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## Aid and Comfort

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Dr. Robin Polt, University of Arizona Pharmacology researchers at the University of Arizona are looking at ways to make the body's own chemicals more effective at relieving severe pain. The implications on the battlefield are considerable, and these researchers are aiming for nothing less than bringing about the obsolescence of morphine.

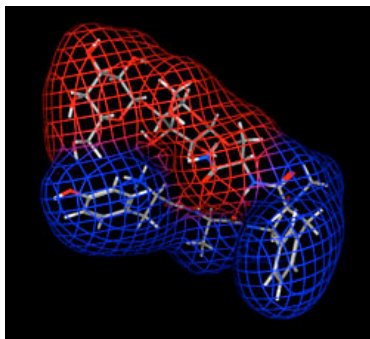
Since prehistoric times, opiates, a class of plant compounds, have been used to relieve pain. The opiate drug morphine came into use in the early 1800s, and it is still used to relieve severe pain. Morphine is used as a benchmark against which other analgesics (pain relievers) are compared. Some small opioid molecules, such as morphine, delivered to the blood stream are capable of passing into the brain, making them some of the most powerful analgesics.

In previous wars, soldiers and Marines were issued doses of morphine to carry in their backpacks, but this practice was discontinued when the Food and Drug Administration (FDA) classified morphine as a controlled substance. Now, Army corpsmen and Navy medics must administer morphine to wounded warfighters. Dosages must be carefully monitored to avoid overdose, which can cause acute opioid toxicity, respiratory depression, and death. Continued use can lead to physical dependence and addiction. The euphoric and hallucinogenic effects of morphine can lead to its abuse as a recreational drug.

As the military pushes for smaller units to conserve manpower, the effects of a wounded soldier or Marine on morphine are felt more acutely. Once the drug is administered, the warfighter must be relieved of his or her weapon, and two healthy warfighters must monitor the warfighter to ensure that he or she does not wander off or cause harm to himself or others.

Dr. Robin Polt, a chemistry professor at the University of Arizona, has worked since 1992, with funding from the Office of Naval Research (ONR) and the

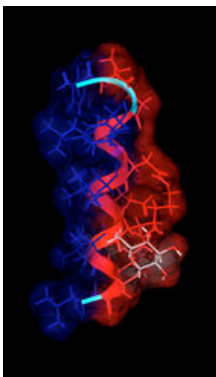
enkephalins into powerful analgesics, with the aim of rendering morphine obsolete. Enkephalins are proteins belonging to the class of endorphins, the compounds that produce the "runner's high". The human body produces enkephalins naturally.



Glycosylated enkephalin molecule. Graphics courtesy of Dr. Robin Polt. Enkephalins engage the opioid receptors with high specificity and can produce strong analgesic effects when delivered to the brain. However, difficulties in their administration and stability, and an inability to deliver more than very small amounts through the blood brain barrier, has hampered any efforts to use these compounds as practical pain relievers.

Polt has modified synthetic enkephalins with glycogen, disaccharide sugar that allows the compounds to pass into the brain. ONR has funded his work from the very early compound discovery stages to the current work, which involves animal testing for pharmacokinetic and toxicological properties. Acretia, a drug development company based in Lexington MA, has licensed the glycopeptide compounds from the University of Arizona. Acretia is raising capital to take these compounds through clinical trials and market them to a large drug manufacturer, which will then bring the commercial product to market.

ONR's goal is to move this project at an accelerated pace so that the drug can enter Phase I clinical trials about a year from now. The Marine Corps warfighting labs plan to assist in moving the project along. The U.S.



Marine Corps Glycosylated endorphin molecule. would like to see these drugs introduced into the field, ideally as over-the-counter products, but at least as "nonscheduled" compounds.

So far, testing has shown that many of the glycopeptide drugs are more potent than morphine, and some show no adverse toxicology. They have not shown signs of addiction in mice, but it is unknown whether they present the potential for abuse by humans. The drugs are expected to induce no cognitive impairment and are non-sedative, which in some cases will allow the warfighter to bring himself or herself to safety with minimal loss of capacity (other than that caused by the injury).

Michael Given, ONR program officer for Casualty Care and Management and

Applications for Combat Casualty Care, is impressed with the pace at which this study is proceeding. "[Polt has] made remarkable progress," he said.

Given continued, "From preclinical studies we know this drug is as potent as morphine, without morphine's adverse effects such as respiratory depression. We also know that it produces sedation only at 50-times the normal dose so it should not impair cognitive performance. If it is also non-addictive then we have a serious home run. Hopefully we'll get similar results when administered to humans in upcoming clinical trials. But even if we improve only the safety profile when compared to morphine, well that's a significant advancement in itself. However, I think we are going to do substantially better than that."

For more information, see:  
Robin Polt's web page  
<http://www.chem.arizona.edu/polt>  
U.S. Patent Application 20060148679  
(July 2006)

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