

# Functions of alpha-Synuclein in Neurotransmitter Release

<https://neurodegenerationresearch.eu/survey/functions-of-alpha-synuclein-in-neurotransmitter-release-2/>

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### Country

USA

## Title of project or programme

Functions of alpha-Synuclein in Neurotransmitter Release

## Source of funding information

NIH (NINDS)

## Total sum awarded (Euro)

€ 1,341,789.91

## Start date of award

15/02/2014

## Total duration of award in years

3

## The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

## Keywords

alpha synuclein, neurotransmitter release, Exocytosis, Vesicle, Recycling

## Research Abstract

DESCRIPTION (provided by applicant): Parkinson's disease (PD) is the second most common neurodegenerative disease, which affects 1.8% of people over the age of 65 years. One clinic hallmark of PD is formation of intracellular proteinaceous inclusions, termed Lewy Bodies, in the

brain neurons. The main constituent of the Lewy Bodies is alpha-synuclein, which is found to accumulate in neurons in both familial forms of PD and sporadic PD. Therapeutic strategies for PD patients have not been very successful, because clinical symptoms occur at a stage when the neuronal functions have been damaged to an extent hard to rescue. Improvement of the therapeutic strategies depends on better understanding of the pathophysiological development of PD, including presymptomatic neuronal dysfunctions induced by alpha-synuclein accumulation. Increased level of alpha-synuclein has previously been found to impair neurotransmitter release prior to the symptomatic PD. However, mechanisms causing such impairment are poorly understood. Because alpha-synuclein is mainly expressed in nerve terminals, which are usually too small for using the highly sensitive electrophysiology methods, previous studies could not directly evaluate contributions of many essential presynaptic factors, such as action potential, voltage dependent calcium entry, and vesicle recycling through endocytosis. In order to identify the primary cellular and molecular targets of elevated alpha-synuclein in nerve terminals, our studies will take advantage of the calyx of Held, a large mammalian synapse which is accessible to patch-clamp techniques. In preliminary experiments, we found that elevated alpha-synuclein inhibited vesicle exocytosis at the calyx synapse. This observation provides the foundation to further investigate the mechanisms underlying the inhibited exocytosis by elevated alpha-synuclein. In Aim 1, we will determine the interaction between elevated alpha-synuclein and calcium signaling. In Aim 2, we will determine whether elevated alpha-synuclein reduces exocytosis by affecting vesicle pool, endocytosis and mobilization. In Aim 3 we will determine whether the mechanisms identified at the calyx apply to midbrain dopaminergic neurons, which are related to the development of neurodegeneration. Achieving these aims can provide crucial information on how accumulation of alpha-synuclein causes the impairment of synaptic transmission prior to the symptomatic neurodegenerative disorders. This project can shed light on the process of pathophysiological changes in PD, and help the development of new therapeutic approaches targeting to these changes.

### **Lay Summary**

**PUBLIC HEALTH RELEVANCE:** Changes in endogenous alpha-synuclein levels have been linked to neurodegenerative diseases including Parkinson's diseases and dementia with Lewy bodies. The current project aims to identify the initial mechanisms by which oversupply and/or removal of alpha-synuclein impairs neuronal communication. Information gained from our studies is expected to enrich our knowledge of presymptomatic dysfunctions in Parkinson's disease and provide clues for future development of effective therapeutic strategies to treat the related diseases.

### **Further information available at:**

#### **Types:**

Investments > €500k

#### **Member States:**

United States of America

#### **Diseases:**

Parkinson's disease & PD-related disorders

#### **Years:**

2016

#### **Database Categories:**

N/A

**Database Tags:**

N/A