Norepinephrine in Health and Disease

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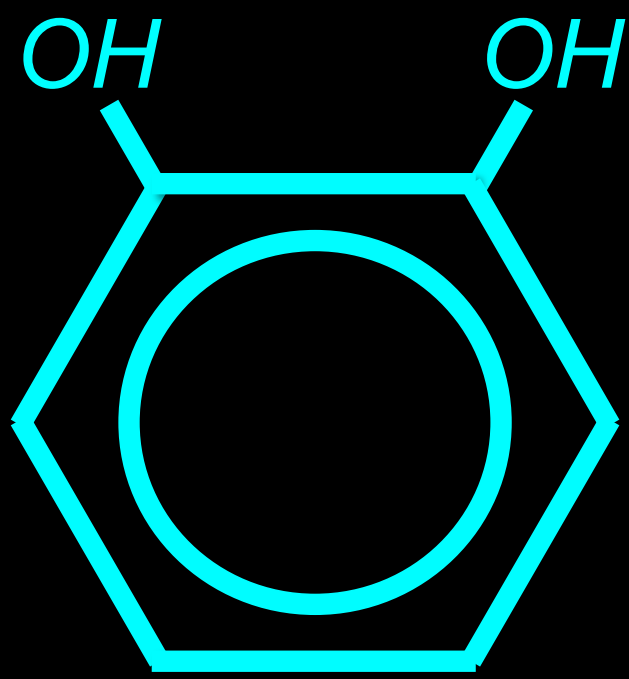
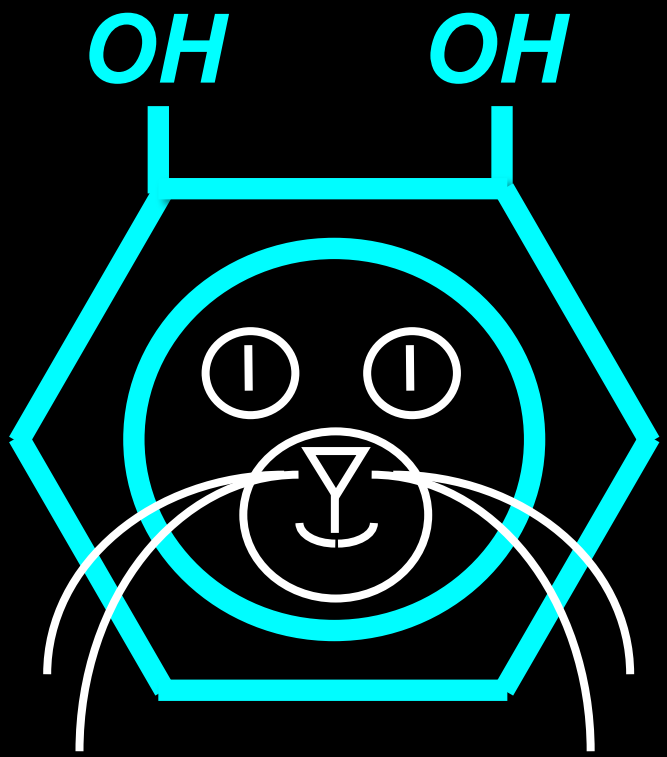
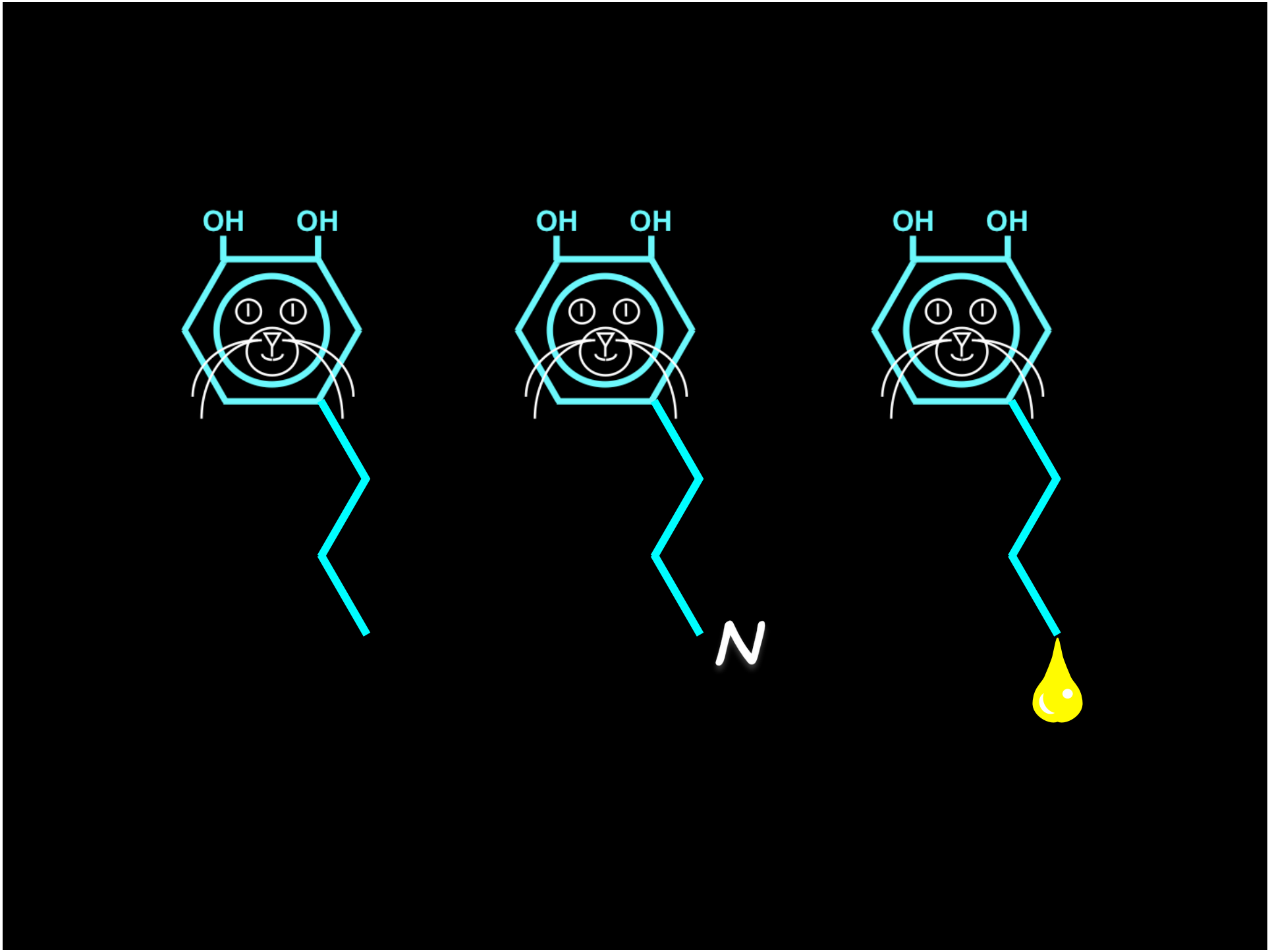
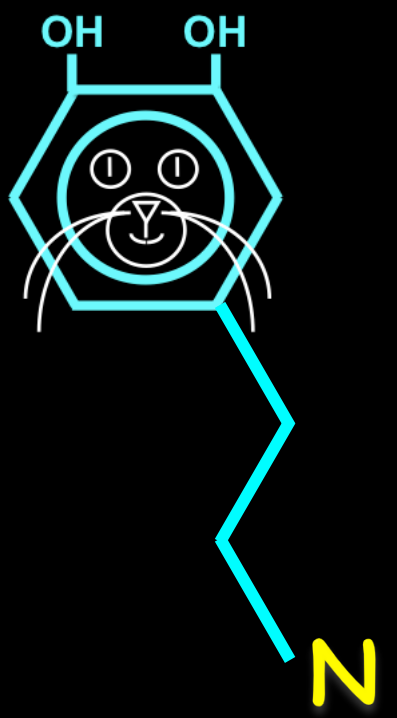

OH
OH

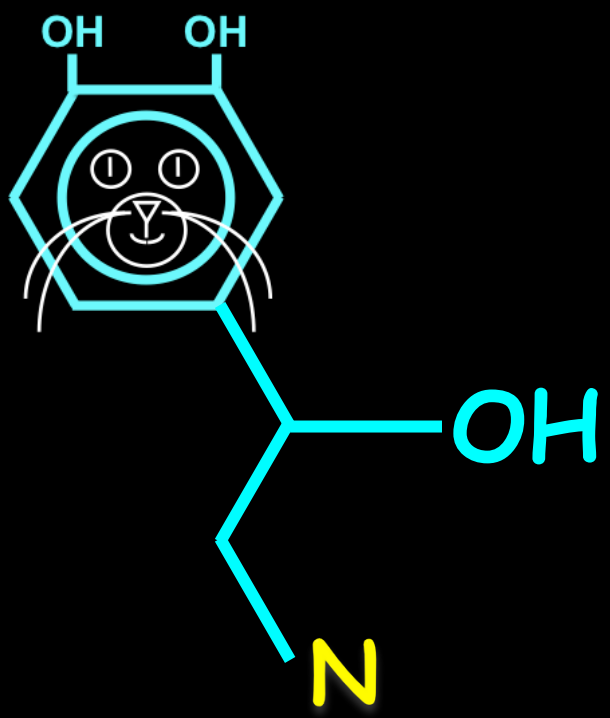

OH
OH


OH
OH
OH
OH
OH
OH
N

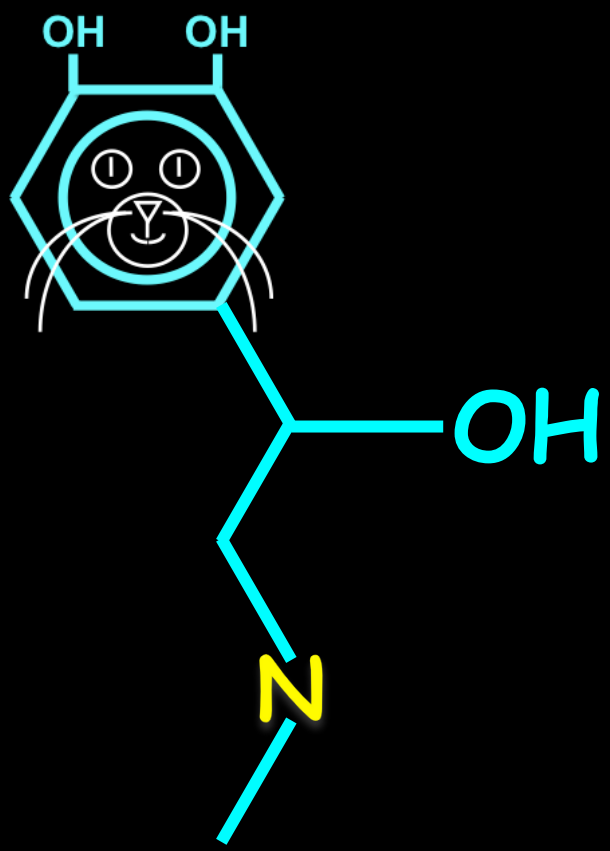
Dopamine

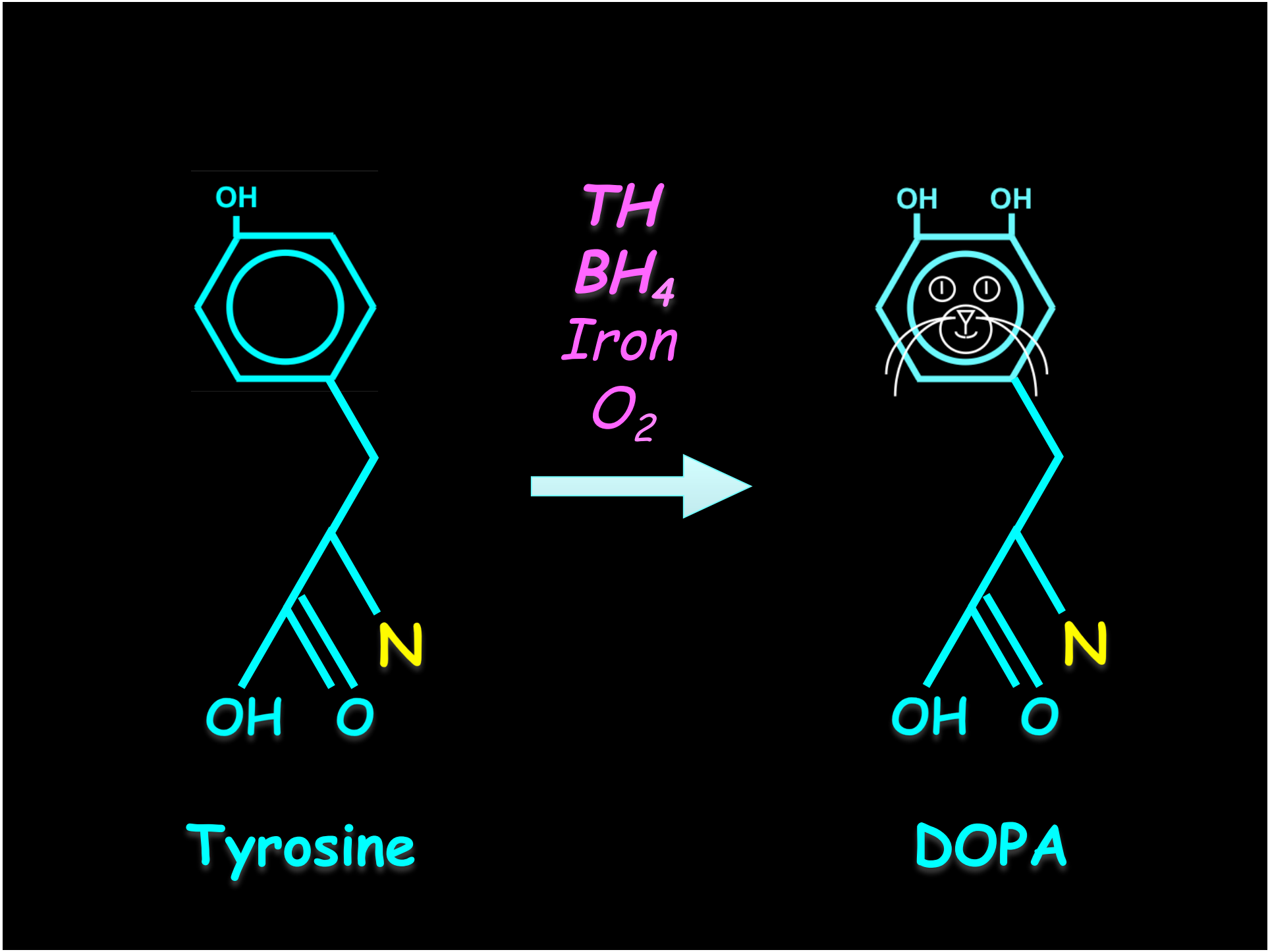


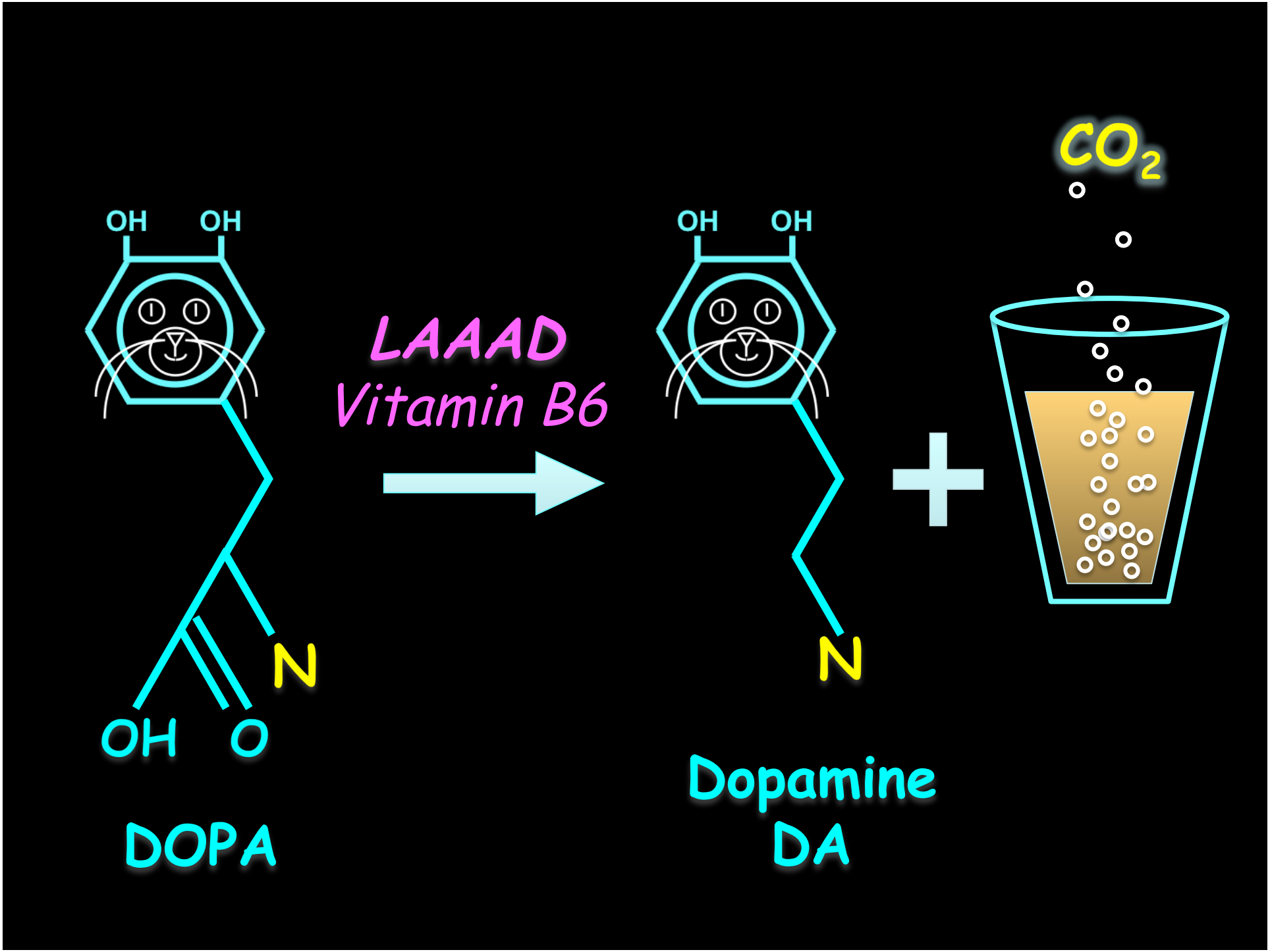
Norepinephrine

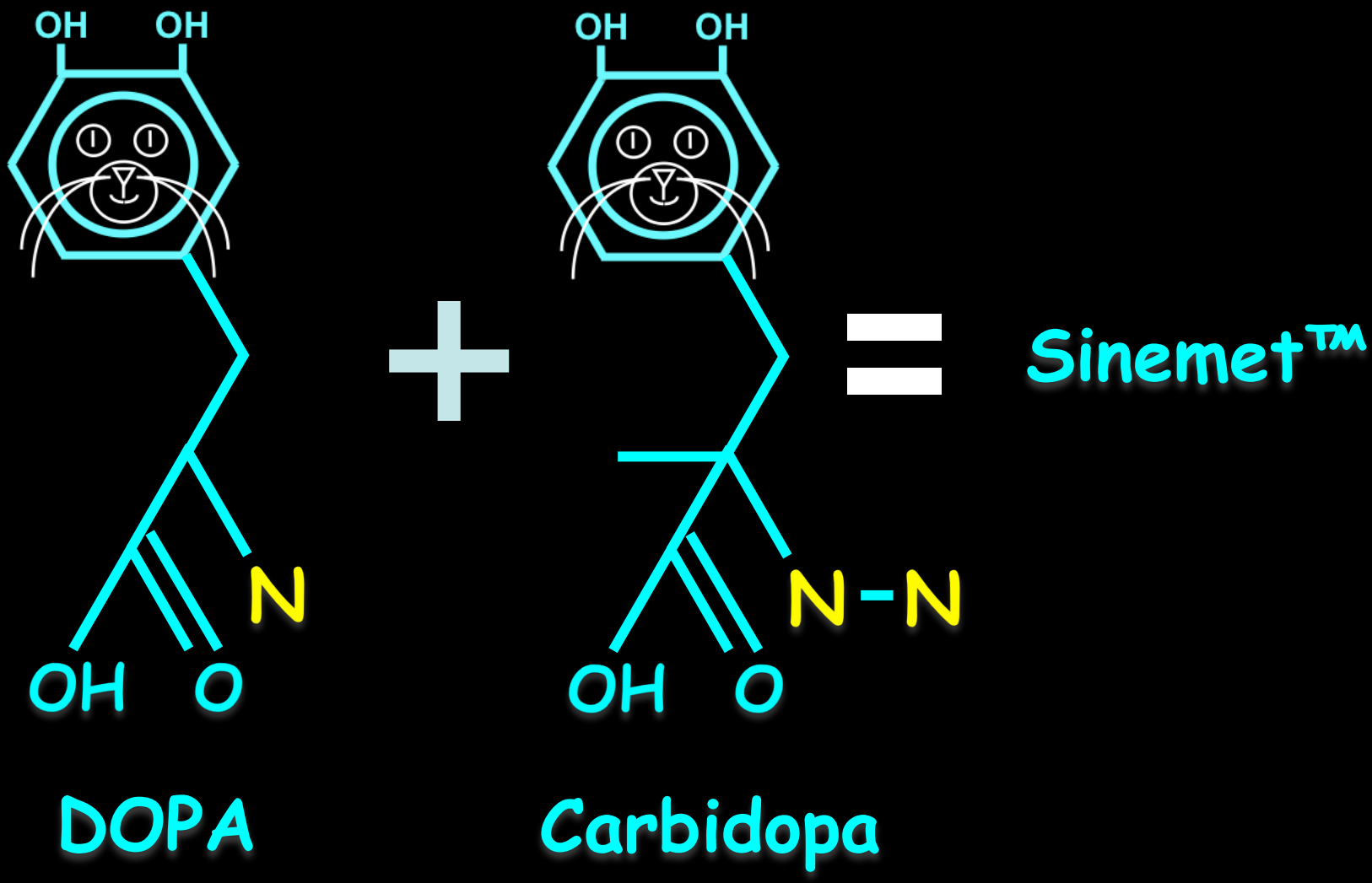


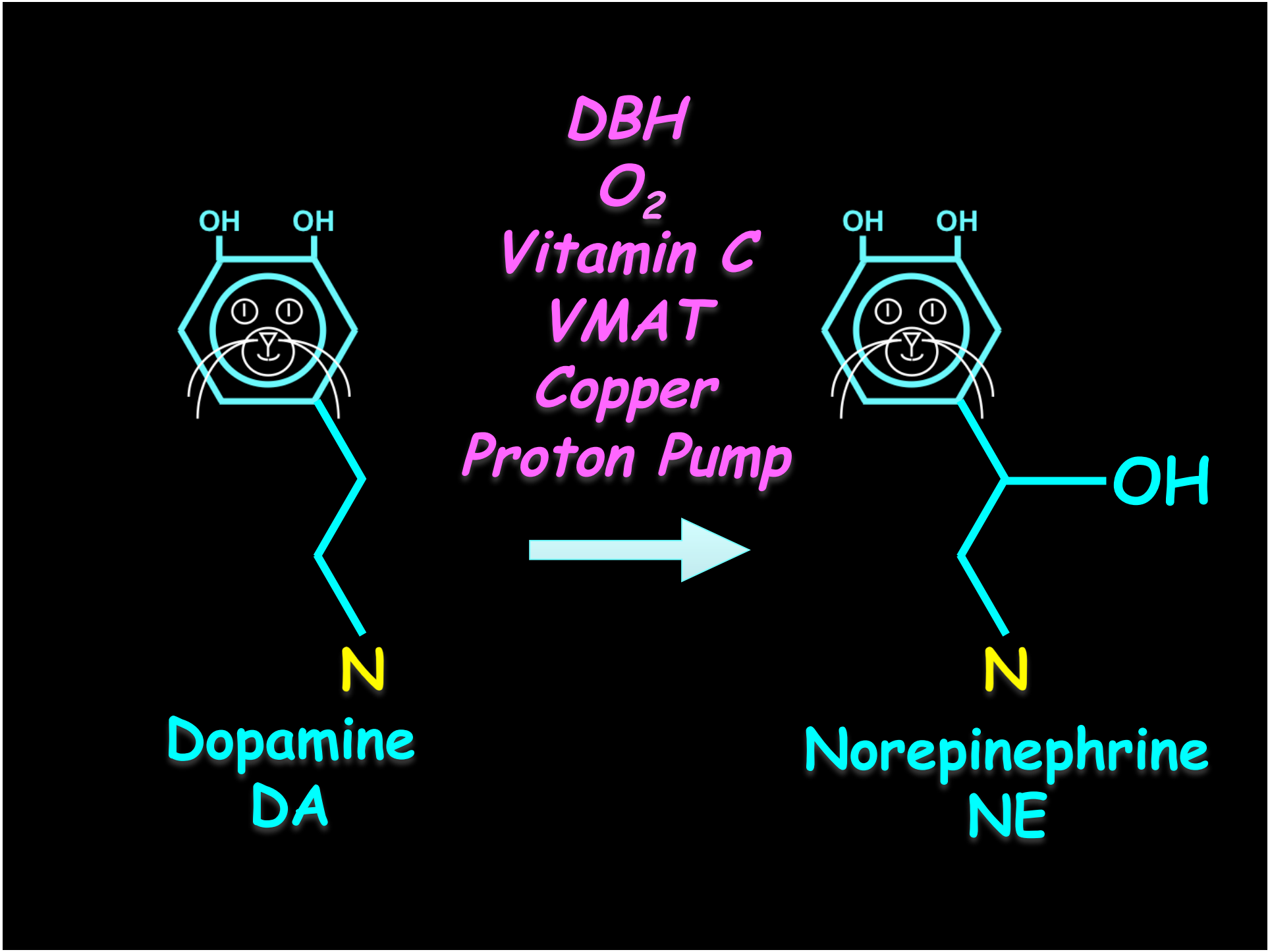
Epinephrine

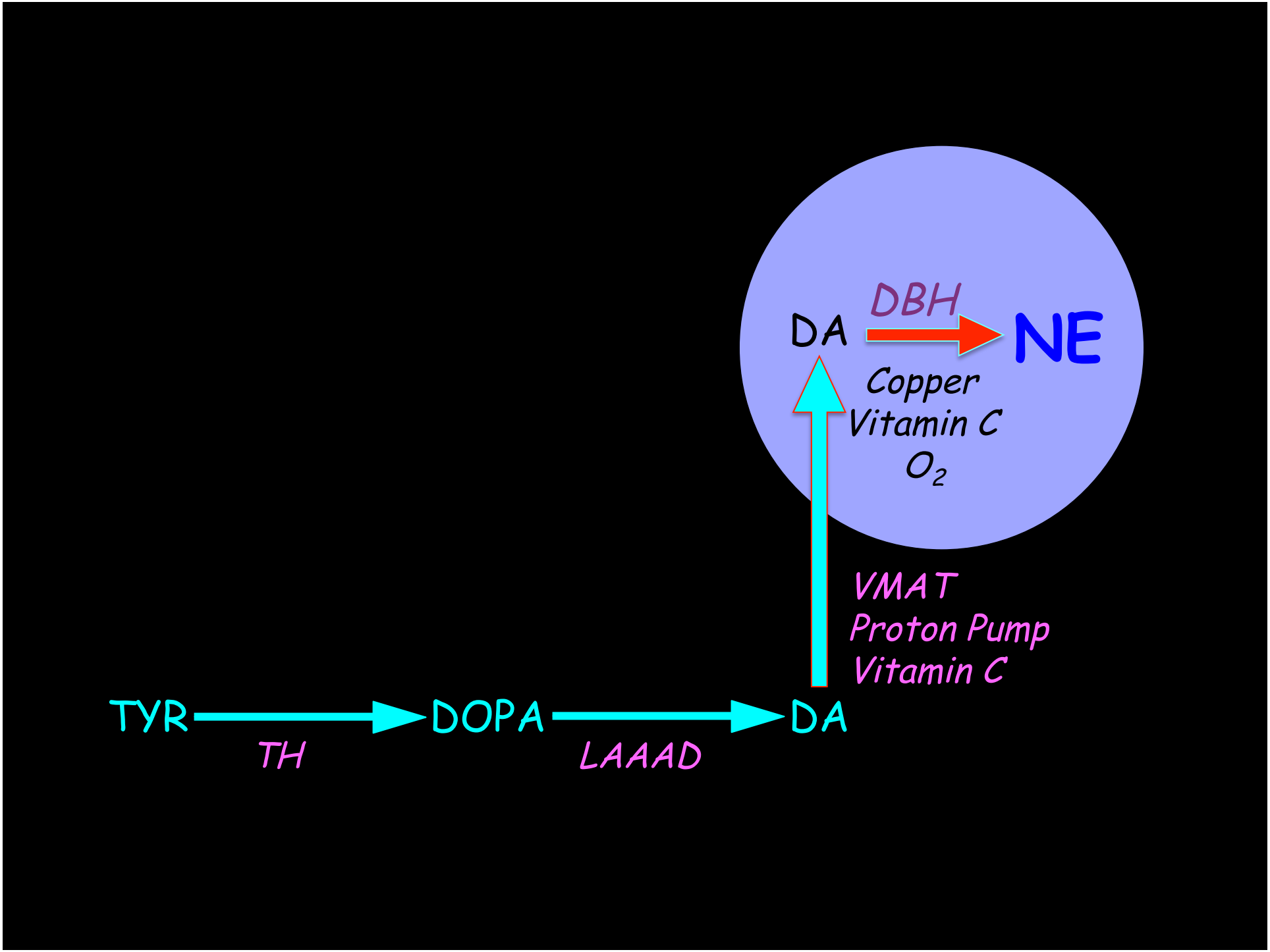


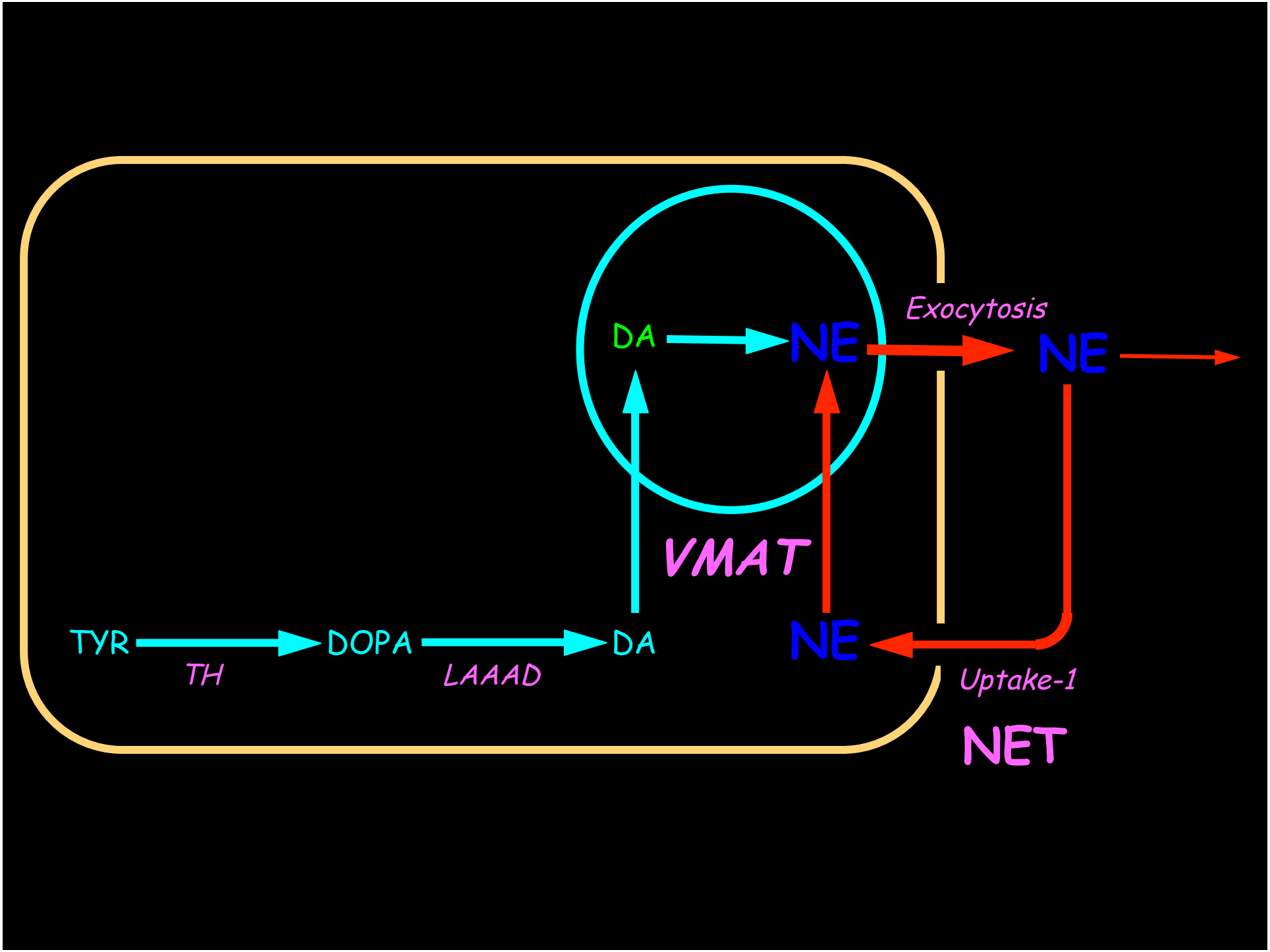

OH
N
OH
O
TH
BH4
Iron
O2
OH
OH
N
OH
O
Tyrosine
DOPA

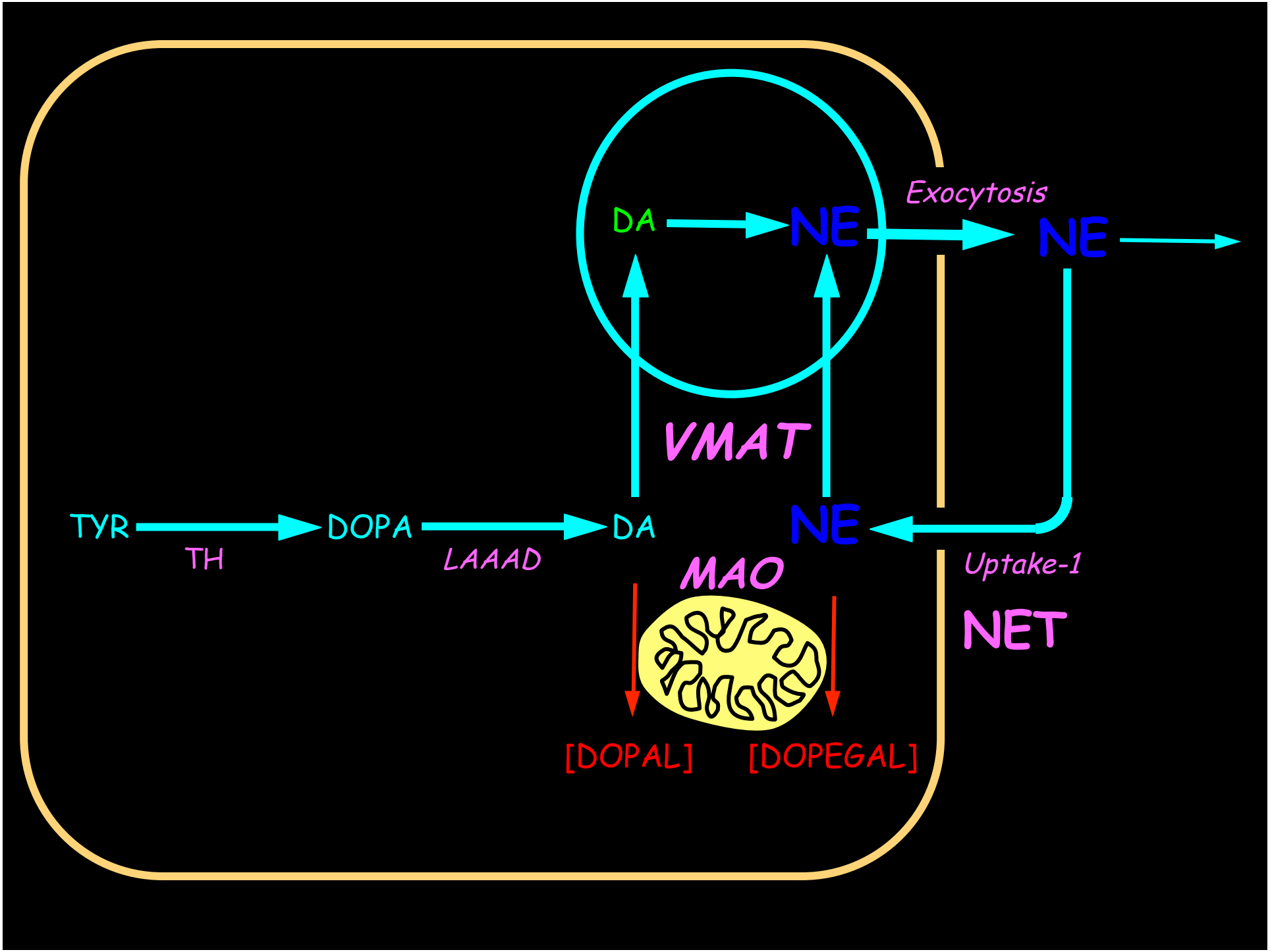

OH
OH
N
OH
O
DOPA
LAAAD
Vitamin B6
OH
OH
N
Dopamine
DA
CO_2

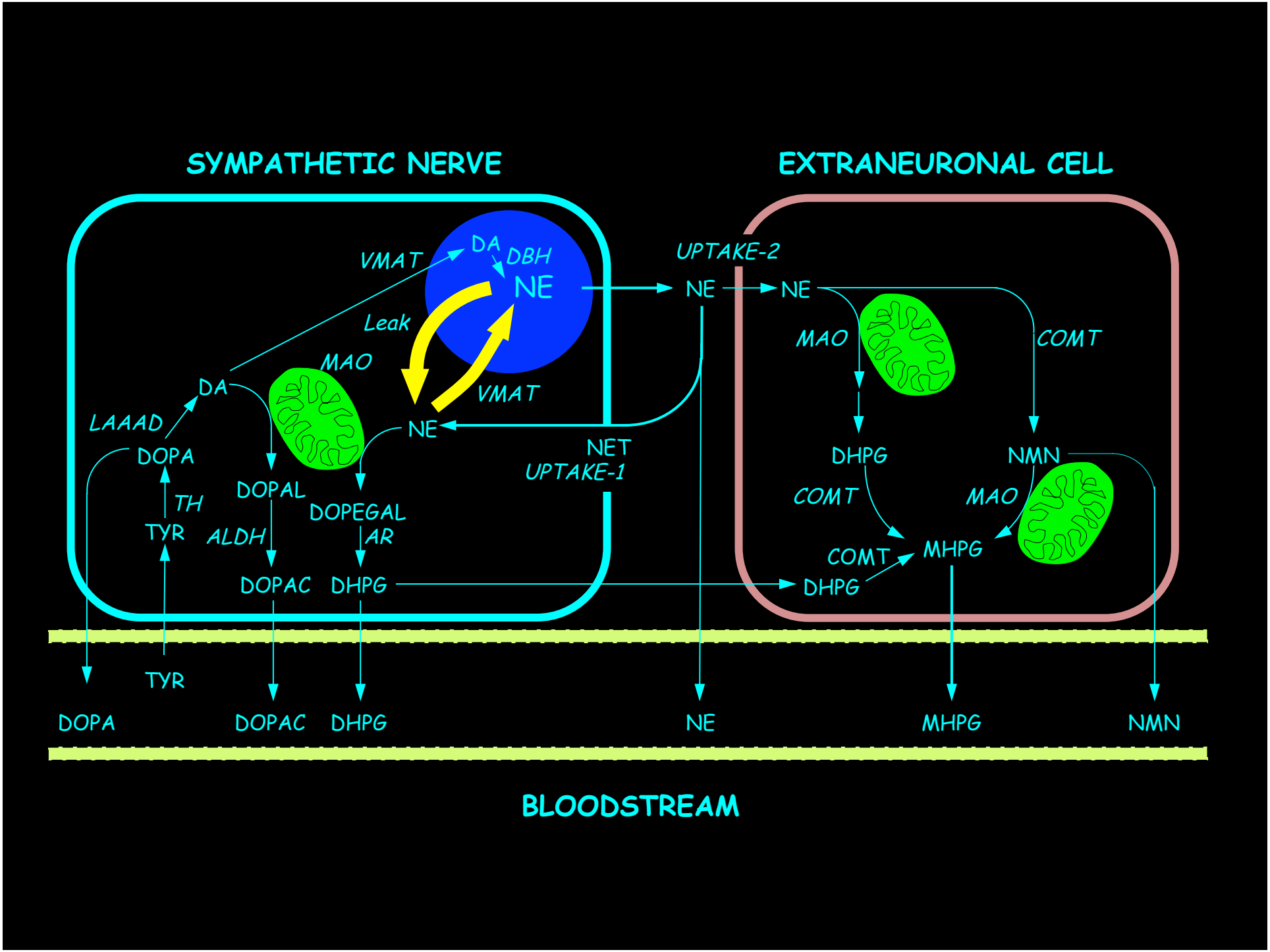

OH
OH
N
OH
O
DOPA
OH
OH
N-N
OH
O
Carbidopa
Sinemet™


DBH
O2
Vitamin C
VMAT
Copper
Proton Pump
OH
OH
N
Dopamine
DA
OH
OH
OH
N
Norepinephrine
NE


DA
DBH
NE
Copper
Vitamin C
O_2
VMAT
Proton Pump
Vitamin C
TYR
TH
DOPA
LAAAD
DA


DA
NE
Exocytosis
NE
VMAT
TYR
TH
DOPA
LAAAD
DA
NE
Uptake-1
NET


DA
NE
Exocytosis
NE
VMAT
TYR
TH
DOPA
LAAAD
DA
NE
MAO
Uptake-1
NET
[DOPAL]
[DOPEGAL]


SYMPATHETIC NERVE
EXTRANEURONAL CELL
VMAT
DA
DBH
NE
Leak
MAO
VMAT
DA
LAAAD
DOPA
TH
TYR
DOPAL
ALDH
DOPEGAL
AR
DOPAC
DHPG
NE
NET
UPTAKE-1
UPTAKE-2
NE
NE
MAO
COMT
DHPG
COMT
NMN
MAO
COMT
MHPG
DHPG
TYR
DOPA
DOPAC
DHPG
NE
MHPG
NMN
BLOODSTREAM

Sympathetic Noradrenergic System (SNS) Underactivity or Failure

Drugs

Diabetes

Parkinson disease (PD)

Cancer (paraneoplastic)

Multiple system atrophy (MSA)

Spinal cord injury

Pure autonomic failure

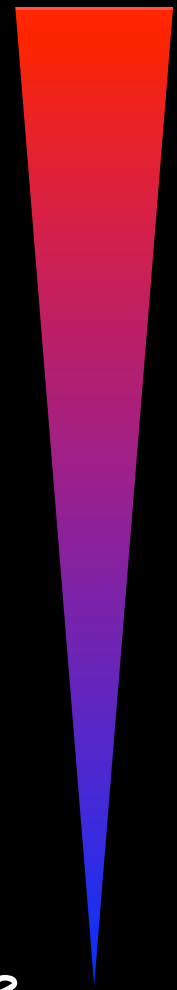
Amyloidosis

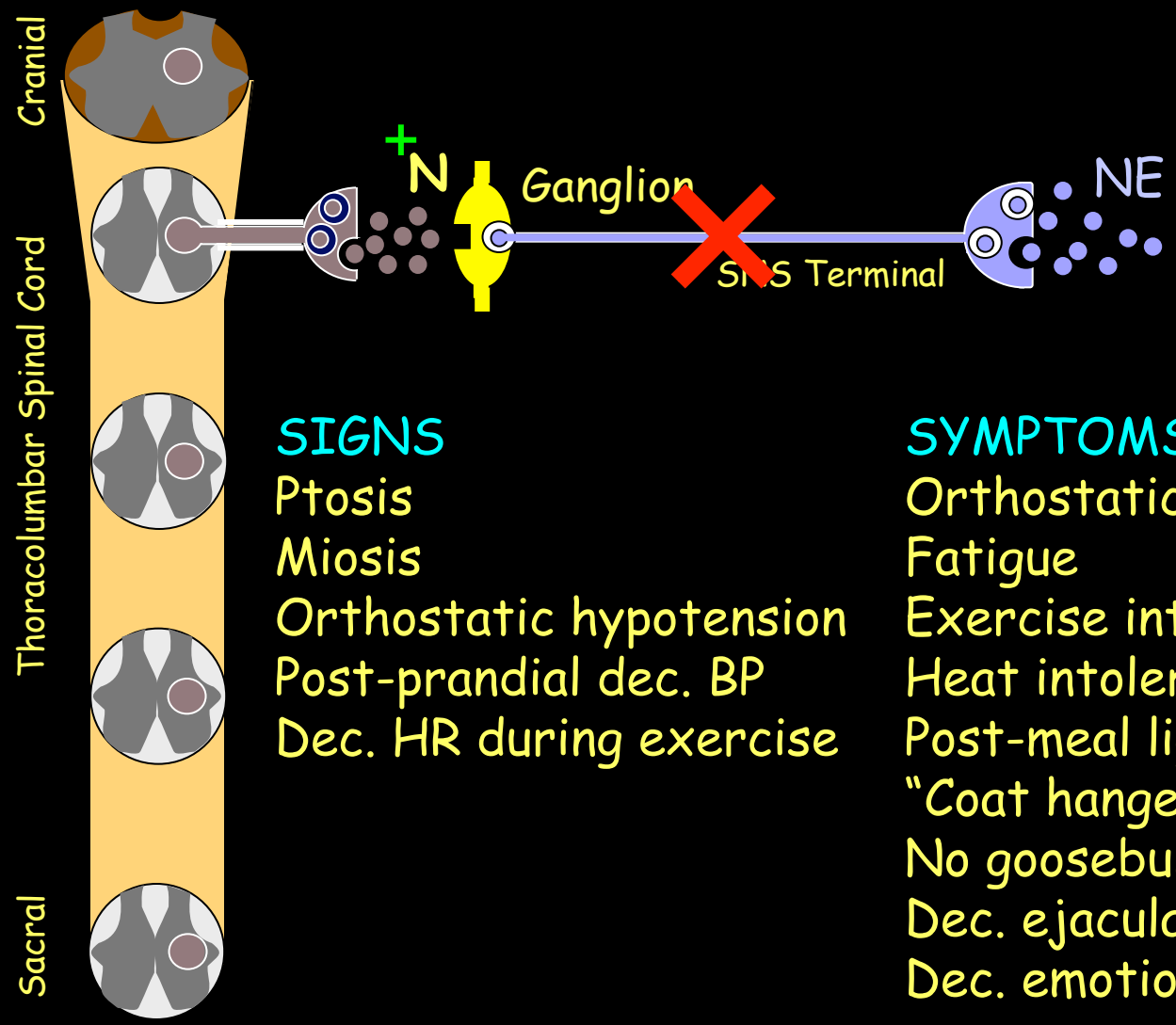
Familial dysautonomia

Dopamine-beta-hydroxylase deficiency

Acquired sensory and autonomic neuropathy

Autoimmune autonomic ganglionopathy





Spinal Cord

SIGNS

Ptosis
Miosis
Orthostatic hypotension
Post-prandial dec. BP
Dec. HR during exercise

SYMPTOMS

Orthostatic intolerance
Fatigue
Exercise intolerance
Heat intolerance
Post-meal lightheadedness
"Coat hanger" phenomenon
No goosebumps
Dec. ejaculation
Dec. emotional intensity

Sympathetic Noradrenergic System (SNS) Failure

Orthostatic intolerance & hypotension

Post-prandial lightheadedness & hypotension

Heat intolerance & hypotension

Fatigue

Tendency to slow pulse rate during exercise

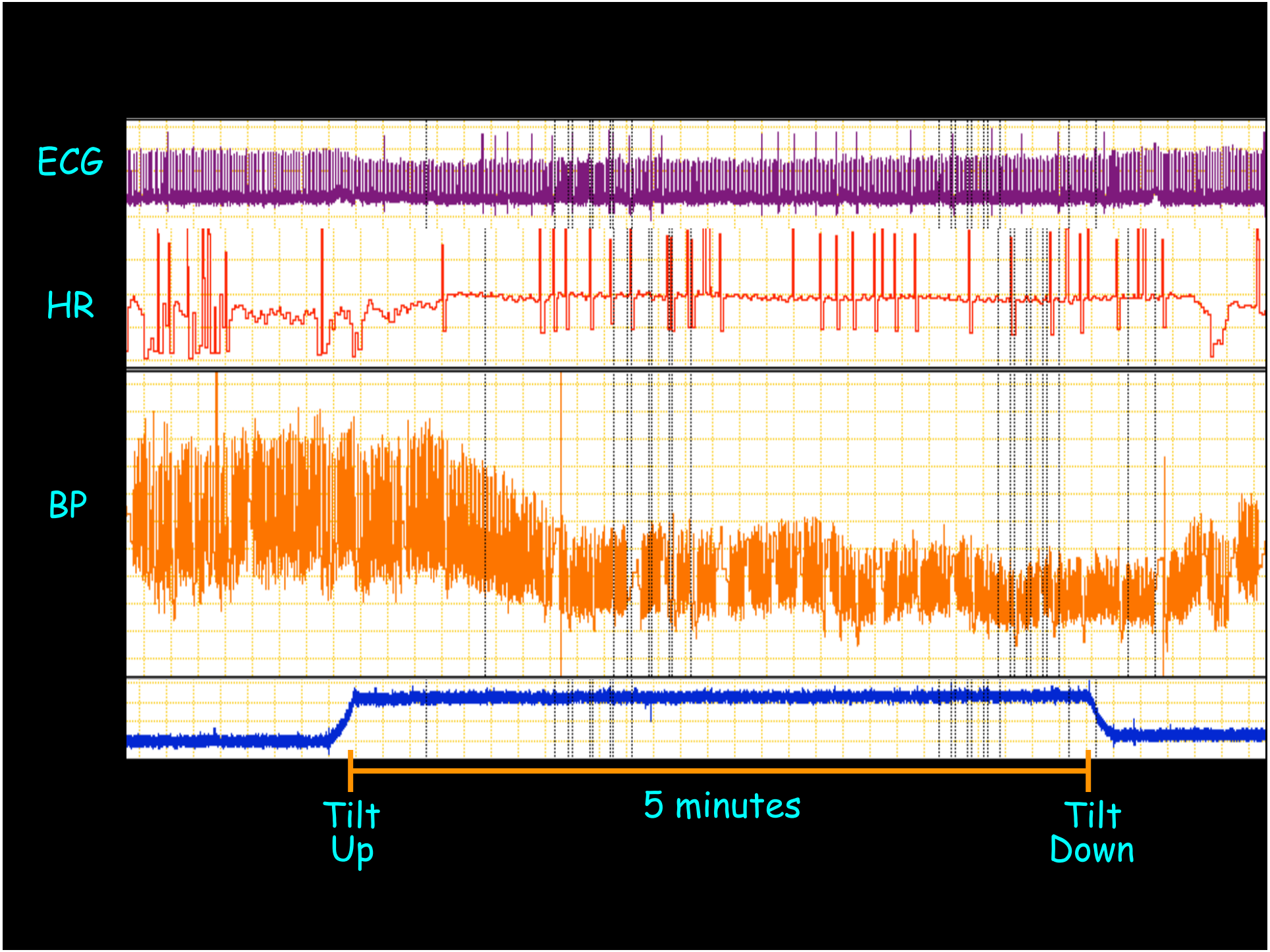
"Coat hanger" pain

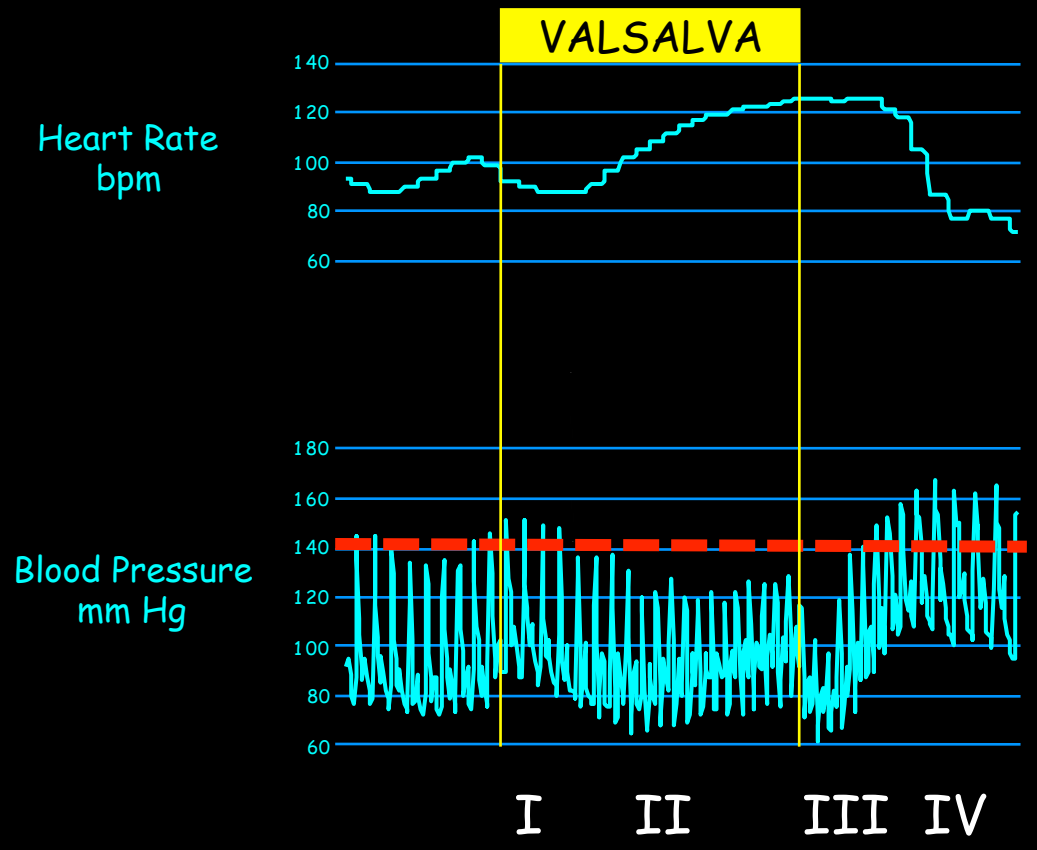
Droopy eyelids (ptosis)

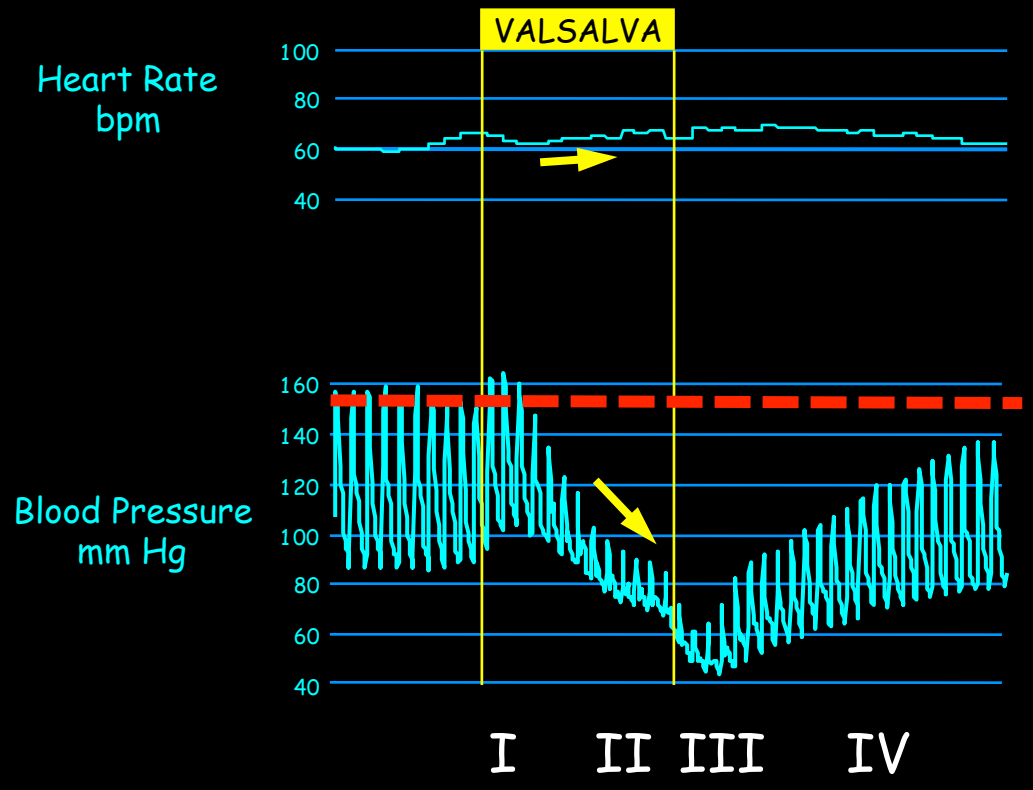
Decreased ability to ejaculate

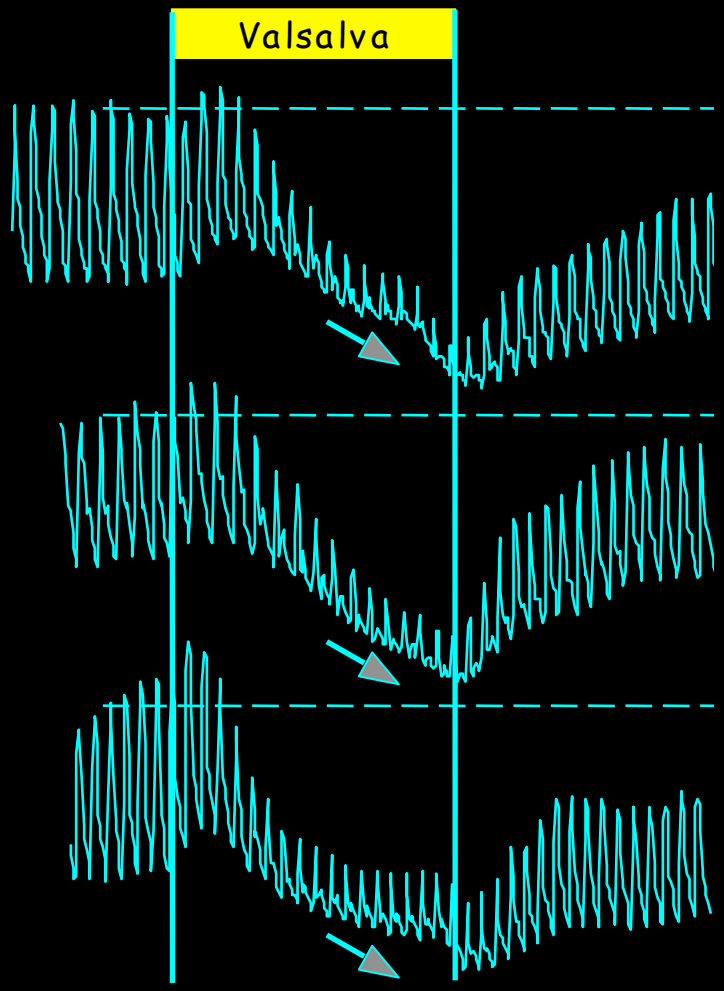
Tendency to constricted pupils

No goosebumps


ECG
HR
BP
Tilt
Up
5 minutes
Tilt
Down


VALSALVA
Heart Rate
bpm
140
120
100
80
60
180
160
140
120
100
80
60
Blood Pressure
mm Hg
I
II
III
IV

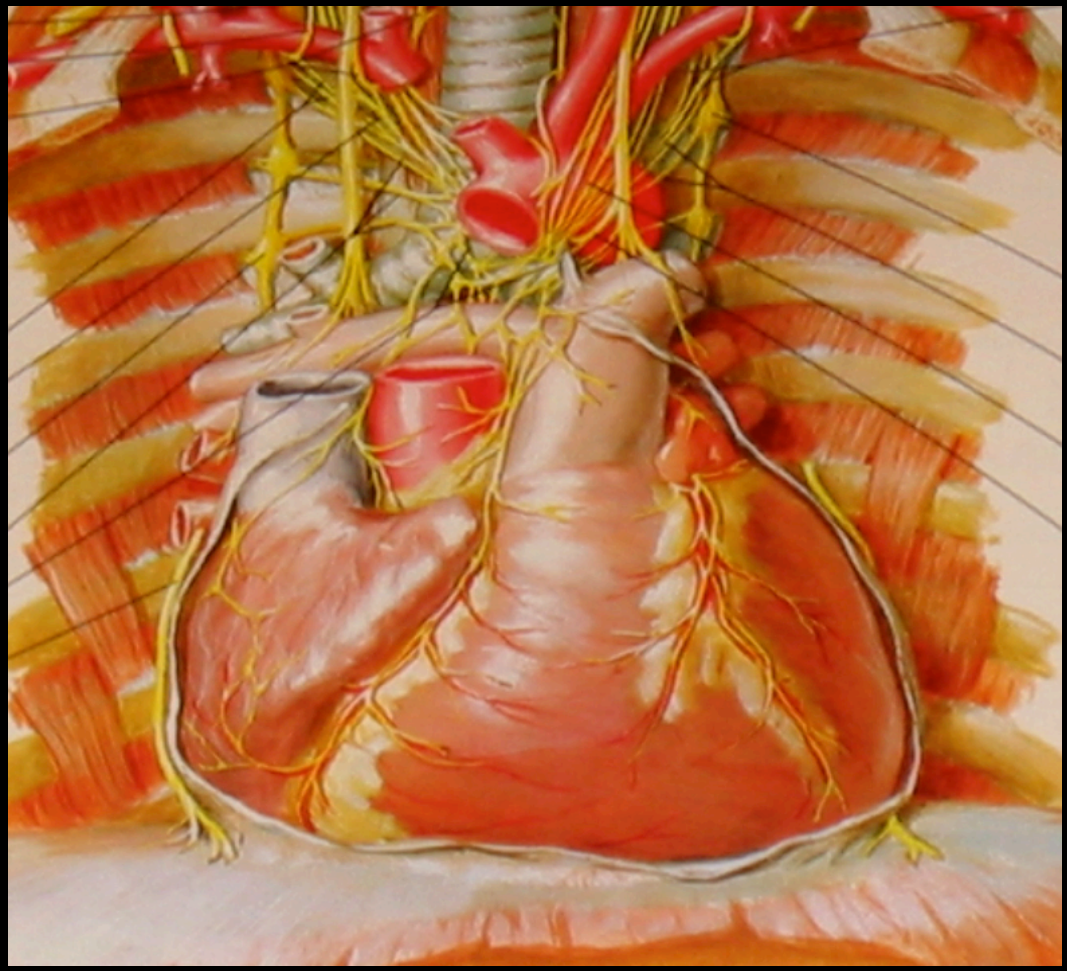

VALSALVA
Heart Rate
bpm
100
80
60
40
160
140
120
100
80
60
40
Blood Pressure
mm Hg
I
II
III
IV

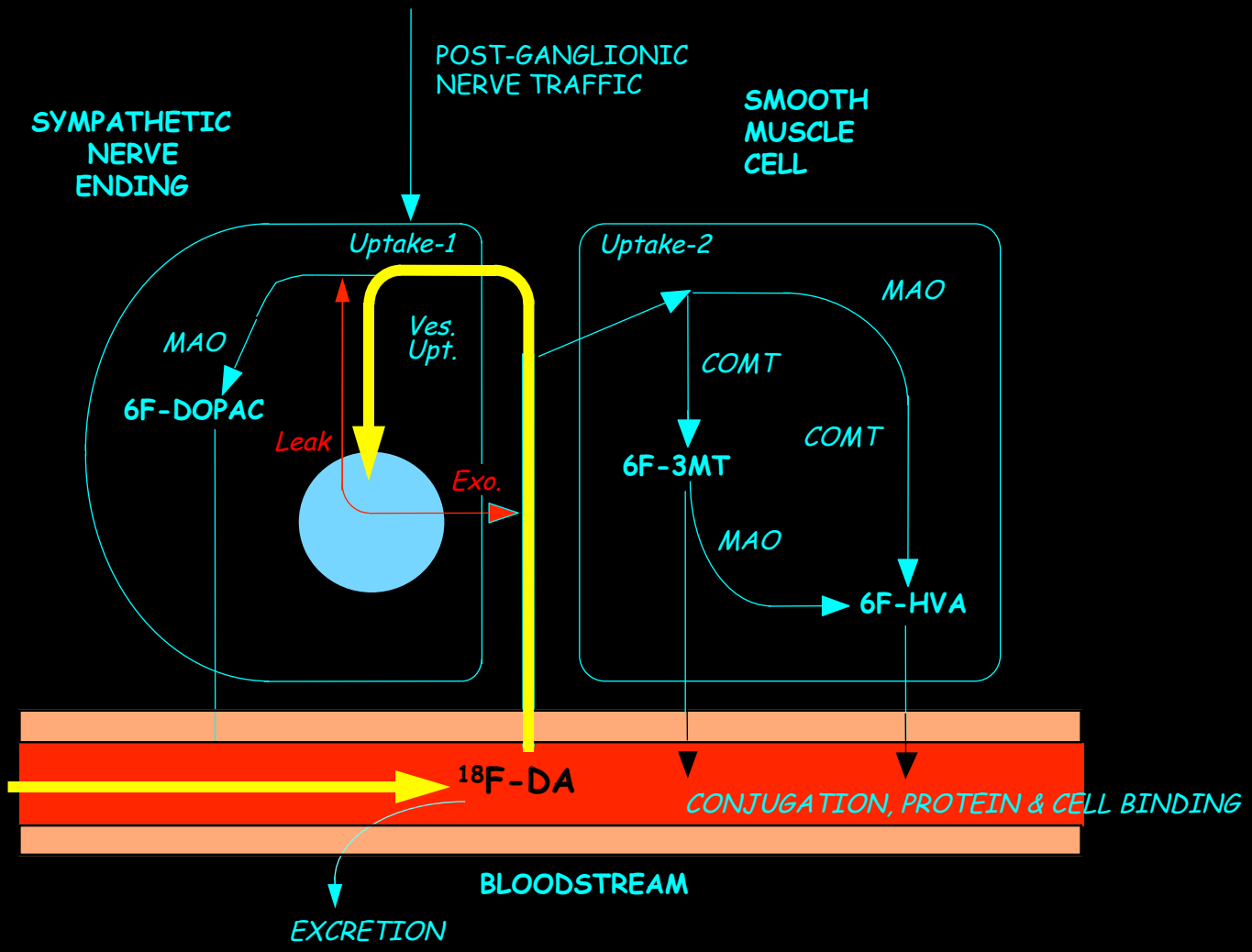


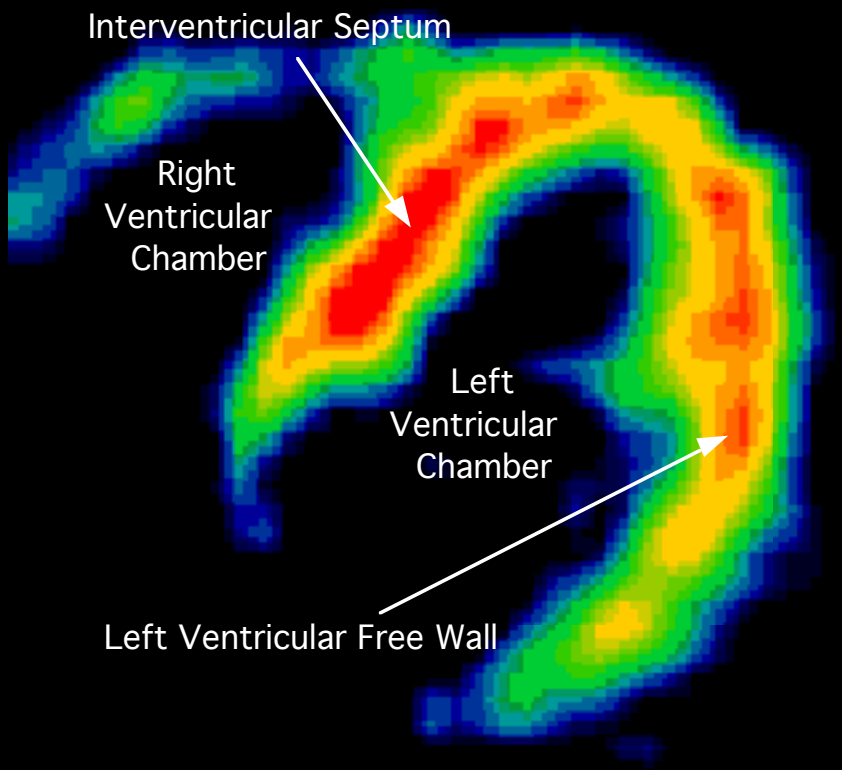
PD+OH

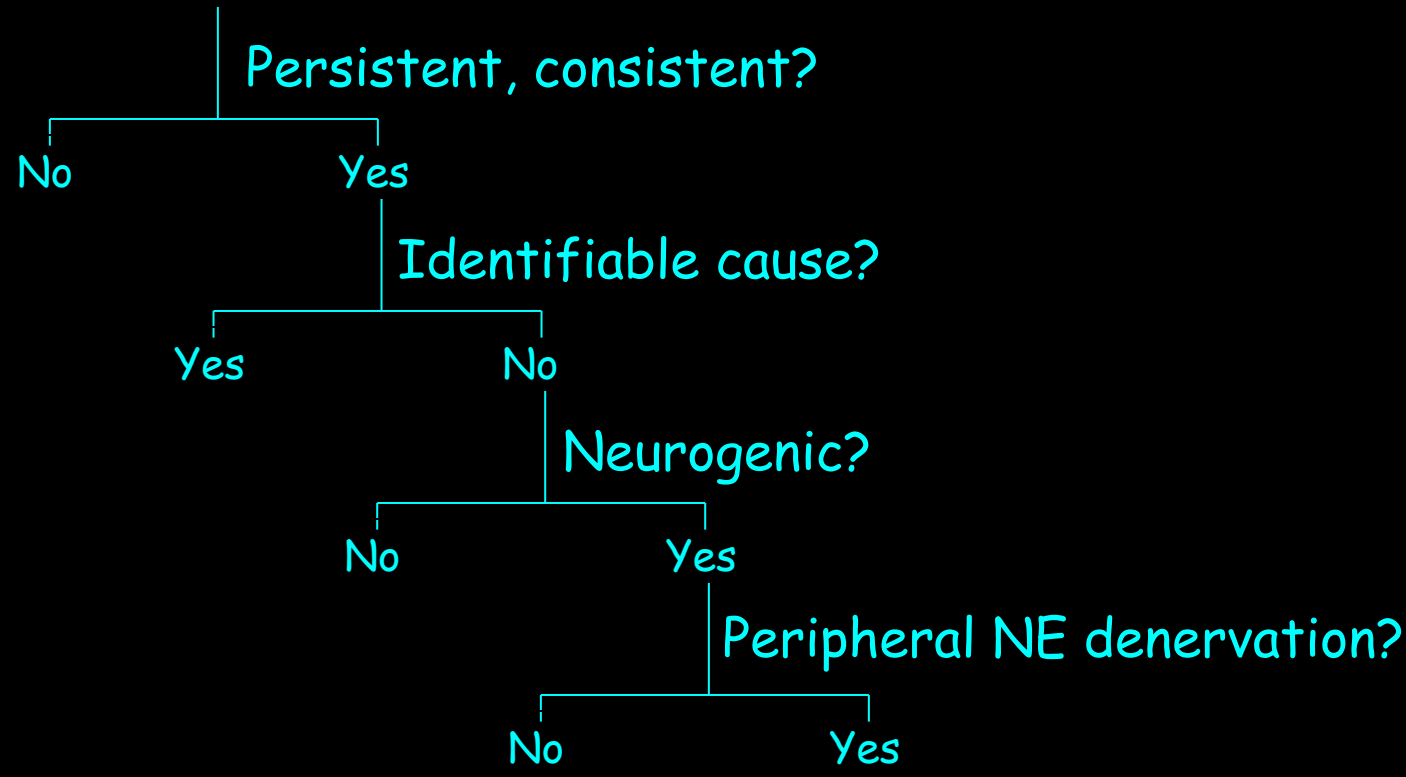
PAF

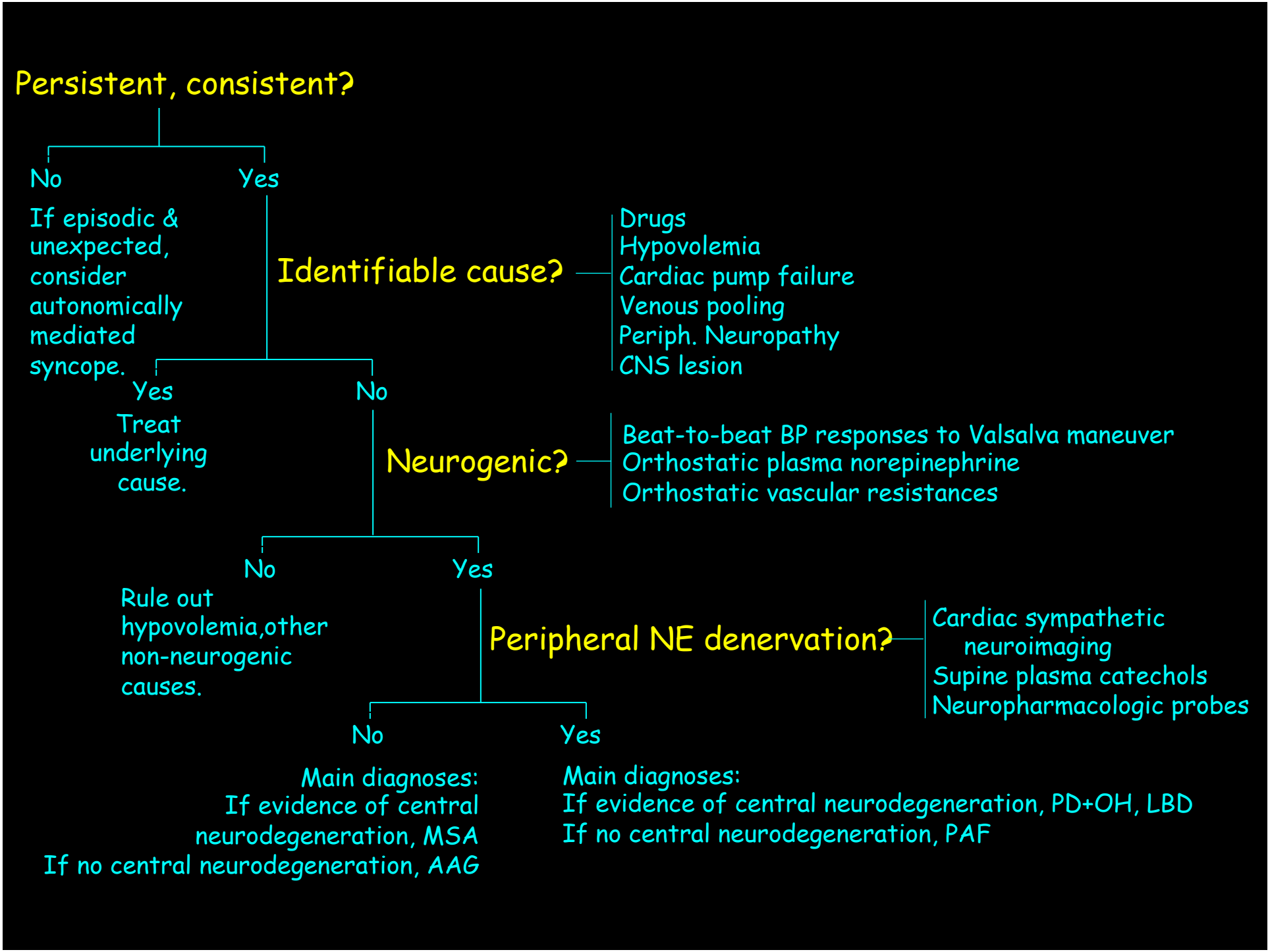
MSA

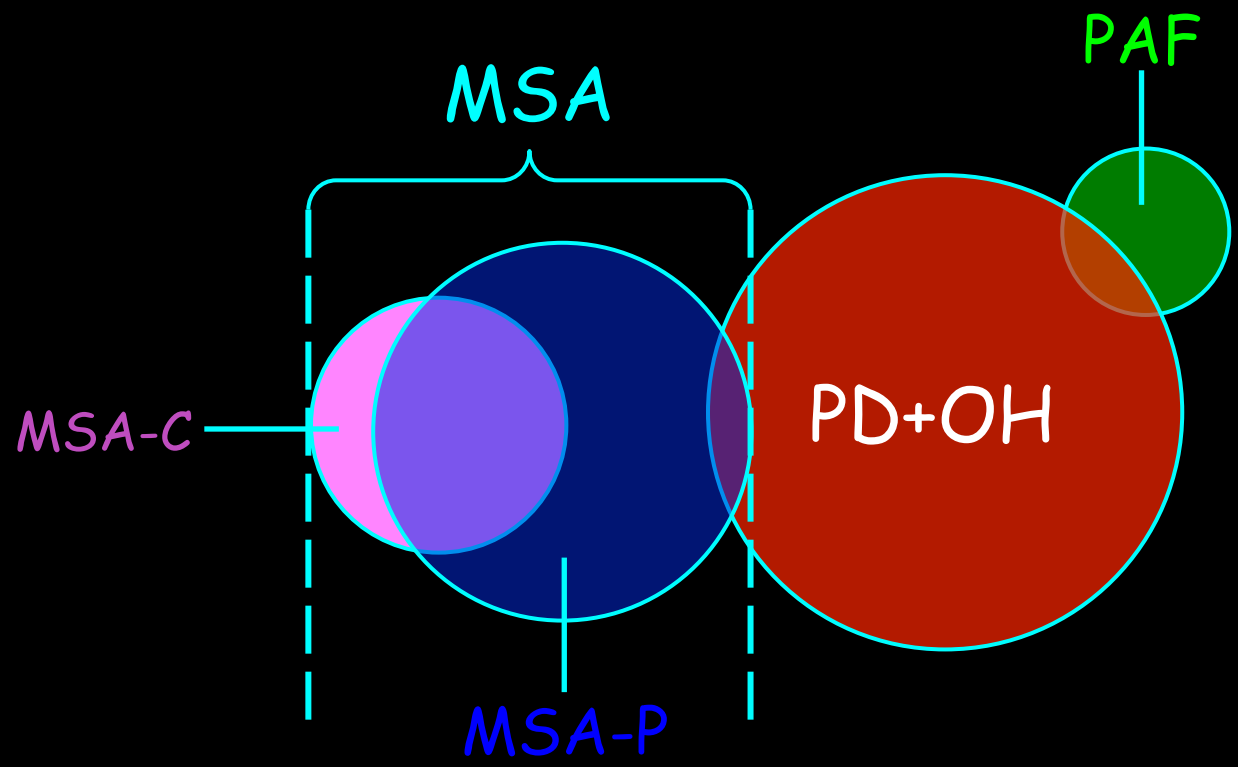


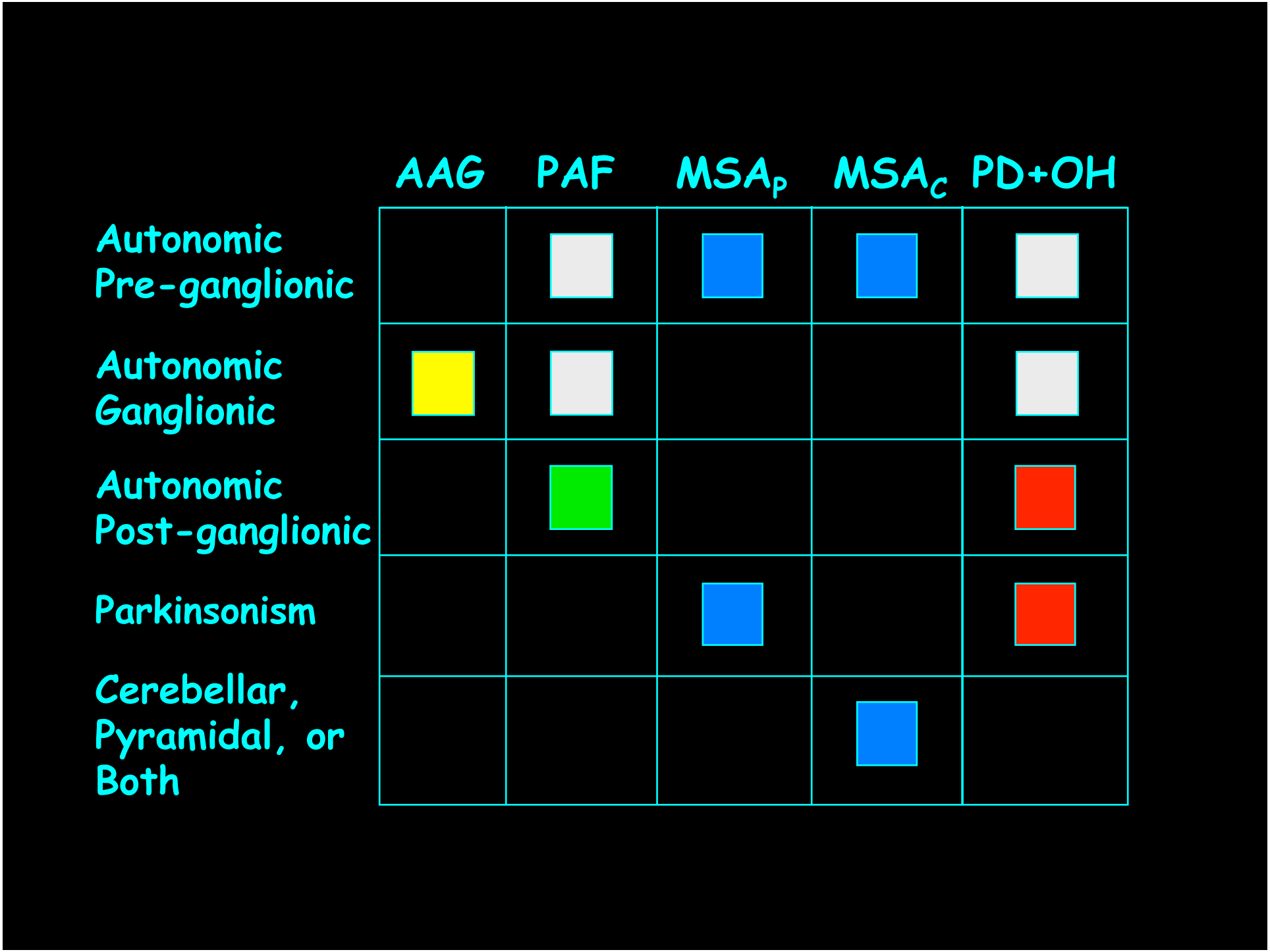

POST-GANGLIONIC
NERVE TRAFFIC
SYMPATHETIC
NERVE
ENDING
SMOOTH
MUSCLE
CELL
Uptake-1
Uptake-2
MAO
Ves.
Upt.
MAO
6F-DOPAC
Leak
Exo.
COMT
COMT
6F-3MT
MAO
6F-HVA
18F-DA
CONJUGATION, PROTEIN & CELL BINDING
BLOODSTREAM
EXCRETION

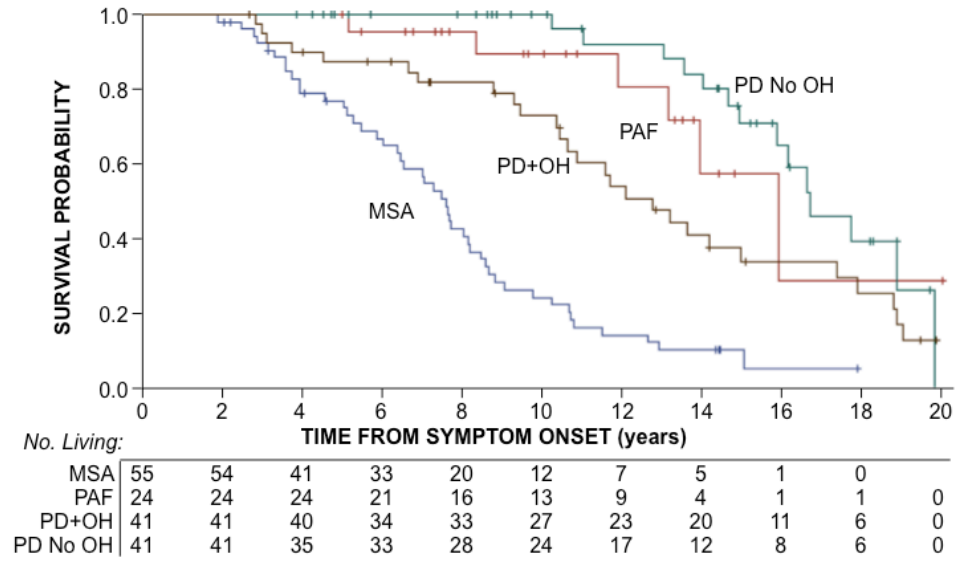

Interventricular Septum
Right
Ventricular
Chamber
Left
Ventricular
Chamber
Left Ventricular Free Wall


Persistent, consistent?
No
Yes
Identifiable cause?
Yes
No
Neurogenic?
No
Yes
Peripheral NE denervation?
No
Yes


Persistent, consistent?
No
If episodic & unexpected, consider autonomically mediated syncope.
Yes
Identifiable cause?
Drugs
Hypovolemia
Cardiac pump failure
Venous pooling
Periph. Neuropathy
CNS lesion
Yes
Treat underlying cause.
No
Neurogenic?
Beat-to-beat BP responses to Valsalva maneuver
Orthostatic plasma norepinephrine
Orthostatic vascular resistances
No
Rule out hypovolemia,other non-neurogenic causes.
Yes
Peripheral NE denervation?
Cardiac sympathetic neuroimaging
Supine plasma catechols
Neuropharmacologic probes
No
Main diagnoses:
If evidence of central neurodegeneration, MSA
If no central neurodegeneration, AAG
Yes
Main diagnoses:
If evidence of central neurodegeneration, PD+OH, LBD
If no central neurodegeneration, PAF

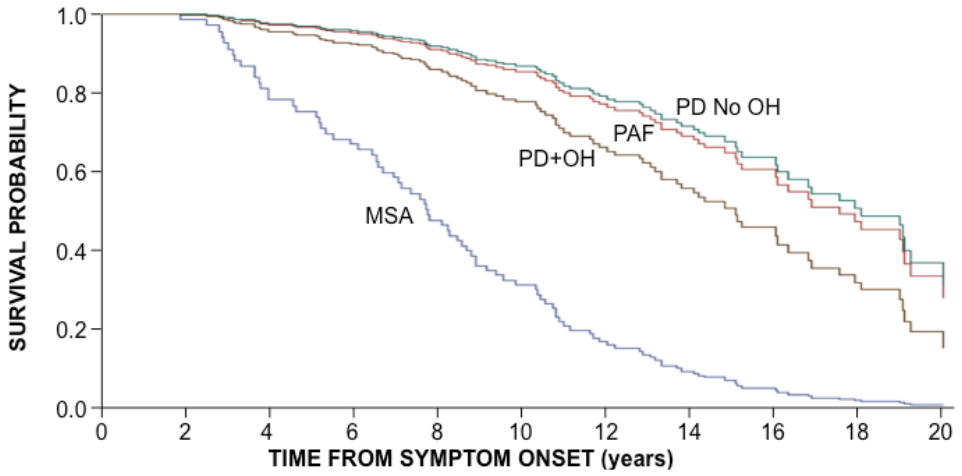

MSA
PAF
MSA-C
PD+OH
MSA-P

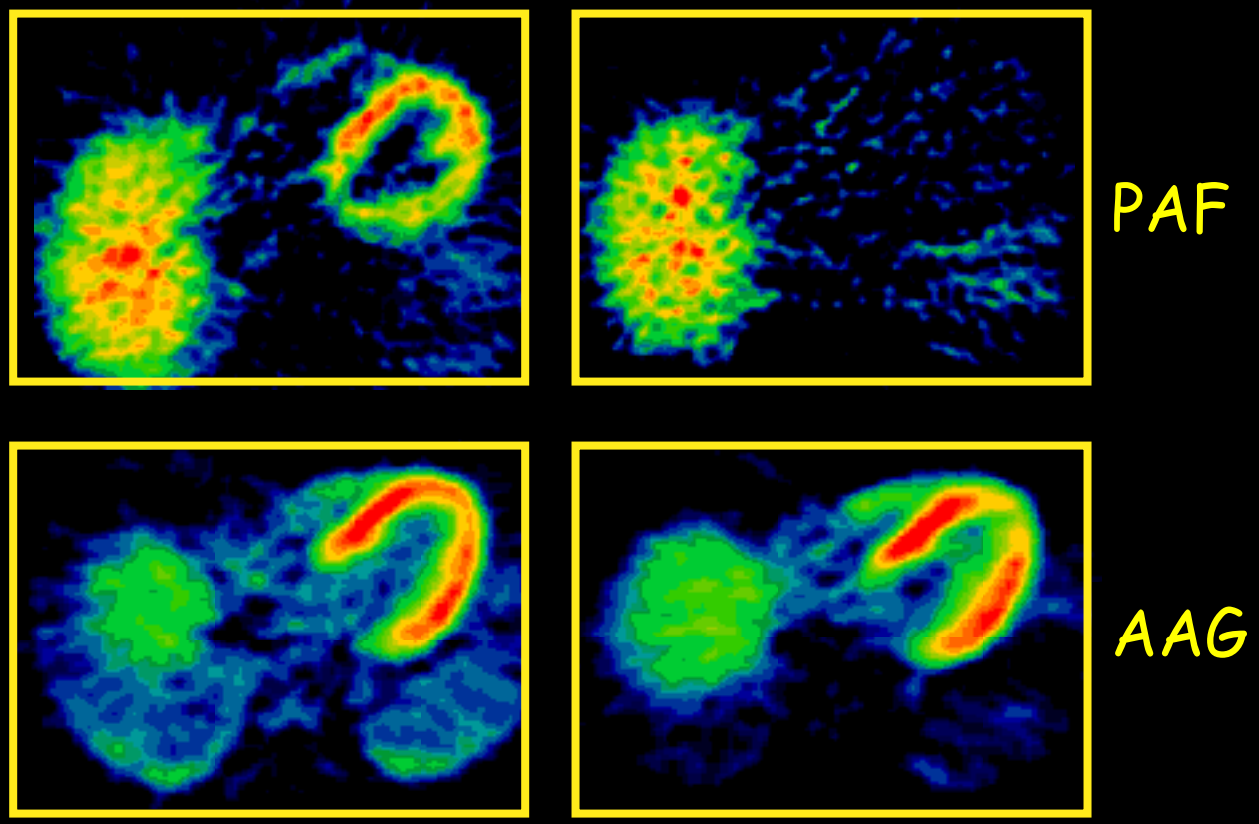

AAG
PAF
MSAp
MSAc
PD+OH
Autonomic Pre-ganglionic
Autonomic Ganglionic
Autonomic Post-ganglionic
Parkinsonism
Cerebellar, Pyramidal, or Both

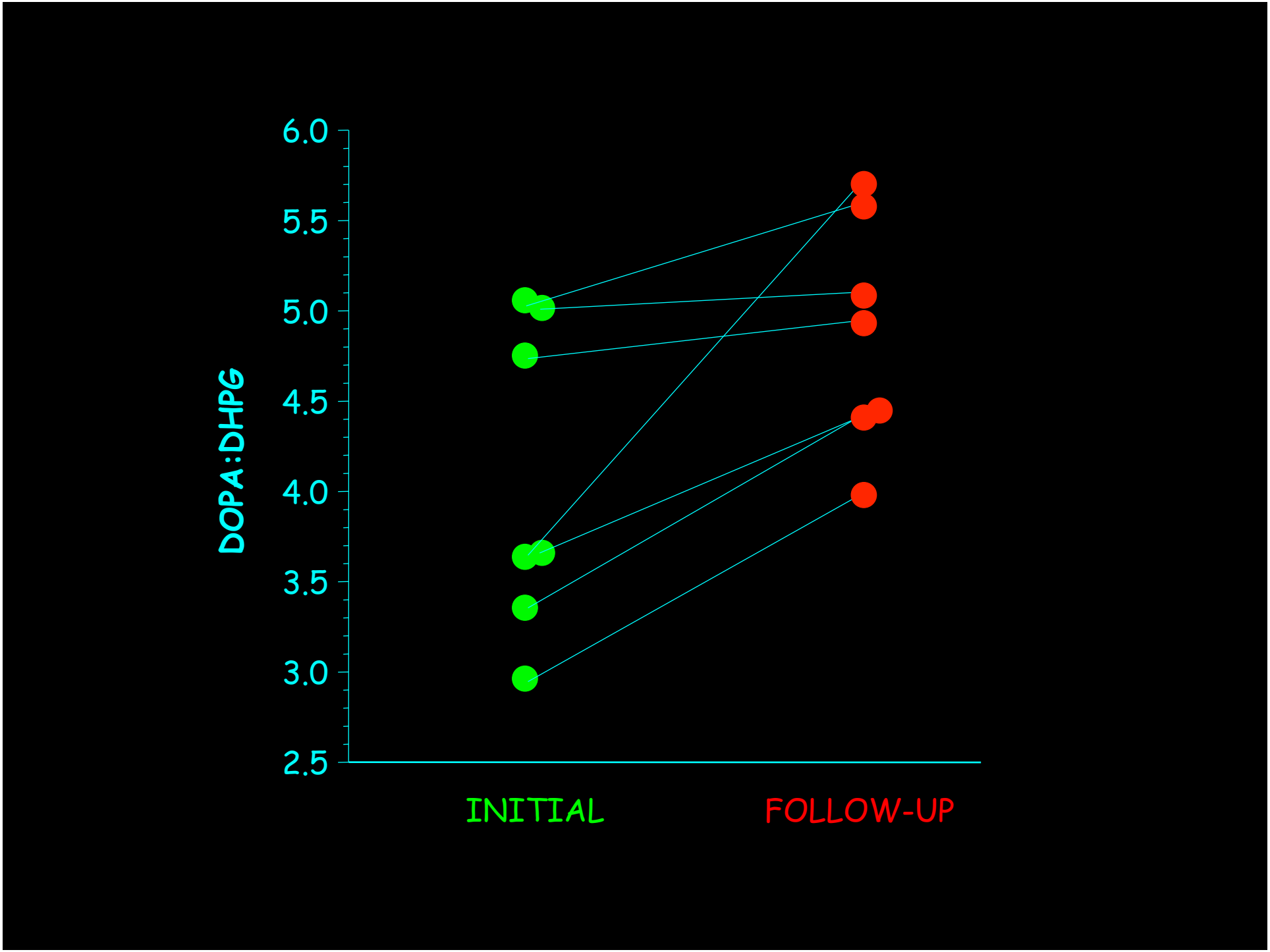


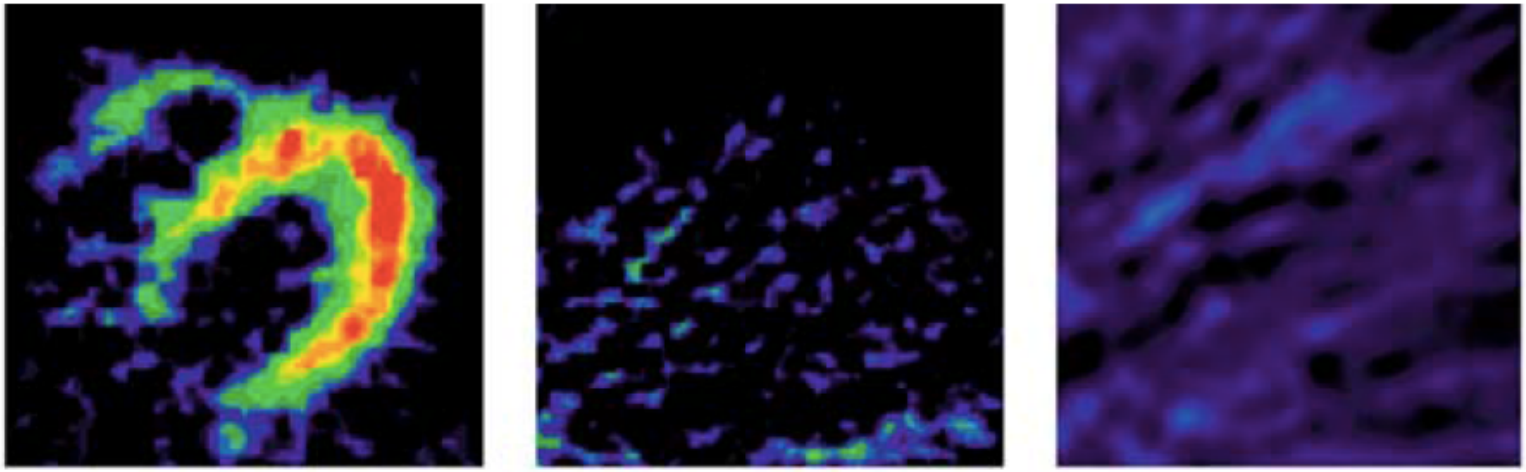
No. Living:

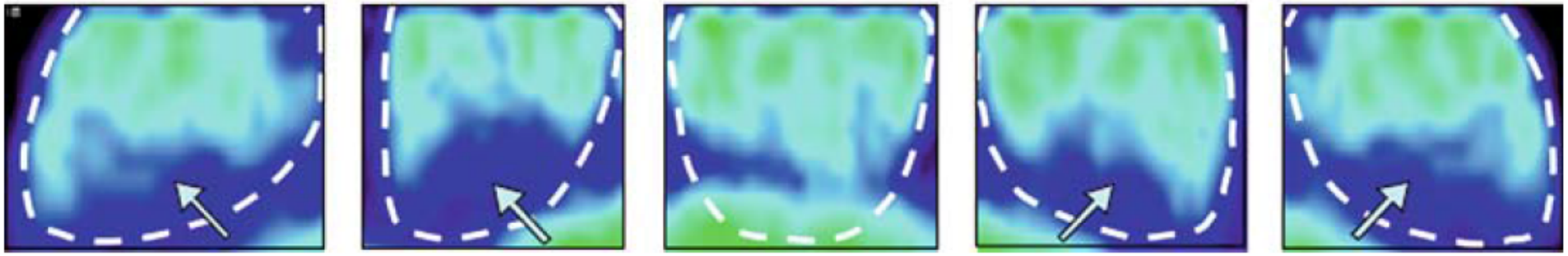
MSA	55	54	41	33	20	12	7	5	1	0
PAF	24	24	24	21	16	13	9	4	1	1	0
PD+OH	41	41	40	34	33	27	23	20	11	6	0
PD No OH	41	41	35	33	28	24	17	12	8	6	0

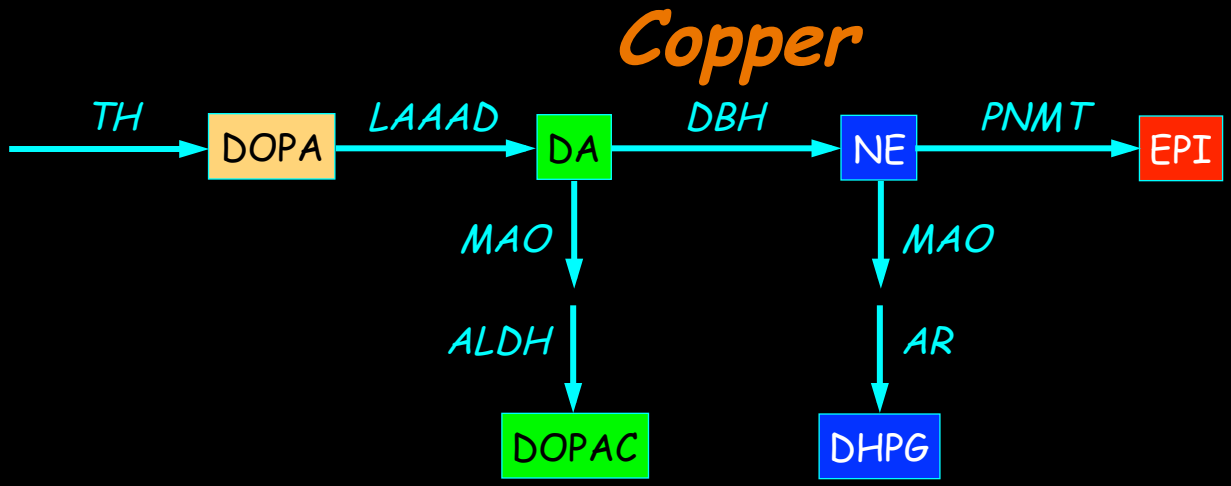


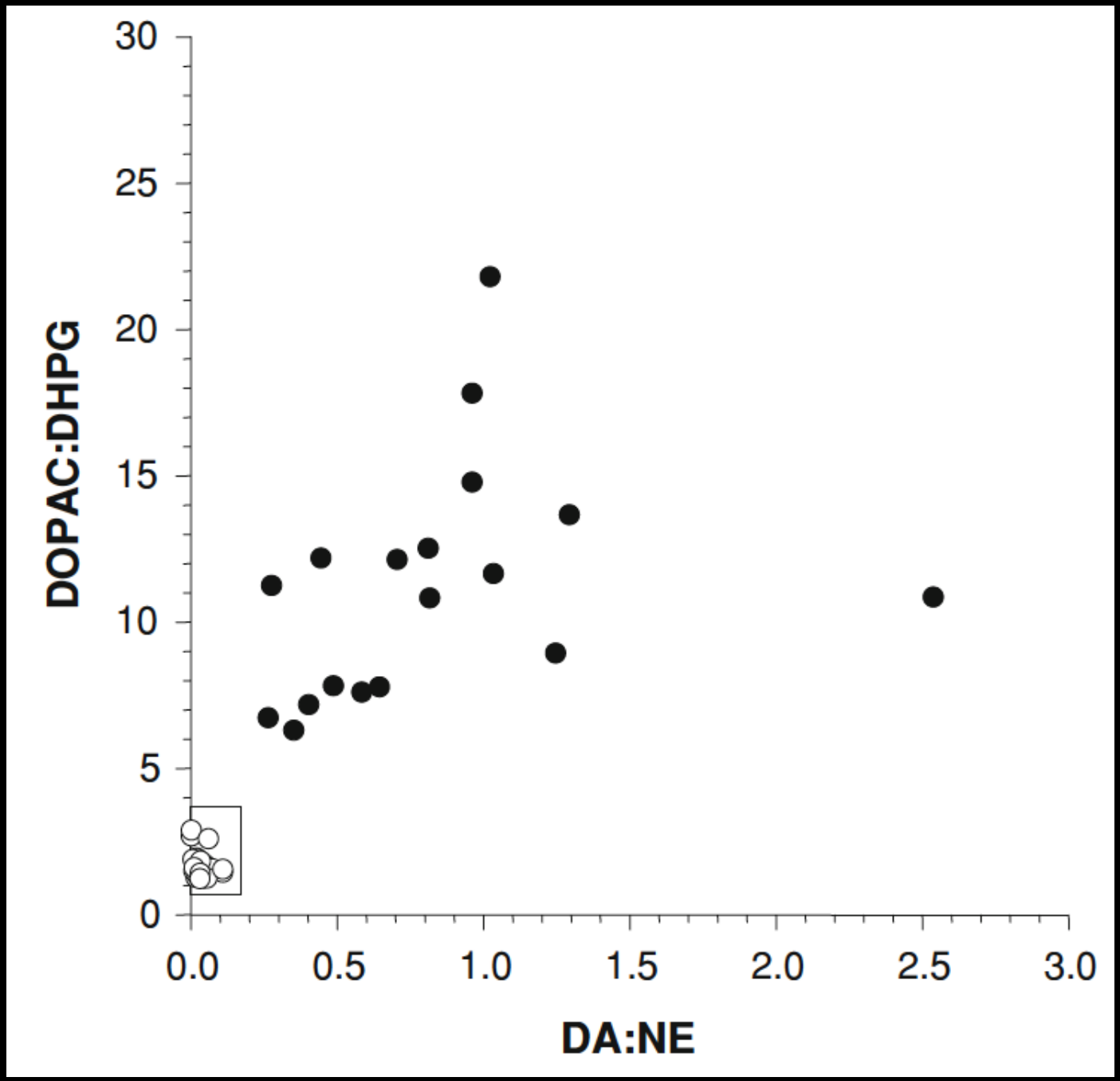

PAF
AAG
$^{13}NH_3$
^{18}F-DA


6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
DOPA:DHPG
INITIAL
FOLLOW-UP


Normal
PAF
FD


L Lat.
LAO
Ant.
RAO
R Lat.


Copper
TH
DOPA
LAAAD
DA
DBH
NE
PNMT
EPI
MAO
MAO
ALDH
AR
DOPAC
DHPG


DOPAC:DHPG
30
25
20
15
10
5
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
DA:NE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neonatal Diagnosis and Treatment of Menkes Disease

Stephen G. Kaler, M.D., M.P.H., Courtney S. Holmes, B.S., M.T., David S. Goldstein, M.D., Ph.D., Jingrong Tang, M.D., Ph.D., Sarah C. Godwin, B.S., Anthony Donsante, Ph.D., Clarissa J. Liew, M.D., Susumu Sato, M.D., and Nicholas Patronas, M.D.

ABSTRACT

BACKGROUND

Menkes disease is a fatal neurodegenerative disorder of infancy caused by diverse mutations in a copper-transport gene, *ATP7A*. Early treatment with copper injections may prevent death and illness, but presymptomatic detection is hindered by the inadequate sensitivity and specificity of diagnostic tests. Exploiting the deficiency of a copper enzyme, dopamine-β-hydroxylase, we prospectively evaluated the diagnostic usefulness of plasma neurochemical levels, assessed the clinical effect of early detection, and investigated the molecular bases for treatment outcomes.

METHODS

Between May 1997 and July 2005, we measured plasma dopamine, norepinephrine, dihydroxyphenylacetic acid, and dihydroxyphenylglycol in 81 infants at risk. In 12 newborns who met the eligibility criteria and began copper-replacement therapy within 22 days after birth, we tracked survival and neurodevelopment longitudinally for 1.5 to 8 years. We characterized *ATP7A* mutations using yeast complementation, reverse-transcriptase–polymerase-chain-reaction analysis, and immunohistochemical analysis.

II-3, Age 32 mos

From the Unit on Pediatric Genetics, Program in Molecular Medicine, National Institute of Child Health and Human Development (S.G.K., J.T., S.C.G., A.D.), the Clinical Neurocardiology Section (C.S.H., D.S.G.), and the Electroencephalography Section (C.J.L., S.S.), National Institute of Neurological Disorders and Stroke, and the Imaging Sciences Program, Mark O. Hatfield Clinical Center (N.P.) — all at the National Institutes of Health, Bethesda, MD. Address reprint requests to Dr. Kaler at the National Institute of Child Health and Human Development, National Institutes of Health, Bldg. 10, Rm. 5-2571, 10 Center Dr., MSC 1832, Bethesda, MD 20892-1832, or at kalers@mail.nih.gov.

N Engl J Med 2008;358:605-14.

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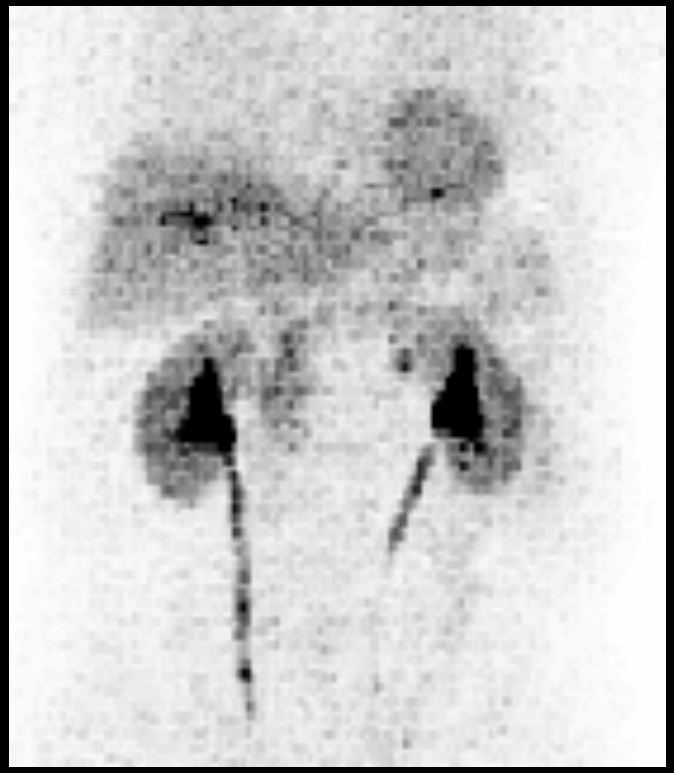
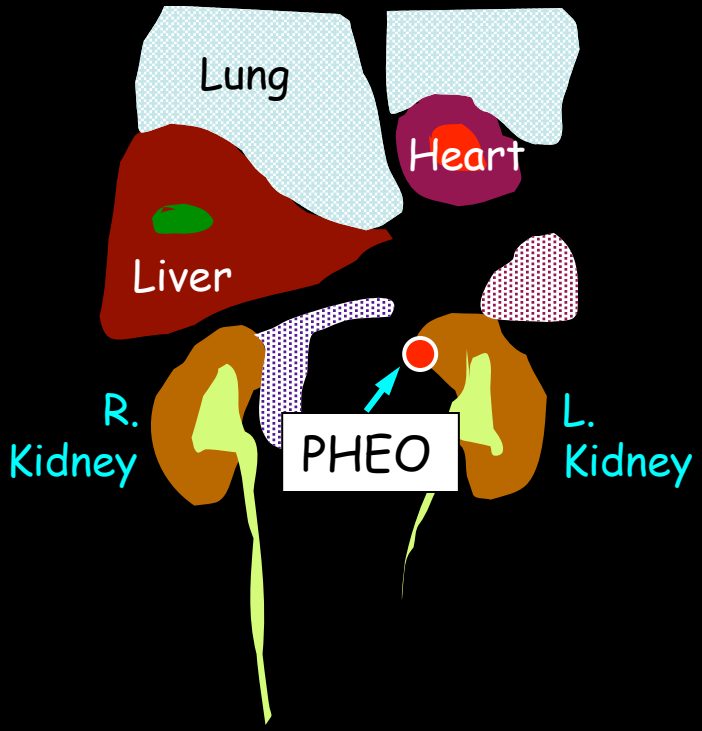
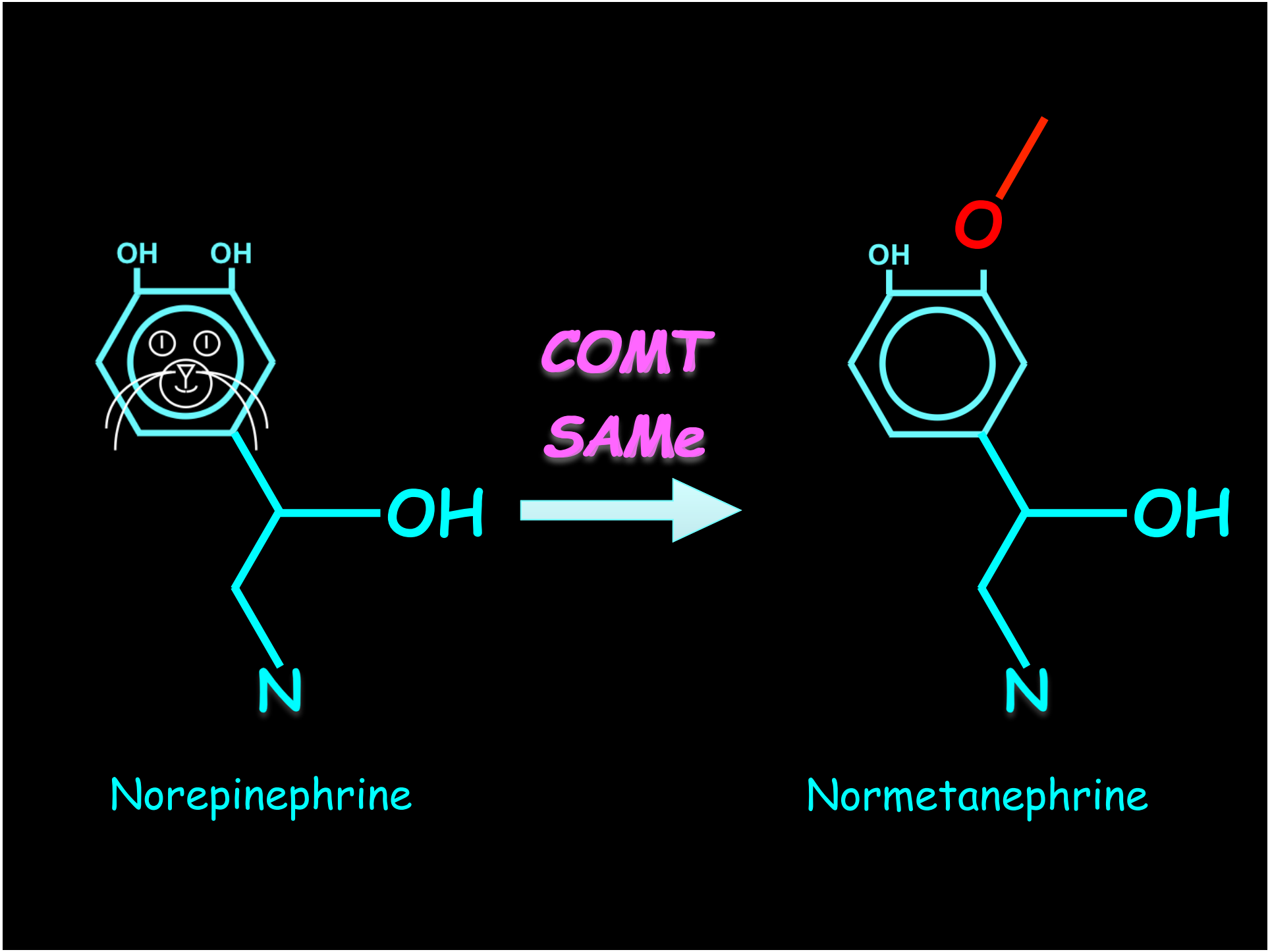
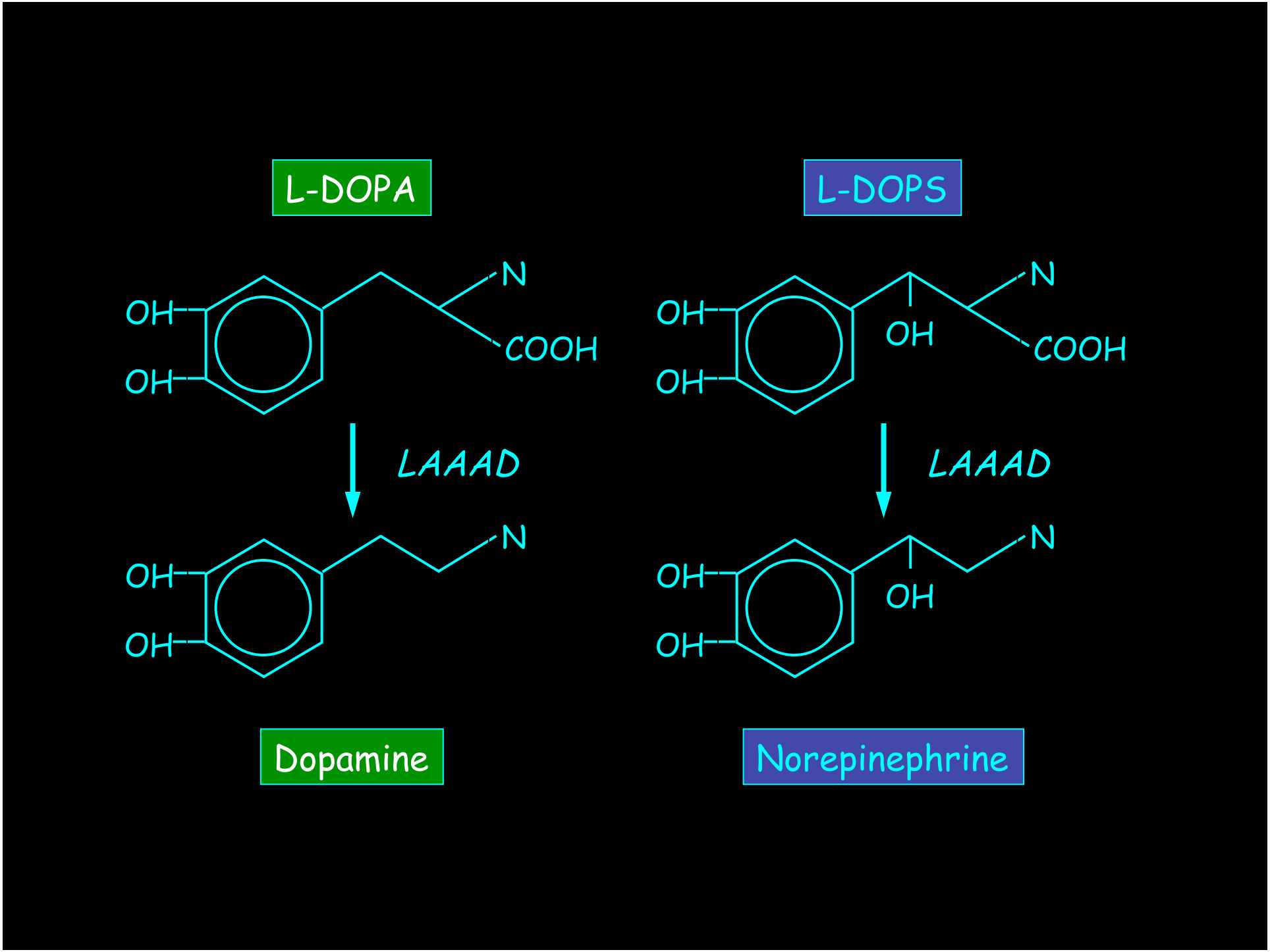
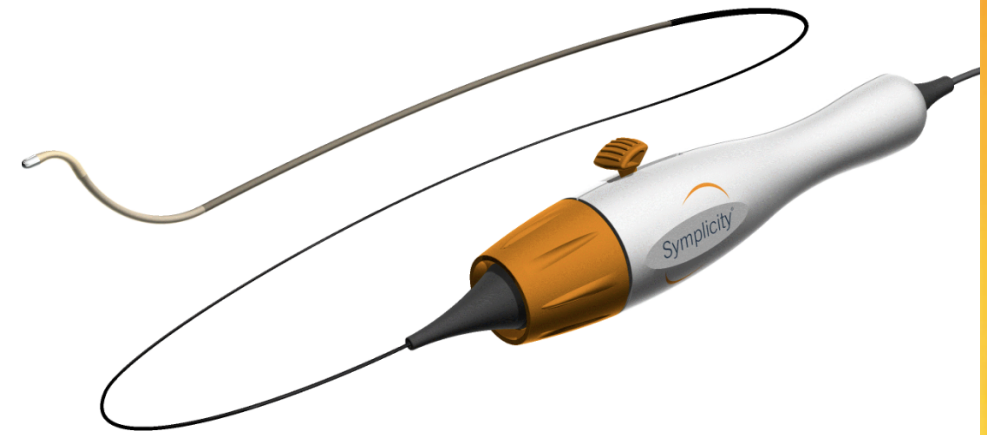
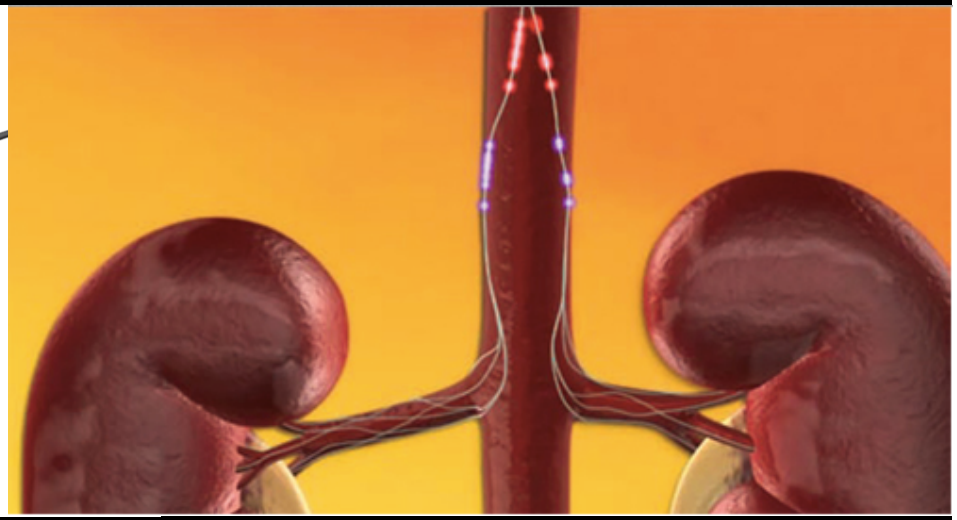



Lung
Heart
Liver
R.
Kidney
PHEO
L.
Kidney

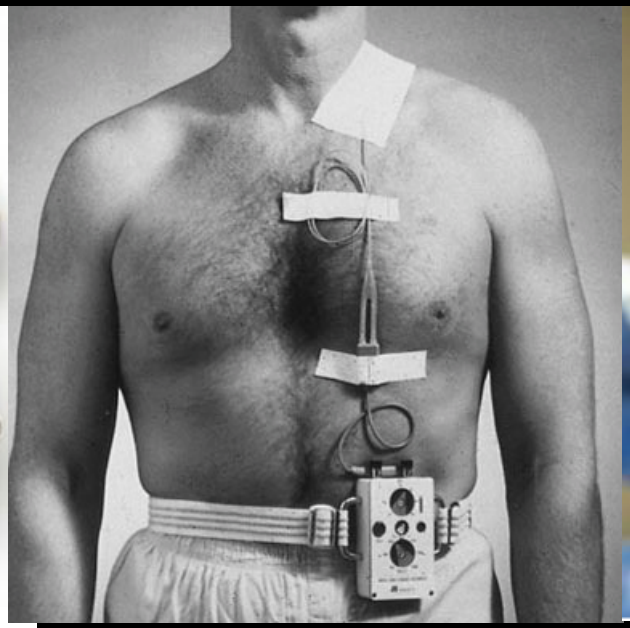

OH
OH
OH
N
COMT
SAMe
O
OH
OH
N
Norepinephrine
Normetanephrine


L-DOPA
OH
OH
N
COOH
LAAAD
OH
OH
N
Dopamine
L-DOPS
OH
OH
OH
N
COOH
LAAAD
OH
OH
OH
N
Norepinephrine

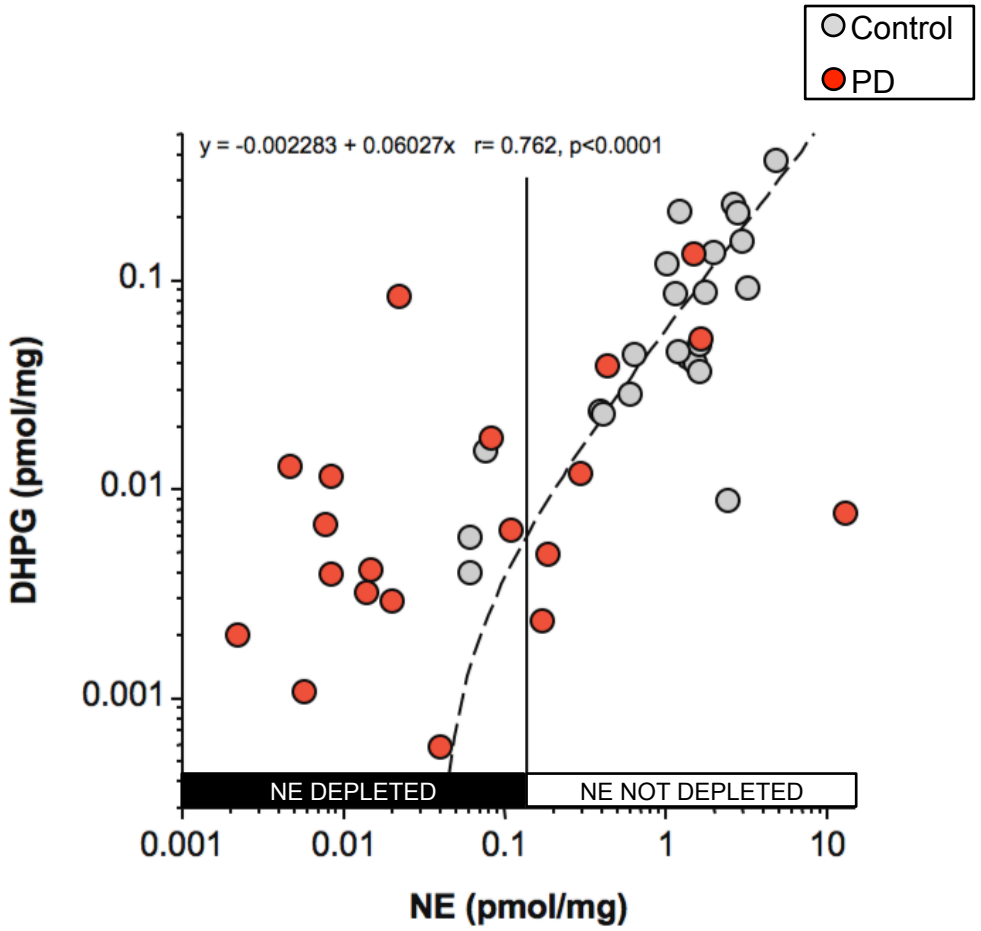

Symplicity

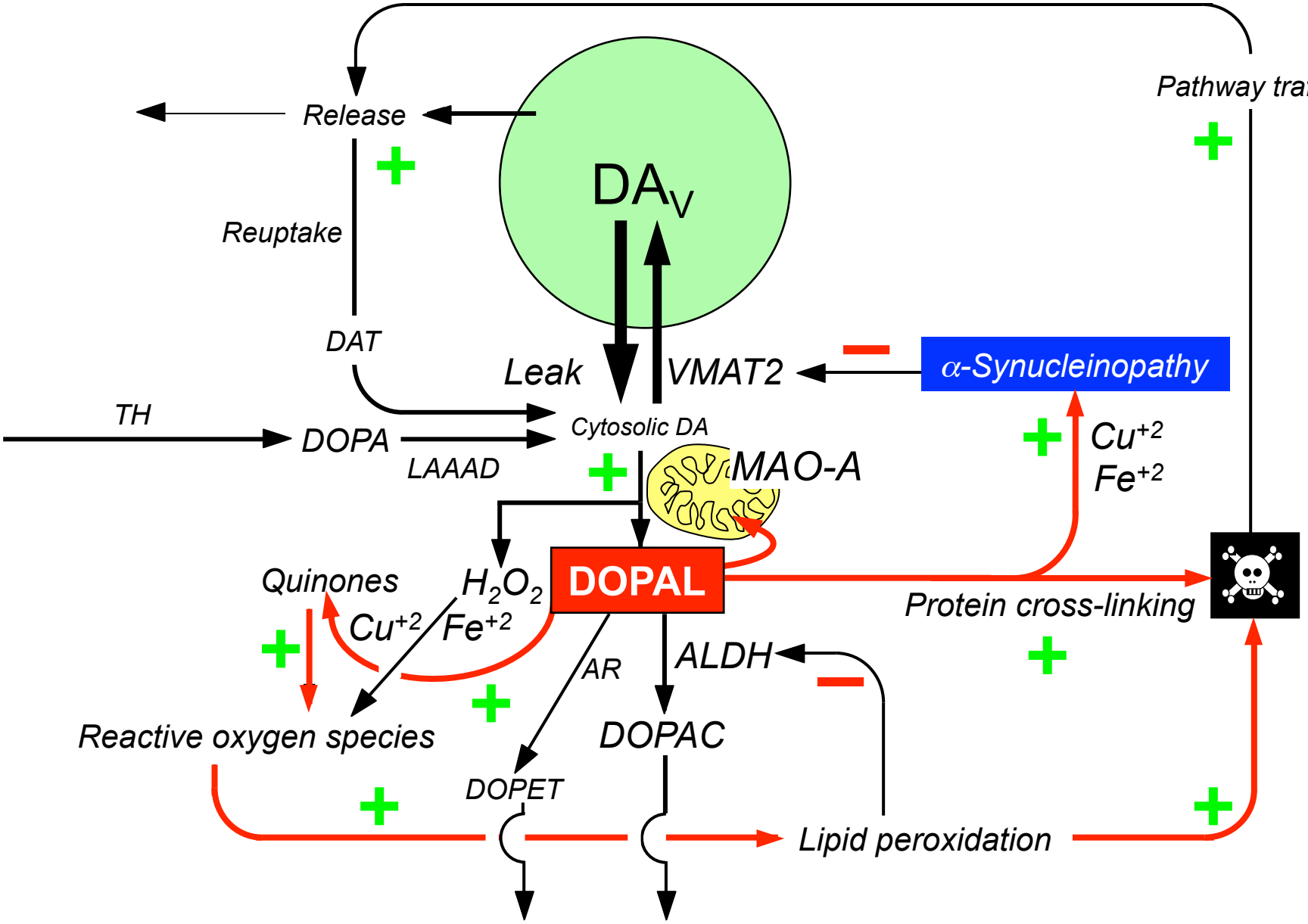


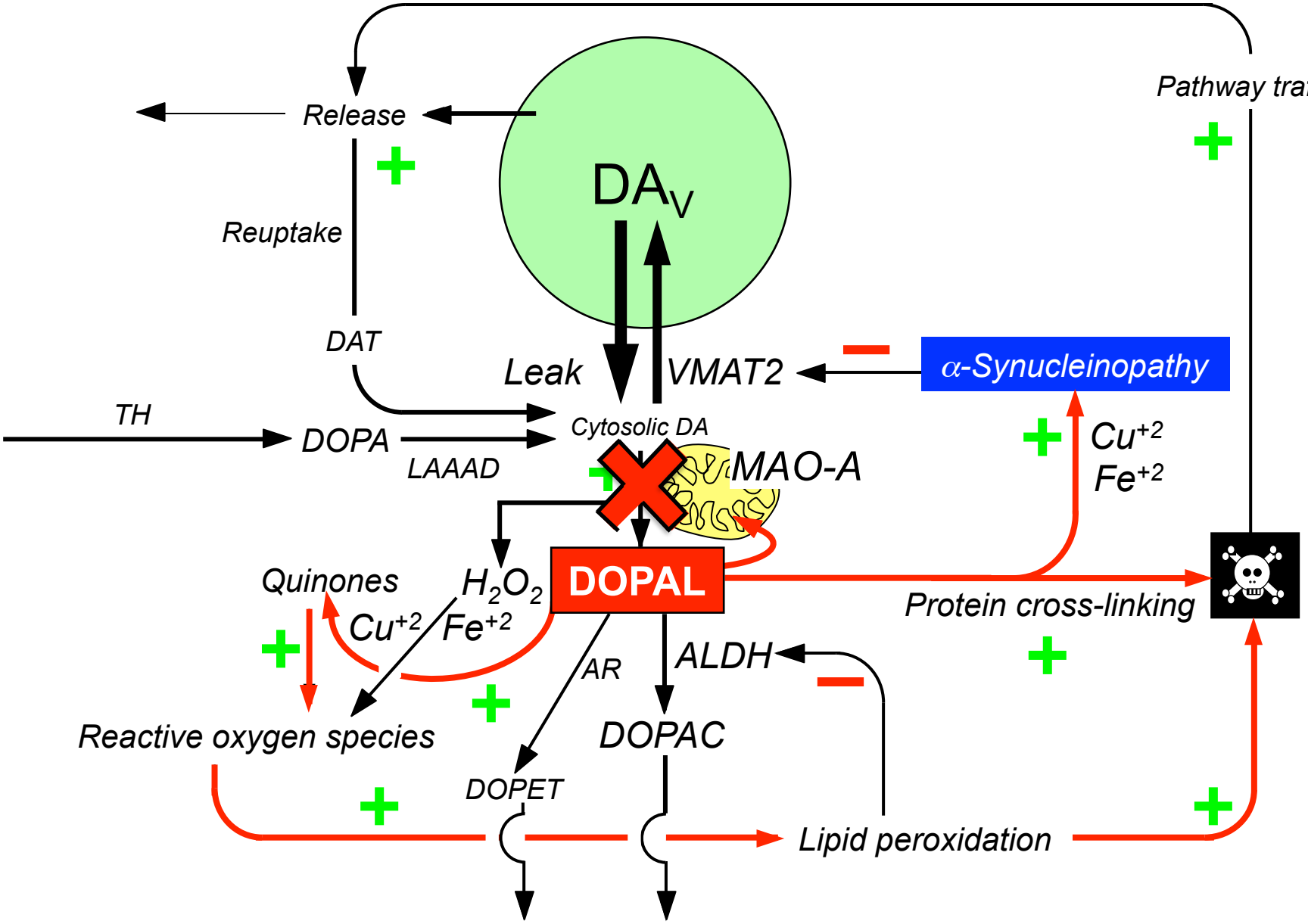

5
8
2
12
1.5
25
1.1
MA
100
140
70
180
60
200
50
RATE
MEDTRONIC
PACEMAKER

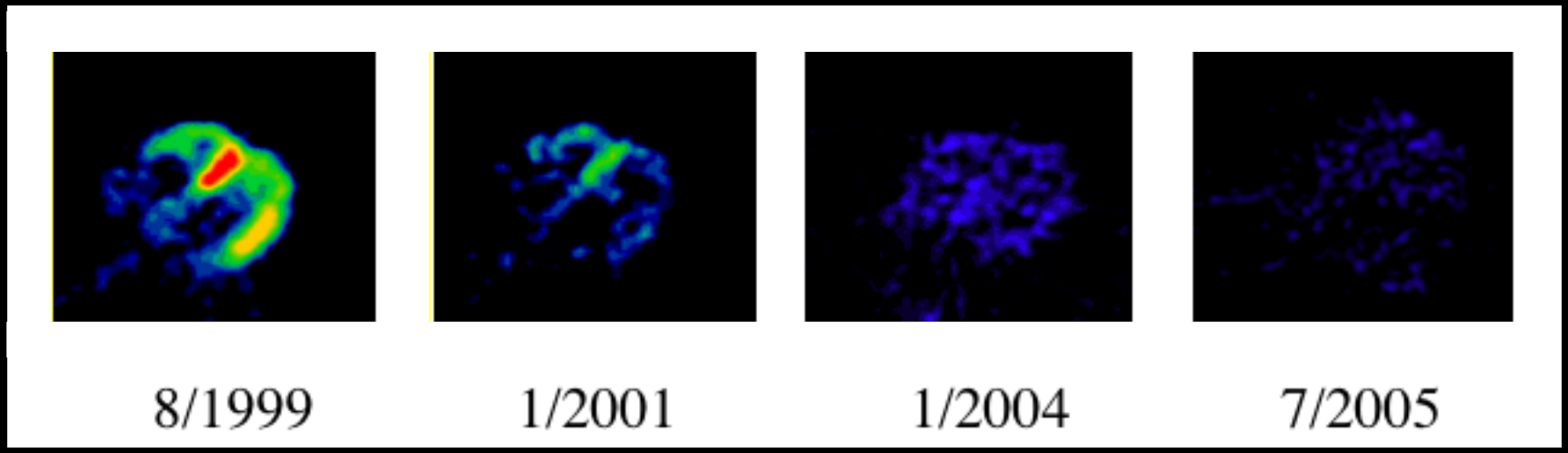


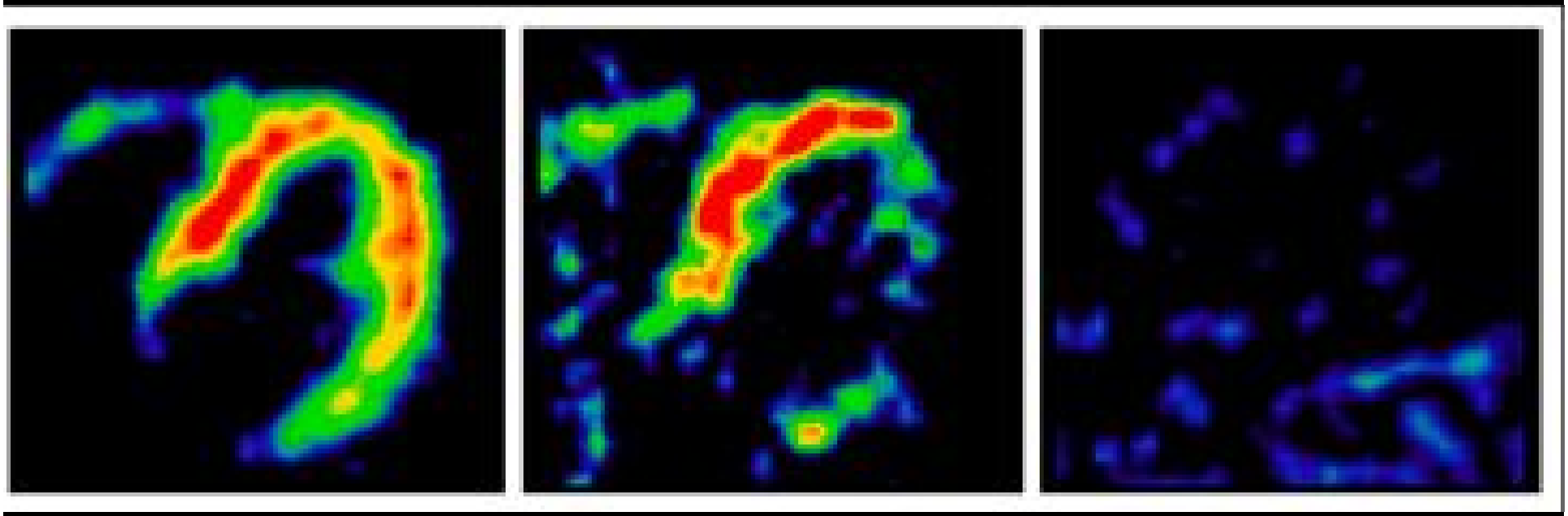

CVRx
Barostim
neo

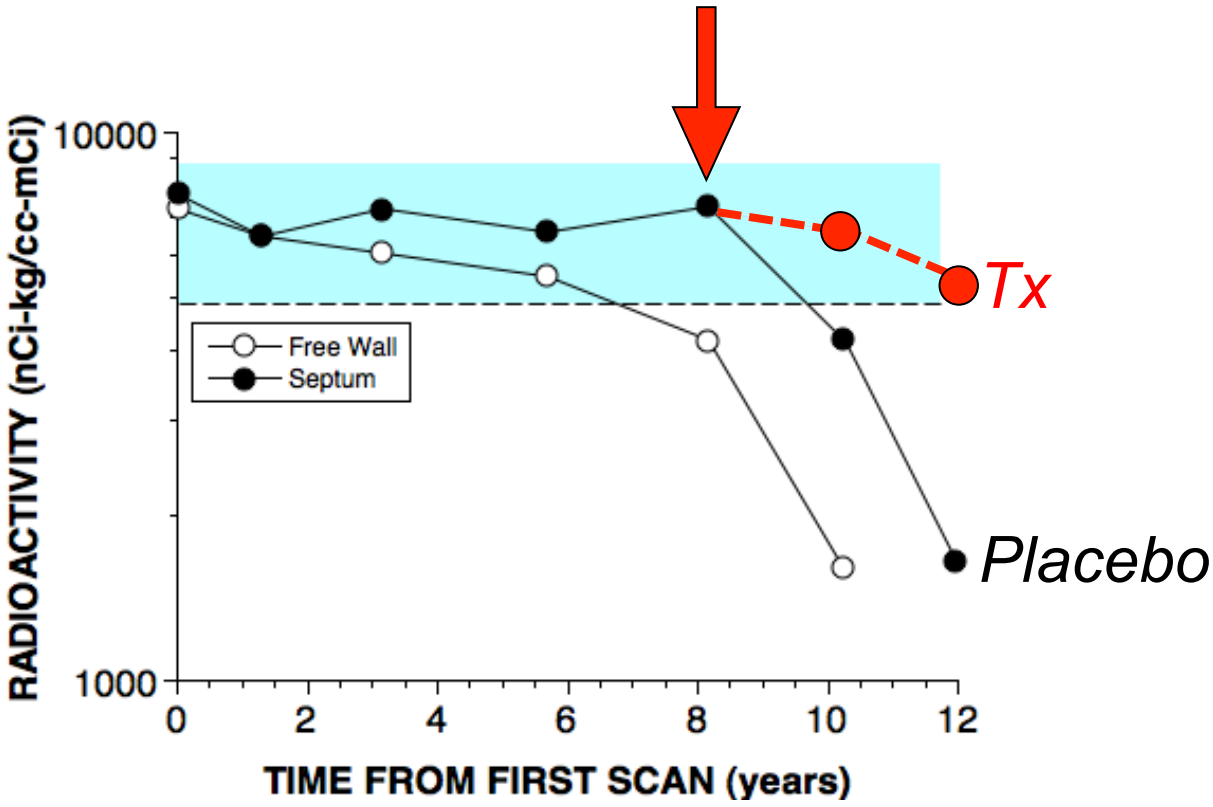

Control
PD
y = -0.002283 + 0.06027x r= 0.762, p<0.0001
DHPG (pmol/mg)
0.1
0.01
0.001
NE DEPLETED
NE NOT DEPLETED
0.001
0.01
0.1
1
10
NE (pmol/mg)


Pathway traffic
Release
Reuptake
DAT
DA$_V$
Leak
VMAT2
α-Synucleinopathy
TH
DOPA
LAAAD
Cytosolic DA
MAO-A
Cu^{+2}
Fe^{+2}
Quinones
H$_2$O$_2$
DOPAL
Cu^{+2}
Fe^{+2}
Protein cross-linking
AR
ALDH
Reactive oxygen species
DOPET
DOPAC
Lipid peroxidation

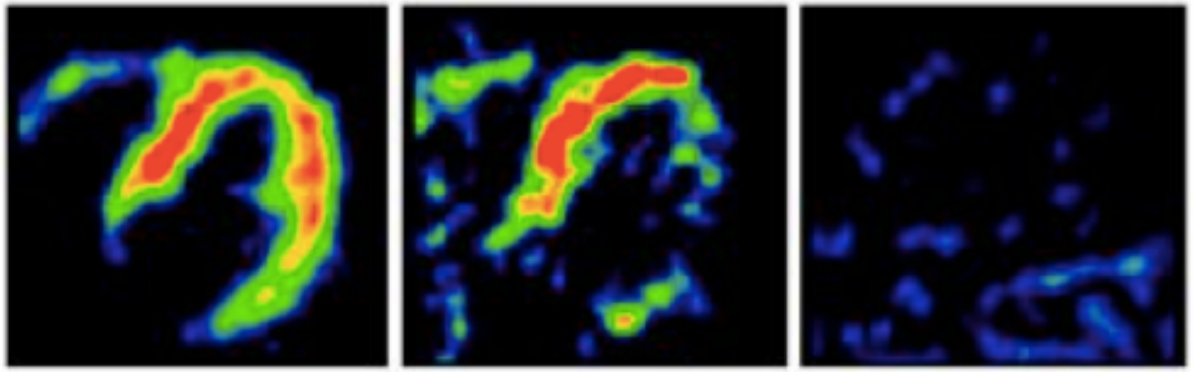

Pathway traffic
Release
Reuptake
DAT
DA$_V$
Leak
VMAT2
α-Synucleinopathy
TH
DOPA
LAAAD
Cytosolic DA
MAO-A
Cu^{+2}
Fe^{+2}
Quinones
H$_2$O$_2$
DOPAL
Cu^{+2}
Fe^{+2}
Protein cross-linking
ALDH
AR
Reactive oxygen species
DOPAC
DOPET
Lipid peroxidation


8/1999
1/2001
1/2004
7/2005




RADIOACTIVITY (nCi-kg/cc-mCi)
10000
1000
0
2
4
6
8
10
12
TIME FROM FIRST SCAN (years)
Free Wall
Septum
Tx
Placebo

Principles of Autonomic Medicine



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