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"Identifying sources of dynorphin inputs to the BNST that are recruited by social stress"

Experiencing repeated social stress is an important risk factor for developing anxiety, depression, and substance use disorders (SUD). For instance, those who drink alcohol in negative social contexts to reduce social anxiety are more likely to meet DSM criteria for an alcohol use disorder (AUD). The neural mechanisms by which social stress increases vulnerability to developing AUD are not fully understood, though recent work suggests that the dynorphin-kappa opioid receptor system plays an important role. Dynorphin is a neuropeptide whose expression is increased by stress in a variety of limbic/motivation related regions of the brain. Dynorphin binds to the kappa opioid receptor (KOR) to have an inhibitory effect on neuronal activity. These Dynorphin-KOR binding interactions have been implicated in the neural processes by which stressful events precipitate alcohol and drug use.

Our previous work focused on localizing these interactions within the brain and understanding their involvement in stress escalated drinking. We found that antagonizing KORs throughout the brain, and more specifically in a region called the bed nucleus of the stria terminalis (BNST), attenuates stress escalated drinking. These KORs are located on terminals of basolateral amygdala (BLA) cells that project to the BNST. This was an interesting finding because the BLA is a known regulator of behavioral response to stress and regulates alcohol consumption.

We predict that stress causes dynorphin release within the BNST and this dynorphin acts on KORs located on BLA cell terminals in the BNST. Our current work focuses on identifying sources of dynorphin inputs to the BNST that are recruited by social stress. We have identified four potential sources of dynorphin: local dynorphin expressing cells within the BNST, and dynorphin expressing cells projecting to the BNST from other brain regions, which include the central amygdala (CeA), dorsal raphe (DR), and the parabrachial nucleus (PBN). By understanding this we can modulate these neurons, explore drug targets that are selectively expressed in these cells, and identify novel therapeutic targets for AUDs.

Retro AAV targeting was used prior to the study to label neuronal inputs to the BNST with eGFP. We found GFP labeled cells in several brain regions that project to the BNST including the basolateral and central amygdala, insular cortex, and parabrachial nucleus. We subjected mice to ten days of our social defeat stress paradigm followed by a period of intermittent access alcohol consumption. We performed RNA scope analysis to visualize three mRNA targets in each of our aforementioned brain regions of interest: eGFP, which marks neurons that input to the BNST, cFOS, a marker for neurons that are activated by social stress, and dynorphin, which indicates dynorphin expression. Colocalization of these markers indicates cells that produce dynorphin, project to the BNST and are recruited by social stress. This work is ongoing and will inform our understanding of regional involvement within the brain in dynorphin-KOR mediated stress escalated drinking.