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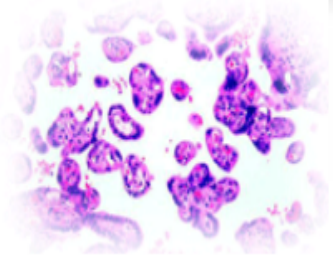

Additional therapeutic options in Parkinson's disease according to a neuronal network

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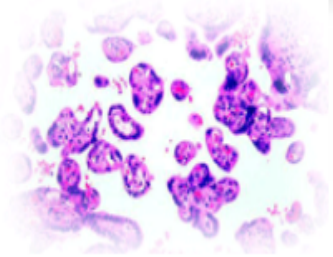

Werner, F.M.; Coveñas, R.

Introduction: In Parkinson's disease exists a dopaminergic cholinergic and GABAergic glutaminergic neurotransmitter imbalance in the extrapyramidal system. The development of neuronal networks in the basal ganglia, the thalamus and the cortex could contribute to derive additional pharmacological options.

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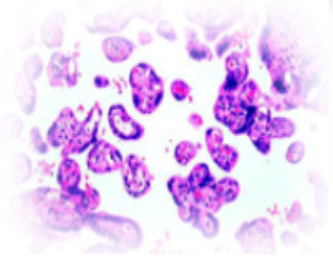

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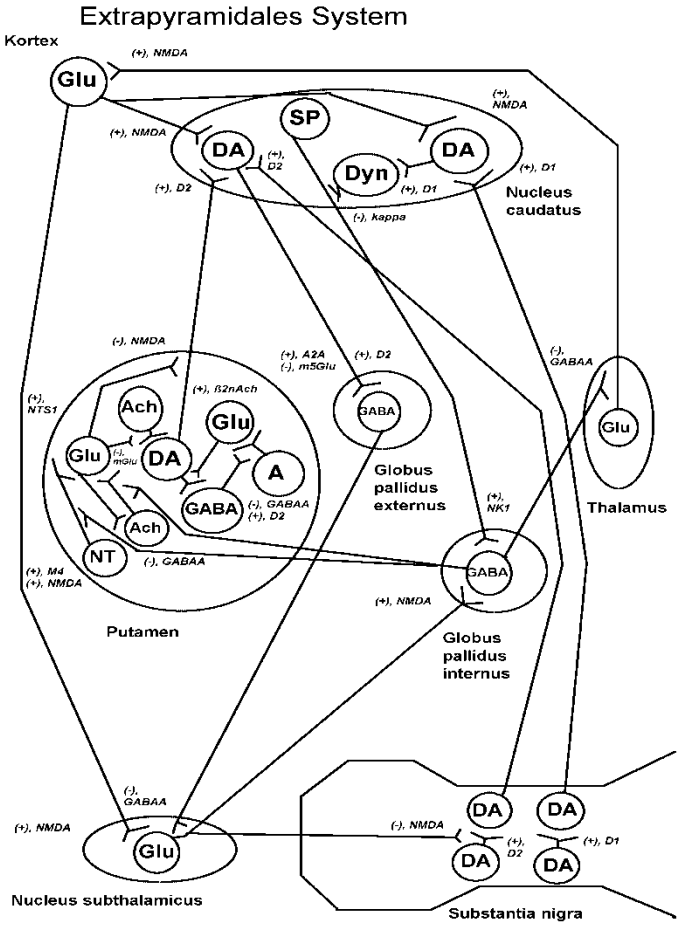
Material/methods: The neuronal network can be described as follows: Dopaminergic neurons from the substantia nigra weakly activate other dopaminergic neurons in the caudate nucleus via **D_1** and **D_2** receptors. The **D_1** dopaminergic neurons transmit a weak activating impuls to dynorphin neurons which inhibit substance P neurons via kappa receptors. The latter neurons transmit a weak postsynaptic excitatory impulse via **NK_1** receptor to GABAergic neurons in the globus pallidus internus. **D_2** dopaminergic neurons weakly activiate GABAergic neurons in the globus pallidus externus, which inhibit glutaminergic neurons in the nucleus subthalamicus via **$GABA_A$** receptors.



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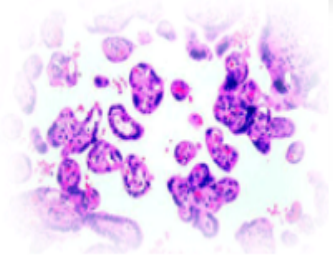

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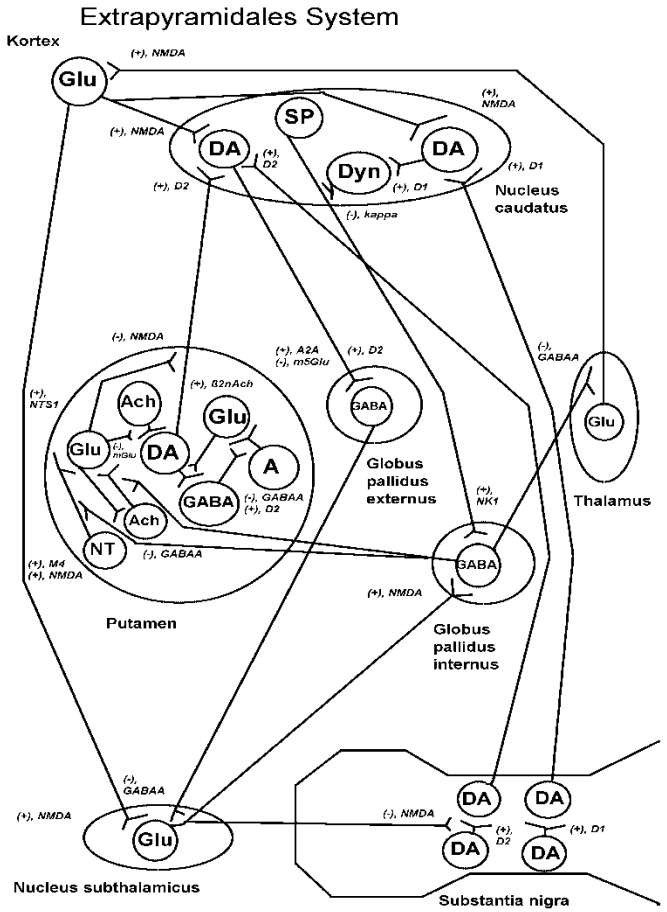
The latter neurons strongly inhibit via **NMDA** receptors dopaminergic neurons in the substantia nigra and transmit an activating impulse via **NMDA** receptors to GABAergic neurons in the globus pallidus internus. The GABAergic neurons in this nucleus inhibit glutaminergic neurons in the thalamus which transmit an activating impulse to glutaminergic neurons in the cortex. The cortical glutaminergic neurons can activiate $\mathbf{D_1}$ and $\mathbf{D_2}$ dopaminergic neurons in the caudate nucleus via **NMDA** receptors and activate other glutaminergic neurons in the nucleus subthalamicus.



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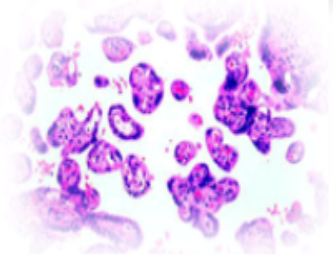

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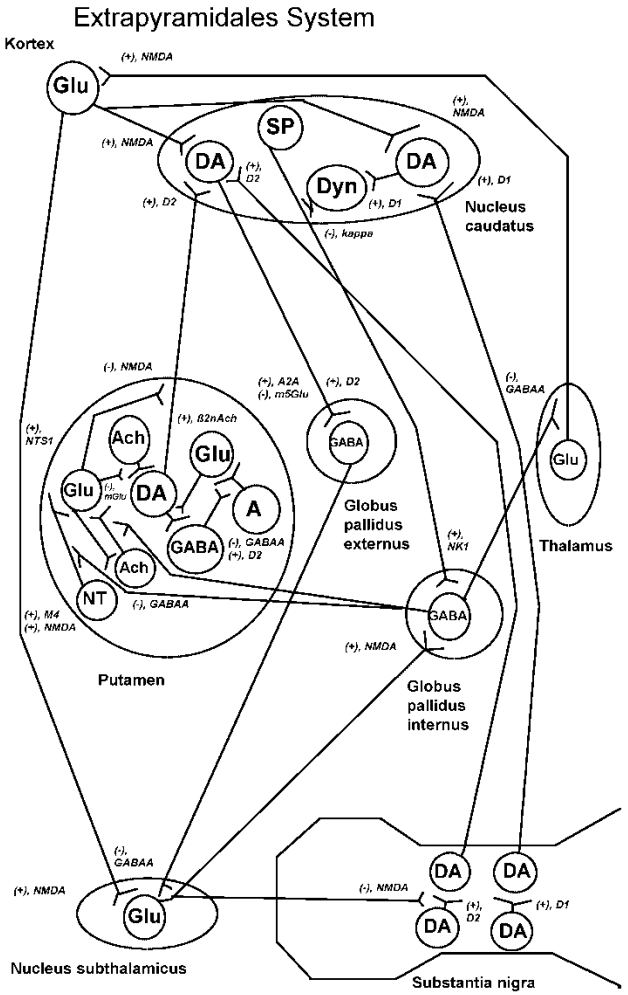
The GABAergic neurons in the globus pallidus internus weakly inhibit via **$GABA_A$** receptors muscarinic cholinergic and neurotensin neurons in the putamen. The muscarinic cholinergic and neurotensin neurons with a high activity transmit a strong activating impulse respectively via **M_4** and **NTS_1** receptors to glutaminergic neurons. The latter neurons strongly presynaptically inhibit dopaminergic neurons via **NMDA** receptors. Nicotinic cholinergic neurons activate dopaminergic neurons via **ß2 nAch** receptors, and adenosine neurons activate via **A_{2A}** receptors glutaminergic neurons which strongly inhibit dopaminergic neurons via the **subtype 5** of the metabotropic glutamate receptors. The **D_2** dopaminergic neurons in the putamen are connected to other dopaminergic neurons in the caudate nucleus.



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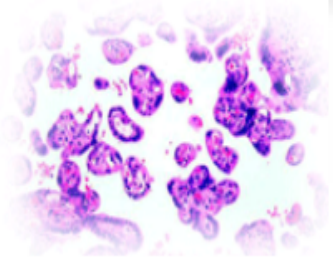

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Results: In addition to l-dopa combined with a decarboxylase inhibitor, dopamine agonists, **M_4** antagonists, **NMDA** antagonists and inhibitors of enzymes degrading dopamine, the following drugs can be administered according to the neuronal network:

- Antagonists of the **subtype 5** of the metabotropic glutamate receptors, e.g. **m5Glu** receptor antagonists, which increase dopamine levels through a reduced presynaptic inhibition,
- **A_{2A}** adenosine antagonists, which reduce the presynaptic glutaminergic inhibition of dopaminergic neurons,
- **ß2 nAch** agonists, which stimulate the **ß2** subreceptor of the nicotinic cholinergic receptors and activate dopaminergic neurons,
- **NTS_1** antagonists, which reduce the presynaptic glutaminergic inhibition of dopaminergic neurons.

Discussion: It can be concluded that it is important to examine such neuronal networks in order to coordinate a multimodal pharmacotherapy in Parkinson's disease.

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