Early Growth and Ageing


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Abstract
Effects of in utero and early life conditions on adult health and disease such as cardiovascular disease and type 2 diabetes are well documented by epidemiological and clinical observations. Animal models including intrauterine artery ligation, maternal restriction of iron, protein or general caloric intake, provide invaluable tools to understand mechanisms linking early growth and later diseases in adult life. In addition, the rodent model of maternal protein restriction has revealed that longevity can be influenced either positively or negatively by early growth patterns. Recent rapid advances in the ageing field using model organisms involving caloric restriction and genetic mutation as well as gene overexpression demonstrated the importance of insulin/IGF-1 signaling pathways, oxidative damage and SIRT1 in the regulation of lifespan. Studies using rodent models of maternal protein restriction suggest that alteration in insulin metabolism, changes in expression of antioxidant defense systems and in levels of oxidative damage (including telomere attrition) may also play a key role in regulation of lifespan by the early environment. It is suggested that neuroendocrine systems and epigenetic modification may be the potential mechanisms underlying beneficial or detrimental effects of early growth on the regulation of lifespan. Further studies in this area are warranted.

Introduction
It is now well established that growth patterns in fetal and early postnatal life can have consequences on long-term health including risk of developing traditionally adult-onset diseases such as type 2 diabetes and cardiovascular disease. More recently, it has been demonstrated that early growth patterns can influence longevity. There is strong evidence from both human and animal studies that the environment and in particular nutrition play an important role in mediating these relationships.
Epidemiological Data

Barker [1] was the first to report relationships between fetal growth and adult disease using UK-based cohorts. The author demonstrated that there was a linear relationship between birthweight and risk of developing cardiovascular disease, type 2 diabetes and metabolic syndrome. The increased risk of disease was substantial in low birthweight individuals with the lowest birthweight individuals being at 6-fold increased risk of type 2 diabetes and at 18-fold increased risk of the metabolic syndrome. It was subsequently demonstrated that the relationship between birthweight and type 2 diabetes occurred in monozygotic twins [2]. The genetic identity of monozygotic twins suggests that the relationship between early growth and type 2 diabetes can be independent of genotype.

Thrifty Phenotype Hypothesis

In light of the epidemiological observations, it was proposed that early nutrition played a key role in mediating the relationships between early growth and adult disease. Hales and Barker termed this the ‘Thrifty Phenotype Hypothesis’ [3]. They proposed that in response to impaired nutrient supply, the growing fetus will make adaptations in utero in order to maximize metabolic efficiency regarding the storage and usage of fuels, to increase chances of immediate survival postnatally. This included sparing the growth of the brain at the expense of other tissues such as the endocrine pancreas as well as programming metabolism in a manner that promoted fuel storage. The programming of such a phenotype would continue to be beneficial if conditions of poor nutrition were extended into postnatal life. However, in the presence of adequate or plentiful nutrition, these adaptations become detrimental and predispose to the development of obesity and metabolic dysfunction.

Importantly, this hypothesis recognized that there are interactions between early growth and later nutritional exposure. Those that were growth restricted during fetal life, but subsequently grow rapidly and achieve a higher bodyweight, were most affected. These individuals typically had an increased adiposity in childhood and later adult life, and are insulin resistant [4].

Accelerated Early Postnatal Growth

The importance of rates of growth during early postnatal life has become apparent from a number of epidemiological studies. A study of 7-year-old South Africans revealed that those children with low birthweights but who
underwent rapid childhood weight gain had the worst glucose tolerance [5]. Similar deleterious effects of poor fetal growth followed by rapid postnatal growth have been observed in a cohort of Finnish men and women [6]. It was also observed that individuals who developed type 2 diabetes had below average birthweights but above average heights at age 7 and age 15. This again suggests that the increased risk of diabetes associated with small size at birth is further increased by high growth rates in childhood. Rapid growth during early life has also been associated with increased risk of cardiovascular disease. A study in Finland showed that the highest death rate from coronary heart disease occurred in men who were thin at birth but whose weight caught up postnatally such that they had an average or above average body mass from the age of 7 years [7].

Animal Models

A large number of animal models have been established to investigate the mechanisms underlying the relationship between early growth patterns and longer-term metabolic health. Despite the differences in model design, the resulting metabolic outcomes in these models are remarkably similar. This suggests that disruption in fetal and early growth may act through common mechanisms to produce the adult phenotype. However, few of these have focused directly on effects on ageing and longevity.

Global Caloric Restriction

A reduction in maternal caloric intake, of varying severities, has been widely used to induce intrauterine growth restriction (IUGR) in both rodent and other large animal models. In one relatively severe model, pregnant rat dams restricted to 30% of ad libitum intake during gestation produce offspring that are hyperphagic, hyperinsulinemic, develop obesity and hypertension and exhibit reduced activity levels [8]. In a more moderate model, food restriction to 50% of control intake in rat dams from day 10 of pregnancy also resulted in low birthweight offspring. These studies identified that low birthweight animals, cross-fostered to and suckled by control-fed dams, undergo early catch-up prior to weaning. In adulthood, these offspring displayed an increased bodyweight, adiposity and had raised circulating leptin concentrations compared with control animals. Similarly, a persistent reduction in β-cell mass in the pancreas has been demonstrated in offspring of 50% food-restricted rat dams, indicating that inappropriate development of the endocrine pancreas is likely causal in the later glucose intolerance and insulin-deficient phenotypes [9].
Intrauterine Artery Ligation

A disruption in blood flow to the fetus, causing uteroplacental insufficiency, is the most common cause of IUGR in human pregnancy in developed countries. Experimentally, this can be induced through ligation of the uterine arteries, in either a unilateral or bilateral manner. In the rat, offspring develop a diabetic phenotype, associated with reduced insulin secretion and decreased insulin action. Recent studies suggest that this is related to a progressive change in the epigenetic regulation of the transcription factor Pdx1 postnatally, leading to a permanent decrease in the expression and function of this transcription factor [10].

Hypoxic Model

Reduced oxygen delivery during fetal life has profound effects on the development of the cardiovascular system and increases risk of hypertension and heart disease in later life. Exposure to a hypoxic environment (9.5% oxygen compared with ~21% in normoxic conditions) has been reported to induce severe IUGR and to affect both litter size and offspring weight at birth [11]. In neonatal offspring of rat dams exposed to chronic hypoxia during pregnancy, heart weights were increased. Offspring displayed increased blood pressure and reduced recovery from ischemia/reperfusion events, which would be expected to predispose to increased risk of cardiovascular events in later life [12].

Maternal Iron Restriction

Maternal anemia is common during human pregnancy, and has long-term detrimental effects on offspring health, including increased risk of cardiovascular events and behavioral and learning problems. Experimental manipulations in which rat dams are iron-restricted during pregnancy gives rise to offspring of low birthweight who have increased heart weights at birth and exhibit hypertension in later life [13].

Glucocorticoid Overexposure

An overactive hypothalamic-pituitary-adrenal (HPA) axis is one feature that is common in growth-restricted humans, with low birthweight individuals having higher circulating cortisol levels in adulthood compared with those of normal birthweight [14]. Thus, high levels of glucocorticoid (GC) exposure are associated with fetal growth retardation. In both human
pregnancy and experimental animals, fetal GC concentrations are determined not only by circulating maternal levels, but also by placental conversion of active GC to inactive forms, by the placental 11β-HSD2 enzyme. It has been demonstrated that birthweight is directly related to the expression and function of this enzyme, with low levels of 11β-HSD2 resulting in an increase in GC exposure and a reduction in birthweight. Treatment of pregnant rat dams with dexamethasone, a synthetic GC able to freely cross the placenta induces fetal growth restriction [15]. This manipulation results in a significant reduction in birthweight, and subsequent outcomes include disrupted glucose homeostasis and increased blood pressure [15].

Maternal Protein Restriction

The rodent maternal low protein (LP) model is possibly one of the best-characterized animal models used to investigate the effects of early growth on long-term metabolic health. It produces offspring with a phenotype very similar to that of the human metabolic syndrome [16]. The model involves feeding either a control diet (C), containing 200 g/kg protein, or an isocaloric diet having reduced 80 g/kg protein, to female rodents during pregnancy and/or lactation. Growth restriction during gestation gives rise to offspring with a reduced birthweight, and if the LP diet is continued throughout lactation, these animals remain permanently smaller even when weaned onto a control diet. We have shown a wide range of programmed metabolic disturbances arising from these early life dietary manipulations. In general, offspring of LP dams show improved glucose handling capabilities in early adult life, but undergo a greater age-related decline in glucose tolerance and have alterations in insulin signaling pathways in muscle and adipose tissue [17].

In an extension of this LP protocol, crossover groups have been included to assess the differential effects of reduced growth at different stages of early development. The crossing of LP offspring to control-fed dams for the period of lactation results in a rapid growth during this period (recovered offspring), and conversely crossing control offspring to LP fed dams during lactation (postnatal low protein; PLP animals) slows growth and permanently reduces body size. One of the most striking findings was that rapid growth during lactation significantly reduces lifespan in male rats, whereas a slowing of growth during this period increases longevity [18]. More recently, the LP crossover model was applied in mice and these studies again replicated these findings on lifespan [19], and in addition showed that PLP animals are resistant to weight gain when given access to a highly palatable diet from weaning [20], suggesting programmed changes in energy balance systems.
Mechanisms Linking Early Growth and Ageing

The mechanistic basis by which early growth rates affect longevity remained largely unknown. However, recent advances in research into molecular mechanisms underlying the regulation of ageing process in model organisms provide insight into candidate mechanisms.

Caloric Restriction and Ageing

It has been consistently demonstrated that caloric restriction (CR) increases lifespan in both invertebrates and vertebrate animals. In rodents, CR – typically 60 or 70% of the amount of food consumed by the ad libitum-fed littermates – robustly extends lifespan whether it is started early or later in life [21]. One mechanism by which protein restriction during lactation increases longevity could therefore be through a programmed reduction in food intake. PLP offspring have a permanently reduced food intake and like caloric restricted animals are small in body size and have reduced insulin levels. The mechanisms by which CR increases longevity have not been fully elucidated. However, one molecule that has been suggested to play a pivotal role in CR animals is SIRT1. SIRT1 is an NAD-dependent histone deacetylase which can regulate metabolism in multiple tissues by regulating the activities of critical transcription factors such as FOXO1, PPARα, PPARγ and PGC-1α [22]. Transgenic mice overexpressing SIRT1 showed a phenotype resembling CR [23]. Interestingly, a recent study revealed that SIRT1 is recruited to double-strand breaks and is required for efficient DNA repair [24]. Our recent studies revealed that SIRT1 was also increased in PLP offspring, further demonstrating the phenotypic similarity between these animals and CR models [25].

Insulin/IGF-1 Signaling Pathways and Ageing

Disruption of genes involved in the insulin/IGF-1 signaling pathways can increase lifespan. Such increase in lifespan can be observed in both invertebrate and vertebrate species, implying that the molecular mechanisms governing lifespan are highly conserved [26]. Female mice heterozygous for the IGF-1 receptor gene disruption live longer [26]. Paradoxically, long-lived humans and rodents generally demonstrate increased insulin sensitivity. However, this may reflect the divergent actions of insulin including mitogenic and metabolic pathways. PLP rat kidneys have significantly increased expression of insulin receptor, Akt1 and Akt2 as well as increased phosphorylation at Ser473, indicative of increased sensitivity to the metabolic actions of insulin [25]. Although recuperated rats also showed increased expression of Akt1 and Akt2, there was no increase in phosphorylated Akt, suggesting impaired Akt phosphorylation and therefore insulin action in these animals [25]. Thus, it is clear that alterations in early growth rate, influenced by maternal nutrition, can lead to changes in the expression of insulin-signaling molecules and whole body insulin sensitivity very early in life, which may eventually affect lifespan.
Oxidative Stress, Telomeres and Ageing

The oxidative stress theory of ageing (also known as the free radical theory of ageing) suggests that reactive oxygen species are produced during normal metabolism and can cause oxidative damage to DNA, proteins and lipids. This can cause cellular senescence/apoptosis and ultimately contribute to the ageing process. The importance of antioxidant defense systems and DNA damage in regulating lifespan has been supported by the observation that mice with enhanced expression of the antioxidant enzyme catalase live longer, whereas mutation in genes responsible for DNA repair or genetic manipulation that causes mitochondrial DNA damage result in premature ageing [27].

Telomeres are tandem repeats of the sequence TTAGGG located at chromosomal ends. Telomere DNA-binding proteins, which recognize and bind to these sequences, are thought to protect chromosomal ends from being recognized as broken DNA ends. In somatic cells, due to the lack of telomerase expression, the length of telomeres shortens with each cell division/DNA replication. Critically shortened telomeres can trigger cellular senescence [28]. The G-rich nature of the telomeric DNA repeats renders them particularly susceptible to oxidative damage. It has been shown that single-stranded breaks preferentially accumulate in the telomeric regions under conditions of oxidative stress, which eventually can cause accelerated telomere shortening [28]. Conditions of increased oxidative stress can therefore lead to increased telomere shortening and premature cell senescence. Although cellular senescence is an essential tumor suppression mechanism, it can contribute to ageing by compromising tissue homeostasis and function. Telomere shortening is associated with ageing and age-related pathologies. Thus, although it still remains to be determined as to whether telomere shortening is a cause or a consequence of ageing, telomeres can serve as biomarkers of ageing and age-related diseases.

We have demonstrated extensive effects of early growth and nutrition on rates of telomere shortening and antioxidant defense capacity. Age-dependent telomere shortening is slowed in kidneys and aortic tissues of long-lived PLP rats. In contrast, recuperated animals demonstrate accelerated telomere shortening in kidney, aorta and pancreatic islets. These differences in telomere length are accompanied by differences in expression of antioxidant enzymes. Expression of a number of antioxidant enzymes is increased in PLP animals and can be detected as early as weaning in some tissues. Therefore, PLP rats seem to experience less oxidative damage, presumably through the enhanced expression of the antioxidant defense system, resulting in less single-strand breaks in telomeric regions and reduced telomere shortening [29]. Conversely, recuperated rat offspring demonstrate age-associated impairment of antioxidant defenses. In addition, increased expression of p21 and p16 was observed in recuperated animal tissues [29]. Upregulation of p21 and p16 is associated with the process of cellular senescence and p16 has been recently identified as a biomarker of ageing [30]. It is therefore conceivable that accelerated growth may lead to compromised antioxidant defense sys-
Chen/Cottrell/Ozanne

Fig. 1. Potential mechanisms linking early growth and lifespan. Growth during early life can be influenced by maternal nutrition and health as well as postnatal dietary conditions. Normal fetal development followed by slow postnatal growth is associated with increased lifespan, whereas in utero growth restriction followed by rapid postnatal catch-up growth leads to shortened lifespan. It is suggested that in animals of normal birthweight, slow growth during early life reduces oxidative stress, due at least in part to enhanced antioxidant defense systems, and delayed cellular senescence. This may lead to improved metabolism and immunity which ultimately contribute to increased longevity. Conversely, rapid catch-up growth of low birthweight animals will result in increased oxidative stress, possibly due to impaired antioxidant defense systems, and accelerated telomere shortening. This may lead to accelerated cellular senescence and/or apoptosis which in turn can cause compromised metabolic profiles and impaired cardiovascular functions (common adult diseases) and ultimately premature ageing and early death. Neuroendocrinological change and epigenetic modification indicated in the ‘black box’ are potential mechanisms underlying the beneficial or detrimental effects brought about by the altered early growth.

tems, increased oxidative stress, accelerated telomere shortening and cellular senescence and ultimately shortened lifespan.

Conclusion

Effect of in utero and early life conditions on adult health and disease is well documented by epidemiological and clinical studies. Animal models provide
Invaluable tools to understanding mechanisms linking early growth and later diseases in adult life. In addition, the rodent model of maternal protein restriction has revealed that longevity can be influenced either positively or negatively by early growth. Recent rapid advances in the ageing field using model organisms involving CR and genetic mutation as well as gene overexpression demonstrated the importance of insulin/IGF-1 signaling pathways, oxidative damage and some key molecules such as SIRT1 in the regulation of lifespan. Studies using rodent models of maternal protein restriction suggest that alteration in insulin metabolism, changes in expression of antioxidant defense systems and in levels of oxidative damage (including telomere attrition) may play a key role in regulation of lifespan. As proposed in figure 1, changes in neuroendocrine systems and epigenetic modification may be the potential mechanisms underlying the beneficial or detrimental effects of early growth on the regulation of lifespan. Further studies in this area are warranted.

References

Discussion

Dr. Mobarak: What was your definition of ageing in rodents?

Dr. Ozanne: We ultimately measured the lifespan, but telomere shortening is a surrogate measure of ageing at the cellular level, and p16 is probably the best biomarker of cellular ageing that there is [1], so we have both the actual longevity data [2] as well as the cellular differences [3].

Dr. Makrides: Thank you very much for a wonderful presentation. I just wanted to ask for some clarification about the 8 and 20% diets. I am not familiar with rat diets, so I wanted to know whether the percentages are weight percent or the percentage of energy. If it is the percentage of energy, what is it that actually went up when the protein went down? If weight percent then did the low-protein animals also have a lower energy intake?

Dr. Ozanne: The percentages are percentages by weight, and so when something goes down, something else has to go up, so they have increased carbohydrate compared to the controls.

Dr. Hüppi: I was particularly fascinated by the change in oxidative protection in the offspring that were suckled by a growth-restricted mother. Do you have any speculation on how this antioxidant protection gets to the neonate? Is it by milk?

Dr. Ozanne: It’s a very good question and the answer is that we don’t know. We don’t have milk composition data, so we know that the mothers have reduced protein, but we don’t know whether that is reflected by reduced protein in the milk. It may or
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it may not be as dramatic, there may be more effects on some amino acids than others, so what the signal is between the mother and the pup, we don't know. We don't know the mechanisms by which they increase their antioxidant defense enzymes, but it's a permanent effect because the expression data I showed were from the animals when they were 12 months of age.

Dr. Haschke: My question addresses the different protein needs of animals and humans. If you look at breastfed infants, the percentage of energy consumed as protein would be 10%. Can you elaborate what means 20 or 8% for the animals?

Dr. Ozanne: Twenty percent is the standard protein content of an experimental rodent diet. The literature suggests that for a pregnant rat, the minimum protein requirement is 12%, so the 8% is only modestly below the recommended protein content of a pregnant rat diet.

Dr. Ziegler: What do you know about the central nervous system of your animals?

Dr. Ozanne: We haven't looked at that at all, so we don't have any data on the central nervous system.

Dr. Cooke: When you feed a low-protein diet and a relatively high energy diet, what happens to body composition of these animals?

Dr. Ozanne: The recuperated animals have increased fat mass, and the postnatal protein animals have dramatically reduced fat mass.

Dr. Wainaina: In pediatrics, we are worried when the catch-up growth doesn't occur by 6 years. When you are talking about animals, how can you extrapolate this to humans?

Dr. Ozanne: I think we have to be cautious in extrapolating the findings from animal models to humans, so in the rodent context it's them catching up to the same weight as the control animals, we are not looking at the crossing of centiles. In terms of the mice when they were cross-fostered, they caught up by 1 week of age, so it's a very early accelerated growth.

Dr. Domelöff: What do these rodents die of? What is the cause of death really, you said they don't have atherosclerosis.

Dr. Ozanne: Mice don't get atherosclerosis because of their lipid profile. The most common cause of death is kidney failure, and so the recuperated animals are more albuminuric than the controls and the postnatal low protein animals are less albuminuric; so, it's consistent with them having differences in renal function but we don't know exactly whether that's the cause of death or not.

Dr. Ziegler: I know the low-protein model is the most widely used to produce prenatal growth reduction, but I wonder how good a model is it for human intrauterine growth reduction which is mostly due to placental dysfunction. Is it really protein that's limiting human fetal growth or is it something else?

Dr. Ozanne: Two answers to that; firstly, a recent study by Olsen et al. [4] in Denmark showed that maternal daily protein intake correlated with birthweight in a contemporary human cohort. Secondly, we are using the low protein model as a model and in all those models that I listed, the phenotype is very similar, so it would appear that there are some fundamental mechanisms operating when a fetus is in a suboptimal environment. We don't know the precise driver of that response. It could be differences in insulin, differences in glucocorticoids, so we are not using the model because we think it's only protein that's causing low birthweight in humans but simply because as a model it's causing a phenotype which is very similar at the whole body and molecular level to what we see in low birthweight humans.

Dr. Nem Yun Boo: In some developing countries such as African countries or India, small for gestational age is very common. Based on all the studies of antenatal starvation and postnatal deprivation, theoretically we should see more diabetes, atherosclerosis, hypertension in all these countries when they experience overnutrition.
Dr. Ozanne: I think that’s exactly the point; to establish the detrimental effects, you need postnatal overnutrition or certainly adequate nutrition to conflict with what is happening in utero. So if you are in a nation where you are born small but then you continue to grow slowly postnatally you are fine. It is in populations going through the transition from a relatively poor diet to rich western diet where type 2 diabetes and cardiovascular disease are increasing.

Dr. Cooke: Do you see any sex differences?

Dr. Ozanne: In rats like in humans, the males live shorter than the females. The data I showed you was from males; we see similar effects in females but everything is shifted to a slightly longer lifespan. At the same age, female rat telomeres are longer than male rat telomeres [5].

Dr. Lucas: I would quite like you to explore a little bit more if you could this business of extending lifespan in animal models. When I gave my presentation I pointed out that we tended to ignore the possibility that public health and clinical interventions could shift the theoretical biological lifespan of humans to the right, we just focus more on increasing the chances of getting there. The studies of McCay and perhaps also your studies in Nature could be interpreted by saying that you would not extend the lifespan but you would actually reduce lifespan in those who had rapid postnatal growth. So are there actually models where you extend the expected biological lifespan of experimental animals and can that give us any clues to what could be done in a human population?

Dr. Ozanne: Certainly, from animal models of permanent caloric restriction, so by restricting to usually between 70 and 60% of ad libitum intake, it is possible to increase both median and maximum lifespan [6, 7]. Obviously, that’s quite a big reduction in ad libitum food intake, and I think trying to introduce that into a human population would be extremely difficult, which is why people are looking more at caloric restriction mimetics [8]. In terms of the programming effects on longevity, the animals that were born small and experienced catch-up growth have a reduced median and maximum lifespan, but the animals who have an increased average lifespan don’t have an increase in maximum lifespan [9].

Dr. Lucas: When you study risk markers for cardiovascular disease in humans, the inference is that you’ll then go on to get cardiovascular disease or have an increased chance of doing so, but since the laboratory animals that you study don’t actually go on to get atherosclerotic disease what do these risk markers mean, I mean what do the components of a metabolic syndrome actually mean in a rat?

Dr. Ozanne: As I said before, rodents don’t get cardiovascular disease unless you put them on a genetic background that makes them susceptible. They develop insulin resistance, and the most insulin-sensitive ones are the ones that live longer. It’s known in human populations that the centenarians are very insulin sensitive [10], so a good insulin sensitivity also seems to be a good marker of a long as well as healthy lifespan.

Dr. Hüppi: What happens if you continue to feed the offspring by the growth-restricted mother, you don’t cross-foster, does that correct the oxidative stress situation or are they reverting then to your sort of recuperating group?

Dr. Ozanne: We haven’t looked in terms of the oxidative stress markers; however, it does eliminate the effect on the lifespan [11].

Dr. Ke: Is it really protein deficiency, energy deficiency or energy excess that is important, and are there any models in this respect?

Dr. Ozanne: In our model, the caloric intake of the mothers is identical in the two groups, but there are models where people have looked at caloric restriction during pregnancy and lactation, and that also causes a very similar phenotype in terms of insulin resistance, glucose intolerance, hypertension, so I think all the different models seem to induce a very similar phenotypic outcome.
Dr. Nem Yun Boo: Regarding the postnatal low-protein diet of animals when compared to controls, do you test the neurodevelopmental function? If these animals live longer, are they able to function better or worse?

Dr. Ozanne: I think they function metabolically very well because they have increased insulin sensitivity, they have reduced albuminuria, they have increased adiponectin, their cholesterol levels are reduced compared to controls, so everything about their profile suggests that they are living longer and are living longer healthily as well.

Dr. Nem Yun Boo: My question was, do they have a better neurological functioning?

Dr. Ozanne: We haven’t done any behavioral studies on them, but there is nothing obvious to suggest that they are depressed.

Dr. Lucas: In my presentation earlier and no doubt in the talk to Dr. Singhal’s presentation an argument is put forward that postnatal growth is more influential than fetal growth in terms of later risk factors for heart disease, and in fact you could potentially explain the fetal origins hypothesis in terms of postnatal catch-up growth. Can you apportion the fetal vs. postnatal influences in some kind of approximate way in a rodent model. I mean is that looking similar to the humans?

Dr. Ozanne: In the rodent models of low birthweight, they catch up, so as well as being in utero growth restricted they are growing rapidly during the early postnatal period, so dissecting between the two is actually quite difficult. It’s not easy to stop the catch-up unless you place them into a very large litter.

Dr. Lucas: What about feeding them badly both prenatally and postnatally?

Dr. Ozanne: If you feed them the low-protein diet prenatally and postnatally, they get a diabetic phenotype [12]. However, feeding the low-protein diet during pregnancy and lactation has no effect on their lifespan, so the two periods seem to cancel each other out, but they do get a diabetic phenotype.

Dr. Rosenfeld: I am surprised that you haven’t discussed the potential role of the IGF system in your model because in addition to animal models such as the ones you have described, there are numerous animal models of congenital growth retardation associated with various defects in the growth hormone-IGF axis that are also associated with comparable longevity. It seems to me that that’s a potential unifying theme between the nutritional models and the growth models.

Dr. Ozanne: We focused on insulin because we originally came from a diabetes perspective. Interpreting plasma IGF-I data is complicated by the different binding proteins, but I agree that it would be an interesting area to address.

References


