Effects of activation of cholinergic, noradrenergic, and serotonergic systems on respiratory impairment in Alzheimer's disease

Alzheimer disease (AD), a neurodegenerative, age-related disorder, is the most common reason of dementia with over 45 million people worldwide affected. Apart from impairment of memory and multiply, cognitive dysfunctions resulting in progressive impairment and finally in disability, disturbances of respiration such as respiratory dysrhythmias, shortness of breath, bronchitis, pneumonia, and sleep apea that worsens cognitive functioning, have been observed in many AD patients. Respiratory diseases are the cause of death in 55% of AD patients, including the most frequent aspiration pneumonia caused by noncooperation of swallowing and breathing. Respiratory problems, although significant and worsening life comfort, are still undiagnosed and untreated. Their cause and nature are still not understood.

The aim of the project is to examine the mechanisms of respiratory changes, using stressing stimuli (hypoxia and hypercapnia) testing the efficiency of the respiratory system, in two models imitating AD: transgenic AβPP V717I mice and strepozotocin (STZ) intracerebroventricular injected rats.

Examination of the activity of two respiratory nerves: phrenic and hypoglossal, indicating alteration in the central nervous control of breathing will be performed and this will shed new light on the mechanism of the increased number of apnea episodes appearing in AD patients. Long term facilitation phenomenon, which in a healthy organisms has a compensatory effect on recurrent apnea, as it improves ventilation after an episode of apnea, will be investigated in AD models. We also will try to affect the observed respiratory impairment with activation of cholinergic, serotonergic, and noradrenergic systems. All of them are well known to be disrupted in AD and are involved in respiratory control; central chemosensitivity, state-dependent modulation of breathing and respiratory motor output. Hypoglossal and phrenic nerves have cholinergic, noradrenergic and serotonergic innervation. Therefore, we hypothesize that stimulation of some of these systems may be effective in reversing or reducing some respiratory deficits including apnea. Additionally, we will compare changes in respiratory responses between the transgenic and pharmacological models of AD, mimicking early-onset familial AD and sporadic AD, respectively. The utility of both models in studies of respiratory disturbances present in AD will be assessed.

The experiments will be performed in rats bilaterally intracerebroventricularly injected with streptozotocin and transgenic AβPP V717I mice. Ventilatory measurements will be carried out in a whole body rodent plethysmograph in normoxic, hypoxic, and hypercapnic conditions in rats and mice treated with activators of all three systems (rivastigmine, fluoxetine, reboxetine). Hypoglossal and phrenic nerve activity, as a nervous output to the diaphragm and upper airway muscles, respectively, will be studied during air breathing and during acute hypoxia in STZ injected rats before and after stimulation of cholinergic and serotonergic systems. To evaluate cognition problems in STZ rats, the object recognition test will be performed. To explain the mechanism of the observed respiratory changes the activity of acetylcholinesterase in brain tissue homogenates (hippocamus, brainstem) and the presence of amyloid β in the brainstem areas involved in the regulation of breathing will be performed. Additionally brainstem impairments in serotonergic and noradrenergic neurotransmitter systems in both models will be assessed via HPLC analysis of the content serotonin and noradrenaline.

The current research will provide the novel insight into the possible pathological mechanisms of respiratory dysfunctions specific to Alzheimer disease and the contribution of the cholinergic, serotonergic, or noradrenergic systems to pathological breathing. Positive effects of cholinergic, serotonergic, or adrenergic system activation could give additional important information for designing new therapies of respiratory disorders present in AD patients.