REPORT

Progesterone
May Improve Outcomes from Brain Injury

New Research from Donald G. Stein, PhD

Why do some females recover from brain injury much faster and more completely than males? With more than 3 million people chronically disabled from traumatic brain injury, the answer may have far-reaching implications for the treatment of traumatic brain injury, stroke, and other neurological disorders.

For the past twenty-five years, neuroscientist Donald G. Stein, PhD and his colleagues have been investigating this question and have discovered something remarkable—that the hormone progesterone confers profound neuroprotective effects that improve outcomes and reduce mortality following brain injuries. These findings may be relevant to research on treatments for a variety of other conditions affecting the central nervous system, including stroke, spinal cord injury, and multiple sclerosis. Here, we’ll unravel the neuroprotective effects of progesterone.

PROGESTERONE PROTECTS BRAIN TISSUE AS WELL AS FETAL TISSUE

Progesterone provides powerful neuroprotection to the fetus, particularly in late pregnancy, when it helps suppress neuronal excitation that can damage delicate new brain tissue. Dr. Stein and his colleagues at Emory University in Atlanta have continued to develop, test, and prove the theory that in addition to protecting the fetal brain, progesterone also protects and heals injured brain tissue.

“If you think about progesterone as a developmental hormone that has evolved to protect the fetus, the findings that it can help with the repair of brain injury should not be surprising,” Dr. Stein says. “Many of the processes that follow a brain injury or a stroke, as the brain tries to repair itself, are similar, but not identical to, processes that take place during the development and differentiation of the fetal nervous system.”

In the 1970s and 1980s, Dr. Stein submitted a number of grant applications to the National Institutes of Health (NIH) to fund animal research on progesterone in traumatic brain injury, but at first, none of the applications were funded. It seemed to many of his peers that as a “female hormone,” progesterone simply could not have such an important role in promoting recovery from brain injury.

Dr. Stein persisted in his research at Clark University in Worcester, Massachusetts and then at Rutgers University in New Jersey, with the help of a few committed students. Together they learned that female rats that had surgical injury to the frontal cortex of the brain lost the ability to solve a spatial memory task. These rats’ brains also showed dramatic evidence of brain swelling (cerebral edema).

Rats that had high circulating levels of progesterone performed much better after injury than did those without elevated progesterone, and even more surprisingly, had hardly any brain swelling.

To compare responses to injury under conditions of high progesterone, Dr. Stein’s group allowed half of the rats to continue normal estrus cycles and induced a state of pseudo-pregnancy in the remaining rats by mild mechanical stimulation of the cervix.

“When we do this procedure, the animal acts as if she has been impregnated, so her progesterone levels go up relative to estrogen and stay elevated for about 6 to 10 days,” Dr. Stein explains. “When the animals were high in progesterone when the brain injury was inflicted—and this is just natural circulating levels of progesterone; it had nothing to do with giving them additional hormones—the outcome was much better on a series of behavioral tests. When we looked at the brains of these
animals, we noted that the females with higher levels of progesterone at the time of the injury had much less cerebral edema.

Even more exciting in terms of potential implications for treatment was that progesterone injections given after brain injury also reduced edema and were equally effective in both males and females. The reduced brain swelling seen with progesterone treatment was accompanied by better performance on a water maze and by less degeneration of brain cells in areas with connections to the injured area.6

A few years later, Dr. Stein, then Dean of the Graduate School and Vice Provost at Rutgers University, led a team that discovered that progesterone injections in rats were still effective in reducing brain swelling and functional impairment even if treatment was delayed up to 24 hours after injury.7

“At first, I would say that many people in mainstream neuroscience and medicine were pretty dubious about our research because it just seemed to be too good to be true,” Dr. Stein says. “There are now about 100 papers showing evidence of the efficacy of progesterone that I think even all those doubtful people are beginning to think that maybe we ought to give this treatment a chance.”

PROGESTERONE SAFE, EFFECTIVE IN HUMAN TRIALS FOR TRAUMATIC BRAIN INJURY

Ultimately, these consistent, promising results from well-done, methodologically sound animal experiments could no longer be ignored. Scientists who had been skeptical began confirming the findings of Dr. Stein’s team, and the NIH and US Centers for Disease Control (CDC) began funding small pilot projects.

All this pre-clinical research then led to a clinical trial known as ProTECT II, led by physicians Arthur Kellermann and David Wright at Grady Hospital in Atlanta, with nationally-recognized health expert Dr. Sanjay Gupta also on the team.8 One hundred patients with moderate to severe traumatic brain injury were randomly assigned to receive standard of care treatment for head injury (with no progesterone), or identical standard of care treatment plus three days of intravenous progesterone to reach levels about triple the highest natural levels seen at the end of pregnancy. Seventy percent of the patients in ProTECT had severe head injury based on the standard Glasgow Coma Scale at the outset of treatment.

“Normally the mortality rate for patients with severe brain injury here and nationwide is about 30-33% in the patients given state of the art or standard of care treatment,” Dr. Stein says. “We found that the mortality rate in the progesterone-treated group was cut to 13%, so it was more than a 50% reduction in mortality rate.”

These results were especially exciting given the delay in starting progesterone administration. Although the animal studies suggest that progesterone may be helpful if given as late as 24 hours post-injury,7 the benefits were greatest if treatment was given within the first 2 hours. Some patients were accepted into the ProTECT study up to 11 hours after injury, because the need to obtain informed consent from relatives delayed starting treatment. Both groups had similar rates of adverse and serious adverse events. An independent safety monitoring board picked by the NIH did not attribute any serious adverse event to treatment with progesterone.

“Unfortunately, no funding was provided in this first study to do any long-term follow up, but the clinicians were able to show that at 30 days survival, using a disability rating scale measure of 5 different measures of functional activity the patients with moderate head injury were substantially better with progesterone than those just given standard of practice care,” Dr. Stein said.

WHAT YOU NEED TO KNOW: PROGESTERONE IN TRAUMATIC BRAIN INJURY

- In animal models, functional recovery after traumatic brain injury is often better in animals with high levels of circulating progesterone, considered by many a female sex hormone. Brain swelling is also reduced in these animals.
- Administering progesterone to male or female brain-injured rats reduces brain swelling and improves motor and functional recovery. These benefits occur even if progesterone treatment is delayed up to 24 hours, which is of great potential importance to treatment of humans with traumatic brain injury.
- In an Emory University clinical trial of 100 patients with moderate to severe traumatic brain injury who all got standard-of-care treatment, adding progesterone treatment reduced the death rate by more than 50% compared with placebo. In the patients with moderate head injury, recovery of function was substantially better with progesterone plus standard care than with standard care alone.
- An independent clinical trial in China has shown similar benefits with progesterone treatment in head injury. In both trials, progesterone was safe and well tolerated.
PROGESTERONE HAS MULTIPLE MECHANISMS OF ACTION IN BRAIN INJURY

“Clearly, one of the most beneficial effects of progesterone is on cerebral edema,” Dr. Stein says. “But one of the great benefits of progesterone that enables it to work in head injury is that it acts on a number of different injury mechanisms.”

Progesterone acts not only on a specific progesterone receptor in the cell nucleus, but also on different receptors in the cell membrane to achieve different effects beneficial in head injury. In response to injury, glial cells, which are critical to normal brain function, release protein-like compounds known as inflammatory cytokines. This triggers inflammation, which leads to edema, which in turn causes the entire brain to swell and function abnormally.

Progesterone “dramatically reduces the expression of the genes that trigger cells to release these inflammatory cytokines,” Dr. Stein says. Animal studies have shown that progesterone, and its metabolite allopregnanolone, enhance the production of a protein that inhibits the molecular chain reaction leading to brain swelling.

Another mechanism by which progesterone relieves cerebral edema is its contrasting effects on water channel proteins called aquaporins. Progesterone downregulates, or decreases, aquaporin activity in the injured brain tissue, while upregulating, or enhancing, aquaporin activity in the walls of the cerebral ventricles. This may help with drainage of the excess fluid from the region of the injury.

Through still another mechanism, progesterone upregulates the expression of genes that inhibit programmed cell death called apoptosis, thereby helping to prevent death of injured brain cells.

Neurons within the brain and spinal cord normally communicate rapidly by transmitting electrical impulses along nerve fibers. Speed of neurotransmission is improved by myelin, a protective coating along the nerve fiber, which may be disrupted in various types of injury and in disease processes such as multiple sclerosis. The neuroprotective and even regenerative qualities of progesterone may include its effects on myelin.

“In the nervous system, progesterone also stimulates cells in the spinal cord and brain to make more myelin,” Dr. Stein says. “This is one of the reasons why progesterone derivatives are being tested in clinical trials in France and Italy to treat multiple sclerosis (a disease in which myelin is disrupted). Women with multiple sclerosis who become pregnant show a marked reduction of their symptoms, which get worse again when progesterone drops immediately after birth and estrogen levels kick back in. It’s possible that the symptoms regress during pregnancy because the progesterone is stimulating the expression of genes that produce more myelin.”

Additional impressive effects of progesterone in traumatic brain injury include its ability to control excitotoxicity, or heightened responsiveness of injured brain cells that may cause seizure activity, and its ability to help restore the damaged blood-brain barrier that normally protects against intrusion of unwanted substances into brain tissue.

In untreated brain injury, not only do brain cells die in the injured area, but nerve cells in other brain regions connected by nerve fibers to the injured area also die by a process known as retrograde degeneration. Dr. Stein has noted that progesterone appears to reduce neuronal death related to retrograde degeneration following brain injury.

“The key thing that I want to stress is that progesterone does a lot of things at the [structural] level to help rescue neurons that might otherwise die as a result of the trauma,” Dr. Stein says. “Progesterone is involved in many different processes that help to repair and reorganize damaged brain tissue, and that’s why I think it’s so effective.”

Compared with other experimental treatments for traumatic brain injury, progesterone offers a number of advantages: it is lipid-soluble and quickly crosses the blood-brain barrier to allow rapid onset of action; it has a long history of safe use in both men and in women; and it can be given intravenously through an injection site in the arm or leg. Its effects on a variety of receptors in different locations allow a host of neuroprotective actions.

“A lot of drugs have failed—the ProTECT II trial was the first successful trial for traumatic brain injury in 40 years,” Dr. Stein says. “And one of the reasons I think progesterone has worked is because it does not target just one specific receptor mechanism.”

SUMMARY

■ Progesterone normally acts by a variety of mechanisms to protect the brain during fetal development, and it may act by similar mechanisms to promote recovery in the injured brain.
■ Other neurological conditions for which progesterone might prove an effective treatment include stroke, pediatric brain injury, multiple sclerosis, and/or possibly even such neurodegenerative diseases as Alzheimer’s disease.
Progesterone is a powerful hormone that has been proven to confer profound neuroprotective effects that improve outcomes and reduce mortality following brain injuries. Donald Stein, PhD, has been at the forefront of testing progesterone and discovered that giving intravenous progesterone to male or female brain-injured rats reduces swelling in the brain and helps motor and functional recovery. In a clinical trial involving 100 human patients with moderate to severe traumatic brain injury, adding progesterone reduced the death rate by almost 60% compared with placebo.

If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-866-864-3027.

DISCLOSURES

The Brain Research Laboratory at Emory is currently supported by funding from the NIH-NINDS and the Department of Defense. Dr. Stein and some of his colleagues have applied for patent protection for the use of progesterone in the treatment of central nervous system injury and as such may benefit financially as a result of the outcomes of this research described above. The University and the principal investigators have recently entered into a licensing agreement with BHR Pharmaceuticals, a manufacturer of progesterone, and both the institution and the individual investigators may benefit financially from the use of this agent.

DISCLAIMER

Dr. Stein recognizes that products may be sold using some of the hormones discussed above and he states that, “In no way am I endorsing any of these commercially available products. The basic research we have conducted does not implicitly or explicitly endorse or recommend the use of any commercial product currently available.”

References

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