

**Plenary Session / EC – US Workshop: Early life programming of obesity
Lecture 3: Programming of the appetite regulatory system**

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Abstract

It is well established through epidemiological studies in humans that there is a relationship between poor fetal growth and subsequent development of type 2 diabetes, obesity, insulin resistance and other features of the metabolic syndrome. The detrimental effect of poor early growth is exaggerated if it is followed by accelerated postnatal growth. For example it has been shown that those children born small for gestation age but who then grew rapidly during early postnatal life were fatter later on in childhood. In contrast slow growth during the lactation period appears to be protective against future obesity and metabolic disease independently of growth *in utero*. It has also been shown that the degree of weight gain during the first week of life in humans associates positively with later obesity. The mechanistic bases of these relationships are not understood. However, accumulating evidence has emerged over the last 15 years to suggest that early environmental factors, such as nutrition, play an important role. It has been suggested that these effects arise through permanent (programmed) changes in tissue structure and function. Studies of individuals who were *in utero* during the Dutch Hunger Winter have shown a direct relationship between maternal nutrition, glucose tolerance and obesity in the offspring. Further support for the importance of the fetal environment has come from studies of monozygotic twins who were discordant for type 2 diabetes. These revealed that the diabetic twins had significantly lower birth weights than their non-diabetic co-twins. In addition, it has been demonstrated that breast-fed infants, who in general experience a lower plane of nutrition compared to formula-fed infants are at reduced risk of obesity and cardiovascular disease.

A number of animal models have been established to investigate the mechanisms by which the early environment influences long term risk of obesity and metabolic health. The most extensively studied is the maternal low protein model where rodents are fed a low (8 %) protein diet during pregnancy and/or lactation and the offspring compared to those from dams fed an isocaloric 20 % protein diet. Both control and low protein offspring are weaned onto the same standard laboratory chow fed *ad libitum*. This maternal dietary manipulation leads to a low birth weight and offspring development many features of the metabolic syndrome including type 2 diabetes. The glucose intolerance is associated with β cell dysfunction and insulin resistance. The insulin resistance is accompanied by changes in expression of key components of the insulin-signalling cascade including protein kinase C ζ and the p110 β (catalytic) subunit of PI 3-kinase in muscle and adipocytes. Similar differences in insulin signalling protein expression are observed in tissue biopsies from young men who had a low birth weight. Cross fostering studies have enabled more defined critical time windows to be identified. If offspring born to low protein-fed dams are suckled by control dams during the lactation period, they undergo rapid postnatal growth. These "recuperated" offspring gain excess weight when weaned onto standard laboratory chow and are more susceptible to diet-induced obesity. They also have a substantially reduced longevity. In contrast offspring of control dams that are suckled by low protein fed dams grow slowly during lactation, gain less weight when weaned onto standard laboratory chow are resistant to diet induced obesity and have an increased longevity.

The differences in susceptibility to weight gain observed in the maternal low protein model are associated with changes in expression of hypothalamic genes such as the leptin receptor. Expression of ObRb, the signalling form of the leptin receptor is increased in the arcuate nucleus of the hypothalamus of the obesity resistant animals exposed to protein restriction during suckling. It is known that leptin action has different effects in early postnatal life compared to during adult life. Whereas in adulthood the main action of leptin is metabolic (i.e. to reduce food intake and increase energy expenditure), in early postnatal life it has a neurotrophic action and no effect on food intake or energy expenditure. Programmed changes in leptin action may therefore mediate its effects through changes in both neuronal development and therefore structure as well as through regulation of energy balance. The fundamental molecular mechanisms by which a phenomenon that occurs very early in life has phenotypic consequence many years later are only just starting to emerge. These may include epigenetic mechanisms such as changes in DNA methylation or histone acetylation leading to programmed changes in gene expression.