UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title
RGS4 ligands in Parkinson's disease
2)Abstract (max 500 words)
Regulators of G-protein signaling (RGS) are signal transduction proteins which couple to heterotrimeric G-protein coupled receptors (GPCRs). RGS proteins bind to the Gα-GTP complex and accelerate its intrinsic GTPase activity, promoting the formation of Gα-GDP and the reassembly of Gαβγ trimer. This causes the termination of GPCR-driven intracellular signaling. RGS proteins are grouped into five subfamilies (R4, R7, R12, RA and RZ) based on sequence homology. They interact with $G\alpha_i$, $G\alpha_o$, $G\alpha_{12/13}$ but not $G\alpha_s$, and show a variable degree of receptor and G-protein specificity. Morari group has provided original evidence that RGS4 is involved in neuroleptic-induced parkinsonism and that RGS4 receptor blockade reverses it (Blazer 2015). Moreover, they proved that RGS4 blockade potentiates the antidyskinetic action of NOP receptor agonists in a model of levodopa-induced dyskinesia (Pisanò 2023). Striatal RGS4 expression and levels appear to be downregulated in models of experimental parkinsonism although whether this is a cause, a consequence or a simple epiphenomenon of dopamine depletion needs to be ascertained. The project aims at elucidating the contribution of RGS4 to Parkinson' disease and the potential of RGS4 ligands as therapeutic agents. We will use pharmacological inhibitors of RGS4 in neurodegenerative and etiological murine models of Parkinson's disease. RGS4 knockout mice will be tested for their sensitivity to parkinsonian toxins or triggers. Stereological techniques will be used to monitor neurodegeneration in the substantia nigra. Western blot and immunohistochemistry will be used ex-vivo to study signaling pathways in the basal ganglia and cerebral cortex. In vivo techniques will be used to monitor dopamine, glutamate and GABA levels as markers of nigro-striatal and striato-nigral pathways activity in the basal ganglia.