Healing hormone provides hope for brain injury

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For years Donald Stein persisted in his research despite many naysayers, who are now quiet. Credit: Jack Kearse

If Don Stein were the kind of man who listened to what others said, he would have shut down his lab years ago. The Emory neuroscientist spent more than two decades investigating progesterone as a treatment for traumatic brain injury (TBI)—a pursuit that was unappreciated at best and maligned at worst. A naturally occurring hormone was too simple a solution to too complex a problem, according to the prevailing wisdom.

Today Stein stands if not on the threshold of vindication, at least within the general neighborhood. After better-than-hoped-for results from the first human trial, progesterone is being tested in two nationwide phase 3 trials and also internationally in more than 20 countries.

And Stein is now expanding his scope to test whether progesterone can work its magic in other conditions, such as stroke, pediatric TBI, and brain tumors.

"I've spent most of my professional career pursuing this line of work," says Stein, Asa Candler Professor of Emergency Medicine and director of the department's Brain Research Laboratory. "Seeing our work in worldwide clinical trial is exciting, but what would really be gratifying would be to know that the work we did actually ended up helping a lot of people to live more healthy and fulfilling lives."

A positive outcome from the trial could mean just that. Researchers have tried unsuccessfully for decades to develop an acute treatment for TBI.

"The graveyard for drugs and promising therapies for TBI is extensive," says David Wright, associate professor in emergency medicine. "There have been many attempts, but zero have made it past a phase 3 clinical trial in something that is epidemic in this country."

All those failures stemmed from looking at the problem the wrong way, contends Stein. "One of the main reasons every single drug has failed is the persistent approach to target one gene, one pathway, one receptor, thinking you are going to find a magic bullet to treat a very, very complex disorder," says Stein.

Indeed, with TBI the initial injury is just the beginning. Even a very localized trauma results in a cascading release of inflammatory factors that cause swelling, tissue breakdown, and programmed cell death.

"When you have a brain injury, you have a systemic disease," says Stein. "Every organ in the body is affected. So if you are just treating one spot in the brain or one pathway, you're going to fail."

Progesterone, on the other hand, works at multiple genes, multiple pathways, and multiple receptors. Not only is it able to stem the devastating inflammatory cascade, it actually helps repair the damage. "If you tear down a building, are you just going to leave the rubble?" says Stein. "No, you're going to clear it away and rebuild. That's where progesterone shines. It's a developmental hormone that is involved through the entire gestation of the fetus. So here you have an agent that not only blocks all these toxic events, but it also stimulates regenerative repair."

Progesterone certainly took a step toward proving its worth in the small 100-patient phase 2 trial. Stein and his team were merely hoping to demonstrate that the high dose of the hormone used was safe, so they could proceed to a larger trial. Any evidence of efficacy would be gravy. They got gravy.

"Much to our surprise, we saw a50% reduction in death in the treatment group, which was just over the top," says Wright. "And in a certain subgroup, we also saw functional improvement. That shifted the whole curve from keeping people alive to actually making them better."

For Stein, applying these positive findings to other conditions only makes sense. "Everything we do has to do with brain injury," he says. "Whether it's from a head trauma, a stroke, or a tumor, it's still an injury to the brain."

In collaboration with the Pediatric Emergency Care Applied Research Network (PECARN) and the University of Michigan, his lab is looking into the effect of progesterone on younger TBI victims. "There is

currently very little that can be done for children with severe brain injuries—that's a wide open field," says Stein. "But we need to make sure if we are working with a powerful developmental hormone it's going to be as safe and effective in kids and not produce any untoward effects. This work is still in very preliminary stages."

Much further along is Stein's research using progesterone to treat stroke victims. When rats were given progesterone after having an induced stroke, they experienced about 70% less brain damage than rats in the control group and had 50% to 60% greater functional recovery. "We did gait scans to check the use of all limbs, a maze to test memory, a grip analysis to test grip, and many other functional assessments," says Fahim Atif, a researcher in Stein's lab. "In all areas, the progesterone rats performed significantly better than the control rats."

In the laboratory, researchers also are investigating the timing of progesterone administration, treating animals up to 24 hours after their stroke. "The only FDA-approved drug for stroke has a very narrow window—it must be given within 3-1/2 hours of the stroke," says Atif. "As a result, less than 5% of the stroke population gets it. And even those 5% are at risk for serious side effects, such as brain hemorrhage. If progesterone proved effective even after a 24-hour delay—as it has in animal models with TBI—it could provide a much safer treatment for many, many more people than is currently available."

Stein and his team of research scientists hope to wrap up the pre-clinical work and move the stroke study into human trials in the near future. "Progesterone promises to have an even more profound influence on stroke than it has on TBI," says Stein.

Stein's lab is having even more success in improving outcomes in animal models of trauma and stroke when progesterone is combined with vitamin D. "Vitamin D is actually a hormone, like progesterone, and it

acts on many different biochemical pathways, like progesterone," says Stein. "We started working with vitamin D hormone at the urging of Mahlon DeLong, the former chair of neurology here at Emory. It turns out that both the very young and the elderly often suffer from vitamin D deficiency and this can impair the processes of healing after traumatic brain injury or stroke. When used in combination, the two hormones work better than either does alone. In a study we just published, there was significantly less brain damage and more functional recovery in stroke-induced rats that got progesterone and vitamin D in combination than in rats that got progesterone or vitamin D alone."

Another area of research was stumbled upon serendipitously. When working on a project to develop a synthetic version of progesterone that might be more effective in treating brain injury than the native form of the hormone, Atif happened to use tumor cells in his testing. As a part of the screening process, he found that high doses of progesterone were toxic to the cells. "At first I was sure I did something wrong, so I repeated it about 10 more times and got the same result each time," says Atif.

Subsequent research confirmed his findings. Mice treated with high-dose progesterone had a 50% reduction in neuroblastoma tumor size after only eight days. The hormone induced cell death and inhibited vascular growth. "We published this work last year in the journal *Molecular Medicine*, and we are very encouraged by the findings," says Atif. "Especially since every chemotherapy drug has severe side effects and progesterone appears to have none. It specifically kills the cancer cells but is absolutely safe for healthy, normal cells. We are now testing it with other types of brain tumors, such as glioblastoma and astrocytoma."

Finally, Stein's lab is working with the Department of Chemistry and the laboratory group of Dennis Liotta, the Samuel Candler Dobbs Professor of Chemistry, to modify progesterone to make it viable for use in the

field, particularly in combat situations. "In a military situation, if you can help it, you don't want to have to start an IV and keep it going," says Stein. "You want something that you can get in quickly and easily, that can be used in all conditions, from -40 degrees to 120 degrees, that is highly stable so you don't need to replace it every two weeks, and that lasts in the system until you can get the injured person to a hospital. And that's what we're trying to develop."

It's hard to overstate the impact Stein's work will have if the phase 3 trial shows progesterone's efficacy in treating TBI. "Others have said if this works, it will dramatically change emergency care and treatment of brain injury, and that it could become standard of care around the world," says Stein. "But the real beauty is that progesterone is really cheap, it's easy to administer, and it doesn't require high technology. So you can't get away with charging vast amounts of money for it, and there's no reason it couldn't be available all over the world."

Provided by Emory University