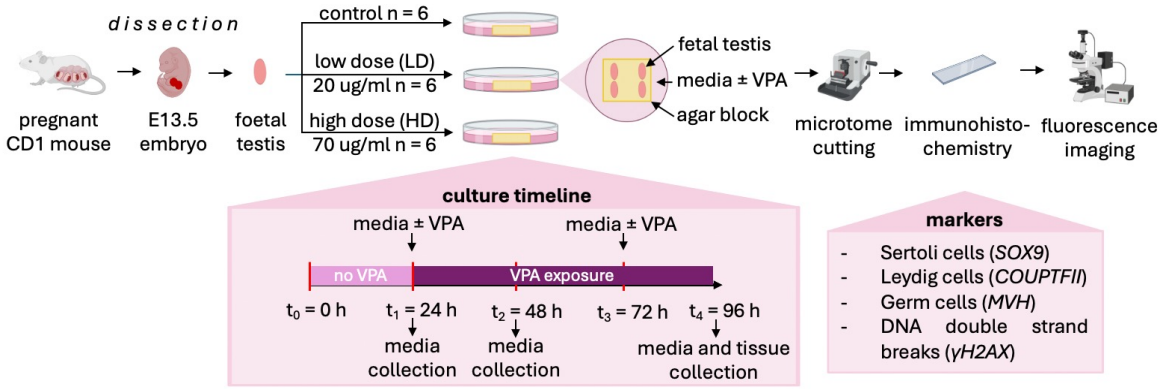
Investigation into the effects of sodium valproate on the developing fetal mouse testis *in vitro*

Adomas Liugaila & Agnes Stefansdottir
Biomedical Sciences, University of Edinburgh, Scotland, U.K.

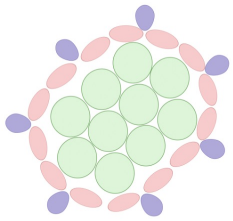
INTRODUCTION

Epilepsy is the most common neurological disorder in UK, with approximately one-third of patients being females of reproductive age. Management of epilepsy is critical during pregnancy, as intense seizures can lead to severe consequences for the developing fetus. On the contrary, anti-epileptic drugs (AEDs), which are used to alleviate symptoms of epilepsy, can also cause fetal malformations. For example, sodium valproate (SV) is an AED, which is contraindicated to have teratogenic effects on the developing fetus. Moreover, in 2024 the Medicines and Healthcare products Regulatory Agency (MHRA) issued a national patient safety alert advising that SV prescriptions for all patients under 55 will be required to be signed off by two independent specialists. Despite this, research examining the impact of SV exposure on fetal testis has been limited. Therefore, the aim of the project was to study the impact of SV on the morphology and function of the fetal mouse testis *in vitro*.

METHODS

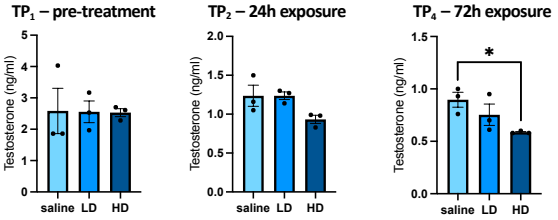


MORPHOLOGY



RESULTS: testosterone

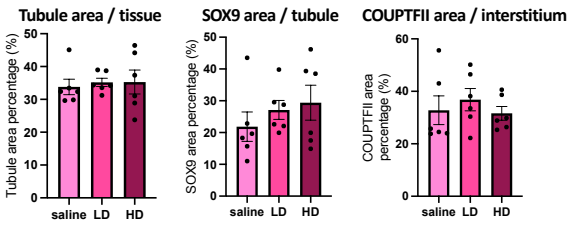
72-hour (at TP_4) SV exposure significantly reduced testosterone levels in HD group ($p = 0.0214$)

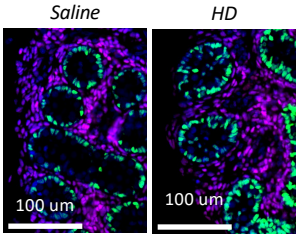


RESULTS: tubules, Sertoli-, Leydig cells

SV did not affect tubule area or Leydig cells, but there was a dose-dependent trend in an increase of SOX9 area per tubule

DAPI SOX9 COUPTFII

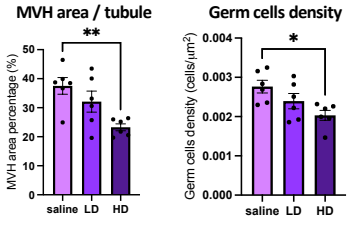


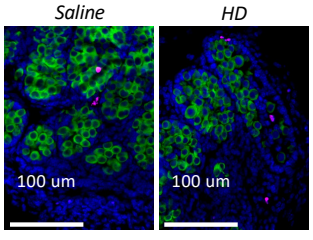


RESULTS: germ cells and DNA damage

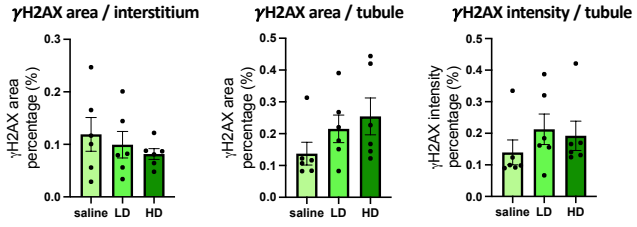
SV exposure significantly reduced MVH area ($p = 0.0077$) and germ cells density ($p = 0.0217$) in a dose-dependent manner

DAPI MVH γH2AX





SV exposure does not cause DNA double strand breaks in interstitial cells, but there is a strong dose-dependent trend observed in cells found within the tubules ($p=0.0838$)



DISCUSSION & CONCLUSION

Our research showed that clinically-relevant concentrations of SV reduce the number of germ cells in fetal testes, while Leydig- and Sertoli cells remained unaffected. SV concentrations were chosen according to umbilical cord serum levels, which range from 5.4 – 72.1 ug/ml, while the exposure window reflects the 2nd trimester of pregnancy. It is hypothesized that during this time the 'masculinization programming window' takes place, when reduction in testosterone can have long-term detrimental effects on reproductive health. However, future research is needed to confirm the same trends *in vivo*, with longer than 72h SV exposure windows to reflect the real-life exposure window.

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