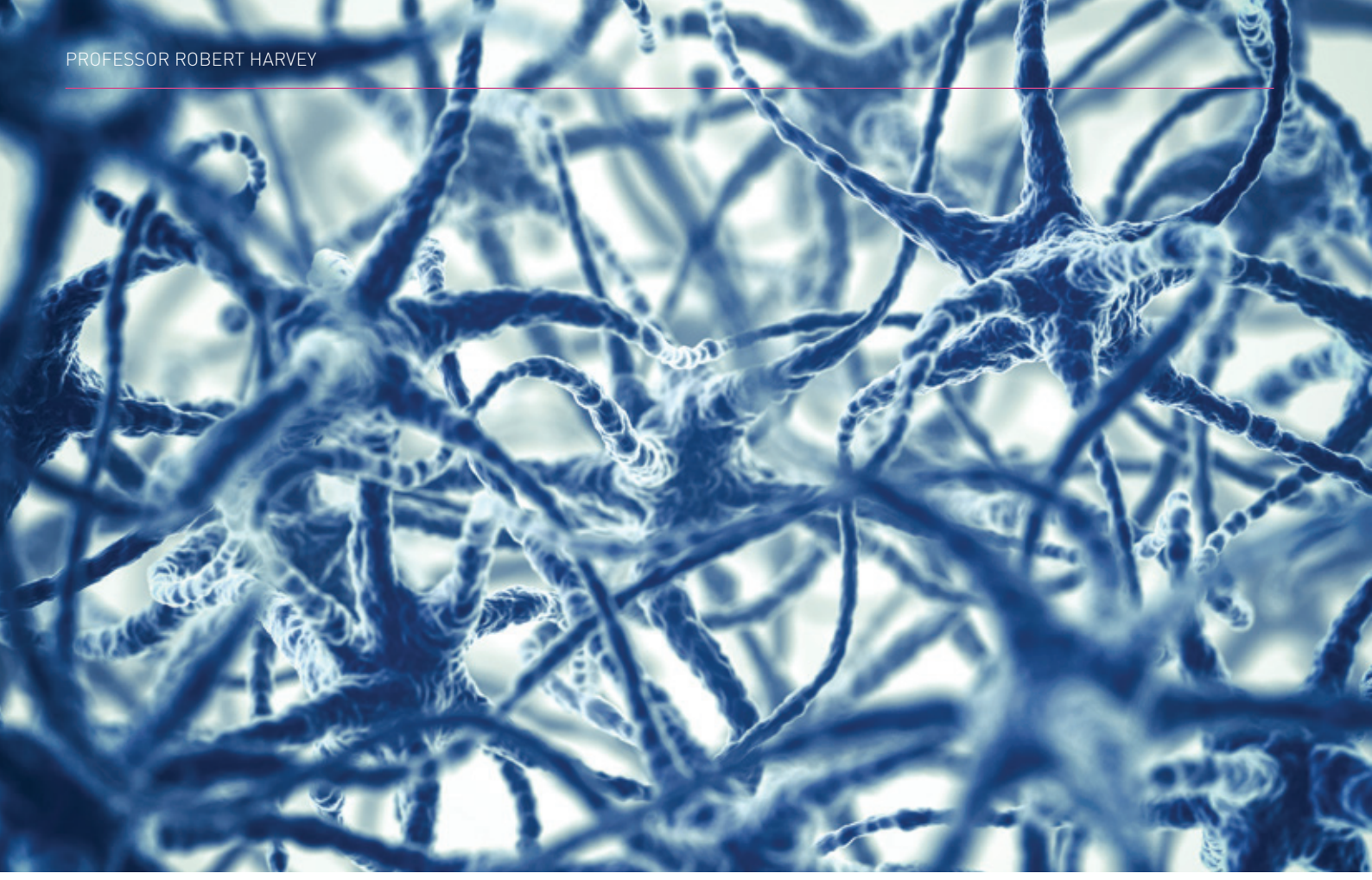


Towards translational neuroscience

Professor Robert Harvey has devoted his research career to studying the molecular neurobiology of inhibitory neurotransmission mediated by glycine and γ-aminobutyric acid. Here, he discusses his current roles, research aims and fruitful partnerships

You are currently based in the School of Pharmacy at University College London (UCL). Can you provide an overview of the work you are undertaking?

I have over 25 years of experience studying the biological roles of inhibitory and excitatory neurotransmitter receptors, transporters and associated proteins in health and disease. My research has a strong translational aspect, aiming to convert basic science discoveries into clinical applications, such as improved genetic diagnostics, patient care and pharmacological treatments. I am also Associate Director for Research at the UCL School of Pharmacy, a role that involves research strategy and management. In addition, I contribute to several university committees at faculty level, including the Faculty of Life Sciences Senior Management Group and the UCL Open Access Academic Advisory Group.

How has your career led you to your current position?

After completing a PhD in Natural Sciences at the University of Cambridge, UK, I worked in Hamburg, Germany, for five years as a postdoctoral research assistant. I was fortunate enough to be awarded a Max-Planck fellowship in Frankfurt with Heinrich Betz, who stimulated my interest in glycine receptors and transporters. I have run my own research group at the School of Pharmacy at UCL since 1998, and was promoted to Professor in 2007.

What is the motivation for your research into hyperekplexia, more commonly known as startle disease?

It is a rare neurological disease that affects humans as well as several animal species, including dogs, horses and cattle. The identification and functional characterisation of mutations in genes involved in this disease have improved both genetic diagnostics and patient care – a strong motivation to continue forging a fuller understanding of startle disease.

Can you discuss your role as professor? What do you enjoy most about teaching students at the beginning of their scientific careers?

Today, professors have so many different roles that it is easy to lose count. For example, in addition to my existing responsibilities, I recently learnt aspects of website design in order to redevelop the UCL School of Pharmacy website. As for teaching, it is an activity I particularly enjoy – and I currently lecture first-year students on genetics, second-year students on cardiovascular diseases and final-year students on substance abuse. I am very proud of our students who are completing

a Master's degree in Pharmacy as they are highly professional and have a great attitude for learning. I also find that hosting students for final-year research projects is very rewarding – especially seeing them learn research methods, become experts on a topic and develop the necessary skills they need to become lifelong learners in such a short space of time.

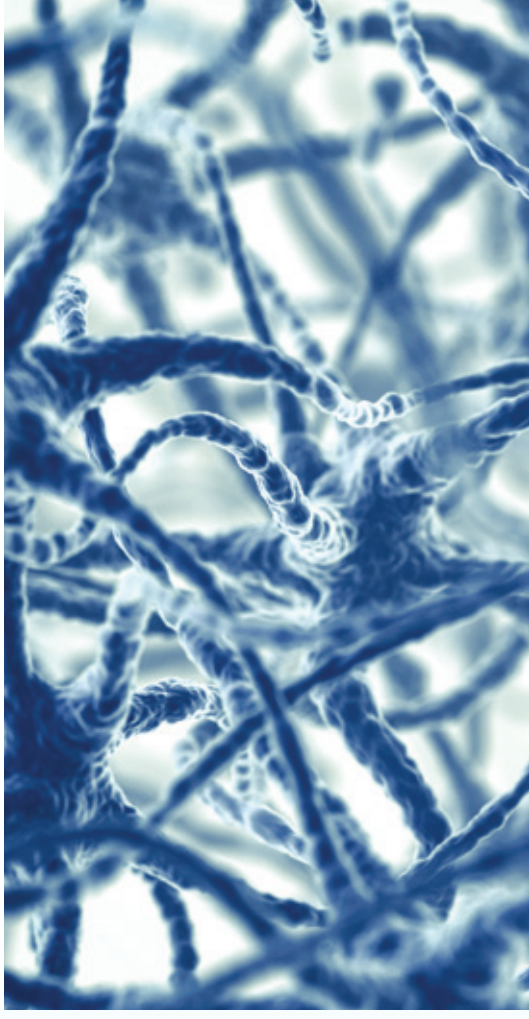
How does collaborative research benefit your work?

Collaboration is essential in my field as projects often operate across different disciplines; for example, they encompass aspects of genetics, biochemistry, molecular biology and electrophysiology. With modern communications, collaborative projects can operate over international boundaries; we have many partners in Europe and further afield in countries such as Japan and the US. By pooling our resources and expertise, these joint initiatives often make significant contributions to the scientific knowledge base and result in publications in high-impact journals. However, they are also a great way to learn new scientific techniques.

Moreover, collaborators often become lifelong friends and provide one another with interesting opportunities and experiences. For example, I was recently fortunate enough to spend a week in Japan with a long-term collaborator, Hiromi Hirata, who was kind enough to take me to a restaurant serving Fugu – a fish which can be fatal if prepared incorrectly!

Where do you see your career taking you in 10 years' time?

I hope that I will still be running a successful, funded research programme that addresses fundamental questions in health and disease. A senior leadership role in an academic setting is also a strong possibility; I would be very open to the prospect of running a thriving research department that works in the area of translational neuroscience.



Startle disease and faulty genes

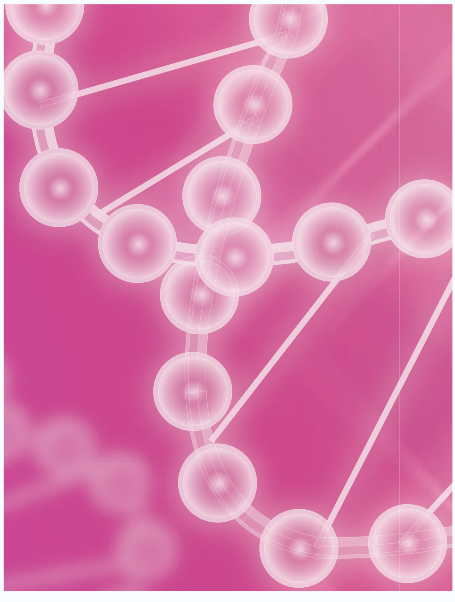
In an attempt to enhance genetic diagnostics and patient care, researchers based in the School of Pharmacy at **University College London** are investigating the biological roles of inhibitory and excitatory neurotransmitter receptors, transporters and proteins in neurological diseases

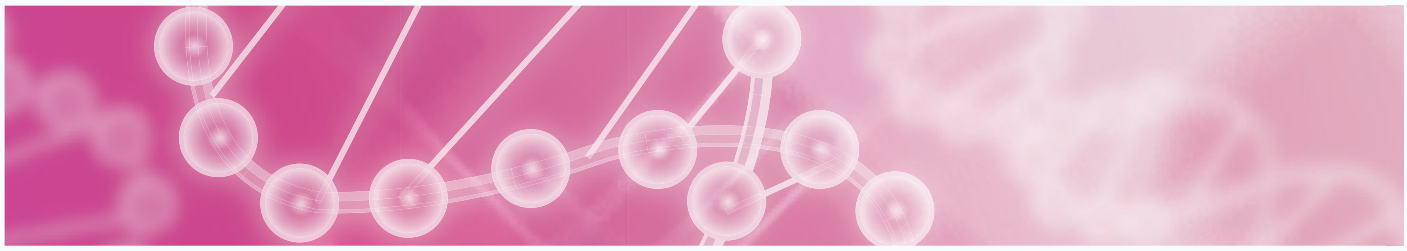
KNOWN AS STARTLE DISEASE, hyperekplexia is an inherited condition that affects newborn babies. Characterised by exaggerated responses triggered by unexpected sound, touch or visual stimuli, this disorder causes the chest and throat muscles of infants to freeze, their limbs to go rigid and – in some cases – their breathing to stop. Startle disease is also associated with swallowing and weaning difficulties and is a potential cause of sudden infant death.

This disease is extremely distressing for parents of the affected infant. Fortunately, however, treatments are available. The benzodiazepine Clonazepam is one of the most commonly used drugs, while the life-saving Vigevano manoeuvre – which involves the forced flexion of the head and limbs towards the trunk of the body – can help combat the effects of acute muscle stiffness and apnoea. Although the clinical symptoms of this condition tend to gradually diminish throughout the first year of life, in some cases the pronounced startle response and muscle stiffness can continue into adulthood, putting sufferers at risk of serious injuries and loss of ambulation as a result of sudden and unprotected falls.

MAKING INSIGHTS

Hyperekplexia was first recognised in 1962, when it was described in a paper entitled 'An unidentified hereditary disease' in *The Lancet* by two Dutch researchers, Drs O Kok and G W Bruyn. Although its exact incidence remains unknown today, startle disease is extremely rare and has been estimated to affect approximately 1,000 people worldwide. Disorders that resemble hyperekplexia have also been identified in animals, including mice, dogs, cattle and horses – often at a much higher prevalence than in humans, and with fatal consequences.





With an overarching emphasis on clinical translation, Harvey and his colleagues are committed to converting their scientific discoveries into practical applications that include improved genetic diagnostics, patient care and pharmacological treatments

One prominent researcher whose work has fundamentally advanced understanding of the underlying genetic causes of startle disease is Robert Harvey, Professor of Molecular Neuroscience and Genetics and Associate Director for Research at the School of Pharmacy at University College London (UCL). In recent years, he has conducted numerous game-changing studies that have mined the complex mechanisms that underpin these diseases in both humans and animals. With an overarching emphasis on clinical translation, Harvey and his colleagues are committed to converting their scientific discoveries into practical applications that include improved genetic diagnostics, patient care and pharmacological treatments.

INVESTIGATING GENETICS

The gene mutations that cause startle disease trigger communication and cell signalling defects in the spinal cord and brainstem, in turn causing exaggerated startle reactions, abnormal muscle movements and other characteristic symptoms. A number of different genes are associated with the disease – most of which play a role in producing proteins found in neurons and governing how they respond to the neurotransmitter glycine. The majority of cases are known to be caused by mutations in the gene *GLRA1*, which encodes the glycine receptor α1 subunit. Mutations in *GLRA1* lead to the production of a flawed receptor that is unable to respond properly to glycine. More recently, Harvey and Professor Mark Rees at the University of Swansea, UK, have identified numerous startle disease mutations in *GLRB,* encoding the glycine receptor beta subunit.

However, by drawing on a range of cutting-edge technologies and techniques – including polymerase chain reaction, DNA sequencing, and cellular and computational models of receptor and transporter function and dysfunction – Harvey and Rees highlighted a major role for another gene in startle disease: *SLC6A5*. Their studies have provided conclusive evidence that missense, nonsense and frameshift mutations in *SLC6A5* – the gene responsible for encoding the presynaptic glycine transporter known as GlyT2 – result in symptoms such as hypertonia, a pronounced startle response to tactile or acoustic stimuli and life-threatening apnoea episodes in early infancy. In contrast to individuals with hyperekplexia caused by *GLRA1* mutations, individuals with *SLC6A5* mutations show high rates of neonatal apnoea episodes, developmental delay and difficulties with speech acquisition, demonstrating that there is variation between the symptoms depending on the affected gene.

Importantly, this innovative research not only proves that *SLC6A5* is a key gene involved in startle disease, but also uncovers the first human neurological disorder connected to alterations in a Na^+/Cl^--dependent transporter for a classical fast neurotransmitter. The implications of these findings are significant, as they imply that in other human diseases linked to defects in postsynaptic receptors, similar symptoms could be induced as a result of defects in the cognate presynaptic neurotransmitter transporter. Additionally, the results highlight the necessity of including both presynaptic and postsynaptic causes of startle disease in genetic screening tests for the disease. Improved genetic diagnoses mean that babies with the disease can be monitored and properly treated, thus dramatically improving quality of life.

DRIVING CLINICAL BENEFITS

Ultimately, by unveiling their crucial roles in health and disease, Harvey's research has transformed understanding of the postsynaptic inhibitory glycine receptors and the cognate presynaptic glycine transporter. Indeed, his findings have linked both dysfunctional inhibitory transmission of glycine and defects in receptor-associated clustering molecules associated to a range of serious disorders such as autism, anxiety, epilepsy, inflammatory pain, intellectual disability and rhythmic breathing. Going forwards, these receptors and transmitters could prove to be excellent therapeutic targets for those disorders.

Recent studies conducted by Harvey and his colleagues have highlighted that genetic defects in genes for NMDA receptor subunits – namely, GluN2A and GluN2B – cause various forms of childhood epilepsy, intellectual disability, autism and schizophrenia. The initial results imply that many of the genetic changes identified in these children lead to the over-excitation of neurons via gain-of-function mutations

FOCUS ON FUNDING

Harvey has had enormous success in securing funding for his research. In 2012, for instance, he received two prestigious awards totalling £500,000. More recently his team has obtained a grant worth £794,896 from the Medical Research Council to investigate the role of excitatory NMDA receptors in neurological disease.

At a time when competition for research funding is increasingly fraught and intense, he shares some guidance for achieving success in this area: "My advice to junior investigators is to take plenty of time and write a well-structured, compelling application that addresses a fundamental set of questions," he states. "Having your grant application read and critiqued by experienced scientists is essential – and studying examples of previously successful funding applications can also be very informative."

in NMDA receptor genes. As a result, the researchers are currently planning to explore the potential of glycine transporters as therapeutic targets. Indeed, inhibiting the glycine transporter GlyT1 increases the activity of excitatory NMDA-type glutamate receptors, which play a key role in learning and memory processes. "Inhibiting GlyT1 could be a potential remedy against the cognitive and affective deficiencies we observe in schizophrenic patients," Harvey elucidates. "Additionally, because GlyT1 can suppress alcohol intake in rodents, it may also be of use in the treatment of alcohol dependency in humans."

Looking to the future, Harvey hopes his research at UCL will continue to bring tangible clinical benefits to the lives of those who are affected by startle disease and related diseases, such as childhood epilepsies. However, therapeutic advances are dependent on increasing knowledge about the complex molecular and physiological effects of glycine reuptake inhibition. In view of this, Harvey and his team are aiming to continue forging innovative insights into new possibilities for the control of glycinergic transmission in an attempt to realise the full potential of glycine receptors and transporters as therapeutic targets.

REAL-WORLD IMPACT

Harvey is passionate about conducting basic research with real-world impact. For instance, the discovery that mutations in the GlyT2 gene can lead to startle disease associated with breathing difficulties has meant that parents of affected infants can be provided with specialist heart rate and breathing monitors and given training in life-saving resuscitation techniques.

Dedicated to maximising the impact of his research, Harvey is also devoted to engaging with the public and delivering both national and international lectures about his illuminating discoveries. He has had many speaking engagements in Europe, North America and Australia.

PROMOTING ANIMAL WELFARE

Harvey and his colleagues have devoted several studies to examining the causes of genetic defects of startle disease in dogs and cattle. Their findings have had important implications for promoting animal welfare and increasing economic return for farmers. For example:

- The use of artificial insemination through elite sires in cattle breeding has increased the frequency of recessive genetic disorders in livestock. In response, Harvey and his collaborators have demonstrated that the use of genome-wide, high-density single nucleotide polymorphism panels, together with the typical structure of livestock populations, increases the positional identification of defect-causing genes and mutations. This enables at-risk mating to be avoided as a result of marker-assisted selection against the defects and as such has had a positive impact on breeding practices
- Tests conducted on Belgian Blue calves on a UK farm, along with a sample of Belgian Blue sires, led Harvey and his team to develop a series of cost-effective tests for the congenital muscular dystonia type 2 allele. These tests can be used to confirm a diagnosis, identify carriers and inform breeding strategy in the future
- Further studies have found that startle disease in Irish Wolfhounds is linked to a microdeletion in the *SLC6A5* gene – and have also pinpointed a total of 13 carriers of this deletion in related animals. Harvey and his collaborators aim to use these results to guide future breeding strategies and lead to the development of viable therapeutics

STARTLE DISEASE AND THE ROLE OF GLYCINE

OBJECTIVES

- To gain a deeper understanding of the genetic mutations responsible for startle disease, a rare neurological disorder
- To explore glycine receptors and transporters as therapeutic targets for epilepsy, inflammatory pain and other disorders

KEY COLLABORATORS

Dr Julia Dallman, University of Miami, USA

Dr Hiromi Hirata, Center for Frontier Research, National Institute of Genetics, Japan

Professor Joe Lynch, Queensland Brain Institute, Australia

Professor Mark Rees, Institute of Life Science, Swansea University, UK

Dr Maya Topf, Birkbeck, University of London, UK

Professor Diane Shelton, University of California, San Diego, USA

Professor Trevor Smart, University College London (UCL), UK

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ROBERT HARVEY obtained his PhD in Natural Sciences (Biochemistry) from the University of Cambridge, UK, in 1991. Following postdoctoral studies at the Institute for Cell Biology and Clinical Neurobiology, Hamburg, Germany (1991-96) and the Max-Planck-Institute for Brain Research, Frankfurt, Germany (1996-98), he moved to the UCL's School of Pharmacy as Lecturer in 1998. He is now Professor of Molecular Neuroscience and Genetics and Associate Director for Research. His main area of interest is neurotransmission mediated by glycine, GABA and glutamate. His research also has a strong translational aspect – he aims to convert basic science discoveries into clinical applications, such as improved genetic diagnostics, patient care and pharmacological treatments.