SSA PhD Studentship Final Report

Final Report 2021

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Targeting *Drosophila* $GABA_B$ receptors alters alcohol addiction phenotypes

RESEARCH REPORT

It is well known that alcoholic beverages are freely consumed worldwide, and as a result, overconsumption has both negative health and socioeconomic consequences. Whilst ethanol, the alcohol found within commercially available beverages, has some known direct targets, the exact mechanisms of the complex neurological responses to the consumption of ethanol remains to be elucidated. Many neurotransmitter systems have been implicated in the acute and chronic responses to ethanol. Among these, the $GABA_B$ receptor mediated signalling pathways have been identified in playing a potential role in Alcohol Use Disorder (AUD) with $GABA_B$ drugs being used with some success as a treatment.

This research has sought to understand and explore the $GABA_B$ receptors in ethanol induced behaviours, using the fruit fly, *Drosophila melanogaster* as a model. The $GABA_B$ receptor agonist, SKF 97541 and the antagonist CGP 54626 were given to *Drosophila* to alter the fly's sensitivity to ethanol and to explore the effect that these compounds had on ethanol induced preference behaviours. In order to reliably use the *Drosophila* model to elucidate the mechanisms by which ethanol alters behaviours such as sensitivity, tolerance and preference, previously reported behavioural paradigms assays were used to model these addiction-like behaviours. Additionally, *Drosophila* genetic were exploited to modify gene expression to confirm results found in pharmacological studies and interventions. I found that targeting the $GABA_B$ receptor with the agonist SKF 97541, enhanced the sensitivity of the flies to ethanol in terms of the time needed to reach sedation. The agonist reduced the development of ethanol induced preference for high ethanol concentrations in both a cue induced preference assay and a natural olfactory preference assay. In contrast to the agonist SKF 97541, the $GABA_B$ antagonist CGP 54626, successfully reduced *Drosophila* sensitivity to ethanol but also reduced the development of preference although not to the same extent as the agonist (See here for published work).

To conclude, the results that I generated provide new evidence that the $GABA_B$ receptor is involved in both the response to ethanol and in complex mechanisms that are related to behaviours that characterise AUD. Furthermore, genetically modified flies with downregulated $GABA_B$ gene expression confirmed findings that were consistent with pharmacological interventions, further confirming the importance of the $GABA_B$ receptor as a target for AUD.

PUBLICATIONS, PRESENTATIONS, AWARDS AND CONFERENCES

During my PhD, I was fortunate to be given the opportunities and support to present and communicate my research. I have shared my works as peer reviewed academic publications and by presenting my work at both national and international conferences, as oral poster presentations and as an invited speaker.

Publications

- **Ranson, D.C.,** Ayoub, S.S., Corcoran, O. and Casalotti, S.O. (2020). Pharmacological targeting of the GABAB receptor alters Drosophila's behavioural responses to alcohol. *Addiction Biology*. 25(2). Available at: doi.org/10.1111/adb.12725.

- Aleyakpo, B., Umukoro, O., Kavlie, R., **Ranson, D.C.,** Thompsett, A., Corcoran, O. and Casalotti, S.O. (2019). G-Protein αq gene expression plays a role in alcohol tolerance in *Drosophila melanogaster. Brain and Neuroscience Advances.* 3(1). Available at: doi.org/10.1177/2398212819883081.

Presentations

Oral Presentations

- *British Pharmacological Society (2019). Targeting of the $GABA_B$ receptor alters the development of cue induced preference to ethanol in Drosophila.*
- *London Fly Meeting, Francis Crick Institute (2019). Pharmacological and genetic targeting of $GABA_B$ receptors alter alcohol-induced behaviours in Drosophila.*
- *Society for the Study of Addiction (2018). The role of Gamma-aminobutyric acid B receptors in alcohol related behaviours in Drosophila models of ethanol tolerance.*

Poster Presentations

- *British Pharmacological Society (2019). Targeting of the GABAB receptor alters the development of cue induced preference to ethanol in Drosophila.*
- *British Pharmacological Society (2018). Drosophila Sensitivity and Tolerance to Ethanol is Altered by GABAB Receptor Drugs.*
- *Federation of European Neuroscience, Germany (2018). Pharmacological Modulation of Alcohol Tolerance via $GABA_B$ receptors in Drosophila melanogaster.*

Awards

2021

- British Pharmacological Society/Laboratory Animal Science Association Event Bursary.

- *2019*
- British Pharmacological Society/Laboratory Animal Science Association Event Bursary.
- British Neuroscience Association Travel Bursary.
- British Pharmacological Society Travel Bursary.
- Guarantors of Brain Travel Bursary.
- Society for the Study of Addiction Open Access Bursary Award.

- *2018*
- Best late breaking research poster abstract award**.** *British Pharmacological Society*.

- *2017*
- Society for the Study of Addiction PhD Sponsorship.

Conferences Attended

2021

- British Pharmacological Society/Laboratory Animal Science Association event/workshop, Online.
- Society for the Study of Addiction annual conference, Online.

2020

- British Pharmacological Society annual conference, Online.
- Society for the Study of Addiction annual conference, Online.
- Society for the Study of Addiction PhD symposium, Online.

2019

- British Pharmacological Society annual conference, Edinburgh, Scotland.
- British Neuroscience Association annual conference, Dublin, Ireland.
- British Pharmacological Society annual conference, London, England.
- British Neuroscience Association Xmas symposium, London, England.

2018

- Society for the Study of Addiction annual conference, Newcastle, England.
- Society for the Study of Addiction PhD symposium, Newcastle, England.
- NC3R's 2019 Funding Highlight Notice Launch, London, England.

- Federation of European Neurosciences conference, Berlin, Germany.

2017
- British Pharmacological Society annual conference, London, England.
- Society for the Study of Addiction annual conference, Newcastle, England.