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Promising new drug targets identified for Huntington's disease

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Research funded by the Wellcome Trust has provided a number of promising new drug targets for Huntington's disease, a neurodegenerative disease. Scientists at the University of Cambridge have identified a number of candidate drugs to investigate further which encourage cells to "eat" the malformed proteins that lead to the disease.

Huntington's disease is one of a number of degenerative diseases marked by build up of a malformed proteins in brain cells, mainly in the basal ganglia and the cerebral cortex. Normally, cells dispose of or recycle their waste material, including unwanted or misfolded proteins, through a process known as autophagy, or 'self-eating'.

The group of Professor David Rubinsztein, a Wellcome Trust Senior Clinical Fellow at the University of Cambridge, has previously shown that stimulating autophagy in the cells can be an effective way of preventing the malformed proteins from building up. However, there are currently no treatments available that slow the neurodegeneration in people with Huntington's disease. Rapamycin, an immunosuppressant used to lower the body's natural immunity in patients who receive kidney transplants, is the most promising candidate drug currently available but can have significant side effects.

Now, in research published today online in the journal *Nature Chemical Biology*, Professor Rubinsztein and colleagues have shown that a number of FDA-approved drugs for treatments such as migraine and hypertension are able to stimulate autophagy in fruit flies and zebrafish

through unexpected pathways.

"By screening a number of drugs that have already been shown to be safe in humans, we have been able to identify some unexpected and very promising pathways involved in Huntington's," says Professor Rubinsztein. "In collaboration with Cahir O'Kane's group in Cambridge and Summit Plc, we have shown that these drugs can alleviate the toxicity of the Huntington's disease mutation in cell-based, fly and zebrafish models. The big question for us is whether they will do the same in humans."

One of the drugs tested, verapamil, which is currently used to treat high blood pressure and heart arrhythmias (among other indications), inhibits the influx of calcium into cells which, in turn, appears to regulate autophagy. Similarly, clonidine, currently used to treat hypertension or migraine, appears to work on autophagy by decreasing levels of cAMP, a molecule that is important in many biological processes.

If the drugs can stimulate autophagy effectively over long-term periods in human brains, then they may have the potential to help delay the onset of Huntington's disease. The candidate drugs are relatively safe and well tolerated when used to treat the diseases they were designed for. A minimal side-effect profile would be highly desirable for a drug treatment aiming to delay the onset or slow the progress of Huntington's. Such drugs may need to be taken for decades, and even moderate side effects may discourage people from taking them over a long period.

"We know the genetics of Huntington's disease and can predict the majority of people at risk," says Professor Rubinsztein. "If we can find a safe, well tolerated drug, then a person at risk could be placed on a drug regime to help prevent onset. It is much easier to stop something happening than having to treat it once it has started."

Professor Rubinsztein and colleagues will shortly begin testing the drugs in other animal models to evaluate their safety and efficacy.

Source: Wellcome Trust