Cardiovascular Health

PHYS3008 Frontiers in Physiology

Programming Developmental Disease Risk

Intrauterine growth restriction involves a birth weight of less than $2.5\ kg$.

In the developed world, intrauterine growth restriction is most often caused by placental insufficiency.

intrauterine growth restriction can be caused by maternal undernutrition, and can be caused by maternal disease.

Intrauterine growth restriction involves adaptions that help the foetus to survive and that cause an increased adult disease risk of diabetes, obesity, osteoporosis, cardiovascular disease, and renal disease.

The majority of babies born small experience accelerated growth in the first six months of life, which is protective against the adult diseases associated with intrauterine growth restriction.

Intrauterine growth restriction is modelled in rats by bilateral uterine vessel ligation, which causes an altered maternal endocrine environment, impairs mammary development during pregnancy, triggers early lactogenesis, and reduces milk quality and quantity during lactation.

Restricted male rats have a greater risk of cardiovascular disease and renal disease than restricted female rats.

Restricted male rats have high blood pressure.

Restricted female rats have normal blood pressure.

Exercise training can restore pancreatic beta-cell mass in restricted rats.

Fostering restricted rats on control mothers causes early accelerated growth.

Pregnancy in stressed restricted female rats increases their risk of diabetes and renal disease, and causes transgenerational disease transmission.

The transgenerational transmission of nephron deficiency is not sustained postnatally.

The transgenerational transmission of high blood pressure, which is specific to male rats, is sustained postnatally.

Developmental Origins of Cardiorenal Disease

15% of birth size is genetically determined.

2% of birth size is sex-dependent.

Insulin-like growth factors, thyroid hormones, insulin, and glucocorticoids promote foetal growth.

Excess glucocorticoids inhibit foetal growth.

The placenta is involved in nutrient transport, endocrine production, immunity, and preventing excessive glucocorticoid exposure to the foetus.

For every foetal weight, there is an optimal placental weight.

Humans have a hemochorial placenta.

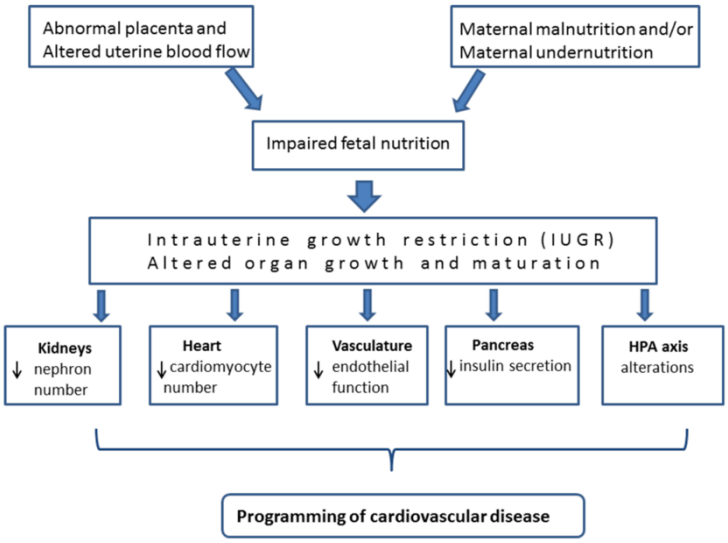
Rodents have a discoid placenta.

Sheep have a multicotyledonary placenta.

Cows, pigs, and horses have an epitheliochorial placenta.

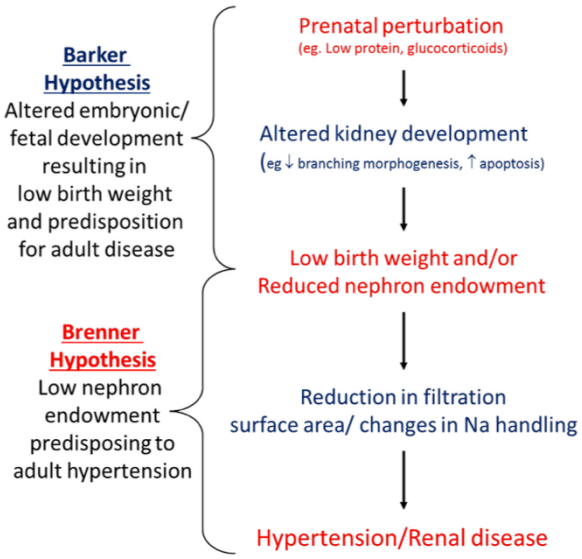
Intrauterine growth restriction can be modelled in rodents by maternal stress, hypoxia, hyperthermia, glucocorticoid administration, reduced maternal nutrient intake, or bilateral uterine vessel ligation.

Intrauterine growth restriction can be modelled in sheep by carunculectomy.



Programming of cardiovascular disease.

Adults that were born small have reduced nephron endowment, glomerular hypertrophy, and greater risk of kidney disease.



The Barker hypothesis and the Brenner hypothesis.

Males that were born small are at an increased risk of hypertension than females that were born small despite similar kidney deficits.

Leptin is a pro-inflammatory adipokine that activates the JAK-STAT pathway and the PIP3 pathway, and is involved in appetite suppression and increasing energy expenditure.

In all mammals, a leptin surge occurs following organogenesis.

Intrauterine growth restriction causes a reduced or delayed plasma leptin concentration during the post-organogenesis leptin surge.

Leptin administration post-organogenesis causes accelerated growth.

Fostering restricted rats on control mothers causes an increased plasma leptin concentration, accelerated growth, and normalised blood pressure.

Impact of Obesity on Next Generation

Obesity is a low-grade inflammatory condition that is clinically defined as a BMI greater than 30.

Obesity is associated with cardiovascular disease, diabetes, metabolic disease, and chronic kidney disease.

Adipocytes secrete cytokines, chemokines, and hormone-like factors.

Increased caloric intake causes adipocyte hyperplasia and adipocyte hypertrophy.

In advanced obesity, adipocytes undergo apoptosis, which recruits inflammatory cells and causes adipocyte dysfunction.

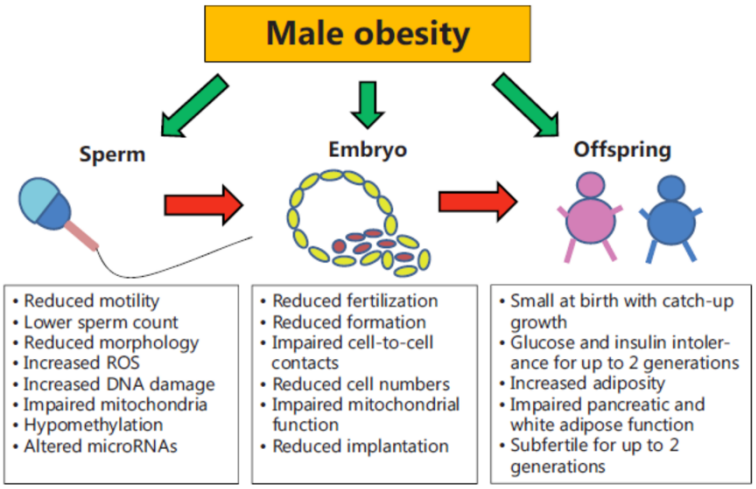
Being obese during pregnancy increases the risk of cardiovascular disease and diabetes in the mother.

Being obese during pregnancy increases the risk of obesity, cardiovascular disease, and diabetes in the offspring.

Obesity-related dysbiosis can cause an increased birth weight of offspring, which may be due to an increased microbe-derived plasma endotoxin concentration.

Breastfeeding, vaginal delivery, and maternal probiotic use can prevent dysbiosis in offspring.

Limited animal studies have demonstrated that offspring of obese fathers can develop metabolic syndrome and male infertility.



Effects of male obesity on offspring.

Disease outcomes in individuals that were born small are exacerbated with 'second-hits', which include a poor diet, old age, an unhealthy lifestyle, pregnancy, and being male.

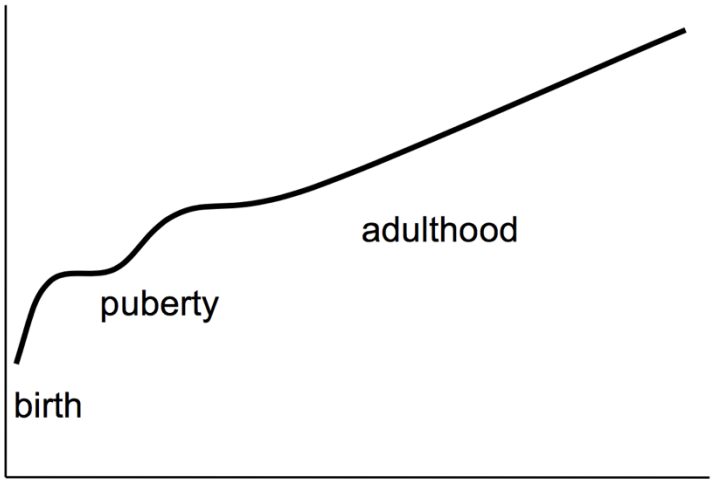
Male rats that were born small and consume a high-fat diet have exacerbated renal dysfunction.

Female rats that were born small and consume a high-fat diet have exacerbated glucose intolerance.

Preventing Genetic Destiny

50% of blood pressure is genetically determined.

Blood pressure is influenced by rare coding sequence alleles that can affect blood pressure by $5\ mm\ Hg$, and common non-coding alleles that can affect blood pressure by less than $1\ mm\ Hg$.

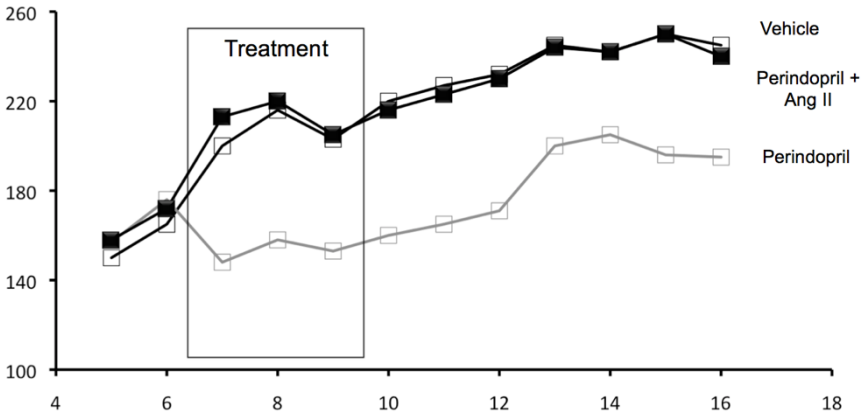


Lifetime blood pressure.

High parental blood pressure and high personal blood pressure early in life predisposes an individual to high blood pressure later in life.

High blood pressure is associated with high plasma renin concentration and high renal vascular resistance.

The divergence of the blood pressure of spontaneously hypertensive rats and control rats occurs around adolescence.



Effect of short-term renin-angiotensin system inhibition during adolescence on blood pressure in spontaneously hypertensive rats.

The long-term effect of short-term blood pressure reduction during adolescence on blood pressure is not observed when calcium channel blockers are used, and is not observed in all strains of hypertensive rat.

In human trials, a long-term effect of short-term blood pressure reduction during adulthood on blood pressure is not observed.

Interrogating the Coding and Non-Coding Genome

30% of essential hypertension is genetically determined.

Genome-wide association studies find associations between single nucleotide polymorphisms and phenotypes.

Microarrays can be used to detect single nucleotide polymorphisms.

Copy number variations can affect essential hypertension risk.

ncRNA regulates the transcription genes and the translation of mRNA.

RNA sequencing can be used to identify RNA.

Microarrays can be used to quantify RNA.

Searching for Genetic Clues

Searching for genetic clues can involve linkage disequilibrium mapping, linkage studies, association studies, transcriptomics, proteomics, bioinformatics, and systems biology.

Linkage disequilibrium studies determine the correlation between nearby alleles on the same chromosome.

Genome-wide association studies do not identify gene-gene interactions, gene-environment interactions, and rare coding variants.

Genome-wide association studies are prone to bias due to population stratification.