Ethanol-initiated oxidative DNA damage in *Brca1* knockout mice

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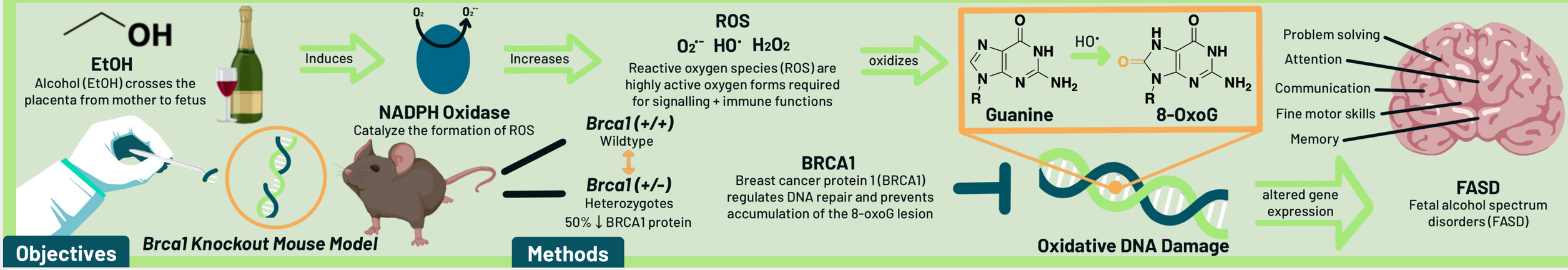
Introduction

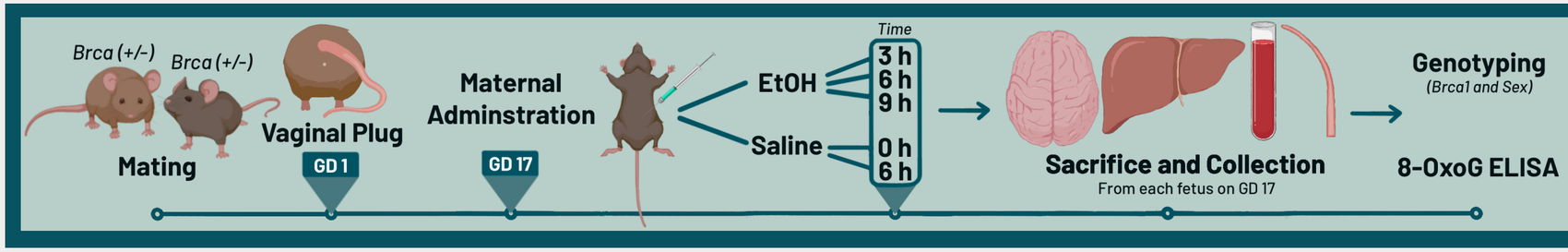


Objectives

Determine in fetal brains with maternally administered ethanol treatment:

- **I) Time of peak 8-oxoG formation.**
- **II) Effect of saline on 8-oxoG levels.**
- **III) Effect of *Brca1* genotype on 8-oxoG levels.**
- **IV) Effect of sex on 8-oxoG levels.**

Methods



Results

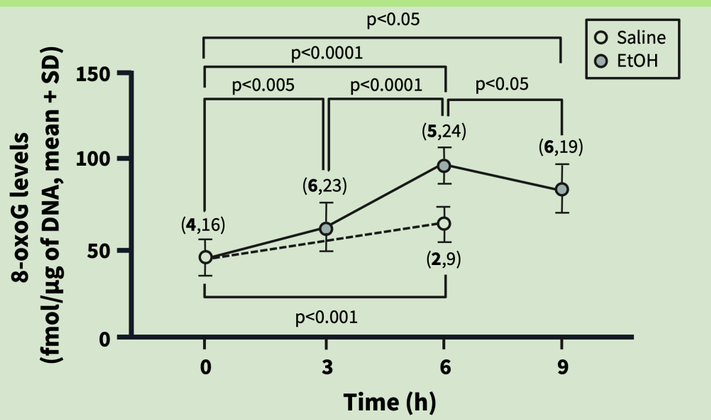


Figure 1. Time course for EtOH-initiated DNA oxidation (8-oxoG) in murine fetal whole brain. EtOH maximally increased 8-oxoG at 6 h by ~87% compared to 0 h saline and ~44% compared to 6 h saline. Saline enhanced 8-OxoG by ~30% from 0 to 6 h. (**x**,y) = (# of litters, # of progeny).

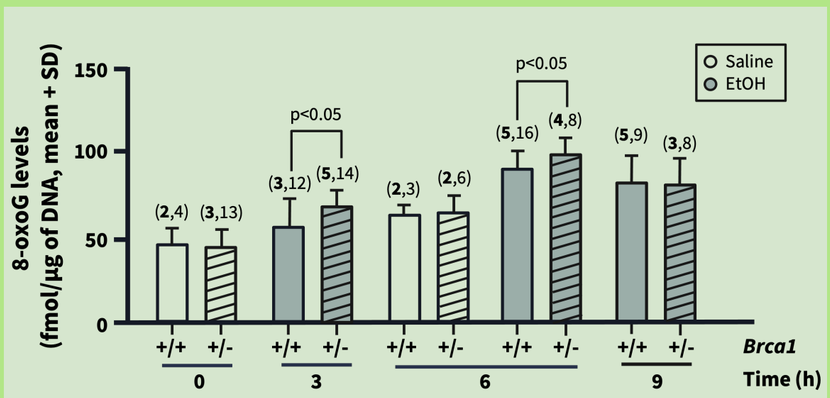


Figure 2. Impact of deleted *Brca1* allele on EtOH-initiated DNA oxidation (8-oxoG) in murine fetal whole brain. Same sample set as *Figure 1*. *Brca1* +/- fetal brains had ~20% higher 8-oxoG levels than *Brca1* +/+ with EtOH at 3 h. *Brca1* +/- had ~10% higher 8-oxoG levels than *Brca1* +/+ with EtOH at 6 h. (**x**,y) = (# of litters, # of progeny).

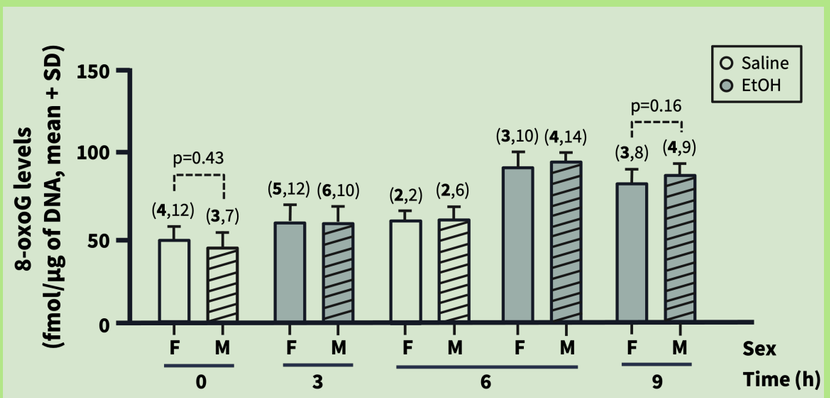


Figure 3. Sex comparison for EtOH-initiated DNA oxidation (8-oxoG) in murine fetal whole brain. Same sample set as *Figure 1*. No significant differences were observed between sexes. (**x**,y) = (# of litters, # of progeny).

Conclusion

I) Peak DNA oxidation (8-oxoG) in fetal brains was observed at **6 h** after maternal **ethanol** administration which will be used in future biochemical studies.

II) Increased 8-oxoG in fetal brains treated with **saline** suggests that maternal saline injection may enhance fetal ROS-producing NOX enzymes.

III) Increased 8-oxoG in ***Brca1* +/-** vs. ***Brca1* +/+** fetal brains shows that BRCA1 may protect the fetus from oxidative DNA damage.

IV) Sex differences in EtOH-initiated neurodevelopmental outcomes previously observed must be due to biochemical events following 8-oxoG formation in fetal brains.

Future Directions

- Determine the mechanism of saline injection-induced DNA oxidation.
- Quantify blood ethanol concentrations via gas chromatography-mass spectrometry.
- Quantify DNA strand breaks via single-cell gel electrophoresis (comet assay).

Acknowledgements and References

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Drake, D. M., & Wells, P. G. (2021). Novel mechanisms in alcohol neurodevelopmental disorders via BRCA1 depletion and BRCA1-dependent NADPH oxidase regulation. *Redox Biology, 48,* 102148. https://doi.org/10.1016/J.REDOX.2021.102148