

# Investigating the physiological factors affecting development in early life

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## INTRODUCTION and AIMS:

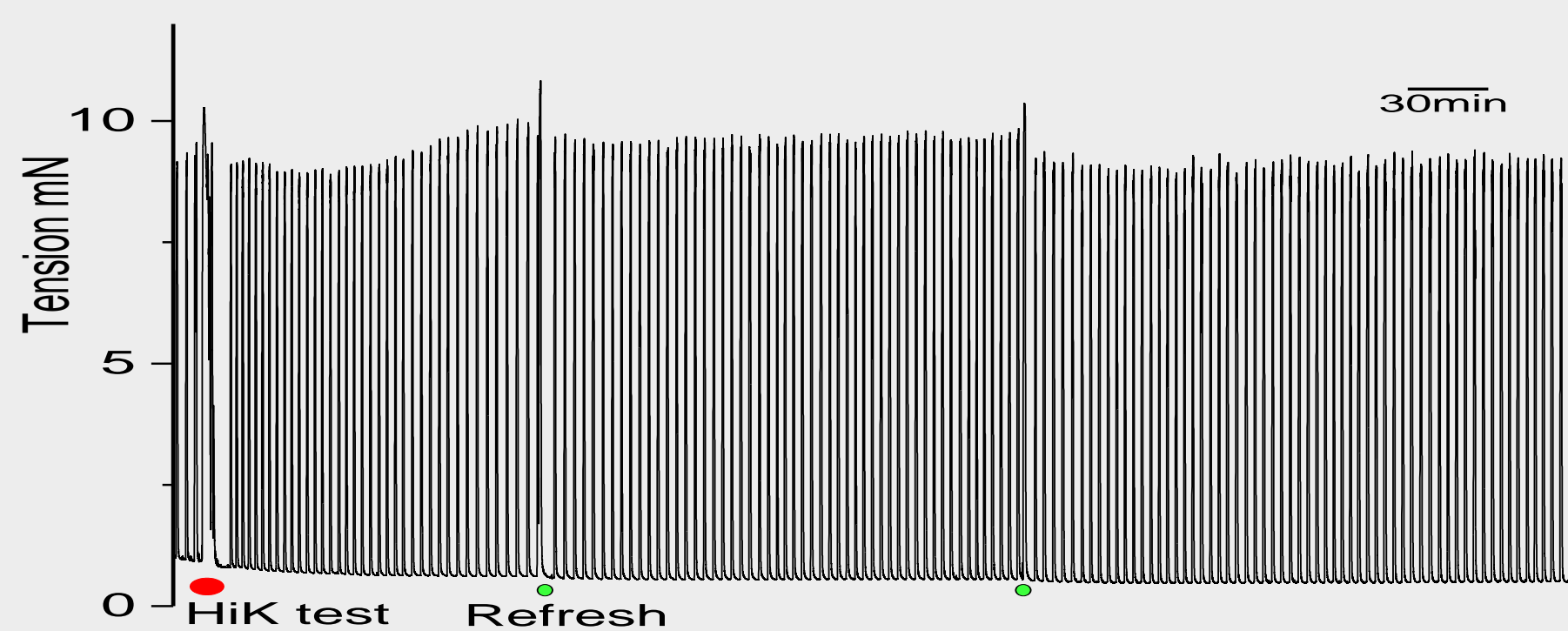
During the early stages of life, we are susceptible to physiological and environmental factors which, can occur *in utero* and can impact development, birth, and life post-partum. We investigated the way in which the uterine environment can impact the delivery of a fetus and how defects in fetal development can affect the life of the offspring after it is born. The two main aims of our studies were:

- To handle and effectively record data from sheep myometrial tissue under varying conditions and analyse the results.
- To electrically stimulate and record contractions from sheep renal arteries, to assess the link between renal agenesis and hypertension.

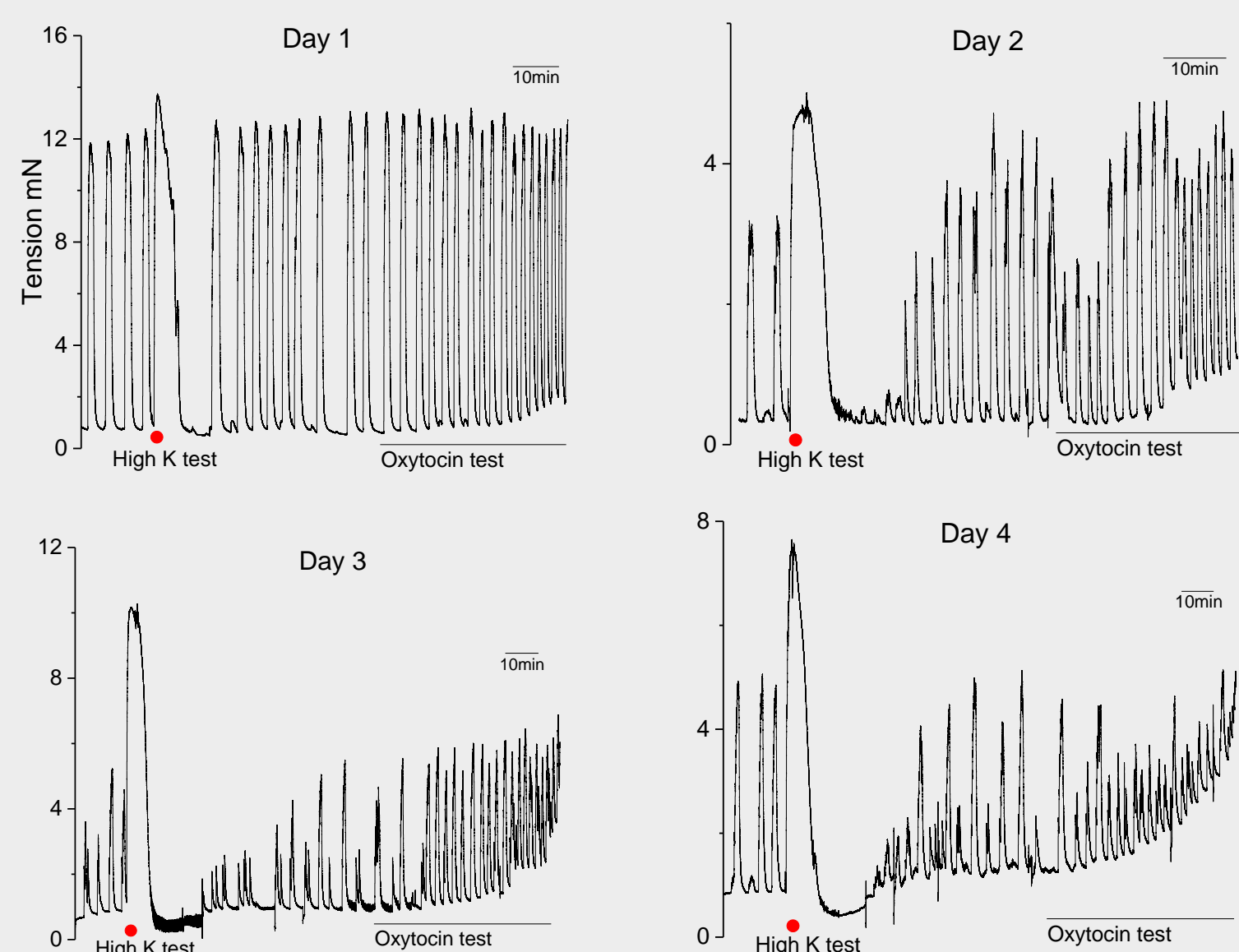
## STUDY 1: Failure to Progress in Labour

Failure to progress (FTP) occurs when labour lasts longer than 20 hours and usually results a caesarean section delivery, however this delivery has been shown to cause immune diseases in the subsequent offspring.<sup>[1]</sup> For this reason, we need to reduce the number of women failing to progress, which requires us knowing the mechanism causing the failure through myometrial (uterine) tissue studies.

- We investigated the theory that once the uterus is removed from the body it undergoes severe changes and hence cannot function properly. We studied myometrial tissue over the course of 24 hours to observe if there were any dramatic changes, and also looked at the effect of stretching the tissue on its functionality.



[Fig. 1] Contractions remain consistent and unchanged over the course of 24 hours.



[Fig. 2] Tissues remain functional for up to 4 days, response to OT is proportional to the time the tissue is stretched for.

## Results and Discussion:

This study provides evidence that the tissue can be effectively maintained outside the body for up to 24 hours when untreated (Fig.1) and up to 4 days when kept under tension (Fig. 2).

This therefore proves that myometrial tissue can be used *in vitro* to study tissue from both normal women and those failing to progress. Further studies will include genetically manipulating the samples by culturing them with different siRNAs to investigate potential genetic causes of FTP

## References:

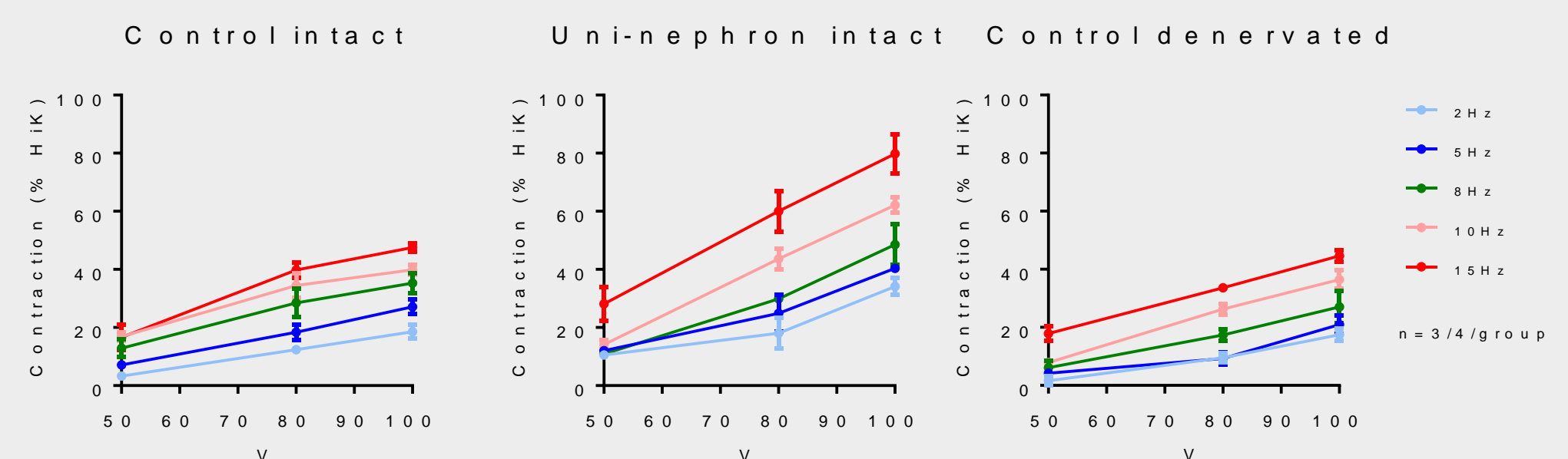
[1] Foundation NK. Living With One Kidney. [cited 09/08/2017]; Available from: <https://www.kidney.org/atoz/content/onekidney>

[2] Neuj J, J. R. Cesarean Versus Vaginal Delivery: Long term infant outcomes and the Hygiene Hypothesis. *Clinical Peritanology*. 2011;38:321-31

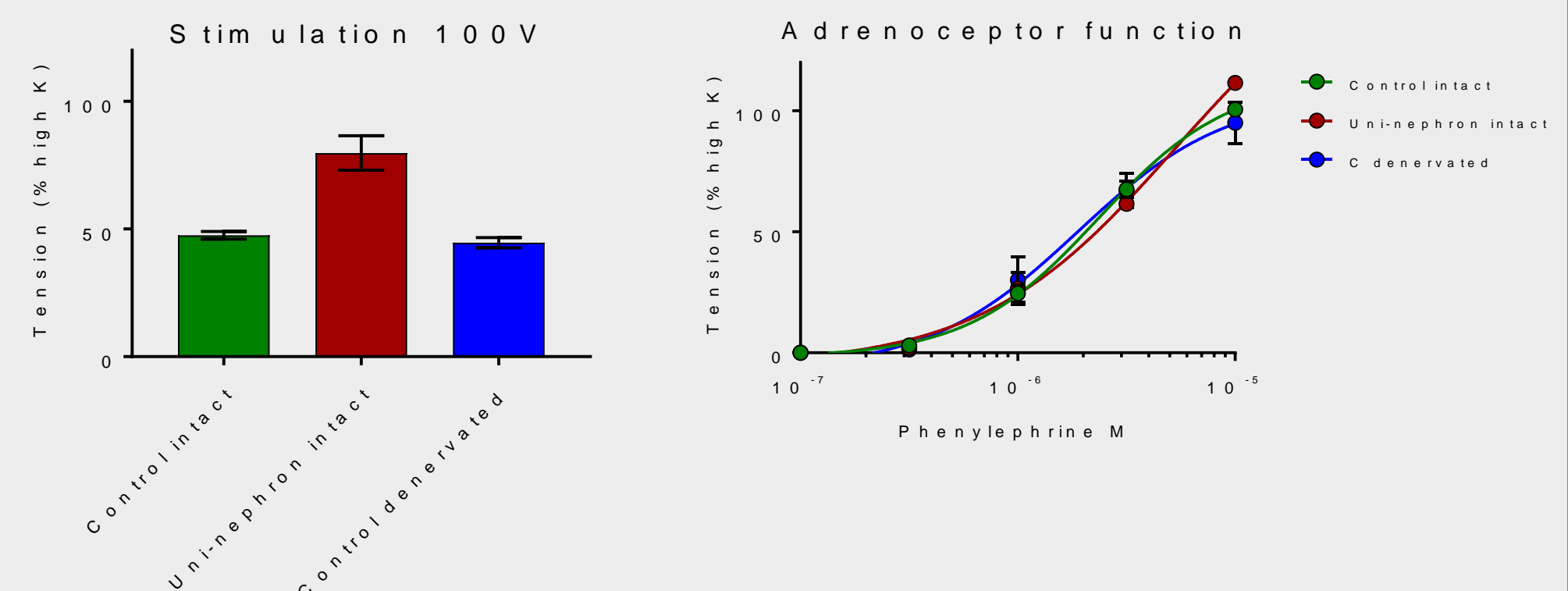
## STUDY 2: Relationship between renal agenesis and hypertension

Children born with only one kidney (renal agenesis) or only one functioning kidney most often develop high blood pressure, hypertension, later in life.<sup>[2]</sup> The nerves that enter the kidney cause the arteries in the kidney to contract which reduces blood flow and the kidney reacts by producing hormones that increase blood pressure. We considered whether the hypertension in those born with only one kidney reflects problems with the nerves on the arteries and investigated this possibility by measuring contractions in the renal artery following stimulation of these nerves.

- We used electrical currents (at varying frequencies and voltages) to stimulate the nerves.
- We performed these experiments in tissue samples from three groups of sheep, at 2 years of age:
  1. Control intact (with 2 normal functioning kidneys).
  2. Sheep that had had one kidney removed on day 20 of pregnancy - uni-nephrectomy.
  3. Control denervated arteries - renal nerves damaged later in life.
- We also tested the response of the arteries to phenylephrine, which acts on the artery in a manner identical to that of nerves. This tests if there was a change in the ability of the artery to respond to the actions of the nerves.



[Fig. 3]: An increase in stimulating voltage recruits a greater number of nerves to act on the renal artery, increasing contraction (standardized as % HiK contraction).



[Fig. 4]: Tension (% HiK tension) at max. stimulation of 100v across all models

[Fig. 5]: Contractile responsiveness to phenylephrine remained unchanged.

## Results & Discussion:

Prior to this study, blood pressure was measured in these sheep. While animals in the 2 control groups had normal blood pressure, those born with one kidney (uni-nephrectomised) displayed hypertension.

- Arteries from uni-nephrectomised sheep had increased sensitivity to the contractions induced by nerves (Fig 3).
- Tension was increased ~1.5 fold compared with controls (Fig 4). This did not result from a change in the muscle of the artery, as adrenoceptor function was the same in all 3 groups (Fig 5).

An increase in the number of nerves in the renal artery following uni-nephrectomy is likely, and this will be tested using microscopic study of reserved kidney tissues from these sheep. This study provides a possible mechanism by which being born with only one functioning kidney leads to the development of hypertension.

I would like to thank my supervisor, Prof. Helena Parkington, and the other lab members who supported me throughout this project and allowed me to shadow their work. I would also like to thank Newcastle University for awarding me with a research scholarship which enabled me to complete this project.