The role of inflammation in healthy and natural neurodegenerative states of the sensorimotor pathway responsible for song production

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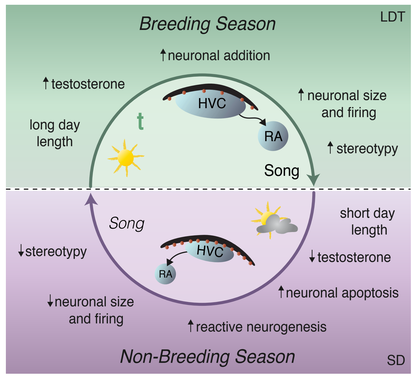
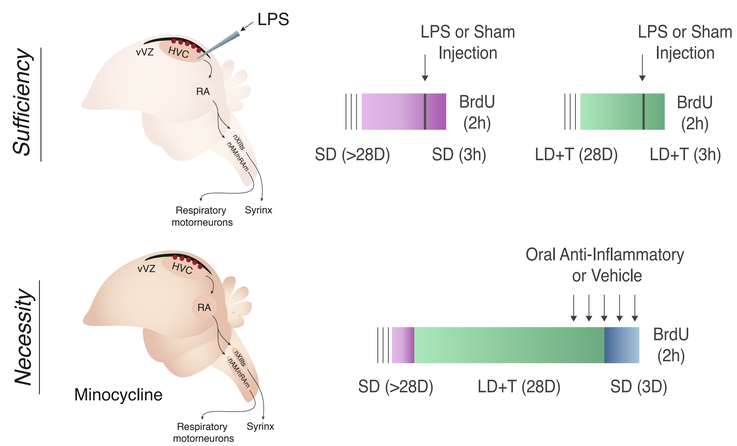
Background

Neuroinflammation is typically considered a negative response following neuronal injury and damage. Neuroinflammation can, however, play a beneficial role in the healthy adult brain. For example, ramified microglia elicit positive effects through neuronal and synapse pruning to maintain proper neuronal number and connections. To identify the role of inflammation in both healthy and natural degenerative states, we utilized the natural seasonal regression of the motor pathway responsible for song production in Gambel's white-crowned sparrow. As male sparrows transition from breeding to nonbreeding conditions, nearly 25% of HVC neurons undergo apoptosis. As a consequence, neural stem cell proliferation in the nearby ventricular zone increases – a process termed natural reactive neurogenesis. Using this unique model of natural and rapid neurodegeneration, we show that inflammation mediates reactive neurogenesis.



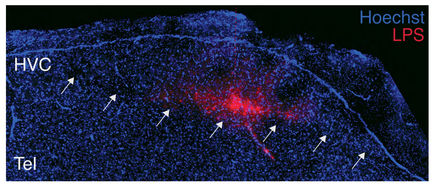
Materials and Methods

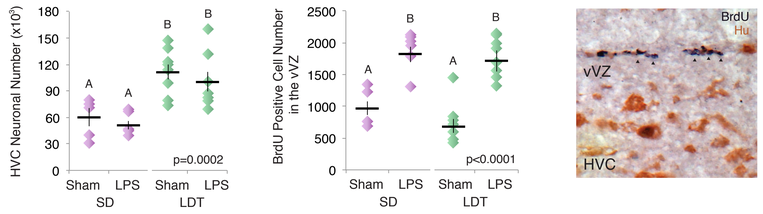
Adult male Gambel's white-crowned sparrows (*Zonotrichia leucophrys gambelli*) were experimentally manipulated to test for the necessity and sufficiency of inflammation within HVC to confer an increase in neural stem cell (NSC) proliferation in the nearby ventricular zone.



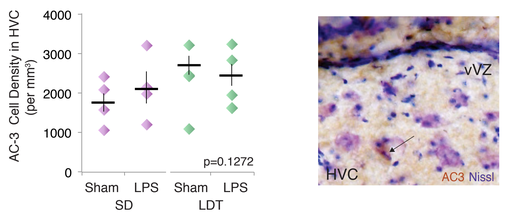
Locally-induced inflammation within HVC drives increase in neural stem cell proliferation regardless of HVC state

Microinjection of 1µg of LPS into HVC rapidly increased NSC proliferation in the ventral ventricular zone (vVZ) of birds maintained in stable breeding and nonbreeding conditions.



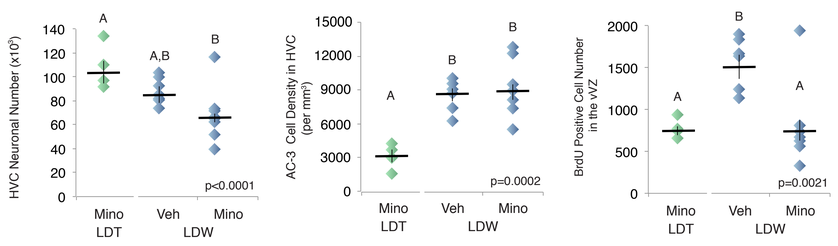


LPS did not increase HVC cell death over 3 hours. These data suggest that inflammation within HVC is sufficient to drive rapid NSC proliferation.



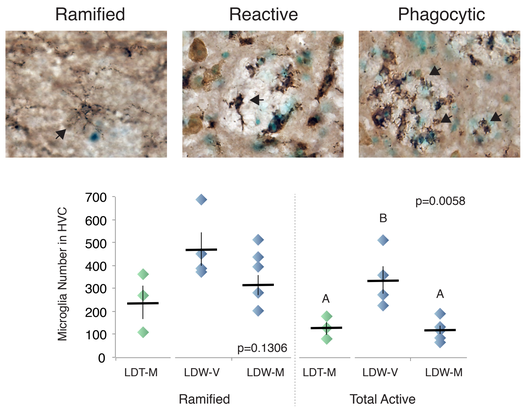
Oral anti-inflammatory prevents reactive neurogenesis upon natural neuronal apoptosis in HVC

Birds were administered oral doses of the anti-inflammatory, minocycline twice a day begining two days before seasonally-induced apoptosis within HVC. Minocycline – an inhibitor of microglial activation – prevented reactive neurogenesis following HVC neuronal apoptosis.

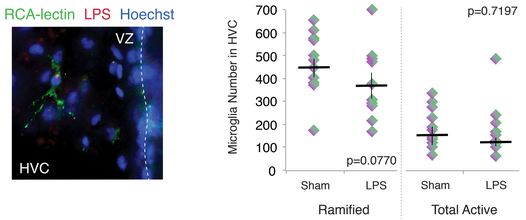


Reactive and activated microglia confer inflammatory state of HVC during natural neuronal apoptosis

Microglia were classified and quantified based on morphological state. Microglia activation increased with HVC apoptosis. Minocycline reduced microglia reaction to local inflammation but did not affect basal levels of ramified microglia.

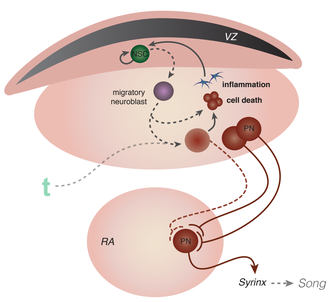


LPS microinjection did not alter transition of microglia morphology from the ramified state, suggesting morphology alone is not sufficient for assesing rapid microglial responses.



Conclusions

- Local LPS rapidly induces NSC proliferation in the vVZ
- Inflammation-induced NSC proliferation does not vary between LDT and SD
- Inhibition of microglial activation prevents reactive natural neurogenesis
- Microglia localize to HVC and exert pro-proliferative effects in the nearby NSC niche that supplies HVC with new neurons



Acknowledgements

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