Molecular and cellular determinants of dopamine-related brain diseases

https://www.neurodegenerationresearch.eu/survey/molecular-and-cellular-determinants-of-dopamine-related-brain-diseases/

Principal Investigators

Gilberto Fisone

Institution

Karolinska Institute

Contact information of lead PI
Country

Sweden

Title of project or programme

Molecular and cellular determinants of dopamine-related brain diseases

Source of funding information

Swedish Research Council

Total sum awarded (Euro)

€ 435,256

Start date of award

01/01/2016

Total duration of award in years

4

Keywords
Research Abstract
This Research Proposal aims at the study of brain diseases linked to dysfunctional dopamine transmission, such as Parkinson’s disease (PD), drug addiction and schizophrenia. We will use mouse models of disease combined with pharmacological and transgenic approaches for the identification of neuronal and molecular targets for therapeutic interventions. Work is based on 3 Specific Aims, which will be achieved during a 5-year period. Specific Aim 1 focuses on chromatin modifications and signaling processes involved in the motor complications (dyskinesia) caused by prolonged administration of L-DOPA, which represent a major problem in the pharmacotherapy for PD. L-DOPA-induced dyskinesia (LID) has been linked to abnormal

signal transduction in the medium spiny neurons of the striatum, which are the principal target of L-DOPA. We showed that, in these neurons, abnormal gene expression associated with LID correlates with increased levels of histone H3 marked by Lys trimethylation and Ser28 phosphorylation (S28p). Recently, we found that LID is also associated with S28p occuring at genomic regions marked by histone H3 acetylation at Lys27 (K27ac). We will characterize the regulation of H3K27acS28p associated with dyskinesia and use genome-wide analyses to assess the impact of H3K27acS28p in LID. These studies will be performed using a protocol developed in our laboratory, in collaboration with Dr. Klaus Hansen (University of Copenhagen). LID is also accompanied by activation of mammalian target of rapamycin complex 1, which affects degradation of cytoplasmic proteins by inhibiting autophagy. We found that, in the striata of dyskinetic mice, decreased autophagy leads to accumulation of the protein p62, which is implicated in synaptic plasticity and receptor trafficking. We will study the role of p62 in regulating the trafficking of receptors previously implicated in dyskinesia. We will also examine the role of p62 in LID, using p62 knock out mice. Recently, we found that S28 phosphorylation of H3K27me3 and H3K27ac is also increased in response to administration of addictive (amphetamine) and antipsychotic (haloperidol) drugs. In Specific Aim2, we will use ChIP-seq to assess H3K27me3S28p and H3K27acS28p across the genome in mice treated with amphetamine, morphine and haloperidol. These studies will be carried out using the same techniques employed in Specific Aim 1 and will help to understand the molecular basis of the maladaptive processes implicated in drug addiction and of the extrapyramidal motor complications produced by typical antipsychotics. Cognitive and psychiatric symptoms are a major clinical challenge in the treatment of PD. In Specific Aim 3 we will employ a mouse model of PD displaying memory deficits, depression- and anxiety-like behaviors, to assess the ability of cannabinoid, histamine and glutamate receptor antagonists, to counteract these conditions. In these experiments we will use behavioral tests previously used for the optimization of the model. Interestingly, the behavioral abnormalities described above are paralleled by disrupted gamma oscillations in the hippocampus, a brain region critically involved in memory. Gamma oscillations are rhythmic patterns of electrical activity implicated in cognitive processes and depression. We will determine which specific neurons in the hippocampus are involved in the impairment of gamma oscillation observed in the mouse model of PD. Similar studies will be performed in cortical areas, which are also involved in cognitive and affective processes. Drugs that revert memory and mood-related deficits (cf. above) will be also tested for their ability to rescue gamma oscillations in the PD mouse model. These studies will identify molecular and neural targets implicated in non-motor symptoms of PD and open new vistas for the design of broader therapeutic interventions.

Further information available at:

Types:
Investments < €500k

Member States:
Sweden

Diseases:
N/A

Years:
2016

Database Categories:

N/A

Database Tags:
N/A