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Alternative Pain Management via Endocannabinoids in the Time of the Opioid Epidemic: Peripheral Neuromodulation and Pharmacological Interventions

Ming Tatt Lee, PhD[1,3], **Ken Mackie, MD**[4,5], **Lih-Chu Chiou, PhD**[1,2,6]

[1]Department of Pharmacology, College of Medicine, National Taiwan University, Taipei 10051, Taiwan

[2]Graduate Institute of Brain and Mind Sciences, College of Medicine, National Taiwan University, Taipei 10051, Taiwan

[3]Faculty of Pharmaceutical Sciences, UCSI University, Kuala Lumpur 56000, Malaysia.

[4]Gill Center for Biomolecular Research, Indiana University, Bloomington, Indiana 47405, USA.

[5]Department of Psychological and Brain Sciences, Indiana University, Bloomington, Indiana 47405, USA.

[6]Graduate Institute of Acupuncture Science, China Medical University, Taichung 40402, Taiwan.

Abstract

The use of opioids in pain management is hampered by the emergence of analgesic tolerance, which leads to increased dosing and side effects, both of which have contributed to the opioid epidemic. One promising potential approach to limit opioid analgesic tolerance is activating the CNS endocannabinoid system, via activation of CB_1 receptors (CB_1Rs) in the descending pain inhibitory pathway. In this review, we first discuss preclinical and clinical evidence revealing the potential of pharmacological activation of CB_1Rs in modulating opioid tolerance, including activation by phytocannabinoids, synthetic CB_1R agonists, endocannabinoid degradation enzyme inhibitors, and recently discovered CB_1R positive allosteric modulators. On the other hand, as nonpharmacological pain relief is advocated by the US-NIH to combat the opioid epidemic, we also discuss contributions of peripheral neuromodulation, involving the electrostimulation of peripheral nerves, in addressing chronic pain and opioid tolerance. The involvement of supraspinal endocannabinoid systems in peripheral neuromodulation-induced analgesia is also discussed.

[*]**To whom correspondence should be addressed:** Professor Lih-Chu Chiou, Graduate Institute of Pharmacology, College of Medicine, National Taiwan University, No. 1, Jen-Ai Rd., Section 1, Taipei 100, Taiwan. Phone: 886-2-2312-3456 ext 88323; FAX: 886-2-2341-4788; lcchiou@ntu.edu.tw.

Data Availability Statement

Data sharing is not applicable to this article because no new data were created or analysed in this study.

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The authors declare no conflict of interest.

Keywords

Opioid epidemic; opioid tolerance; endocannabinoids; CB_1 receptor; monoacylglycerol lipase; fatty acid amide hydrolase; peripheral neuromodulation

1. Opioid epidemic

The opioid epidemic is an issue of great concern in Northern America and many European countries (OECD, 2019) due to a continuously increasing death rate from misuse or overuse of opioids. In 2018, opioids contributed to more than two-third of overdose deaths in the US (US-CDC, 2020), exerting an enormous economic burden to the healthcare system (Hagemeier, 2018). Opioids are commonly prescribed for relieving cancer pain, postoperative pain or severe neuropathic pain. However, patients often continued to consume opioids even though opioids are categorized as a second or third-line treatment for chronic neuropathic pain (Urits *et al.*, 2020). This is possibly due to persistent painful conditions or postsurgical opioid over-prescription (Neuman *et al.*, 2019). Besides prescription opioids, improper disposal of leftover opioids and the availability of over-the-counter opioids have also substantially contributed to opioid misuse (Sobczak and Gorynski, 2020). Repeated opioid use leads to analgesic tolerance, dependence, and abuse (Skolnick, 2018). Increasing dosing of opioids for better pain control also increases the risk of constipation and respiratory depression, due to the excessive activation of opioid receptors in gastrointestinal and respiratory systems. The latter leads to opioid overdose death. In fact, the consumption of opioids for relieving non-cancer pain, as compared with other analgesics, positively correlates with an increased risk of all-cause mortality (Ray *et al.*, 2016). Thus, unresolved chronic pain and potentially mismanaged opioid administration are significant contributors to the ongoing opioid crisis (Skolnick, 2018). Although there are several non-opioid analgesic options, opioids retain their central role in the approach of many practitioners to pain management, despite inconclusive or negative findings in benefit to risk analyses.

2. Opioids, endorphins, and descending pain inhibition

2.1. Opioid-induced analgesia

There are four members in the opioid receptor family, μ- (MOR), κ- (KOR) and δ- (DOR) opioid receptors as well as NOP receptors (NOR) (Alexander *et al.*, 2019). The analgesic effect of clinically used opioids is mainly mediated by MORs, which are abundantly expressed in neuronal tissues involved in the descending pain inhibitory pathway, including the periaqueductal gray (PAG), rostral ventromedial medulla (RVM) and spinal cord, as well as in sensory nerve endings (Stein, 2016). MOR activation leads to neuronal inhibition by activating G protein-coupled-inward rectifying K^+ (GIRK) channels and/or inhibiting Ca^{2+} channels, both mechanisms can contribute to opioid-induced analgesia. GIRK channel activation induces neuronal membrane hyperpolarization and thus directly inhibits neuronal excitability, which probably contributes to the analgesic effect of opioids at peripheral and spinal levels (Nockemann *et al.*, 2013). Ca^{2+} channel inhibition at nerve terminals either leads to reduced glutamate release at the spinal dorsal horn or produces disinhibition in the PAG by reducing GABA release onto the glutamatergic neurons in the PAG, which project

to the RVM, and subsequently suppress nociceptive transmission at the spinal cord (Bagley and Ingram, 2020).

2.2. Opioid tolerance and the descending pain inhibitory pathway

Repeated application of MOR agonists typically elicits MOR desensitization (Williams *et al.*, 2013) and internalization (Koch and Hollt, 2008) via β-arrestin-2- and/or PKA-dependent pathways, both of which may contribute to analgesic tolerance of opioids. The descending pain inhibitory pathway, where MORs are densely expressed, plays an important role in the generation of analgesic tolerance, especially the PAG. Direct microinjection of morphine into the PAG induced a stronger analgesic effect and quickly elicited analgesia tolerance, compared to injection at the dorsal raphe nucleus (Campion *et al.*, 2016). Similar susceptibility of the PAG to morphine analgesic tolerance was observed in another comparative study between PAG and RVM (Morgan *et al.*, 2005). These data demonstrated that opioid-sensitive neurons in the PAG play a prominent role in the development of opioid analgesic tolerance. Indeed, electrophysiological studies in PAG slices of morphine tolerant mice, found reduced responsiveness of the PAG neurons towards an MOR agonist, suggesting down-regulation of MOR number and/or dysfunctional MOR activity (Bagley *et al.*, 2005).

2.3. Endogenous opioids in PAG stimulation-induced analgesia and stress-induced analgesia

Electrical stimulation of the PAG was able to produce analgesia, which is mediated by endogenous opioids in rodents (Cannon *et al.*, 1982) and humans (Young and Chambi, 1987). This PAG stimulation-produced analgesia (PAG-SPA) was naloxone-sensitive (Akil *et al.*, 1976), mediated by a mechanism similar to morphine analgesia, and exhibited analgesic tolerance after repeated administrations (Mayer and Hayes, 1975). PAG-SPA is known to exhibit crosstalk with the neuronal circuit involved in the phenomenon of stress-induced analgesia (SIA) (Terman *et al.*, 1985), an evolutionarily conserved, self-protecting mechanism in mammals engaged during life-threatening situations. During stress, endogenous opioids, *e.g.*, β-endorphin (Rubinstein *et al.*, 1996), are released to induce analgesia via activating the descending pain inhibitory pathway.

In addition to opioid-dependent PAG-SPA, a naloxone-insensitive PAG-SPA was also reported (Yaksh *et al.*, 1976), but its mechanism(s) remained unclear for decades. Similarly, opioid-independent SIA was also reported (Terman *et al.*, 1986), which, unlike opioid-dependent SIA, did not develop tolerance after repeated induction (Suplita *et al.*, 2008). The opioid-independent form of SIA was, very much later, revealed to be mediated, at least in part, via the endocannabinoid (eCB) system (Hohmann *et al.*, 2005; Lee *et al.*, 2016; Lee *et al.*, 2020). Thus, it is not surprising that the (endo)cannabinoid system has been regarded as a viable alternative pharmacological target for analgesia, although the efficacy of its clinical application remains inconclusive. In some countries, cannabinoids have been suggested as second- or third-line treatments for chronic pain (Urits *et al.*, 2020).

3. Cannabinoid-induced analgesia

3.1. Cannabinoid pharmacology

Cannabinoids include phytocannabinoids, synthetic cannabinoids and eCBs, as reviewed by Schurman *et al.* (2020). Phytocannabinoids are isolated from marijuana and hemp (*Cannabis sativa*), where Δ9-tetrahydrocannabinol (THC) is the major psychomimetic constituent. Synthetic cannabinoids, such as CP-55,940, WIN-55,212, levonantradol, *etc*, have been synthesized for research or drug development purposes and have higher affinity and often higher efficacy at cannabinoid receptors, as compared to THC. eCBs are endogenous ligands of cannabinoid receptors. They are notable for being synthesized on demand, unlike classical neurotransmitters that are pre-synthesized, stored in vesicles of nerve terminals, and rapidly released following increases in nerve terminal calcium. Anandamide (AEA) and 2-arachydononylglycerol (2-AG) are two main eCBs, and both are well documented for their roles in analgesia. 2-AG, in particular, appears to be synthesized in postsynaptic neurons and then travels retrogradely to activate presynaptic cannabinoid CB_1 receptors (CB_1Rs) to inhibit neurotransmitter release. The synthesis and degradation of these two eCBs are enzymatically regulated, which will be discussed in the later section.

Cannabinoids can produce several biological activities via CB_1Rs and CB_2Rs, such as analgesia, anti-emesis, hyperthermia, appetite stimulation, anti-spasticity, anti-epilepsy, anti-inflammation and anti-tumorigenesis (Alexander and Molina-Holgado, 2019). Among these, the analgesic effect mediated by CB_1Rs is noteworthy, although CB_2Rs also have a role in pain regulation (Iyer *et al.*, 2020). CB_1Rs are expressed in neuronal tissues along the descending pain inhibitory pathway, including the PAG (Bouchet and Ingram, 2020; Lau and Vaughan, 2014), RVM and spinal cord (Kelly and Chapman, 2001), as well as in some peripheral nerves endings (Kelly *et al.*, 2003). At the cellular level, CB_1R activation, via $G_{i/o}$ protein activation, leads to inhibition of adenylyl cyclase, activation of K^+ channels, and inhibition of Ca^{2+} channels, which can contribute to the analgesic effects of cannabinoids (Alexander and Molina-Holgado, 2019).

Interestingly, opioids and cannabinoids share the same cellular action mechanisms and a similar regional distribution in the descending pain inhibitory pathway (Wilson-Poe *et al.*, 2012), while both exert their analgesic effects through their respective receptors (Lau and Vaughan, 2014). Cannabinoids can also activate the descending pain inhibitory pathway, which encompasses the midbrain PAG and its downstream RVM, and ultimately inhibit pain transmission at the spinal cord (Bouchet and Ingram, 2020). Through its distinct pharmacological receptors and profiling, the cannabinoid system is regarded as a main non-opioid analgesic mechanism to complement opioid analgesia in the descending pain inhibitory pathway, especially in the PAG (Lau and Vaughan, 2014). Thus, cannabinoids are well-positioned to be a non-opioid alternative in pain management.

3.2. Cannabinoids and pain relief

Through their evaluation in multiple preclinical pain models, both phytocannabinoids and synthetic cannabinoids have been reported to suppress acute and chronic pain, mainly, via CB_1Rs (Narouze, 2020). However, like opioids, the tolerance development is also a concern

when using cannabinoids as an alternative pain-relieving agent. Like MORs, prolonged activation of CB_1Rs may result in β-arrestin-dependent desensitization (Daigle *et al.*, 2008; Nguyen *et al.*, 2012), which may contribute to analgesic tolerance of cannabinoids. The analgesic effect of repeated low doses of THC, although less susceptible to tolerance development (McKinney *et al.*, 2008), was found to be associated with cognitive dysfunction in rodents (Sarne *et al.*, 2011). Clinically, substantial human studies unfortunately also indicated a limited efficacy of using CB_1R agonists in relieving chronic non-cancer pain (Stockings *et al.*, 2018). Often, the therapeutic benefits of CB_1R agonists are limited by the risk or emergence of adverse psychoactive effects.

3.3. Endocannabinoids and pain relief

Besides exogenous agonists, pharmacological activation of CB_1Rs can be achieved via increasing eCB levels through inhibiting their respective degradation enzymes, *i.e.* fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) for AEA and 2-AG, respectively (Donvito *et al.*, 2018). At CB_1Rs, AEA is a low efficacy agonist, whereas 2-AG is a high efficacy agonist, although AEA has a higher affinity than 2-AG (Narouze, 2020). An electrophysiological study has shown that inhibiting either FAAH or MAGL enhanced GABAergic transmission via CB_1Rs in rat PAG slices (Lau *et al.*, 2014), which can lead to PAG disinhibition, subsequently activating the descending pain inhibitory pathway and inducing analgesia (Guindon *et al.*, 2013; Lau and Vaughan, 2014). Several *in vivo* preclinical studies also confirmed the analgesic effect of eCB degradation inhibitors in various animal models of inflammatory and neuropathic pain, as reviewed previously (Donvito *et al.*, 2018; Hossain *et al.*, 2020). It is noteworthy that majority of these preclinical studies demonstrated that eCB degradation inhibitors possess antiallodynic and/or anti-hyperalgesia effect in inflammatory and neuropathic pain models (Donvito *et al.*, 2018; Hossain *et al.*, 2020), insufficient finding are available in the literature to demonstrate whether both classes of eCB degradation inhibitors (FAAH and MAGL inhibitors), can enhance pain threshold in naïve animals, similar to opioids.

Nonetheless, similar to exogenous CB_1R agonists, repeated CB_1R-activation by eCBs, especially by 2-AG, can also cause analgesic tolerance. This was used to explain the underlying cause of analgesic tolerance observed in repeated administrations of MAGL inhibitors, such as JZL184 and KML29 (Crowe *et al.*, 2017; Schlosburg *et al.*, 2010), due to the eCB overload phenomenon (Lichtman *et al.*, 2010). Repeated administrations of a low dose of JZL184, which was expected to modestly increase level of 2-AG and activate CB_1Rs in a manner similar to low doses of THC, seems to induce analgesia without tolerance in mice (Kinsey *et al.*, 2013). On the other hand, although repeated administration of exogenous AEA caused analgesic tolerance (Welch, 1997), repeated administration of its degradation enzyme (FAAH) inhibitor generally does not elicit analgesic tolerance (Kiso *et al.*, 2020; Slivicki *et al.*, 2018a; Slivicki *et al.*, 2019), but see Okine et al. (2012).

To date, the successful application of FAAH and MAGL inhibitors in pain management is at the preclinical stage only. An earlier clinical study with an FAAH inhibitor, PF-04457845, did not show significant analgesia in phase II trial in patients with osteoarthritic pain (Huggins *et al.*, 2012). The phase I clinical trial of another FAAH inhibitor, BIA 10–2474,

was terminated early due to flaws in research design and a likely off target effect (Kaur *et al.*, 2016). A clinical study of an MAGL inhibitor, ABX-1431, for experimental pain and peripheral neuropathy is completed, but the results have not been revealed (Deng and Li, 2020). Further clinical studies may be planned to investigate the efficacy of FAAH and/or MAGL inhibitors in humans.

Recently, Hohmann's group identified a novel pharmacological approach to enhance eCB-CB_1R-mediated analgesia without tolerance by using a positive allosteric modulator (PAM) of CB_1Rs. This PAM retained its analgesic efficacy after chronic administration without tolerance in animal models of inflammatory pain and chemotherapy-induced neuropathic pain (Slivicki *et al.*, 2018b). This pharmacological manipulation has the potential to enhance eCB-CB_1R transmission at low or normal levels of eCBs and thus minimize the occurrence of CB_1R desensitization due to eCB overload. However, further studies will be needed to determine its role in managing chronic pathological pain in humans.

4. Opioid-sparing effects by cannabinoids in opioid-tolerant subjects

4.1. Synergistic analgesia between opioids and cannabinoids

Concurrent activation of MORs and CB_1Rs was found to synergistically induce analgesia in preclinical studies, where co-administration of THC with opioids, including morphine and codeine, was found to increase the potency of opioids by 1.2–24.8 folds, as compared with the group co-administered with the vehicle of THC (Cichewicz, 2004). Thus, co-administration of opioids with cannabinoids is considered to be a potential strategy to reduce the amount of opioid needed to produce analgesia, *i.e.*, provide an opioid-sparing effect, in chronic opioid users. If co-administration of a cannabinoid reduces the amount of opioid needed for satisfactory analgesia, this may be a way to decrease the development of opioid analgesic tolerance. In this section, we will discuss the preclinical and clinical evidence of the opioid-sparing effect of cannabinoids.

In rodents, systemic administration of a CB_1R agonist together with morphine can induce synergistic analgesia in neuropathic (Kazantzis *et al.*, 2016) and inflammatory (Chen *et al.*, 2019) pain models. Interestingly, several studies also showed synergistic analgesia when morphine was co-administered with an ineffective dose of cannabinoids (Alsalem *et al.*, 2019), or when both morphine and cannabinoids were at sub-effective doses (Smith *et al.*, 2007). The PAG is an important site of action for this synergistic analgesia. Repeated intra-PAG (*i.pag.*) microinjections of a CB_1R agonist enhanced the analgesic efficacy of subsequent *i.pag.* morphine injection without producing analgesic tolerance (Wilson *et al.*, 2008). Thus, the synergistic analgesic effect of cannabinoids with low doses of opioids may be utilized to reduce opioid tolerance. Interestingly, a continuation study by the same group showed that the analgesic synergism between CB_1R and MOR agonists in rat PAG is bidirectional (Wilson-Poe *et al.*, 2013). Nevertheless, an asymmetrical analgesic synergism was reported when CB_1R and MOR agonists were systemically administered (Vigano *et al.*, 2005). In morphine (*i.p.*)-tolerant rats, *i.p.* injection of a CB_1R agonist can induce analgesia, but not *vice versa*. The synergistic analgesia produced by opioids and cannabinoids was also reported in nonhuman primates (Nilges *et al.*, 2019), a preclinical model known to closely mimic human responses.

However, the outcomes of clinical studies examining cannabinoid/opioid interactions are not as consistently promising as expected from preclinical studies (Nielsen *et al.*, 2017). In healthy volunteers, cannabis enhances the analgesic effects of sub-threshold oxycodone (Cooper *et al.*, 2018). However, coadministration of dronabinol with oxycodone not only did not enhance oxycodone-induced analgesic effect, but it also increased abuse- and impairment-related subjective responses in healthy volunteers (Babalonis *et al.*, 2019). In patients suffering from chronic non-cancer pain, indeed some studies showed a positive correlation of enhanced opioid analgesia with cannabis co-administration (Degenhardt *et al.*, 2015) and some patients consider using cannabinoids as a substitution for opioids (Takakuwa and Sulak, 2020). However, in cancer pain patients with optimized opioid therapy, add-on administration with a cannabinoid did not show superior pain relief as compared with placebo (Lichtman *et al.*, 2018). Meta-analysis studies also indicated that no significant opioid reduction was achieved by medical cannabis or CB_1R agonists in patients with postoperative pain (Abdallah *et al.*, 2020), non-cancer chronic pain (Okusanya *et al.*, 2020) and cancer-related chronic pain (Boland *et al.*, 2020). Furthermore, some clinical studies indicated that cannabinoid treatment is associated with higher pain intensity (Liu *et al.*, 2019), increased opioid consumption (Bhashyam *et al.*, 2018), and enhanced opioid abuse potential (Babalonis *et al.*, 2019) in patients with acute or postoperative pain. Furthermore, a history of cannabis use can increase the tendency of inpatient opioid use (Dalal *et al.*, 2020).

4.2. Synergistic analgesia between opioids and eCBs

As for the potential synergistic effect of eCBs on opioid analgesia, either through inhibiting eCB degradation or CB_1R PAMs, so far, only preclinical studies are available. When administered alone, an FAAH inhibitor or MAGL inhibitor, which was known to increase AEA or 2-AG levels, significantly inhibited chemotherapy-induced (Guindon *et al.*, 2013) and chronic constriction injury (CCI)-induced (Kinsey *et al.*, 2009) neuropathic pain in mice, via CB_1Rs as analgesia was prevented by pretreatment with a CB_1R antagonist. Table 1 compiles the available reports on the opioid-sparing and analgesic tolerance-preventive effects of eCB degradation enzyme inhibitors. Co-administration of a selective MAGL inhibitor with a sub-effective dose of morphine was synergistic in eliciting analgesia in formalin-induced inflammatory pain in rats (Clapper *et al.*, 2018) or in CCI-induced neuropathic pain in mice (Wilkerson *et al.*, 2016). Interestingly, repeated co-administrations of these agents did not show analgesic tolerance (Wilkerson *et al.*, 2016). A similar opioid-sparing effect was observed in rodents co-treated with morphine and a selective FAAH inhibitor (Hasanein and Ghafari-Vahed, 2016; Slivicki *et al.*, 2018a) or a dual FAAH/MAGL inhibitor (Wilkerson *et al.*, 2017). Repeated co-administrations of an FAAH inhibitor (Fotio *et al.*, 2020; Hasanein and Ghafari-Vahed, 2016) or a dual inhibitor (Wilkerson *et al.*, 2017) with morphine also prevented or attenuated morphine analgesic tolerance.

Fig. 1 (A & B) depicted a working model of the possible signaling pathway in the PAG explaining how eCB degradation enzymes restore analgesia in opioid-tolerant conditions. Briefly, downregulation of MORs in GABA interneurons of the PAG following repeated exposure to exogenous opioids, causes analgesic tolerance as it impairs opioid-induced disinhibition signaling onto the projection neuron that is required to activate the descending

inhibitory pathway (Bagley and Ingram, 2020; Bouchet and Ingram, 2020). Pharmacological inhibition of MAGL and/or FAAH, via their respective inhibitors, causes an accumulation of eCBs that can activate the CB_1Rs on GABA interneurons, thus restoring the disinhibition signaling in the PAG (Fig. 1A). On the other hand, a recent study demonstrated that a CB_1R PAM co-administered with morphine augmented the analgesic effect of morphine and prevented the development of morphine tolerance (Slivicki *et al.*, 2020). This may be attributed to an enhancement of the effect of eCBs on presynaptic CB_1Rs on GABAergic terminals of PAG neurons, leading to the restoration of PAG disinhibition, which was impaired during opioid-tolerant conditions (Fig. 1B). Taken together, similar to preclinical studies of CB_1R agonists, eCB degrading enzyme inhibitors and a CB_1R PAM showed convincing analgesia and attenuated opioid tolerance, but further clinical studies will need to be conducted to provide translational validity of their pharmacotherapeutic potentials.

It is noteworthy that the abovementioned preclinical studies on the analgesic effect of cannabinoids and eCBs use acute neurogenic pain (thermal or mechanical), inflammatory pain or chronic neuropathic pain (surgical-, chemotherapy-, or diabetic induced) models. Although they are often assumed to be translationally relevant for clinical pain, they may not adequately mimic the multidimensionality of clinical pain conditions, *e.g.*, the motor, neurological and psychological complications (Finn *et al.*, 2021) associated with chronic pain in humans. Further studies are required to collectively examine the potential effects of cannabinoids and eCBs on the full multidimensionality of clinical pain conditions in humans.

5. Peripheral neuromodulation and chronic pain relief

5.1 Peripheral neuromodulation

The search for pharmacological replacements for opioid analgesics is regarded as an important component to resolve the opioid crisis (Yaksh *et al.*, 2018). However, the financial and time costs of novel drug development are considerable barriers to a rapid solution. The US National Institute of Health has recognized that nonpharmacological treatments of pain may be an alternative approach to address chronic pain as well as the opioid crisis (Abbasi, 2018). Peripheral neuromodulation may be one of the feasible options.

The main principle of peripheral neuromodulation involves the application of electrical stimulation on the peripheral nerves to achieve therapeutic effects, including analgesia (Slavin *et al.*, 2015). In an early implementation, peripheral modulation was achieved via peripheral nerve stimulation (PNS), where large electrodes were implanted next to the target nerves via open surgery (Slavin *et al.*, 2015). Gradually, several less invasive procedures of peripheral neuromodulation were introduced, including transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation (PENS), and ultrasound-guided percutaneous PNS (pPNS). TENS involves delivering transcutaneous electrical stimulation through intact skin to activate the underlying nerve fibers (Teoli and An, 2021). When TENS is applied to an acupoint is referred as transcutaneous acupoint electrical stimulation (TEAS) (Liang *et al.*, 2019). PENS is conducted via inserting acupuncture-like needles into the dermatome(s) of the target peripheral nerve (Ghoname *et al.*, 1999). The later ultrasound-guided pPNS was developed by percutaneously inserting stimulating

electrodes to the target nerve guided under ultrasound, utilizing similar principles as conventional PNS while avoiding an invasive open surgery (Gabriel and Ilfeld, 2021).

5.2. Analgesic mechanisms of peripheral neuromodulation

5.2.1. Opioid-dependent—Since the first report of peripheral nerve stimulation for pain management in 1967 (Wall and Sweet, 1967), the Gate Theory of Pain or Gate Control Theory is attributed as the underlying mechanism (Melzack and Wall, 1965). This theory posits that nociceptive transmission via Aδ and C fibers can be interfered with by non-painful stimuli on Aβ fibers, with the spinal dorsal horn as the "gate" to suppress pain transmission to the brain. However, the gate theory cannot explain the systemic analgesia or the pain relief at the location distal to the stimulating point of peripheral neuromodulation (Gozani, 2019). Thus, mechanisms other than the gate theory may be involved.

Endogenous opioids are one of the candidates that contribute to peripheral neuromodulation-induced analgesia. PNS can increase β-endorphin levels in human cerebrospinal fluid (CSF) (Clement-Jones *et al.*, 1980; Salar *et al.*, 1981). Direct PAG electrostimulation can also induce β-endorphin elevation in the CSF (Amano *et al.*, 1980), which contributes to SPA in humans (Hosobuchi *et al.*, 1979). Thus, it is likely that PNS can activate the opioid system in the brain, releasing β-endorphin that subsequently triggers the PAG-RVM-spinal descending inhibitory pathway. Indeed, Sluka's group reported that peripheral neuromodulation-induced analgesia can be reversed by blocking opioid receptors at PAG (DeSantana *et al.*, 2009), RVM (Kalra *et al.*, 2001) and spinal (Sluka *et al.*, 1999) levels in rats with inflammatory pain. Preclinical reports on naloxone-sensitive peripheral neuromodulation are also available in the literature (Chen *et al.*, 1996; Jorum and Shyu, 1988).

5.2.2. Opioid-independent—The opioid-dependent analgesic effects induced by peripheral neuromodulation or SPA, similar to morphine-induced analgesia, also develop tolerance after repeated stimulations, and displayed cross-tolerance to morphine in humans (Leonard *et al.*, 2011; Young and Chambi, 1987) and rats (Mayer and Hayes, 1975). Nonetheless, numerous longitudinal studies have found that peripheral neuromodulation can surprisingly induce long-term analgesic effects, ranging from months to decades (Cohen *et al.*, 2019; Johnson and Goebel, 2016; Kupers *et al.*, 2011). Thus, tolerance-prone opioid signaling is unlikely to be the underlying mechanism. Indeed, the SPA induced by PAG stimulation in rats was only partially reversed by naloxone (Akil *et al.*, 1976; Morozova and Zvartau, 1986) at the dose that completely reversed morphine-induced analgesia, suggesting an involvement of a non-opioid mechanism in the PAG, which is supported by a later clinical study (Young and Chambi, 1987).

Similarly, the evidence supporting that a naloxone-insensitive mechanism can contribute to peripheral neuromodulation-induced analgesia has been reported in humans since 1981. In patients with primary dysmenorrhea, Walker and Katz (1981a) found that repeated electrostimulation at the radial, median and/or saphenous nerves exerted a prolonged systemic analgesic effect that was naloxone-insensitive and did not show cross-tolerance with morphine. Their next publication in the same year emphasized that the same mode of PNS did not develop analgesic tolerance after repeated treatments (Walker and Katz, 1981b).

The authors claimed that this was the first clinical evidence that described a “non-opioid pathway can produce lasting pain relief in patients with severe clinical symptoms” (Walker and Katz, 1981a).

The studies conducted in nonhuman primates by Willis’s group also demonstrated the involvement of a non-opioid mechanism in the analgesia induced by peripheral neuromodulation. For instance, electrostimulation at the tibial, sciatic or median nerve significantly suppressed neuronal activity in the spinothalamic tract (STT) activated by painful sural nerve stimulation, suggesting a central participation in peripheral neuromodulation (Chung *et al.*, 1984b). Naloxone slightly but significantly reversed the suppression induced by tibial nerve stimulation on the elicited STT neuronal activity (Chung *et al.*, 1984a). Furthermore, TENS at the hindlimb nerves also inhibited STT neuronal activity and induced analgesia (Foreman *et al.*, 1975) in a manner not reversed by naloxone (Lee *et al.*, 1985). These data suggested an opioid-independent mechanism contributes to peripheral neuromodulation-induced analgesia.

5.2.3. Involvement of eCBs—Among reported analgesic mechanisms other than opioids, the eCB system in the PAG is the most likely candidate involved in peripheral neuromodulation-induced analgesia. The first report indicating that the PAG eCB system can be activated by peripheral neuromodulation was demonstrated by Longhurst’s group in a study investigating the cardiovascular suppressive effect induced by peripheral neuromodulation in rats. They found that electrical stimulation at PC5 (*Jianshi*) and PC6 (*Neiguan*) acupoints, *i.e.* electroacupuncture at PC5-PC6, reduced GABA levels in the PAG in a manner reversed by a CB_1R antagonist (Fu and Longhurst, 2009). PC5 and PC6 acupoints are known to overlie the median nerve (Joo Oh *et al.*, 2012). Chiou’s group subsequently substantiated that median nerve stimulation (MNS) can trigger a CB_1R-mediated inhibition of GABA release, i.e. disinhibition, in the PAG (Chen *et al.*, 2018). That is, MNS at the PC6 acupoint (MNS-PC6) significantly suppressed the hot-plate nociceptive response in normal mice and mechanical allodynia in CCI-mice, via a CB_1R-mediated disinhibition in the PAG through an endogenous orexin-initiated eCB signaling (Chen *et al.*, 2018). This will be discussed in section 6. The same study also indicated that MNS-PC6-induced analgesia is naloxone-insensitive, in agreement with earlier studies in humans (Walker and Katz, 1981a; Walker and Katz, 1981b) and nonhuman primates (Lee *et al.*, 1985) that found an opioid-independent mechanism underlying this form of peripheral neuromodulation-induced analgesia.

Besides MNS, stimulation of other peripheral nerves by the electroacupuncture procedure can also induce analgesia via the CB_1R-mediated disinhibition mechanism in the PAG. A study reported that electroacupuncture at acupoints GB30 (*Huantiao*) and GB34 (*Yanglingquan*), a procedure similar to percutaneous sciatic nerve stimulation (Shao *et al.*, 2015), significantly suppressed inflammatory and neuropathic pain responses in mice via CB_1R-mediated inhibition of GABA neurons in the PAG (Zhu *et al.*, 2019). In addition to the PAG, eCB-CB_1R transmission in the periphery and spinal cord are also involved in peripheral neuromodulation-induced analgesia. TENS of the hindpaw of mice was found to induce analgesia, accompanied by increased anandamide and CB_1R expression in paw, spinal, and PAG tissues (de Oliveira *et al.*, 2020).

5.3 Opioid-sparing effect of peripheral neuromodulation providing pain relief in opioid-tolerant subjects

In clinical practice, the treatment duration of prescription opioids in an opioid-naïve postoperative patient strongly correlates with the likelihood to develop opioid dependence, which may lead to unintentional overdose or misuse of opioids. In addition to pharmacological intervention with cannabinoids, peripheral neuromodulation has been demonstrated to have opioid-sparing effects in patients with postoperative pain (Gabriel and Ilfeld, 2021). Table 2 summarizes the available literature on the opioid-sparing effect of peripheral neuromodulation. In patients with varied chronic pain conditions, direct PNS of the forearm nerves (ulnar, median or radial nerves) by implanted electrodes has been reported to remarkably reduce opioid consumption in 23 out of 24 (Strege *et al.*, 1994) and 8 out of 9 (Deer *et al.*, 2010) patients. Recently, clinical reports indicated that percutaneous PNS at the femoral and sciatic regions provided adjunct analgesic effect in patients receiving total knee arthroplasty surgery and led to an earlier cessation of opioid consumption (Ilfeld *et al.*, 2019). Several placebo-controlled clinical studies also demonstrated that the consumption of opioids to relieve postoperative pain was significantly reduced by TENS treatment at the dermatome of the skin incision sites in patients receiving major spinal surgery (Unterrainer *et al.*, 2010) or major gynecological procedures (Hamza *et al.*, 1999; Wang *et al.*, 1997). Interestingly, transcutaneous acupoint stimulation (TEAS) treatments also significantly reduced post-operative opioid consumption with the stimulating acupoints including the LI4 (*Hegu*) acupoint (Lan *et al.*, 2012; Wang *et al.*, 1997) targeting the radial nerve (Umemoto *et al.*, 2019), the ST36 (Zusanli) acupoint (Chen *et al.*, 1998; Lan *et al.*, 2012) targeting the sciatic nerve (Jung *et al.*, 2018), and the PC6 acupoint (Lan *et al.*, 2012) targeting the median nerve (Chen *et al.*, 1998) (Table 2). Besides acute postoperative pain, the requirement for oral opioids in patients with lower back pain was reported to be relieved by regional PENS or pPNS of the lower back (Kapural *et al.*, 2018). Interestingly, a reduction in opioid consumption by TENS was accompanied by decreased cortisol levels 24 h after surgery (Szmit *et al.*, 2021), suggesting that the TENS procedure reduces stress.

To the best of our knowledge, until now, only one preclinical study has investigated the potential beneficial effect of peripheral neuromodulation in opioid-tolerant animals. Taking advantage of the naloxone-insensitive analgesic effect induced by MNS-PC6 (Chen *et al.*, 2018), Chiou's group revealed that analgesic tolerance did not develop after repeated MNS-PC6 treatments in mice with neuropathic pain. They also found that MNS-PC6 was able to provide significant analgesia in neuropathic mice that had developed tolerance to escalating doses of morphine (Lee *et al.*, 2021). MNS-PC6-induced analgesia is mediated by an eCB (2-AG)-mediated disinhibition of the PAG, a sequence after activation of orexin 1 receptors (OX_1Rs), a type of G_q protein-coupled receptors (G_qPCRs) (Fig. 1C). This study indirectly supports the notion that the eCBs, which are synthesized on demand and released under optimal spatial (in the synaptic cleft) and temporal (upon OX_1R activation) conditions can induce analgesia without causing eCB overload and tolerance, an important distinction to the effect of pharmacological elevation of eCBs (Lichtman *et al.*, 2010), thus avoiding CB_1R desensitization. Although the mechanistic findings from the preclinical model are somewhat in line with prior clinical reports of peripheral neuromodulation-induced analgesia, it should

be noted that these studies may not fully reflect other neurological and psychological aspects of chronic pain and/or opioid use disorders, thus further studies should be conducted.

6. Involvement of the orexin-eCB signaling in the PAG in analgesia induced by peripheral neuromodulation and stress

The orexin system consists of two hypothalamic neuropeptides, orexin-A and orexin-B, and two receptors, OX_1 and OX_2. Orexins are well-known to be involved in arousal, hormonal, metabolic and cardiovascular functions (Li and de Lecea, 2020), and also in pain regulation (Chiou et al., 2010). Using electrophysiological and behavioral approaches, Chiou's group has reported that the analgesic effect induced by MNS-PC6 is opioid-independent (Chen *et al.*, 2018), as observed in the opioid-independent form of SIA (Lee *et al.*, 2016; Lee *et al.*, 2020). Both modes of analgesia share the same disinhibition mechanism mediated by an endogenous orexin-initiated eCB cascade, as first revealed in the PAG (Ho *et al.*, 2011). This mechanism can lead to analgesia via activating the descending pain inhibitory pathway. As depicted in Fig. 2, when orexin neurons in the lateral hypothalamus are activated by acute stress (Lee *et al.*, 2016) or MNS-PC6 (Chen *et al.*, 2018), orexins are released in the PAG to activate postsynaptic OX_1 receptors (OX_1Rs), a G_qPCR, resulting in the synthesis of 2-AG via a phospholipase C (PLC)–diacylglycerol lipase (DAGL) enzymatic pathway. 2-AG then produces retrograde inhibition of GABA release by activating CB_1Rs on GABAergic terminals, leading to disinhibition of the PAG excitatory neurons that project to the RVM that in turn send inhibitory inputs to the spinal cord, culminating in the activation of the descending pain inhibitory pathway that is constituted by the PAG–RVM–spinal cord circuit and ultimately leading to analgesia (Ho *et al.*, 2011). It is noteworthy that activation of other G_qPCRs in the PAG, *e.g.* $mGlu_5$ receptors was shown to cause GABA disinhibition via a similar downstream signaling pathway (Drew *et al.*, 2008) and mediate SIA in mice (Lee *et al.*, 2020). Further studies will need to be carried out to discern their possible involvement in peripheral neuromodulation-induced analgesia.

7. Conclusions and future perspectives

Opioid analgesics are the "gold standard" in pain management and remain irreplaceable, although their chronic clinical use is limited by several unwanted side effects, especially the analgesic tolerance that leads to a dose escalation and ultimately increases the risk of respiratory depression. Therapeutic interventions to delay the emergence of opioid tolerance or maintain the analgesic efficacy after repeated opioid dosing may be achieved by activating the cannabinoid system in the descending pain inhibitory pathway. Mechanistic studies in laboratory animals support this notion, including the finding that exogenous cannabinoids (Chen *et al.*, 2019) or inhibitors of eCB degradation (Wilkerson *et al.*, 2017; Wilkerson *et al.*, 2016) have an opioid-sparing effect by preventing opioid analgesic tolerance. However, inconclusive findings were reported in the clinical setting (Le Foll, 2021), and often the analgesic benefits of cannabinoids were masked by their neurocognitive side effects (Yanes *et al.*, 2019). As direct CB_1R activation is subject to tolerance as well, the cannabis-use history and the amount of cannabinoid intake may need to be established to ensure a higher success rate in clinical trials. Recent advancement in cannabinoid pharmacology

is the introduction of CB_1R PAMs, which have been reported to be devoid of analgesic tolerance and cannabimimetic side effects, such as hypothermia and catalepsy in rodents (Ignatowska-Jankowska *et al.*, 2015; Slivicki *et al.*, 2018b). Thus, CB_1R PAMs seem to be a promising therapeutic agent for opioid-independent chronic pain control, provided that the efficacy is translated in clinical studies. Furthermore, their safety pharmacology and toxicology profiles should be established to ensure an adequate therapeutic window when used for chronic pain management.

On the other hand, peripheral neuromodulation via activating the eCB system in the descending pain pathway may be a potential alternative nonpharmacological option for chronic pain management. Since its clinical introduction in the 1960s, peripheral nerve stimulating devices have evolved, due to the advancement of biomedical technology, from surgically implanted electrodes to minimally invasive miniature implants (Banks and Winfree, 2019), and even more recently simplified to non-invasive wearable devices (Kong and Gozani, 2018). Thus, peripheral neuromodulation has become easily accessible. Extensive mechanistic studies (Chen *et al.*, 2018; Lee *et al.*, 2021) in animals have supported the involvement of endocannabinoids in the analgesic mechanism of peripheral neuromodulation by MNS. It can be speculated that this mode of opioid-independent analgesic management may be easily achieved by wearable devices in patients with opioid tolerance, providing satisfactory clinical outcomes, and thus may be of great benefit in palliative care or reducing opioid use and lessening the opioid crisis. Although clinical case studies and animal studies both showed similar efficacy in pain suppression, larger-scale randomized control trials for peripheral neuromodulation in opioid-tolerant patients should be conducted to discern the efficacy in this unique patient population.

Clinically, prescription opioids and chronic pain are both reported to be associated with depression and anxiety (Rosoff *et al.*, 2021). The opioid and endocannabinoid systems in periaqueductal gray are known to, at least in part, be involved in these neuropsychiatric disorders. Furthermore, other domains of opioid use disorders, such as dependence, withdrawal, rewards, etc. have been demonstrated to be subject to cannabinoid-opioid interactions (Mohammadkhani and Borgland, 2020; Norris *et al.*, 2019). Nonetheless, the neuropsychiatric interactions between opioid and cannabinoid systems would be another interesting and crucial topic of review.

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Abbreviations:

2-AG	2-arachidonoylglycerol
BBB	blood brain bar

CB1R	CB1 receptor
CB2R	CB2 receptor
CCI	chronic constriction injury
CSF	cerebrospinal fluid
DAGL	diacylglycerol lipase
DOR	δ-opioid receptor
eCB	endocannabinoid
i.p.	intraperitoneal injection
FAAH	fatty acid amide hydrolase
GIRK	G protein-coupled-inward rectifying K+ channels
G_qPCRs	G_q protein-coupled receptors
KOR	κ- opioid receptor
LH	lateral hypothalamus
MAGL	monoacylglycerol lipase
MOR	μ-opioid receptor
MNS	median nerve stimulation
MNS-PC6	median nerve stimulation at PC6 acupoint
NOR	NOP receptor
OX_1R	OX_1 receptor
PAG	periaqueductal gray
PAM	positive allosteric modulator
PLC	phospholipase C
PNS	direct peripheral nerve stimulation
PostOP	post-operation
pPNS	ultrasound-guided percutaneous peripheral nerve stimulation
RVM	rostral ventromedial medulla
s.c.	subcutaneous injection
SIA	stress-induced analgesia
SPA	stimulation-produced analgesia

STT	spinothalamic tract
TEAS	transcutaneous acupoint electrical stimulation at acupoint
TENS	transcutaneous electrical nerve stimulation
THC	Δ9-tetrahydrocannabinol

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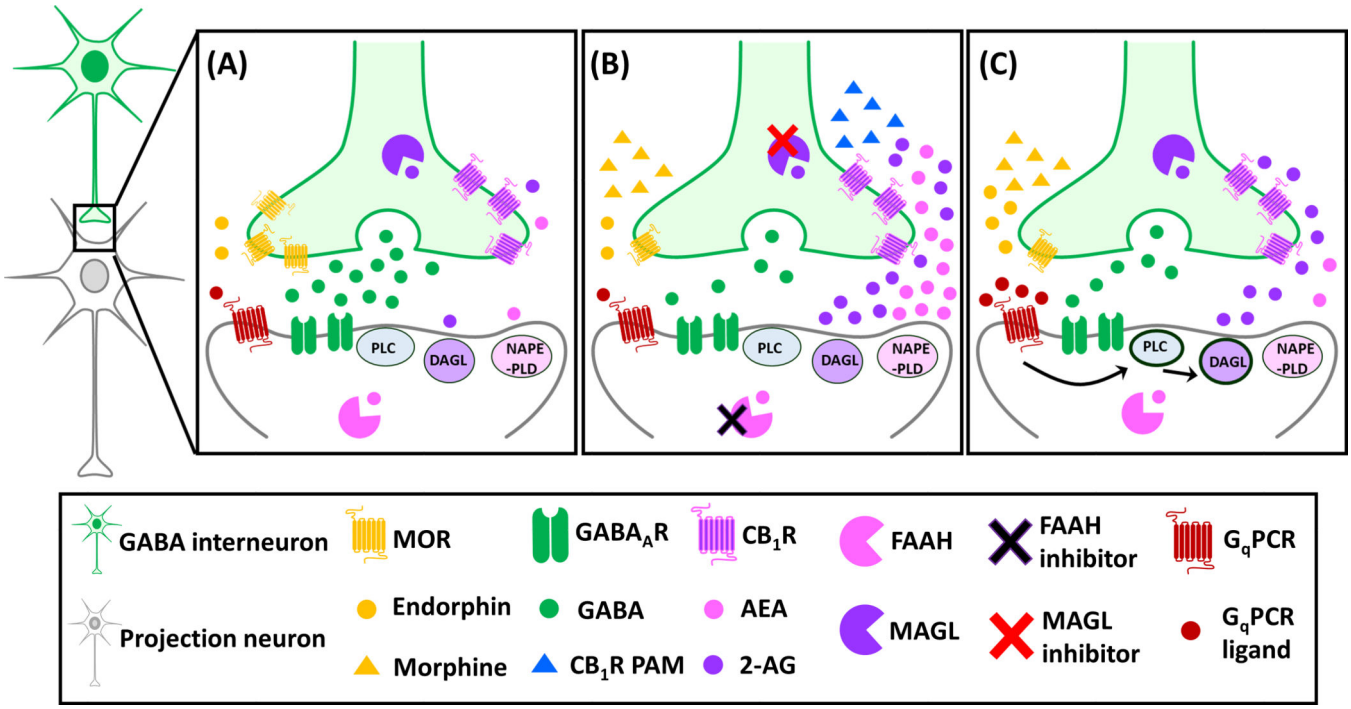
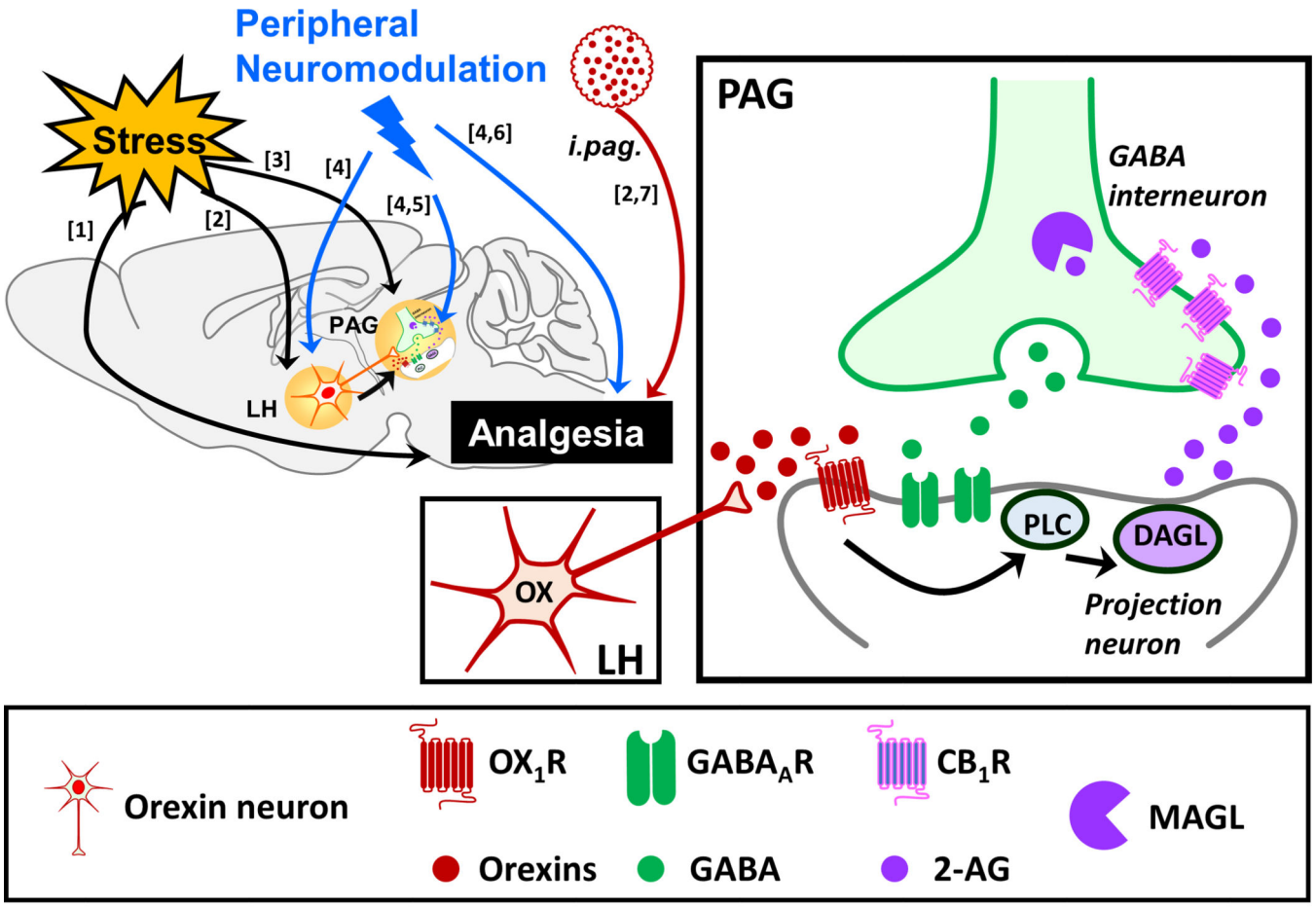


Fig. 1. A working model of possible interactions between opioids and endocannabinoids in the periaqueductal gray (PAG) in control (A) and opioid-tolerant conditions during pharmacological (B) and peripheral neuromodulation (C) interventions.

(A) Under control condition, the glutamatergic projection neuron (grey neuron) in the PAG receives GABA (green circles) inhibitory transmission via $GABA_A$ receptors (green receptors). The inhibition of GABA release from the presynaptic GABA interneuron (green neuron) (disinhibition) can be achieved via presynaptic activation of either μ-opioid receptors (MORs, yellow receptors) by endorphins (yellow circles) or CB1 receptors (CB_1Rs, pinkish-purple receptors) by endocannabinoids (eCBs), i.e., 2-arachidonoylglycerol (2-AG, purple circles) or anandamide (AEA, pink circles). The levels of 2-AG and AEA are regulated by their respective degradation enzymes, monoacylglycerol lipase (MAGL, purple circular sectors in the presynaptic GABAergic terminal) or fatty acid amide hydrolase (FAAH, pink circular sectors in the postsynaptic neuron). **(B)** During opioid-tolerant conditions, the expression of MORs on GABA interneurons is downregulated due to repeated treatments with exogenous opioids, e.g., morphine (yellow triangles), leading to a reduced inhibition of GABAergic transmission by opioids, *i.e.,* reduced disinhibition. This reduction of disinhibition on the postsynaptic glutamatergic projection neuron can possibly be restored by pharmacological inactivation of eCB degradation enzymes with an MAGL inhibitor (red cross) and/or an FAAH inhibitor (black cross), or by a CB_1R positive allosteric modulator (PAM). **(C)** On the other hand, the reduction of disinhibition on the postsynaptic projection neuron during opioid-tolerant conditions can also be achieved via peripheral neuromodulation through an opioid-independent and cannabinoid-dependent mechanism. That is, electrostimulation at peripheral nerves, *e.g.,* the median nerve, can lead to activation of the Gq protein-coupled receptors (G_qPCRs) by increasing the release of G_qPCR ligands (e.g., orexins or glutamate) in the PAG. Via the phospholipase C (PLC)-diacylglycerol lipase (DAGL) pathway, 2-AG can be synthesized and produce retrograde inhibition of GABA

release via presynaptic CB_1Rs. The images of neurons, ligands and receptors are adapted from Illustration Toolkit Neuroscience by Motifolio.



1. Lewis *et al*, 1980
2. Lee *et al*, 2020
3. Lee *et al*, 2016
4. Chen *et al*, 2018
5. Fu and Longhurst *et al*, 2009
6. Lee *et al*, 2021
7. Ho *et al*, 2011

Fig. 2. A proposed working model demonstrating the involvement of orexin-initiated endocannabinoid signaling in stress- and peripheral neuromodulation-induced analgesia.

The periaqueductal gray (PAG) is known to be a pivotal brain region mediating the supraspinal analgesic effect of orexins (red circles) as intra-PAG (*i.pag.*) microinjection of orexin was shown to produce analgesia in rodents via activation of OX_1 receptors (OX_1Rs, red receptor) in the projection neuron (grey neuron). Through the phospholipase C (PLC)–diacylglycerol lipase (DAGL) pathway, activation of OX_1Rs leads to the production of 2-arachidonoylglycerol (2-AG, purple circles), an endocannabinoid (eCB) that travel retrogradely to activate presynaptic CB_1 receptors (CB_1Rs, pinkish-purple receptor) on the terminal of the GABA neuron (green neuron), resulting in decreased GABA (green circles) release, and thus disinhibition of the projection neuron, leading to analgesia. This orexin-initiated eCB signaling in the PAG was reported to mediate opioid-independent stress- and peripheral neuromodulation-induced analgesia, via activating orexin neurons (red neuron) in the lateral hypothalamus (LH). The numbers in square brackets refer to the numbers assigned to the supporting studies depicted below the schemas. The images of neurons, ligands and receptors are adapted from Illustration Toolkit Neuroscience by Motifolio.

Table 1.

Synergistic effects on opioid analgesia induced by endocannabinoids.

Pain Model	Animal	eCB enhancer		Interaction with morphine		Reference
		AEA	2-AG			
		FAAH inhibitor	MAGL inhibitor	Acute morphine[a] (Dose)	Repeated morphine[b] (Dose, days)	
Inflammatory pain (formalin test)	SD rat		ABD-1970	Synergistic analgesia (2.49 mg kg^{-1}, *s.c.*)		Clapper *et al.*, 2018
Neuropathic pain (CCI)	C57BL/6J mouse		MJN110	Synergistic analgesia (0.82 mg kg^{-1}, i.p.)	Reduced tolerance (0.82 mg kg^{-1}, 2× day^{-1}, 6 days)	Wilkerson *et al.*, 2016
Acute pain (tail-flick)	Wistar rat	URB597			Reduce tolerance (10 mg kg^{-1}, 2× day^{-1}, 7 days)	Hasanein and Ghafari-Vahed, 2016
Neuropathic pain (chemotherapy)	C57BL/6J mouse	URB597 URB937		Reduction of morphine ED50		Slivicki *et al.*, 2018a
Neuropathic pain (CCI)	C57BL/6J mouse	SA-57 (dual inhibitor)		Reduction of morphine ED50	Without tolerance (1.12 mg kg^{-1}, 2× day^{-1}, 5 days)	Wilkerson *et al.*, 2017
Acute pain (tail-immersion)	CD1 mouse	URB597		No interaction (15 mg kg^{-1}, *s.c.*)	Reduced tolerance (15–30 mg kg^{-1}, 2× day^{-1}, 7 days)	Fotio *et al.*, 2020
		URB937		No interaction (15 mg kg^{-1}, *s.c.*)	No interaction (15–30 mg kg^{-1}, 2× day^{-1}, 7 days)	
Neuropathic pain (chemotherapy)	C57BL/6J mouse	GAT211 (CB1R PAM)		Reduction of morphine ED50	Without tolerance (10 mg kg^{-1}, 1× day^{-1}, 20 days)	Slivicki *et al.*, 2020

[a]The acute dose of morphine when co-administrated with the eCB enhancer.

[b]The repeated doses of morphine and treatment duration when co-administrated with the eCB enhancer. URB597 is a BBB-permeable and URB937 is a BBB-impermeable FAAH inhibitors. SA-57 is an FAAH and MAGL dual inhibitor. 2-AG: 2-arachidonoylglycerol; AEA: anandamide; CB1R PAM: CB1 receptor positive allosteric modulator; CCI, chronic constriction injury; eCB, endocannabinoid; FAAH, fatty acid amide hydrolase; *i.p.*, intraperitoneal injection; MAGL, monoacylglycerol lipase; *s.c.*, subcutaneous injection; SD rat, Sprague Dawley rat.

Table 2.

Opioid-sparing effect of peripheral neuromodulation in chronic pain or postoperative pain relief in clinical setting.

Pain types	Subject[a]	Target nerve (Acupoint)	Stimulation Mode	Opioid	Opioid Reduction (PostOP time)[b]	Reference
Chronic peripheral nerve pain	American (24 vs 0)	Ulnar/ Median/ Radial	PNS	Narcotics (Meperidine)	Opioid cessation in 23/24 patients.	Strege *et al.* (1994)
Chronic pain (Carpal tunnel syndrome)	American (9 vs 0)	Median	PNS	Oral narcotics	Opioid reduction in 8/9 patients.	Deer *et al.* (2010)
Postoperative (total knee arthroplasty)	American (7 vs 0)	Femoral/ sciatic	pPNS	Oxycodone	Opioid cessation: 45–60 to 6 days.	Ilfeld *et al.* (2019)
Postoperative (major spinal surgery)	Austrian (14 vs 11)	Dermatome of incision site	TENS	Piritramide	62.1%.	Unterrainer *et al.* (2010)
Postoperative (major gynaecological procedures)	American♀ (25 vs 25)	Dermatome of incision site	TENS	Morphine	50% (24 hr) 53% (overall).	Hamza *et al.* (1999)
Postoperative (lower abdominal surgery)	American♀ (25 vs 25)	Radial (LI4)	TEAS	Hydromorphone	34% (24 hr) 46% (overall).	Wang *et al.* (1997)
Postoperative (total abdominal hysterectomy/ myomectomy surgery)	American♀ (25 vs 25)	Sciatic (ST36)	TEAS /TENS	Hydromorphone	39% (24 hr) 38% (overall).	Chen *et al.* (1998)
Postoperative (total hip arthroplasty)	Chinese; (30 vs 30)	Median (PC6) /Radial (LI4) /Sciatic (GB31-ST36)	TEAS	Fentanyl	37% (24 hr) 31% (48hr).	Lan *et al.* (2012)
Postoperative (inguinal hernia repair)	Polish (24 vs 23)	Radial (LI4)/ Dermatome of incision site	TEAS /TENS	Morphine	51.6% (24 hr).	Szmit *et al.* (2021)

[a]The number of subjects in the treatment and placebo groups, respectively. Both genders were recruited, unless specified.

[b]The opioid reduction percentage 24 hours post-operation or overall. PNS: direct peripheral nerve stimulation; PostOP: post-operation; pPNS: ultrasound-guided percutaneous peripheral nerve stimulation; TEAS: transcutaneous acupoint electrical stimulation at the GB31 (*Fengshi*), LI4 (*Hegu*), PC6 (*Neiguan*) or ST36 (*Zusanli*) acupoint. TENS: transcutaneous electrical nerve stimulation.