Pathophysiology of dyskinesia and behavioral disorders in non-human primates: Insights from multimodal imaging

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Résumé

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Parkinson's disease (PD) is a complex disorder with both motor and non-motor symptoms. Besides the dopaminergic (DA) neuronal loss, serotonergic (5-HT) neurons from the raphe nuclei also degenerate in PD. Interestingly, the dysfunction of the 5-HT system is associated with tremor and L-DOPA-induced dyskinesia (LID). There is also a link between 5-HT dysfunction and non-motor symptoms such as fatigue, depression, anxiety and apathy. The aim of our research was to investigate the causal role of this 5-HT lesion, besides the DA one, in the parkinsonian symptomatology via the development of a monkey model exhibiting a double DA/5-HT lesion using sequentially MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and MDMA (or ecstasy). The severity of MPTP-induced parkinsonism was inversely correlated with DA and 5-HT cell losses. It was also correlated with striatal decreases of [11C]PE2I availability (the DA transporter radioligand) and with increases of mean diffusivity (MD) within the caudate nucleus and the anterior cingulate cortex (ACC). In severely-lesioned MPTP monkeys, chronic L-DOPA treatment induced dyskinesia whose severity correlated with MD decreases and [11C]DASB (the 5-HT transporter radiotracer) increases in both the ventral striatum and the ACC. In moderately-lesioned MPTP monkeys, L-DOPA induced neuropsychiatric-like symptoms whose severity correlated with 5-HT transporter availability in the posterior ventral putamen. Monkeys were then treated with MDMA and the neurotoxic effects were evaluated by multimodal imaging as for MPTP. A decrease of SERT availability was evidenced by PET imaging in the basal ganglia, thalamic and raphe regions. Using DTI, MDMA lesions were detected by fractional anisotropy (FA) increases in the caudate nucleus and the ACC. The impact of MPTP and MDMA was also investigated on 5-HT markers by immunohistochemistry. Depending on its administration regimen, MPTP could lead to a decrease of both 5-HT fibers and cells, while MDMA did only affect 5-HT fibers. After MDMA, there was a reduction or even abolition of LID, in agreement with the fact that i) MDMA is effective in reducing LID in rats, ii) there is a beneficial role of administrating 5-HT1A or 5-HT1A/1B agonists in dyskinetic monkeys or PD patients

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and that iii) antidepressants acting at the SERT level offer an interesting anti-dyskinetic strategy. After MDMA, there was also a reduction or even abolition of neuropsychiatric-like disorders, suggesting that 5-HT fibers may sustain their expression via the same aberrant processing of L-DOPA in non-motor regions. The higher SERT to DAT ratio, the higher the risk to develop adverse effects such as LID, impulsive compulsive disorders and visual hallucinations, depending on the cerebral regions involved. Finally, given the fact that 5-HT deficits can be detected early in *de novo* PD patients and that the pathological process could affect the raphe before reaching the substantia nigra, we wondered what would be the impact of an early 5-HT lesion on parkinsonian symptoms. Prior MDMA administration worsened MPTP-induced parkinsonism (and associated DA cell loss) and affected both the 5-HT and DA systems. MDMA neurotoxicity towards 5-HT fibers was well demonstrated in non-human primates. Its neurotoxicity towards the DA system was well accepted in mice and rats but is new in monkeys. As MDMA causes oxidative stress, it may favor vulnerability of DA neurons to subsequent MPTP. Interestingly, while bradykinesia, rigidity and freezing were not affected by prior MDMA administration, tremor, arm posture and spontaneous activities (homecage activity, spontaneous movements) were significantly impacted. To conclude, this double lesioned macaque model can reproduce the DA and 5-HT injuries observed in PD patients. However, MPTP and MDMA are not specific to lesion the DA and 5-HT systems, and MDMA does not kill 5-HT raphe somas. Despite these limits, the use of MDMA has an impact on parkinsonian symptomatology. When administrated after MPTP, MDMA alters pre-established LID and neuropsychiatric-like behaviors. When administrated prior MPTP, MDMA aggravates parkinsonism.

Mots-Clés: dyskinesia, multimodal imaging, NHP