The tVTA: a new member of basal ganglia with therapeutic potential

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Title of project or programme

The tVTA: a new member of basal ganglia with therapeutic potential

Source of funding information

ANR

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4.0

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract

The loss of dopamine neurons in Parkinson’s disease leads to the dysfunction of the brain basal ganglia circuit, associated with motor and non-motor symptoms whose management remains challenging. A recently defined brain structure, the tail of the ventral tegmental area (tVTA), was shown to control dopamine systems and its inhibition improves basal ganglia functions. As such, this structure may offer a new target for therapies. tailPARK is a neuroscience project starting

with a question of fundamental research: what is the anatomical and physiological place of the tVTA in the basal ganglia circuit? Based on published and our preliminary data, the project further develops towards the preclinical validation of a proof-of-concept concerning the tVTA as neuroanatomical target for symptom management in Parkinson’s disease. To reach its objectives, tailPARK gathers teams from 3 institutional laboratories, with complementary expertises applied to a same question. Beyond the increased knowledge in the control of basal ganglia activity, this project has the potential to pave the way for addressing current unmet medical needs.
Midbrain dopamine neurons project to a number of brain regions where dopamine exerts a modulatory influence. Mirroring their physiological roles, dopamine systems are also implicated in the aetiology, symptoms and treatment of neurological and psychiatric disorders. The dopamine structures belong to the larger basal ganglia circuit, and understanding the controls of basal ganglia is necessary to understand its pathological impairments and to search for novel therapeutic targets for improving pathological deficits. Parkinson’s disease is the second most frequent neurodegenerative disease. Known for its motor symptoms, Parkinson’s disease also has deleterious non-motor consequences including pain, anxiodepressive disorders and deficits in executive functions. Patients consulting for Parkinson’s disease display around 14 symptoms as a mean at early stage of the disease, and over 20 at later stage, which stresses out the need to take this complexity into consideration in preclinical research. While slowing the neurodegenerative process is a major therapeutic goal, improving yet unmanaged symptoms in already installed disease remains also critical. One of the objectives of tailPARK concerns such symptoms’ management. In this context, newly discovered brain structures can help improving our knowledge of normal brain functions and of brain disorders, and may provide new neuroanatomical targets for treatments. The project concerns the tVTA, a brain structure that exerts a major inhibitory control on dopamine systems. Discovered in rodents, the tVTA has now been described in the primates. Recently, two of tailPARK partners demonstrated that the tVTA controls motor functions, and that its bilateral ablation improves motor performances and motor skill learning. Preliminary data suggest that inhibiting the tVTA may be beneficial in models of Parkinson’s disease.
From normal to pathological brain functioning, these data raise the questions of tVTA integration within basal ganglia circuitry at fundamental level, and of the therapeutic potential of tVTA targeting at preclinical level. tailPARK was designed to answer these questions, by assessing the anatomical and functional links between the tVTA and the basal ganglia, and by testing the therapeutic potential of targeting the tVTA in Parkinson’s disease, using a combination of animal models and taking into consideration motor, pain-related and anxiodepressive-related symptoms. To reach these objectives, this 4-year project gathers 3 laboratories with complementary expertises: a specialist in neuroanatomy and behaviour, a specialist in electrophysiology, and a specialist in Parkinson’s disease and its models. Project completion will provide brain maps of tVTA/basal ganglia inter-relations, and preclinical assessment of tVTA inhibition in a context of Parkinson’s disease.

Lay Summary
Further information available at:

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Investments > €500k

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