The Dopamine Receptor D3 and Pramipexole: from Parkinson Disease to Pathological Gambling

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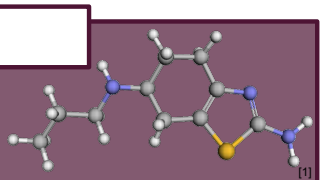
Introduction


[1]

Parkinson Disease (PD) is a progressive neurodegeneration that causes motor impairment. This results from the death of dopaminergic neurons and the consequent depletion of dopamine in the striatum.

Dopamine replacement therapies include levodopa and dopamine agonists (DAs). The latter are competent and commonly prescribed drugs; Pramipexole is one of them.

Pramipexole is effective and alleviates the motor symptoms of PD but it has been associated with the development of Impulse Control Disorders (ICDs). These comprise several psychiatric disorders characterized by impulsivity, failure to resist temptations and inability to learn from negative outcomes.

Aims

- To find results that depict the percentage of patients who develop Impulse Control Disorders, which of them were pramipexole-treated patients and which are the most frequent ICDs.
- To find results that determine the binding affinity of pramipexole to the D3 receptor, in comparison to other dopamine agonists and other receptors.
- To find results that demonstrate the localization of the D3 dopamine receptor to limbic areas of the brain.

Materials & Methods

Frequency of ICDs. Cross-sectional study [2]

3090 PD patients under treatment >1year
Evaluation of pathological gambling, compulsive sexual behavior, compulsive buying and binge-eating disorder

Radioligand binding assays [3]

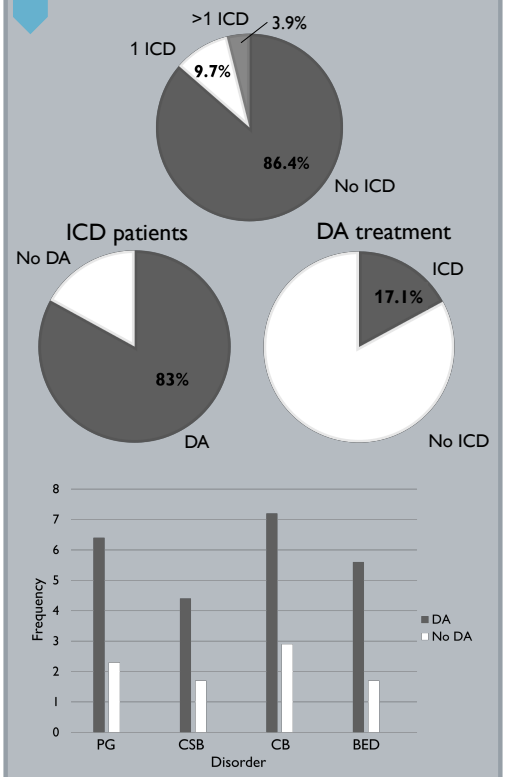
[^{3}H]pramipexole and [^{3}H]spiperone

Localization of the D_3 dopamine receptor [4]

In situ hybridization histochemistry
Human D_3 receptor cDNA
Nissl staining

Results

ICD diagnosis in overall patients



420/3090 patients (13.6%) diagnosed with ICD.
↳ 120 patients ≥ 2 ICD , 300 = 1 ICD

83% of ICD patients under treatment with a DA.
17.1% of the patients taking a dopamine agonist developed ICDs.

All types of ICDs are more frequent in dopamine agonist-treated patients.

1. Competition assay using [^{3}H]spiperone

Dissociation constant	D_{2L}	D_3
$K_{H\ (nM)}$	2.07±0.32	0.49±0.09
$K_{L\ (nM)}$	139±32	2.78±0.45
$K_{GppNHp\ (nM)}$	701±49	2.4±0.09

2. Saturation assay using [^{3}H]pramipexole

	K_D (nM)	B_{max} (pmol/mg)
D_{2L}	1.26±0.25	0.70±0.22
D_{2S}	0.96±0.13	0.58±0.06
D_3	0.22±0.03 2.27±0.56	3.00±1.00 5.30±0.60

3. Indirect competition assay using ↓[^{3}H]pramipexole

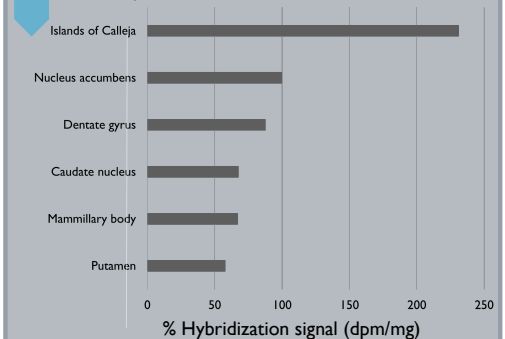
Ki (nM)	D_{2L}	D_{2S}	D_3
Pramipexole	3.9±0.2	3.3±0.3	0.5±0.1
Bromocriptine	2.5±0.4	4.8±0.8	12.2±1.7
Quinpirole	1.8±0.3	1.5±0.1	0.96±0.03

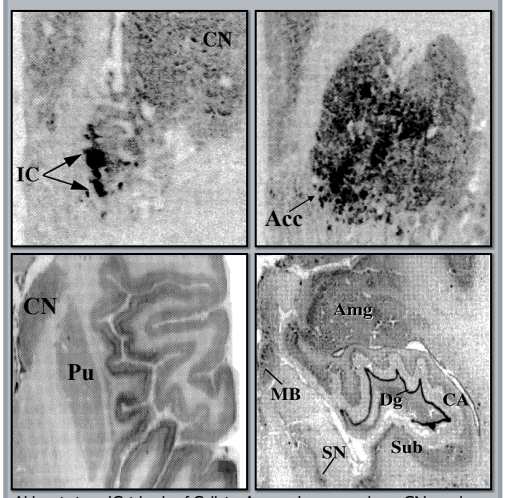
1. Pramipexole has a clear preference for the binding to D_3, when compared to one of the isoforms of the D_2 receptor.

2. Two populations of binding sites with significantly different affinities at the D_3 receptor.
$D_3B_{max} > D_2B_{max}$ → D_3 more binding capacity
$D_2K_d \approx 5.7\ D_3K_{d(high)}$ and more affinity

3. $D_2K_i \approx 7D_3K_i$ → High selectivity of pramipexole for D_3
Pramipexole has the greatest binding affinity at D_3, when compared to other DAs

D_3 receptor mRNA expression



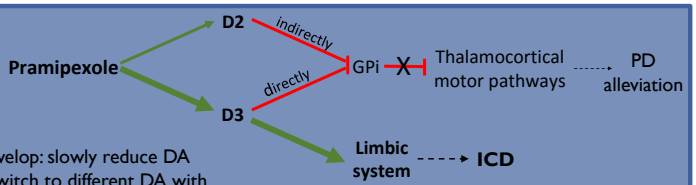


Abbreviations. IC: islands of Calleja, Acc: nucleus accumbens, CN: caudate nucleus, Pu: putamen, MB: mammillary body, Dg: dentate gyrus. [4]

↑↑↑D_3 expression in areas that are part of or associated with the limbic system.
↓ D_3 expression in areas related to motor function.
Dual localization → D_3 involved in both behavioral and motor functions

Conclusions

There is a clear association between DA treatment and ICD. This must be recognized as early as possible due to adverse personal and financial consequences.



Before starting a pramipexole treatment:
- Consider risk factors (early PD onset, novelty seeking, hypomania, impaired planning, family history of alcohol abuse). [5]
- Evaluate risk/benefit ratio.
- Adjust dose and therapy to each case.

If ICD develop: slowly reduce DA dose or switch to different DA with lower affinity for the D_3 receptor

Future: elucidate the exact molecular mechanism responsible for the convergence of PD and ICD, as it is not clear yet.
Further functional imaging studies and genome wide association studies. [6]

References

[1] DrugBank www.drugbank.ca
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