Resveratrol appears to restore blood-brain barrier integrity in Alzheimer's disease

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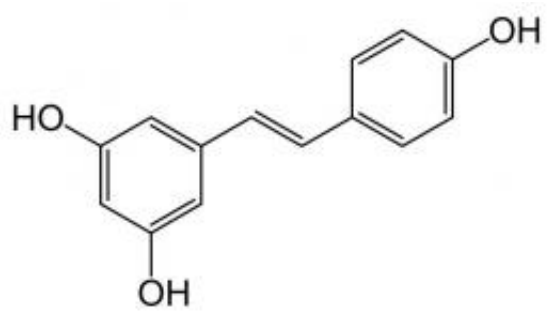

Skeletal formula of trans-resveratrol. Image: Wikipedia

Resveratrol, given to Alzheimer's patients, appears to restore the integrity of the blood-brain barrier, reducing the ability of harmful immune molecules secreted by immune cells to infiltrate from the body into brain tissues, say researchers at Georgetown University Medical Center. The reduction in neuronal inflammation slowed the cognitive decline of patients, compared to a matching group of placebo-treated patients with the disorder.

The laboratory data provide a more complete picture of results from a clinical trial studying resveratrol in Alzheimer's disease that was first reported in 2015. The new findings will be presented at the Alzheimer's Association International Conference 2016 in Toronto on July 27th.

The Alzheimer's disease brain is damaged by inflammation, thought to

be due to a reaction to the buildup of abnormal proteins, including Abeta40 and Abeta42, linked to destruction of neurons. Researchers believe that heightened inflammation—which was historically thought to come only from "resident" brain immune cells—worsens the disease. According to the researchers, this study suggests that some of the immune molecules that can cause inflammation in the blood can enter the brain through a leaky blood-brain barrier.

"These findings suggest that resveratrol imposes a kind of crowd control at the border of the brain. The agent seems to shut out unwanted immune molecules that can exacerbate brain inflammation and kill neurons," says neurologist Charbel Moussa, MD, PhD, scientific and clinical research director of the GUMC Translational Neurotherapeutics Program. "These are very exciting findings because it shows that resveratrol engages the brain in a measurable way, and that the immune response to Alzheimer's disease comes, in part, from outside the brain."

Resveratrol is a naturally occurring compound found in foods such as red grapes, red wine, raspberries and dark chocolate. GUMC researchers, led by R. Scott Turner, MD, PhD, tested the substance in 119 patients, the largest nationwide phase II clinical trial to study high-dose pure synthetic (pharmaceutical-grade) resveratrol in individuals with mild to moderate Alzheimer's. The study was published Sept. 11, 2015 in *Neurology*.

The new part of the resveratrol study examines specific molecules in the cerebrospinal fluid (CSF) taken from participants with biomarker-confirmed Alzheimer's disease—19 were given a placebo, and 19 treated daily for a year with resveratrol, equivalent to the amount found in about 1,000 bottles of red wine.

Previous studies with animals found that age-related diseases—including Alzheimer's—can be prevented or delayed by long-term caloric restriction (consuming two-thirds the normal caloric intake). The

researchers studied resveratrol because it mimics the effects of caloric restriction by also activating proteins called sirtuins.

In this new study, Moussa and Turner found that treated patients had a 50 percent reduction in matrix metalloproteinase-9 (MMP-9) levels in the cerebrospinal fluid. MMP-9 is decreased when sirtuin1 (SIRT1) is activated. High levels of MMP-9 cause a breakdown in the blood-brain barrier, allowing proteins and molecules from the body to enter the brain. Normally low MMP-9 levels maintain the barrier, say the researchers.

"These new findings are exciting because they increase our understanding of how resveratrol may be clinically beneficial to individuals with Alzheimer's disease. In particular, they point to the important role of inflammation in the disease, and the potent anti-inflammatory effects of resveratrol," says Turner, director of GUMC's Memory Disorders Program and co-director of the Translational Neurotherapeutics Program.

They also found that resveratrol increased the level of molecules linked to a long-term beneficial or "adaptive" immune reaction, suggesting involvement of inflammatory cells that are resident in the brain, says Moussa. "This is the kind of immune response you want—it is there to remove and degrade neurotoxic proteins."

"A puzzling finding from the resveratrol study (as well as immunotherapy strategies for Alzheimer's under investigation) is the greater shrinkage of the brain found with treatment. These new findings support the notion that resveratrol decreases swelling that results from inflammation in Alzheimer's brain," says Turner. "This seemingly paradoxical effect is also found with many of the drugs that are beneficial for patients with multiple sclerosis—another brain disease characterized by excessive inflammation."

Moussa says that resveratrol should be further tested in a phase III study, but the agent, by itself, is unlikely to be a complete treatment for Alzheimer's. It does not inhibit destruction of brain neurons by tau, another protein aggregate involved in the disease, so a likely beneficial treatment would combine resveratrol with an agent that targets tau, he says.

More information: Resveratrol activates CSF Sirtuin1/Matrix Mettaloproteinase-9 and regulates inflammation in Alzheimer's disease, Alzheimer's Association International Conference 2016.

Abstract

Alzheimer's disease (AD) is a neurodegenerative process associated with brain accumulation of amyloid-beta (Aβ) peptides including Aβ40/42 and hyper-phosphorylated Tau (p-Tau) tangles, leading to cognitive impairment. An elevation of Sirtuin 1 (SIRT1) level decreases matrix metalloproteinase-9 (MMP-9) expression and activity, altering macrophage and neutrophils activity. The SIRT1 pathway is also involved in AD and Resveratrol activates several neuroprotective pathways involving Sirtuin. (trials patients treated with 2g of res). We selected AD patients that have less than 600ng/ml CSF Aβ42 (definite AD?) and used Milliplex ELISA to measure changes in CSF biomarkers of the SIRT1/MMP9 pathway. Resveratrol significantly reduces (50%) CSF MMP9 levels and attenuates loss of CSF Aβ40 and Aβ42 in AD patients compared to placebo. There was no change in CSF MMP2 and MMP10 as well as total Tau or p-Tau181. Resveratrol increases the level of macrophage-derived chemokine (MDC/CCl22) that is produced by macrophages and dendritic cells and is upregulated by TH2-type cytokines, such as IL-4, which is also increased. Resveratrol increases monocyte-specific chemokine-3 (MCP-3/CCL7), which regulates macrophage function and interacts with MMPs. These data suggest that Resveratrol activates the SIRT1/MMP9 pathway, leading to regulation of neuro-inflammation. Taken together these data provide evidence that

CSF MMP9 is a target of Resveratrol activity, leading to regulation of neuro-inflammation and reduction of brain Aβ40/42.

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