EARLY LIFE ORIGINS OF THE INSULIN RESISTANCE SYNDROME IN THE AGED GUINEA PIG

A thesis submitted for the degree of
DOCTOR OF PHILOSOPHY

by

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November 2007
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ABSTRACT

In human populations, perturbed growth in early life and ageing have been identified as risk factors for the development of the 'Insulin Resistance Syndrome' (IRS). The consequences of restricted prenatal growth on postnatal function have been investigated using numerous experimental models of intrauterine growth retardation, mainly in the rat. These studies have shown that some, but not all aspects of postnatal function that are programmed in humans, are also programmed in the rat. In addition, few experimental studies have investigated the effect of perturbed postnatal growth on adult function, or whether ageing amplifies the effects of events in early life. Therefore this study was designed to determine firstly, whether the IRS develops with increasing age in the guinea pig as it does in the human, and secondly whether the development of this syndrome is more pronounced in aged offspring which have undergone spontaneous fetal growth restriction and accelerated growth in the neonatal period.

Whole body insulin sensitivity of glucose metabolism, subcutaneous adiposity and skeletal muscle mass were reduced, while visceral adiposity and fasting concentrations of plasma glucose, insulin, triglycerides and total cholesterol were increased, in aged (14 months) compared to young adult (4 months) guinea pigs. An increase in resting systolic, diastolic and mean arterial blood pressure and pulse pressure was also observed in offspring with increasing age.

Spontaneous fetal growth restriction in the guinea pig reduced size at birth, but increased the neonatal fractional growth rate for weight in male and female offspring. In aged female offspring, small size at birth was associated with decreased whole body insulin sensitivity of glucose metabolism, increased fasting concentrations of plasma glucose and insulin, impaired glucose tolerance and elevated resting systolic and mean arterial blood pressure, pulse pressure and heart rate. An increased neonatal fractional growth rate for weight was associated with elevated fasting concentrations of plasma glucose and triglycerides in aged females, while a low fractional growth rate for weight during the neonatal period increased resting systolic blood pressure. In aged male offspring, large size at birth was associated with decreased whole body insulin sensitivity of glucose metabolism and increased fasting concentrations of...
plasma insulin, while disproportionate fetal growth, as indicated by a low ponderal index at birth, was associated with increased fasting concentrations of plasma total cholesterol. A low fractional growth rate for weight during the neonatal period decreased whole body insulin sensitivity of glucose metabolism and increased fasting concentrations of plasma free fatty acids in aged males, while an increased neonatal fractional growth rate for weight was associated with elevated fasting concentrations of plasma triglycerides and raised resting pulse pressure and heart rate.

In conclusion, the guinea pig appears to be a suitable animal model of ageing, displaying many of the metabolic, cardiovascular and anthropometric changes seen in humans. Furthermore, the effects of perturbed prenatal and early postnatal growth on the development of the IRS in the aged guinea pig exhibit a sexually dimorphic pattern, however the mechanisms responsible for the emergence of this syndrome in a gender-specific manner remain to be determined.