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Military funds research on how nicotine impairs bone healing

Goal to speed smokers' recovery from combat injuries

Researchers have received a grant from the U.S. Department of Defense to study ways in which nicotine from cigarette smoke may interact with stem cells to slow the healing of bone injuries.

Smoking has been shown to delay skeletal healing by as much as 60 percent following fractures. Slower healing means a greater chance of re-injury and can lead to chronic pain and disability. The obvious solution is for smokers to quit when they get hurt, but studies show that just 15 percent can.

The military is interested in the issue because about 34 percent of military personnel smoke, compared to 25 percent in the general population, according to the Air Force Medical Support Agency. Long-term health concerns aside, military experts say smoking reduces soldiers' readiness to fight by impairing night vision, weakening the immune system and lengthening healing time. The problem is especially poignant now because more than 14,000 soldiers have been injured in Iraq since 2003, with about 65 percent of the injuries including orthopedic damage to extremities.

One goal of the research then is to determine, based on biochemical evidence, the window of time during which healing has the greatest chance of being delayed by cigarette smoke. Smokers could then be advised to quit for a specific time period to afford them their best chance of healing. Beyond the time window, researchers hope a better understanding of the mechanisms involved will lead to treatments that speed healing in persistent smokers and in all patients with bone injuries.

"Smoking reduces the rate at which the two sides of a fracture come together," said Michael Zuscik, Ph.D., assistant professor in the Department of Orthopaedics at the University of Rochester Medical Center, recipient of the $1.4 million DOD grant. "We

believe this new research will establish for the first time the mechanisms by which nicotine interferes with the healing process, and identify ways to prevent it." Zuscik's work hinges on the theory that nicotine prevents stem cells from maturing into replacement bone.

Healing Machinery

Acetylcholine is a neurotransmitter, a biochemical with the first purpose of passing on nerve impulses that enable muscles to flex. The neurotransmitter passes on its signal by attaching to nicotinic acetylcholine receptors (nACHRs), proteins shaped specifically to receive the neurotransmitter, like a lock receives a key, on the surface of the nerve cell receiving the signal. As part of passing on nerve messages carried by acetylcholine, nACHRs must transfer signals from the outer surface of the cells they occur on to their inner compartments. nACHRs can do this because they form gateways that pass through the barrier that separates the outside and inside of cells. nACHRs transfer nerve messages by allowing charged particles (e.g. calcium ions) to flow through their gateways, which in turn sets off actions inside the cell.

The DOD-funded research is based on the discovery that nACHR-enabled calcium flow, along with helping to pass on nerve signals, also regulates the behavior of certain genes. That the body has evolved to use neurotransmitter receptors in this second way, to regulate genes, may explain why the receptors appear on cells that have nothing to do with passing on nerve signals. Central to the problem caused by nicotine is that, although structurally different than acetylcholine, it can bind to and activate the same receptor, nACHR. That may grant nicotine the power to turn on and off genes without regard for the delicate genetic controls that govern acetylcholine's ability to take the same action.

Specifically, researchers plan to confirm that when nicotine binds to nACHRs, it changes calcium flow, which in turn changes the action of cyclic-AMP response element binding protein (CREB). Transcription factors like CREB "turn on" certain sections of the genetic code at the proper times. Medical Center researchers believe that nicotine may cause CREB to distort gene function in the normal, two-step bone healing process, where stem cells become cartilage and then cartilage matures into bone.

They will test the idea that stem cells in the bone marrow (mesenchymal stem cells), which differentiate to form replacement bone after injury, have nACHRs on their

surfaces. Activation by nicotine of such receptors on stem cells could switch on genes that delay the final transition of cartilage into new bone.

"Nicotine leaves the healing process in limbo," Zuscik said. "In the future, we hope to manipulate neurotransmitter receptors, much like researchers have already done in neurology to create drugs for depression, to accelerate bone healing."

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