



Gloria E. Meredith, Ph.D. Professor & Chair

Mechanisms of neurodegeneration and addiction pathology

General Research Interests:

Mechanisms underlying novel therapies for Parkinson's disease

Addiction pathology: structure & function of the amygdala with drug abuse (see poster from Rademacher lab)

Main Research Techniques

Systems approach using neuroanatomy

Behavioral models:

- Mouse and rat models of Parkinson's disease
- Conditioned place preference

Immunohistochemistry

Quantitative approaches to the nervous system including electron microscopy, confocal microscopy and in situ hybridization

Lab Members



Gloria Meredith
Professor
PhD 1983
Georgetown University
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Maud Morshedi, PhD
Previous graduate Student
Now finishing his M.D. degree
Rosalind Franklin University



David Rademacher
Research Assistant Professor
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Nathaniel Klein
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Figen Seiler
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Recent Publications & Funding

FUNDING: R01 NIH/NIDA: Mechanisms underlying reward-related synaptogenesis
R01 NIH/NINDS: Aberrant synaptic plasticity: Impact on dopamine graft outcome

PUBLICATIONS:

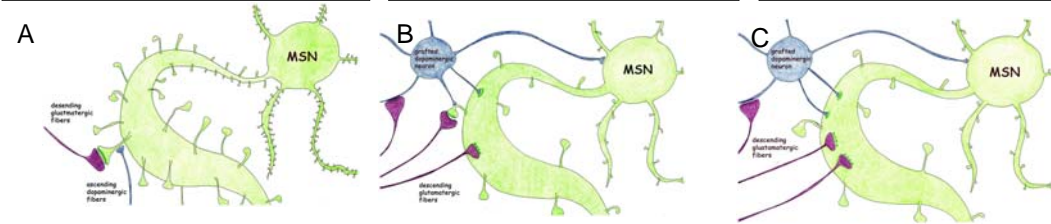
- Rademacher DJ, Kovacs B, Shen F, Napier TC, Meredith GE (2006) The neural substrates of amphetamine conditioned place preference: implications for the formation of context-reward associations. *Eur J Neurosci*, 24:2089-2097.
- Rademacher DJ, Napier TC, Meredith GE (2007) Context modulates the expression of conditioned motor sensitization, cellular activation and synaptophysin immunoreactivity. *Eur J Neurosci* 26:2661-2668.
- Chan CS, Guzman JN, Iljic E, Mercer JN, Rick C, Tkatch T, Meredith GE, Surmeier DJ (2007) 'Rejuvenation' protects neurons in mouse models of Parkinson's disease. *Nature*, 447:1081-1086.
- Potashkin JA, Kang UJ, Loomis PA, Jodelka FM, Ding Y, Meredith GE (2007) MPTP administration in mice changes the ratio of splice isoforms of fosB and rgs9. *Brain Res* 1182:1-10.
- Morshedi MM, Meredith GE (2007) Differential laminar effects of amphetamine on prefrontal parvalbumin interneurons. *Neuroscience* 149:617-624.
- Morshedi MM, Meredith GE (2007) Repeated amphetamine administration induces Fos in prefrontal cortical neurons that project to the lateral hypothalamus but not the nucleus accumbens or basolateral amygdala. *Psychopharmacology*, 197:179-189.
- Geisler S, Marinelli M, DeGarmo B, Becker ML, Freiman AJ, Beales M, Meredith GE, Zahm DS (2007) Prominent activation of brainstem and pallidal afferents of the ventral tegmental area by cocaine. *Neuropsychopharmacology*. doi:10.1038/sj.npp.1301650.
- Meredith GE, Baldo BA, Andrezewski ME, Kelley AE (2008) The structural basis for mapping behavior onto the ventral striatum and its subdivisions. *Brain Struct Funct* doi:10.1007/s00429-008-0175-3.
- Meredith GE, Sonsalla PK, Chesselet M-F (2008) Animal models of Parkinson's disease progression. *Acta Neuropathol* 115:385-398.
- Meredith GE, Totterdell S, Potashkin JA, Surmeier DJ (2008) Modeling PD pathogenesis in mice: Advantages of a chronic MPTP model. *Parkinsonism Relat Disord* 14: S112-S115.
- Morshedi MM, Rademacher DJ, Meredith GE (2008) Increased synapses in the medial prefrontal cortex are associated with repeated amphetamine administration. *Synapse*, in press.

Project: plasticity underlying graft-induced dyskinesias in a rat model of Parkinson's disease

In the healthy striatum, descending glutamatergic fibers from the cortex and thalamus synapse onto the heads of the spines of the resident medium spiny neurons (MSN). This excitatory input is modulated by the ascending dopaminergic fibers from the substantia nigra that synapse onto the necks of these spines.

In the grafted striatum, there was a significant change in the distribution of symmetrical to asymmetrical (presumably excitatory synapses). Grafted dopaminergic fibers made more atypical connections onto MSN dendrites and perikarya.

The increase in asymmetrical TH+ endings seen following grafting was exacerbated in the immune-challenged striatum. The shift in the distribution of TH+ synaptic targets increased in the immune-challenged striatum.



Hypothesis and specific aims

Our findings suggest that aberrant synaptic features between TH+ grafted cells and host MSN, result in the development of aberrant behaviors following dopamine cell grafting. Changes in the distribution of TH+ synaptic target and symmetry and the increased asymmetrical input onto grafted cell bodies suggest that the striatal environment following grafting is one of unregulated hyperdopaminergic activity known to be associated with dyskinesias. Changes in corticostriatal inputs also appear to be associated with dyskinetic behaviors observed post-grafting. Finally, the increases seen in several of the synaptic features with increased host immune response, suggest a possible mechanism by which the immune response may be mediating GIDs.

Our future work hypothesizes that **the loss of dendritic spines on MSNs interferes with the capacity of grafted DA neurons to provide full therapeutic benefit to parkinsonian subjects.**

Specific Aims: Although the primary neurochemical deficiency in Parkinson's disease is related to death of nigral dopamine (DA) neurons that innervate the striatum, it is not clear precisely how this alteration leads to symptoms of the disease. It is clear that DA denervation results in numerous changes in transmitter function and altered neuron morphology. Specifically, the primary site for afferent input from nigral DA neurons and cortical glutamate neurons is medium spiny neurons (MSNs) within the striatum. *The numerous dendritic spines found on normal MSNs are critical sites for synaptic integration of DA and glutamate signaling, which is essential for normal motor behavior.* In advanced PD there is a marked atrophy of dendrites and spines on these neurons. Similar pathology is observed in mice and rats with severe DA depletion (e.g.: Day et al, 2006). Importantly, a new mechanism involving dysregulation of intraspine Cav1.3 L-type Ca²⁺ channels has been found to account for spine loss following striatal DA depletion. Administration of the calcium channel antagonist nimodipine to rats, or the absence of these channels in transgenic mice prevents spine loss despite severe DA depletion. The impact of altered dendritic morphology of MSNs in the parkinsonian striatum on therapeutics such as DA cell replacement or traditional pharmacotherapy remain unclear. However, it would be anticipated that an absence of these critical input sites in the parkinsonian striatum would make it difficult: 1) for grafted DA neurons to re-establish normal connections needed for therapeutic benefit, and 2) for standard pharmacotherapy to recapitulate normal physiological responses in the face of altered synaptic connectivity. The proposed set of studies is aimed at addressing two primary issues related to DA-glutamate maladaptive synaptic plasticity in the parkinsonian brain. The first set of studies will examine whether degenerative changes in spine density of MSN impacts DA graft efficacy. A second set of studies will examine whether altered spine morphology plays a role in the development of levodopa-induced and/or DA graft-induced dyskinetic behavior.

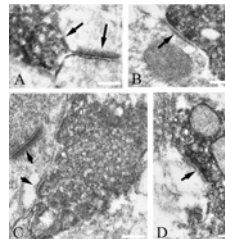


Figure: Electron micrographs illustrating the synapses of grafted neurons in the striatum.