## Health & Physiology

# Treating Alzheimer's disease with a known anticoagulant: insights from lab mice

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ABSTRACT

*Alzheimer's disease (AD) is a neurodegenerative disorder with vascular alterations such as reduced brain blood flow. Treatment with a direct oral anticoagulant available in the market delays the onset of AD in mice: animals did not show memory loss or decreased cerebral circulation, and they presented reduced brain inflammation, vascular damage, and decreased amyloid deposits, typical signs of AD.*
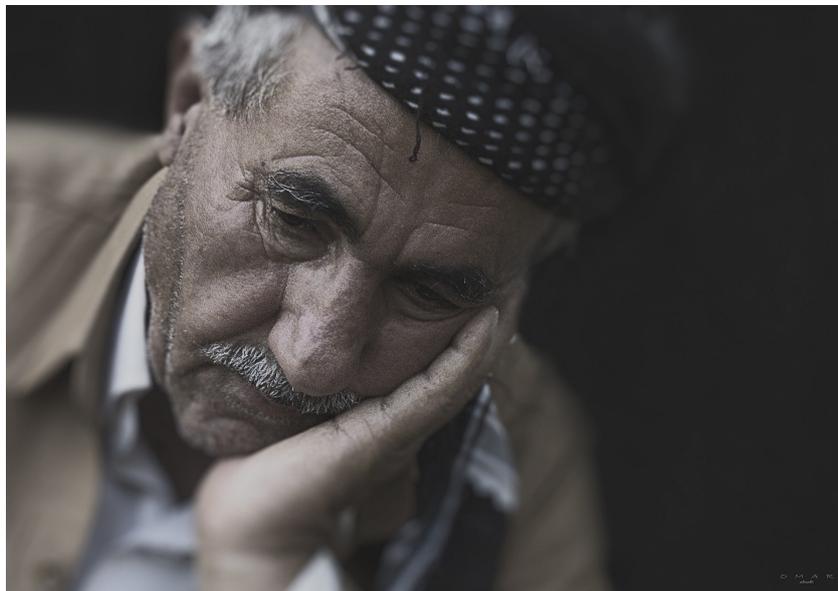
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Alzheimer's disease (AD) is the most common form of dementia and has been long described as a disease of neurons. Although this is true (neurons are indeed sick and eventually die during AD), the events leading to this are numerous, and not all of them have been evaluated with the same devotion. This disorder was discovered more than a century ago when in 1906 the German physician Alois Alzheimer described the neuropathological changes observed in August D., a woman who "had lost herself". After many years of developing memory problems and disorientation, she died in her fifties with plaques, neurofibrillary tangles, and atherosclerotic changes in her brain. The plaques

and tangles have been intensively studied since then, becoming the core of the research in the AD field. However, August D's autopsy revealed that her brain also presented "arteriosclerosis of the small cerebral vessels". Such evidence implies the presence of vascular pathology in this neurodegenerative disease.

We now know that a vascular component is present in an important proportion of the AD patients and contributes to when and how fast the pathology progresses. Indeed, research has linked this disease to a reduction in the cerebral circulation, which results in an insufficient supply of nutrients and

oxygen to brain cells, leading to their death. A few years ago, we discovered an underlying chronic pro-thrombotic state in AD that influences its progression: blood clots form faster and degrade slower. This entails that clots stick around longer than they should be, contributing to a decreased cerebral blood flow and neuroinflammation. Then, if a pro-coagulant state is influencing how AD progresses, why not use an anticoagulant to treat this disorder? In fact, atrial fibrillation patients that undergo long-term anticoagulation present a decreased dementia risk. Also, traditional anticoagulants such as warfarin and heparin have been suggested to be beneficial in AD. However, these anticoagulants have several limitations, such as the administration route and the increased risk of bleeding. That prompt us to investigate whether dabigatran, a direct oral anticoagulant with decreased risk of intracranial bleeding, may be more suitable to normalize the pro-thrombotic state in AD. Therefore, we combine physiological and molecular analyses and demonstrate that long-term anticoagulation with dabigatran effectively slows disease progression in a mouse model of AD. We easily administrated dabigatran to the mice in the food, and we observed that the treatment inhibited the abnormal formation of fibrin clots in the AD brain, hence preserving blood flow. This drug, in turn, also had a beneficial effect on controlling neuroinflammation, maintaining the integrity and functionality of the blood-brain barrier, and reducing amyloid, the main pathological hallmark of AD. More importantly, we measured whether the treatment had an impact on improving cognitive performance in the AD mice. We subjected our treated mice to the Barnes maze, a task that consists of placing the mice under a bright light in a circular table with 20 holes equally distributed in the periphery. Only one of those holes is connected to a dark/"safe" box. Mice are afraid of open spaces, so those with proper memory remember the location of the escape box by using the visual cues placed around the Barnes maze. AD mice did not remember where that box was, while mice treated with dabigatran perfectly located it.

AD is a multifactorial disorder. Efforts should be focused on developing multidrug individualized therapies if we want to win the battle against it.
We should target the various processes contributing to an individual's pathology instead of the "one target, one treatment" approach that has not been successful thus far. Our studies indicate that one of the pathological mechanisms worth targeting in AD is the pro-coagulant state that, in combination with other disease-modifying compounds, might be instrumental in improving disease pathogenesis.

AD patients with a pro-coagulant state need to be identified and treated accordingly. Dabigatran is already on the market approved for indications such as the prevention of stroke in patients with non-valvular atrial fibrillation and the treatment of venous thromboembolism. Importantly, generics will probably be available in the upcoming years. Even though dabigatran is one of the direct oral anticoagulants that presents a low risk of intracranial bleeding, the risk is still present. Dosing will need to be carefully evaluated by a heart-brain team of experts to ensure its use outweighs any bleeding risk. Although further studies are needed to warrant its use in the clinic, this study opens the door to the use of dabigatran as a possible treatment to normalize cerebral circulation in AD patients.