

AMPA- and GABA(A) receptor signalling and corticospinal motor neuron excitability in mouse models of ALS

<https://www.neurodegenerationresearch.eu/survey/ampa-and-gabaa-receptor-signalling-and-corticospinal-motor-neuron-excitability-in-mouse-models-of-als/>

Principal Investigators

Professor M Farrant

Institution

University College London

Contact information of lead PI Country

United Kingdom

Title of project or programme

AMPA- and GABA(A) receptor signalling and corticospinal motor neuron excitability in mouse models of ALS

Source of funding information

MRC

Total sum awarded (Euro)

€ 656,803

Start date of award

01/07/2013

Total duration of award in years

3.0

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Research Abstract

We will determine functional characteristics of excitatory and inhibitory influences on identified CSMNs in brain slices prepared from SOD1(G93A) 'ALS' mice at different stages of disease

progression. Cells will be retrogradely labelled with FluoroGold or latex beads applied to the cervical spinal cord. We will determine the active and passive electrical properties of the neurons and establish any general alterations in their properties at different stages of the disease. We will then examine the contribution of calcium-permeable AMPARs and their auxiliary proteins (TARPs and CNIHs) to synaptic and extrasynaptic signalling. We will record pharmacologically isolated AMPAR-mediated macroscopic currents and synaptic currents. The contribution of specific proteins will be determined by comparing the kinetics, voltage-dependence, calcium-permeability, conductance and pharmacology of synaptic and extrasynaptic receptors with those of recombinant receptors expressed with specific auxiliary subunits in tsA201 cells. To determine how GABAergic signalling is altered during disease progression, we will quantify the relative contribution to charge transfer of phasic and tonic GABA(A)R activation. We will distinguish between pre- and postsynaptic changes by examining pharmacologically isolated mIPSCs (amplitude and kinetics, and the conductance of the underlying channels). To determine the origin of changes in tonic GABA(A)R-mediated currents will examine the properties of native receptors in outside-out somatic patches and compare these with those of recombinant GABA(A)Rs expressed in tsA201 cells. We will assess the impact of GABA(A)R activation on cell excitability and potential changes in chloride homeostasis in recordings using the gramicidin perforated-patch technique to preserve intracellular chloride. Our research will contribute to the understanding of normal brain function and highlight potential strategies for limiting excitotoxic damage of motor neurons in ALS.

Lay Summary

Further information available at:

Types:

Investments > €500k

Member States:

United Kingdom

Diseases:

Motor neurone diseases

Years:

2016

Database Categories:

N/A

Database Tags:

N/A