Addictive behavior

https://doi.org/10.1038/s44220-024-00300-7

Hypocretin receptor antagonists prevent opioid addiction

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The opioid abuse epidemic is a major health concern that requires new pain management strategies. Findings now show that suvorexant, a dual hypocretin receptor antagonist, reverses the anatomical and circuit alterations induced by opioids and decreases addictive behavior while maintaining the analgesic properties of the drugs.

The World Health Organization (WHO) estimates that approximately 480,000 people die annually from opioid abuse. This death toll, which surpasses those from gun violence and automobile accidents, is a major health concern. An overwhelming majority of patients with an opioid use disorder (OUD) report that their initial exposure was due to a medical prescription for pain management[1]. The importance of exploring alternative pain management strategies or curbing the addictive nature of opioids while retaining their pain-relieving properties cannot be overstated. However, this requires that we understand how brain circuits are altered by opioid use. In this issue of *Nature Mental Health*, McGregor et al.[2] aimed to better understand the impact of opioids on hypocretin signaling in addiction-related neural circuitry in mice. Importantly, the authors found that the use of the dual hypocretin receptor antagonist suvorexant reversed the anatomical and circuit alterations induced by opioids and decreased addictive behavior, without preventing opioid-mediated analgesia. This suggests that suvorexant could be used in combination with opioids for pain management while limiting the risk of substance abuse in patients.

Hypocretin, a neurotransmitter discovered in the 1990s, is exclusively synthesized by a specific group of neurons in the lateral hypothalamus[3]. Hypocretin signaling is involved in sleep–wake control and reward-seeking behavior such as addiction[4]. Narcolepsy is

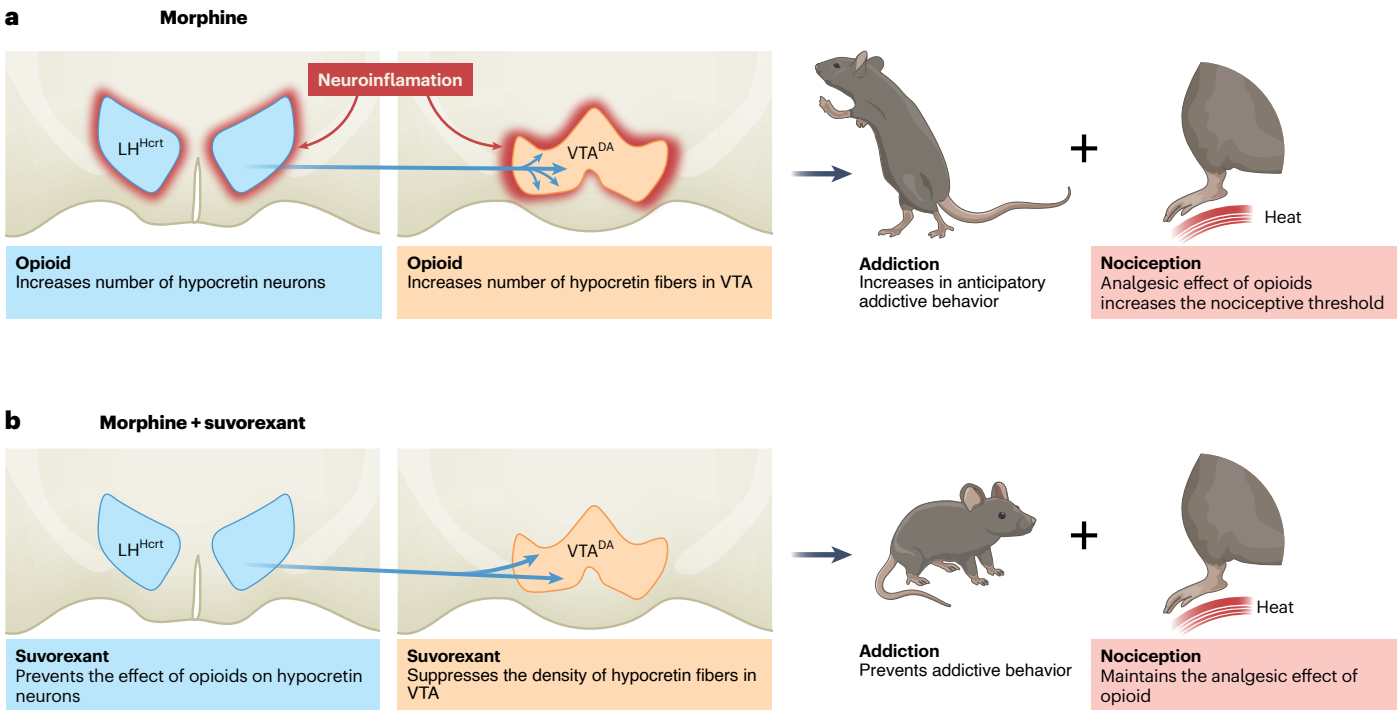

Fig. 1 | Suvorexant, a dual hypocretin receptor antagonist, prevents opioid alteration of hypocretin neurons and addictive behaviors while maintaining analgesia. a, Morphine causes an increase in the number of hypocretin neurons in the lateral hypothalamus (LH^{Hcrt}), the density of hypocretin axonal fibers in the VTA and the number of dopamine neurons in the VTA (VTA^{DA}), and causes neuroinflammation by increasing the number of activated microglia. These changes are associated with anticipatory addictive behavior and an increased nociceptive threshold in response to heat, indicative of analgesia. **b**, The preemptive administration of suvorexant 60 minutes before morphine prevents the effect of opioids on hypocretin neurons and microglia. This prevents addictive behavior while maintaining the analgesic properties of morphine.

a sleep disorder characterized by the loss of hypocretin-secreting cells. Narcolepsy symptoms such as sleepiness are treated with drugs that have strong abuse potential (for example, amphetamines and γ-hydroxybutyrate), yet people with narcolepsy rarely experience drug abuse[5]. Interestingly, postmortem studies show that people with heroin addiction have a 54% increase in the number of hypocretin neurons compared to healthy controls[6]. Chronic administration of morphine in mice triggers a similar increase in the number of hypocretin neurons, and this increase is due to heightened hypocretin synthesis by individual neurons and not to neurogenesis[6]. Similar effects are also reported in rats following chronic cocaine or fentanyl administration[7].

In this issue, McGregor et al.[2] administered morphine to mice daily for 14 days and analyzed its effect on hypocretin neuron numbers and morphology using immunohistochemistry and microscopy. They first confirmed that the opioid-mediated increase in hypocretin cell numbers is dependent on functioning opioid receptors by using naltrexone, an opioid receptor antagonist. They also found that the opioid-mediated increase in hypocretin cell numbers was not due to other cell types (such as GABA or melanin-concentrating hormone (MCH) neurons) starting to synthesize hypocretin de novo. Instead, the increase in hypocretin cell numbers was due to an increased production of hypocretin in hypocretin neurons. Other cell types in the lateral hypothalamus, such as MCH neurons, were unaffected by opioid administration, indicating that the opioid effect on morphology and hypocretin expression is cell type specific.

Next, the authors aimed to determine whether blocking hypocretin receptors with suvorexant, a dual hypocretin receptor antagonist, would limit the opioid-mediated increases in hypocretin cells[2]. To do this, they injected suvorexant in mice 60 minutes before injecting morphine, repeating this daily over a 2-week period. They found that suvorexant prevented the opioid-mediated increase in hypocretin neurons seen when morphine was administered alone. They also found that in addition to increasing the number of hypocretin cells, morphine increased the density of hypocretin axonal fibers in the ventral tegmental area (VTA), one of the main nuclei in the addiction pathway (Fig. 1). Importantly, when suvorexant was pre-emptively given before morphine, hypocretin fiber density in the VTA was reduced compared to that in the morphine-only group. This establishes a potential link between the effects of opioids on hypocretin neurons and the modulation of 'addiction circuits'.

Neuroinflammation has been observed in patients suffering from chronic OUD and contributes to the maintenance of substance abuse[8]. Hence, McGregor et al.[2] wanted to determine whether suvorexant could also limit this aspect of substance abuse. They found that morphine administration activated microgliosis by increasing the number of microglia and the size of their soma in both the lateral hypothalamus and the VTA and that suvorexant prevented this inflammatory effect. Thus, both opioids and hypocretin directly affect microglia (Fig. 1).

Finally, the authors tested the effect of suvorexant on the addictive behavior of mice following chronic morphine injection[2]. They found that blocking hypocretin receptor function prevented opioid-mediated anticipatory behaviors that characterize chronic morphine addiction. In addition, administration of suvorexant diminished the opioid withdrawal symptoms induced by naloxone. More importantly, blocking hypocretin receptors with suvorexant did not interfere with the analgesic effect of morphine: mice subjected to a nociceptive test – in which the floor of their cages was progressively heated – maintained a high nociceptive threshold with morphine even when suvorexant was present. This demonstrates the beneficial effect of suvorexant for preventing addictive behavior while maintaining the analgesic effects of opioids (Fig. 1).

The study by McGregor et al.[2] conducted in mice has important and pragmatic implications for the current opioid abuse epidemic in the human population[1]. For example, their findings suggest that dual hypocretin receptor antagonists have the potential to mitigate addictive anticipatory behaviors without compromising the analgesic efficacy of opioids. This dual action holds promise for the development of combination therapies to provide pain management while minimizing the risk of substance abuse. This treatment combination could easily be tested in patients given that suvorexant has few side effects[9]. Patients with OUD often report suffering from insomnia[10], and suvorexant, which is commonly prescribed as a sleeping aid[9], could also contribute to resolving this symptom of OUD.

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Published online: 23 August 2024

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Competing interests

The authors declare no competing interests.