Medical Xpress

New knowledge on the pharmacology of dopamine stabilizers

February 24 2012

A study from Karolinska Institutet in Sweden shows that a new drug for Huntington's disease – pridopidine or dopamine stabiliser ACR16 – might operate via previously unknown mechanisms of action. Researchers have found that at very low concentrations, ACR16 binds to the sigma-1 receptor, a protein in the brain important to neuronal function and survival. This new knowledge can be used to develop future treatments for schizophrenia, involuntary Parkinsonian tremors and neurodegenerative diseases.

"It's conceivable that some of the beneficial effects of dopamine stabilisers are mediated via the sigma-1 receptor," says principal investigator Daniel Marcellino of the Department of Neuroscience. "Our results suggest a formerly overlooked aspect of dopamine stabiliser pharmacology."

Dopamine stabilisers are a new class of drug substance originally developed by Swedish Nobel laureate Professor Arvid Carlsson. In clinical trials, these substances have revealed promising results against neurological and neuropsychiatric conditions that currently lack suitable treatment, such as schizophrenia and the dyskinesia (involuntary tremors) caused as an adverse effect of Parkinson's drugs.

Pridopidine or dopamine stabiliser ACR16 (also known as Huntexil), is in an advanced phase of clinical trials (phase III) for the relief of the motor symptoms of Huntington's disease, an incurable disease caused by neuronal degeneration in certain parts of the brain. The disease, which is

hereditary, is characterised by motor and subsequent psychiatric disorders, leading to a protracted death. There is currently only one drug registered for the relief of Huntington's symptoms, but as it has several adverse effects there is a strong demand for alternative treatment options.

Dopamine stabilisers are thought to exert their beneficial effects primarily via the dopamine D2 receptor, which is a well-known site of action for drugs for Parkinson's disease and schizophrenia. However, in a study published recently in the scientific journal *Molecular Psychiatry*, researchers at Karolinska Institutet have shown that ACR16 and another dopamine stabiliser (-)-OSU6162 also bind to the sigma-1 receptor in low concentrations.

"We found that ACR16 binds to the sigma-1 receptor at concentrations 100 times lower than those reported for interaction with the D2 receptor," says Dr Marcellino. "This is extremely interesting since experimental studies have shown that sigma-1 receptor ligands have positive effects in schizophrenia and protect against cell death in neurodegenerative conditions."

More information: "The dopamine stabilizers ACR16 and (−)-OSU6162 display nanomolar affinities at the σ-1 receptor" K Sahlholm, P Århem, K Fuxe & D Marcellino,, *Molecular Psychiatry* advance online publication 21 February 2012; doi: 10.1038/mp.2012.3

Provided by Karolinska Institutet