KJP

Korean J Pain 2023;36(4):405-407
https://doi.org/10.3344/kjp.23258
pISSN 2005-9159, eISSN 2093-0569

Editorial

Towards precision pain management—the case for targeting DRP1 in remifentanil-induced hyperalgesia

Ki Tae Jung

Department of Anesthesiology and Pain Medicine, Chosun University Hospital, School of Medicine and Medical College, Chosun University, Gwangju, Korea

Received September 6, 2023; Accepted September 9, 2023

Handling Editor: Francis S. Nahm

Correspondence: Ki Tae Jung
Department of Anesthesiology and Pain Medicine, Chosun University Hospital, School of Medicine and Medical College, Chosun University, 365 Pilmun-daero, Dong-gu, Gwangju 61453, Korea
Tel: +82-62-220-3223, Fax: +82-62-223-2333, E-mail: mdmole@chosun.ac.kr

Even though it is widely used in surgery as a potent and short-acting opioid analgesic, remifentanil also causes opioid-induced hyperalgesia (OIH), as opioids paradoxically can increase sensitivity to painful stimuli [1]. The exact mechanisms behind remifentanil-induced hyperalgesia (RIH) are not entirely understood but have been attributed to various factors. Prevention and treatment for RIH are not easy and unpredictable. Tapering or discontinuation is not universally effective and may not be applicable in acute settings where remifentanil is often used [2]. And while adjuvant therapies such as N-methyl-D-aspartate (NMDA) receptor antagonists or alpha-2 agonists may have a role in managing OIH, more evidence is required [3,4].

In the last issue of the Korean Journal of Pain, the research of Zhou et al. [5] provided insight into a potential therapeutic strategy for RIH and reinforced the importance of the dynamin-related protein 1 (DRP1)-mitochondria-reactive oxygen species (ROS) pathway in pain modulation. Upregulation of DRP1, a key protein involved in mitochondrial fission, can lead to excessive mitochondrial fission, which may contribute to mitochondrial dysfunction [6]. Dysfunctional mitochondria may produce excessive ROS, activating pain pathways [7]. DRP1-mediated mitochondrial fission has been shown to play a role in synaptic plasticity [8]. Given that neural plasticity is one of the essential factors in the development of chronic pain and possibly OIH [9], DRP1 upregulation could be a contributing factor.

In this study, antisense oligodeoxynucleotides against DRP1 (AS-DRP1), administered intrathecally, relieved pain behavior due to RIH via downregulation of the DRP1-mitochondria-ROS pathway. By reducing DRP1 expression, hyperactivity of the spinal NR2B subunit of the NMDA receptor associated with neural hyperexcitability was reduced [10,11]. These findings emphasize the role of the DRP1-mitochondria-ROS-NMDA pathway in the development of RIH. Inhibiting DRP1 in the spinal cord with AS-DRP1 may offer an effective treatment or prevention of RIH.

Interestingly, the authors used antisense oligodeoxynucleotide (ASO) drug delivery methods. ASOs are short, synthetic strands of DNA or RNA that specifically bind to a designated RNA target [12]. By binding to target mRNA, they can modulate post-transcriptional gene expression, preventing the mRNA from being translated into a pro-

tein, such as DRP1. Treatments using ASOs have been approved for neuromuscular diseases, such as spinal muscular atrophy and Duchenne muscular dystrophy [13], and research is ongoing regarding the use ASOs to target oncogenes and neurodegenerative diseases like Alzheimer's and Huntington's. The application of ASOs might provide advantages even in pain medicine [13]. ASOs offer the advantage of gene-specific targeting with minimal off-target impacts, making them suitable for precision and personalized pain management strategies. They also can be rapidly developed to meet unmet and emerging clinical needs without starting from scratch. Enhanced delivery technologies may improve effectiveness and enable more precise drug delivery, which could potentially reduce the doses of drugs administered. However, there are challenges to overcome, such as the difficulty in extrahepatic delivering oligonucleotides efficiently, unintended effects on other cellular processes, and potential immune responses to the ASOs [13].

In summary, the study posited a connection between RIH and the DRP1-mitochondria-ROS pathway. Understanding the role of DRP1 and mitochondrial fission in OIH could lead to new therapeutic strategies, such as (AS-DRP1), to mitigate the development of OIH in patients on opioid therapy. In addition, ASO drugs have the potential to rapidly address unfulfilled and emerging clinical needs. These advancements will offer optimism that presently incurable pain conditions may soon become treatable through precision genetic medicine.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed for this paper.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

No funding to declare.

AUTHOR CONTRIBUTIONS

Ki Tae Jung: Concept/writing/manuscript preparation.

ORCID

Ki Tae Jung, https://orcid.org/0000-0002-2486-9961

REFERENCES

1. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology 2006; 104: 570-87.
2. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician 2011; 14: 145-61.
3. Cohen SP, Christo PJ, Wang S, Chen L, Stojanovic MP, Shields CH, et al. The effect of opioid dose and treatment duration on the perception of a painful standardized clinical stimulus. Reg Anesth Pain Med 2008; 33: 199-206.
4. Lee C, Kim YD, Kim JN. Antihyperalgesic effects of dexmedetomidine on high-dose remifentanil-induced hyperalgesia. Korean J Anesthesiol 2013; 64: 301-7.
5. Zhou S, Pan Y, Zhang Y, Gu L, Ma L, Xu Q, et al. Antisense oligodeoxynucleotides against dynamin-related protein 1 reduce remifentanil-induced hyperalgesia by modulating spinal N-methyl-D-aspartate receptor expression in rats. Korean J Pain 2023; 36: 316-27.
6. Gibellini L, Bianchini E, De Biasi S, Nasi M, Cossarizza A, Pinti M. Natural compounds modulating mitochondrial functions. Evid Based Complement Alternat Med 2015; 2015: 527209.
7. Tsushima K, Bugger H, Wende AR, Soto J, Jenson GA, Tor AR, et al. Mitochondrial reactive oxygen species in lipotoxic hearts induce post-translational modifications of AKAP121, DRP1, and OPA1 that promote mitochondrial fission. Circ Res 2018; 122: 58-73.
8. Atkins K, Dasgupta A, Chen KH, Mewburn J, Archer SL. The role of Drp1 adaptor proteins MiD49 and MiD51 in mitochondrial fission: implications for human disease. Clin Sci (Lond) 2016; 130: 1861-74.
9. Petersen-Felix S, Curatolo M. Neuroplasticity--an important factor in acute and chronic pain. Swiss

Med Wkly 2002; 132: 273-8.
10. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000; 288: 1765-9.
11. Paoletti P, Bellone C, Zhou Q. NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. Nat Rev Neurosci 2013; 14: 383-400.
12. Mohan A, Fitzsimmons B, Zhao HT, Jiang Y, Mazur C, Swayze EE, et al. Antisense oligonucleotides selectively suppress target RNA in nociceptive neurons of the pain system and can ameliorate mechanical pain. Pain 2018; 159: 139-49.
13. Roberts TC, Langer R, Wood MJA. Advances in oligonucleotide drug delivery. Nat Rev Drug Discov 2020; 19: 673-94.