American College of Neuropsychopharmacology

www.nature.com/npp

HOT TOPICS

Developing breakthrough psychiatric treatments by modulating G protein-coupled receptors on prefrontal cortex somatostatin interneurons

Nicole A. Crowley[1]✉ and Max E. Joffe[2,3,4]✉

Neuropsychopharmacology (2022) 47:389–390; https://doi.org/10.1038/s41386-021-01119-x

Prefrontal cortex (PFC) interneurons expressing the neuropeptide somatostatin (SST-INs) are implicated in the etiology of several psychiatric diseases [1, 2]. Emergent findings from animal models now demonstrate that PFC SST-INs are essential in orchestrating adaptive affective behaviors and that aberrant SST-IN signaling is involved in maladaptive emotive responses. An exemplary recent study by Cummings and Clem revealed that synaptic potentiation through SST-IN microcircuits mediates associative fear learning in male mice [3], suggesting shared or similar molecular mechanisms likely contribute to affective behavioral alterations in disease-relevant models. Indeed, studies from our laboratories have revealed that stress and chronic alcohol consumption alter SST-IN function [4, 5]. These studies, along with others linking SST-IN function with generalized fear, chronic pain, and acute psychosis, provide great motivation for developing translational approaches to manipulate SST-IN activity. Modulating PFC SST-INs may therefore provide avenues towards ameliorating anxious and depressive symptoms in diseases like major depressive disorder, anxiety disorders, and substance and alcohol use disorders. Nonetheless, continuing to probe how exactly SST-IN modulation affects PFC circuit function remains a key question for continued research. Recent findings suggest some SST-INs (i.e., X94 cells) inhibit other types of INs to facilitate cortical disinhibition [3], revising and updating the canonical SST-IN dendritic inhibition motif. Thus, positive and negative modulation of distinct subclasses of SST-INs harbors great diversity in opportunities for developing new SST-IN-directed treatments to sculpt PFC circuit function (Fig. 1).

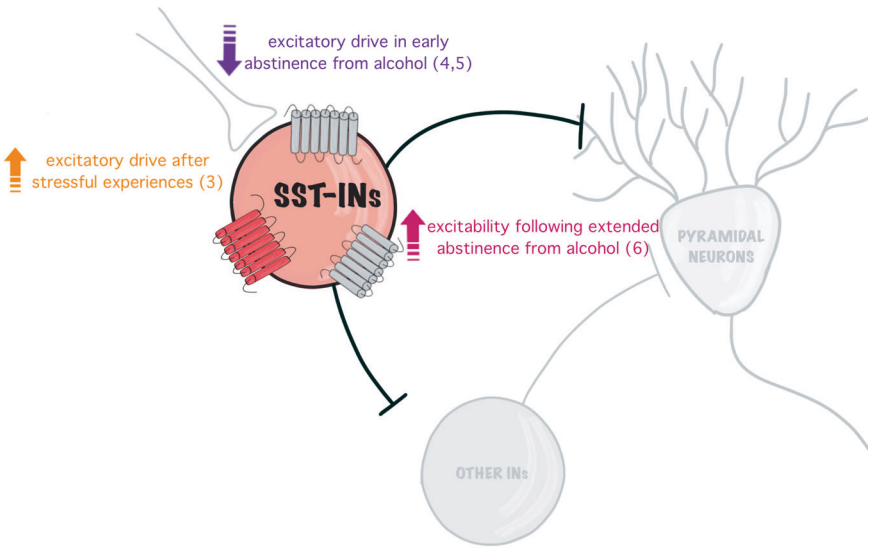

Fig. 1 Unique GPCRs expressed on PFC SST-INs may be leveraged as novel therapeutic targets for treating psychiatric disorders. Adaptations to PFC SST-INs have been observed in postmortem studies and across several preclinical models related to psychiatric disease. SST-INs exhibit unique proteomes relative to other cell types in PFC; therefore, targeting GPCRs on SST-INs represents an avenue towards circuit-specific modulation via conventional pharmacology. Proof of this concept is found in new findings indicating chemogenetic approaches and small molecule modulators of $mGlu_1$ or $mGlu_5$ receptors can modulate PFC SST-INs and disease-relevant behaviors. GPCR G protein-coupled receptor, IN interneuron, PFC prefrontal cortex, SST somatostatin.

[1]Department of Biology, Pennsylvania State University, University Park, PA, USA. [2]Department of Pharmacology, Vanderbilt University, Nashville, TN, USA. [3]Warren Center for Neuroscience Drug Discovery, Franklin, TN, USA. [4]Vanderbilt Center for Addiction Research, Nashville, TN, USA. ✉email: nzc27@psu.edu; max.joffe@vanderbilt.edu

Published online: 2 August 2021

SST-INs display unique patterns of transcript expression, splicing variants, and cell signaling pathways relative to other types of neurons in the PFC [1]. Based on this, there exists tremendous potential to harness endogenous cell type-specific mechanisms to manipulate discrete PFC microcircuits via conventional neuropharmacology. To this end, G protein-coupled receptors (GPCRs) deserve our continued attention as pharmacologically accessible targets for therapeutic intervention. GPCRs are generally expressed at the cell surface, where they respond to neurotransmitters, hormones, and other signals by initiating amplified cascades of intracellular signaling. While many widely expressed GPCRs have been explored as targets for psychiatric medications, INs contain vast untapped potential to modulate neurocircuit function through receptors with unique or limited expression patterns. For example, $mGlu_1$ metabotropic glutamate receptors are enriched in SST-INs and expressed in those cells as an uncommon splicing variant. We recently discovered that $mGlu_1$ receptors potentiate excitatory transmission on SST-INs but not neighboring pyramidal cells. Consistent with these actions, small molecule modulators conferred microcircuit-specific effects on PFC microcircuit function and disease-relevant behaviors. Studies from our labs and others leveraging chemogenetics confirm that GPCR-based manipulation of PFC SST-INs can modulate disease-relevant behaviors in animal models [6].

These new and cutting-edge examples provide exciting proof-of-concept that GPCR modulation of SST-INs can be efficacious in preclinical models related to disease. Moving forward, some less-abundant receptor subtypes for acetylcholine, monoamines, and SST itself, represent potentially straightforward paths to develop microcircuit-specific GPCR modulators. Contemporary single-cell transcriptomics studies offer extraordinary, unbiased insight into candidate GPCRs expressed in limited populations of INs as well. Leveraging these valuable datasets to develop means to modulate SST-INs and other IN subtypes will provide great opportunities for developing breakthrough treatments for psychiatric disease.

REFERENCES

1. Prevot T, Sibille E. Altered GABA-mediated information processing and cognitive dysfunctions in depression and other brain disorders. Mol Psychiatry. 2021;26:151–67. https://doi.org/10.1038/s41380-020-0727-3.
2. Duman RS, Sanacora G, Krystal JH. Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. Neuron. 2019;102:75–90. https://doi.org/10.1016/j.neuron.2019.03.013.
3. Cummings KA, Clem RL. Prefrontal somatostatin interneurons encode fear memory. Nat Neurosci. 2020;23:61–74. https://doi.org/10.1038/s41593-019-0552-7.
4. Joffe ME, Winder DG, Conn PJ. Contrasting sex-dependent adaptations to synaptic physiology and membrane properties of prefrontal cortex interneuron subtypes in a mouse model of binge drinking. Neuropharmacology. 2020;178:108126. https://doi.org/10.1016/j.neuropharm.2020.108126.
5. Dao NC, Suresh Nair M, Magee SN, Moyer JB, Sendao V, Brockway DF. et al. Forced abstinence from alcohol induces sex-specific depression-like behavioral and neural adaptations in somatostatin neurons in cortical and amygdalar regions. Front Behav Neurosci. 2020;14:86. https://doi.org/10.3389/fnbeh.2020.00086.
6. Dao NC, Brockway DF, Suresh NM, Sicher AR, Crowley NA. Somatostatin neurons control an alcohol binge drinking prelimbic microcircuit in mice. Neuropsychopharmacology.2021. https://doi.org/10.1038/s41386-021-01050-1.

ACKNOWLEDGEMENTS

We thank members of the Crowley laboratory, the Warren Center for Drug Discovery, and the Vanderbilt Center for Addiction Research for helpful discussions related to this topic. We also thank Dr. P Jeffrey Conn for supporting research led by MEJ with NIH grants.

AUTHOR CONTRIBUTIONS

MEJ conceived the topic for this commentary. NAC and MEJ contributed equally to manuscript preparation.

FUNDING INFORMATION

NAC is supported by NIH grant R21AA028088 and a NARSAD Young Investigator Award from the Brain and Behavior Research Foundation. MEJ is supported by NIH grant K99AA027806.

COMPETING INTERESTS

This commentary was prepared in the absence of any personal, professional, or financial relationships considered a conflict of interest.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to N.A.C. or M.E.J.