The Effect of Chemogenetic DREADD Manipulation in the Ventral Dentate Gyrus of Chronically Stressed Females on the Behavioral Antidepressant Response

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Background

• The most widely prescribed class of antidepressants are selective serotonin reuptake inhibitors (SSRIs), which increase serotonin, a mood-regulating monoamine neurotransmitter, by blocking reuptake. One type of SSRI is fluoxetine (FLX), also known as Prozac. Despite the popularity of SSRIs, approximately 3 patients do not remit after treatment (Rush et al., 2006).

• Mice that retain a long latency to eat in the NSF after chronic FLX treatment are considered non-responders, whereas mice with shorter latencies after chronic FLX treatment are considered responders. Therefore, NSF permits the grouping of FLX-treated animals into responders and non-responders to SSRI treatment (Samuels & Hen, 2011).

• Inhibition of the ventral dentate gyrus is important for the behavioral response to antidepressant treatment (Bagot et al., 2015; Kheirbek et al., 2013). Deletion of 5-HT1A receptors (Gi-coupled heteroreceptors) from ventral dentate gyrus (vDG) in the DG abolishes the behavioral effects of SSRIs (Samuels et al., 2015).

• Published results from Samuels lab observed that responders to FLX have less DG cFos expression than non-responders to FLX and stress controls after completion of the NSF. Given that cFos is an indicator of neuronal activity within an area, this data suggests that response to FLX is related to a decrease in activation of the DG GCs.

• DREADDS are a chemogenetic method of cell manipulation used to influence levels of cell activity. Different DREADDs increase Gq- or Gi-mediated signaling to alter membrane potential, either increasing (Gq) or decreasing (Gi) the probability that an action potential will occur (Roth, 2016).

• Our current hypothesis is that Gi-DREADD-mediated inhibition of ventral DG GCs will mimic an antidepressant response, while Gq-DREADD-mediated activation of ventral DG GCs will induce anxiogenic behavioral responses. We hypothesize that Gi-DREADD-mediated inhibition of DG GCs can convert female FLX non-responders into responders. We hypothesize that Gq-DREADD-mediated stimulation of DG GCs can convert female FLX responders into non-responders.

Methods

• Light Dark
• Elevate Plus Maze (EPM)

Results: Ventral DG DREADD-mediated Regulation of Behavior

Figure 1. (a) Timeline of Gq-DREADD and Gi-DREADD-mediated manipulation in SIS (b) Timeline of Treatment Reversal for Responders and Non-Responders.

• Many pre-clinical models exclude the use of female subjects, despite the fact that nearly twice the number of women suffer from MDD than men. This exclusion is historically due to antiquated ideas of behavioral variations from the hormonal changes of the estrous cycle (Shorsky, 2019). Social instability stress (SIS) is a chronic stress paradigm, effective in both males and females. SIS involves frequent changes in the housing environment, in which the introduction of novel cage mates replaces the control of the course of several weeks creates a social imbalance.

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Results: Confirmation of DREADD Activation

• Behavioral response to FLX is associated with a decrease in DG GC activity, with chronic inhibition of the vDG via DREADDS mediating antidepressant-like behavioral responses in both stress and non-stress backgrounds.

• Chronic stimulation of the vDG via DREADDS mediate an anxiogenic response in non-stress backgrounds and a minimal anxiogenic response in stress backgrounds.

• Behavioral non-responders to FLX can be converted into behavioral responders following chronic inhibition of the vDG via DREADDS.

• Behavioral FLX responders are converted into non-responders following chronic chemogenetic stimulation of the vDG.

• This study, along with unpublished data from Samuels lab investigating DREADD-mediated inhibition and stimulation in the vDG of males stressed by chronic corticosterone (a stress hormone) administration suggests that DREADD-mediated modulation of the DG is independent of stress.

• Due to the complex etiology of MDD, further investigation of treatment resistant depression and independence from the type of stressor, can help novel research focus on the role of DG in physiology that allows it to differentially respond to antidepressant treatment.

• It is apparent that more research into the neural circuitry that underlies the behavioral response to antidepressant treatment is necessary in order to develop novel pharmacotherapies; however, our results demonstrate that the vDG plays an essential role in this response.

References


Crosby, T. E. (2019). Novel pharmacotherapies; however, our results demonstrate that the vDG plays an essential role in this response.

Acknowledgements

I would like to thank my faculty mentor, Dr. Benjamin Samuels, and my graduate mentor, Christine Yohn, for their guidance and support. I would like to extend my gratitude to the undergraduate research assistants in Dr. Samuels’s lab for their help, especially Sandria Ashamalla and Debbie Ma.