Protein is potential target for memory drugs

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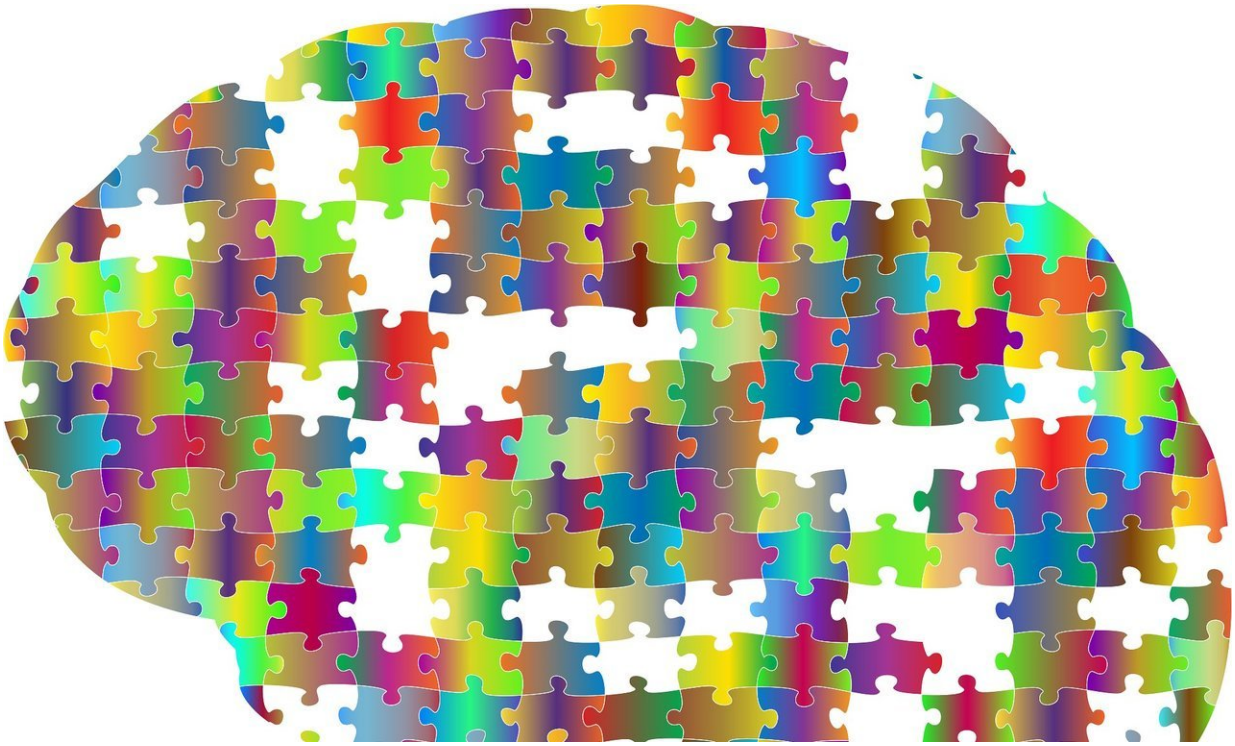

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Researchers at the University of Toronto Mississauga (UTM) have determined that the presence of a particular protein in the brain may suppress the brain's ability to learn, making it a potential precursor to memory loss in later life.

In a paper published in the current issue of *Cell Reports*, Iva Zovkic, an

assistant professor of psychology at UTM, and colleagues in Britain, Maine, Tennessee and Alabama, focused their attention on the H2A.Z protein, which Zovkic first linked to memory formation during her postdoctoral fellowship at the University of Alabama at Birmingham. Although their research focused on mice, this protein is present in the human brain and may be associated with some similar outcomes.

"Identifying H2A.Z as a unique protein that is involved with memory and increases with aging could be a big deal for creating genetic or pharmaceutical therapies for age-related cognitive decline and dementia," says Zovkic. "H2A.Z is a relatively specific therapeutic target."

Using young adult and late middle-aged mice, the researchers determined the role of H2A.Z in memory formation. To induce memory, each group of mice was placed in a new box; they eagerly ran around and explored this new environment. The mice were then exposed to a negative stimulus. The next time mice were placed in this box, they simply froze in place—they had learned to associate the box with the negative experience.

To understand how the experience produced long-term memory, the researchers examined the mice brains half an hour after their exposure, measuring changes in H2A.Z protein binding to DNA. They found that H2A.Z protein binding was reduced on approximately 3,000 genes, allowing the activation of many genes related to memory. In other words, reducing the H2A.Z protein during learning was linked to the mice's ability to remember what had happened to them the first time they entered the box.

"We have thousands of experiences each day, but we only remember things that are in some way important to us," says Zovkic. "This experiment used a very straightforward learning experience to illustrate

that H2A.Z apparently serves to suppress memory, and the removal of this protein appears to...allow long-lasting memories to form."

In addition, the researchers found that H2A.Z levels in the hippocampus—often called the brain's "memory centre"—increase as mice reach late-middle age. Given that high levels of H2A.Z appear to inhibit memory, and that H2A.Z is one of only a handful of proteins that can be produced in neurons, this increased concentration may be a harbinger of future memory loss. The authors plan to test the hypothesis that very old mice, who tend to show age-related memory decline, will have even higher levels of H2A.Z. Similar studies are planned for Alzheimer's disease.

"We're always trying to find molecular bases for memory, and discovering how genes related to memory are turned on and off is a step in a positive direction," says Zovkic.

More information: Learning and Age-Related Changes in Genome-wide H2A.Z Binding in the Mouse Hippocampus. *Cell Reports*. DOI: doi.org/10.1016/j.celrep.2018.01.020 |

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