Estrogen and Dain Bramage: Lessons From Songbirds

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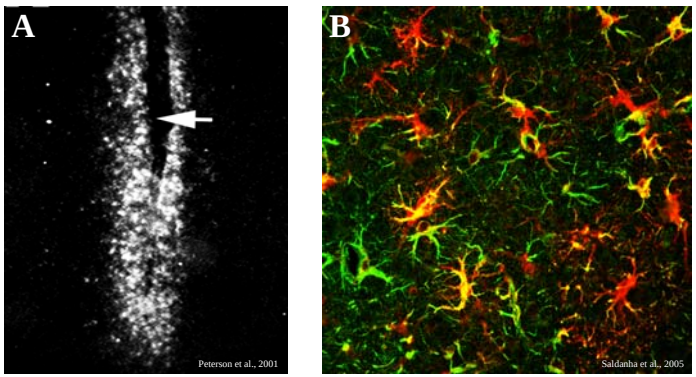
INTRODUCTION

In vertebrates, brain injury is followed by a wave of secondary degeneration. This cellular degeneration is believed to be primarily responsible for the many symptoms of brain damage caused by stroke, Alzheimer's and Parkinson's disease (Mattson et al., 2000).

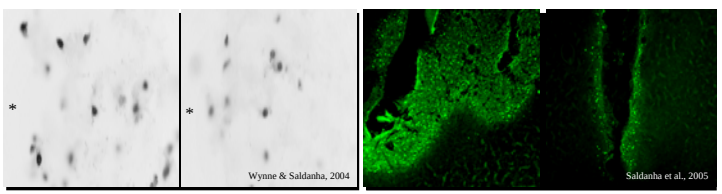
Brain injury increases the production of the enzyme aromatase (*estrogen (E)-synthase*) in mammals (Garcia-Segura et al., 1999, 2002) and songbirds (Peterson et al., 2001, 2004; Wynne & Saldanha, 2004; Saldanha et al., 2005).

This upregulation occurs in glial cells surrounding brain damage.



(A) Aromatase mRNA is increased around mechanical injury.
(B) Aromatase cells co-express glial proteins (yellow).

Local estrogen synthesis by glial aromatase inhibits cellular degeneration and decreases injury size in songbirds (Wynne & Saldanha, 2004; Saldanha et al., 2005).



Fadrozole **Saline** **Fadrozole** **Fadrozole + E**

Blocking aromatase increases cellular degeneration 72hrs following brain injury in the songbird (Wynne & Saldanha 2004).

E-replacement decreases cellular degeneration 72hrs following brain injury in the songbird (Saldanha et al., 2005).

DOES INHIBITION OF INJURY-INDUCED AROMATASE AFFECT THE DYNAMICS OF THE WAVE OF SECONDARY DEGENERATION FOLLOWING INSULT TO THE BRAIN?

The zebra finch is an excellent model for these studies.

- This species expresses abundant aromatase.
- The brain is the primary source of E in males.
- Injury to the brain causes rapid aromatase synthesis.

EXPERIMENTAL DESIGN AND METHOD

Adult male zebra finches received injuries with needles containing either fadrozole (fad; an aromatase inhibitor) or saline (sal; control) into contralateral hemispheres. Birds survived 0, 2, 6, 24, 72hrs, 2 or 6 weeks following injury.

RESULTS

INHIBITION OF AROMATASE REVEALS THE WAVE OF SECONDARY DEGENERATION FOLLOWING BRAIN INJURY

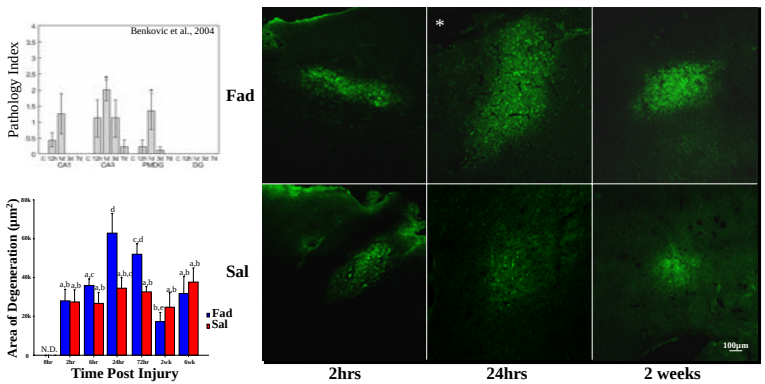


Figure 1: Cellular degeneration in representative subjects across time following injury. Saline injury did not show a wave of secondary degeneration that is typically found in mammals. Blocking aromatase activity with fadrozole revealed a wave of secondary degeneration with an increase in the area of degeneration at 24 (*) and 72hrs post injury.

AROMATASE INHIBITION DISSAPATED 2 WEEKS POST-INJURY

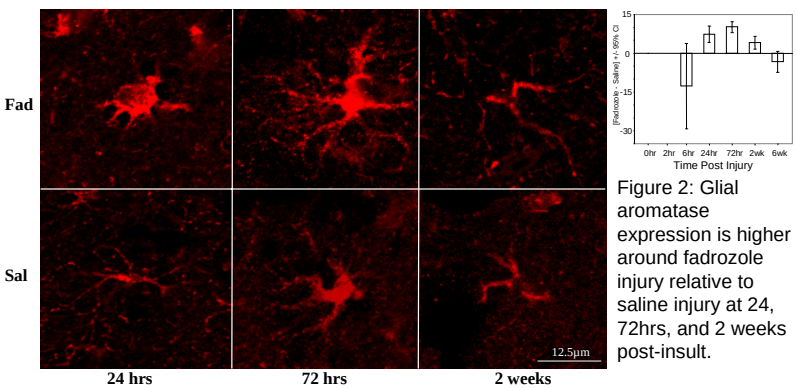


Figure 2: Glial aromatase expression is higher around fadrozole injury relative to saline injury at 24, 72hrs, and 2 weeks post-insult.

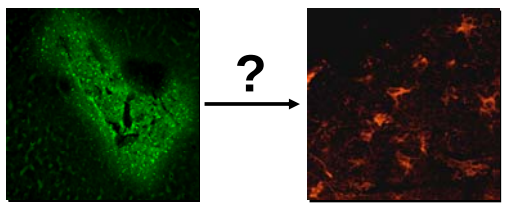
SUMMARY AND CONCLUSIONS

- Aromatase is upregulated in glial cells around injury.
- Glial aromatase limits brain injury size by decreasing cell death around insult.
- Glial aromatase limits cell death through at least E dependent pathways.
- Songbirds have an undetectable wave of secondary degeneration following brain injury.
- A wave of secondary degeneration is, however, revealed upon inhibition of local aromatase.

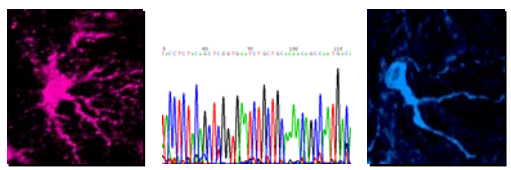
IN SONGBIRDS, INJURY INDUCED UPREGUATION OF GLIAL AROMATASE IS ROBUST ENOUGH TO SEVERELY DAMPEN THE WAVE OF SECONDARY DEGENERATION CHARACTERISTIC OF MAMMALIAN BRAIN INJURY.

SONGBIRDS ARE EXCELLENT MODELS TO STUDY BRAIN DAMAGE AND REPAIR.

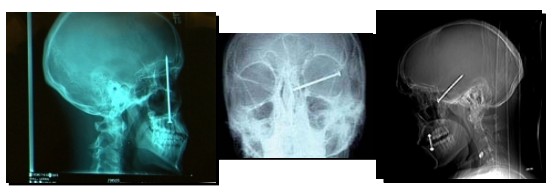
FUTURE RESEARCH QUESTIONS



What is it about degeneration that regulates the upregulation of gene expression in reactive glia?



Is glial aromatase different from neuronal aromatase?



Does glial aromatase modulate the repair of degenerating brain circuits?

ACKNOWLEDGEMENTS
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