BIOGRAPHICAL SKETCH

NAME: Daniel J. Foster, PhD

eRA COMMONS USER NAME: fosterdj

POSITION TITLE: Research Instructor, Vanderbilt Center for Neuroscience Drug Discovery

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Bucknell University; Lewisburg, PA	BS	05/2005	Biochem/Cell Biology
University of Michigan; Ann Arbor, MI	PhD	05/2010	Pharmacology
Vanderbilt University; Nashville, TN	Postdoc	12/2015	Pharmacology

A. Personal Statement

The focus of my research is elucidating the molecular mechanisms whereby neurotransmission is regulated with the ultimate goal of identifying and validating novel therapeutic targets with which to treat psychological disorders. I have a broad scientific background in biochemistry, pharmacology, and neuroscience with specific expertise in studying the cellular, physiological, and behavioral effects of muscarinic acetylcholine receptor (mAChR) activation in both physiological and pathological conditions. During my undergraduate studies at Bucknell University, and subsequent graduate career at the University of Michigan, I received comprehensive training in biochemistry and molecular pharmacology with a particular emphasis on studying the signal transduction pathways of G-protein coupled receptors (GPCRs) and how these pathways alter ion channel and transporter function in neuronal cells. I built on these skills during my postdoctoral studies at the Vanderbilt Center for Neuroscience Drug Discovery under the mentorship of Dr. Jeff Conn by receiving world class training in the molecular pharmacology of allosteric modulators as well as in electrophysiological and electrochemical techniques for studying neuronal communication. In my current position as a Research Instructor in the Department of Pharmacology at Vanderbilt University, my research is focused on determining how acetylcholine signaling through mAChRs can regulate striatal biology by modulating dopaminergic and glutamatergic neurotransmission. I have made numerous contributions that have advanced our understanding of how individual mAChR subtypes regulate basal ganglia function and have extensive experience using multidisciplinary approaches to validate receptors as therapeutic targets in preclinical models of numerous central nervous system diseases. My previous training, motivation, and ability to establish and participate in successful collaborations make me well-suited to successfully carry out the proposed research project. These studies will provide critical mechanistic details that will inform drug discovery efforts with the goal of providing desperately needed novel therapeutic strategies to treat psychological disorders.

B. Positions and Honors

Positions and Employment

Graduate Student, Dept. of Pharmacology, University of Michigan, Ann Arbor, MI (2005-2010)
Postdoctoral Research Fellow, Dept. of Pharmacology, Vanderbilt University, Nashville, TN (2010-2015)
Research Instructor, Dept. of Pharmacology, Vanderbilt University, Nashville, TN (2015 – present)

Ad hoc Review Positions

Journal of Neurochemistry (2010-present), Neuroscience (2015-present), ACS Chemical Neuroscience (2015-present), Neuropharmacology (2016-present)

Awards and Honors

Thomas Baum travel award (2010), ASPET travel award (2008), Rackham travel award (2008), Dow Chemical scholarship (2001-2005), Bucknell University Scholarship (2001-2005)

Professional Memberships

2008-present: The American Society for Pharmacology and Experimental Therapeutics
2011-present: The Society for Neuroscience
2014-present: Member: Vanderbilt Brain Institute
2017-present: Member: International Basal Ganglia Society
2017-present: Member: Vanderbilt Kennedy Center

C. Contribution to Science

Therapeutic potential of M_4 receptor modulation of neurotransmission in the basal ganglia

The M_4 muscarinic acetycholine receptor (mAChR) holds great promise as a therapeutic target with which to treat numerous CNS disorders including movement disorders, Alzheimer's disease, and schizophrenia. Clinical evidence using mAChR agonists have suggested that activating these receptors can both reduce psychotic symptoms and enhance cognitive deficits in patients with Alzheimer's disease or schizophrenia. However, peripheral side effects mediated primarily through M_2 and M_3 receptors have limited the clinical utility of muscarinic agonists. Excitingly, M_4-selective allosteric modulators have demonstrated antipsychotic efficacy in numerous preclinical models without the adverse side-effect profile seen with mAChR agonists. While these studies provide compelling evidence that selective activation of M_4 receptors is sufficient to see antipsychotic-like effects, not much is known about the mechanism whereby these receptors mediate these effects. All currently available antipsychotics act by reducing dopamine receptor signaling and consistent with this my work found that activation of M_4 receptors could reduce dopamine release in the striatum. Using genetically modified mice I identified a subpopulation of M_4 receptors expressed on direct pathway spiny projection neurons was critical to both the effects on dopamine release and antipsychotic-like behavioral efficacy. Furthermore, we discovered that this population of M_4 receptors communicated with dopamine terminals through a cannabinoid-mediated pathway involving the CB_2 receptor. These studies provide insight into how M_4 receptors regulate dopamine release and highlight the potential utility of both M_4- and CB_2-selective compounds as novel therapeutic targets for schizophrenia. In addition to being expressed on spiny projection neurons, M_4 is also expressed on cholinergic interneurons and cortical glutamatergic inputs to the striatum making it uniquely placed to modulate basal ganglia circuitry. In early stage Huntington's disease excessive glutamatergic and dopaminergic signaling in the striatum is thought to be maladaptive and ultimately lead to striatal degeneration observed later in disease progression. Since M_4 activation can reduce both striatal glutamatergic and dopaminergic signaling we hypothesized that M_4-selective activation may normalize hyperactive signaling and slow or prevent disease progression. Excitingly, we have found that M_4 downregulation of glutamatergic signaling in the striatum was even more robust in HD mice than in control littermates and administration of M_4 modulators could prevent the onset of motor deficits in these mice. My work continues to examine the mechanisms whereby different populations of M_4 receptors can regulate the basal ganglia. These studies will be critical to determining the biological role of the M_4 receptor and potential utility of M_4-selective therapies to treat a wide range of CNS disorders.

1. **Foster DJ**, Wilson JM, Remke DH, Mahmood MS, Uddin MJ, Wess J, Patel S, Marnett LJ, Niswender DM, Jones CK, Xiang Z, Lindsley CW, Rook JM, Conn PJ. Antipsychotic-like effects of M4 positive allosteric modulators are mediated by CB2 receptor-dependent inhibition of dopamine release. *Neuron* (2016) PMC5033724
2. Pancani T**, Foster DJ,** Moehle MS, Bichell TJ, Bradley E, Bridges TM, Klar R, Poslusney M, Rook JM, Niswender CM, Jones CK, Wood MR, Bowman AB, Lindsley CW, Xiang Z, Conn PJ. Allosteric activation of M4 muscarinic receptors improve behavioural and physiological alterations in early symptomatic YAC128 mice. *Proceedings of the National Academy of Sciences* (2015) PMC4653197
3. **Foster DJ**, Choi DL, Conn PJ, Rook JM. Activation of M1 and M4 muscarinic receptors as potential treatments for Alzheimer's disease and schizophrenia. *Neuropsychiatric Disease and Treatment*. (2014) PMC3913542.

M_5 muscarinic receptor regulation of dopaminergic signaling

The M_5 muscarinic receptor has a highly restricted expression pattern where it is primarily expressed in midbrain dopamine neurons indicating that targeted intervention at this receptor could be useful for treating numerous disease in which dopaminergic signaling is disrupted such as substance abuse and schizophrenia. During my post-doctoral studies I helped to characterize the very first M_5–selective pharmacological compound that was discovered as a result of intensive medicinal chemistry efforts at the Vanderbilt Center for Neuroscience Drug Discovery. Using molecular pharmacology techniques in I found this novel compound to be highly selective for the M_5 subtype where it acted as a positive allosteric modulator (PAM). In acute brain slices using electrophysiological recordings I discovered that selective activation of M_5 increased the intrinsic excitability of dopamine neurons, providing the first direct evidence that M_5 activation could alter dopamine neuron physiology. To see if M_5 could modulate the release of dopamine directly, we collaborated with Dave Sulzer at Columbia University where I was trained in performing cyclic voltammetry experiments to directly monitor dopamine release in brain slices. Using this technique, I found that activation of M_5 in the striatum caused a significant reduction in dopamine release. This unexpected finding suggested that spatially distinct populations of M_5 receptor have opposing effects on dopamine neurons, with M_5 receptors expressed on DA neuron cell bodies leading to increased dopamine neuron excitability, and activation of M_5 in DA neuron terminals suppressing dopamine release. Unfortunately, this compound does not possess properties suitable for *in vivo* studies and efforts to further optimize M_5-selective compounds are currently ongoing. While much is left to be determined regarding the systemic effects of M_5 modulation, these studies characterizing and utilizing the very first M_5-selective small molecule provide direct evidence that M_5 activation can modulate dopaminergic signaling.

1. **Foster DJ**, Gentry PR, Lizardi-Ortiz J, Bridges TM, Wood MR, Niswender CM, Sulzer D, Lindsley CW, Xiang Z, Conn PJ. M5 receptor activation produces opposing physiological outcomes in dopamine neurons depending on the receptor's location. *The Journal of Neuroscience*. (2014) PMC3935086.
2. **Foster DJ**, Jones CK, Conn PJ. Emerging approaches for treatment of schizophrenia: modulation of cholinergic signaling. *Discovery Medicine* 14(79): 413-20, (2012) PMC3726271

Signal pathways mediating $mGlu_5$ PAM antipsychotic-like efficacy

It is becoming increasingly clear that G-protein coupled receptors are complex signaling machines that can adopt multiple conformations and induce signaling through a multitude of downstream signaling pathways. Agonists or allosteric modulators can induce “signal bias” by stabilizing some, but not all, of the active confirmations of a given receptor leading to selective activation of certain downstream signaling pathways. The ability to pharmacologically target not only a given receptor, but to selectively activate a specific signaling pathway at that receptor, provides unprecedented selectivity that could be leveraged to design efficacious drugs with reduced side-effect liability. While lots of examples of signal bias have been demonstrated *in vitro*, very few studies have been able to translate the importance of signal bias to the efficacy and side-effect profiles of drugs observed *in vivo*. As part of a collaborative effort between the Vanderbilt Center for Neuroscience Drug Discovery and Janssen Pharmaceuticals, I was able to participate in studies that differentiated what signaling pathways were important for $mGlu_5$-mediated antipsychotic activity and which pathways mediated adverse seizure activity. One signaling pathway of potential importance to both $mGlu_5$ efficacy and to unwanted seizure liability was the ability of $mGlu_5$ compounds to enhance NMDA receptor signaling. I performed whole-cell patch clamp experiments to determine what $mGlu_5$ compounds potentiated NMDA currents in CA1 hippocampal neurons and what compounds demonstrated signal bias by potentiating calcium responses, but not enhancing NMDA currents. Excitingly, we found that compounds that did not potentiate NMDA signaling could still mediate antipsychotic-efficacy. This suggests that $mGlu_5$ compounds can be designed so as to avoid NMDA receptor activation and reduce the seizure liability highlighting the potential utility of compounds displaying signal bias to provide therapeutic benefit.

1. **Foster DJ**, Conn PJ. Allosteric modulation of GPCRs: new insights and potential utility for treatment of schizophrenia and other CNS disorders. *Neuron* (2017) PMC28664928
2. Rook JM, Xiang Z, Lv X, Ghoshal A, Dickerson JW, Bridges Tm, Johnson KA, **Foster DJ**, Gregory KJ, Vinson PN, Thompson AD, Byun N, Collier RL, Bubser M, Nedelcovych MT, Gould RW, Stauffer SR, Daniels JS, Niswender CM, Lavreysen H, Mackie C, Conde-Ceide S, Alcazar J, Bartolome-Nebreda JM, Macdonald GJ, Talpos JC, Steckler T, Jones CK, Lindsley CW, Conn PJ. Biased mGlu5-positive allosteric modulators provide efficacy without potentiating mGlu5 modulation of NMDAR currents. *Neuron* (2015) PMC4443790

Cell volume regulation and modulation by G-protein couple receptors

My graduate thesis aimed to determine the molecular mechanisms whereby neurons and astrocytes actively maintain a constant volume through the coordinated regulation of ion channels and transporters. Maintenance of cell volume in the central nervous system (CNS) is critical due to the physical restrictions of the skull and pathological conditions under which these processes are overwhelmed (such as congenital heart failure, renal failure, acute trauma, or water poisoning) can have deleterious effects on CNS function and result in death. My work focused on how the activation of G-protein coupled receptors (GPCRs) could regulate these processes. These studies identified numerous receptors including muscarinic acetylcholine receptors (mAChRs) that could facilitate normalization of swollen cell volumes by inducing the release of both organic and inorganic osmolytes. Interestingly, while mAChR activation during cell swelling induced the release of both inorganic and organic osmolytes, it also induced the reuptake of inorganic osmolytes such as K^+. This highlights an important mechanism whereby receptor activation can lead to the selective loss of relatively inert compounds such as taurine while maintaining K^+ homeostasis and suggests that targeted pharmacological interventions leading to activation of these receptors could provide a novel treatment for conditions in which brain swelling is observed.

1. Fisher SK, Heacock AM, Keep RF, **Foster DJ**. Receptor regulation of osmolyte homeostasis in neural cells. *Journal of Physiology*, 588, 3355-64 (2010) PMC2988502
2. **Foster DJ**, Heacock AM, Fisher SK. Muscarinic receptor stimulation of D-aspartate uptake into human SH-SY5Y neuroblastoma cells is attenuated by hypoosmolarity. *Journal of Pharmacology and Experimental Therapeutics*, 333, 297-309 (2010) PMC2846019
3. **Foster DJ**, Vitvitsky VM, Banerjee R, Heacock AM, Fisher SK. Muscarinic receptor regulation of osmosensitive taurine transport in human SH-SY5Y neuroblastoma cells. *Journal of Neurochemistry* 108, 437-49 (2009) PMC2865146
4. **Foster DJ**, Heacock AM, Keep RF, Fisher SK. Activation of muscarinic cholinergic receptors on human SH-SY5Y neuroblastoma cells enhances both the influx and efflux of K^+ under conditions of hypo-osmolarity. *Journal of Pharmacology and Experimental Therapeutics* 325, 457-65 (2008). PMID: 18281593

A complete list of published works can be found in My Bibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/daniel.foster.1/bibliography/44032433/public/?sort=date&direction=descending

D. Research Support

Ongoing

NARSAD Young Investigator Award Foster (PI) 01/15/2016 – 01/14/2018
Brain & Behavior Research Foundation Elucidating the Mechanisms of Anti-psychotic efficacy of M4 PAMs

This project is focused on determining what populations of M_4 receptors and what downstream signaling pathways mediate the antipsychotic-like effects seen with M_4 positive allosteric modulators (PAMs) in preclinical models of schizophrenia.

Completed

F32MH095285 Foster (PI) 07/01/2011 – 06/30/2014
NIH/NIMH NRSA Postdoctoral Fellowship Elucidation of M_5 neurophysiology using allosteric modulators

The long-term goal of this award was to utilize novel allosteric modulators of the M_5 muscarinic receptor (mAChR) to elucidate the physiological consequence of M_5 receptor activation in dopaminergic neurons.

T32GM007767 Hollenberg (PI) 07/01/2006 – 06/30/2008
NIH/NIGMS Predoctoral Training Grant Interdepartmental training in pharmacological sciences

As a predoctoral student I participated in this training which provided students with a strong foundation in basic pharmacological principles, biochemistry, and medicinal chemistry.