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Samuel J. Rose Date

**A new mouse model of l-DOPA-responsive dystonia**

By

Samuel J. Rose

Doctor of Philosophy

Graduate Division of Biological and Biomedical Science

Neuroscience

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**A new mouse model of l-DOPA-responsive dystonia**

By

Samuel J. Rose

B.S., University of Georgia, 2008

Advisor: Ellen J. Hess, PhD

An abstract of a dissertation submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

In partial fulfillment of the requirements for the degree of

Doctor of Philosophy in Neuroscience

2015

**Abstract**

A new mouse model of l-DOPA-responsive dystonia

By

Samuel J. Rose

Dystonia is a neurological movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements or postures. Abnormal dopamine neurotransmission is associated with many different dystonic disorders. For instance, mutations in genes critical for the synthesis of dopamine, including GTP cyclohydrolase 1and tyrosine hydroxylasecause l-DOPA-responsive dystonia. Despite evidence that implicates abnormal dopamine neurotransmission in dystonia, the precise nature of the dopaminergic defects that result in dystonia is not known. To better understand these defects, we generated a knockin mouse model of l-DOPA-responsive dystonia that recapitulates the human p.381Q>K TH mutation (c.1141C>A). Mice homozygous for this mutation (DRD mice) had reduced TH activity throughout the brain and striatal dopamine concentration that were ~1% of normal. Although the gross anatomy of the nigrostriatal dopaminergic neurons was normal in DRD mice, the microstructural target of corticostriatal synapses was affected; corticostriatal input in DRD mice showed a shift away from synapses on dendritic spines towards dendrites themselves. DRD mice displayed the core behavioral features of the human disorder, including dystonia that worsened throughout the course of the active phase, and improvement in the dystonia in response to both l-DOPA and trihexyphenidyl. Administration of D1- or D2-type dopamine receptor agonists reduced the dystonic movements while administration of D1- or D2-type dopamine receptor antagonists worsened the dystonia, suggesting that both receptors mediate the dystonic movements. Further, D1-dopamine receptors were supersensitive; adenylate cyclase activity, locomotor activity and stereotypy were exaggerated in DRD mice in response to the D1-dopamine receptor agonist SKF 81297. D2-dopamine receptors responses were blunted or altered in DRD mice with an increase in adenylate cyclase activity and blunted behavioral responses after challenge with the D2-dopamine receptor agonist quinpirole. Together, the findings here implicate developmental dopamine loss within a specific range in the development of dystonia. Further, they implicate maladaptive changes to dopamine receptor responses as important factors for this disorder.

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**List of Abbreviations**

l-DOPA = 3,4- l-dihydroxyphenylalanine

DRD = l-DOPA-responsive dystonia

DA = dopamine

NE = norepinephrine

DOPAC = 3,4-dihydroxypheynlacetic acid

5-HT = serotonin

5-HIAA = 5-hydroxyindoleacetic acid

l-DOPS = 3,4-l-dihydroxyphenylserine

BH4 = tetrahydrobiopterin

cAMP = cyclic adenosine monophosphate

GCH1 = guanosine triphosphate cyclohydrolase 1

TH = tyrosine hydroxylase

DAT = dopamine transporter

VMAT2 = vesicular monoamine transporter 2

AADC = aromatic acid decarboxylase

D1DAR = D1-type DA receptor

D2DAR = D2-type DA receptor

AC = adenylate cyclase

vGluT1 = vesicular glutamate transporter 1

vGluT2 = vesicular glutamate transporter 2

SNc = substantia nigra pars compacta

SNr = substantia nigra pars reticulata

VTA = ventral tegmental area

GPi = internal globus pallidus

GPe = external globus pallidus

STN = subthalamic nucleus

MSN = medium spiny neuron

Ctx = cerebral cortex

Hipp = hippocampus

Cbm = cerebellum

MAO = monamine oxidase

COMT = catechol-o-methyltransferase

PKA = cAMP-dependent protein kinase A

ERK = extracellular signal-regulated kinase

CaMKII = CaM-phospokinase 2

DARPP-32 = 32-kD DA and cAMP-regulated phosphoprotein

DBS = deep brain stimulation

LTD = long term depression

6-OHDA = 6-hydroxydopamine

MPTP = 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine

PD = Parkinson’s disease

LID = l-DOPA-induced dyskinesia

HPLC = high performance liquid chromatography

FDG-PET = [18F]-fluorodeoxyglucose positron-emission tomography

fMRI = functional magnetic resonance imaging

Neo = Neomycin resistance cassette

PCR = polymerase chain reaction

qRT-PCR = quantitative reverse transcriptase PCR

TBS = Tris-buffered saline

NGS = normal goat serum

s.c. = subcutaneous