Boosting natural brain opioids may be a better way to treat anxiety

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Boosting natural brain opioids may be a better way to treat disabling emotions, says new research revealing their role in regulating critical brain circuits affecting fear and anxiety.

Published in *Nature Communications* by University of Sydney scholars, the findings suggest medications that boost the effect of natural brain opioids might be a better way to reduce anxiety than 'receptor-binding' opioid drugs like morphine, which have major side effects.

Fear and anxiety help defend us against harm, and are largely controlled via neural circuits of interconnected nerve cells and synaptic activity in the brain's amygdala that allow neurons to pass electrical or chemical signals to each other.

Specialised neural circuits control these emotions, but disturbances in the circuits can cause prolonged and disabling emotional responses that are out of proportion to threatening events.

These disturbances are thought to underlie many anxiety disorders such as phobias and post-traumatic stress disorder, which affect up to a million Australians each year.

Anxiety disorders affect 14 per cent of Australians but are poorly managed by commonly prescribed medications such as benzodiazepines and 5HT-reuptake inhibitors.

"These drugs weren't developed to treat anxiety but they're widely used because of chance findings suggesting their clinical usefulness," says the University of Sydney's Associate Professor Elena Bagley, who led the research.

"Many experts agree that better anxiety treatments will come when science uncovers how the neural circuits and endogenous or naturally occurring opioids regulate fear and anxiety.

"The precise action of these natural opioids in the brain is poorly understood, but better insights are critical because these opiods control how we acquire and store fear memories and regulate our emotional responses once a threat has passed."

Experiments in mice have shown that 'deleting' the natural opioid enkephalin, which is heavily expressed in the brain's amygdala, increases their fear, anxiety and aggressiveness. By contrast, increasing enkephalin or reducing its breakdown reduces these behaviours.

While this effect of enkephalin suggests that it is anxiety-inhibiting, when it binds to different receptors in the amygdala, it exerts opposing effects, depending on which one it binds to.

For example, when it binds to the mu-opioid receptor, enkephalin promotes anxiety, but when it binds to the delta-opioid receptor, it inhibits it.

"Given this complexity, understanding the cellular actions of natural opioids at these two receptors is critical if we hope to use opioid-related medications

for emotional issues," says Dr Bagley.

"Our findings show that opioids produced and released by our own brain cells strongly regulate these critical neural circuits that are important for fear responses.

"We also show that we could boost the actions of these endogenous opioids using a novel pharmacological approach."

More information: Bryony L. Winters et al, Endogenous opioids regulate moment-to-moment neuronal communication and excitability, *Nature Communications* (2017). DOI: 10.1038/ncomms14611

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