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RESEARCH HIGHLIGHT

Calcitonin receptor signal: a potential target for opioid use disorder?

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If we were to ask any addiction neuroscience researcher about their main scientific goal and dream, the overwhelming response would undoubtedly be to discover treatments and targets that can prevent and disrupt the various phases of drug addiction. Throughout the history of our field, this has been the shared objective for our community, spanning several decades [1]. Despite the noble intentions, fervent efforts, and significant investments, the stark reality remains that treatment options have remained largely unchanged [2]. This stagnation in the state of the art has increasingly caused disappointment and raised doubts about the validity of our field. While this background may sound cynical and pessimistic, it is important to note that this is not the end. As scientists in the addiction neuroscience field, we acknowledge our past mistakes and failures. Nevertheless, we persist in our pursuit of creating and proposing new solutions and approaches. We are committed to learning from our previous missteps and are dedicated to the ongoing exploration of innovative avenues [3].

In recent years, there has been a growing interest in exploring potential pharmacotherapies to treat drug addiction. Among various approaches, one significant area of focus has been targeting neuropeptides and their receptors within the gut-brain axis [4]. Calcitonin receptors (CTRs) have emerged as a particularly promising example in this regard. Pharmacological activation of CTRs has shown promise in reducing drug-induced activation of the mesolimbic dopamine system and drug taking. However, the role of CTRs in opioid addiction remains a critical area for investigation. This is because current therapies for opioid addiction predominantly rely on the use of full or partial mu opioid receptor agonists and antagonists, which are considered effective treatments. However, given the current opioid epidemic and the urgent need for more effective treatments, investigating the involvement of CTRs and other signaling pathways could provide new avenues for developing more targeted and potentially more effective treatments for opioid addiction. In this issue of *Neuropsychopharmacology*, Zhang et al. [5] delve into this topic to further expand our understanding of the involvement of CTRs in opioid self-administration with a specific emphasis on the nucleus accumbens (NAc) shell because of its pivotal role in mediating opioid-related behaviors.

In this comprehensive paper, the authors initially embarked on an impressive endeavor to characterize cell type-specific patterns of CTRs expression in the NAc. They employed a wide array of state-of-the-art techniques, ranging from immunohistochemistry to single nuclei RNA sequencing and fluorescent in-situ hybridization in combination with transgenic rats expressing Cre recombinase under the Drd1 or Drd2 promoter, enabling the identification of specific cell types. Through this multi-faceted approach, the authors successfully unraveled the anatomical expression of CTRs on D1R- and D2R-expressing medium spiny neurons (MSNs) within the medial shell subregion of the NAc. Furthermore, the authors discovered that *Calcr* transcripts were expressed at higher levels in D2R-expressing MSNs than in D1R-expressing MSNs. Although these findings provide valuable insights into the expression pattern differences of CTRs in distinct neuronal populations within the NAc, the specific functional role of CTRs in either D1R- or D2R-expressing MSNs in the context of opioid self-administration remains unknown.

Thus, the authors examined the cell type-specific role of CTRs expressed on both D1R- and D2R-expressing MSNs in opioid self-administration. To accomplish this, they employed transgenic rats and used Cre-dependent CTR knockdown viruses that were injected into the medial NAc shell. The efficiency of the knockdown viruses was validated and confirmed using immunohistochemistry and fluorescent in-situ hybridization reporting a *Calcr* transcript expression reduction of ~50% in rats infused with the knockdown viruses versus rats that were infused with the control viruses. The authors trained the rats for oxycodone self-administration under a fixed-ratio 1 or progressive ratio reinforcement schedules, with doses of 0.06 or 0.15 mg/kg/infusion, over 10 sessions lasting 3 h each. The authors found that decreased CTR expression, in D1R-expressing neurons of medial NAc shell enhanced the acquisition of oxycodone self-administration and increased motivation to self-administer oxycodone. In contrast, decreased CTR expression in D2R-expressing neurons of medial NAc shell decreased acquisition of oxycodone self-administration and reduced motivation to self-administer oxycodone. Importantly, the effects observed were specific to oxycodone self-administration. There were no effects of cell type-specific knockdown of CTR expression on acquisition of sucrose self-administration in drug-naïve rats.

Together, these findings highlight the cell type-specific and bidirectional effects of endogenous CTR signaling in the NAc on opioid self-administration. Reduction of CTRs in D1R-expressing MSNs decreased opioid self-administration, whereas reductions of CTRs in D2R-expressing MSNs increased opioid self-administration. The comprehensive characterization of functional,

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neuroanatomical, and sequencing aspects of *Calcr*-expressing cells in the NAc by Zhang and colleagues is commendable, as it significantly expands our understanding of the central mechanisms underlying the effects of CTRs in the context of opioid self-administration. This study paves the way for exploring new potential targets for opioid addiction. However, it should be noted that this is just the beginning of an extensive and critical line of research. Many unanswered questions remain, such as elucidating the precise molecular mechanisms mediating the effects of CTR activation on opioid-taking behaviors, generalizing these findings to female rats, and perhaps most important, identifying a way to translate these results to phase 1 and 2 clinical trials to determine efficacy of this novel mechanism to human opioid addiction. This necessitates implementing iterative and bidirectional processes, where insights from preclinical studies inform clinical research, and clinical observations guide further preclinical investigations. Given the importance and potential impact of this work, there is a collective sense of urgency to initiate these processes promptly.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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