Potential Role of Cholesterol in the Migration of Neurons Containing Gonadotropin-Releasing Hormone

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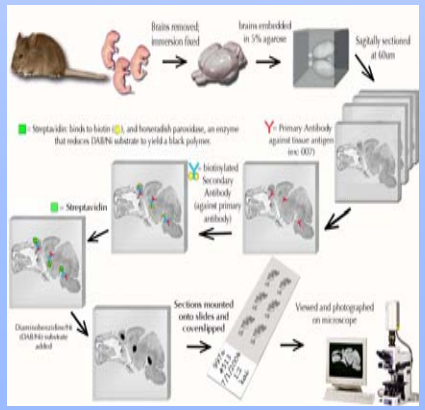
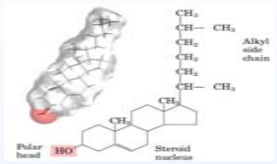
Introduction

- Signaling by Sonic Hedgehog (Shh) is instrumental in the development of midline facial and forebrain structures
- Signaling by Shh can be dependent upon conjugation with cholesterol. Structural abnormalities related to cholesterol depletion may be a result of a failure of Shh signaling
- Disorders resulting in cholesterol depletion are often characterized in part by developmental malformations, including holoprosencephaly
- Neurons that synthesize gonadotropin releasing hormone (GnRH; controls the reproductive axis) originate in the nasal compartment and migrate into the brain along a route that may depend upon proper Shh signaling
- The current study was conducted to assess whether cholesterol-depleted enzyme Dhcr24-/- mice would affect the unique migration of GnRH neurons as they migrate to the brain

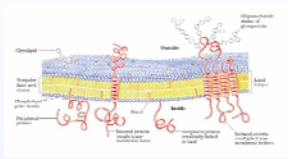
Methods

Heads from fetuses at embryonic day 16 & 18 were immersion fixed. Dhcr24 knockout (-/-) and heterozygous (+/-) mice were used and neurons containing GnRH were labeled via immunocytochemistry. Immunoreactive neurons were counted in the brain versus nasal compartment.

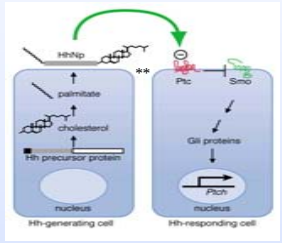




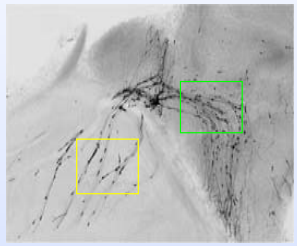
Structure of cholesterol



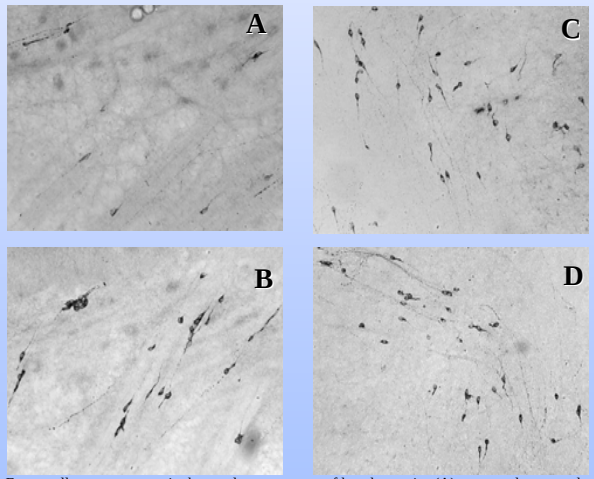
Cholesterol is an integral component of membrane lipid rafts and could potentially influence cell signaling



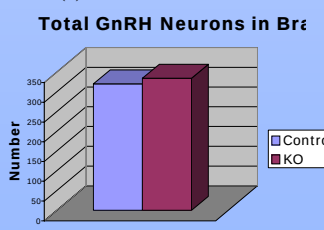
Cholesterol can be conjugated to Sonic Hedgehog.



The region where the nasal compartment (yellow box) & brain (green box) pictures were taken.

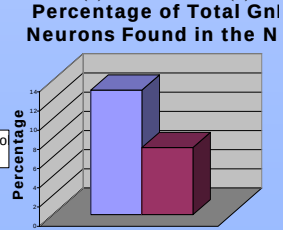


Fewer cells were apparent in the nasal compartment of knockout mice (A) compared to control mice (B). More cells were counted in the brains of knockout (C) versus control mice (D).



Total number of GnRH neurons found in the brain and nasal compartment.

Groups were not statistically different.



Percentage of the total number of neurons found in the nose

KO significantly lower than control ($p = 0.01$)

Conclusions

- Cholesterol depletion produced mice with fewer GnRH neurons in the nasal compartment and more in the forebrain
- Cholesterol depletion did not influence the total number of GnRH neurons. Thus, migration out of the nasal compartment may have increased
- Fibers that guide GnRH neurons were fully intact and there was no evidence of holoprosencephaly or midline defects
- Alternative roles for cholesterol in signaling during development may be based on its utilization in plasma membrane lipid rafts or in signaling through alternative and selective pathways
- These results suggest that in the GnRH migratory pathway, signaling to GnRH neurons that may require cholesterol may play a role in a normal inhibition of the migration of GnRH neurons

Future Analyses

- Finer analysis of GnRH neuron location in brain regions
- Additional analysis of tissue condition between KO and control sections

Acknowledgements

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