



Research Project Proposal

Academic year 2016-2017

Project Nº 15 ASIGNADO

Title: Screening of dopamine D1/D2 receptor heteromers in the striatum of the long-tailed macaque. Changes following dopaminergic manipulation.

Department/ Laboratory Basal Ganglia Neuroanatomy Laboratory, Neurosciences Program, Center for Applied Medical Research (CIMA)

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Summary

Although it has long been widely accepted that dopamine receptor types D1 and D2 form heteromers in the striatum, the presence of such heteromers has recently been challenged in a recent article appearing in *Molecular Psychiatry* (Frederick et al., *Mol Psychiatry* 2015; 20:1373-1385). Using a number of in vitro and ex vivo techniques, together with behavioral analysis in mice, these authors failed to find any conclusive evidence supporting the presence of these heteromers, despite the large body of literature supporting the opposite. Indeed and most importantly, the so-called in situ proximity ligation assay (PLA) was used to provide the final morphological proof of the lack of D1/D2 heteromers. However, they have followed a somewhat unconventional PLA technique. In this regard, we strongly believe that the selected PLA protocol has prevented these authors to accurately detect D1/D2 heteromers. Here we will be using what we think is the most appropriate variant procedure of the PLA technique to accurately demonstrate the presence of D1/D2 receptor heteromers across different striatal territories of *Macaca fascicularis*, together with putative physiological regulation after nigrostriatal dopamine denervation and dopamine repletion. Experiments will be carried out in control macaques as well as in MPTP-treated macaques (with and without levodopa-induced dyskinesia).

References

Frederick, A.I., Yano, H., Trifilieff, P., Vishwasrao, H.D., Biezonski, D., Mészáros, J., Urizar, E., Sibley, D.R., Kellendonk, C., Sonntag, K.C., Graham, D.L., Colbran, R.J., Stanwood, G.D., Javitch, J.A., 2015. Evidence against dopamine D1/D2 receptor heteromers. *Mol. Psychiatry*. 20, 1373-1385.

Dziedzicka-Wasylewska, M., Faron-Górecka, A., Andrecka, J., Polit, A., Kúsmider, M., Wasylewski, Z., 2006. Fluorescence studies reveal heterodimerization of dopamine D1 and D2 receptors in the plasma membrane. *Biochemistry* 31, 2424-



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Guigoni, C., Doudnikoff, E., Li, Q., Bloch, B., Bezard, E., 2007. Altered D1 dopamine receptor trafficking in parkinsonian and dyskinetic non-human primates. *Neurobiol. Dis.* 26, 452-463.

POSSIBILITY OF PhD

YES*

* (PhD grant required)