Blood pressure – a window of opportunities…

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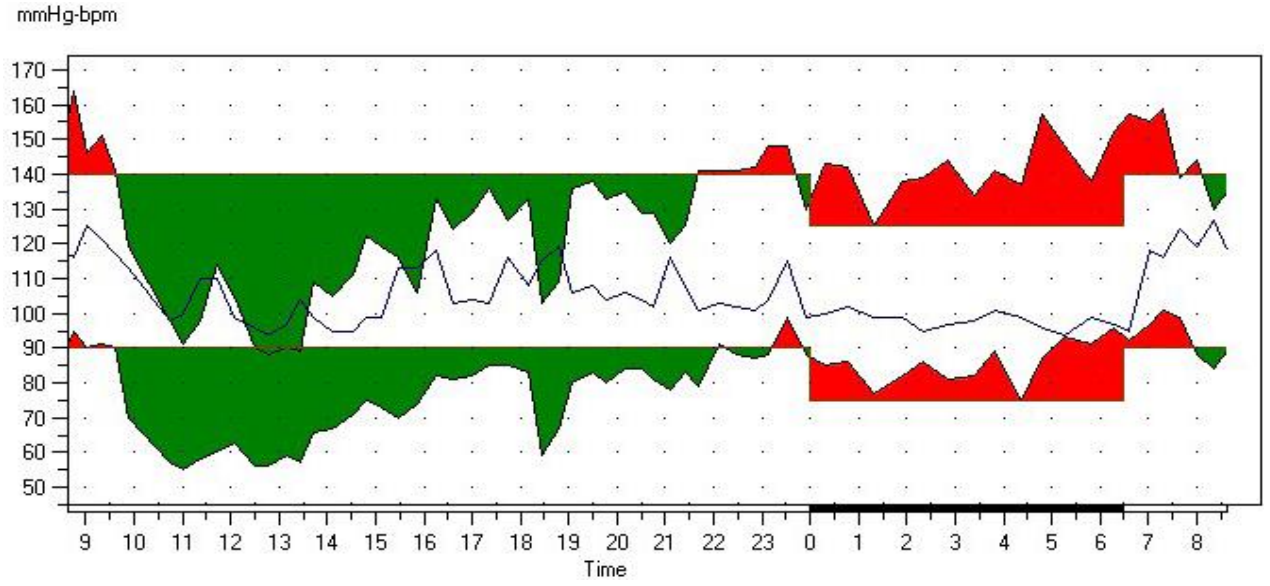
Blood pressure control in PD:

78 y/o female, PD for 12 years, on sinemet, weakness, recurrent falls, distal radius fracture, miserable!



Association Between Supine Hypertension and Orthostatic Hypotension in Autonomic Failure

David S. Goldstein, Sandra Pechnik, Courtney Holmes, Basil Eldadah, Yehonatan Sharabi

Abstract—Supine hypertension occurs commonly in primary chronic autonomic failure. This study explored whether supine hypertension in this setting is associated with orthostatic hypotension (OH), and if so, what mechanisms might underlie this association. Supine and upright blood pressures, hemodynamic responses to the Valsalva maneuver, baroreflex-cardiovagal gain, and plasma norepinephrine (NE) levels were measured in pure autonomic failure (PAF), multiple-system atrophy (MSA) with or without OH, and Parkinson's disease (PD) with or without OH. Controls included age-matched, healthy volunteers and patients with essential hypertension or those referred for dysautonomia. Baroreflex-cardiovagal gain was calculated from the relation between the interbeat interval and systolic pressure during the Valsalva maneuver. PAF, MSA with OH, and PD with OH all featured supine hypertension, which was equivalent in severity to that in essential hypertension, regardless of fludrocortisone treatment. Among patients with PD or MSA, those with OH had higher mean arterial pressure during supine rest (109±3 mm Hg) than did those lacking OH (96±3 mm Hg, $P=0.002$). Baroreflex-cardiovagal gain and orthostatic increments in plasma NE levels were markedly decreased in all 3 groups with OH. Among patients with PD or MSA, those with OH had much lower mean baroreflex-cardiovagal gain (0.74±0.10 ms/mm Hg) than did those lacking OH (3.13±0.72 ms/mm Hg, $P=0.0002$). In PAF, supine hypertension is linked to both OH and low baroreflex-cardiovagal gain. The finding of lower plasma NE levels in patients with than without supine hypertension suggests involvement of pressor mechanisms independent of the sympathetic nervous system. **(*Hypertension*. 2003;42:136-142.)**

Key Words: hypertension, essential ■ hypotension ■ Parkinson's disease ■ autonomic nervous system ■ sympathetic nervous system ■ norepinephrine

Objectives

- Blood pressure regulation abnormalities in PD
- Neurogenic OH
- Selective post-ganglionic sympathetic denervation
- Mechanisms
- Biomarkers of disease process – PD Risk
- Future prevention and disease-modifying intervention

Orthostatic Hypotension Common in PD

Senard et al.	J Neurol Neurosurg Psychiatry 1997;63:584-9	58%
Bellon et al.	Dtsch Med Wochenschr 1996;121:1077-83	65%
Micieli et al.	Neurology 1987;37:386-93	54%

Orthostatic hypotension defined by $\geq$ 20 mm Hg fall in systolic blood pressure between supine and upright 5 minutes.

How do we establish a neurogenic nature of OH in PD?

Contemporary Reviews in Cardiovascular Medicine

Neurogenic Orthostatic Hypotension

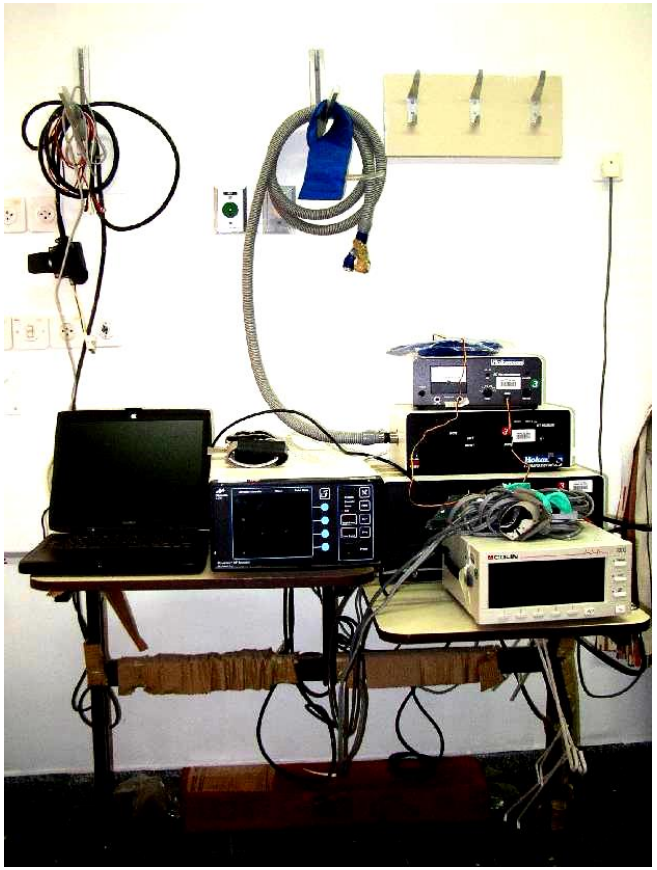
A Pathophysiological Approach

David S. Goldstein, MD, PhD; Yehonatan Sharabi, MD

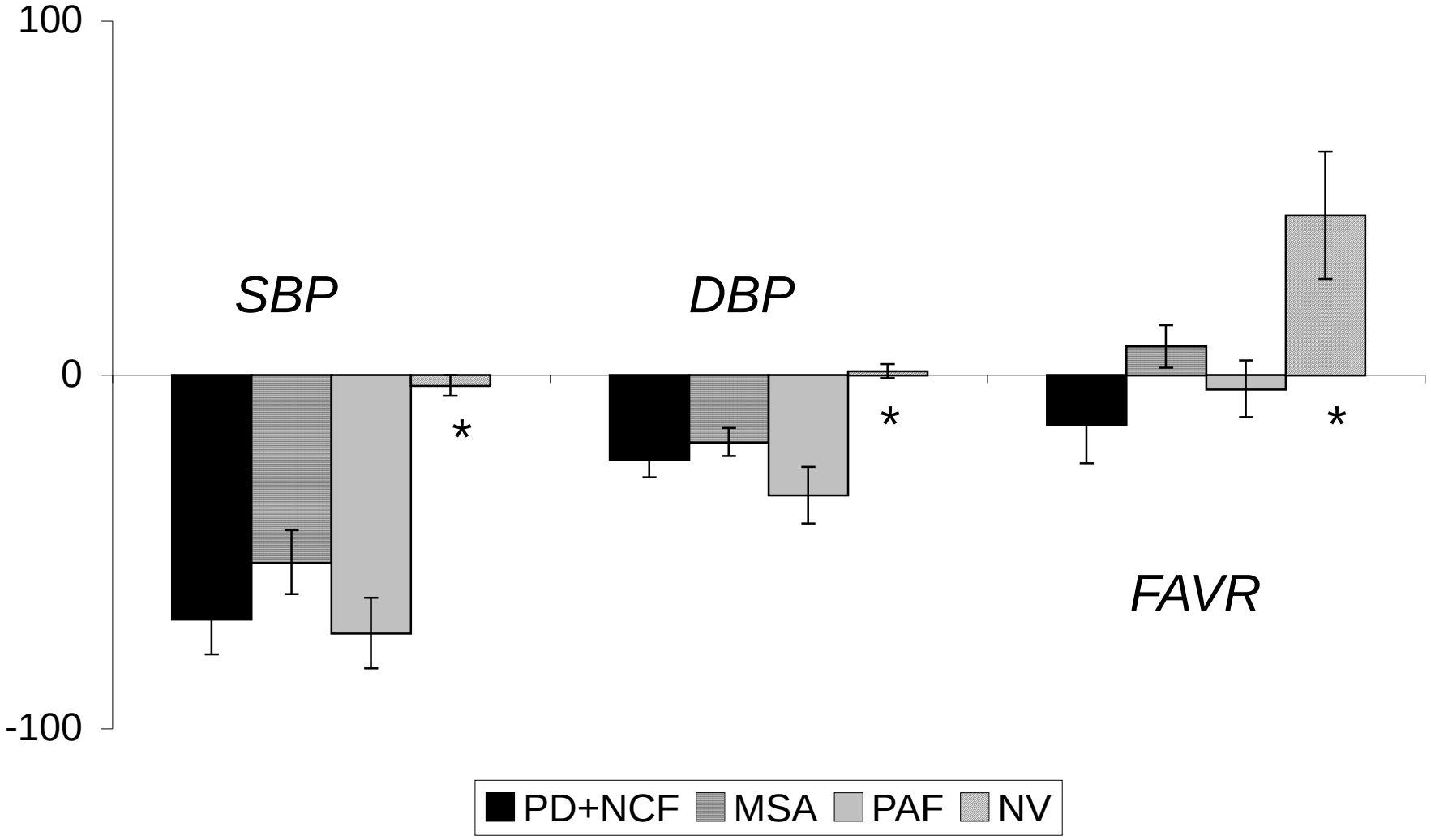
Circulation 2011

Clinical Autonomic Lab

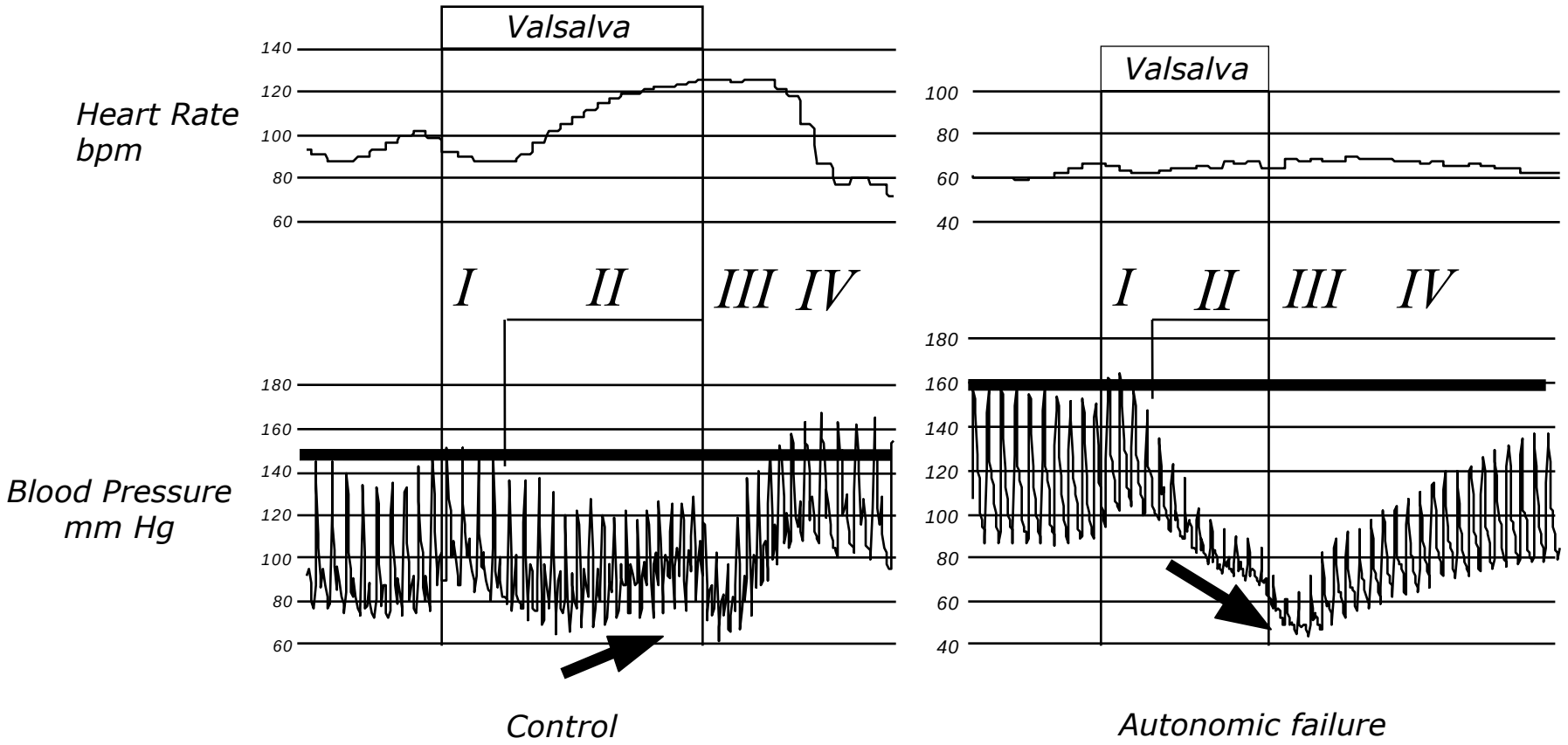
- Beat to beat BP monitor
- ECG
- Forearm blood flow
- Plasma CA measurements (HPLC)
- Neuroimaging (MIBG or FDA PET)



HEMODYNAMIC RESPONSES TO ORTHOSTASIS



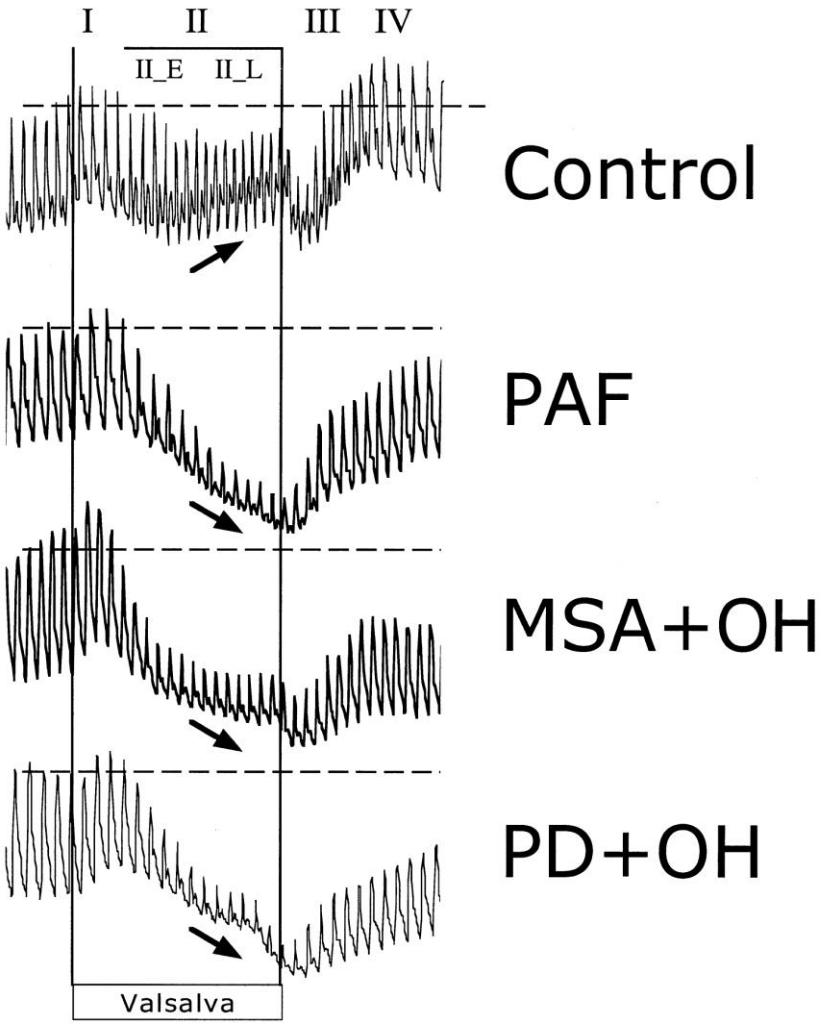
Valsalva maneuver



Lessons from Primary Chronic Autonomic Failure Syndromes

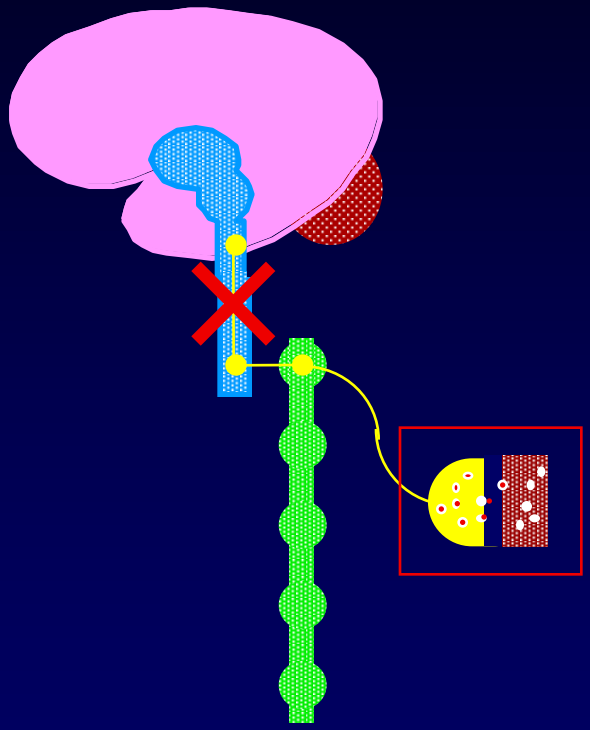
- PAF
- MSA
- PD+NOH

BP responses to the Valsalva maneuver in a control patient and in patients with OH associated with PAF, MSA, and PD

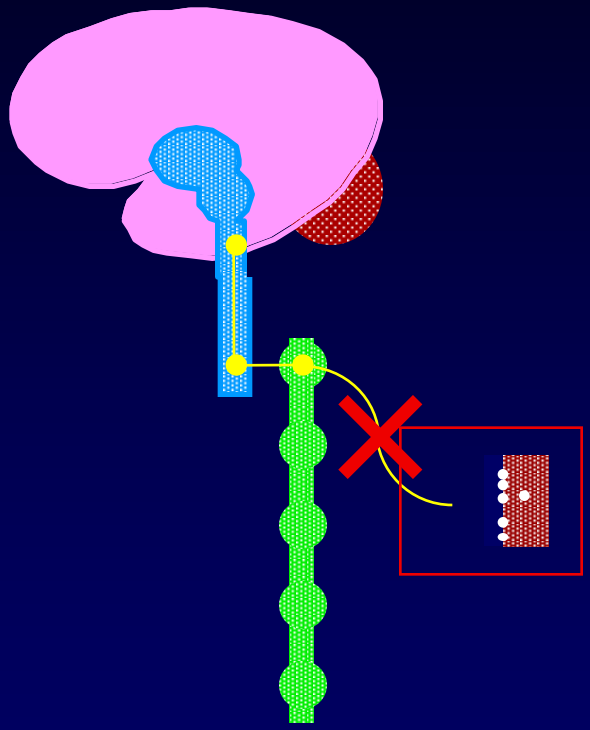


Goldstein, D. S. et al. Hypertension 2003;42:136-142

Where is the Lesion?



Pre-Ganglionic



Post-Ganglionic

Original Article

CLINICAL
NEUROPHARMACOLOGY

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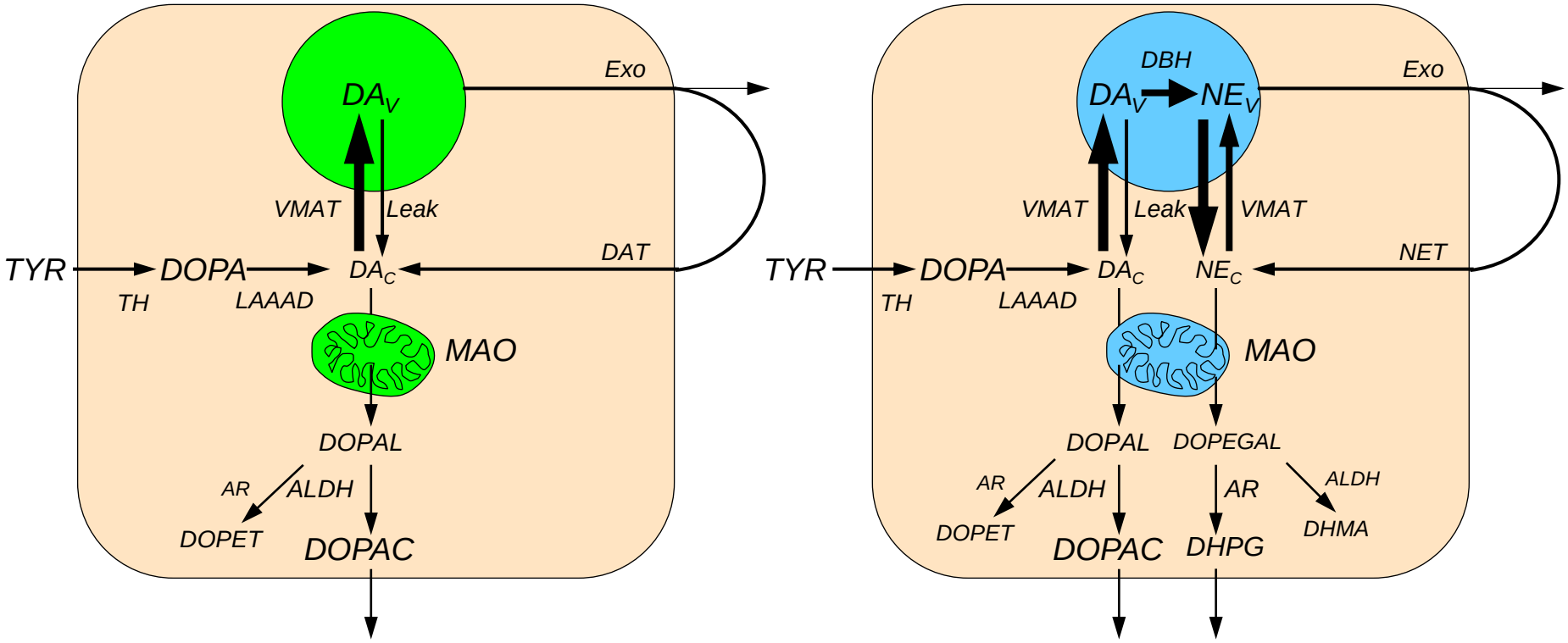
Neuropharmacologic Distinction of Neurogenic Orthostatic Hypotension Syndromes

Yehonatan Sharabi, MD, Basil Eldadah, MD, PhD, Sheng-Ting Li, MD, PhD, Rhaguveer Dendi, MD, Sandra Pechnik, RN, Courtney Holmes, CMT, and David S. Goldstein, MD, PhD

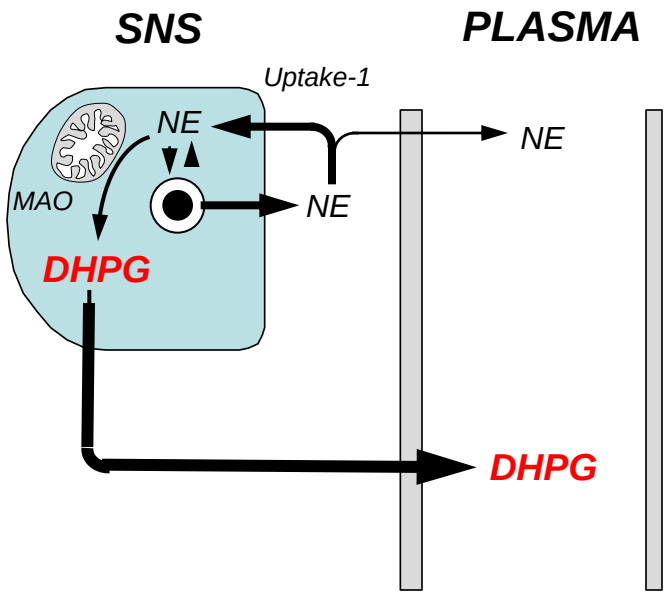
Sympathetic Noradrenergic Tests

- *Plasma DHPG & NE*
- *Microdialysate DHPG*
- *Tyramine*
- *Isoproterenol*
- *Trimethaphan*
- *Yohimbine*

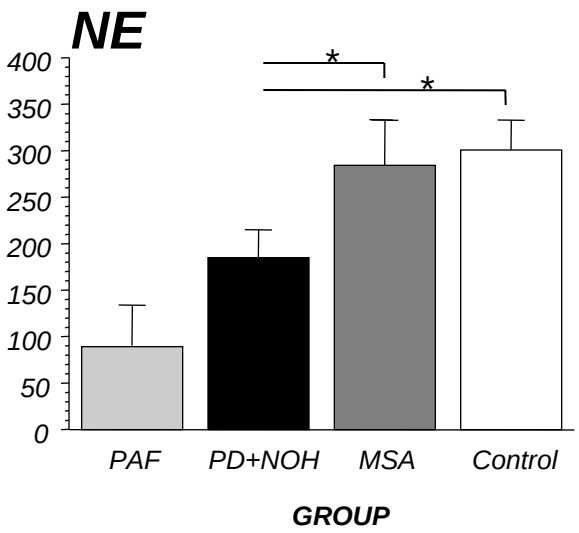
FIGURE 1

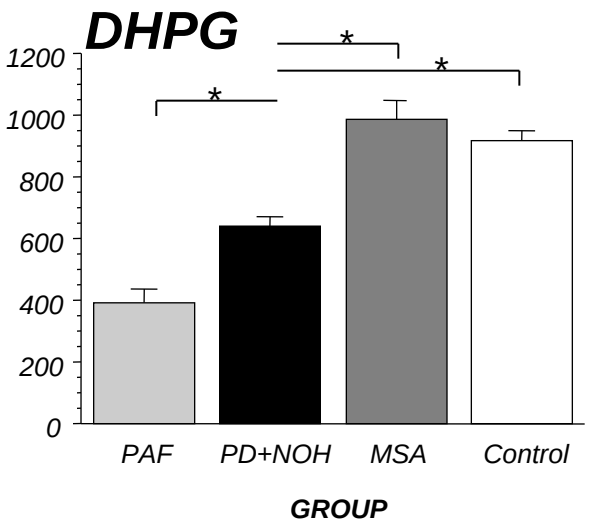

DA_V
Exo
VMAT
Leak
TYR
DOPA
DA_C
DAT
TH
LAAAD
MAO
DOPAL
AR
ALDH
DOPET
DOPAC
DBH
DA_V
NE_V
Exo
VMAT
Leak
VMAT
NET
TYR
DOPA
DA_C
NE_C
TH
LAAAD
MAO
DOPAL
DOPEGAL
AR
ALDH
AR
ALDH
DOPET
DOPAC
DHPG
DHMA

DHPG vs. NE Sources

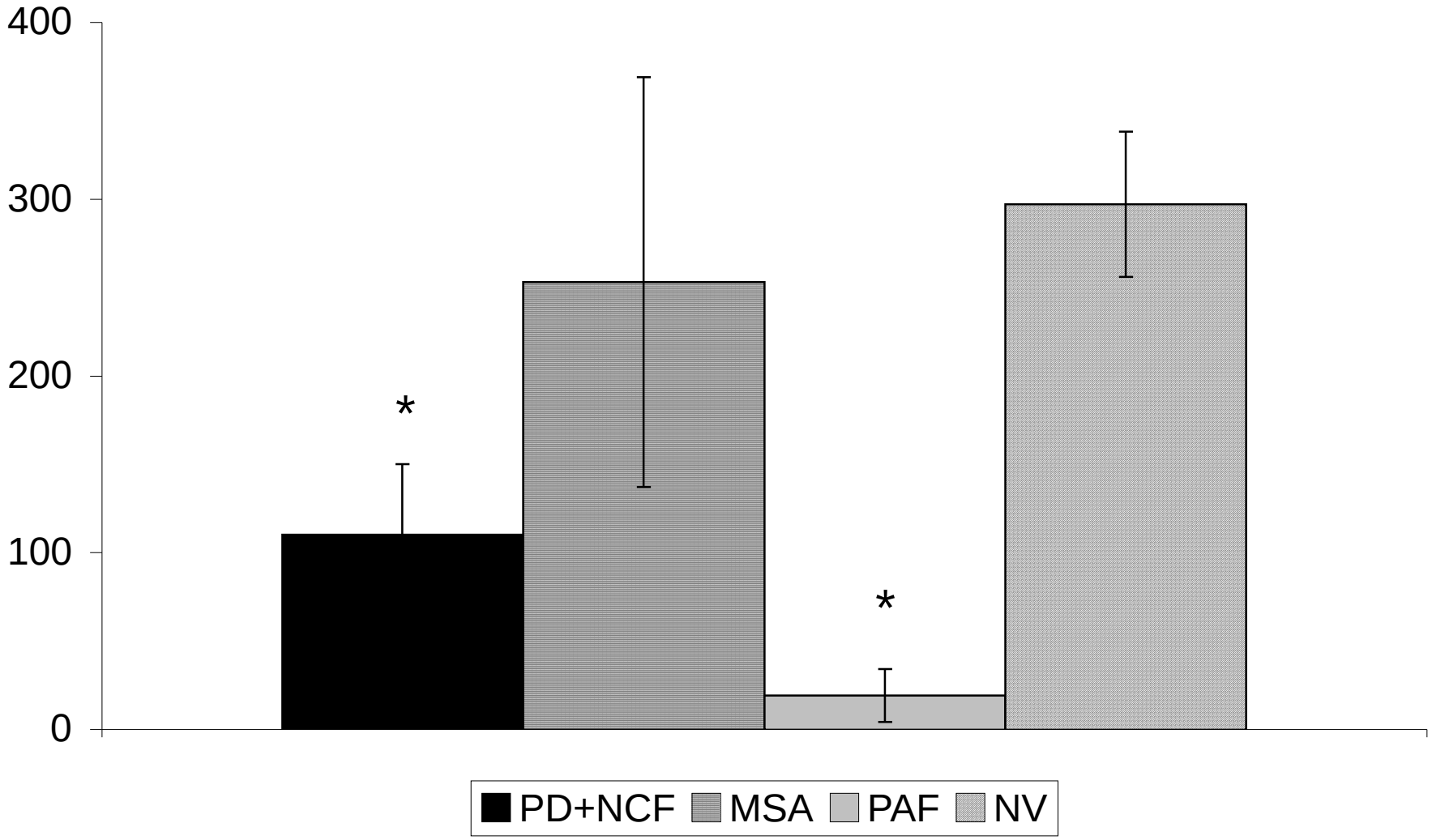


PLASMA CATECHOLS (pg/mL)

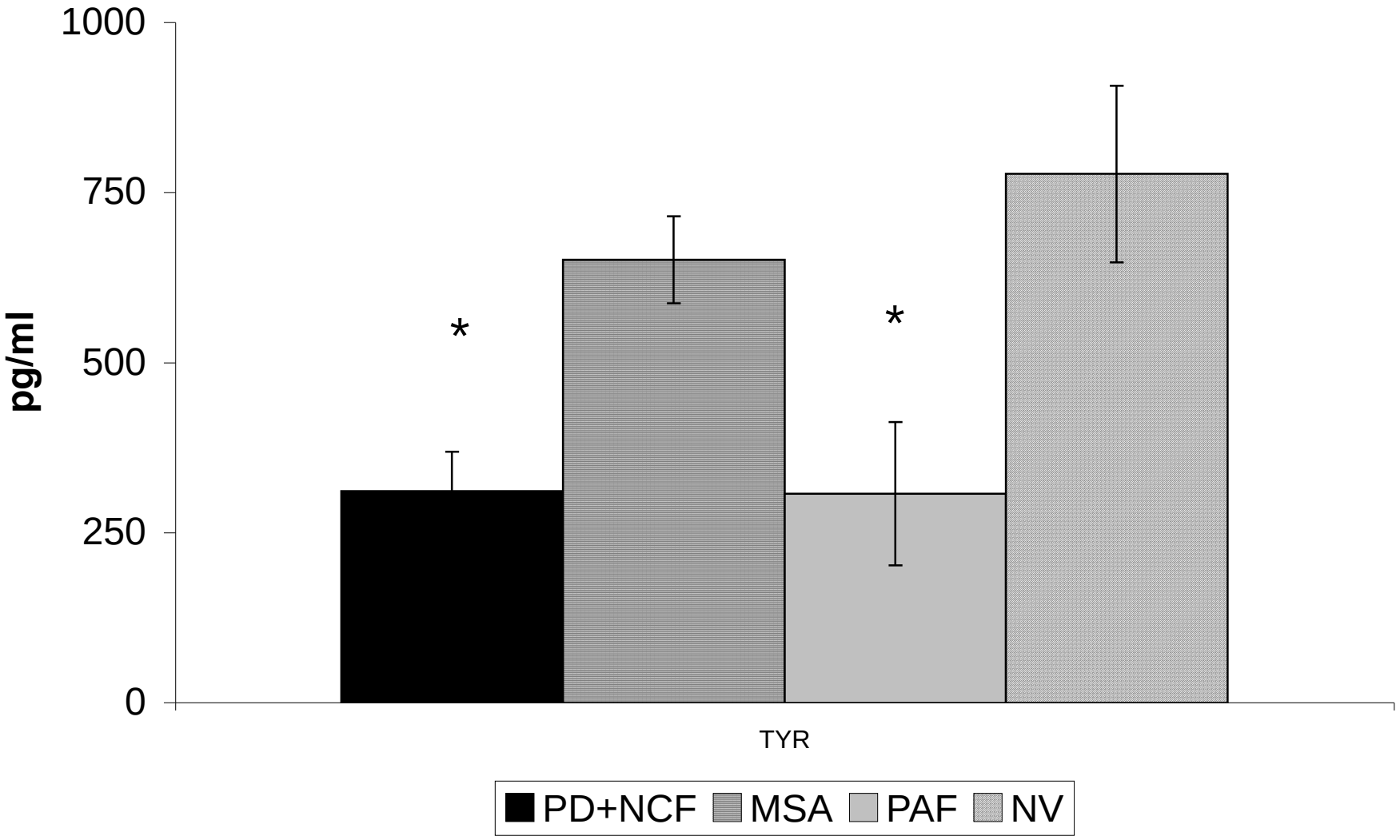


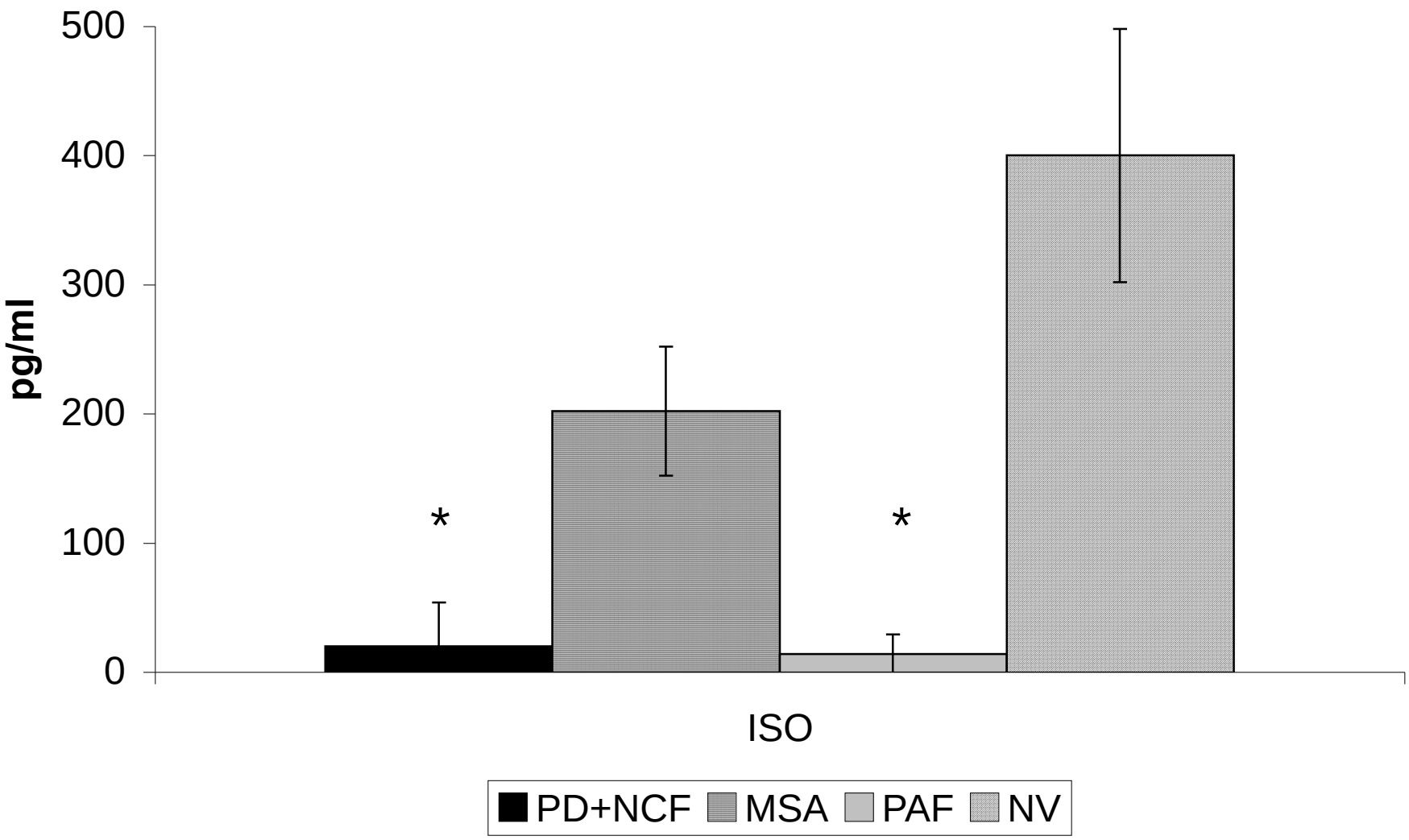


NE RESPONSES TO ORTHOSTASIS



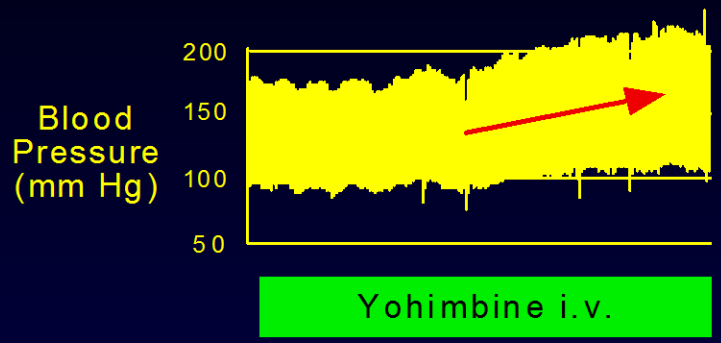
DHPG RESPONSES TO TYRAMINE

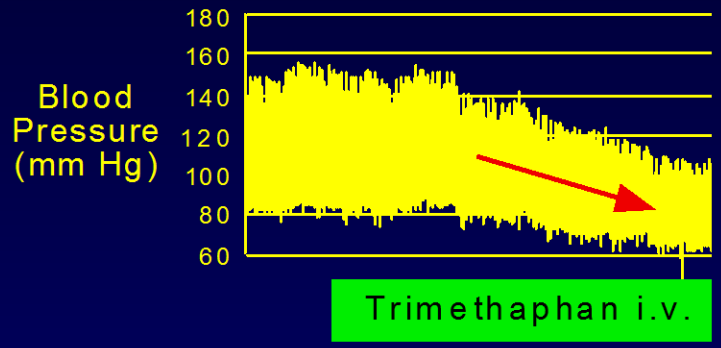



NE RESPONSES TO ISOPROTERENOL
500
400
300
200
100
0
pg/ml
*
*
ISO
PD+NCF
MSA
PAF
NV

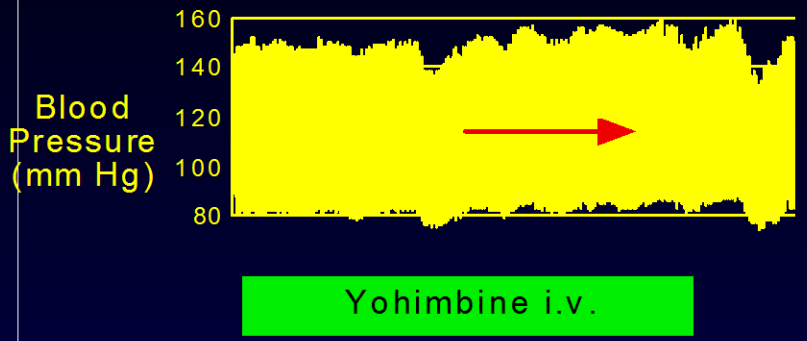
Yohimbine & Trimethaphan

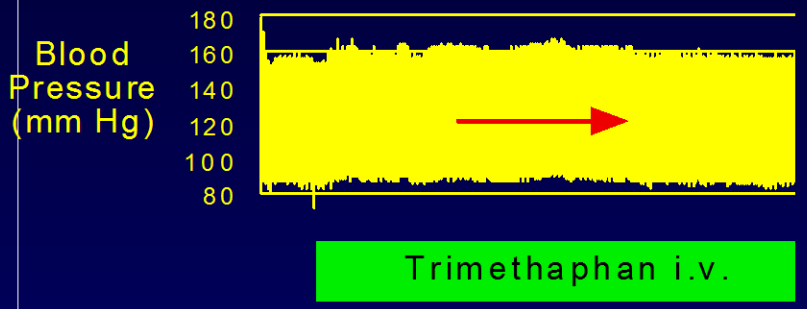
MSA+SNF

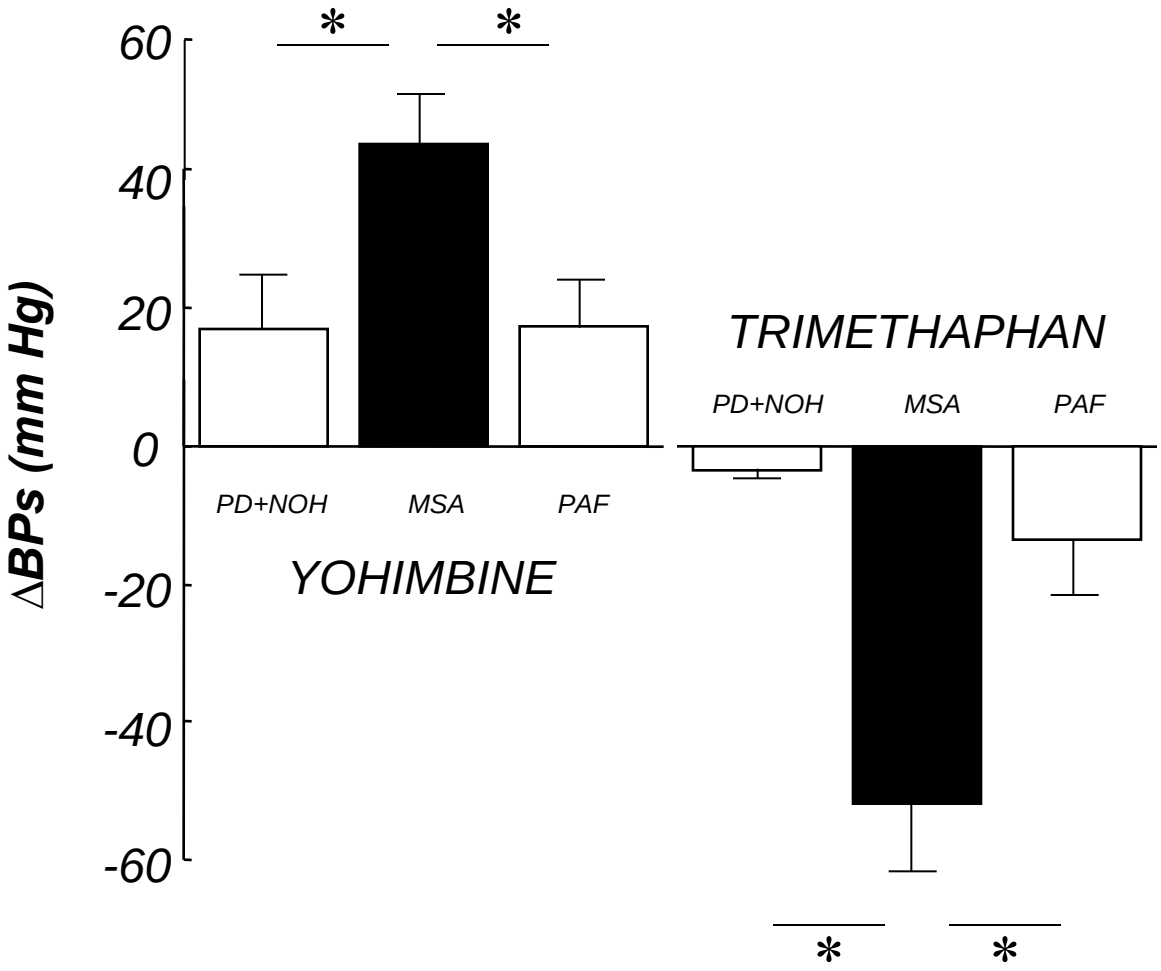




Park+SNF





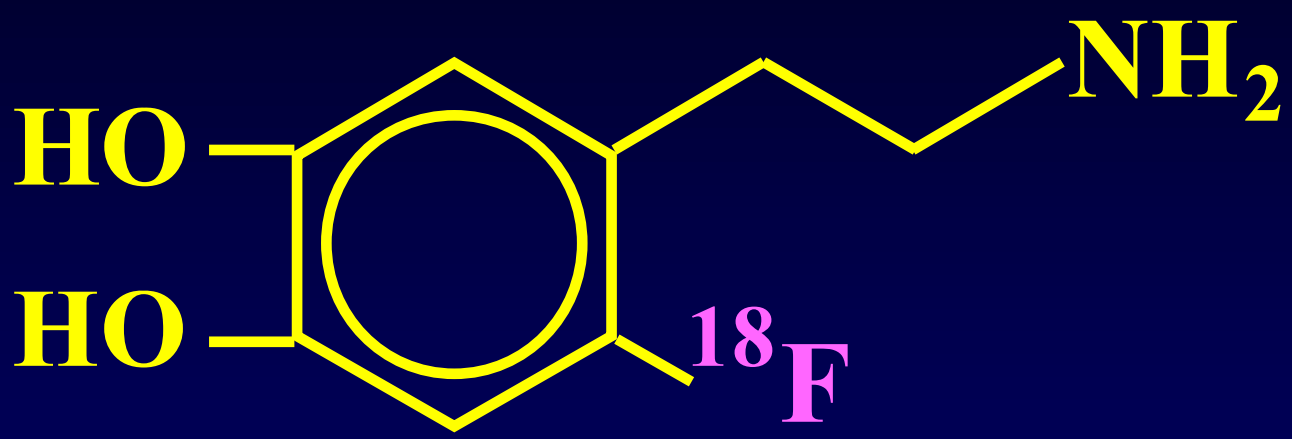

60
40
20
0
-20
-40
-60
ΔBPs (mm Hg)
*
*
PD+NOH
MSA
PAF
YOHIMBINE
TRIMETHAPHAN
PD+NOH
MSA
PAF
*
*

Cardiac ^{123}I-MIBG in PD

First Author	Journal	Year	Finding
Orimo	Neurology	2001	123I myocardium in PD, not MSA
Taki	Eur J Nucl Med	2000	123I myocardium in PD, not MSA
Reinhardt	Eur J Nucl Med	2000	123I myocardium in PD, not MSA
Druschky A	J Neurol Sci	2000	123I myocardium in PD, not MSA
Takatsu	J Nucl Med	2000	123I myocardium in PD, not MSA
Takatsu	JAMA	2000	123I myocardium in PD, not MSA
Braune	Neurology	1999	123I myocardium in PD, not MSA
Orimo	J Neurol Neurosurg Psychiatry	1999	123I myocardium in PD, not MSA
Satoh	J Nucl Med	1999	123I myocardium in PD, not MSA
Yoshita	Nucl Med Commun	1998	123I myocardium
Yoshita	J Neurol Sci	1998	123I myocardium in PD, not PSP
Braune	Acta Neurol Scand	1998	Dec. 123I myocardium
Satoh	Nippon Rinsho	1997	Dec. 123I myocardium

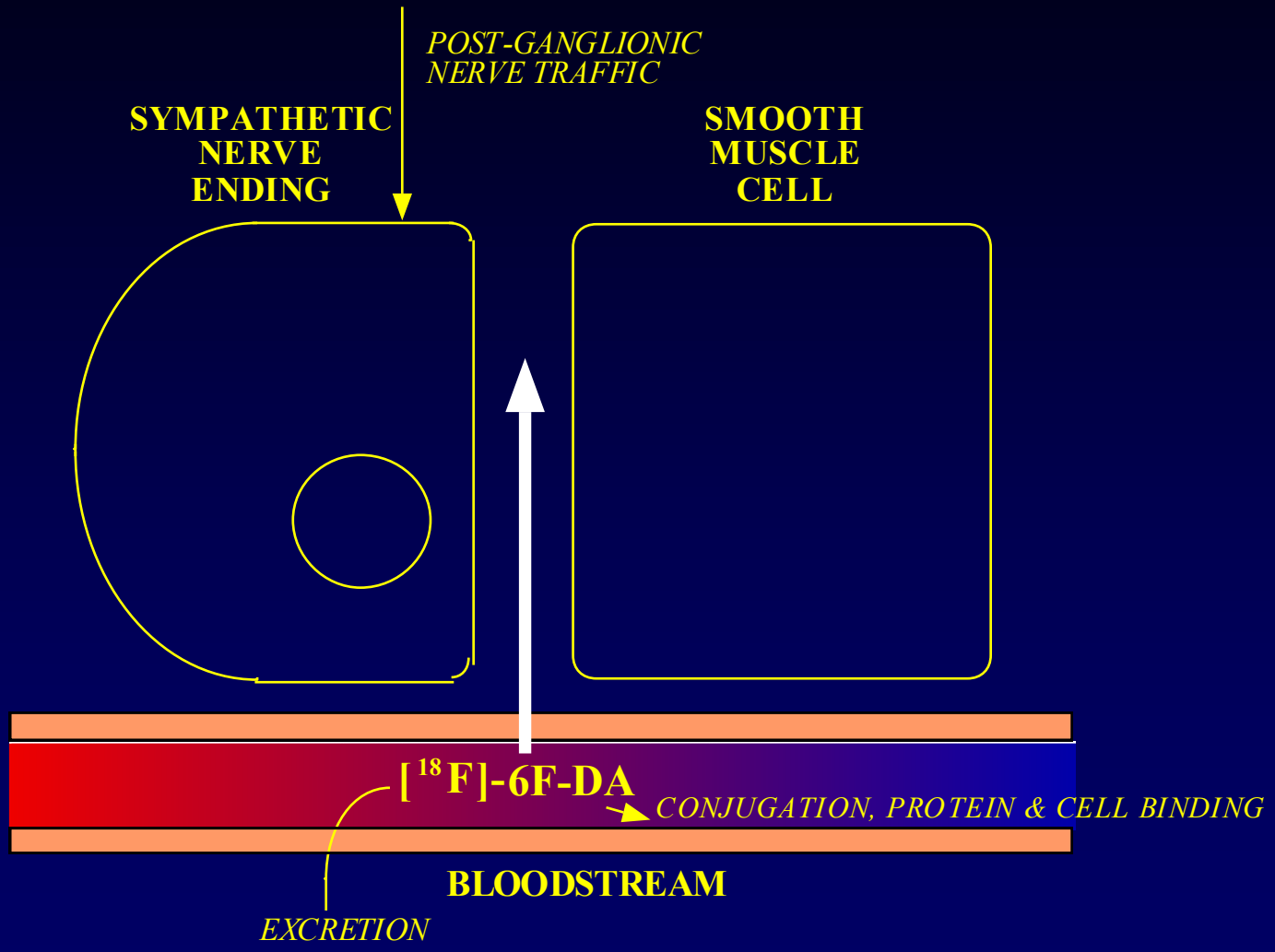
- Low cardiac ^{123}I-MIBG in PD, not MSA.
- Heart-selective, independent of AF, related to severity of PD & age.

6-[^{18}F]Fluorodopamine



Goldstein et al., Circulation 1990;81:1606-1621

Fate of 6-[^{18}F]Fluorodopamine

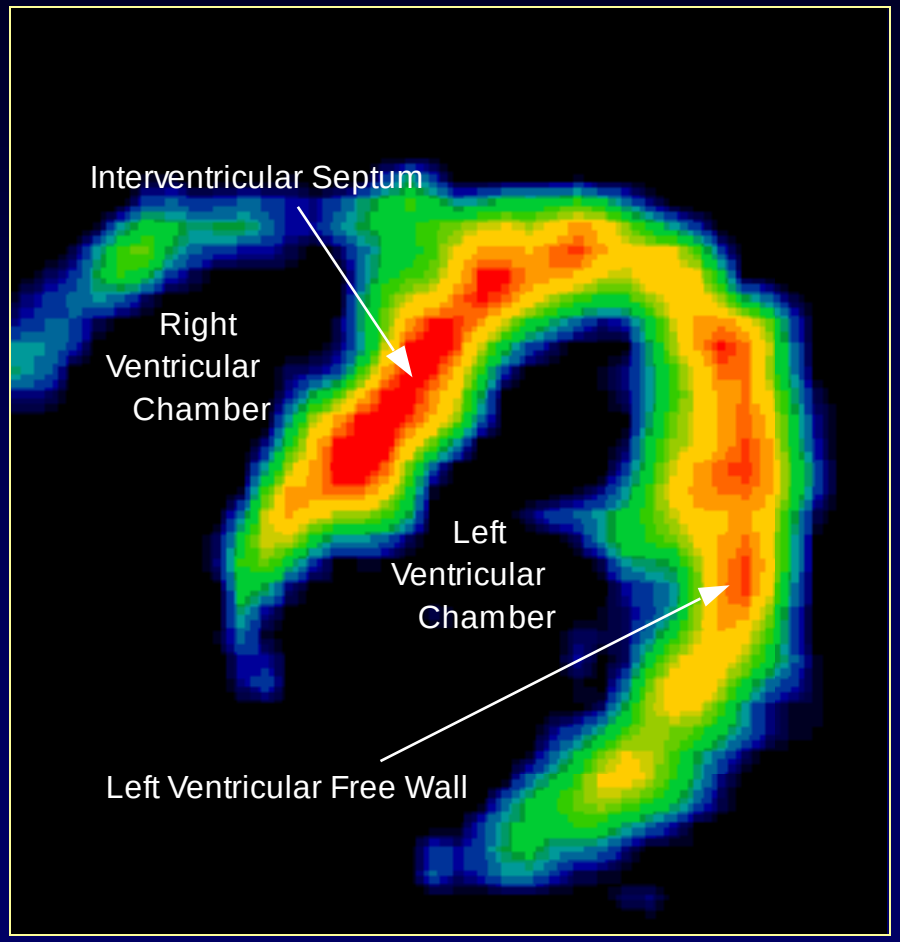


Goldstein et al., J Am Coll Cardiol 1993;22:1961-1971.

Sympathetic Nerves in the Heart

Front

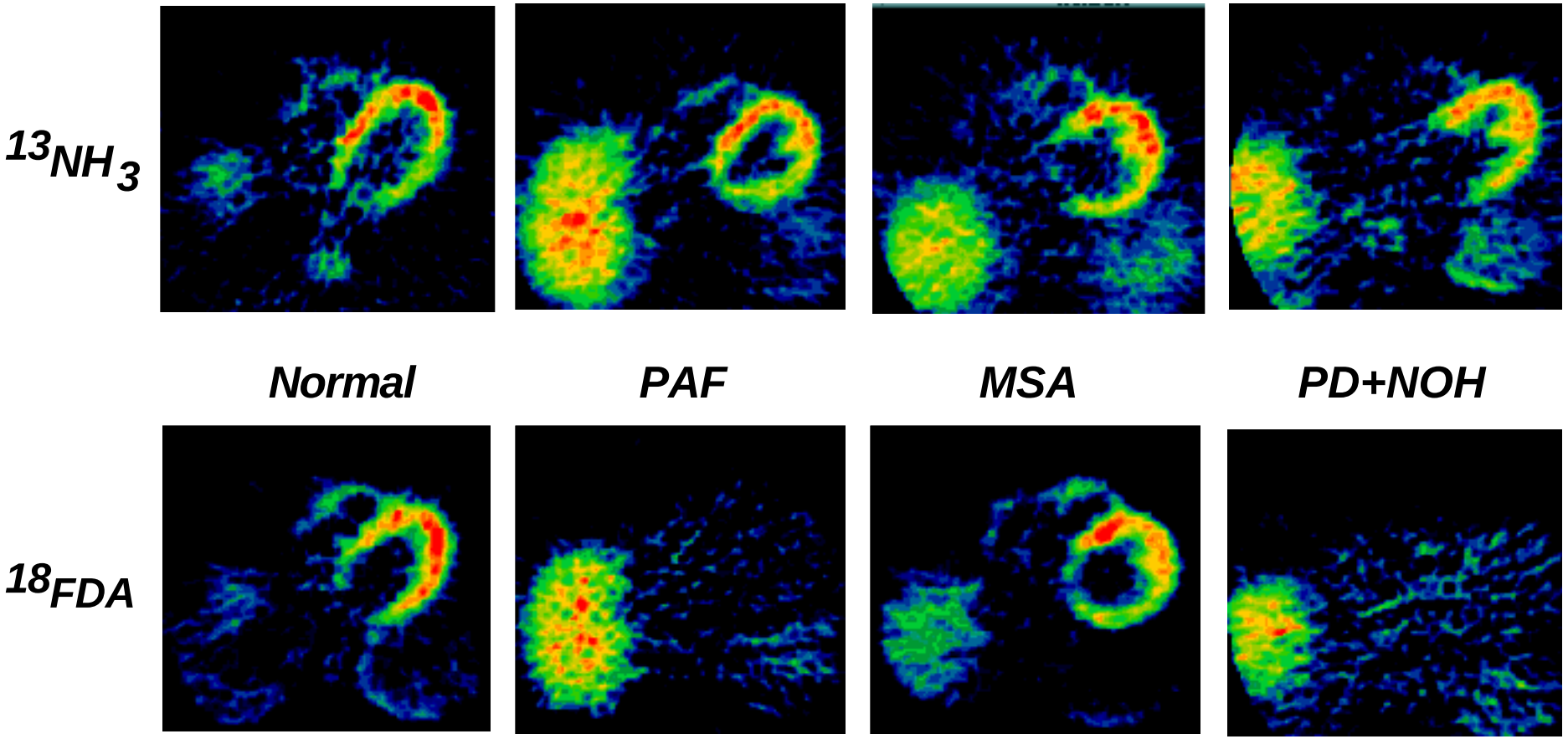
Right



Left

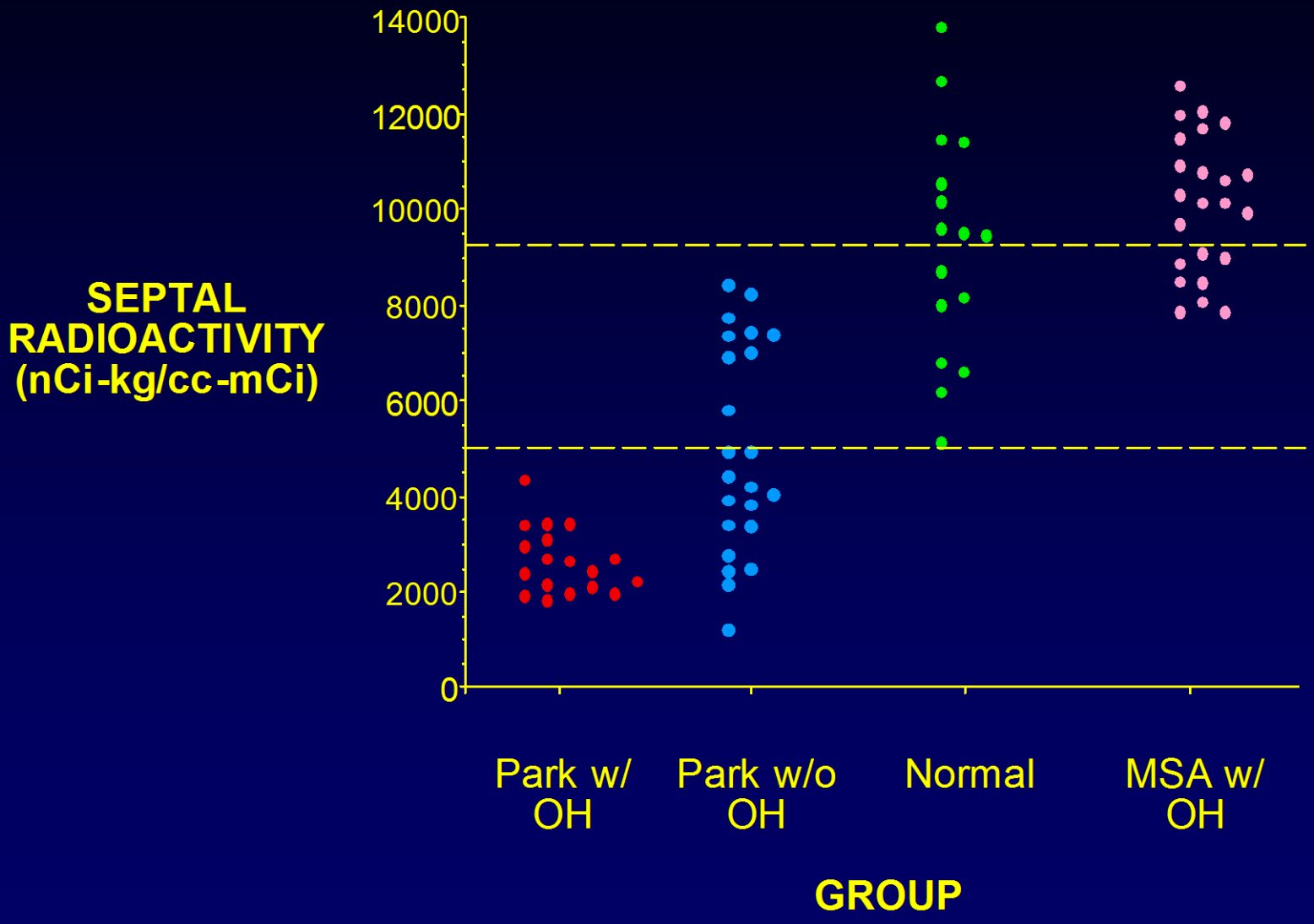
Back

PET Scanning in Autonomic Failure



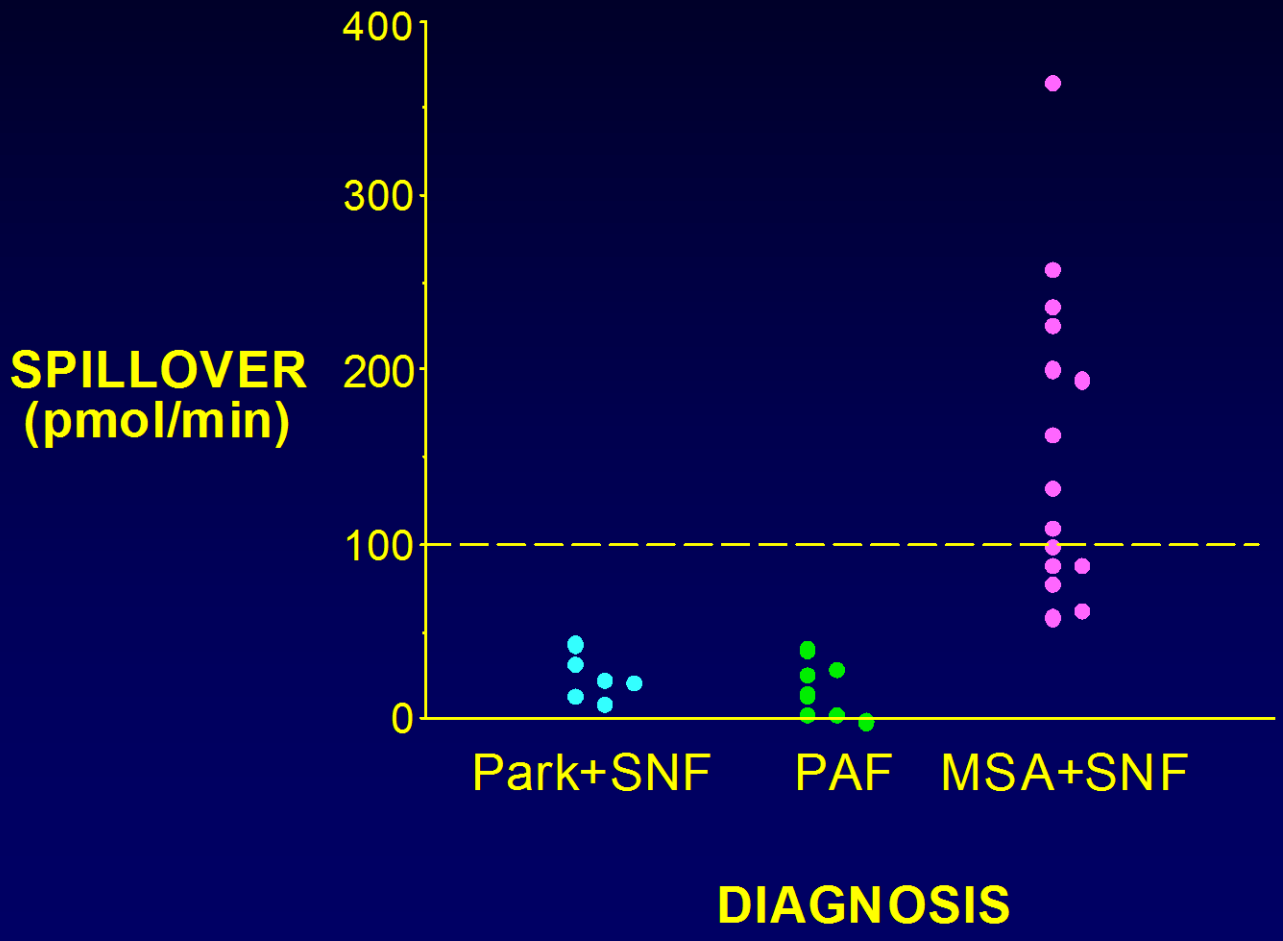
Goldstein et al., N Engl J Med 1997;336:696-702.

Cardiac Sympathetic Denervation in PD



Goldstein et al., Neurology 2002;58:1247-1255

Cardiac NE Spillover



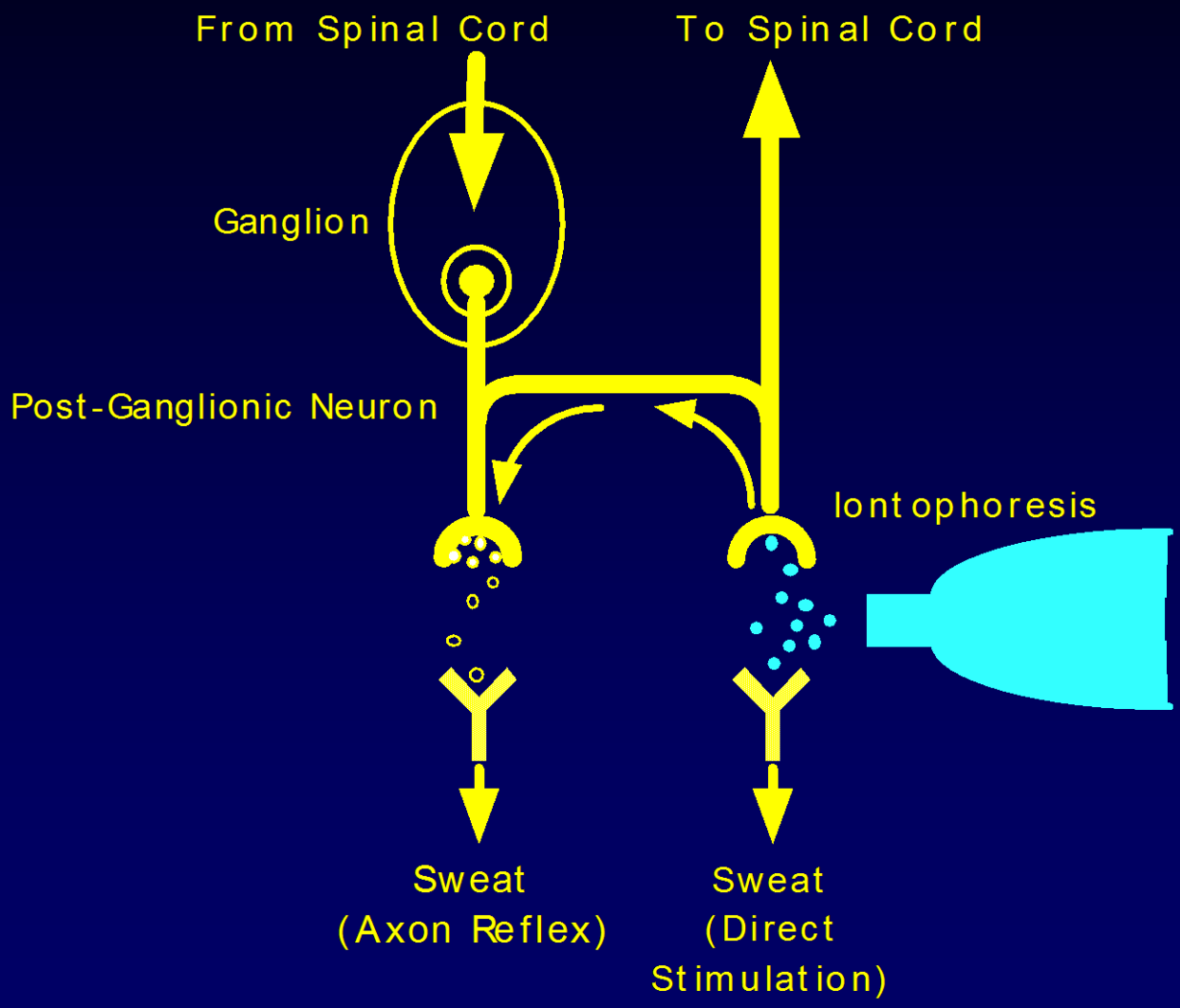
Neurotransmitter specificity of sympathetic denervation in Parkinson's disease

Y. Sharabi, MD; S.-T. Li, MD, PhD; R. Dendi, MD; C. Holmes, CMT; and D.S. Goldstein, MD, PhD

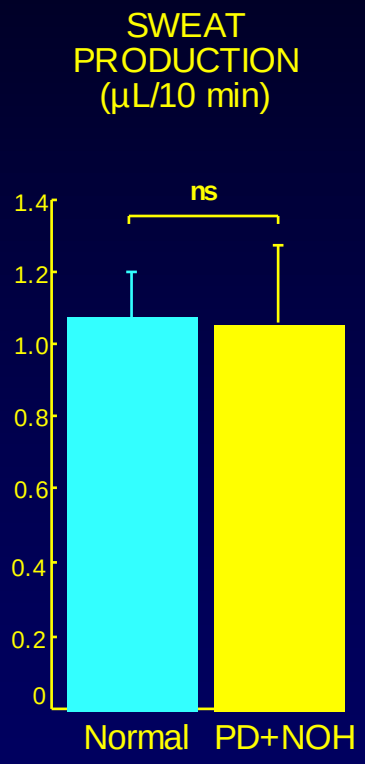
Abstract—In PD, orthostatic hypotension reflects sympathetic noradrenergic denervation. The authors assessed sympathetic cholinergic innervation by the quantitative sudomotor axon reflex test (QSART) in 12 patients who had sympathetic neurocirculatory failure, markedly decreased cardiac 6-[^{18}F] fluorodopamine-derived radioactivity, and subnormal plasma norepinephrine increments during standing. All 12 had normal QSART results. The sympathetic nervous system lesion in PD involves loss of postganglionic catecholaminergic but not cholinergic nerves.

NEUROLOGY 2003;60:1036–1039

QSART

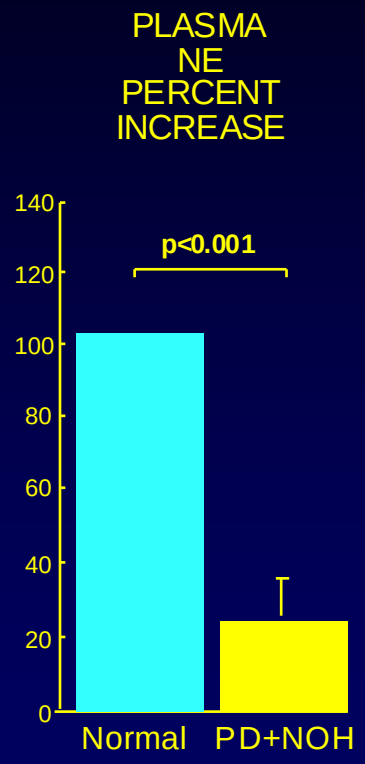

From Spinal Cord
To Spinal Cord
Ganglion
Post-Ganglionic Neuron
Iontophoresis
Sweat
(Axon Reflex)
Sweat
(Direct
Stimulation)

Cholinergic vs. Noradrenergic Lesion



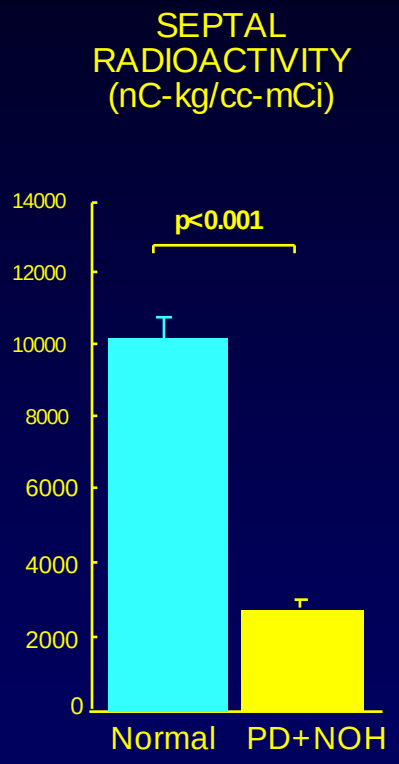
SYMPATHETIC
CHOLINERGIC

NORMAL



SYMPATHETIC
NORADRENRGIC

ABNORMAL



SYMPATHETIC
NORADRENRGIC

ABNORMAL

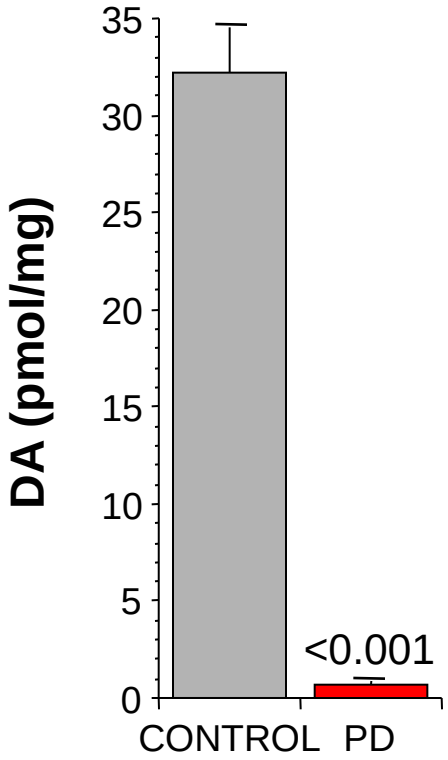
Movement Disorders
Vol. 23, No. 12, 2008, pp. 1725–1732

Generalized and Neurotransmitter-Selective Noradrenergic Denervation in Parkinson's Disease with Orthostatic Hypotension

Yehonatan Sharabi, MD, Richard Imrich, MD, PhD, Courtney Holmes, CMT, Sandra Pechnik, RN, and David S. Goldstein, MD, PhD*

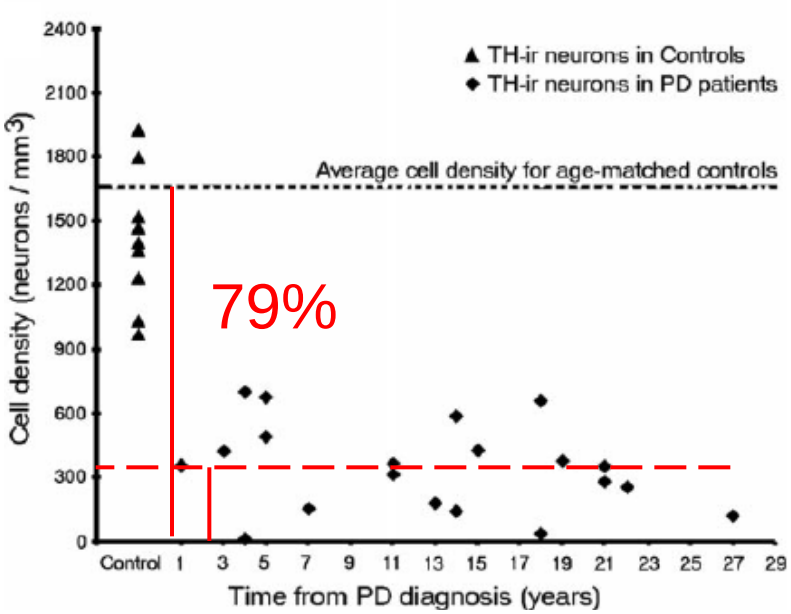
Clinical Neurocardiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA

Putamen DA Depletion: Biochemical *Sine Qua Non* of PD

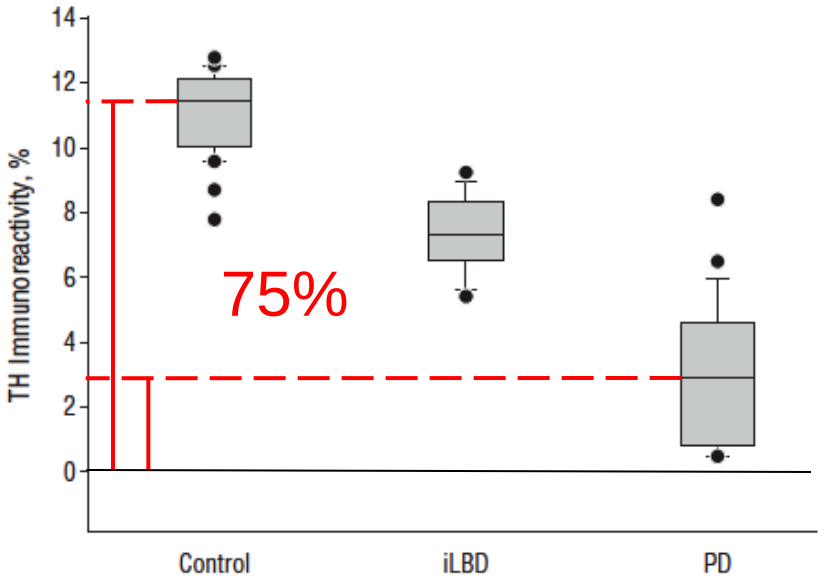


All patients with PD have markedly decreased putamen DA.

Kish et al., N Engl J Med 1988;318:876-880



Kordower et al., Brain 2013;136:2419-2431



DelleDonne et al., Arch Neurol. 2008;65:1074-1080

ELSEVIER

Parkinsonism and Related Disorders 14 (2008) 600–607

Parkinsonism & Related Disorders

www.elsevier.com/locate/parkreldis

Biomarkers to detect central dopamine deficiency and distinguish Parkinson disease from multiple system atrophy

David S. Goldstein [a,*], Courtney Holmes [a], Oladi Bentho [a], Takuya Sato [a], Jeffrey Moak [b], Yehonatan Sharabi [a], Richard Imrich [a], Shielah Conant [c], Basil A. Eldadah [a,b,c]

[a] *Clinical Neurocardiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, USA*
[b] *PET Department, Clinical Center, National Institutes of Health, Bethesda, MD 20892, USA*
[c] *Geriatrics and Clinical Gerontology Program, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA*

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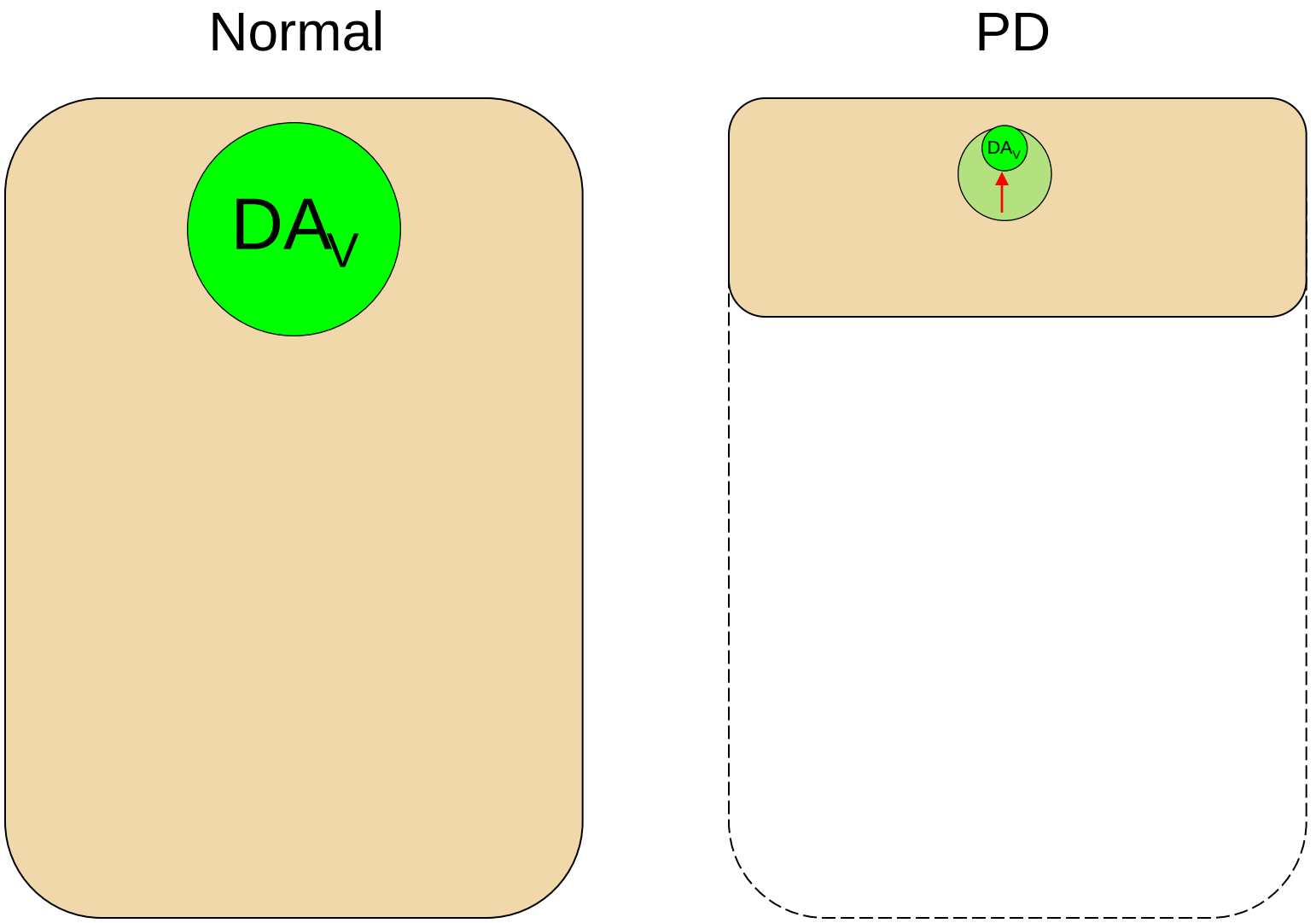
So far…

DA deficiency in CNS

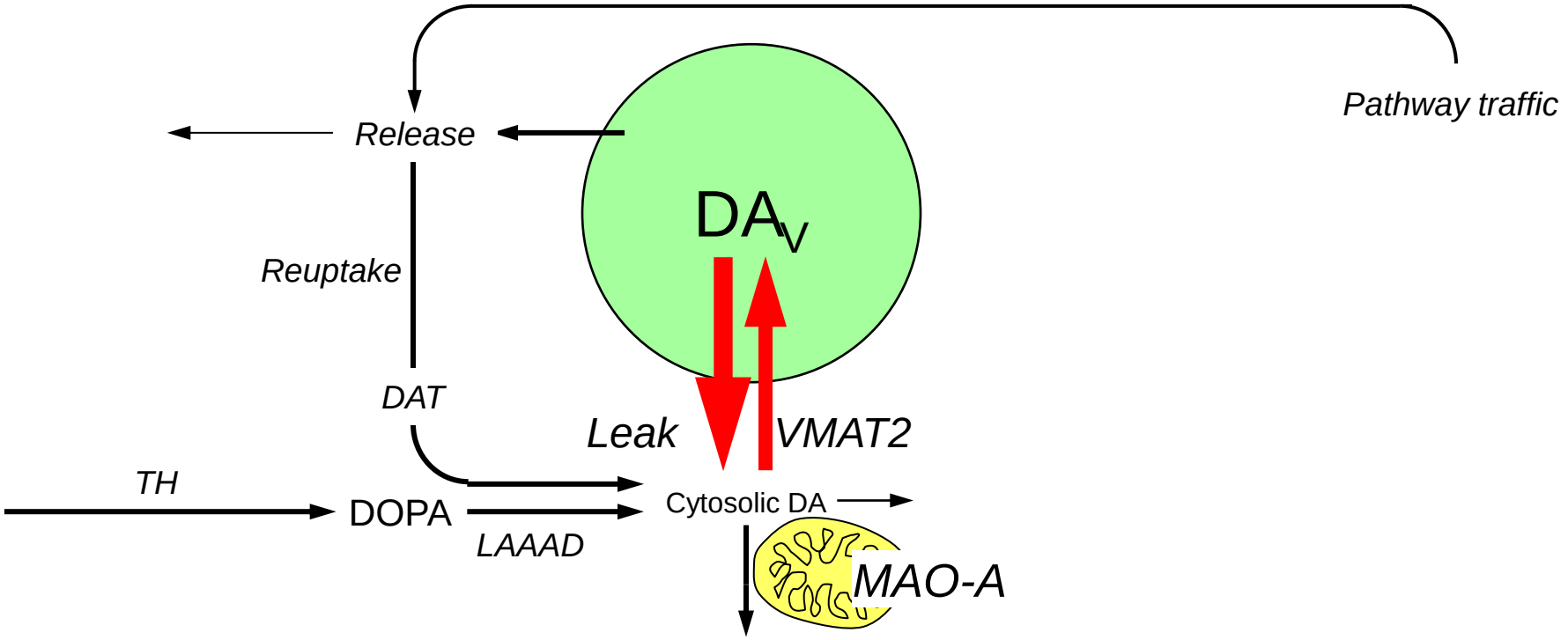
NE deficiency in periphery

Catecholamines – the smoking gun

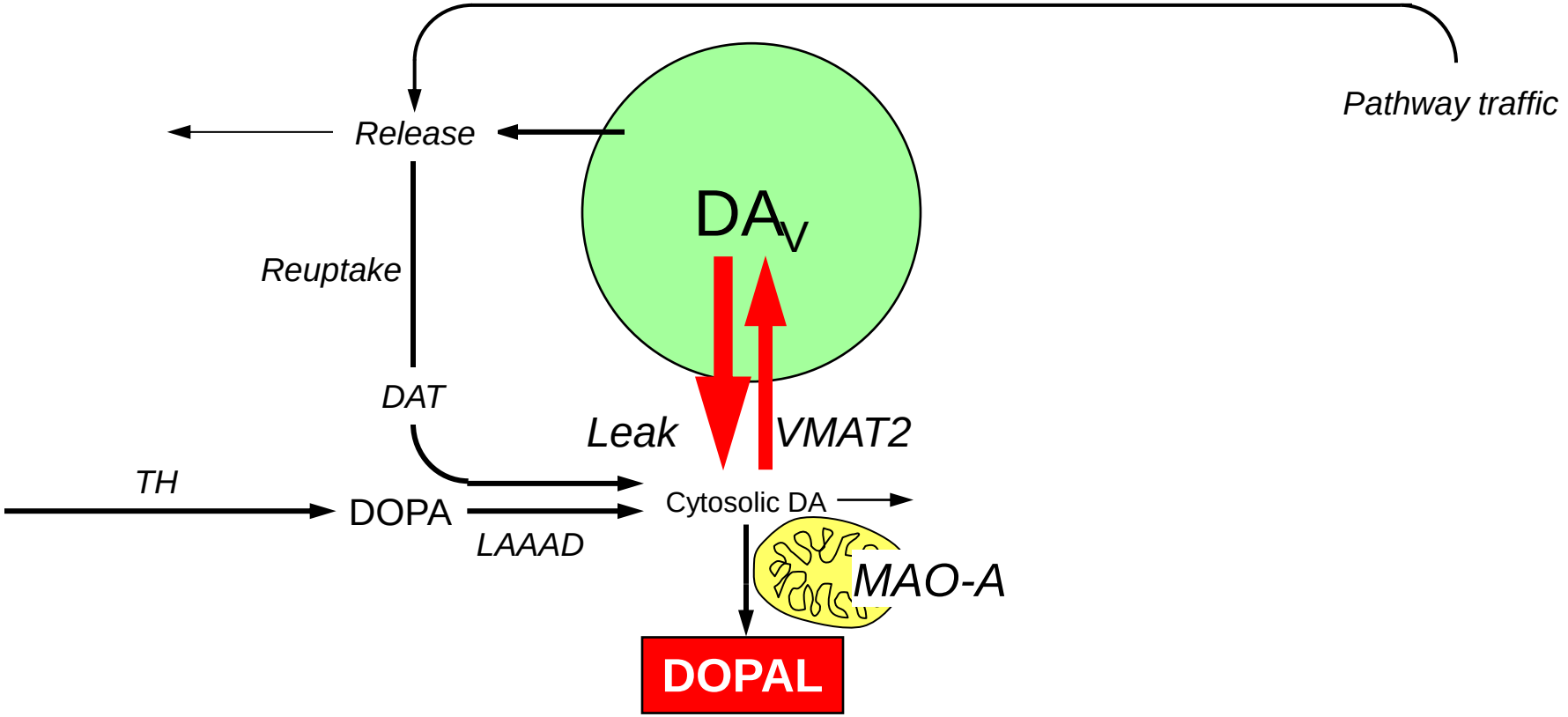
The Quest Begins with a Paradox



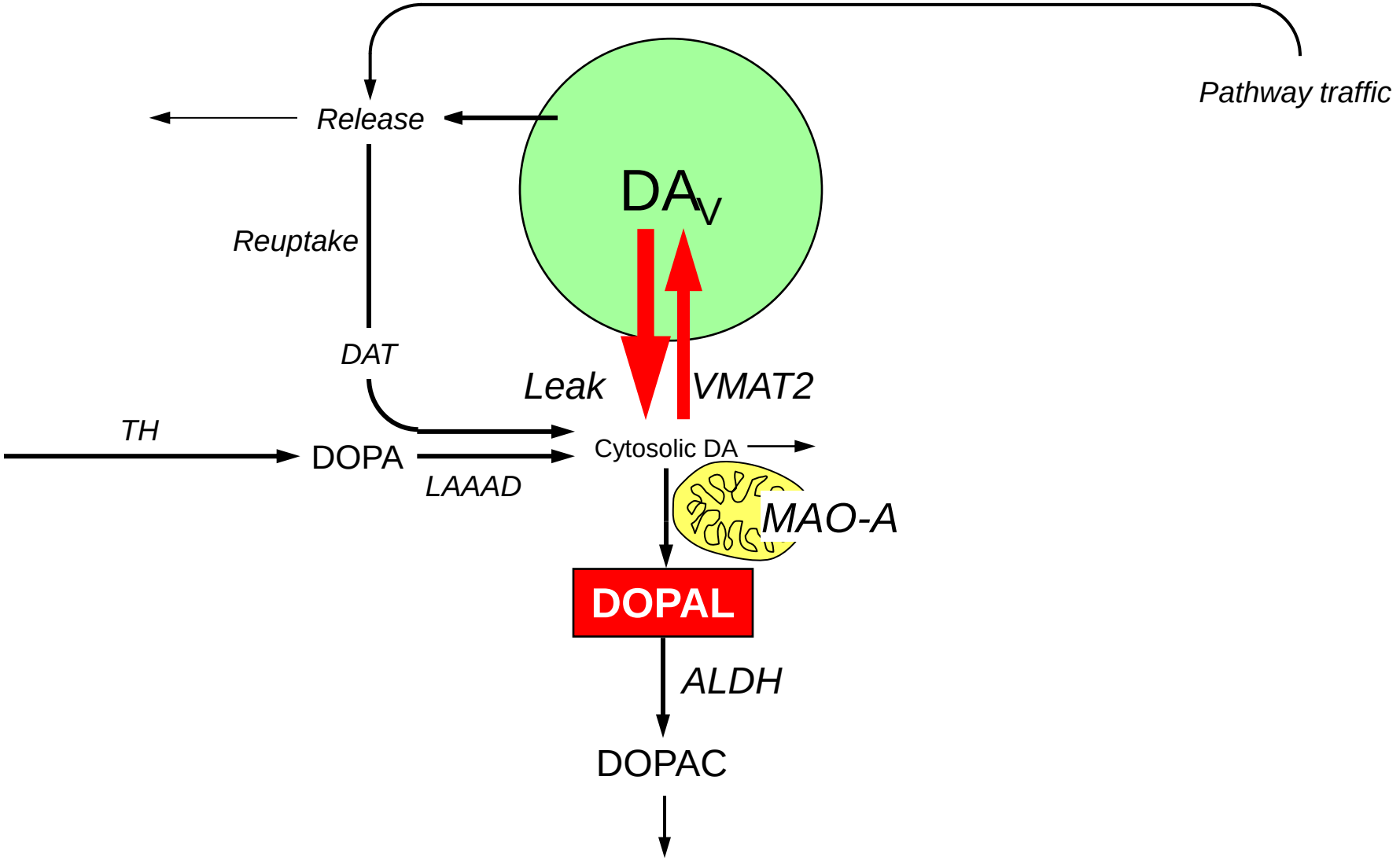
Vesicular Sequestration-Oxidative Deamination Balance



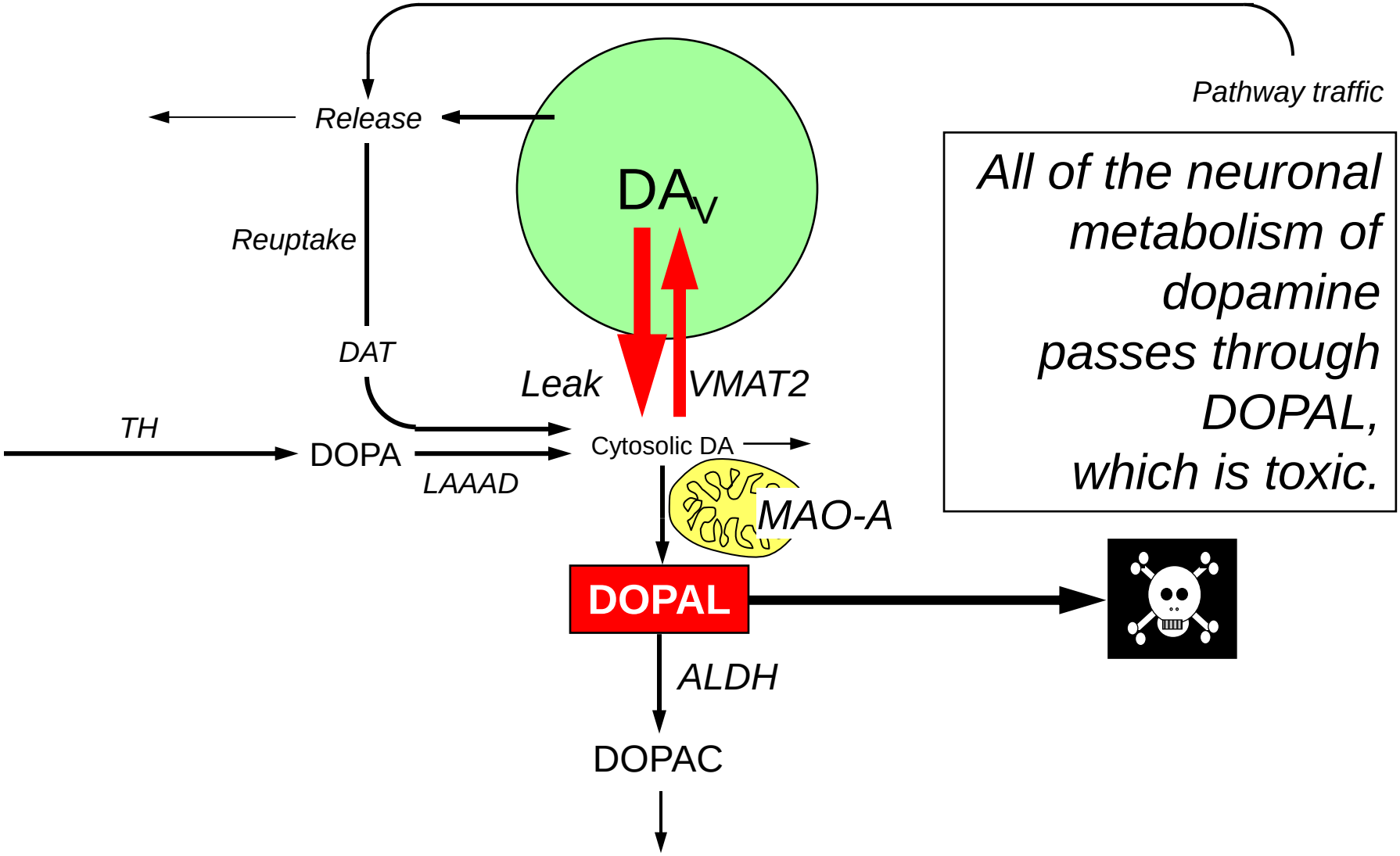
Vesicular Sequestration-Oxidative Deamination Balance



Vesicular Sequestration-Oxidative Deamination Balance

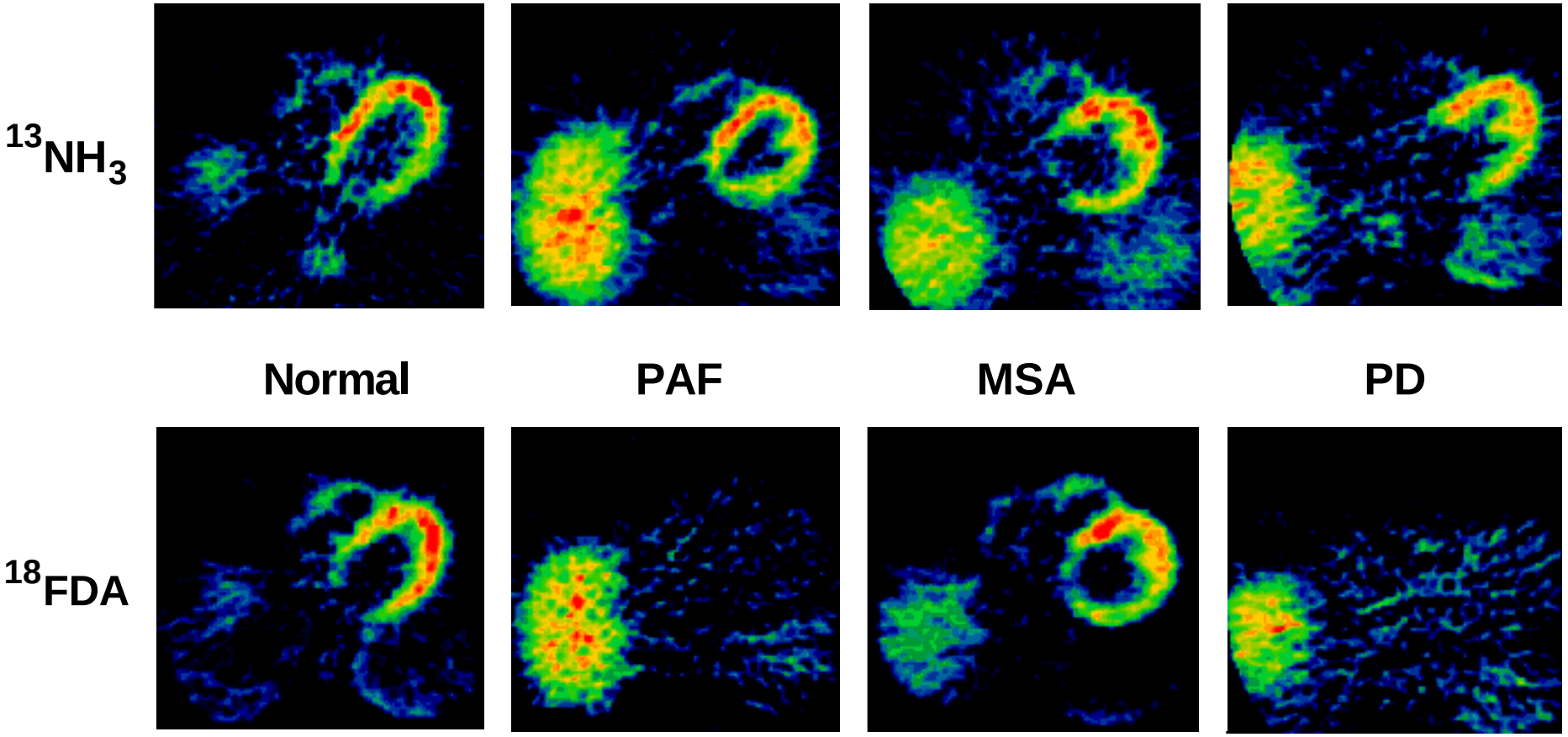


Vesicular Sequestration-Oxidative Deamination Balance



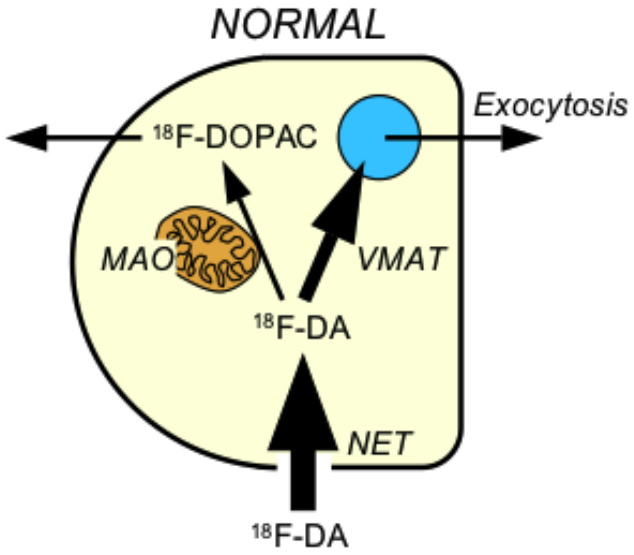
All of the neuronal metabolism of dopamine passes through DOPAL, which is toxic.

Is Vesicular Sequestration Decreased in PD?



Goldstein et al., N Engl J Med 1997;336:696-702

Is Vesicular Sequestration Decreased in PD?



Goldstein et al. JCI 2011;121:3320-3330

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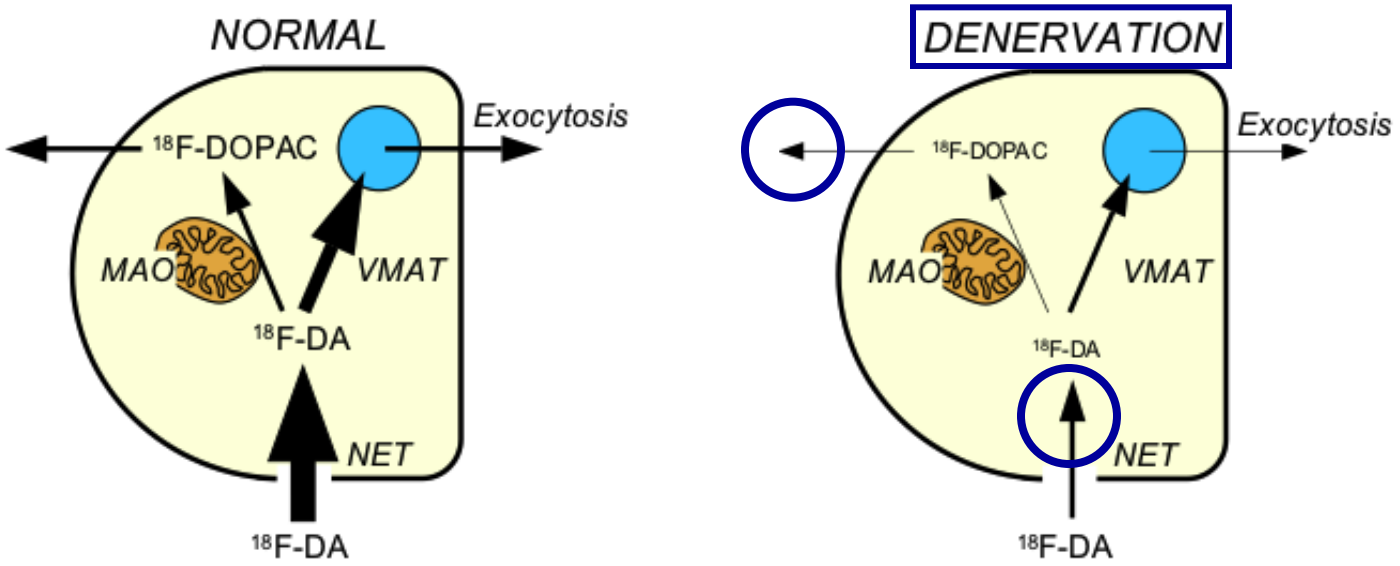

Goldstein et al. JCI 2011;121:3320-3330

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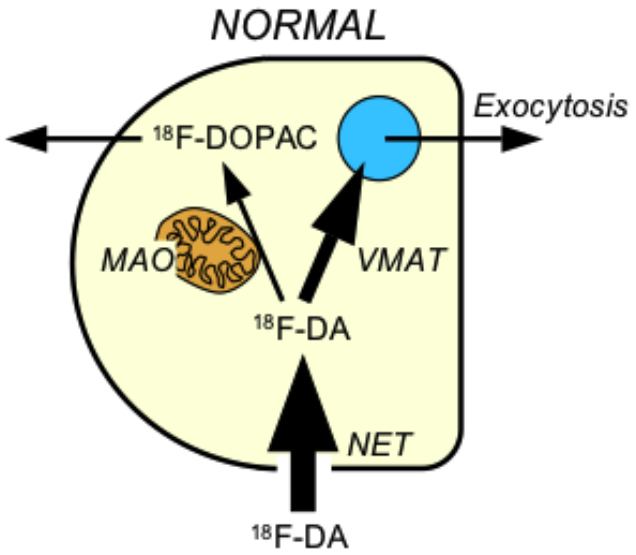

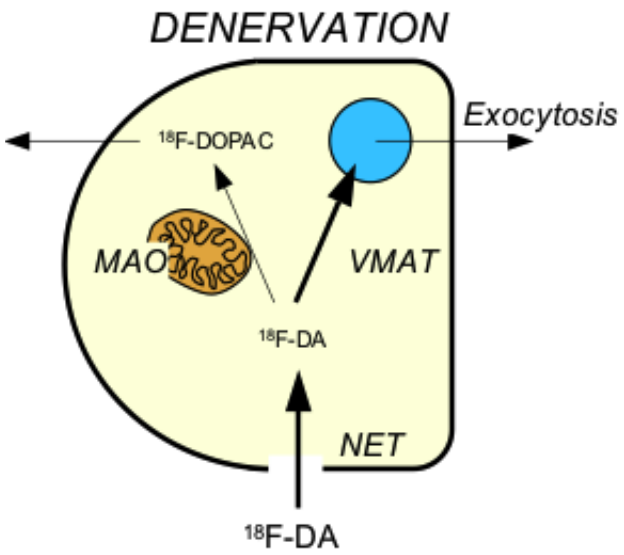

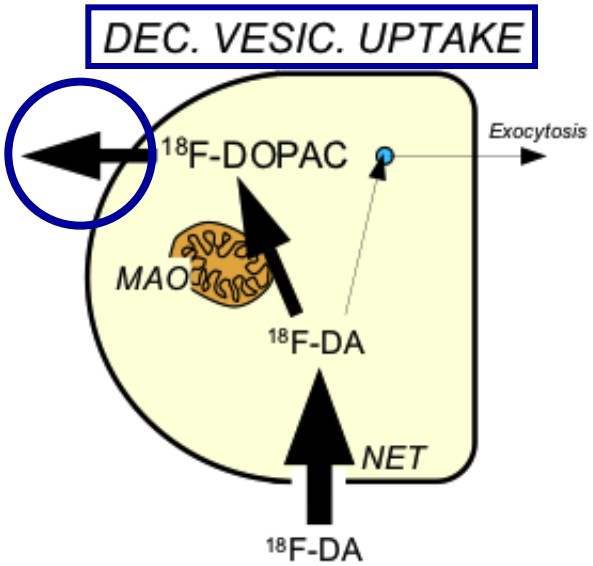

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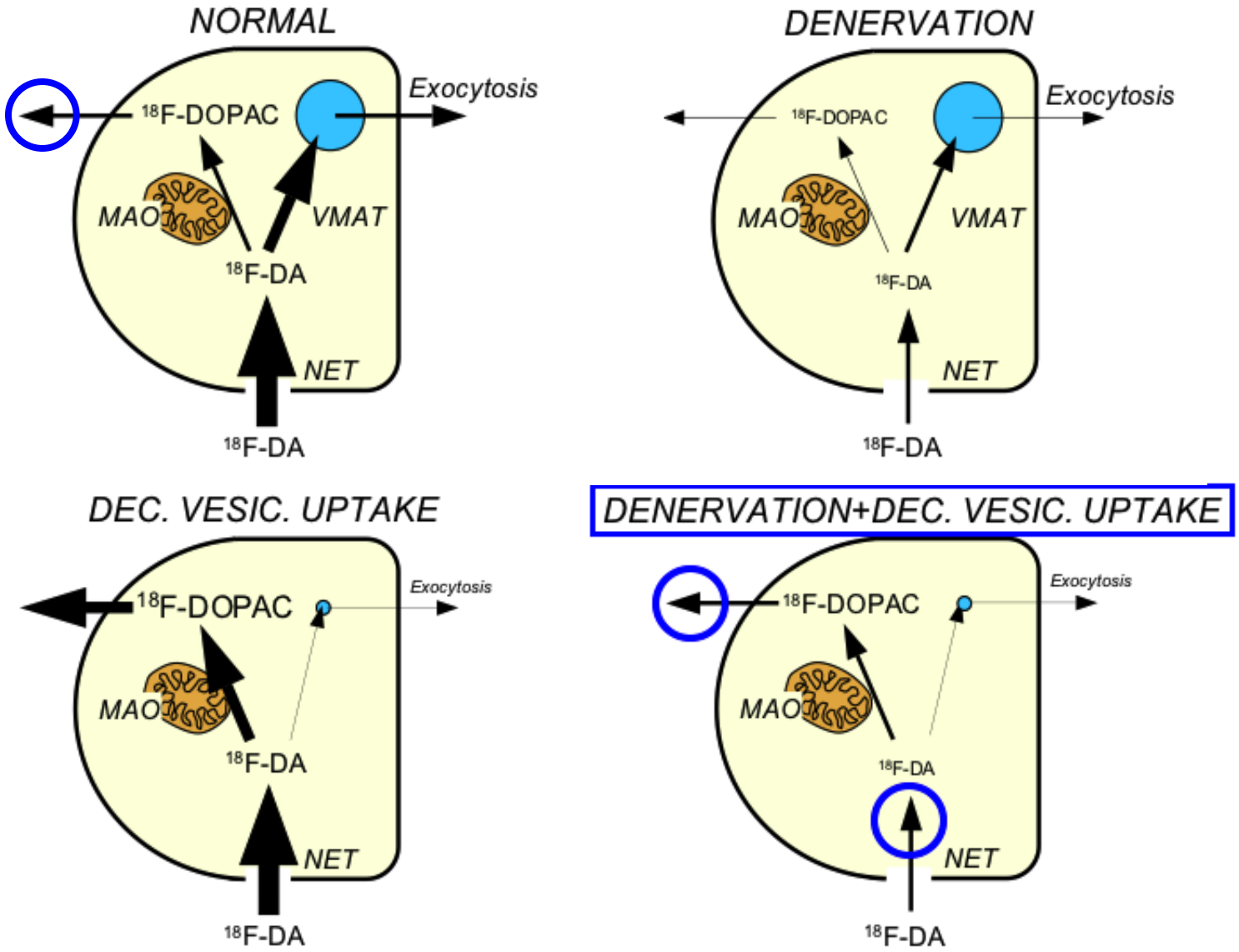
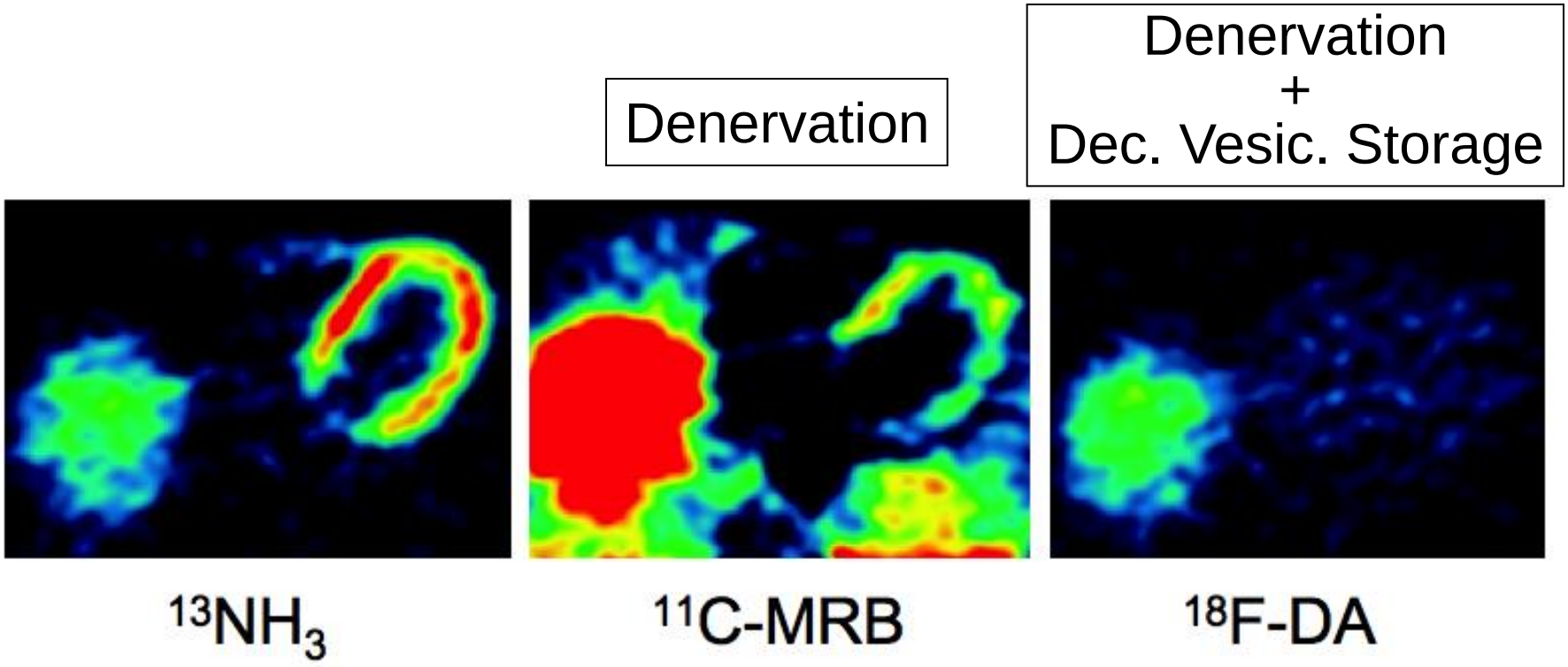


Goldstein et al. JCI 2011;121:3320-3330

Visualization of Decreased Vesicular Sequestration



Comparison of ^{18}F-dopamine vs. ^{11}C-methylreboxetine scans visualizes decreased vesicular storage in vivo

Goldstein et al. (unpublished)

Research article

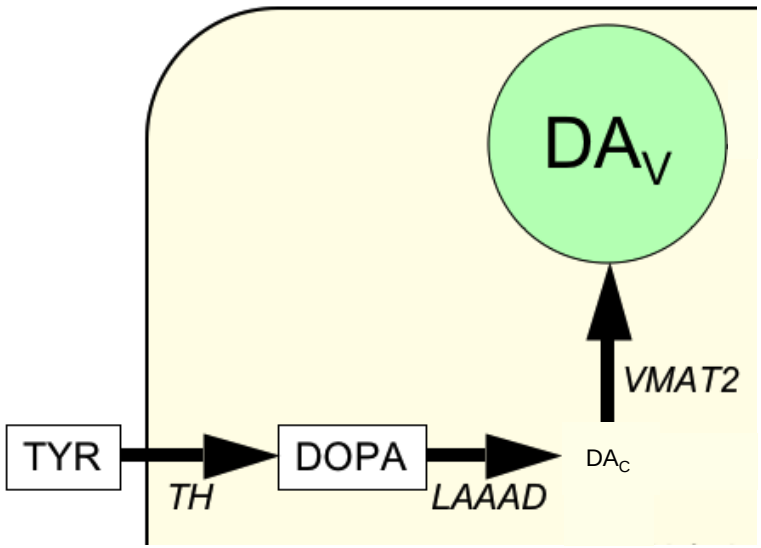
Intra-neuronal vesicular uptake of catecholamines is decreased in patients with Lewy body diseases

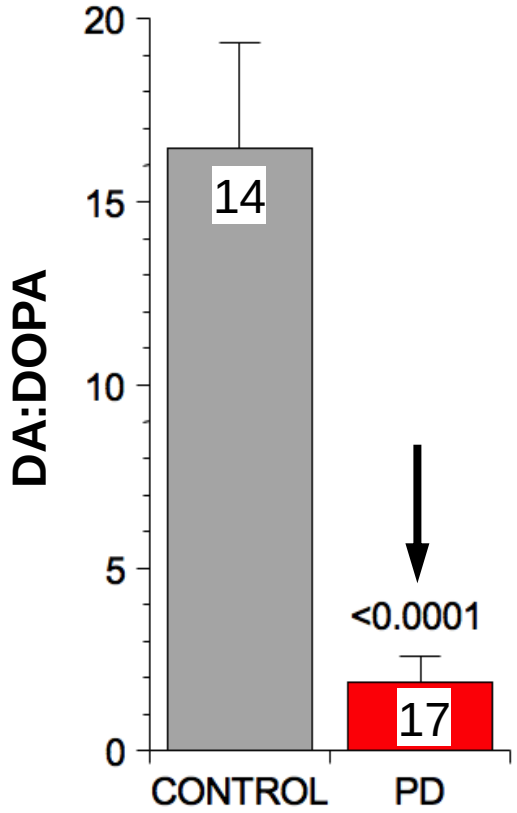
David S. Goldstein, Courtney Holmes, Irwin J. Kopin, Yehonatan Sharabi

Clinical Neurocardiology Section, National Institute of Neurological Disorders and Stroke (NINDS), NIH, Bethesda, Maryland, USA.

JCI, 2011

Is Vesicular Sequestration Decreased in PD?

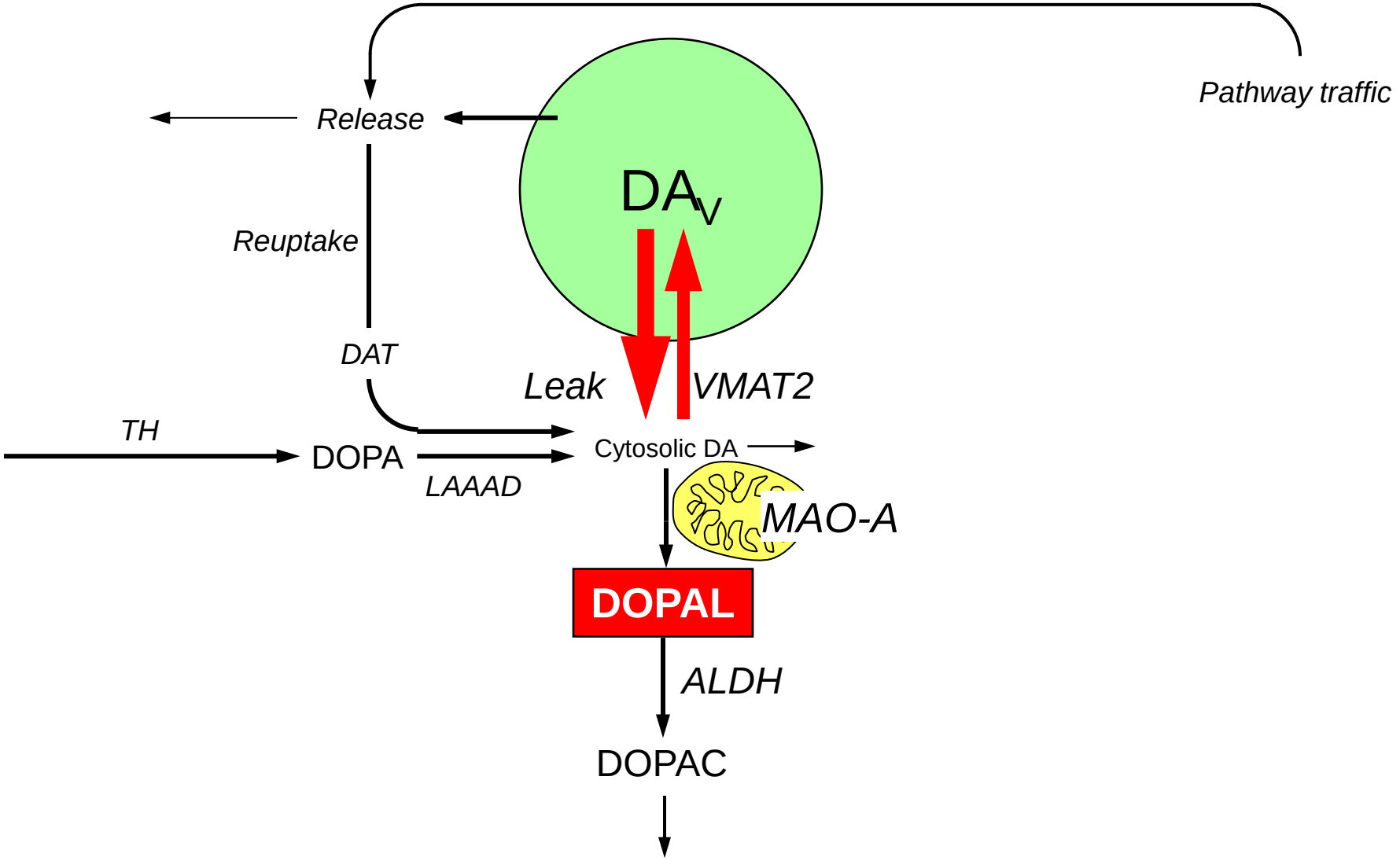




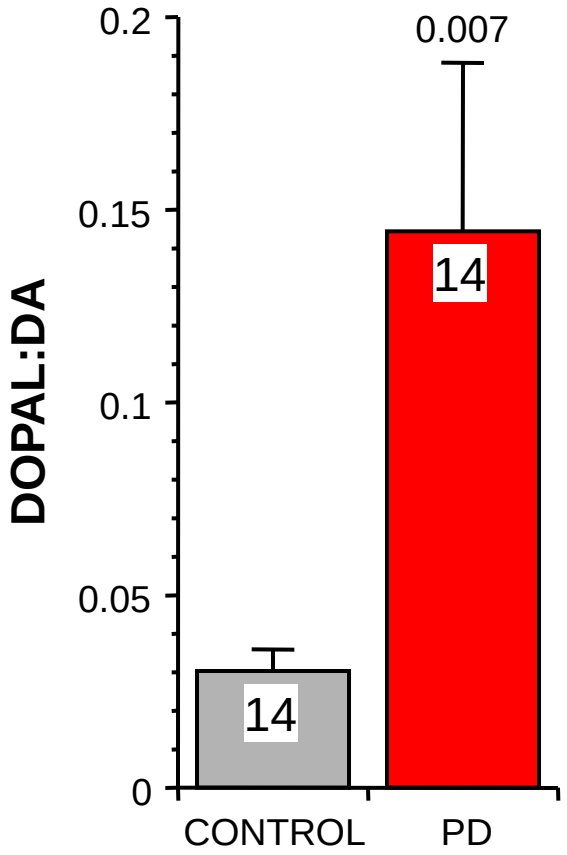
Low DA:DOPA ratios indicate decreased vesicular sequestration of cytoplasmic DA in PD putamen.

Goldstein et al., J Neurochem 2013;126:591-603

Vesicular Sequestration-Oxidative Deamination Balance



Is DOPAL Built Up in PD Putamen?



We obtained post-mortem neurochemical evidence for DOPAL buildup with respect to DA in PD putamen.

Goldstein et al., J Neurochem 2013;126:591-603

Journal of Neurochemistry

JNC

JOURNAL OF NEUROCHEMISTRY | 2013 | 126 | 591–603

doi: 10.1111/jnc.12345

ORIGINAL ARTICLE

Determinants of buildup of the toxic dopamine metabolite DOPAL in Parkinson's disease

David S. Goldstein,* Patti Sullivan,* Courtney Holmes,* Gary W. Miller,† Shawn Alter,† Randy Strong,‡ Deborah C. Mash,§ Irwin J. Kopin* and Yehonatan Sharabi*¶

*Clinical Neurocardiology Section, Clinical Neurosciences Program, Division of Intramural Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA

†Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

‡Department of Pharmacology, University of Texas Health Science Center and South Texas Veterans Health Care Network, San Antonio, Texas, USA

§Miller School of Medicine, University of Miami, Miami, Florida, USA

¶Sackler Faculty of Medicine, Tel Aviv University, Tel-HaShomer, Israel

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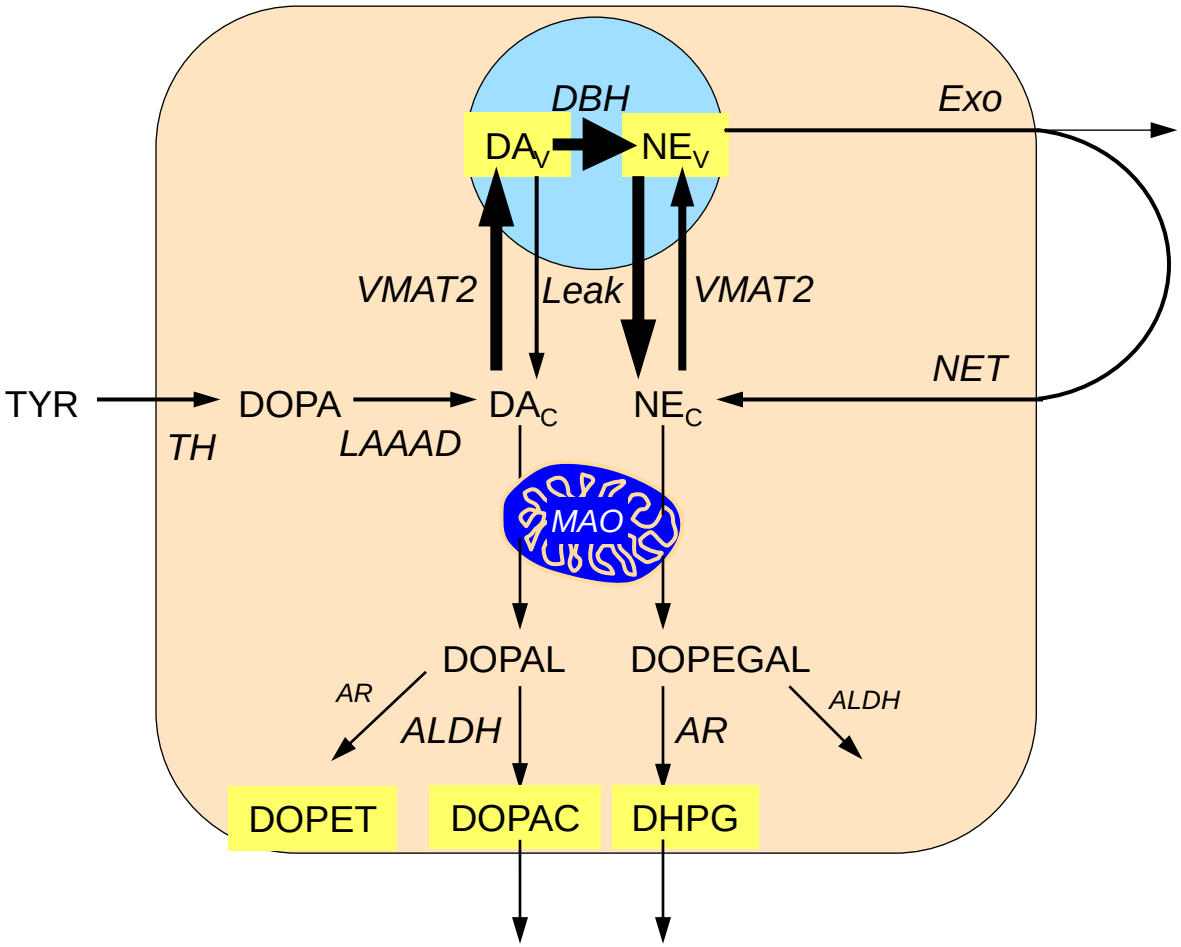


DHPG:NE

DOPAC:DA

DA:NE

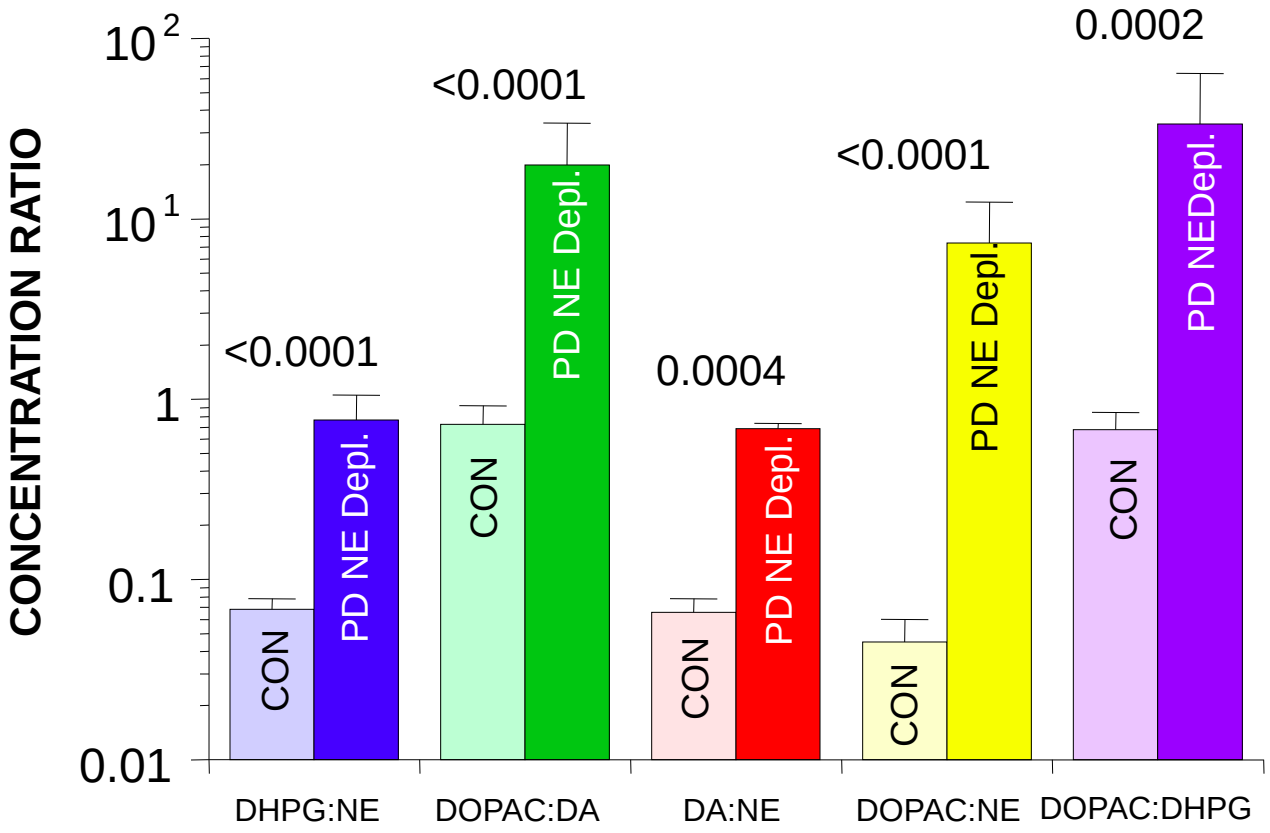
DOPAC:NE

DOPAC:DHPG

We used a novel post-mortem neurochemical approach to assess vesicular sequestration in cardiac sympathetic nerves in PD.

Goldstein et al .J Neurochem 2014 (PMID 24848581)

Is Vesicular Sequestration Decreased in PD?



By all 5 indices, PD patients have a vesicular sequestration-to-oxidative deamination shift in sympathetic nerves.

Goldstein et al .J Neurochem 2014 (PMID 24848581)

Journal of Neurochemistry

JNC

JOURNAL OF NEUROCHEMISTRY | 2014 | 131 | 219–228

doi: 10.1111/jnc.12766

ORIGINAL ARTICLE

A vesicular sequestration to oxidative deamination shift in myocardial sympathetic nerves in Parkinson's disease

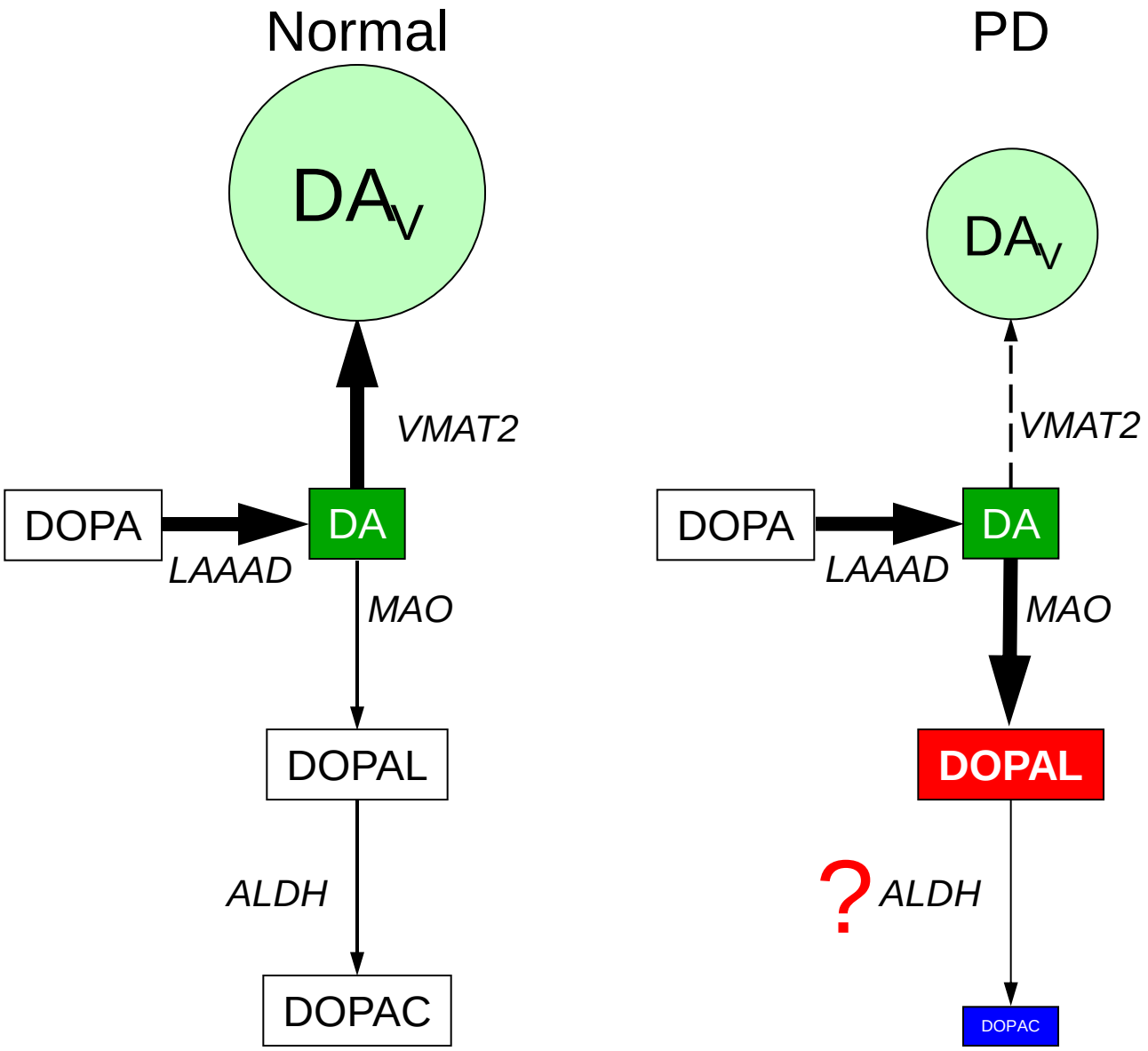
David S. Goldstein,* Patricia Sullivan,* Courtney Holmes,* Gary W. Miller,† Yehonatan Sharabi‡ and Irwin J. Kopin*

*Clinical Neurocardiology Section, CNP/DIR/NINDS/NIH, Bethesda, Maryland, USA

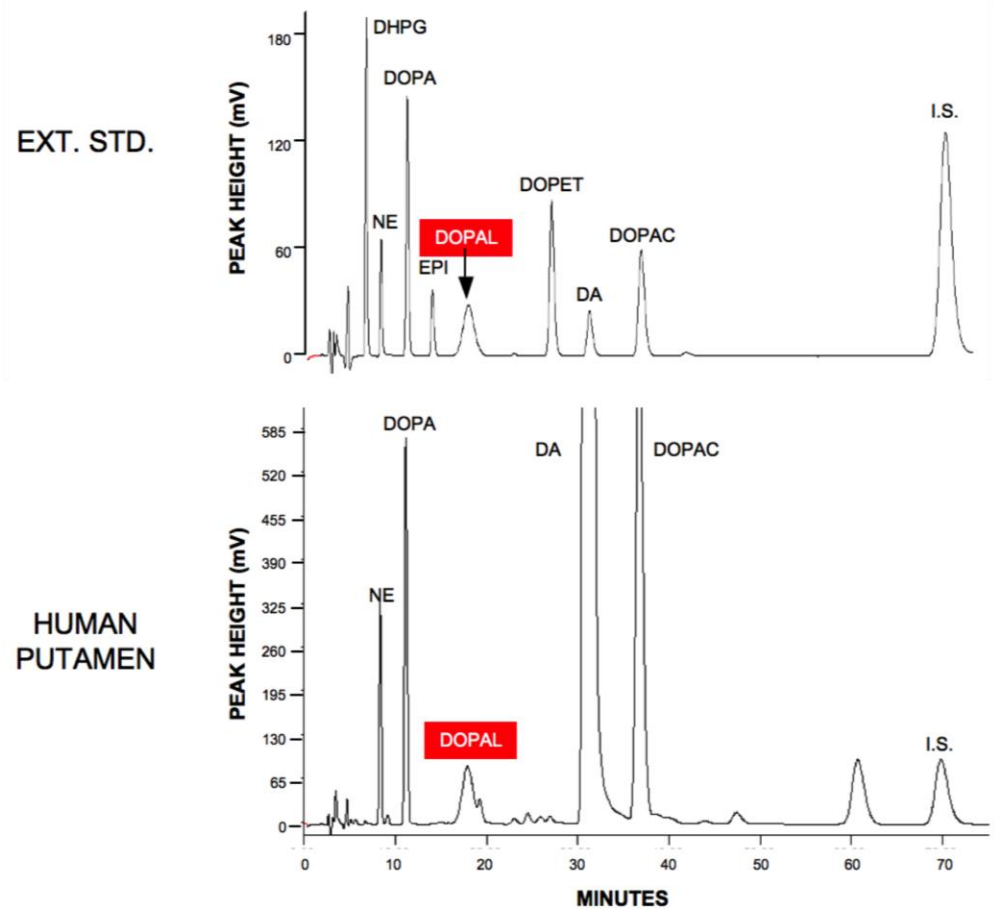
†School of Public Health, Environmental Health, Emory University, Atlanta, Georgia, USA

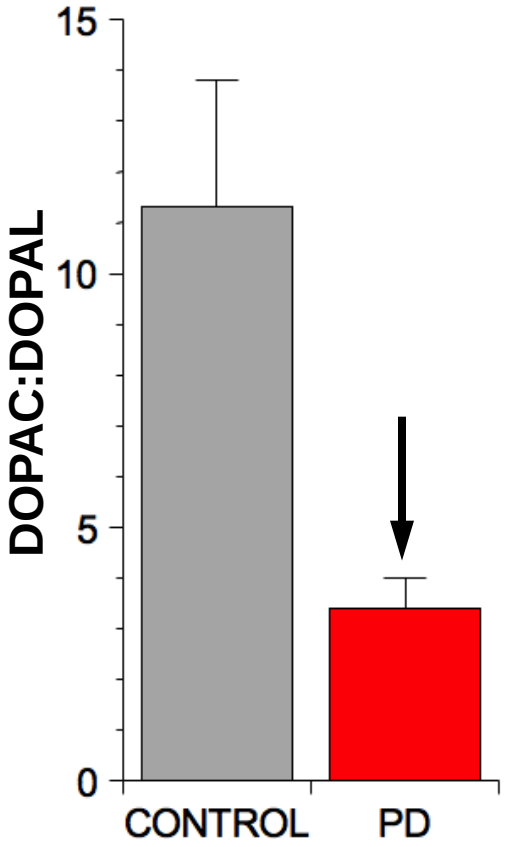
‡Hypertension Unit, Chaim Sheba Medical Center, and Tel Aviv University, Tel-HaShomer, Israel

Is ALDH decreased in PD?



Is ALDH decreased in PD?

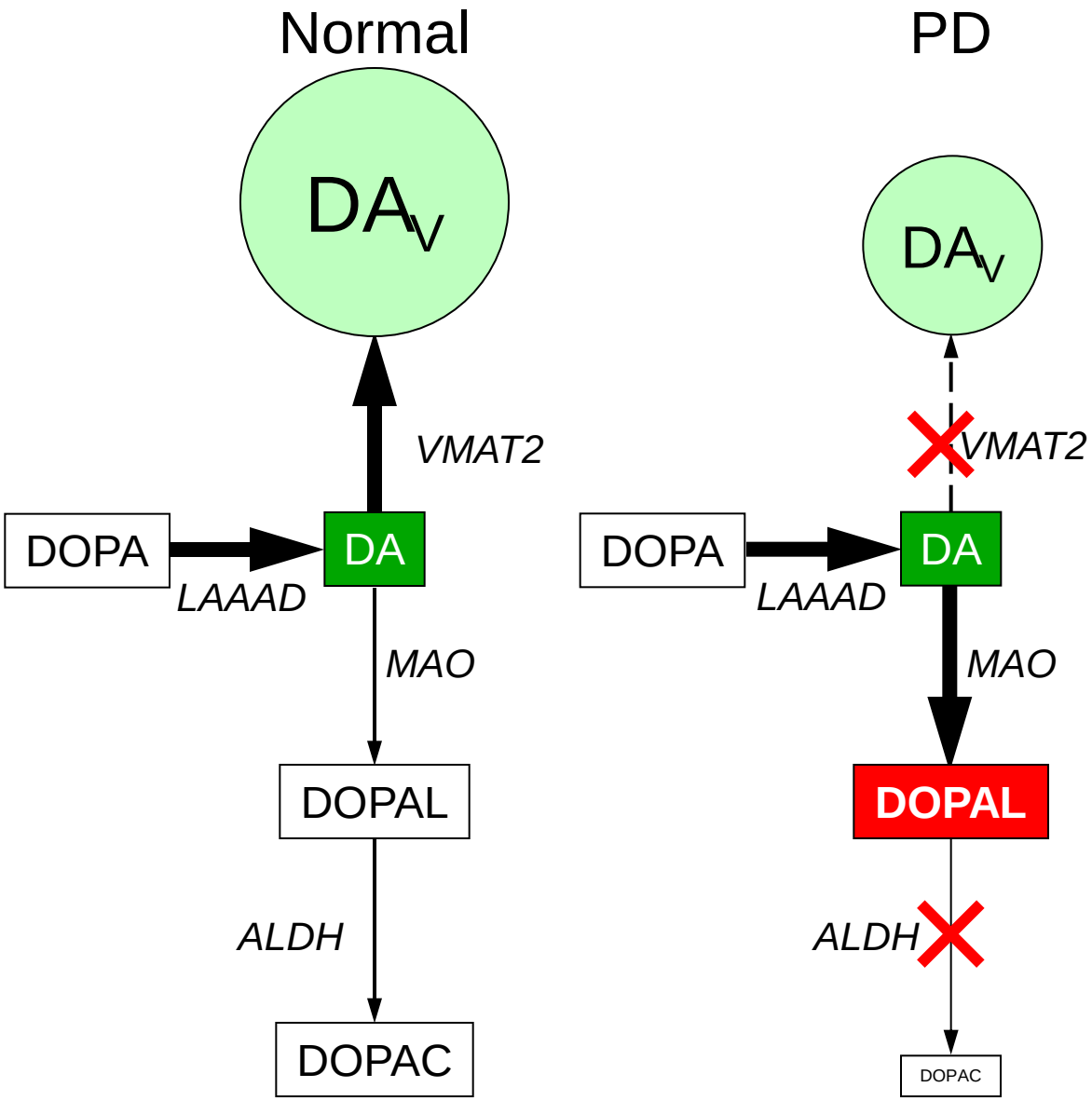




From assays of DOPAC and DOPAL, we obtained post-mortem neurochemical evidence for decreased ALDH activity in PD putamen.

Goldstein et al., J Neurochem 2013;126:591-603

Is DOPAL Built Up in PD Putamen?



Journal of Neurochemistry

JNC

JOURNAL OF NEUROCHEMISTRY | 2012 | 123 | 932–943

doi: 10.1111/j.1471-4159.2012.07924.x

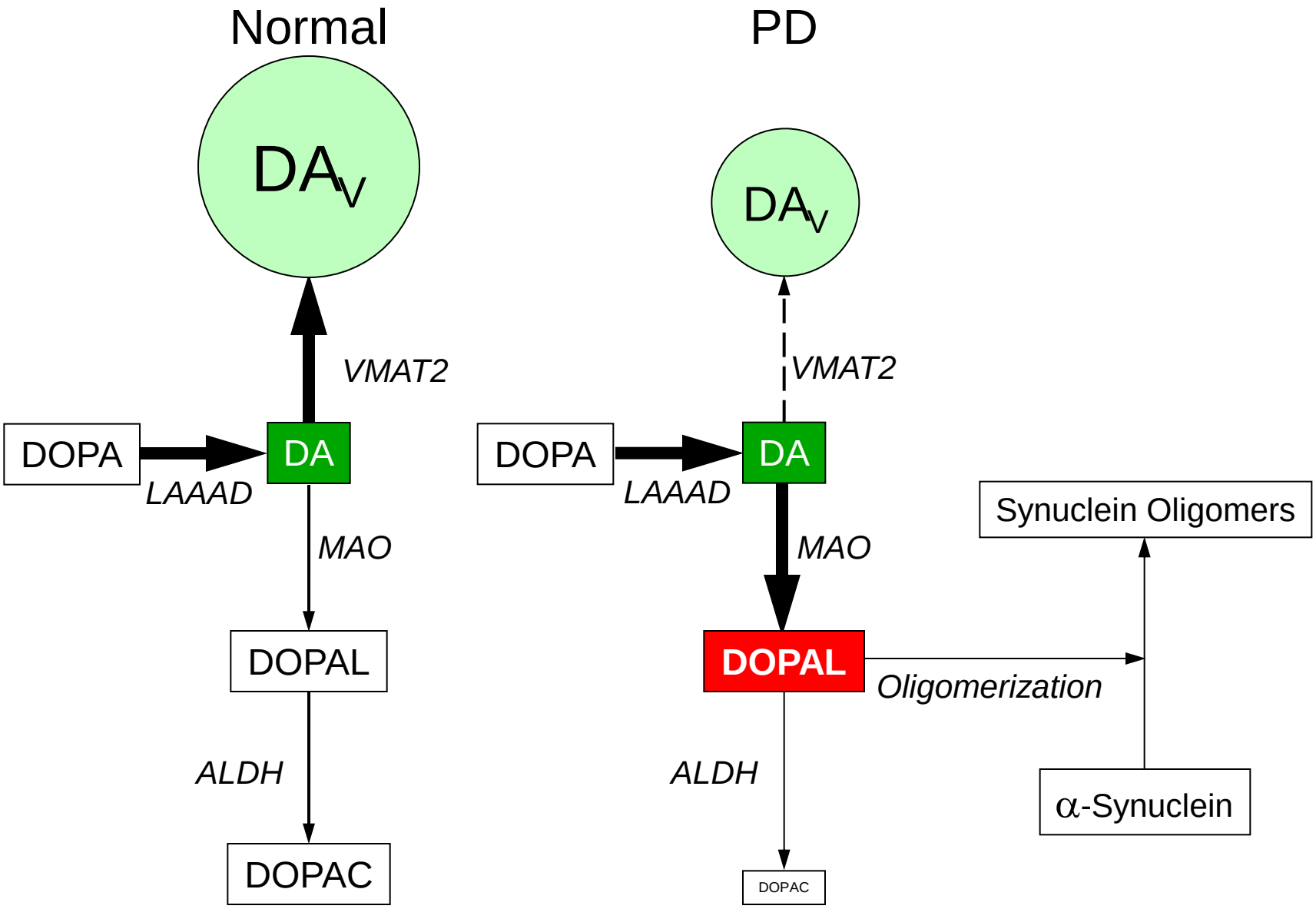
ORIGINAL ARTICLE

Vesicular uptake blockade generates the toxic dopamine metabolite 3,4-dihydroxyphenylacetaldehyde in PC12 cells: relevance to the pathogenesis of Parkinson's disease

David S. Goldstein, Patti Sullivan, Adele Cooney, Yunden Jinsmaa, Rachel Sullivan, Daniel J. Gross, Courtney Holmes, Irwin J. Kopin and Yehonatan Sharabi

Clinical Neurocardiology Section, CNP/DIR/NINDS/NIH, Bethesda, MD, USA

Does DOPAL Oligomerize Alpha-Synuclein?



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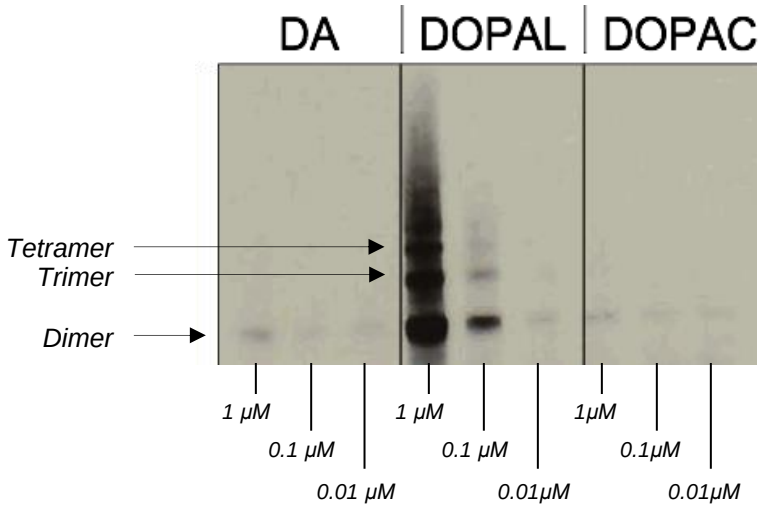
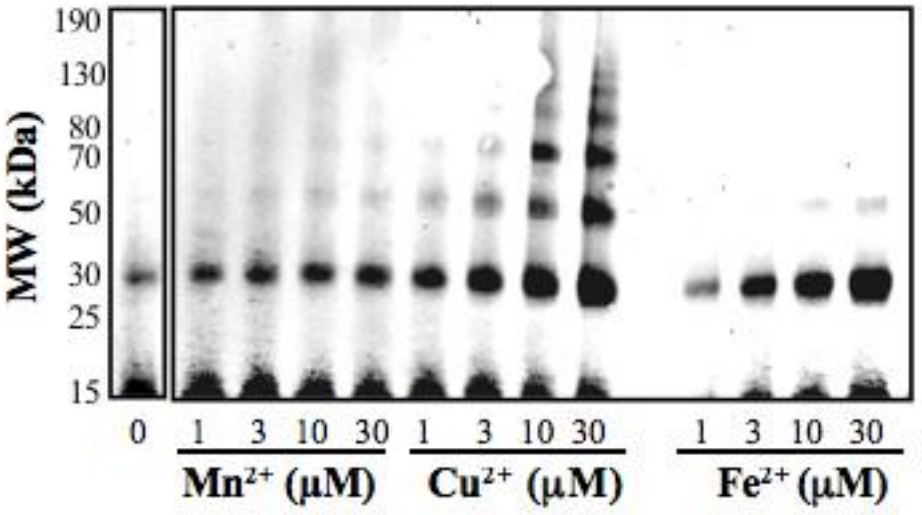
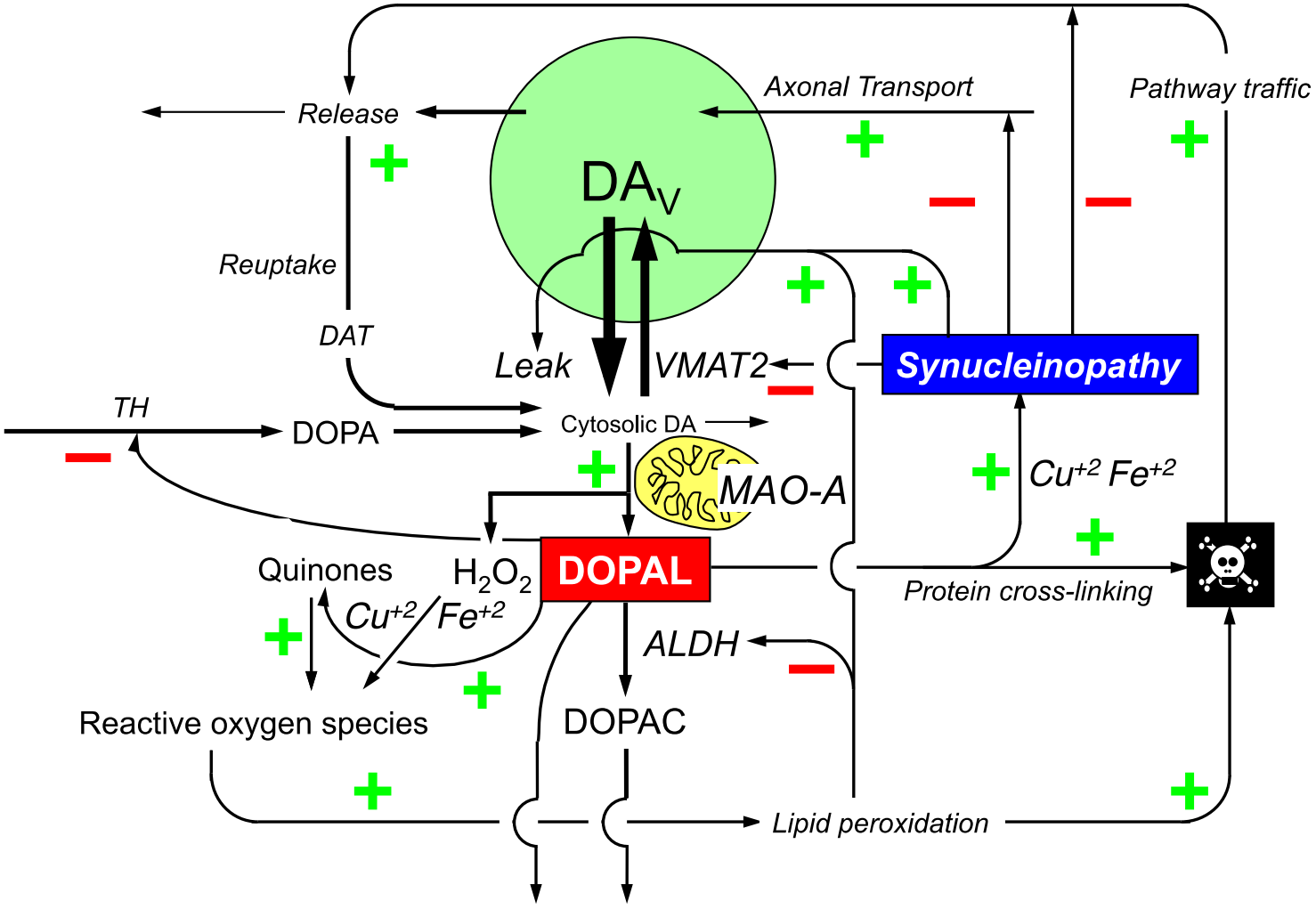




DOPAL potently oligomerizes ⟨-synuclein.
Divalent metal cations augment the oligomerization.

Jinsmaa et al. Neurosci Lett 2014;569:27-32

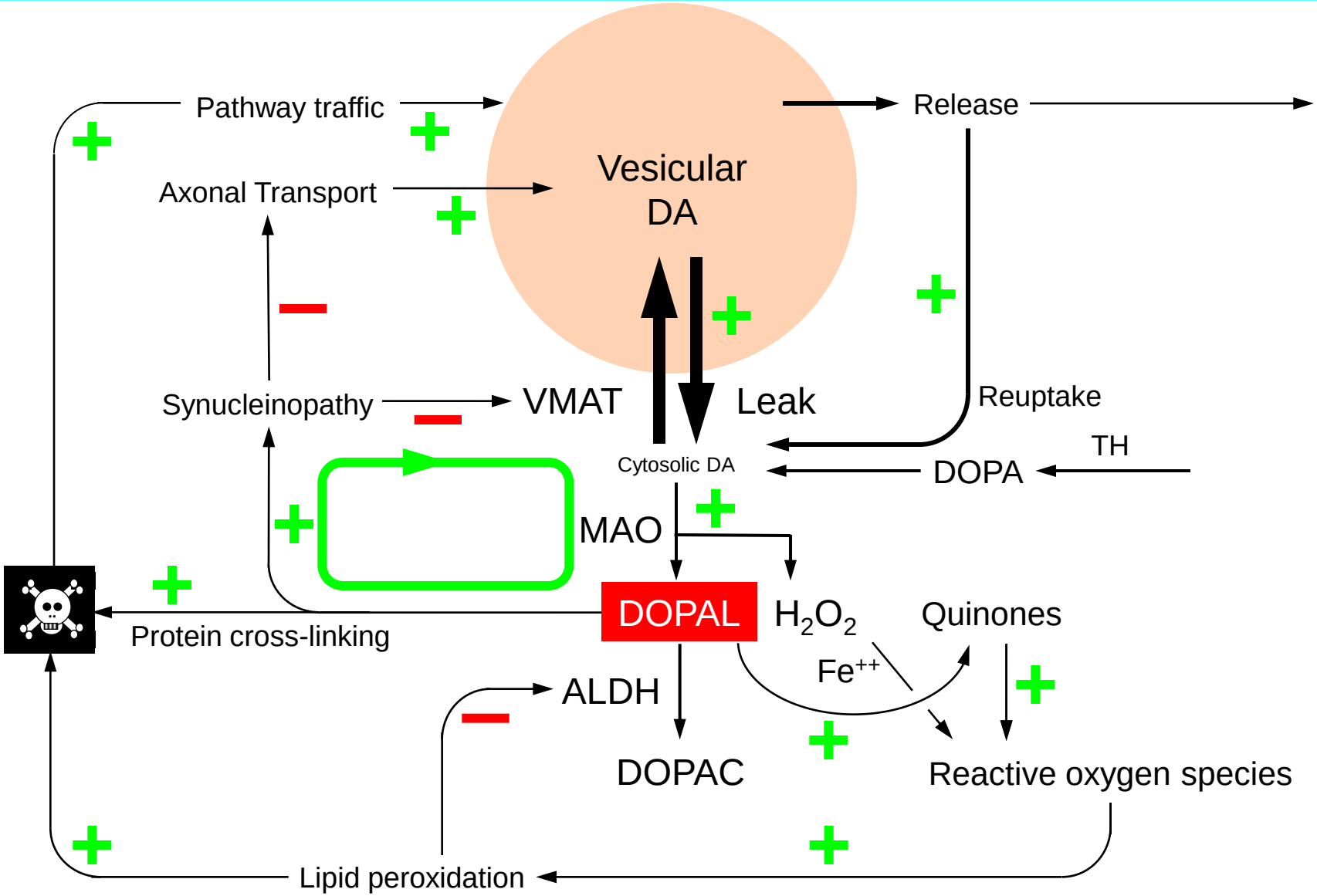
DOPAL-Synuclein Interactions



DOPAL and α-synuclein as nodes in a pathophysiologic nexus

Goldstein et al. Pharmacol Ther 2014 (PMID 24945828)

Concepts of Scientific Integrative Medicine



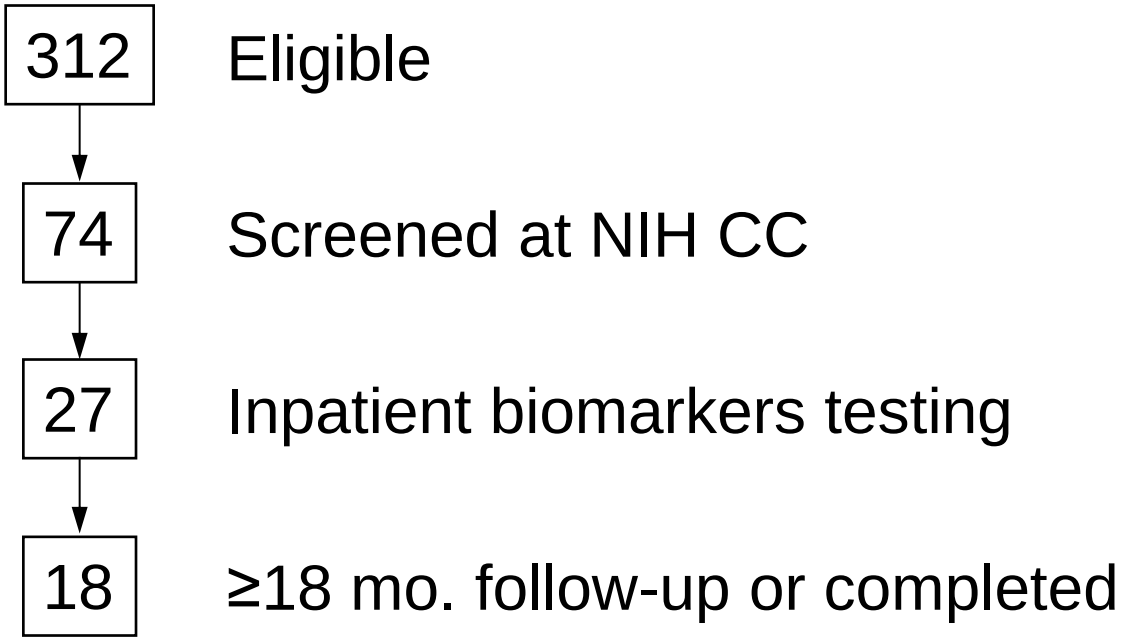
Prevention and disease modifying intervention?

PD-Risk project

Goals

- Determine whether people with statistical risk factors have biomarkers of catecholamine deficiency.
- Determine whether people with abnormal biomarkers develop PD during several years of follow-up.
- Risk factors: family history of PD, decreased sense of smell, dream enactment behavior, orthostatic intolerance (≥3 to be eligible)

PDRisk Study Progress to Date



Pharmacology & Therapeutics 144 (2014) 268–282

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Associate editor: G. Eisenhofer

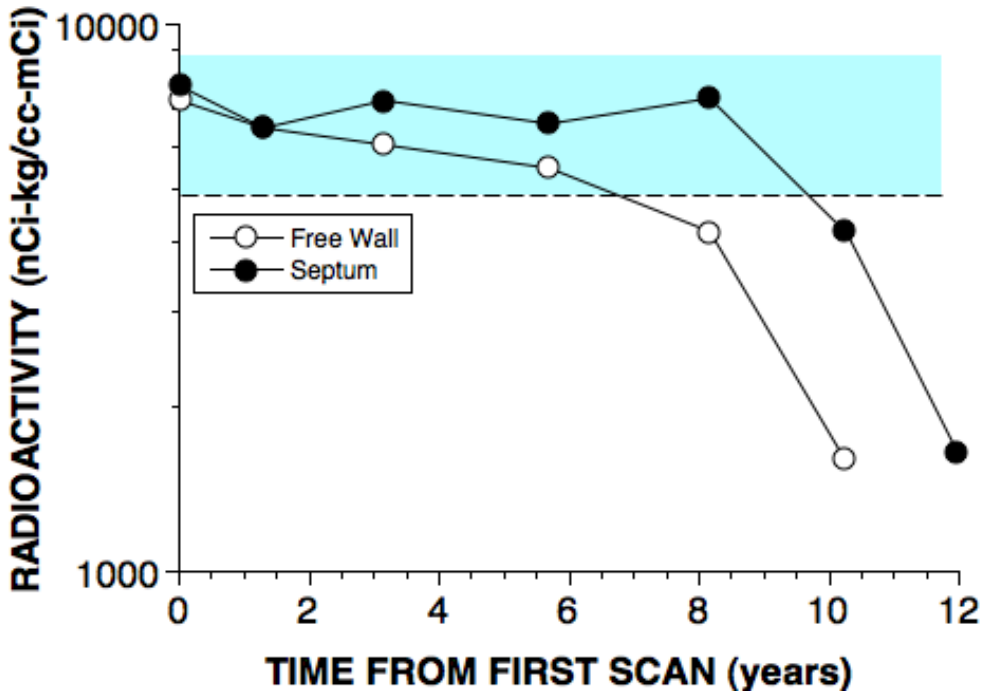
Catecholamine autotoxicity. Implications for pharmacology and therapeutics of Parkinson disease and related disorders ☆

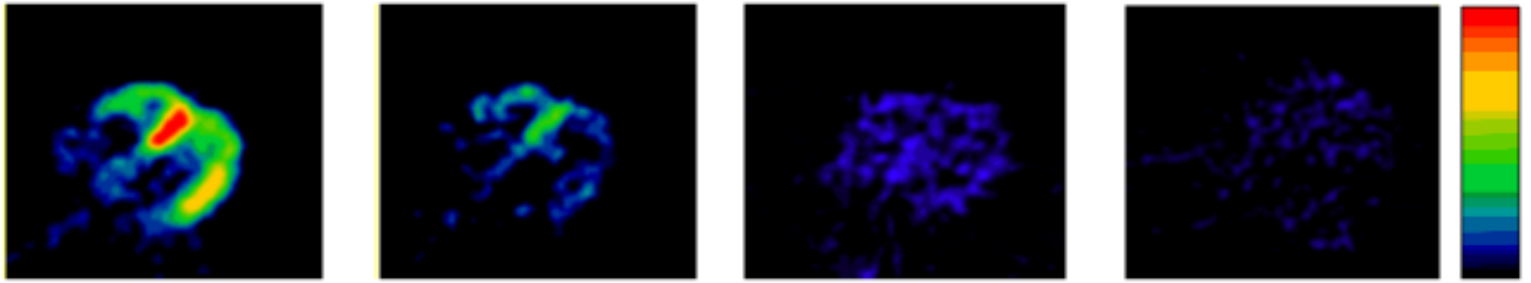
David S. Goldstein [a,*], Irwin J. Kopin [a], Yehonatan Sharabi [b]

[a] Clinical Neurocardiology Section, Clinical Neurosciences Program, Division of Intramural Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

[b] Tel-Aviv University Sackler Faculty of Medicine, Tel-Aviv, Israel

How Can One Test for Slowing of Neurodegeneration?

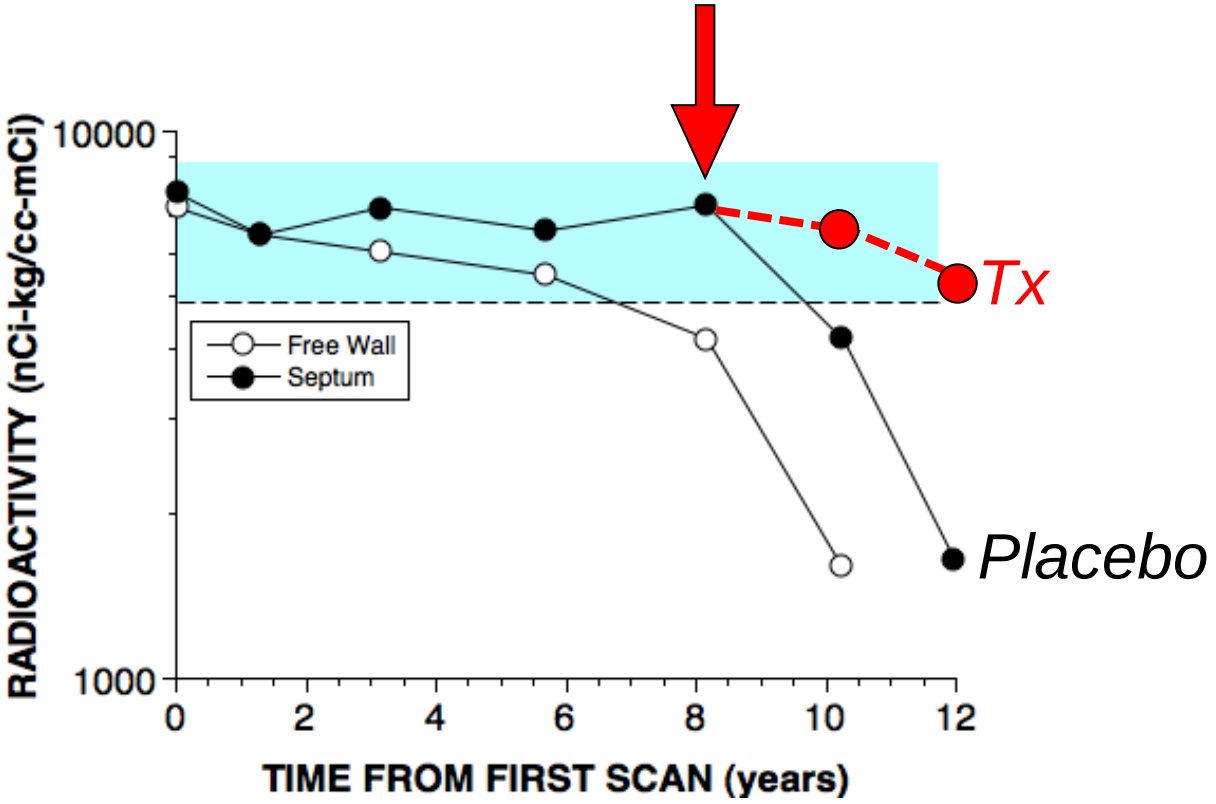




Initial Evaluation | 1.3 years | 4.3 years | 5.8 years

Jain & Goldstein, Neurobiol Dis 2012;46:572–580

How Can One Test for Slowing of Neurodegeneration?



Conclusions

- Catecholamine depletion in PD is determined by denervation and decreased vesicular storage.
- Decreased vesicular storage and decreased ALDH tend to build up up DOPAL, which is toxic and oligomerizes alpha-synuclein.
- The catecholaldehyde hypothesis and concepts of scientific integrative medicine lead to novel, testable treatment and prevention strategies.