Study reveals a new target for developing treatments for depression

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A new CAMH study shows for the first time that people experiencing clinical depression have higher levels of a brain protein called MAO-B. The finding—published online today in *JAMA Psychiatry* - opens the

door to a new area of exploration for developing depression treatments. Depression affects an estimated 15 per cent of people over their lifetime, and is the leading cause of disability worldwide.

"Half of the people with depression had higher MAO-B levels than those without the illness," says Dr. Jeffrey Meyer, Canada Research Chair and Scientist in CAMH's Campbell Family Mental Health Research Institute. "The most commonly prescribed antidepressants aren't designed to act on this brain protein, making this a new focus for developing treatments different from the usual medications." Most antidepressants work on the brain chemical serotonin.

MAO-B plays roles in keeping the brain healthy, including getting rid of an excess of the brain chemicals dopamine and norepinephrine, and creating signals promoting the turnover and death of old cells. "The brain needs these functions," says Dr. Meyer, senior author of the study. "But when MAO-B levels are elevated, we see this as an imbalance that may lead to depression." For example, higher levels of MAO-B may deplete dopamine and norepinephrine, which are involved in brain pathways that are essential for maintaining a healthy mood and experiencing enjoyment. At the same time, higher levels of MAO-B, through a process called oxidative stress, may affect memory and concentration.

In the past, MAO-B was thought to be unimportant in depression, so the only antidepressant medications that target it have extremely difficult side-effects or tend to be very expensive. For example, in the case of a medication called EMSAM, available in the U.S. only, costs may be up to a couple thousand dollars monthly. For these reasons, less than 1% of people with depression take an antidepressant medication that affects MAO-B.

This new CAMH study is the first that looks at MAO-B in the prefrontal cortex, the large brain area involved in our most complex thinking

behaviours, such as planning and decision-making. A unique chemical brain imaging agent enabled the researchers to observe MAO-B in this brain region using a type of brain imaging called positron emission tomography. Essential development of this brain imaging agent took place over several years at CAMH to make this study possible.

The study was conducted in 40 adults, half with depression and half with no depression. Post-doctoral Research Fellow Sho Moriguchi was first author of the study.

On average, MAO-B was 26% higher in the prefrontal cortex among people with depression when compared with people without the illness.

The researchers also showed that a longer duration of depression was strongly associated with higher levels of MAO-B in the prefrontal cortex, as well as in other brain regions.

A future research direction will be to develop other low-cost biological predictors, such as blood or genetic tests, which could be used to identify which individuals with depression have elevated levels of MAO-B and would benefit from specialized treatment.

To date, MAO-B levels have not been well addressed by current antidepressant medications but Dr. Meyer believes this is solvable. "A promising opportunity is that there are existing medications, developed for Alzheimer's disease and Parkinson's disease, that reduce MAO-B levels, are well tolerated and could be used safely with other antidepressants," says Dr. Meyer. "Studying these medications in people with depression may uncover new treatments for people who don't respond to our commonly used antidepressants."

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