Vascular drug found to improve learning and memory in middle-aged rats

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A team of Arizona psychologists, geneticists and neuroscientists has reported that a safe and effective drug used to treat vascular problems in the brain has improved spatial learning and working memory in middle-aged rats. Although far from proving anything about human use of the drug, the finding supports the scientific quest for a substance that could treat progressive cognitive impairment, cushion the cognitive impact of normal aging, or even enhance learning and memory throughout the life span.

The finding appears in the February issue of *Behavioral Neuroscience*, which is published by the American Psychological Association. The drug in question, Fasudil, has been used for more than 10 years to treat vascular problems in the brain, often helping with recovery from stroke.

In this study, the researchers injected hydroxyfasudil, the active form of Fasudil, into middle-aged (17-18 months old) male rats daily starting four days before behavioral testing and continuing throughout testing. Injection made it easy to give the drug to rats, but people take it in pill form.

Rats were tested on the water radial-arm maze, which assessed how well they remembered which of the radiating arms had a reward, a sign of accurate spatial learning and working memory. Rats given a high dose (0.3750 mg per kg of weight) of hydroxyfasudil successfully remembered more items of information than those given a low dose (0.1875 mg per kg). Both dosed groups performed significantly better

than control-group rats given saline solution. On this same test, the high-dose group showed the best learning (fewest total errors) and best working memory (measured two different ways).

For every test of learning, the scores of the low-dose group fell between the scores of the no-dose and high-dose groups, meaning that learning and memory boosts depended on the size of the dose.

The findings suggest that hydroxyfasudil may be involved in two crucial cognitive processes, learning and working memory, both involving the hippocampus. The mechanism is unclear, but hydroxyfasudil's parent drug, Fasudil, is known to protect the brain by dilating blood vessels when blood flow is curtailed. In the body, Fasudil breaks down into the more potent hydroxyfasudil molecule, which the authors hypothesize may alter memory by affecting the function of a gene called KIBRA. The authors recently demonstrated that KIBRA may play a role in memory in healthy young and late-middle-aged humans.

The authors wrote that their findings may have clinical relevance: "The collected findings and the relative safety of Fasudil support [its] potential ... as a cognitive enhancer in humans [who] have age- or neurodegenerative-related memory dysfunction."

Thus, said lead author Matthew Huentelman, PhD, "We have identified a drug that seems to benefit both the cardiovascular system, which it was originally designed to do, and the central nervous system, a new indication. We are actively exploring options for a clinical trial in the areas of cognitive impairment and dementia using the well-tolerated pro-drug Fasudil."

Co-author Heather Bimonte-Nelson, PhD, added that, "Fasudil shows great promise as a cognitive enhancer during aging. The effects in our aging animal model were robust, showing enhancements in both learning

and two measures of memory. The possibility that these findings may translate to benefits to human brain health and function is very exciting."

Hydroxyfasudil inhibits the activity of Rho-kinase enzymes, which have been shown to inhibit Rac, a vital protein that supports key cellular functions. The authors speculated that blocking Rho-kinase enables Rac, in turn, to activate more of an enzyme called protein kinase C-zeta, which may in turn affect the KIBRA protein.

Article: "Peripheral Delivery of a ROCK Inhibitor Improves Learning and Working Memory," Matthew J. Huentelman, et al., *Behavioral Neuroscience*, Vol. 123, No. 1.

Source: American Psychological Association