Early nutrition and phenotypic development: ‘catch-up’ growth leads to elevated metabolic rate in adulthood

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Resting metabolic rate (RMR) is responsible for up to 50% of total energy expenditure, and so should be under strong selection pressure, yet it shows extensive intraspecific variation and a low heritability. Environmental conditions during growth are thought to have long-term effects through ‘metabolic programming’. Here we investigate whether nutritional conditions early in life can alter RMR in adulthood, and whether this is due to growth acceleration or the change in diet quality that prompts it. We manipulated dietary protein levels during the main growth period of zebra finches (*Taeniopygia guttata*) such that an episode of poor nutrition occurred with and without growth acceleration. This produced different growth trajectories but a similar adult body mass. Only the diet that induced growth acceleration resulted in a significant (19%) elevation of RMR at adulthood, despite all the birds having been on the same diet after the first month. This is the first study to show that dietary-induced differences in growth trajectories can have a long-term effect on adult metabolic rate. It suggests that modification of metabolic efficiency may be one of the mechanisms mediating the observed long-term costs of accelerated growth, and indicates links between early nutrition and the metabolic syndrome.

Keywords: energetics; bird; growth; protein; metabolic syndrome

1. INTRODUCTION

There is a growing awareness of the importance of individual differences in physiological processes, and a recognition that these differences may come about as a consequence of the environmental conditions in which individuals develop. One such physiological trait that shows pronounced variation is resting metabolic rate (RMR), the minimal rate of metabolism of a post-absorptive animal at rest when measured under standardized conditions and when corrected for body size (Hulbert & Else 2004). In higher animals, RMR makes up a significant fraction of total energy costs (e.g. up to 50% in both endotherms and ectotherms; Cruz-Neto & Bozinovic 2004; Steyermark *et al.* 2005) and so has profound effects on energy budgets. It is therefore surprising that a trait likely to be under strong selection pressure shows substantial variation among individuals within a species, with some individuals respiring at three times the RMR of others of the same size and sex (Cruz-Neto & Bozinovic 2004; Labocha *et al.* 2004; Steyermark *et al.* 2005).

In the few published studies that have tracked this physiological variation over time, it has been found to be repeatable in full grown individuals in a stable state, indicating that the RMR of adults is a consistent trait

(Rønning *et al.* 2005). However, the narrow-sense heritability of RMR has been shown to be low (Nespolo *et al.* 2003; Labocha *et al.* 2004), and there is evidence that environmental effects early in development may influence metabolic rate at adulthood (Verhulst *et al.* 2006). The most probable cause of such an effect is the pattern of nutrition during growth and development. It has been suggested that physiological traits are set, often referred to as being ‘programmed’, by the nutritional environment experienced during early growth (Desai *et al.* 1995; Gluckman *et al.* 2007) as a result of tissue remodelling or changes in cell differentiation, organ growth and/or cell signalling (Bertram *et al.* 2001; McMillen & Robinson 2005; Langley-Evans 2006).

Such alterations in physiological processes may serve to ‘match’ individual phenotypes to the environment that they are most likely to encounter as adults (Hales & Barker 2001; Monaghan 2008). However, there may be adverse long-term effects if the environment changes in the meantime; in particular, a change during development from a low protein to a richer diet is associated with a much greater risk of metabolic disorders such as hypertension and glucose metabolism, collectively termed the metabolic syndrome (Ozanne & Hales 1999; Langley-Evans 2006), in later life. Circumstantial evidence suggests that these metabolic disorders may be linked to the acceleration of growth that often follows an increase in the nutritional content of the diet (‘catch-up’ or compensatory growth; Metcalfe & Monaghan 2001; Hales & Ozanne 2003; Singhal *et al.* 2007). However, there is a lack of experimental studies in

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which diet is manipulated with and without compensatory growth being induced, and where individuals are followed into adulthood.

Given this background, we experimentally investigated whether RMR in adulthood is influenced by the pattern of nutrition and growth early in life. Growth trajectories were manipulated by controlling (and in some cases switching) the protein content of the diet during the period of early growth. Specifically, we predicted that those animals which had undergone accelerated growth, prompted by a change from a low-protein diet to a high-protein one, would show a significant perturbation of adult RMR in comparison with those experiencing a diet or dietary switch not associated with growth acceleration. The study was carried out on zebra finches *Taeniopygia guttata*, chosen because their RMR at adulthood has previously been found to be affected by the brood size in which they are reared (and hence possibly their access to food; Verhulst *et al.* 2006) but is stable once adulthood is reached (Rønning *et al.* 2005); moreover, they exhibit catch-up growth after early protein deprivation (Birkhead *et al.* 1999; Blount *et al.* 2003). We show for the first time that metabolic rate can be set by early growth trajectory, and that it is highest in animals that have earlier undergone accelerated growth.

2. MATERIAL AND METHODS

Pairs of stock adult birds were placed in breeding cages and allowed to breed. Most chick growth takes place during the first 30 days after hatching; so we divided this into two 15-day periods during which the quality of the diet was manipulated. Thus on the hatching of the first egg, we randomly allocated the families to receive either a high- (H) or a low (L)-quality rearing diet for the first 15 days of chick growth. The main difference between the two diets was their protein content; the low diet comprised roughly 12% protein by dry weight, while the high diet comprised 40% protein (see electronic supplementary material for further details). The chicks were given identifying ink marks at hatching, and numbered metal rings when 10–12 days old. When half of the chicks within a brood reached 15 days of age, the brood was again randomly allocated either the high- or low-quality diet for the next 15 days, thereby creating four different rearing diet groups (HH, HL, LH and LL). This enabled us to separate the effects of poor nutrition throughout growth (LL birds) from those of a brief episode of poor nutrition (both the LH and the HL groups), and to separate the effects of diet switching from those of growth acceleration, which we expected to occur only in the LH group. HH birds would grow well throughout development and so acted as a control. The chicks were separated from their parents when 30 days old (age 30.48 ± 1.43 days) and subsequently housed in single-sex groups of 6–7 birds. The diet provided from 30 days onwards was the same for all birds and was the one used initially for the parental birds (see electronic supplementary material).

To examine the effect of the diets on growth patterns, we took measurements (tarsus and wing length to the nearest 0.1 mm using calipers and body mass using an electronic balance (± 0.01 g) of the chicks at hatching, at 15 days (but prior to any diet switch), at 30 days (but prior to the transfer to the common diet) and at 200 days (i.e. when fully adult)). Growth rates were expressed as the daily change between

each measurement, with mass or size at the start of each interval included as a covariate.

RMRs were measured at approximately 15, 30 and 200 days. We determined RMR by measuring oxygen consumption in an open flow, push-through respirometry system (see electronic supplementary material for details). In each measurement session, four randomly selected birds were fasted overnight (from approx. 17.00 hours) and then placed singly in metabolic chambers in darkness the following morning (at approx. 09.00 hours); the fifth chamber was kept empty to provide a baseline reading. The birds immediately became inactive when placed in the darkness of the chambers. Their body mass was measured immediately before and after the experiment (± 0.01 g), and the average was used as a covariate in the subsequent analyses of metabolic rate. Oxygen levels in each of the five chambers were measured for 6 min during a 30 min cycle, and this cycle was repeated for 2 hours; the levels were calibrated with reference to those in the empty reference chamber. The lowest stable ($10 + \text{min}$) oxygen consumption recorded in each chamber during the last 30 min of the experiment was used to calculate the birds' RMR.

Only birds that survived to 200 days, and thus could be followed into adulthood, were included in any analyses; this produced total sample sizes of 48 HH, 42 HL, 52 LH and 40 LL birds, derived from 15, 13, 16 and 15 broods, respectively, although sample sizes for individual analyses were in some cases smaller due to missing measurements. Analyses of the effects of diet treatment on growth or RMR were performed using mixed model repeated measures ANOVAs, with the parental breeding round (1 or 2) as the repeated variable, and the bird's family and individual identity as random factors. The sex of the bird and the size of brood in which it hatched were initially included as fixed factors in all analyses, as were all interactions, but non-significant terms were sequentially dropped to produce minimal adequate models. Analyses were performed using SPSS v. 14.0 (www.spss.com); tests are two-tailed and p values less than 0.05 are considered significant; means are quoted $\pm$ s.e.

3. RESULTS

Chicks allocated to the high- or low-protein diet for the first 15 days did not differ in hatching body mass ($F_{1,169.8} = 0.478$, $p = 0.49$). Those on the low-protein diet were slower to gain mass (figure 1a, table 1) such that by 15 days, there was a significant difference in body mass between the H and L treatment groups (11.96 ± 0.13 versus 11.30 ± 0.13 g, $F_{1,183.9} = 13.08$, $p < 0.001$). There was a significant impact of brood size on body mass at 15 days (table 1), with, as would be expected, birds in bigger broods gaining less body mass than those in smaller broods (linear regression, $r = -0.27$, $F_{1,184} = 14.28$, $p < 0.001$), the correlation being particularly strong in the L group ($r = -0.39$, $F_{1,91} = 15.93$, $p < 0.001$). There was no sex effect on growth rate or body mass at this stage.

As expected, the transfer of chicks from a low-quality diet to a high-quality one (LH group) induced growth acceleration in body mass (0.200 ± 0.008 versus 0.177 ± 0.009 g d⁻¹ for LL birds, figure 1b). There was no effect of sex or brood size on any measure of growth rate over this time period. The rate of body mass gain between 30 and 200 days (figure 1c, table 1) did not differ significantly among the treatment groups. There was a significant

Figure 1. Body mass gain (g d^{-1}) of zebra finch chicks reared (a) initially on a low (L)- or high (H)-quality diet during the first 15 days, (b) then re-allocated to H or L diets until the age of 30 days (HH, high throughout; HL, high for 15 days then low, etc) and (c) thereafter put on the same diet and followed until the age of 200 days. Asterisks indicate significant diet treatment differences (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, see table 1 and text for further details and statistics).

interaction between diet treatment and sex on body mass gain during this period (table 1), with females of the LL group gaining more body mass than males (3.30 ± 0.37 versus 1.74 ± 0.40 g, respectively) while the opposite pattern was observed in the LH group (2.17 ± 0.33 versus 1.71 ± 0.34 g, respectively). However, the slightly higher rate of mass gain in the LL birds was such that by adulthood, there was no difference in final body mass among diet groups (16.33 ± 0.32 (HH), 16.50 ± 0.34 (HL), 16.59 ± 0.30 (LH) and 16.43 ± 0.35 g (LL), $F_{3,172.4} = 0.13$, $p = 0.944$) or between the sexes ($F_{1,173.8} = 0.83$, $p = 0.36$).

After correcting for body mass by including it as a covariate, RMR at 15 days was affected by the diet treatment experienced up to that point (high or low protein, table 2). The L diet treatment birds had higher

Table 1. Mixed model analyses of the effect of diet treatment on body mass gain of zebra finches reared under the four diet treatments. (Analyses controlled for sex, brood size at hatching, body mass at the start of each period and sex interactions with diet treatments when a sex effect was found. Non-significant terms (other than diet) were excluded from the final analysis. * indicates an interaction term.)

	d.f.	<i>F</i>	<i>p</i>
<i>body mass gain 0–15 days</i>			
diet treatment (H or L)	182.03	13.48	<0.001
brood size at hatching	183.03	18.86	<0.001
diet treatment* brood size at hatching	181.76	4.86	0.029
<i>body mass gain 15–30 days</i>			
diet groups (HH, LL, HL, LH)	174.03	4.38	0.005
body mass at 15 days	174.65	45.19	<0.001
<i>body mass gain 30–200 days</i>			
diet groups (HH, LL, HL, LH)	169.53	1.23	0.299
body mass at 30 days	163.55	6.77	0.010
sex	170.09	1.22	0.271
sex* diet groups	170.20	2.83	0.040

Table 2. Mixed model analyses of the effect of diet treatment on standard metabolic rate (W per bird) of zebra finches measured at three different ages (15, 30 and 200 days). (The analyses were run on 36 (15 days), 134 (30 days) and 174 birds (200 days). For all statistical tests, we controlled for family (diet treatment nested within), sex, brood size at hatching, body mass at the time of the metabolic measurements, and sex interactions with diet treatments when a sex effect was found. Non-significant terms (other than diet) were excluded from the final analysis.)

	d.f.	<i>F</i>	<i>p</i>
<i>standard metabolic rate at 15 days</i>			
diet treatment (H, L)	17.97	5.73	0.028
body mass (15 days)	11.19	52.05	<0.001
sex	16.41	6.37	0.022
<i>standard metabolic rate at 30 days</i>			
family (diet group)	44.22	2.77	<0.001
diet groups (HH, LL, HL, LH)	121.94	1.46	0.228
body mass (30 days)	133.42	7.50	0.007
brood size at hatching	128.42	7.55	0.007
<i>standard metabolic rate at 200 days</i>			
family (diet group)	71.58	1.71	0.017
diet groups (HH, LL, HL, LH)	109.15	8.45	<0.001
body mass (200 days)	102.46	21.90	<0.001
sex	106.70	4.94	0.028

metabolic rates on average than birds from the H group (0.248 ± 0.008 versus 0.224 ± 0.005 W for birds of the same adjusted mean mass, $F_{1,18.0} = 5.73$, $p = 0.028$, figure 2), neither tarsus length nor its interaction with body mass was significant ($p = 0.173$ and 0.204 , respectively). There was a significant sex effect at this stage, with females having a higher RMR than males (0.249 ± 0.007 versus 0.223 ± 0.006 W for birds of the same adjusted mean mass), but no effect of brood size or family identity. The average RMR did not differ at 30 days among the four treatment groups (figure 2, table 2). There were no sex differences, but both family identity and brood size were significant (with RMR being lower in larger broods; table 2).

Figure 2. Resting metabolic rate (W g^{-1}) of zebra finches in relation to early diet (see figure 1 and text for description of diets). Energy consumption is shown per g of body mass for illustrative purposes, but all the analyses were based on consumption per bird, with body mass included as a covariate. The measurements of metabolic rate were made when the birds were (a–c) 15, 30 and 200 days old before any diet switch (H, high-quality diet; L, low-quality diet; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, see table 2 for statistics). (filled circle, HH; open circle, HL; filled triangle, LH; open triangle, LL; filled square, H; open square, L).

However, by adulthood there was a highly significant difference in adult metabolic rate among the treatment groups (table 2, figure 2), with birds from the LH group having a markedly higher RMR than those from the other three groups (0.330 ± 0.007 versus 0.287 ± 0.008 (HH), 0.285 ± 0.008 (HL), 0.277 ± 0.009 (LL) W, values adjusted for other significant effects; table 2 and pairwise comparisons, $p < 0.001$). Independent of the effect of diet group, the sex difference in RMR persisted into adulthood, with females again exhibiting a slightly higher RMR value than males (0.303 ± 0.006 versus 0.284 ± 0.006 W). The effect of family identity also persisted, but there was no independent effect of brood size during rearing on adult metabolic rate. Since the LH birds differed from the other three treatment groups primarily in having undergone catch-up growth, the association between growth rate and adult metabolic rate was investigated further by adding the gain in body mass between 15 and 30 days to the analysis. The significance of the effects of diet group, adult body mass, family and sex as shown in table 2 remained at the same level ($p < 0.001$, $p < 0.001$, $p = 0.007$, $p = 0.037$, respectively), but mass gain during days 15–30 had an additional independent effect such that the faster the growth during this period, the higher the adult RMR ($p = 0.022$). There was no interaction between diet group and mass gain ($p = 0.661$).

4. DISCUSSION

The diet manipulations were successful in creating significant differences in the growth trajectories of the birds (figure 1). Those initially on a low-protein diet showed early growth retardation and were smaller in mass at 15 days of age. However, while all the birds reached the same mass at adulthood, the pattern of compensation differed according to the dietary schedule. The LH group went through a period of rapid

catch-up growth when transferred from the low-protein diet to the high-protein one. Such a growth acceleration did not occur in the other groups, and instead the LL and HL birds grew at a very slightly higher rate over a protracted period when given access to higher quality food. As a consequence, birds in the four treatment groups reached the same adult mass at 200 days but by different growth trajectories. Such compensatory responses have also been noted in wild animals subjected to natural perturbations to growth, such as are caused by short-term weather fluctuations (Kunz & Ekman 2000; Bjørndal *et al.* 2003; Bize *et al.* 2006).

The dietary switch itself did not appear to induce any short-term metabolic adjustments to changing nutritional conditions, since there was no difference in RMR among the treatment groups when this was measured at 30 days. Rather, the RMR differences were manifest in adulthood, at approximately 170 days after all the birds had been transferred to the same diet, and when they all had the same average mass; the RMR of birds in the LH treatment group in adulthood was between 16 and 19% higher than that of birds in the three other diet groups. That the difference in adult metabolic rate occurred only in the LH group demonstrates that it is associated with the group having experienced a growth acceleration, rather than simply a dietary switch during development or a poor quality diet throughout growth, as experienced by the HL and LL birds, respectively. Moreover, since body mass gain between 15 and 30 days had an effect on adult RMR independently of dietary treatment, adult metabolism seems to be influenced by both the rate of growth acceleration and the protein content of the diet during the late chick stages of development (suggesting the existence of a sensitive period, since there was no effect of the HL diet on RMR).

Growth acceleration may sometimes be associated with reduced metabolic costs during growth itself (Yambayamba *et al.* 1996; Bayne 2000), because one contribution to a faster rate of tissue growth is a reduction in (energetically expensive) protein turnover (McCarthy *et al.* 1994; Samuels & Baracos 1995). In other situations, faster growing animals have greater rates of resting metabolism (McKenzie *et al.* 2003), possibly due to an increased state of readiness to engage in those behaviours (e.g. aggressive or foraging activity) that help to increase food intake and thus fuel the faster growth rate (Herbert *et al.* 2001). It might be suggested that the behavioural modifications proposed to explain the changes in metabolic rate induced by alterations of family size (Verhulst *et al.* 2006) could also be responsible for the differences observed at 15 days in the present study. In this scenario, L diet birds would be more aggressive so as to allow compensation for the lower levels of protein in their diet by acquiring more food. However, a higher rate of begging or aggression is unlikely to be a major factor in metabolic rate modification in the present study, because there was no difference in the metabolic rate at 30 days, when the rates of growth differed mostly between treatment groups and when LH birds should have exhibited the highest begging activity. Furthermore, at the time that the adult measurements were made, the birds had already been on the same ad libitum diet for 170 days, and there was no independent effect of the brood size on adult metabolic rate. Nor can the higher adult RMR of LH birds be

attributed to a higher body mass, since there were no differences in mass between treatments at the time of the metabolic measurements.

A more probable explanation lies in the effect of changing levels of nutrition on developmental processes. Protein restriction can create disproportionate rates of growth in different organs (Desai *et al.* 1996), thus leading to differences in relative organ size, even at adulthood despite full compensation in terms of overall body size. In turn, this could create the observed variation in metabolism, since variation in the relative size of the most metabolically active organs (such as the liver and digestive tract) has been shown to be responsible for some of the inter-individual variation in RMR (Piersma *et al.* 1996; Speakman & McQueenie 1996; Selman *et al.* 2001), although these patterns do not always hold (Burness *et al.* 1998).

Alternatively, the differing levels of protein in the early diet may have caused changes in developmental programming. Eriksson *et al.* (2002) suggested that differential programming of the sympathetic nervous system due to early nutrition (Young & Morrison 1998) was the cause of a correlation between birth size and adult RMR in humans, but little is known of this effect (although this study did not control properly for variation in adult body size). The most probable explanation is via effects on intermediary (especially protein) metabolism that can persist into adulthood (Desai *et al.* 1995). The protein pool of the organism is submitted to a constant cycle of degradation (protein catabolism) and formation (protein anabolism) which controls muscle and enzymatic functions; individuals differ in the rate at which they break down and recycle existing protein (McCarthy *et al.* 1994), although the causes of this variation are unknown. In addition, dietary amino acids can be used as energy precursors as well as for structural somatic (muscle) or reproductive (vitellogenin) proteins; the relative balance of these alternate pathways of intermediary protein metabolism has recently been shown to underlie intraspecific variation in life-history trade-offs (Zera & Zhao 2006) and therefore may be subjected to early life modulation. The molecular basis behind the upregulation in metabolism during the development of endothermy is beginning to be unravelled (Walter & Seebacher 2007). An examination of how amino acid metabolism is programmed in these birds may reveal much about the mechanisms linking growth and metabolic rate.

The longer term consequences of this variation in metabolic rate will also be of interest since RMR is a major contributor to overall energy costs (Hulbert & Else 2004); a high RMR therefore increases the daily food requirement but may also allow a greater workload at peak times (Nilsson 2002). Moreover, RMR has been implicated in the rate of senescence. Rather counter-intuitively, rodents with higher rates of resting metabolism have been shown to have a longer average lifespan (Jackson *et al.* 2001; Speakman *et al.* 2004); the explanation appears to lie in their having greater mitochondrial uncoupling, which leads to a reduced rate of free radical production (and hence slower onset of senescence; Speakman *et al.* 2004). However, it remains to be seen whether the zebra finches in the present study which experienced a switch from a

low-protein diet to a high-protein one early in life subsequently have a longer lifespan (as a result of reduced oxidative damage (Speakman *et al.* 2004)) or a shorter one (due to catch-up growth prompting an increased incidence of metabolic disorders; Ozanne & Hales 1999; Langley-Evans & Sculley 2006).

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