

BRAIN POWER

The mammalian brain is one of the most complex structures known and requires an immense supply of blood, oxygen, and energy to function. It is also highly sensitive to oxygen depletion. Suffering a stroke or being starved of oxygen at birth can cause irreversible brain damage (Basilakos et al. 2015, Rocha-Ferreira E and Hristova M 2015).

However, we know remarkably little about which brain processes can be restored after oxygen depletion, or even after death. **Vrselja et al. (2019) tested whether they could partially restore certain functions to the brains removed from pigs that had been killed 4 hours earlier.**

MIMICKING BLOOD FLOW WITH BRAIN EX

Researchers obtained decapitated heads from pigs killed for food production and removed the brains. To 32 of them they began to supply a perfusate designed to mimic blood flow using a custom artificial vascular system termed BrainEx. A control group of brains were supplied with a control perfusate.

The BrainEx perfusate was hemoglobin-based, cryoprotective, and designed to support the high energy requirements of the brain. The researchers tested how well the brains responded to stimuli during 6 hours of perfusion.

RESTORATION OF BRAIN FUNCTIONS

Even 4 hours after the pigs were killed, the BrainEx system was able to restore blood flow through the main arteries and microvasculature. When a drug, normally used to treat high blood pressure, was administered, the vasculature responded by dilating, in a similar way to how a patient would respond to the same drug. Interestingly, a range of brain cells also restarted their normal functions, displaying their capacity for restoration of activity even after death. Neurons showed spontaneous synaptic activity and did not generally reveal signs of cytotoxic stress. Glial cells responded to lipopolysaccharide (LPS), which resulted in an increase in inflammatory cytokines, suggesting a functioning immune system.

When tested, these brains were able to regain metabolic activity; they consumed glucose and oxygen from the perfusate, and released carbon dioxide, demonstrating a resurgence of their metabolic processes.

The brains supplied with artificial blood flow from BrainEx had preserved cellular structure and cryoarchitecture, and attenuated cell death. Key areas of the brain involved in complex thinking (hippocampus and prefrontal cortex) appeared to look healthy under a microscope. In contrast, brains supplied with a control perfusate showed substantial deterioration across the 6 hour duration of the experiment.

IMPLICATIONS

The kick-starting of cellular and metabolic function several hours after death demonstrates the remarkable resilience of mammalian brains. This finding challenges the notion that the brain goes into irreversible decline shortly after the blood supply is cut off, and the concept that the brain's high energy demands would not sustain cellular function after ATP stores deplete (Harris et al. 2012).

The researchers note that the BrainEx technology needs to be further developed; how long BrainEx could restore and maintain brain functions is still unknown and future experiments could use longer perfusion times. This experiment was halted after 6 hours due to the deterioration of the control brains (Vrselja et al. 2019). This study was so notable that the lead scientist, Nenad Sestan, featured in Nature's "Ten people who mattered in science in 2019."

WHAT DOES THIS MEAN FOR RESEARCH?

Researchers have long been able to study samples of brain tissue, but until now, have not been able to delve into molecular and metabolic processes in an intact mammalian brain hours after death.

The ability to study the connectivity of the whole brain suggests a new class of tool for clinical research. This might make it possible to find the origin of certain brain disorders, and to test drugs for degenerative brain diseases on whole organs (Reardon 2019).

WHAT ARE THE IMPLICATIONS FOR MEDICINE?

It seems that we have underestimated the ability of the brain to recover from damage, raising the question of which functions affected by brain damage are permanent.

In future, with deeper understanding and subsequent policy changes, would it be possible to use a system like BrainEx to extend the time period for resuscitation? Right now this is not possible, in part because of the difficulty of using BrainEx without separating the brain from the skull (Reardon 2019). Although this isn't yet close to being used in humans, it does raise the possibility that in the future, similar technology may not have this limitation.

CAN BRAINEX RESTORE AWARENESS?

It's important to note that the researchers did not observe the kind of brain signals associated with awareness, perception, or other higher-order brain functions. In fact, they kept general anaesthetic available for immediate administration, to avoid inadvertent suffering in the unlikely event that signs of awareness were detected.

It's not clear whether BrainEx is capable of restoring organized global electrical activity in the isolated brain, however, the antagonists in the perfusate may act to dampen any global signals. The researchers raised the ethical considerations of any future system with the capacity to re-activate awareness in isolated brains.

This interesting study builds on years of research suggesting that for our gray matter, life-and-death might not be black-and-white.

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