Exploring PROPOSALS FOR RESEARCH COLLABORATION
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Behavioural therapies for protecting dopamine neurons in a lesion model of Parkinson’s disease
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Abstract

Previous studies have shown that forced use of a limb or running on a treadmill can protect dopamine neurons in animal models of Parkinson’s disease (PD). A variety of behavioural situations designed to encourage physical activity were used in the present research to investigate whether more ‘natural’ increases in behaviour might also spare dopamine in the 6-hydroxydopamine (6OHDA) rat model of PD.

In one study rats performed a task in which they retrieved food pieces placed on one side of the body so as to activate that side affected by the neurotoxin. They did this every day for 10 days starting the day after the 6OHDA lesion. When tested several weeks later, movement was less impaired in rats which had been actively performing the task compared with controls which had not. Analysis of the brains revealed spared dopamine levels in the striatum and neurons in the substantia nigra of the active rats, supporting the idea that physical activity protects dopamine neurons.

In order to stay active, people with PD are often treated with the drug L-dopa. Therefore, it is important to know whether this treatment also affects the survival of dopamine neurons. Rats were treated with L-dopa or with other drugs that either increased (amphetamine) or decreased (alpha-methyl-p-tyrosine) activity during the 10 days immediately following a 6OHDA lesion. Behavioural impairments due to the 6OHDA lesion were reduced in L-dopa treated animals on tests conducted several weeks after the drug treatments, whereas the other two drugs were without effect. However, the improvements in the L-dopa treated group were subtle and not accompanied by improved survival of dopamine neurons. Nevertheless, the results are encouraging that L-dopa treatment does not exacerbate the effect of the lesion.

Environmental enrichment cages were used in a further study to stimulate activity levels. Rats are naturally more active in these large cages which include ladders and running wheels. However, the activity generated by housing in these cages was not sufficient to protect against the damage caused by a 6OHDA lesion. In this and other studies dopamine loss was extensive; it appears that physical activity does not provide protection against large dopamine lesions.

The conclusion from these experiments is that physical activity can protect dopamine neurons, but protection is not guaranteed and may not be sufficient to counter extensive dopamine loss. Further experiments are needed to test this specific prediction that the initial extent of the damage will determine the success of physical therapies as a neuroprotective treatment strategy for PD.
Profile

Lucy Annett is Senior Lecturer in Biological Psychology in the School of Psychology at the University of Hertfordshire. Following her first degree in Psychology and Physiology (PPP) at St. Hilda’s College, University of Oxford, Lucy completed a PhD at the University of London, supervised by Dr. Ros Ridley based at the MRC Clinical Research centre, Harrow, on the role of dopamine in the nucleus accumbens of marmosets. She then worked with Professor Trevor Robbins in the Department of Experimental Psychology, University of Cambridge, on the effects of excitotoxic lesions of the nucleus accumbens in rats. The main focus of her research since then has used animal models to assess novel treatments for Parkinson’s disease (PD). With Professor Stephen Dunnett, then at the Department of Experimental Psychology, University of Cambridge, she investigated the potential of neural transplants to reverse the symptoms of dopamine loss in marmosets with 6-hydroxydopamine lesions. The marmoset model of PD was also used to assess alternatives to neural transplants, including lesions of the subthalamic nucleus and viral vector transfer into the brain of genes that produce dopamine or protect dopamine neurons. In collaboration with Dr. Deniz Kirik and Professor Anders Björklund, viral vector transfer was used to create a new primate model of PD by over-expression of the alpha-synuclein gene. While at the University of Hertfordshire, Lucy has set up a research programme using rat models to investigate potential behavioural therapies for PD and has received support from the Parkinson’s Disease Society, UK for this work. Initial findings suggest that although physical activity can protect dopamine neurons, this is not guaranteed and may not be sufficient to overcome the loss of large numbers of neurons in the more advanced stages of PD.

References


http://www.psy.herts.ac.uk/res/an-models.html

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