Hope for dopamine disorders

Expert neuroscientist and research group leader **Professor Stephanie Cragg** discusses her work on the relationship between neurons, neurotransmitters and Parkinson's disease pathology

Can you describe the work that you are involved with to investigate Parkinson's disease?

My lab uses a powerful electrochemical technology that allows us to study dopamine signals in real time. We have defined fundamental and dynamic mechanisms that determine how dopamine transmission is governed moment-to-moment, and how it reaches its target receptors. We have found that specific receptors and proteins regulate the dopamine circuits selectively involved in Parkinson's disease, and that different receptors operate in the separate dopamine circuits at different stages of drug addiction. The more we can understand these mechanisms, the more we will be able to elucidate potential intervention points that might be targets for improved and specific therapies in dopaminergic disorders.

What are the main characteristics of a Parkinson's disease patient's brain, and how can these characteristics be exploited for therapeutic purposes?

Parkinson's disease pathology is complex, with many brain cells and circuits affected, but the efficacy of the dopamine precursor drug L-DOPA in movement problems is testament to the key role played by the degeneration of dopamine neurons. However, L-DOPA has problems in the long term so alternative therapies are required.

There are several strategies for identifying new therapies. One set of approaches we have been using in our work, including research at the Oxford Parkinson's Disease Centre, UK, involves identifying the earliest neurobiological changes prior to the clinical presentation of the disease, to inform therapies that could halt or offset these disturbances. Not only have we identified that changes to dopamine synapse function are among the earliest neurobiological changes in models of the disease, but also that some other brain circuits might have unexploited potential to offset dopamine disturbances.

How have your links with Parkinson's UK helped the progression of your work?

We have been very fortunate to have received interest and support for some of our work from Parkinson's UK by way of grants and studentships; and through the wider auspices of the Oxford Parkinson's Disease Centre, which was founded in 2010 by Parkinson's UK and the Monument Trust. We host regular lab visits for people affected by Parkinson's disease, which always lead to stimulating interactions. Our links with Parkinson's UK have played a critical role in developing our understanding of the key mechanisms that govern dopamine both in health and in the disease.

Have you faced any difficulties working with nicotine, a substance that is generally only considered for its negative health effects?

No, the importance of understanding the neural effects of drugs such as nicotine seems to be increasingly appreciated. Many of the negative respiratory and cardiovascular effects are due to the smoking of nicotine, rather than its intake itself. Funding bodies are increasingly recognising that there is a growing need to address the causes and treatment of drug addiction, which is a growing problem worldwide, and has now been acknowledged as a disease. The potential of harnessing drug effects to treat dopamine disorders such as Parkinson's disease receives a lot of interest and support from both scientific and non-scientific communities.

In that case, what barriers need to be overcome for a nicotine-related drug to be developed by a drug company for clinical use?

The design of conventional drugs that are specific for particular nicotinic receptor subtypes is difficult. There might be adaptive changes to the types of nicotinic receptors that operate, as probably happens after chronic nicotine exposure, and we also need to understand whether more or less nicotinic receptor activation is helpful for different dopamine disorders.

You have collaborated with researchers from the Institut Pasteur in Paris, France; how has this benefited your work?

We have had productive interactions with colleagues in Paris such as Professors Uwe Maskos and Philippe Faure, who are interested in the mechanisms underpinning nicotine addiction. These colleagues have developed genetically modified mice that enable us to identify the specific nicotinic receptors responsible for gating dopamine release from different neurons associated with Parkinson's disease or nicotine addiction. Together, we have published several high profile research papers on these topics.

Curing neurons

Neuroscientists at the **University of Oxford** are investigating the pathways that lead to dopamine transmission in the brain; their observations challenge long-held beliefs surrounding neural function in this area and could have implications for the treatment of Parkinson's disease and addiction

DOPAMINE IS ONE of the best-known neurotransmitters, and with good reason. This biomolecule is not only central to a number of signalling systems in the brain, including some that account partly for the human ability to learn and perform basic motor functions, but also acts as a chemical signal outside the brain in the blood vessels, kidneys, pancreas and immune system. Most famously, however, dopamine is associated with reward-motivated behaviour; under normal conditions, beneficial actions trigger dopamine release and feelings of pleasure and satisfaction. It is for this reason that many addictive drugs interact with dopamine.

Given this broad range of functions, it is hardly surprising that many health problems are associated with dopamine dysfunction. Schizophrenia, attention deficit hyperactivity disorder (ADHD) and depression have all been linked with dopamine function – but perhaps one of the most notable entries on the list is Parkinson's disease. In the course of this progressive neurological condition, which affects around 127,000 people in the UK alone, the brain's neurons begin to die off, leaving a deficit of dopamine that starts to impact motor function. Although Parkinson's disease is generally a condition of older patients, 5 per cent of sufferers are under the age of 40.

AN UNLIKELY THERAPY

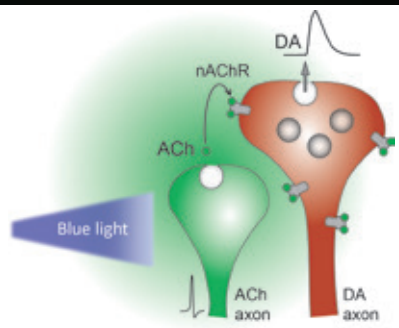
Nicotine is one of the addictive drugs that stimulates dopamine release. This substance activates receptors on dopamine neurons because it is a functional analogue of acetylcholine, another neurotransmitter of the central and peripheral nervous systems. Imbibing nicotine effectively cheats the body's reward system – but the aberrant dopamine signalling that it produces, while enjoyable for the subject, triggers the pathological cascade of addiction.

Interestingly, however, this process may not be all bad. Epidemiological studies have suggested that, while they do put themselves at a significant health risk, smokers are less likely to suffer from Parkinson's disease.

The functions of dopamine and their disruption by disease, as well as the exact mechanism by which drugs such as nicotine boost dopamine, are all subjects that will require further investigation if science is to resolve this intriguing but fragmented picture. The Cragg Group at the University of Oxford's Department of Physiology, Anatomy and Genetics in the UK is interested in exactly these topics, and its investigations under the leadership of Professor Stephanie Cragg have already shed significant light on the area. In particular, their studies support the controversial theory that in the context of Parkinson's disease, nicotine may be an unlikely but useful therapeutic agent.

ASKING ABOUT AXONS

A fundamental and intriguing focus of this team's work has been answering the question



Brief light flashes to optogenetically engineered acetylcholine neurons in the brain drives acetylcholine release which, by acting at nicotine receptors on dopamine axons, directly and powerfully triggers dopamine release in striatum.

> Nicotine acts in a very powerful way on the dopamine axons, which in fact outperform the dendrites and cell body as centres of nicotine-controlled dopamine modulation

ALPHA MICE

Understanding the function of nicotinic receptors in the process of dopamine signal modulation is central to Professor Stephanie Cragg's work, and one of the vital tools that has allowed her group to progress in this area has been the α5 knockout mouse line.

The α5 subunit is one of the components from which nicotinic receptor proteins are constructed. It is particularly interesting because, although nicotinic receptors can be generated with various combinations of subunits, α5 is one key subunit associated with smoking addiction, and its expression is confined to only a few sets of neurons. Currently, there are no drugs that work by targeting these subunits.

Luckily, the Cragg Group had the opportunity to collaborate with colleagues at the Institut Pasteur in Paris, France, who had the necessary expertise to develop this line of rodent models. "Mouse brains are useful because they conserve the key neural systems found in the human brain that regulate our movements," Cragg explains.

Using these custom-made mice, the Oxford scientists determined that α5 positive receptors play an important role in controlling dopamine transmission from the neurons affected by Parkinson's disease, which are also the nerve cells that are most important to habit-forming behaviour. These receptors may therefore be particularly relevant to Parkinson's disease and addiction.

of what exactly nicotine does to dopamine neurons to boost dopamine signalling. Dopamine neurons are apparently distinct from other neurons, both in their structure and their function; their axons, in particular, are unique in that they are extensively branched. In the rat brain, for example, a single dopamine neuron can have half a metre of axons, accounting for more than 99 per cent of the cell's surface. But it is the opposite end of the neuron – the end bearing the dendrites and the cell body – that usually attracts the attention of those studying the way nicotine and acetylcholine act.

It was already known that the axons of dopamine neurons are also home to nicotinic receptors that can mediate responses to nicotine and acetylcholine, but what was not yet certain before Cragg and her collaborators began their investigations was how these receptors on dopamine axons determine dopamine output. Using rodent models developed specifically for the purpose, the scientists probed dopamine function in real time with microelectrodes in slices of rodent brain. With a wealth of evidence already accumulating to suggest that these axons were more than mere electrical relay cables, the scientists tested the strange hypothesis that they could be active processors of neural activity.

CRUCIAL CONTRAST

The results of their study revealed that nicotine acts in a very powerful way on the dopamine axons, which in fact outperform the dendrites and cell body as centres of nicotine-controlled dopamine modulation. This effect can be dependent on neural activity; essentially, one role of the axon receptors is to heighten contrast, making the dopamine highs higher and the lows lower. Therefore, when dopamine neurons change their firing rate – to convey information about a stimulus or precipitate a movement, for example – the nicotine enhances the outcome. This is also the opposite of conditions the team see in Parkinson's disease. While these results are corroborated by behavioural observations in the field, they have proved something of a surprise to many researchers working in this area.

In order to further investigate this phenomenon, the Oxford team has deployed a new tool known as optogenetics, which activates acetylcholine circuits by exposing them to flashes of light. Using this system, the scientists observed that stimulation of the axonal nicotinic receptors was also a direct driver of dopamine release that could dominate other agents. They found that, further to the complex and powerful effects already observed, the axonal receptors could even override the transmissions initiated in the dendrites and cell body. These conclusions have great implications for the current understanding of neural dopamine signalling, overturning the assumption that dopamine and acetylcholine are antagonistic within the striatum.

A NEW MODEL

These effects are promising in the context of novel therapies, and the Cragg Group is already investigating ways of making such therapies a reality. In a new optogenetic mouse model of Parkinson's disease developed in the Oxford Parkinson's Disease Centre, the researchers are attempting to identify whether nicotinic receptors can be exploited to dispel the symptoms of disease. Furthermore, new approaches for stimulating acetylcholine release are also under investigation, and Cragg is enthusiastic about the future of this work: "We have many exciting projects underway and new avenues to explore," she enthuses.

INTELLIGENCE

NICOTINE ADDICTION: A TALE OF TWO TRANSMITTERS

OBJECTIVES

To understand monoamine transmission in the brain, its function, and dysfunction in drug addiction and Parkinson's disease.

KEY COLLABORATORS

Professor Richard Wade-Martins, Oxford Parkinson's Disease Centre, University of Oxford, UK

Professor Uwe Maskos; **Professor Philippe Faure**, Institut Pasteur, Paris, France

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STEPHANIE CRAGG obtained a BA in Natural Sciences at the University of Cambridge, before completing a DPhil in Pharmacology studying neuronal dendrite function at the University of Oxford and New York University (NYU), USA, as a Mary Goodger scholar. She subsequently undertook junior research fellowships and a Beit Memorial Fellowship in Oxford, and then further research at NYU and the University of North Carolina, USA. During this period she helped develop her group's expertise in real-time electrochemical detection and established their programme of study into how monoamine transmission is governed in the brain. Cragg is currently Professor of Neuroscience in the Department of Physiology, Anatomy and Genetics at the University of Oxford and a fellow at Christ Church college. She heads the Brain Monoamine Transmission Laboratory and works as an investigator for the Oxford Parkinson's Disease Centre.