When Chronic Pain Can Suppress the Opioid Kick

New Insights from Preclinical Research

OPIOIDS are widely used for the management of intense acute pain, the management of cancer-related pain, or in an end-of-life palliative context. However, their regular use for chronic noncancer pain remains a subject of debate. Controlled preclinical studies may help to address the complex interaction between opioid pain relief and abuse potential, but they still remain scarce in the literature. In this issue of Anesthesiology, Ewan and Martin show that morphine and heroin lose their capacity to facilitate ventral tegmental area (VTA) self-stimulation when delivered in a neuropathic pain context.

These data support the idea that a chronic pain condition can decrease the hedonic properties of opioids.

Preclinical research on opioid abuse in chronic pain faces technical difficulties, such as experimentally separating pain relief from addiction-related behaviors. Self-administration experiments, a gold standard in preclinical studies on drug abuse, illustrate this difficulty. In these procedures, the animal self-administers the drug by pressing a lever switching a pump connected to an intravenous catheter. At doses high enough to relieve allodynia, the opioid self-administration in neuropathic rats correlates with antiallodynic action, thus making it difficult to evaluate whether self-administration was motivated by the opioid analgesic or rewarding properties. At lower doses, the opioid self-administration was inhibited under neuropathic conditions, but this finding is somewhat limited by the poor allodynia relief observed at these doses. Other authors also have shown that partial nerve injury can reduce morphine molecular action on μ-opioid receptors within the VTA (start point of the brain mesolimbic system that is critical for motivated behaviors), morphine-induced dopamine release in the nucleus accumbens (endpoint of the mesolimbic system), and morphine-induced conditioned place preference. Preclinical data were thus supportive of reduced opioid-rewarding properties in a neuropathic pain context, but it was still unclear whether it was the case for opioid doses strong enough to relieve neuropathic pain symptoms.

In their report, Ewan and Martin elegantly circumvent this technical difficulty by using the intracranial self-stimulation (ICSS) procedure. In this paradigm, rodents press a lever to self-administer rewarding electrical stimulations through an electrode implanted into the brain. ICSS behavior was discovered in the 1950s and has been demonstrated in various mammals, including humans. Historically, ICSS was implemental in the discovery of brain regions that form the brain reward pathways. Most experiments are conducted with the electrode implanted into the medial forebrain bundle, a large fiber pathway within the lateral hypothalamus which includes, among others, the dopamine fibers arising from VTA neurons and projecting to the nucleus accumbens. ICSS behavior is also supported by other brain regions, such as the VTA itself. In the current study, the VTA was chosen because it is the area where opioids act to increase the activity of dopamine neurons. As drugs of abuse are known to alter ICSS behavior, this paradigm was currently used to assess opioid action in rats with spinal nerve ligation, a classic model of neuropathic pain in rodents.

When done in appropriate brain regions, ICSS behavior is robust, highly stable, and not subject to satiety. Usually, researchers study either the “reward threshold” (i.e., minimal electrical intensity sustaining the animal response) or the “curve shifts” as in the current case (i.e., the changes in rate [lever press]–frequency curves). The main parameters obtained from these curves are the maximal response rate and the EF50, the frequency at which rodents emit 50% of their maximal response, which is somewhat analogous to ED50 in pharmacology. After exposure to a drug of abuse, the amount of stimulation required to sustain a response is decreased. This reflects the reward facilitating properties of this drug and results in a leftward shift in the ICSS rate-frequency curve. Ewan and Martin show that morphine tested at antiallodynic doses loses this capacity to shift ICSS behavior in a neuropathic pain context, and heroin requires higher doses to do so. This finding demonstrates that the opioid capacity to facilitate hedonia through mesolimbic system recruitment is blunted in a neuropathic pain condition. On the contrary, the capacity of cocaine to affect ICSS behavior remained intact. This finding shows that neuropathic pain does not specifically blunt the endogenous reward system, but rather suppresses its capacity to respond to opioids, even at antiallodynic doses.

This preclinical work supports the idea of reduced risk of opioid abuse in a neuropathic pain context, but some limitations should be pointed out. ICSS is a heavy procedure to set up and master, requiring surgery, appropriate operant chambers, technical skills and time-consuming procedures. The current data were thus obtained from a limited number of animals, the same animals being used for all tested drugs and doses. Although the stability of ICSS behavior allows...
such protocol, the findings remain to be supported by independent experiments. Moreover, an important aspect of chronic pain treatment by opioids was not considered: its duration. Thus, it remains to be tested whether the blunted ICSS response would be present after long-term opioid treatment. Ideally this should be done by combining long-term self-administration procedure in neuropathic animals with regular assessment of their ICSS behavior, which is challenging but possible.9 Last, the choice of chronic pain model may be important as not all types of acute or chronic pain are clinically sensitive to opioids at usual doses or remain sensitive to them with long-term treatments.

By providing their data on opioid and ICSS behavior in a pain context, Ewan and Martin are nevertheless opening an important research avenue with translational potential and numerous questions to address concerning chronic opioid treatments, potential vulnerability factors such as a past history of dependence or individual susceptibility, or the considered type of chronic pain. These aspects should likely be clarified before concretely considering ICSS procedure for opioid drug comparison in preclinical screening. For neuroscience research, this study also raises the question of the underlying mechanism leading to this altered opioid response of the reward systems under chronic pain. This promising study should help foster interactions between clinicians and basic researchers to promote progress regarding the question of opioid abuse in a pain context.

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References
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