

Nicotinic receptor signalling dysfunction in neurodegenerative disease

<https://www.neurodegenerationresearch.eu/survey/nicotinic-receptor-signalling-dysfunction-in-neurodegenerative-disease/>

Title of project or programme

Nicotinic receptor signalling dysfunction in neurodegenerative disease

Principal Investigators of project/programme grant

Title	Forename	Surname	Institution	Country
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Address of institution of lead PI

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- United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

1584255.49

Start date of award

01-04-2006

Total duration of award in months

48

The project/programme is most relevant to

- Alzheimer's disease and other dementias
- Spinal muscular atrophy (SMA)

Keywords

Research abstract in English

“Nicotinic acetylcholine receptors (nAChRs) play a key role in cholinergic synaptic transmission in the brain and at nerve-muscle junctions. Disorders associated with nAChRs studied by the Sattelle group include Alzheimer’s disease (AD), Rasmussen’s encephalitis and congenital myasthenia syndrome (CMS). The nAChR molecules are assembled from a family of subunits and the many subtypes offer drug targets for AD, CMS and other disorders, e.g. epilepsy, schizophrenia and Parkinson’s disease. Our experimental approaches, which range from the study of single genes through to behaviour, provide multiple points of entry for analysis, new leads for therapy and opportunities for translational medicine.

Genomes of the worm and fly, the first animal genomes to be sequenced, are accelerating progress in understanding the molecular basis of neural signalling. The largest and most diverse nAChR gene family known is under investigation in *C. elegans*. Mutants of particular interest include the x26 allele of the nAChR *unc-63* gene, with a missense C151Y mutation that opens up the extracellular disulfide loop, providing a new animal model for one form of Fast Channel CMS. We have now developed a model for Slow Channel CMS and, importantly, automated phenotyping, which greatly accelerates drug screening in these simple, low-cost, oral delivery disease models. Invertebrate models of AD, CMS, inclusion body myositis, spinal muscular atrophy and muscular dystrophy have all been investigated. In collaboration with MRCT, we are testing the NINDs chemical library containing many approved drugs in attempt to explore their potential utility in meeting unmet clinical needs for rarer degenerative diseases of nerve and muscle. In a new development undertaken in collaboration with colleagues in Cardiff and Cambridge, we are using genome-scale RNA interference (RNAi) studies to leverage added value from genome-wide association studies (GWAS) on Alzheimer’s patients. By this means, we can identify those AD risk factors which most strongly influence amyloid-induced toxicity and we also help pinpoint new molecular targets and pathways for therapeutic intervention.

Our work has attracted Industrial collaborations from Pfizer, Senexis Ltd and Merial in the context of drug discovery as well as medical charities such as The Alzheimer’s Research Trust in the context of understanding Alzheimer’s disease risk factors.”

Lay Summary