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**The mechanism of action of pulsed radiofrequency in reducing pain: a narrative review**

**Abstract**

Pain from nervous or musculoskeletal disorders is one of the most common complaints in clinical practice. Corticosteroids have a high pain-reducing effect, and their injection is generally used to control various types of pain. However, they have various adverse effects including flushing, hyperglycemia, allergic reactions, menstrual changes, immunosuppression, and adrenal suppression. Pulsed radiofrequency (PRF) is known to have a pain-reducing effect similar to that of corticosteroid injection, with nearly no major side effects. Therefore, it has been widely used to treat various types of pain, such as neuropathic, joint, discogenic, and muscle pain. In the current review, we outlined the pain-reducing mechanisms of PRF by reviewing previous studies. When PRF was first introduced, it was supposed to reduce pain by long-term depression of pain signaling from the peripheral nerve to the central nervous system. In addition, deactivation of microglia at the level of the spinal dorsal horn, reduction of proinflammatory cytokines, increased endogenous opioid precursor messenger ribonucleic acid, enhancement of noradrenergic and serotonergic descending pain inhibitory pathways, suppression of excitation of C-afferent fibers, and microscopic damage of nociceptive C- and A-delta fibers have been found to contribute to pain reduction after PRF application. However, the pain-reducing mechanism of PRF has not been clearly and definitely elucidated. Further studies are warranted to clarify the pain-reducing mechanism of PRF.

**Keywords:** Pain; Pain management; [Pulsed radiofrequency treatment](https://www.ncbi.nlm.nih.gov/mesh/68061208); Review

**Introduction**

Most people experience pain due to pathologies of the nervous or musculoskeletal systems [1,2]. When the degree of pain is severe, patients’ quality of life decreases, and their function in daily activities and work deteriorates [1,2]. Therefore, pain control is important in clinical practice. Corticosteroid injections are frequently used [3,4]. However, they can have adverse effects including flushing, hyperglycemia, allergic reactions, menstrual changes, immunosuppression, and adrenal suppression [5,6]. To date, many injection materials have been suggested as substitutes for corticosteroids [7-9]. However, the effectiveness of materials that substitute corticosteroids is generally inferior to that of corticosteroids.

Electrical stimulation is thought to have a pain-reducing effect, and several types of electrical simulations have been used to alleviate pain [10-12]. Of these various stimulations, radiofrequency was found to have a pain-reducing effect similar to corticosteroid injection [13-15]. Continuous radiofrequency (CRF) exposes the target nerves or tissues to high temperatures (70°C–90°C) via continuous electrical stimulation [16]. Nerves or tissues treated with CRF are ablated [16]. The ablation of targeted nociceptive nerve fibers is thought to be the main mechanism of pain reduction after CRF [16]. However, as experiences of CRF use were accumulated, physicians realized that the pain could be effectively controlled even not under such high temperatures [17-19]. Therefore, it was thought that the formation and action of the electrical field around the target nerves or tissues would be a more important mechanism of PRF action than ablation by high temperatures. In 1998, Sluijter et al. [20] first introduced pulsed radiofrequency (PRF). By placing a long resting phase between brief electrical stimulation, PRF does not produce sufficient heat to cause structural damage [20]. Therefore, major complications rarely occur after PRF. Since its introduction, PRF has been widely used for various types of pain, such as neuropathic, joint, discogenic, and muscular pain [21-24] (Fig. 1). ~~~~~~~~~~

**Basic theory of action of pulsed radiofrequency**

CRF supplies high-frequency continuous current to the targeted nerves [16]. The tip of the probe during the CRF procedure is at approximately 80°C and induces coagulative necrosis to target nerve structures around the probe tip [16]. Because the high temperature of a targeted structure decreases rapidly with distance from the electrode tip, lesions caused by the CRF procedure are well-circumscribed [16]. Therefore, other than damage to the targeted area, other tissues are rarely affected. Electrical neurolysis using CRF can inhibit the transfer of pain signals and has been proven to have a pain-reducing effect in various musculoskeletal disorders [25,26]. However, neurolysis can result in various side effects, such as sensory deficits, neuropathic pain, and skin burns [27,28]. ~~~~~~~~~~

**Pain-reducing mechanism of pulsed radiofrequency**

**1. Changes at the molecular level**

1) Decrease of microglial activity

Microglia in the dorsal horn of the spinal cord play an important role in the induction and maintenance of neuroinflammation, resulting in chronic neuropathic pain [31,32]. Activated microglia release various inflammatory cytokines and chemokines that facilitate nociceptive processing at all levels of the neuraxis, including the spinal cord and supraspinal centers. Some previous animal studies have demonstrated the downregulation of microglia in rats with neuropathic pain after the application of PRF [31,32]. In 2013, Cho et al. [31] applied PRF stimulation (voltage, 45 V; pulsed rate, 2 Hz; duration, 2 minutes) to the single dorsal root ganglion (DRG) in 23 Sprague-Dawley rats with sciatica due to herniated discs. After PRF application, mechanical withdrawal thresholds significantly increased, which persisted for 40 days. At 41 days after PRF application, microglia in the spinal dorsal horn were found to be deactivated. In 2016, Cho et al. [32] applied caudal epidural PRF (pulsed rate, 5 Hz; pulse width, 5 ms; duration, 10 minutes) to 35 Sprague-Dawley rats with sciatica due to herniated discs. At 14 days post-PRF, in the sections of the spinal cord from L3, L4, L5, L6, and S1, microglial activation was attenuated in rats with herniated discs. The deactivation of microglia in the spinal dorsal horn after PRF application seems to prevent the progression from acute pain to chronic pain.

2) Reduction of proinflammatory cytokines

Inflammation is associated with acute and chronic neuropathic pain. An increase in proinflammatory cytokines, such as various types of interleukin (IL) and tumor necrosis factor-alpha (TNF-α), has been observed in the DRG and spinal dorsal horn in animal models of neuropathic pain [33,34]. In 2013, Vallejo et al. [35] evaluated the effect of PRF (voltage, 45 V; pulse width, 20 ms; duration, 3 minutes) on the ipsilateral L5 DRG in six rats exhibiting sciatic nerve injury. Following PRF therapy, increased proinflammatory gene expression, such as IL-6 and TNF-α, observed in the sciatic nerve and DRG of rats, returned to baseline values. Along with the decreased activation of proinflammatory gene expression, mechanical allodynia in the hind paw was alleviated. In 2019, Jiang et al. [36] applied PRF (pulse width, 20 ms; pulsed rate, 2 Hz; duration, 2 minutes) on the ipsilateral L5 DRG or sciatic nerve in 20 rats with chronic constriction injury to the sciatic nerve. Mechanical allodynia and thermal hyperalgesia were relieved by PRF application. In addition, the authors found that IL-1β and TNF-α in the peripheral blood were downregulated. This anti-inflammatory effect of PRF appears to result in a reduction of various types of neuromuscular pain.

**2. Changes in neuronal activity**

1) Activation of pain-inhibitory mechanism

Previous animal studies have demonstrated that the noradrenergic descending inhibitory pathway plays an important role in analgesic action [38]. In addition, activation of serotonin receptors, such as 5-HT1, 5-HT2, and 5-HT3, induces analgesic effects [39,40]. In 2009, Hagiwara et al. [41] performed an animal study in rats to evaluate the mechanism of PRF action. They induced unilateral hind paw hyperalgesia by injecting 0.15 mL of Freund’s complete adjuvant and applied PRF at 37°C or 42°C for 3 minutes on the sciatic nerves. The pain-reducing effect of PRF was significantly inhibited by intrathecal injection of the alpha2-adrenoceptor antagonist (yohimbine), the selective 5-HT3 serotonin receptor antagonist (MDL72222), and the nonselective serotonin receptor antagonist (methysergide). Based on their results, they suggested that the pain-reducing effect of PRF is correlated with the enhancement of the noradrenergic and serotonergic descending pain inhibitory pathways.

2) Inhibition of the excitatory nociceptive C-fibers

In 2017, Huang et al. [29] conducted experiments in rats with neuropathic pain induced by left L5 spinal nerve ligation. After PRF stimulation (pulsed rate, 2 Hz; pulse width, 25 ms; duration, 5 minutes) on the left L5 DRG, the excitation of A- and C-afferent fibers was measured by checking the A- and C-components on the evoked field potential recordings. They found that PRF significantly suppressed the C-component overtime after 30 minutes, and this suppression was sustained for at least 140 minutes after PRF. However, the A component was not significantly suppressed after PRF stimulation. Mechanical allodynia and thermal analgesia significantly reduced after 10 and 14 days, respectively. This result indicates that PRF reduces neuropathic pain by inhibiting or suppressing the excitation of nociceptive C-fibers.

**Conclusion**

In this review, we discuss previous studies on the mechanism of pain reduction using PRF. LTD of pain signaling from the peripheral nerves to the central nervous system, deactivation of microglia, reduction of proinflammatory cytokines, an increase in the endogenous opioid precursor mRNA, enhancement of descending pain inhibitory pathway, and inhibition and injury of nociceptive nerve fibers were suggested to contribute to pain reduction after PRF. However, the pain-reducing mechanism of PRF has not been clearly and definitely elucidated. Further studies are warranted to clarify the pain-reducing mechanism of PRF.

**Notes**

**Conflicts of interest**

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

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**Referenc****es**

1. Chang MC. Conservative treatments frequently used for chronic pain patients in clinical practice: a literature review. Cureus 2020;12:e9934.

2. Choo YJ, Chang MC. Effectiveness of orthoses for treatment in patients with spinal pain. Yeungnam Univ J Med 2020;37:84–9.

3. Jang SH, Chang MC, Kwak SG. Follow-up of at least five years after lumbar transforaminal epidural steroid injection for radicular pain due to lumbar disc herniation. Ann Palliat Med 2020;9:116–8.

4. Kwak DG, Kwak SG, Lee AY, Chang MC. Outcome of intra-articular lumbar facet joint corticosteroid injection according to the severity of facet joint arthritis. Exp Ther Med 2019;18:4132–6.

5. Manchikanti L. Role of neuraxial steroids in interventional pain management. Pain Physician 2002;5:182–99.

6. Manchikanti L, Boswell MV, Singh V, Benyamin RM, Fellows B, Abdi S, et al. Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. Pain Physician 2009;12:699–802.

7. Lai WF, Yoon CH, Chiang MT, Hong YH, Chen HC, Song W, et al. The effectiveness of dextrose prolotherapy in plantar fasciitis: a systemic review and meta-analysis. Medicine (Baltimore) 2021;100:e28216.

8. Lee HJ, Ju J, Choi E, Nahm FS, Choe GY, Lee PB. Effect of epidural polydeoxyribonucleotide in a rat model of lumbar foraminal stenosis. Korean J Pain 2021;34:394–404.

9. Riewruja K, Phakham S, Sompolpong P, Reantragoon R, Tanavalee A, Ngarmukos S, et al. Cytokine profiling and intra-articular injection of autologous platelet-rich plasma in knee osteoarthritis. Int J Mol Sci 2022;23:890.

10. O’Connell NE, Ferraro MC, Gibson W, Rice AS, Vase L, Coyle D, et al. Implanted spinal neuromodulation interventions for chronic pain in adults. Cochrane Database Syst Rev 2021;12:CD013756.

11. Wu Y, Zhu F, Chen W, Zhang M. Effects of transcutaneous electrical nerve stimulation (TENS) in people with knee osteoarthritis: a systematic review and meta-analysis. Clin Rehabil 2022;36:472–85.

12. Yoon YS, Ko MH, Cho IY, Kim CS, Bajgai J, Jang HY, et al. Effects of personal low-frequency stimulation device on myalgia: a randomized controlled trial. Int J Environ Res Public Health 2022;19:735.

13. Kim TH, Chang MC. Comparison of the effectiveness of pulsed radiofrequency of the suprascapular nerve and intra-articular corticosteroid injection for hemiplegic shoulder pain management. J Integr Neurosci 2021;20:687–93.

14. Lee DG, Ahn SH, Lee J. Comparative effectivenesses of pulsed radiofrequency and transforaminal steroid injection for radicular pain due to disc herniation: a prospective randomized trial. J Korean Med Sci 2016;31:1324–30.

15. Lim JW, Cho YW, Lee DG, Chang MC. Comparison of intraarticular pulsed radiofrequency and intraarticular corticosteroid injection for management of cervical facet joint pain. Pain Physician 2017;20:E961–7.

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**Figure legends**

**Fig. 1.** The application of pulsed radiofrequency procedure on the lumbar dorsal root ganglion.

**Fig. 2.** The waveforms of continuous radiofrequency (CRF) and pulsed radiofrequency (PRF). While CRF is applied continuously without any resting phase, PRF has a long resting phase between brief electrical stimulation. RF, radiofrequency; Voltage, the amplitude of pulsed radiofrequency current.

**Table 1.** A brief, specific, descriptive title

|  |  |
| --- | --- |
| Variable | Value |
| Door-to-puncture time (hr) | 2.73±0.33 |
| Procedural time (hr) | 2.26±1.1 |
| Coiling techniques |  |
| Simple coiling | 232 (72.5) |
| Stent assisted coiling | 71 (22.2) |
| Balloon and stent assisted coiling | 17 (5.3) |
| Obliteration (RR) |  |
| Class I | 270 (84.3)a) |
| Class II | 45 (14.1) |
| Class III | 5 (1.5) |
| Procedural complication |  |
| Thromboembolic events | 25 (7.8) |
| Intraprocedural rupture | 14 (4.3) |

Values are presented as mean±standard deviation or number (%).

RR, Raymond-Roy classification.

a)Total may not sum to 100% because of rounding.