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Researchers identify possible new targets for treating pain in women

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Women and men experience pain, particularly chronic pain, very differently. The ability of some opioids to relieve pain also differs between women and men. While it has been recognized since the mid-nineties that some narcotic analgesics are more effective in women than men, the reason for this difference was largely unknown.

Narcotic analgesics decrease pain by activating opioid receptors, which are located on nerves that transmit painful sensations. Since levels of mu, delta, and kappa opiate receptors—the three main types of opioid receptor in the brain and spinal cord—are not thought to differ dramatically in men and women, it was difficult to understand why the effectiveness of some painkillers is dependent on sex.

Now, research supported by the National Institute of Drug Abuse (NIDA) has revealed that the same major types of opioid receptor interact differently, depending on sex. The spinal cord of female laboratory animals was found to contain almost five times more kappa-mu heterodimer—a complex of mu-opioid and kappa-opioid receptor—than the spinal cord of male animals. Furthermore, the amount of mu-kappa heterodimer in the spinal cord of the females was about four times higher when their levels of estrogen and progesterone were at their peak. Subsequently, researchers found that both estrogen and progesterone are critical for the formation of mu-kappa opioid receptor heterodimers.

This research was conducted by Alan Gintzler, PhD, professor of

biochemistry, Department of Obstetrics and Gynecology, and his senior collaborators Sumita Chakrabarti, PhD, and Nai-Jiang Liu, PhD, at the State University of New York (SUNY) Downstate Medical Center

The discovery of a mu-kappa opioid receptor complex that is more prevalent in the spinal cord of females than males and that is synchronized with the ebb and flow of ovarian hormones could explain why drugs used to treat pain, such as pentazocine, nalbuphine, and butorphanol—which primarily act on mu-opioid and kappa-opioid receptors—are more effective in women than men. The activation of the kappa-opioid receptor within the kappa-mu-opioid receptor complex could provide a mechanism for recruiting the pain-relieving functions of spinal kappa-opioid receptors without also activating their pain-promoting functions.

The research by Drs. Gintzler, Liu, and Chakrabarti, which was recently published in the Proceedings of the National Academy of Sciences and the *Journal of Neuroscience*, suggests that kappa-mu opioid receptor heterodimers could function as a molecular switch that shifts the action of kappa-opioid receptors and endogenous chemicals that act on them from pain-promoting to pain-alleviating. Kappa-mu opioid receptor heterodimers could serve as a novel molecular target for pain management in women.

Dr. Gintzler's research suggests that physicians should take the stage of the menstrual cycle into account before deciding which drugs to prescribe to treat pain in women. While some drugs might be very effective in treating pain at times when estrogen and progesterone levels are high, they could heighten pain when levels are low. "This consideration could become even more critical in managing pain in postmenopausal and elderly women," said Dr. Gintzler. "Further research is needed to flesh out these possibilities."

The *Journal of Neuroscience* paper appeared in the August 17, 2011 edition.