

Neurobiology

Heart disease and brain blood flow regulation: prelude to dementia

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ABSTRACT

In a recent study, we investigated a crucial brain blood flow regulation mechanism in mouse models of heart disease and dementia. We found that there was a breakdown of this regulation in the brains of mice with heart disease. Furthermore, the combination of heart disease with Alzheimer's led to the trebling of a key Alzheimer's protein in the brain, which could eventually trigger dementia.

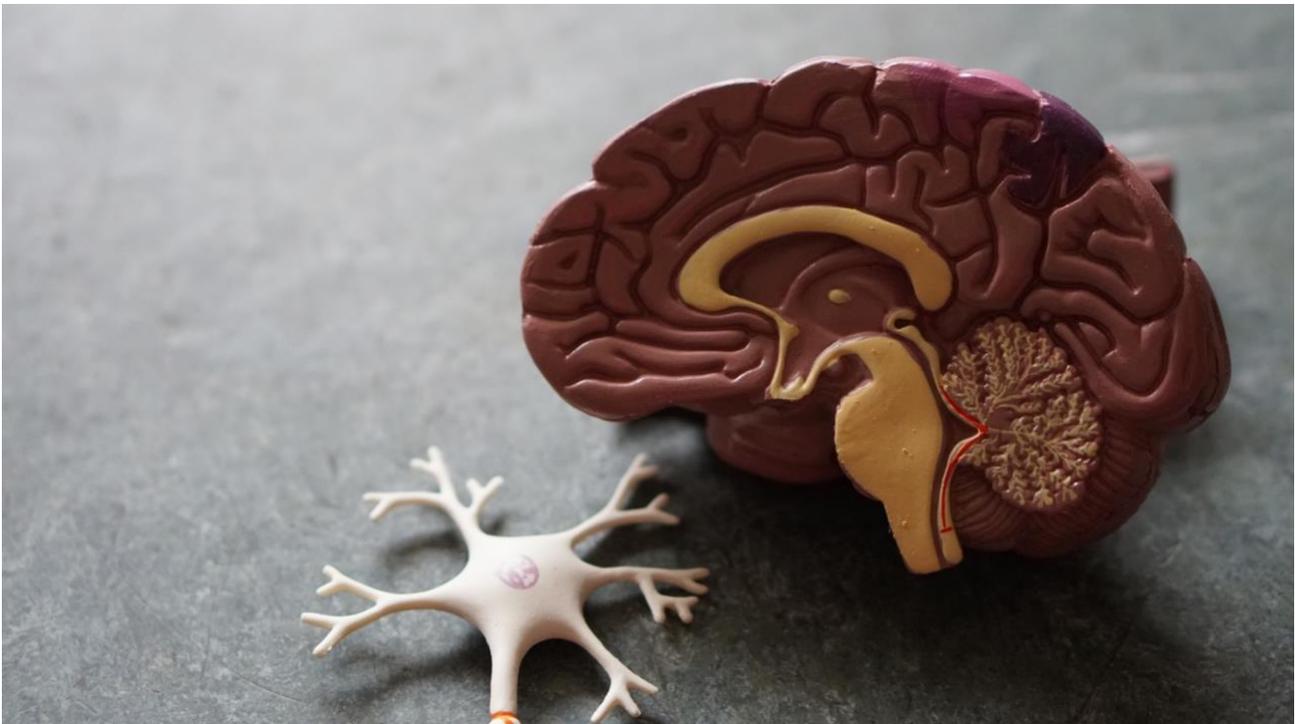


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The brain regulates changes in its own blood flow depending on how active its cells (neurons) are, by a mechanism called *neurovascular coupling*. When neurons become active, they send messages to nearby blood vessels causing them to dilate and bring in more blood. This increased blood flow provides the oxygen and nutrients that neurons need to function properly. The breakdown of this critical mechanism is thought to be involved in many neurological conditions including dementia, stroke, Parkinson's, and motor neuron disease.

In our study, we aimed at investigating whether this regulation mechanism was functional in mouse models of heart disease – a major risk factor for vascular dementia – and in a model that combined heart disease and Alzheimer's. We imaged changes in blood flow in the brain of these mice, as well as recorded their brains electrical activity. Finally, we also examined post-mortem tissue for genetic and protein changes.

We found that, in mice suffering from heart disease, there was a breakdown of *neurovascular coupling*.

Despite having similar levels of neural activity compared to healthy controls, the amount of blood changes decreased in mice with heart disease. This means that for the same amount of neural activity, less blood was arriving at the site of this activity. In addition, the quality of the blood in terms of its overall oxygen levels was also reduced. Heart disease therefore results in poor oxygenation of the brain.

We know from previous studies that when the brain is disturbed – either through injury/damage or infection, a process called cortical spreading depression (CSD) occurs. CSD is a wave of constricting blood vessels in the brain that happens during migraines, epilepsy, brain injury and other conditions. When CSD occurs, the brain does not get enough oxygen, leading to periods of low oxygen levels (*hypoxia*), which can in the long-term have detrimental effects on brain health. Indeed, clinical evidence has found a link between migraine frequency or epilepsy with an increased risk of dementia.

When we disturbed the brains of our disease model mice by inserting an electrode into the brain to cause a minor injury, we found that the CSD in these mice was much more severe compared to healthy controls. The level of constriction was more substantial, and this constriction lasted also much longer in our disease models. Whilst healthy mice did also display CSD, this was less pronounced and recovered quicker, showing that suffering from heart disease has a negative impact on this brain mechanism.

We then went on to examine the post-mortem tissue from all mice to see what differences we could see. Firstly, we wanted to see if a key Alzheimer's protein, *amyloid beta*, was altered in our combined model of heart disease and Alzheimer's compared to Alzheimer's alone. We found that the number of *amyloid beta* plaques were trebled in the brains of the

mixed model compared to Alzheimer's alone. This is significant as it suggests that suffering from a combination of two or more conditions at the same time drastically alters the disease to make it much more severe. This is also reflective of the older populations who tend to have some degree of underlying vascular conditions already.

We also looked at levels of two key inflammatory genes. We found that both were substantially higher in the brains of diseased mice compared to control mice. These findings suggest that inflammation in the brain may be a key driver of disease and the different observations we found.

In summary, we present novel findings relating to heart disease and the breakdown of *neurovascular coupling* leading to reduced blood and oxygen levels in the brain. These changes occur at midlife before the onset of any neurological disease or symptoms relating to dementia. Having a heart disease on top of a genetic predisposition for Alzheimer's can drastically alter the disease course and elevate key Alzheimer's proteins earlier in life. Finally, suffering from a brain injury (or migraines, epilepsy, or infections) can cause profoundly low levels of oxygen in the brain (due to CSD) in patients with heart disease or Alzheimer's – and this may be the reason why symptoms often worsen in patients after falls, injuries and infections.

These novel insights into what happens to the brain of model mice with heart disease and Alzheimer's may provide us with potential therapeutic targets to help prevent or slow down dementia in patients. For example, targeting inflammation in the brain, or elevating oxygen levels could potentially prevent some of the neurological damage seen in these models. Future research targeting such processes could prove useful clinically – though these need to be studied further.