Axonal transport, protein trafficking and neurological disease

https://neurodegenerationresearch.eu/survey/title-of-piaxonal-transport-protein-trafficking-and-neurological-disease/

Title of project or programme

Title of PI Axonal transport, protein trafficking and neurological disease

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
Professor	Christopher	Miller	King’s College London	UK

Address of institution of lead PI

Institution	King’s College London
Street Address	Institute of Psychiatry, De Crespigny Park
City	London
Postcode	SE5 8AF

Country

- United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

1448614.19

Start date of award

06-11-2006

Total duration of award in months

60

The project/programme is most relevant to

- Motor neurone diseases

Keywords

Research abstract in English

The hypothesis that underlies this proposal is that defects in axonal transport and protein trafficking are part of the pathogenic process in three familial forms of amyotrophic lateral sclerosis (ALS). These familial forms are those caused by mutations in the genes encoding copper/zinc superoxide dismutase-1 (SOD1), ALS2/Alsin and vesicle-associated membrane protein-associated protein-B

(VAPB). The aim of the project is to understand how these different genetic insults induce defects in neuronal protein transport. The primary objectives are:-

1) To identify p38 stress-activated kinase phosphorylation sites in neurofilament proteins and to determine how this influences axonal transport of neurofilaments. p38 is activated in ALS, phosphorylates neurofilaments which in turn is known to be a regulator of neurofilament transport. This will be achieved by sequencing neurofilament proteins isolated from neuronal cell bodies in which we have activated p38 by transfection of dominantly-active MKK3. MKK3 is a direct upstream activator of p38. Identified sites will then be mutated to preclude or to mimic permanent phosphorylation and the transport properties of these mutants analysed by monitoring movement of green fluorescent protein (GFP)-tagged variants in transfected cultured neurons.

2) To determine whether ALS mutant SOD1 induces changes in phosphorylation of kinesin and dynein family proteins. These are phosphoproteins and there is emerging evidence that they may be substrates for p38. This will involve proteomic analyses of motor proteins isolated from cells and tissues expressing wild-type or mutant SOD1.

3) To determine how loss of ALS2 influences both fast and slow axonal transport by monitoring movement of GFP-tagged cargoes in living neurons derived from wild-type and ALS2 knockout mice.

4) To gain insight into the mechanisms by which ALS2 may signal to regulate axonal transport and how phosphorylation of ALS2 influences any such signalling.

5) To characterise new transgenic mouse models expressing ALS mutant VAPB that we have recently generated.

6) To determine whether ALS mutant VAPB damages axonal transport and if so, to gain insight into the mechanisms that underlie this effect.
The studies will thus provide information on the mechanisms underlying defective axonal transport in ALS and may reveal new therapeutic targets for this disorder. Since disruption to axonal transport is seen in other neurodegenerative diseases, these results are likely to be informative about pathogenic processes in a number of these disorders.

Lay summary
In which category does this research fall?

- Basic research