

NEUROPLASTICITY IN THE NIGROSTRIATAL SYSTEM OF MPTP-TREATED MICE AT THE PRESYMPTOMATIC AND EARLY SYMPTOMATIC STAGES OF PARKINSONISM

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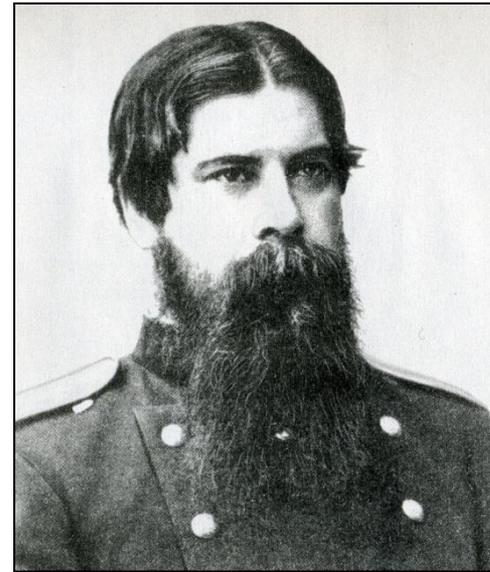
Russian Academy of Sciences

Brain plasticity



Ernesto Lugaro
(1870-1940)

“The Italian psychiatrist E. Lugaro had introduced the term **plasticity** into the neurosciences considering that throughout life the anatomo-functional relations between neurons can be changed in an adaptive fashion to enable psychic maturation, learning, and even functional recovery after brain damage.”



V.M. Bekhterev
(1857-1927)

“... the function of the damaged brain areas is restored due to the undamaged areas. This is accounted for by the reorganization of the interneuronal relations under the information, coming from the target organs.”

Neuroplasticity in the nigrostriatal system of MPTP-treated mice at the presymptomatic and symptomatic stages of parkinsonism

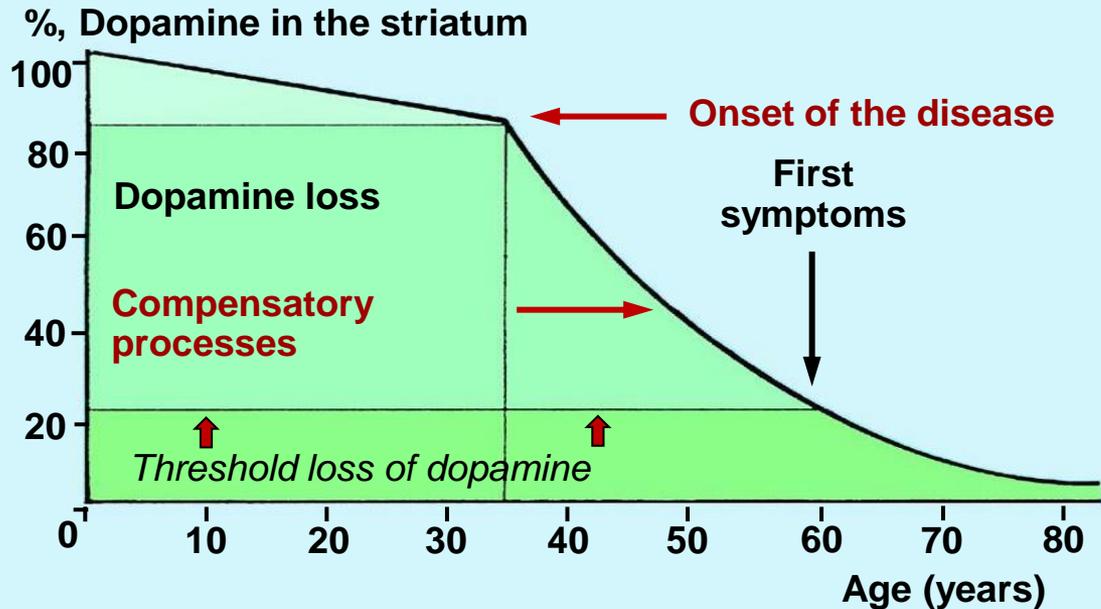
➔ Introduction. New insight into the pathogenesis of Parkinson's disease;

Dopamine turnover in the nigrostriatal system of MPTP-treated mice at modeling Parkinson's disease at the preclinical and early clinical stages with focus on neuroplasticity;

Dopamine production by non-dopaminergic expressing individual enzymes of dopamine synthesis as a mechanism of neuroplasticity under a failure of dopaminergic neurons;

Conclusions.

New insight into the pathogenesis of Parkinson's disease



Pathogenesis:

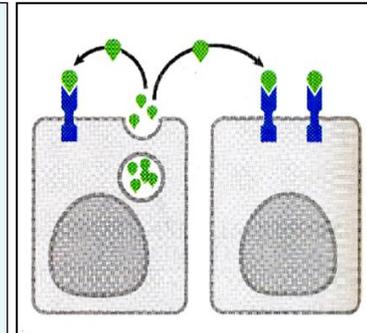
- Neurodegeneration;
- Prion-like propagation;
- **Neuroplasticity**;
- Inflammation

Unspecific mechanisms providing neuroprotection:

- ✓ Stimulation of secretion of the growth factors;
- ✓ Activation of the antioxidant systems.

Specific mechanisms serving to maintain neurotransmission:

- ✓ Stimulation of neurotransmitter secretion;
- ✓ A reduction of the enzymatic degradation of neurotransmitters;
- ✓ Increase of the sensitivity of the target neurons.



Bezard and Gross, 1998. *Prog. Neurobiol.* 55, 93-116; *Trends Neurosci.* 26, 215-221;.

Ugrumov, M.V., 2008. In: *Handbook of Neurochemistry and Molecular Neurobiology. Neurotransmitter Systems*, Springer, Heidelberg, pp. 21-73.

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Neurotoxic (MPTP) models of Parkinson's disease in mice: *Preclinical and early clinical stages*

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, pretoxin) (glial cells)

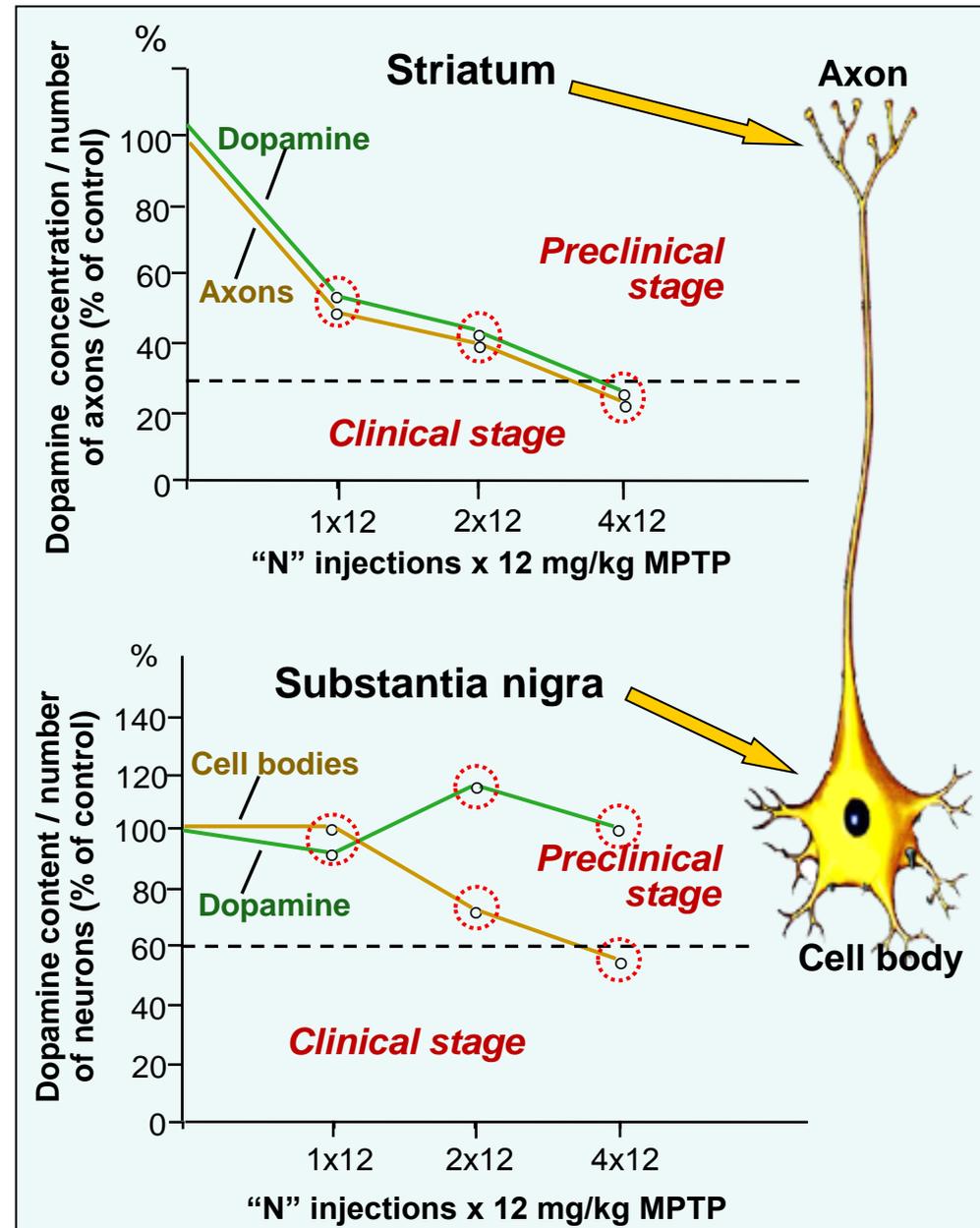
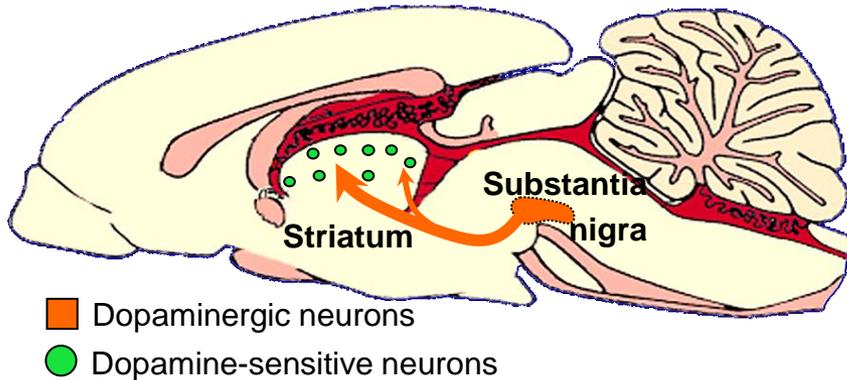


↓

1-methyl-4-pyridine (MPP⁺, toxin)

Injections of MPTP: 1, 2 or 4 times at the individual dose of 12 mg/kg with 2-hours intervals between the injections.

Decapitation: 2 weeks after the treatment



MPTP models in mice of PD at the preclinical and early clinical stages:

Prospect of the use

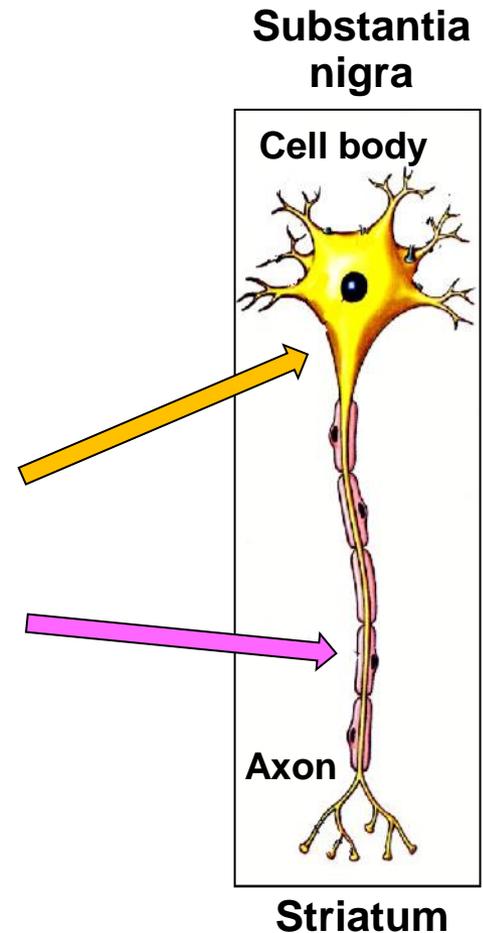
- ❖ Evaluation of the molecular ***mechanisms of neurodegeneration*** in the central and peripheral nervous system;
- ❖ Evaluation of the ***mechanisms of neuroplasticity*** in the central and peripheral nervous system;
- ❖ Search for ***mechanisms triggering a transition from*** preclinical stage to clinical stage;
- ❖ Search for ***peripheral biomarkers*** for the development of preclinical diagnostics of Parkinson's disease;
- ❖ Development of the ***provocation test*** for the diagnostics of Parkinson's disease at the preclinical stage;
- ❖ Development of ***preventive therapy*** in Parkinson's disease:
 - ✓ to slow down neurodegeneration;
 - ✓ to control and improve neuroplasticity;
 - ✓ to deactivate triggers of motor disorders.

Nigrostriatal system in MPTP-treated mice: *Evaluation of functional activity*

Indicators of functional activity:

- ✓ Gene expression, synthesis and activity of tyrosine hydroxylase;
- ✓ Spontaneous and stimulated release of dopamine;
- ✓ Dopamine uptake;
- ✓ Content and turnover of dopamine;
- ✓ Dopamine synthesis by non-dopaminergic neurons;
- ✓ Gene expression and activity of MAO A and B;
- ✓ Gene expression of D2 receptors.

The data obtained for the striatum and substantia nigra as a whole were adjusted to individual nigral cell bodies and striatal axons



Functional activity of the nigrostriatal system in MPTP-treated mice at the presymptomatic and symptomatic stages of parkinsonism

Conclusions

Compensatory processes:

- ✓ An increase of gene expression and activity of tyrosine hydroxylase (TH),
- ✓ An increase of dopamine (DA) release and turnover,
- ✓ A decrease of MAO B activity.

Non-expected results:

- ✓ Regulations of transcription, translation and enzymatic activity of TH are different;
- ✓ An increase of TH activity despite and increase of D2 gene expression.

Triggers of motor disorders:

- ✓ A decrease of DA stimulated release,
- ✓ An increase of DA uptake,
- ✓ An increase of MAO A activity

Object Parameter	Neuron		Neuron	
	Cell body <i>Presympt vs. control</i>	Axon <i>Presympt vs. control</i>	Cell body <i>Presympt vs. sympt.</i>	Axon <i>Presympt vs. sympt.</i>
Tyrosine hydroxylase mRNA	↑	—	↓	—
Tyrosine hydroxylase protein	→	↓	↑	→
Tyrosine hydroxylase activity	↑	↑	↑	→
D2 receptor mRNA	↑	—	↓	—
Dopamine content	↑	→	→	↓
Dopamine release spontaneous / stimulated	→ / ↑	↑ / ↑	↑ / →	→ / ↓
Dopamine uptake	↑	↑	→	↑
Dopamine turnover	→	↑	→	→

↑ Increase; ⇒ No change;
 ↓ Decrease; — No data

Ugrumov et al. (2011) *Neuroscience* 181, 175-188;
 Kozina ... Ugrumov (2014) *J Neurol Sci*, 340:198-207.

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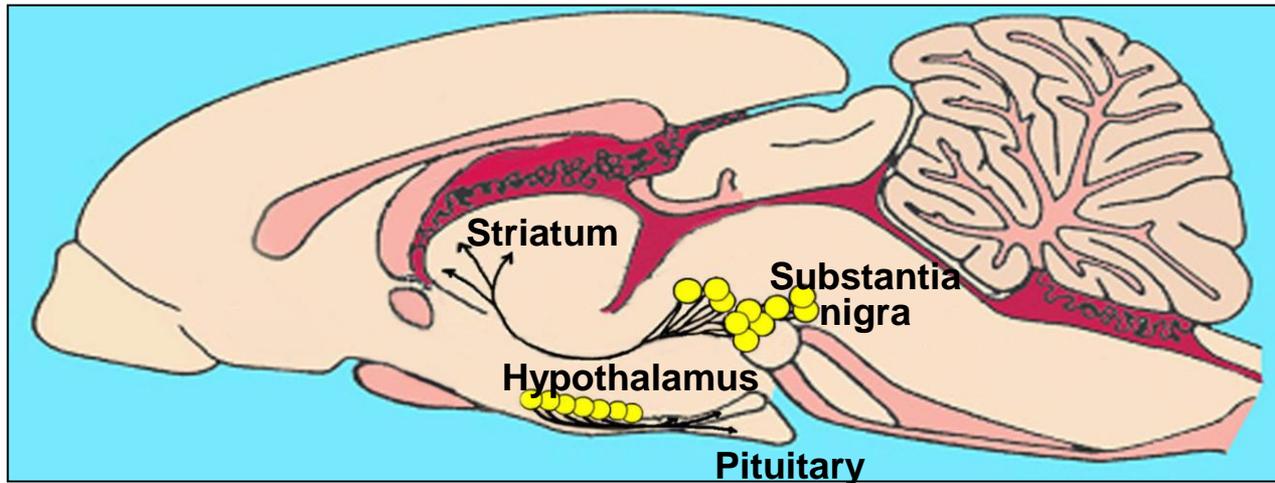
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Neurons partly expressing dopaminergic phenotype



Principal characteristics

Dopaminergic neurons

- ✓ Two enzymes of dopamine synthesis
- ✓ Dopamine membrane transporter
- ✓ Vesicular membrane transporter, type 2

Non-dopaminergic neurons partly expressing dopaminergic phenotype

- ✓ Individual enzymes of dopamine synthesis
- ✓ No dopamine membrane transporter
- ✓ No vesicular membrane transporter, type 2

Meister B., Hökfelt T. (*Sweden*), Steinbusch H.W.M. (*the Netherlands*), Skagerberg G., Lindvall O., Geffard M. (*France*), Joh T., Cuello A.C., Goldstein M. (1988) **Do tyrosine hydroxylase-immunoreactive neurons in the ventro-lateral arcuate nucleus produce dopamine or only L-DOPA?** *J. Chemical Neuroanat.* 1, 59-64.

Hoffman, B.J., Hansson, S.R., Mezey, E., Palkovits, M. (1998). **Localization and dynamic regulation of biogenic amine transporters in the mammalian central nervous system.** *Front. Neuroendocrinol.* 19, 187-231.



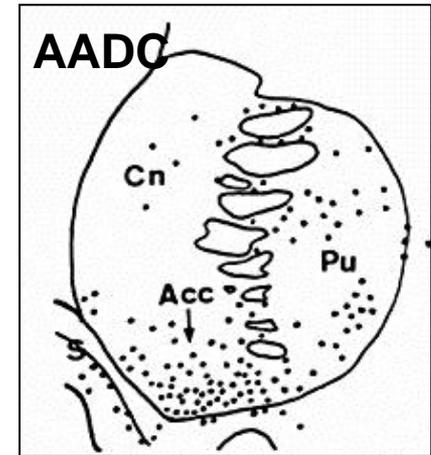
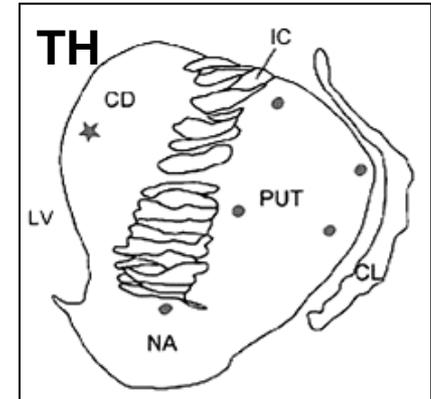
Review

Non-dopaminergic neurons partly expressing dopaminergic phenotype: Distribution in the brain, development and functional significance

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Striatum



(Ikemoto et al., 1997; Cossette et al., 2005)

AADC, aromatic L-amino acid decarboxylase;

DAT, dopamine transporter;

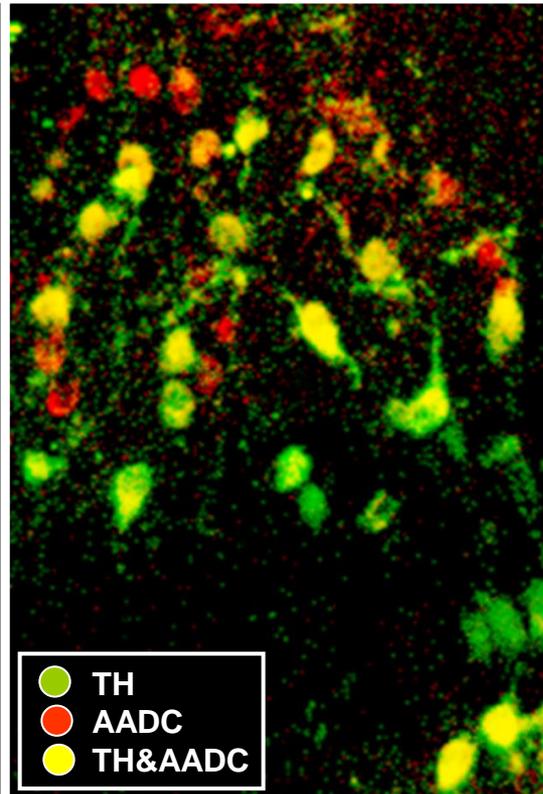
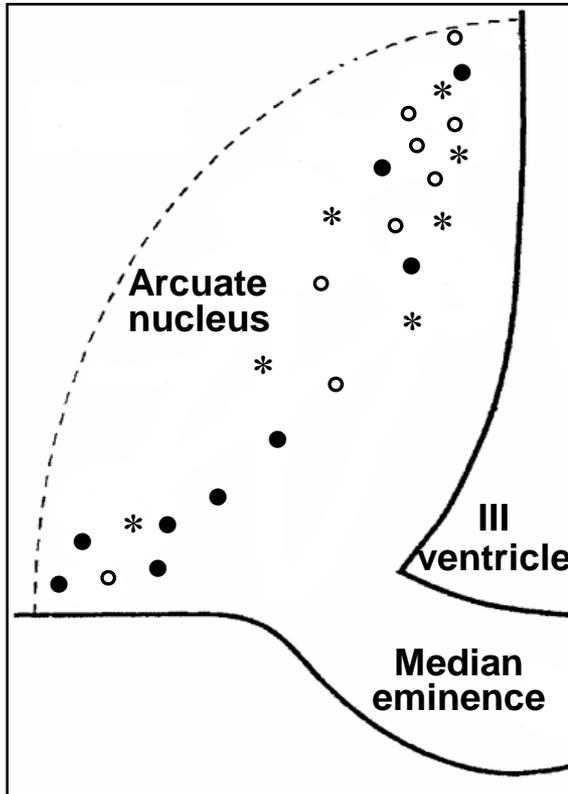
TH, tyrosine hydroxylase.

* Bienzymatic neuron

○ Monoenzymatic AADC neuron

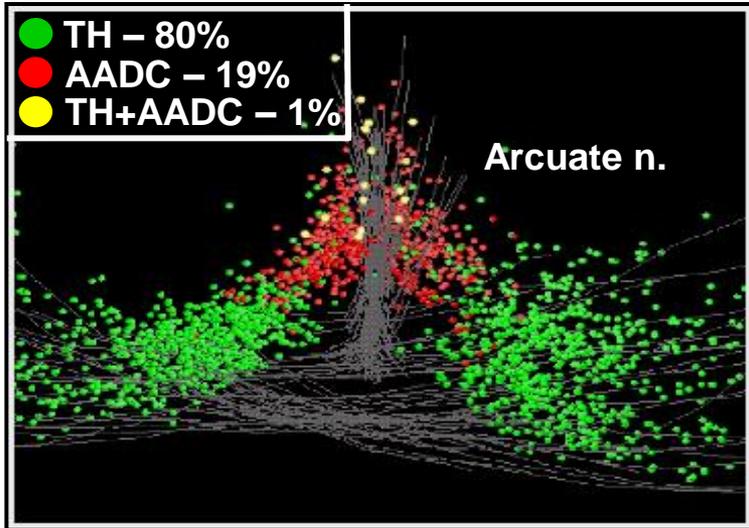
● Monoenzymatic TH neuron

Arcuate nucleus

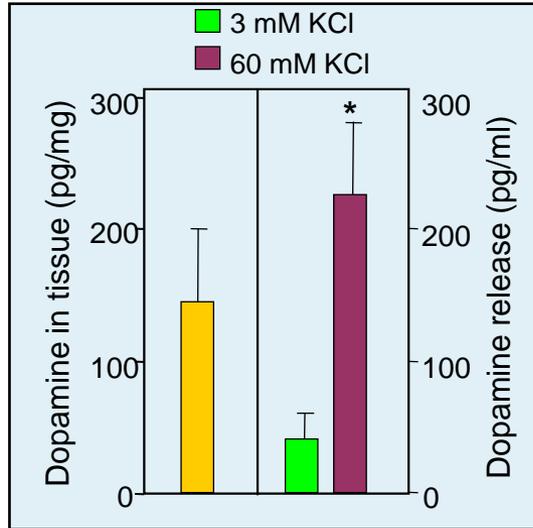


“Cooperative synthesis” of dopamine

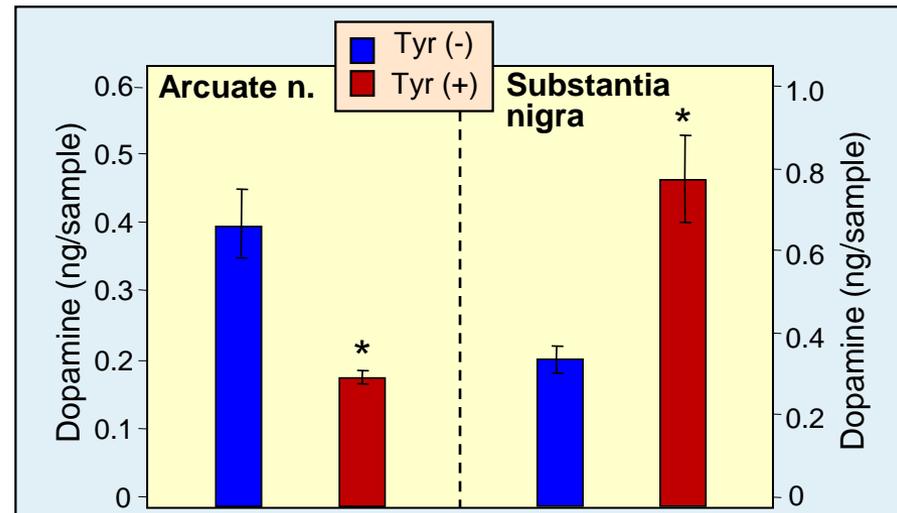
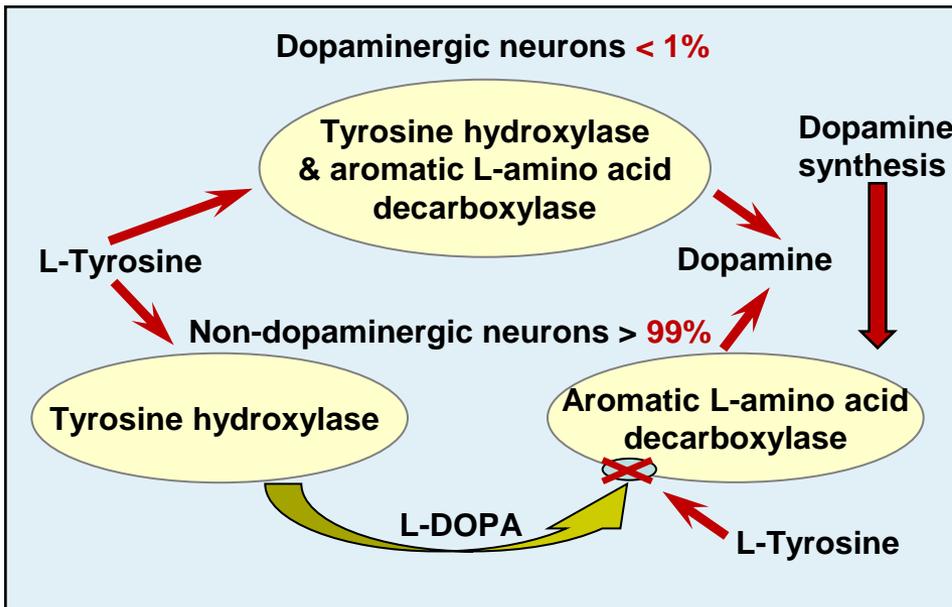
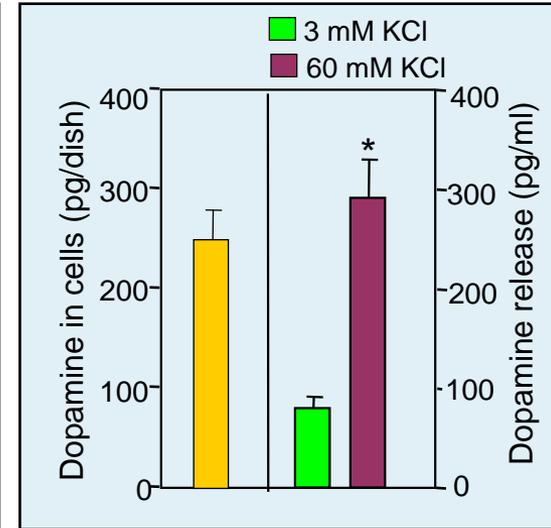
by non-dopaminergic neurons in the arcuate nucleus in rat fetuses



21st embryonic day,
ex vivo

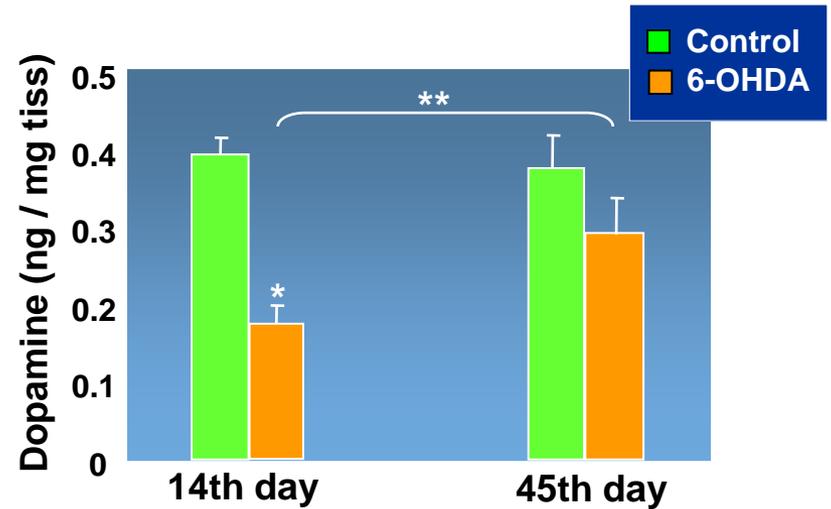
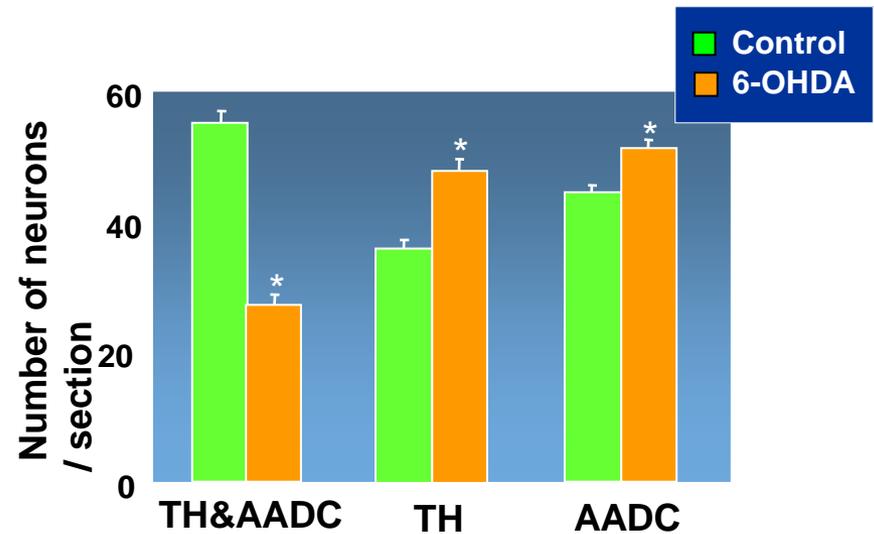
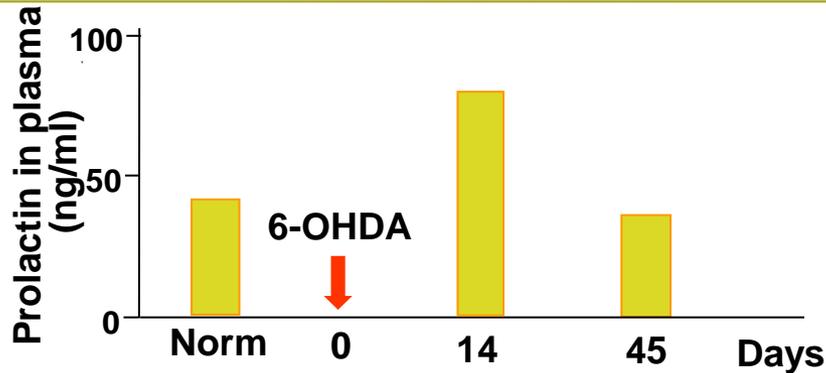
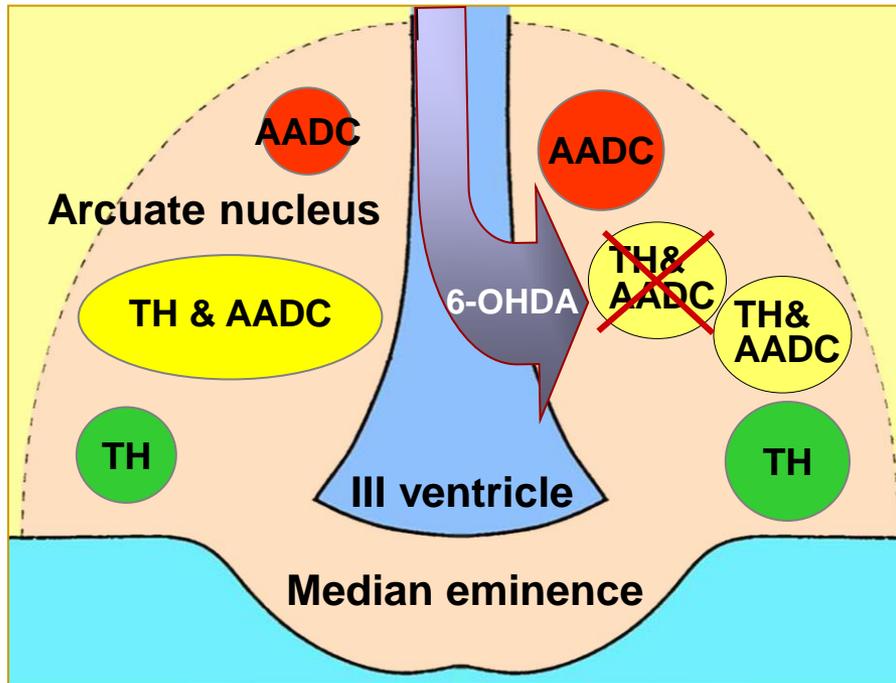


17th embryonic day,
culture



Melnikova, ... Ugrumov (1999) *Neuroscience* 89, 235-241;
Ugrumov et al. (2004) *Neuroscience* 124, 629-635

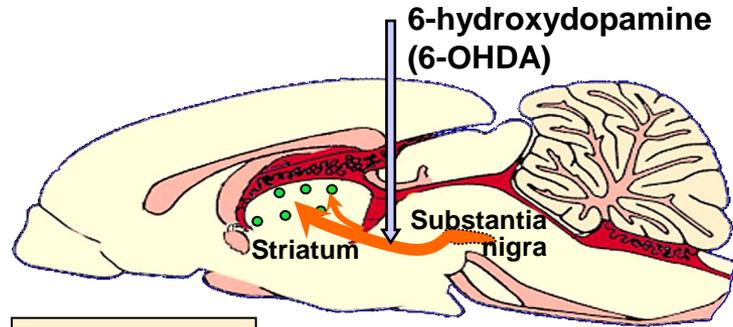
Dopamine synthesis by non-dopaminergic neurons as a compensatory mechanism under a failure of tuberoinfundibular dopaminergic neurons



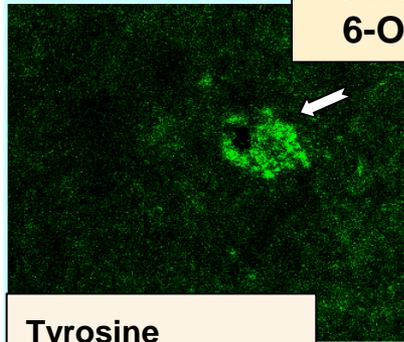
Ershov, Ugrumov et al., 2005, *J. Chem. Neuroanat.* 30, 27-33;
 Ugrumov, 2008. In: *Handbook of Neurochemistry and Molecular Neurobiology. Neurotransmitter Systems*, Springer, Heidelberg, pp. 21-73.

AADC, aromatic L-amino acid decarboxylase;
6-OHDA, 6-hydroxydopamine;
TH, tyrosine hydroxylase

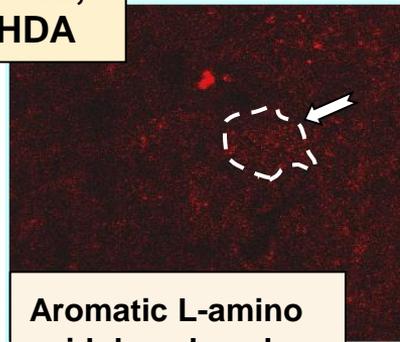
Neurons expressing enzymes of dopamine synthesis in the striatum of rats at 6-OHDA-induced degeneration of nigral dopaminergic neurons



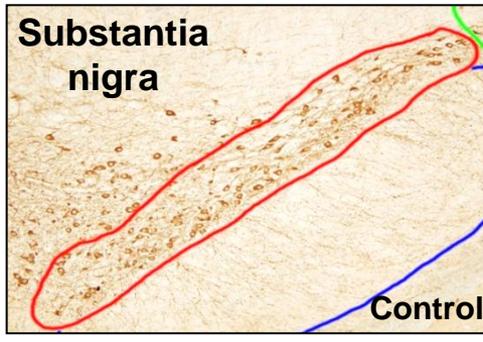
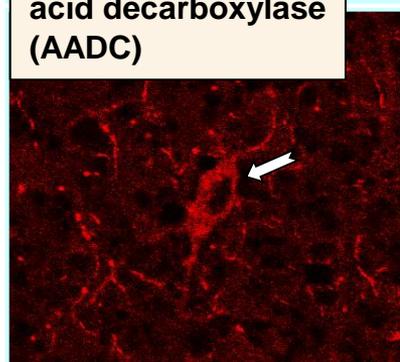
Striatum,
6-OHDA



Tyrosine
hydroxylase (TH)

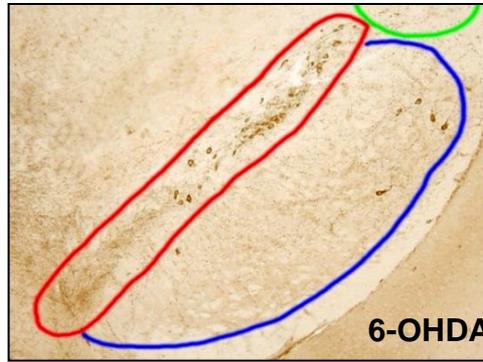


Aromatic L-amino
acid decarboxylase
(AADC)

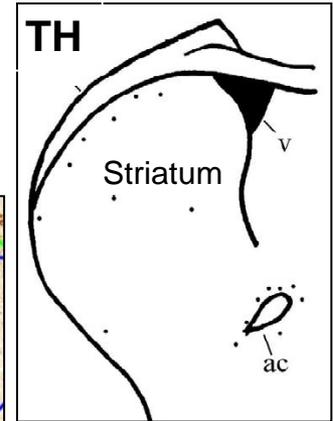


Substantia
nigra

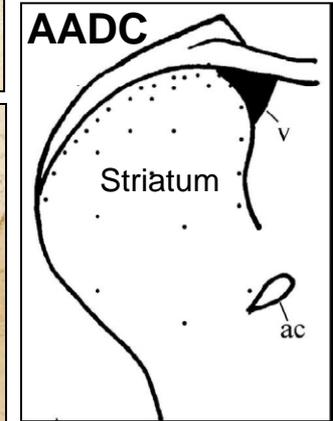
Control



6-OHDA



TH

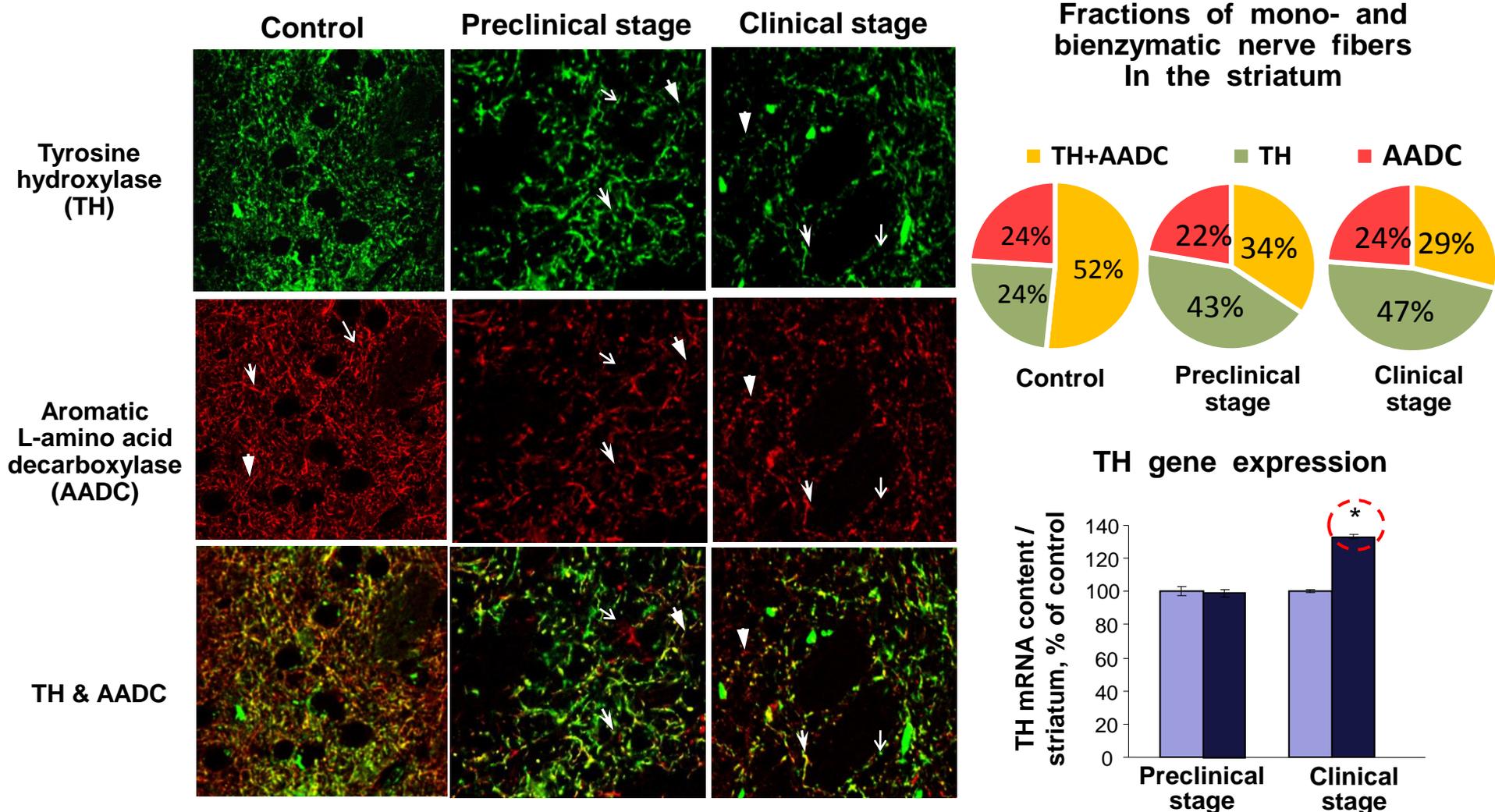


AADC

(Lopez-Real et al., 2003)

Nigrostriatal system in MPTP-treated mice:

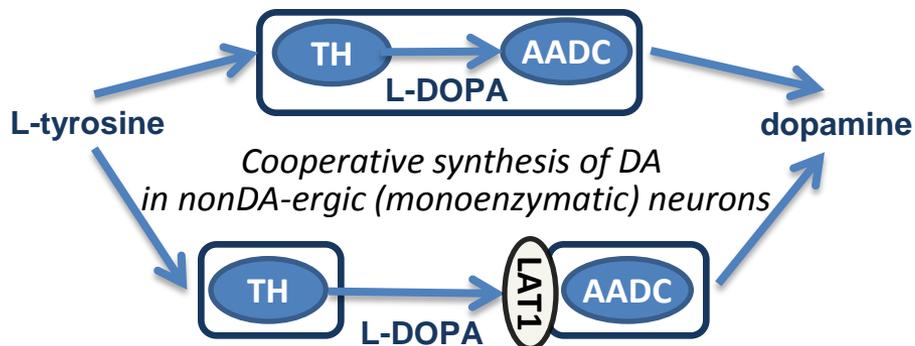
Neurons expressing individual enzymes of dopamine synthesis in the striatum



Conclusion: Degeneration of dopaminergic neurons is followed by an increase of the number of monoenzymatic fibers and an appearance of the neurons expressing tyrosine hydroxylase in the striatum

Cooperative synthesis of dopamine in the striatum of normal and parkinsonian mice

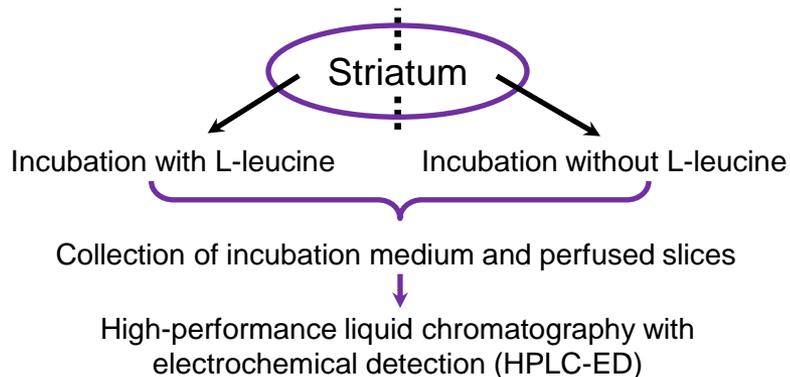
Synthesis of dopamine (DA) in DA-ergic (bienzymatic) neurons



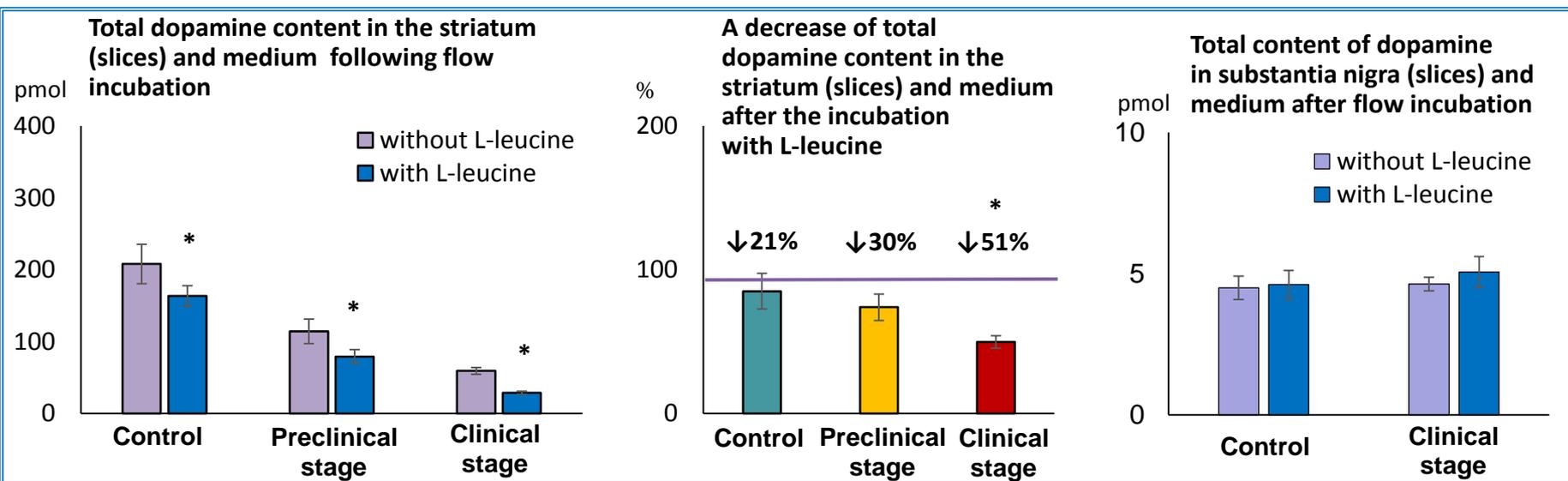
TH – tyrosine hydroxylase, AADC – aromatic L-amino acid decarboxylase, LAT1 – large neutral amino acid transporter.

Design of the experiment

Flow incubation of the striatal slices for 2 hours:

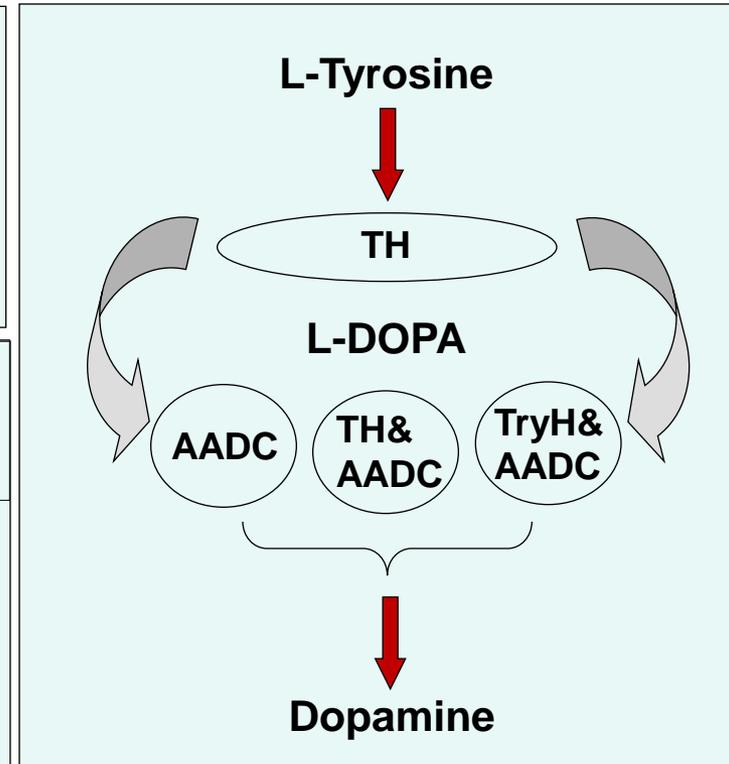
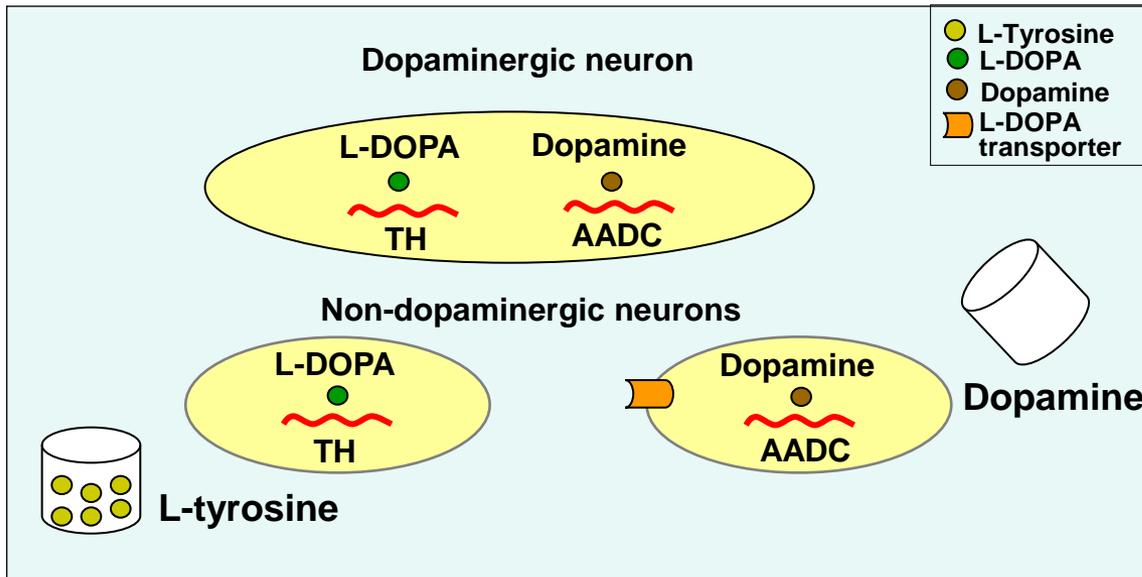


L-leucine is a competitive inhibitor of LAT1 transporter, preventing L-DOPA uptake. Slices of substantia nigra, containing only bienzymatic neurons served as an additional control.



Pathways for cooperative synthesis of dopamine

- ❖ Dopamine is produced by non-dopaminergic neurons expressing individual complementary enzymes of its synthesis in cooperation;
- ❖ Cooperative synthesis of dopamine is a compensatory reaction under a failure of dopaminergic neurons, mostly in neurodegenerative diseases



AADC, aromatic L-amino acid decarboxylase;
 TH, tyrosine hydroxylase;
 TryH, tryptophan hydroxylase

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➔ Conclusions.

Conclusions

- ❖ Experimental models of Parkinson's disease at the preclinical stage and early clinical stage (PD) were developed using MPTP-treated mice;
- ❖ A model of PD at the early clinical stage strongly reproduces the pathogenesis in patients regarding gene expression of α -synuclein and major proteins involved in neurotransmission;
- ❖ Despite a certain degradation of dopaminergic system at the model of PD at the preclinical stage, motor disorders are prevented due to compensatory processes – an increase of the gene expression and activity of tyrosine hydroxylase, an increase of dopamine (DA) release and a decrease of MAO B activity;
- ❖ Dopamine in the striatum is produced besides dopaminergic neurons by non-dopaminergic neurons expressing individual enzymes that is among most efficient mechanisms of neuroplasticity at PD;
- ❖ A transition of the presymptomatic stage to the symptomatic stage, manifested by the onset of motor disorders is provoked by a decrease of DA stimulated release and an increase of DA uptake and MAO A activity.

A nighttime photograph of a cityscape. In the center, a tall, white, rectangular building is under construction, with its upper floors encased in a complex network of golden scaffolding. To the left, another building is illuminated with blue and white lights. In the foreground, a bridge with a dark metal truss structure spans across a river. The river's surface reflects the lights from the buildings and the bridge. The sky is a deep, dark blue.

*Thanks
for your attention*

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