Numerous studies have shown an association between low weight at birth (LBW) and risk of developing insulin resistance and Type 2 diabetes. Our twin studies indicated a non-genetic age dependent origin of insulin resistance and Type 2 diabetes associated with SGA. In order to gain insight into the molecular metabolic defects and mechanisms linking LBW with insulin resistance and other key organ metabolic defects involved in the pathophysiology of Type 2 diabetes, we performed different series of experiments in young and elderly twins, and in particular in young men (aged 19-23 years) with LBW defined as weight at birth at term in the lowest 10 percentile without any family history of diabetes. The control group of the LBW subjects included age matched men with birth weights at term in the upper normal range. While BMI and waist-to hip ratios was similar in the LBW and controls, DXA scan studies documented a higher degree of abdominal obesity in the LBW subjects. Using the gold standard euglycaemic hyperinsulinaemic clamp technique combined with glucose tracers and studies of forearm glucose uptake, we found an impairment of insulin stimulated glycolytic flux and reduced forearm (muscle) glucose uptake in the face of a normal whole body glucose uptake. In addition, we found a significantly decreased insulin secretion rate after oral glucose ingestion after correction for insulin action (disposition index), a paradoxical enhanced insulin suppression of hepatic glucose production and lower fasting plasma glycerol levels suggesting impaired lipolysis. Finally, analysis of skeletal muscle biopsies showed reduced muscle expression of several key proteins involved in insulin signalling and glucose transport including Protein Kinase C-Zeta, the two subunits (p85 and p110) of phosphoinositol-3-kinase and the insulin sensitive glucose transporter GLUT4 in the SGA subjects. In conclusion, LBW is associated with Type 2 diabetes in a non-genetic manner, and programming of multiple organ functions including muscle insulin action and signalling represents early mechanisms responsible for this association.