Fruit-derived resveratrol: Safeguarding brain function after surgery

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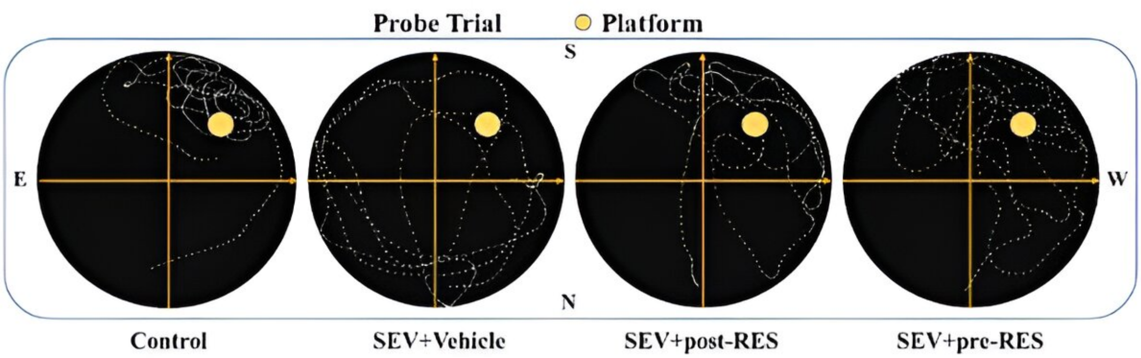

Representative swimming paths of the rats in the probe trial in the four groups. The yellow circles indicate the probe platform. Credit: Bosnian Journal of Basic Medical Sciences

Research by experts from Ningbo Eye Hospital and Hwa Mei Hospital at the University of Chinese Academy of Sciences provides insight into a critical issue facing surgical patients: post-operative cognitive dysfunction (POCD).

Post-operative cognitive dysfunction, commonly abbreviated as POCD, is a neurological complication that some patients experience after undergoing surgical procedures that require anesthesia. It manifests as a noticeable decline in cognitive abilities, specifically impacting areas like learning, memory, concentration, and even causing changes in personality.

According to an article published in the *Bosnian Journal of Basic Medical Sciences*, traditional treatments for POCD mainly focus on regulating nutrition and fluid balance, maintaining electrolytes, and providing psychological support. Some patients are also given neurotrophic drugs to support nerve growth and health.

The issue at hand: Cognitive risks after anesthesia

Anesthesia is a medical practice involving the administration of drugs to block sensation, making patients unconscious or insensitive to pain during surgical or diagnostic procedures. The practice encompasses various forms: general anesthesia for whole-body unconsciousness, regional anesthesia for blocking sensation in a specific body area, and local anesthesia for numbing a particular site.

Anesthetic agents act on the central nervous system by targeting specific neurotransmitter receptors to inhibit nerve impulses, which alters perception, motor function, and consciousness. While essential for pain management in surgeries, anesthesia is not without risks.

Sevoflurane, a widely-used anesthetic, has been identified as a significant factor contributing to postoperative cognitive dysfunction (POCD). Belonging to the fluorinated ether class of anesthetics, sevoflurane is commonly used to induce and maintain general anesthesia. Its rapid onset and offset make it suitable for a variety of surgical procedures.

While generally considered safe and effective, sevoflurane has been linked to certain neurocognitive deficits, including POCD. Research indicates that exposure to sevoflurane can cause pathological changes in the brain, such as amyloid-beta (Aβ) deposition and fibrin tangles in the hippocampus, which are associated with cognitive impairment. Alarmingly, these effects have also been observed in the offspring of rats exposed to the drug during pregnancy.

Given these findings, mitigating the risk factors or symptoms of POCD, especially those induced by sevoflurane, has become an urgent priority for clinicians and researchers alike.

Enter resveratrol: The natural brain protector

Resveratrol, often abbreviated as RES, is a bioactive compound found in certain foods like peanuts, grapes, and blueberries. It has the ability to cross the blood-brain barrier, meaning it can directly interact with the central nervous system (CNS). This compound has garnered attention for its multi-faceted biological effects, including its anti-inflammatory, antioxidant, and anti-apoptotic (cell-death preventing) properties.

In the context of neuroscience and medicine, RES is a known agonist for Silent Information Regulator 1 (SIRT1), a protein that has various neuroprotective roles.

By binding to and activating SIRT1, RES can have a protective effect on the brain. For example, it aids in regulating the growth and differentiation of neurons, can prevent cell death, and has shown promise in combating conditions like Alzheimer's disease. Moreover, RES has demonstrated its capability to modulate pathways like the cAMP/AMPK/SIRT1, which is particularly relevant in providing neuroprotective effects in stroke scenarios. It can also regulate inflammation, offering potential benefits for aging and age-related diseases.

Previous research has shown that RES could improve cognitive impairments in newborn mice that were exposed to sevoflurane (SEV). However, this effect had not yet been studied in adult animal models.

The aim of this study was to fill that knowledge gap. It explored the role of the SIRT1/RhoA signaling pathway in the neurotoxic effects caused by long-term exposure to SEV. Moreover, the study looked into how administering RES before and after surgery could potentially mitigate cognitive impairment in adult rats exposed to SEV.

Experimental Procedures and Protocols

The study used 76 adult male rats of a specific kind called Sprague-Dawley (SD) rats. SD rats are a common type of lab rat that scientists use for research. They're chosen because they're easy to handle and have a well-understood biology, which makes them good for studying how diseases work or how different treatments might work. Think of them as the "standard model" when scientists need to test something in a living creature before they can consider trying it in humans.

These rats weighed between 280–320 grams and were 8–10 weeks old. They were kept in a special, controlled environment that met ethical guidelines for animal research.

How the SEV model works

The "SEV model" is a way to study the effects of the sevoflurane (SEV) on rats. In this experiment, rats are placed in special boxes and breathe in a mixture of 3% sevoflurane and 40% oxygen for six hours. During this time, scientists carefully watch the rats to make sure they're breathing normally and aren't showing any signs of stress.

After the six hours, the rats are allowed to wake up and are returned to their usual living spaces. This model helps researchers understand how long-term exposure to this anesthesia gas might affect the brain and other parts of the body.

As the researchers were interested in RES, they dissolved it in a chemical called dimethyl sulfoxide (DMSO) and then diluted it with saline so it could be easily injected into the rats. DMSO is a chemical that's often used as a "carrier" to help other substances get where they need to go. They injected it into the rats' body cavities at three different doses, either a day before or an hour after the SEV exposure.

Types of tests conducted on rats

Two days after the SEV exposure, the researchers used the Negative Geotaxis Test to check a rat's balance and coordination. In this test, a rat is placed head-down on a sloping board. The goal is to see how quickly the rat can turn itself right-side-up. This helps gauge how well the rat's brain and muscles are coordinating.

Two weeks after the SEV exposure, the researchers placed the rats on a rotating rod to see how long they could stay on it. This is known as the Rotarod Test.

The Rotarod Test is essentially a treadmill challenge for rats. In this test, a rat is put on a spinning rod, and the goal is to measure how long the rat can stay on it without falling off. This helps researchers gauge the rat's balance, coordination, and motor skills. It serves as a way to check for long-term neurological issues in the rat, particularly after being exposed to certain treatments or conditions.

Memory and learning test: About three weeks after the SEV exposure, the researchers used a test known as the Morris Water Maze. This test evaluates how well rats can remember and find a hidden platform in a pool of water. In the Morris Water Maze, a rat is put into a pool with a submerged platform that it can't see. The rat has to swim around until it finds this hidden platform and climbs onto it.

Researchers keep track of how fast the rat locates the platform and how well it remembers the platform's location in subsequent tests. This provides insights into the rat's memory and learning abilities.

Checking protein levels in the brain

Finally, the researchers conducted a biochemical analysis using Western Blotting. This technique measures the levels of specific proteins in the rats' brain tissues, particularly those involved in cell death and signaling pathways, allowing for a detailed understanding of how SEV and RES affect the brain at the molecular level.

Think of Western Blotting like a blood test that's designed to detect specific markers or indicators of a condition. Just as a blood test can identify the levels of cholesterol or glucose to diagnose or monitor certain diseases, Western Blotting identifies specific proteins to understand cellular processes.

After exposing the rats to SEV and/or resveratrol, researchers extracted small samples of the rats' brain tissue and separated them into individual components. Using Western Blotting, they were able to identify specific proteins that serve as markers for various processes, like cell death or survival. By doing so, they gained a deeper understanding of the molecular events taking place inside the rat's brain cells.

Statistical tools used and results of the study

The researchers used specialized statistical tests, like one-way and two-way ANOVA, to make sense of the data. In simple terms, these tests act like advanced calculators to figure out if the changes seen in rats were because of the treatments or just random chance. A key value is "p

In the study, 76 rats were tested, and all survived the different treatments. Three doses of resveratrol were given, and the medium dose worked the best. After being exposed to sevoflurane (SEV), the rats had problems with orientation and weight loss, but resveratrol helped them recover.

Tests also showed that resveratrol improved the rats' balance, motor skills, learning, and memory. At the molecular level, resveratrol acted like a "first-aid kit," reversing changes caused by SEV exposure. Overall, resveratrol seems promising for countering SEV's negative effects on rats' behavior and cellular health.

The study aimed to assess whether resveratrol could mitigate brain damage induced by SEV, a common anesthetic. SEV exposure resulted in brain cell damage and impaired learning and memory in rats.

Resveratrol effectively prevented these issues, particularly when administered preemptively before SEV exposure. This implies that employing resveratrol as a preventive measure could prove especially advantageous for individuals susceptible to postoperative cognitive dysfunction (POCD). Nevertheless, while the study yielded valuable insights, there remain avenues for further investigation. For instance, given the study's exclusive focus on male rats, it's imperative to broaden the research scope to encompass female subjects.

In summary, resveratrol demonstrates significant potential in shielding against brain and cognitive impairments arising from SEV exposure in rats. Administering it prior to exposure appears to amplify its protective efficacy, likely through the SIRT1/RhoA pathway.

More information: Qiaoyun Zhou et al, Resveratrol ameliorates neuronal apoptosis and cognitive impairment by activating the SIRT1/RhoA pathway in rats after anesthesia with sevoflurane, *Bosnian Journal of Basic Medical Sciences* (2021). DOI: 10.17305/bjbms.2021.5997

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