Space Life Sciences Research Highlights

Overproduction of Nitric Oxide May Cause Astronauts' Fainting Spells

Astronauts returning to Earth from space and patients on extended bed rest have one thing in common: Both suffer from fainting spells when they stand upright. NASA-supported investigators have found evidence suggesting that overproduction of nitric oxide—a chemical that dilates blood vessels and thus lowers blood pressure—may explain these fainting spells.

For many astronauts returning from a space mission, being back in Earth's gravitational environment takes some getting used to. As soon as they take off their pressurized space suits, one of the first things they notice is how hard it is to stand upright for more than a few minutes. They feel dizzy and light-headed and can faint unless they quickly sit or lie down.

This condition, known as orthostatic intolerance, is caused by an insufficient flow of blood to the brain. The same symptoms are seen in individuals who, due to illness or injury, have lain prone in bed for a long time.

The underlying mechanisms in the blood vessels that lead to these fainting episodes are not well understood. Recent research findings by NASA-supported investigators at the University of California, Irvine, point to a possible new explanation. In a series of experiments, the investigators showed that nitric oxide, a substance that causes blood vessels to dilate, is overproduced in the blood vessels of rats exposed to simulated microgravity.

Blood Pressure and Gravity

To appreciate the potential significance of these findings, it is necessary to understand how blood pressure normally functions on Earth and what happens to it when an astronaut goes into space or a person undergoes prolonged bed rest.

"When we stand upright on Earth, gravity pulls the blood and other fluids in our bodies toward our feet," explains Ralph Purdy, Ph.D., professor of pharmacology at UC Irvine and principal investigator for the nitric oxide studies. "But our bodies automatically work against gravity to force blood to flow to the heart and the brain. For example, the blood vessels in our lower bodies constrict, pushing blood back up toward the heart."

Standing up, which on Earth can result in orthostatic intolerance, has a different meaning in space. Here the Neurolab crew that flew on STS-90 "stands" for the traditional crew portrait.

Blood pressure in the feet is normally higher than it is around the heart or in the brain. "But in the absence of gravity, or when someone lies prone for an extended period, that pressure gradient disappears," says Purdy. "Blood pressure is the same throughout the body." When astronauts first go into space, they develop puffy faces because the pressure gradient is eliminated and fluids shift toward the head.

Gradually, the circulatory system, like other body systems, adapts to microgravity. When astronauts first return to Earth, their lower-body blood vessels are overly dilated and blood pressure in the brain is at less than half its normal level. This low pressure in the brain causes dizziness and fainting. As the astronauts' bodies readapt to Earth's gravity, however, these symptoms dissipate.

Insufficient Blood Vessel Constriction or Excessive Blood Vessel Dilation?

Patients on prolonged bed rest experience declines in blood pressure and blood volume similar to those that occur in astronauts in space. Researchers have theorized that both microgravity and prolonged bed rest cause changes in blood vessels that reduce their capacity to constrict. Previous research has focused on the possible inhibition of norepinephrine, a chemical that stimulates blood vessels to constrict.

Purdy and his colleagues decided to focus instead on whether another mechanism might play a role, by causing excessive blood-vessel dilation. Nitric oxide, a potent blood vessel dilator, was a candidate. (Nitric oxide has been used for years in many drug treatments and is the active ingredient in nitroglycerin, a medication that improves cardiac circulation by dilating the blood vessels that lead to the heart.)

In a series of experiments, the researchers found that rats kept in a simulated microgravity environment produced excessive amounts of an enzyme, nitric oxide synthase (NOS), in the heart, blood vessels, kidneys, brain, and other tissues. NOS stimulates the production of nitric oxide. Control rats not subjected to simulated microgravity showed no increase in NOS.

The investigators injected rats with an experimental drug, aminoguanidine, that blocks the action of NOS. In the rats kept in simulated microgravity, the injection produced an elevation in blood pressure that was double the increase observed in control rats. "This told us that the rats kept in simulated microgravity had higher levels of nitric oxide in their blood vessels," says Purdy. "Injecting aminoguanidine to block NOS stopped the overproduction of nitric oxide, enabling greater constriction of the blood vessels to occur, and thereby elevating blood pressure."

In another experiment, the team isolated tissues from the rats' lower bodies and measured their ability to constrict in response to the constriction stimulator norepinephrine. They observed a reduced response to norepinephrine in tissues from the rats kept in simulated microgravity compared with that of the control rats. However, when aminoguanidine was added to the solution bathing the tissues, an equivalent response to norepinephrine was seen in the tissues of both groups of rats.

Finally, the researchers analyzed the rats' blood vessels biochemically, using a molecular biology technique known as Western blot analysis. Again, they found excessive levels of NOS in the rats kept in simulated microgravity but not in the control group.

"It is clear from this series of experiments that when nitric oxide is overproduced in blood vessels in animals in simulated microgravity, there is a continuously enhanced stimulus for those vessels to dilate," says Purdy. Thus, overproduction of nitric oxide may contribute to orthostatic intolerance. If this is true, blockade of NOS with aminoguanidine to prevent overproduction of nitric oxide could be an effective treatment for orthostatic intolerance. Purdy and his colleagues are planning to conduct a clinical trial in which bedrest patients who have orthostatic intolerance will be treated with aminoguanidine.

Medications currently used to treat orthostatic intolerance in astronauts—which either promote retention of salt and water by the body, or which increase the body's production of the vessel-constricting chemical norepinephrine—can have undesirable side effects. Improved treatment for this condition would ultimately benefit bedrest patients as well as astronauts, says Purdy.

References

1. Vaziri ND; Ding Y; Sangha D; Purdy RE. Upregulation of NOS by simulated microgravity, potential cause of orthostatic intolerance. *Journal of Applied Physiology* 89(1):338-44, 2000.
2. Sangha DS; Vaziri ND; Ding Y; Purdy RE. Vascular hyporesponsiveness in simulated microgravity: role of nitric oxide-dependent mechanisms. *Journal of Applied Physiology* 88(2):507-17,2000.
3. Purdy RE; Duckles SP; Krause DN; Rubera KM; Sara D. Effect of simulated microgravity on vascular contractility. *Journal of Applied Physiology* 85(4):1307-15,1998.