equality between  $P_{fast}$  and  $P_{refed}$ . The 10 d food-restriction period resulted in a body-weight loss of 30% (compared to 15% in our adult rats). One consequence of this large weight loss was the problem familiar to cross-sectional studies, i.e. that of matching controls. The age-matched controls were 30% heavier by the time of the energy balance measurements, whereas the weight-matched controls were obtained by selection from a younger cohort of *ad libitum*-fed animals. Enough has been said above regarding the existence of individual variability to raise serious questions regarding the effect of such selection on the representativeness of the resulting sample population.

This should not, however, be taken as a dismissal of the possibility that P-ratios can show adaptive changes. On the contrary, we need to know more about the effects of dietary and other biological stresses. For example, how long does it take to establish adaptive responses? How reversible are they? Do they affect both  $P_{fast}$  and  $P_{refed}$ ? At the same time we are sufficiently alive to the puzzling consequences of our own choice of 30–40 d of age (for the longitudinal sequence of measurements on weanling rats) to understand that we must have more information about the pattern of age-related changes in the P-ratio. Our next approach to the problem of establishing the pattern of age changes will, therefore, be based on the use of time-series analysis. Applying this to an extended sequence of measurements of body fat and protein content of normally-fed rats from birth

to maturity (unpublished data) suggested that young rats exhibit at least two large, transient peaks of predominantly lean tissue deposition (i.e. high P-ratios). The first peak is at its maximum around 35 d of age. Our experimental design, with its sequential measurements spanning the period 30–50 d, may well have been confounded by the much lower values preceding and following that peak. The second peak occurs at around 70 d, i.e. within the 59–94 d period of the observations of Dulloo & Girardier (1990).

The figures in Table 1 (p. 108) were derived from the excellent revisit by Dulloo *et al.* (1996) to the data from the Minnesota Experiment. We find it hardly surprising that estimates of  $P_{refed}$  made after the subjects lost 40% of their initial body weight differed significantly from those of  $P_{fast}$  made during the first period of fasting. However, in view of the wide range of the data, and the assumptions regarding tissue composition and energy values involved, we would be cautious of accepting the statistical validity of anything beyond the general direction of the change. Indeed, it is perhaps surprising that the magnitude of the adaptation suggested is so small, given that P-ratios significantly < 0.1 are found at the lower end of the range for human populations. Certainly, it was something of a surprise to Payne and Dugdale that the model gave such convincing simulations of the observed weight changes throughout the entire period, including the first stages of recovery.

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