

Mesenchymal stem cell transplantation reduces opioid tolerance, opioid-induced pain

Published on March 25, 2015 at 5:45 AM

Mesenchymal stem cell (MSC) transplantation reduced opioid tolerance and opioid-induced hyperalgesia caused by daily morphine injections in rats, according to new research. The results could herald stem cell transplantation as an innovative, safe, efficacious and cost-effective therapy to treat pain and opioid tolerance, said researchers, who presented results in a Plenary Research Highlight session at the 31st Annual Meeting of the American Academy of Pain Medicine.

Not only was opioid tolerance prevented when the rats were transplanted with MSC before repeated morphine injections, but tolerance was reversed when the rats were treated after opioid tolerance had developed, results demonstrated.

"MSCs have a remarkable anti-inflammatory effect and a powerful anti-tolerance effect," said the study's principal investigator, Jianguo Cheng, M.D., Ph.D., who led the research team from the Cleveland Clinic, in Ohio. Although clinical trials are still three to five years away, he said, eventually, "The results may apply to millions of patients with a wide range of pain states, including cancer pain and other intractable chronic pain that requires long-term opioid therapy."

Furthermore, Cheng characterized the procedure as practical, in light of readily available sources of stem cells, reliable stem cell technology, the simplicity of transplantation procedures and the fact that clinical trials are already underway involving autoimmune and other diseases.

The Institute of Medicine report on pain in America documented millions who suffer with chronic pain ("Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research." National Academies Press [US]; 2011).

Opioid therapy is a cornerstone component of pain management for many people with severe, ongoing pain; however, side effects such as tolerance and the risks posed by abuse, addiction and drug overdose limit its utility. Tolerance, a physiologic process in which the patient's body adjusts to a dose and no longer achieves pain relief, is a common limitation with opioid therapy. The higher doses that result can limit effectiveness and compromise safety.

Glial cells are of growing interest in pain research and have been implicated in the development of tolerance. Glial cell activity also produces pain through the release of products that excite the nervous system, playing an important role in the spinal cord during nerve injury. Furthermore, the opioids used to treat pain, also can induce glial activity, causing pain relief to drop and unwanted opioid effects, including tolerance, dependence, reward and decreased breathing, to grow. A focus of research, then, is to separate the desired effect of pain relief from the unwanted opioid effects (Watkins et al, Trends in Pharmacological Sciences 2009;30(11): 581-91).

Interest in transplant of stem cells is another maturing research avenue (Hsu et al, Cell Transplant 2007;16(2):133-50). MSCs can differentiate into a variety of cell types and have been investigated for potential repair of damaged neural cells and for calming inflammation in the immune system to promote recovery after traumatic brain injury (Zhang et al, J Neuroinflammation 2013;10(1):106).

Following this line of research, the study investigators wondered whether they could create an anti-tolerance therapy by transplanting MSCs into the intrathecal space surrounding the spinal cord. With approval by the Cleveland Clinic Institutional Animal Care and Use Committee and funding through the Department of Defense's Congressionally Directed Medical Research Programs, they compared the withdrawal thresholds of the hind paws in response to painful mechanical and thermal stimuli in two groups of rats that received daily morphine injections. The first group was treated with MSC transplantation and the control group with phosphate-buffered saline (PBS).

They found that both groups of rats developed morphine tolerance (i.e., reduced responsiveness to morphine) within five to seven days with repeated injections; however, the MSC group demonstrated significant and consistent higher thresholds for paw withdrawal than the PBS group. Furthermore, immunohistochemistry confirmed microglial activation in the spinal cord after repeated daily morphine injections, but the activity was substantially weakened in rats treated with MSC. The animals also maintained normal locomotion, food and fluid intake and body weight gain,

findings that demonstrated safety, Cheng said.

The next step is to translate the experience of animal experiments to clinical trials. Cheng outlined the need to first determine and optimize the key variables of stem cell transplantation, such as sources of cells, routes of administration, number of cells to transplant and the timing of transplantation.

Source:

American Academy of Pain Medicine
