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Study first to pinpoint why analgesic drugs may be less potent in females than in males

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Investigators at Georgia State University's Neuroscience Institute and Center for Behavioral Neuroscience are the first to identify the most likely reason analgesic drug treatment is usually less potent in females than males. This discovery is a major step toward finding more effective treatments for females suffering from persistent pain.

"Opioid-based narcotics (such as morphine) are the most widely prescribed therapeutic agents for the alleviation of persistent pain; however, it is becoming increasingly clear that morphine is significantly less potent in women compared with men. Until now, the mechanism driving the phenomenon was unknown," said Anne Murphy, Ph.D., a Georgia State Professor of Neuroscience and member of the Center for Behavioral Neuroscience, who conducted the research with Dayna Loyd, Ph.D.

Murphy recently solved the mystery with findings printed in the December issue of *The Journal of Neuroscience* that show that previously reported differences in morphine's ability to block pain in male versus female rats are most likely due to sex differences in mu-opioid receptor expression in a region of the brain called the periaqueductal gray area (PAG).

Located in the midbrain area, the PAG plays a major role in the modulation of pain by housing a large population of mu-opioid receptor expressing neurons. Morphine and similar drugs bind to these mu-opioid receptors analogous to a 'lock and key' and, ultimately, tell the brain to

stop responding to pain signals to the nerve cells resulting in the reduced sensation of pain.

Using a series of anatomical and behavioral tests, Murphy and Loyd were able to determine that male rats have a significantly higher level of mu-opioid receptors in the PAG region of the brain compared with females. This higher level of receptors is what makes morphine more potent in males because less drug is required to activate enough receptors to reduce the experience of pain. Interestingly, when they used a plant-derived toxin to remove the mu-opioid receptor from the PAG, morphine no longer worked, suggesting that this brain region is required for opiate-mediated pain relief.

Additional tests also found females reacted differently to morphine depending on the stage of their estrous cycle. These findings indicate that steroid hormones may affect mu-opioid receptor levels in the region of the PAG that are essential for analgesia and also suggest that the actions of morphine are estrous stage-dependent.

"Interestingly, sex is not the only factor that has been shown to affect the potency of various pharmacological agents. Recent studies have reported an influence of age and ethnicity, and further argue for the inclusion of a wide range of study subjects in pain management research," Murphy said. "In addition, despite the rapidly mounting evidence regarding the limitations of opiates in treating persistent pain, opioid-based drugs remain the primary pharmacological tool for pain management. Clearly additional research with the inclusion of female subjects needs to be devoted to determining a more potent treatment for persistent pain in women."

Source: Georgia State University