Moderate Alcohol Drives Splenocyte Transcriptional Changes in a Murine Model of Multiple Sclerosis

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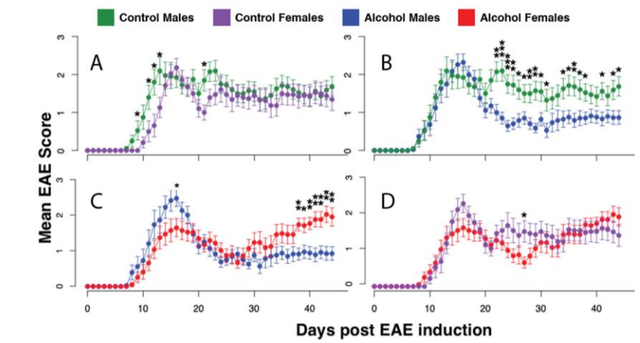
Introduction

Moderate alcohol consumption has been identified as a protective factor against the development and aggravation of several autoimmune conditions[1-3], but the mechanism by which an inflammatory substance can ameliorate autoimmunity is currently unknown. We have previously found that moderate alcohol administration reduces the severity of experimental autoimmune encephalomyelitis (EAE)[4], a mouse model of the central nervous system autoimmune disease multiple sclerosis (MS). However, this result was sexually disparate and the beneficial effects were only observed in alcohol-consuming males. This study examined alcohol's sex-specific alterations to immune activation during EAE onset and recovery via splenocyte gene expression.



References

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Results

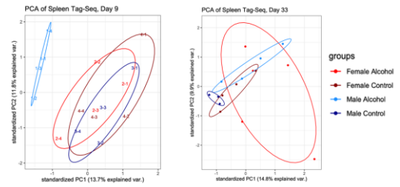


Figure 1. Principal component analysis of splenocyte gene expression by sex and alcohol consumption. Alcohol-consuming males showed distinct splenocyte transcriptional profile during EAE onset (D9) compared to other groups. This effect was lost during the EAE recovery timepoint (D33) (*n=3-5 per group*).

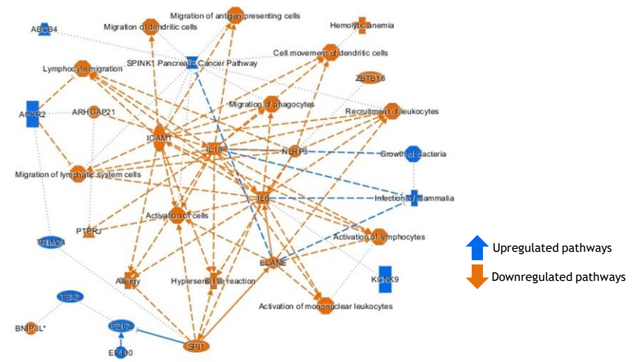


Figure 2. Day 9 post-induction transcriptional pathway analysis. Alcohol consumption downregulated IL-6 and IL-18 expression and associated pathways in splenocytes during EAE onset (*n=3-5 per group*).

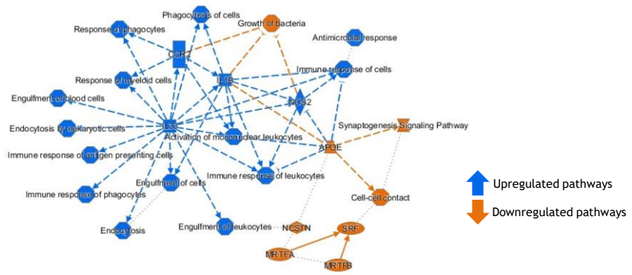
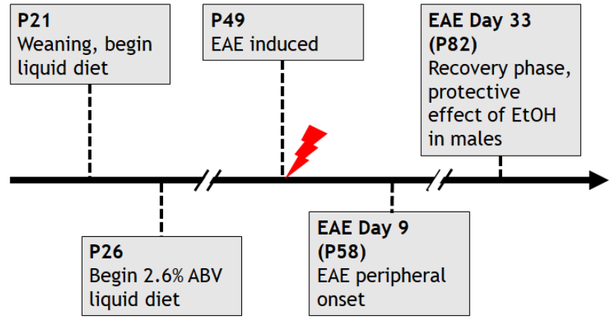


Figure 3. Day 33 post-induction transcriptional pathway analysis. Alcohol consumption upregulated IL-33 expression and phagocytosis-associated pathways in splenic macrophages during EAE recovery (*n=3-5 per group*).

Methods

Male and female C57BL/6 mice (n=16-18 per group) were fed a 2.6% alcohol by volume (ABV) liquid diet (Lieber-DeCarli '82) from 5 days post-weaning for the duration of the experiment, with controls receiving an isocaloric 0% ABV version. EAE was induced at P49. Whole spleens were collected from randomly selected representatives from each group (n=3-5 per group) immediately prior to EAE induction (D0), 9 days post-induction (D9), and 33 days post-induction (D33). Spleens were flash frozen and RNA extracted via Qiagen RNeasy Miniprep Kit for Tag-Seq and analysis. Differential gene expression was analyzed by Ingenuity Pathway Analysis



Conclusions

Moderate alcohol consumption reduces peripheral inflammatory activation in splenocytes during EAE onset via downregulation of IL-6 and IL-18 expression and associated reductions in lymphocyte migration.

During the recovery phase of EAE, alcohol induces increased IL-33 expression and promotes anti-inflammatory pro-phagocytic activation in splenic macrophages.

Future directions:

- Examine whether observed changes are also detectable in resident macrophages of the central nervous system, the microglia.
- Investigate whether differentially activated macrophage-like cells within the central nervous system (CNS) during EAE are resident microglia or peripheral macrophages which have infiltrated and colonized the CNS.