Creation of Music-Induced Analgesia in Chronic Pain Patients through Endogenous Opioid Production: A Narrative Review

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Abstract

Chronic pain affects over 30% of the global population, and reliance on external drugs for treatment has led to major issues, including the present opioid epidemic. A healthier option is necessary, which is why music therapy's analgesic effects have been extensively studied within the last 20 years. Not only is music relatively harmless but given that chronic pain patients require repeated treatment, musical intervention is far more accessible and economical. While the mechanisms underlying music-induced analgesia are relatively unclear, the production of endogenous opioids while listening to music through both the descending pain modulatory circuit and the limbic system, is postulated to play this role. This review describes the brain regions and pathways by which music may trigger the release of endogenous opioids such as enkephalins, endorphins, and dynorphins. More importantly, it discusses the cellular mechanisms through which these neuropeptides are thought to mediate pleasure-induced analgesia in chronic pain patients.

Introduction

Chronic pain patients face a myriad of negative consequences, including financial losses, psychiatric disorders, a significant decrease in quality of life, and lower productivity [1], which is why the need for treatment to combat chronic pain is so high. Unfortunately, the current mainstream treatment options for chronic pain, medication like acetaminophen, gabapentin, and duloxetine, all have severe potential side effects, while opioid therapy risks addiction, hyperalgesia, and overdose. Fortunately, a non-chemical [artificial], non-invasive, and inexpensive treatment exists in music therapy.

To my knowledge no existing literature specifically outlines how endogenous opioid release causes music-induced analgesia in chronic pain through pathways outside the DPMC. This largely includes psychological causes of pain through the limbic system, which music attenuates. The purpose of this review is to illustrate the mechanisms behind endogenous-opioid-based-analgesia in chronic pain patients after they listen to music. This is accomplished through three sections: section 1 establishes the relationship between music and analgesia in chronic pain, section 2 elaborates on the reasons why music leads to endogenous opioid release, and section 3 describes the mechanisms through which endogenous

opioids cause analgesia for chronic pain. If music triggers pleasure-induced analgesia during chronic pain and at the same time elicits endogenous opioid release, then one may conclude that these endogenous opioids are strongly involved in the process of pain relief.

Section 1: Music and Analgesia in Chronic Pain

Although the mechanism underlying music-induced analgesia remains unclear, the relationship between music and its analgesic effect in chronic pain is well documented [2][3][4][5][6]. Such studies typically used subjective-rating scales like the Visual Analogue Scale and the McGill Pain Questionnaire to detect changes in pain perception. A hypothesis that explains the mechanisms behind music-induced analgesia invokes the involvement of endogenous opioids. This is partially because the descending pain modulatory circuit [DPMC] that produces analgesia is mediated heavily by endogenous opioids that can lead to pleasurable emotions while listening to certain genres of music [4]. This link between endogenous opioids is not well-researched but has been proposed in recent literature reviews [7][8]. Having established the relationship between music and analgesia in chronic pain, the following sections aim to illustrate endogenous opioid release as the underlying mechanism.

Section 2: Music and Endogenous Opioids

The pleasure associated with endogenous opioid production has been found to cause pain relief through the brain's reward system. It is believed that music, through multiple media, eventually triggers the release of endogenous opioids associated with pleasure and creates analgesia through pain relief circuits. However, the theory linking music to opioid release is not well-established, leading to a lack of empirical data supporting the reasons outlined in this section. As endogenous opioids elicit pleasure through the neural reward system, the evidence presented here primarily focuses on how music is perceived as a neurobiological reward rather than direct opioid release. Therefore, this section describes how music activates this reward system and causes endogenous opioid release related to pleasure.

Search Strategy

Review articles and primary research papers that were published within the last 30 years were included. They were collected from PubMed and Google Scholar using the search words "music AND opioids", "music AND endorphins", and "pleasure AND music". Some clinical trials were also searched for using an additional search word like "music AND memory AND pleasure" for specificity. Exclusion criteria included a measure or description of pleasure that was not explicitly linked to the neural reward circuit, articles that discussed artificially administered opioids instead of endogenous opioids, and tests involving music mixed with other forms of treatment like meditation. All the papers that have been included were chosen because they demonstrate that listening to music elicits endogenous opioid production.

The Reward System

Within the opioid-based reward system, the neuropeptides enkephalins, endorphins, and dynorphins bind to mu-opioid receptors (MORs), delta opioid receptors (DORs), and kappa opioid receptors (KORs), respectively [9]. These receptors and ligands are mainly found in the cortex, limbic system, and brain stem, and the limbic system consists of mesolimbic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and other regions of the forebrain. The purpose of the reward system is to enforce desirable behavior in an organism, known as instrumental conditioning [10]. The introduction of music is positive reinforcement as the experience of listening is pleasant and acts as a 'reward' in the system, in turn, eliciting endogenous opioid production to create pleasure [11].

This reinforces the idea that listening to music is a positive experience, which creates a desire to listen to it in the future. A similar mechanism is responsible for addictions to exogenous opioids (artificially created) that bind to the receptors to generate pleasure through the same system [12]. Systemic MORs and DORs are specifically involved in positive reinforcement.

While the system is meant to reinforce behavior that increases survival chances, it is often related to stimuli that are simply pleasurable without a direct reward, like listening to music. This section describes how music activates this reward system to cause endogenous opioid release.

Passive Listening

Non-verbal emotional expression

Music's inherent qualities relate to how pleasure is objectively triggered through passive listening. Such qualities, in turn, emphasize how enjoyment is experienced when listening to a song for the first time, regardless of personal preferences. A defining characteristic of music is its similarity to human vocal communication to express emotion using the same non-verbal cues. Pitch accuracy, for example, relies on wave periodicity that creates a fundamental frequency, which is rarely seen in natural sounds except for animal vocalizations [13]. Pitch modulations arose through evolutionary implications, an example being that females have developed greater sensitivity to high-pitch sounds than males because the brain associates it with distress from a baby [14]. Through similar modulations, music also acts as a non-verbal form of emotional expression, which has been corroborated through recent research [15] [16][17][18].

This would affect endogenous opioid release because by listening to music that expresses pleasure or happiness, one would likely feel similar emotions as they would in a natural setting [11]. A hypothesized mechanism for this is dynamic attending theory, which refers to the synchronization between the music and internal signals through the mirror neuron system [19]. In this case, the emotion expressed through the quantitative acoustic qualities previously listed would be translated internally, inducing similar emotions in the listener [11]. This can be seen in studies like Tar et. al, in which techno-music caused strong pleasure due to its characteristics typical of 'happy music' like its strong and rapid rhythmic beat associated with rapid, high-energy movements of excitement [20]. The reward system was associated as part of the pleasurable experience and is thought to be activated through the opioid-receptor-heavy ventral striatum, which has also been linked to activation following exposure to happy facial expressions [11].

Predictability

The patterned nature of music is also significant, partially due to the periodicity of its waves creating pitch. Regularity is one of its defining characteristics, as it has been found that its amplitude modulation, a piece's loudness over time, is fairly steady at 1-2 Hz, and its temporal regularity is fairly consistent through meter [21]. Such regularity is significant because it leads to predictability in musical pieces, which engages the reward system.

The human brain is well adapted to the prediction of future events based on past patterns, as auditory information is typically maintained for long periods [13]. Therefore, soon-following sounds can be connected with those before to create predicted patterns. Specifically, the auditory cortices, dorsolateral frontal regions, and premotor cortex are involved in connecting separate sounds through ventral and dorsal pathways, along with the basal ganglia which calculates beat intervals and perceptually maintains rhythm [22]. Such connections stem from the correlation of separate words and phrases in vocal expression to extract an overarching meaning [23].

Beyond understanding vocal communication, predictability has numerous other benefits that are thought to underscore why it triggers the reward system. One is efficiency, as preparation can increase the speed of information processing, by saving resources by preparing a perceiver for an expected reaction [24]. In addition to pre-directed attention, relevant brain regions are 'pre-activated', which reduces complex processing during the event. The study by Zatorre et al. demonstrated this through music, which showed that the dorsal striatum was most active before a moment causing musical chills, and declined when peak pleasure was reached [25]. Furthermore, the pleasure one gains after an accurate prediction is also relevant, as the desire to prove one's expectations correct heavily influences perception, cognition, and behavior. The satisfaction of accurate predictions is considered a 'reward', which is why the reward system is engaged, as presented in the book *Sweet Anticipation* [26].

While repeated listening and prior knowledge of music enhance the predictability of a piece, predictions can also stem from patterns recognized during a first-time listening experience. This is exemplified through research showing that some pleasure from music lies in the reward of accurate anticipation by exposing participants to songs of varying predictability [27][28][29].

Active Listening

The subjective portion of musical perception is heavily influential. Personal musical preferences are a strong factor affecting such perception, as research has found that self-selected music tends to yield stronger pleasure than 'neutral' or research-chosen pieces, often acting as a control for emotional reactions in experimentation [30][31]. Emotional reactions to self-selected music include a higher frequency of chills, longer durations of chills, greater pupil sizes, and higher levels of comfort through familiarity than neutral music [32]. The anticipation of an expected pleasurable response when listening to previously known music activates the reward system, both through the expectation of the positive stimulus and when directly experiencing the pleasurable response.

Memory

Memory is crucial to musical perception, as its subjectivity is based on past experience and knowledge. The familiarity of self-selected music is due to the memory of its previous listings, and reactions to lyrical content are equally based on personal memories. Furthermore, the memories that are actively recalled are also impactful in shaping this perception to make the listening experience pleasurable [33]. Autobiographical memories are often stirred when listening to music, which can be triggered by any part of a music piece that connects to something familiar. Episodic memories, which are the memories tied to previous listening, are equally significant as a study found that 30% of past popular songs presented to subjects evoked positive autobiographical memories [34][35].

Recalled memories of the past in a positive context typically lead to the creation of nostalgia, which is what activates the reward system and opioid release. The inferior frontal gyrus, cerebellum, insula, and substantia nigra in the reward system are activated with nostalgia-evoking music [36]. Furthermore, it has been suggested that memory and reward systems co-produce the experience of nostalgia [37][38]. In fact, the value of positive autobiographical memories was found to be perceived as similar to monetary rewards [39]. The reward system is also implicated as specifically music-evoked nostalgia is related to reward-seeking and motivation, as the sensation promotes a desire to take risks and pursue valuable goals [40][41].

Movement

While musical interpretations are often individualistic, a generalizable association with music is

movement, typically seen through dance. The brain is thought to be hardwired to generate movement from music. Specifically, the basal ganglia, sensory, motor, and auditory cortexes are activated and communicate to help maintain a beat [42]. Dynamic attending theory, which was previously illustrated in the context of non-verbal emotional expression, is also relevant, as the mirror neuron system could synchronize internal self-sustained oscillations with the beats in music, manifesting in the form of synchronized movement. The already activated motor cortices are largely responsible for this and are often seen through movements like finger tapping. However, this can also be expressed through entrainment with motor imagery, in which one visualizes movement associated with a beat, which has similar effects as physical movement [43].

The pleasure yielded from movement associated with music concerning opioid release is not well-studied, but a possible link could be to the heavily researched connection between exercise and endogenous opioid release, which is also movement-based [44]. Connections between the reward system and movement have also been found to include the striatum and basal ganglia [22].

Section 3: Endogenous Opioids and Analgesia in Chronic Pain

Search Strategy

Systematic reviews, narrative reviews, and primary research papers that were published within the last 30 years were included. They were collected from PubMed and Google Scholar using the search words “opioids AND chronic pain”, “endorphins AND chronic pain”, and “opioids AND chronic pain AND analgesia”. Some studies were also searched for using an additional search word depending on the section, like “opioids AND chronic pain AND depression” for specificity. Exclusion criteria included a focus on acute pain instead of chronic, the use of patients with chronic pain but measuring only acute pain, determining the effect music has on only psychological conditions rather than pain intensity, and measuring opioid levels through dependency on artificial opioids. All the papers that have been included were chosen because they demonstrate that endogenous opioid production produces analgesia in patients with chronic pain.

Chronic Pain

Chronic pain can be defined as pain that remains after a period of 12 weeks following treatment after healing should have taken place, or that persists without any tissue damage [45][46]. Unlike acute pain, which is caused suddenly and has a directly identifiable cause, chronic pain can be created through a wide array of triggers. Furthermore, a certain portion of chronic pain patients are genetically predisposed to the condition, which applies to both the heritability of psychological comorbidities and physical dysregulation [47].

A large portion of chronic pain patients include those who initially had acute pain caused by a tissue injury, but face persisting pain for a prolonged period after physical healing, which is nociceptive chronic pain. Neuropathic, musculoskeletal, inflammatory, and mechanical pain are also physical causes of chronic pain. However, chronic pain is often due to psychogenic factors with identifiable physical causes, acting as a large differentiating factor between chronic and acute pain.

The relationship between chronic pain and psychological comorbidities is bi-directional, as prolonged pain often leads to depression and anxiety [48][49]. Similarly, prolonged stress and sudden stress can give rise to chronic pain, an example being chronic back pain due to sustained high cortisol levels [50]. In such cases, psychological factors may not be the sole cause, but could also exacerbate one’s perception of existing pain’s intensity.

The dysregulation of certain neurotransmitters including dopamine and endogenous cerebral opioids has been linked to the onset of chronic pain in the descending antinociceptive pathways, affecting both psychogenic and physical anomalies [51]. The following sections will delve into the role increased endogenous opioid levels would, in turn, play in the creation of analgesia attenuating chronic pain.

The Descending Pain Modulatory Circuit

The DPMC has been established for endogenous opioids, specifically through the periaqueductal gray (PAG)-rostral ventromedial medulla (RVM) circuit [52]. An overload of noxious stimuli can trigger this circuit to create analgesia, but this section will outline how pleasurable stimuli like music can affect a similar mechanism.

The PAG is a mesencephalic structure responsible for meditating behavior against immediate threats and physical discomfort, including pain management [53]. Furthermore, the structure has a high density of primarily MORs, DORs, and KORs are also expressed, suggesting that opioids are involved in this management [54]. Artificial triggering of the PAG has been found to elicit an analgesic response in both humans and rats, and structures involved in the reward system have been shown to act as endogenous triggers, specifically the VTA, NAc, and hypothalamus. GABA neurons in the VTA send direct inputs to the lateral and ventrolateral portions of the PAG, and the immobility caused by such responses is blocked in the presence of endogenous opioids, likely a form of an analgesic effect trigger [55]. The NAc is, while part of the reward system, also heavily implicated in chronic pain management, as positive activations of the structure accurately predicted analgesic effects in patients with chronic pain, and caused analgesia following b-endorphin injection [56]. The PAG is likely to be part of such a response, as it has been suggested that the NAc, basolateral amygdala (BLA), and dorsal PAG form a circuit responsible for responding to prolonged discomfort, and potentially chronic pain [55]. The NAc has been found to project to the PAG-RVM spinal cord signaling pathway through opioid systems following stressful stimulation [57]. As for the hypothalamus, the lateral hypothalamus has projections that influence the ventrolateral PAG, and such afferent connections have been linked to neuro-adaptive changes following opioid release [55]. The ventrolateral PAG, interestingly, is the most associated with the analgesic circuit and has the most dense enkephalin-containing terminals, and its stimulation directly elicits analgesia in humans that is affected by naloxone [58]. As naloxone is an opioid antagonist, this suggests that ventrolateral-PAG-caused-analgesia is mediated by opioid release. The lateral hypothalamus is heavily implicated in the reward system through its opioid systems, hypothesized to affect orexin and GABA neurons [59][60].

Through the mechanisms illustrated, structures of the reward system activated by music actuate the PAG. The PAG-RVM circuit is well-known as one that mediates analgesic responses, specifically through the inhibition of GABA and glutamate release. The two classes of RVM neurons that respond to noxious stimuli processing are ON and OFF neurons. ON Neuron firing is associated with pain facilitation, while OFF Neuron firing is associated with pain inhibition. Therefore, it can be stated that either a decrease in ON neuron firing or an increase in OFF neuron firing is associated with the production of analgesia, and two separate circuits as illustrated in Bagley and Ingram (2020) responsible for this have been proposed [54].

The first circuit involves ON RVM neurons, as the diagram below outlines the circuit's structure and how endogenous opioids affect it. When an individual is in pain, excitatory PAG neurons are activated and send excitatory signals to the ON RVM neurons, therefore increasing their firing: enhancing pain facilitation. However, when endogenous opioids are produced, they bind to opioid receptors on the

excitatory PAG neurons. The activation of opioid receptors has an inhibitory effect, and so when the opioids bind to these neurons, it inhibits the excitatory signals they were initially sent to the excitatory RVM neurons. Due to the lower number of excitatory signals being sent to the ON RVM neurons, there is a decrease in their firing, which produces analgesia. Figure 1. is a diagrammatic representation of this circuit.

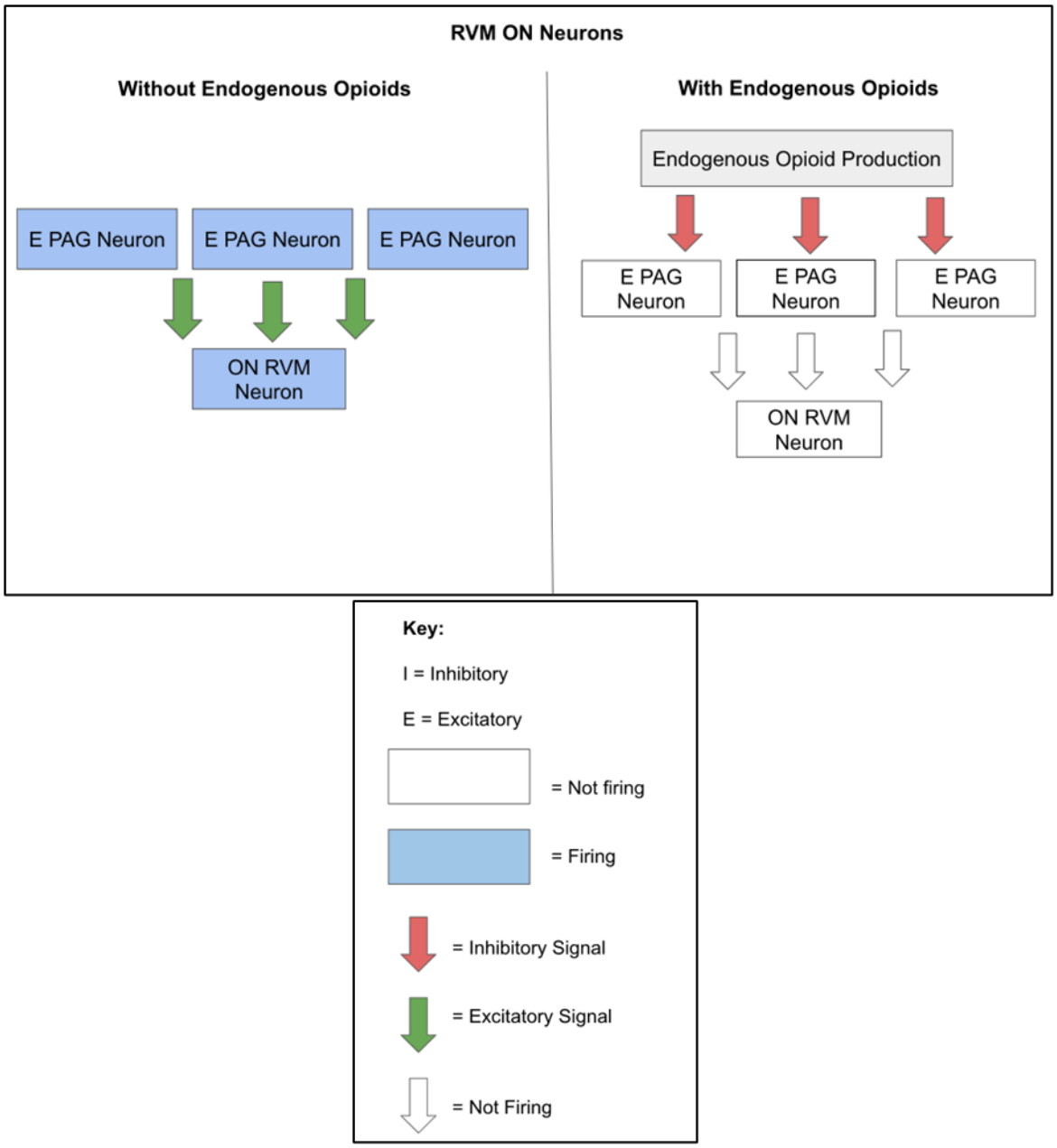

Figure 1. An original diagrammatic representation of the PAG-RVM ON RVM Neuron Circuit, which has been created based on Bagley and Ingram (2020).

The second circuit involves OFF RVM neurons, as Figure 2. outlines the circuit's structure and how endogenous opioids affect it. When an individual is in pain, inhibitory GABA-ergic PAG neurons are activated and send inhibitory signals to excitatory PAG neurons, therefore reducing firing in them. This, in turn, means that excitatory PAG neurons do not produce action potentials to send to OFF RVM neurons, which decreases their firing. However, when endogenous opioids are produced, they bind to opioid receptors on the inhibitory GABA-ergic PAG neurons and have an inhibitory effect similar to the one in the circuit previously described. Due to this, the inhibitory PAG neurons do not fire and do not send inhibitory signals to the excitatory PAG neurons, allowing them to fire. This is referred to as disinhibition. So, since the excitatory PAG neurons are not inhibited anymore, they send excitatory signals to the RVM OFF neurons, increasing their firing rates and producing analgesia.

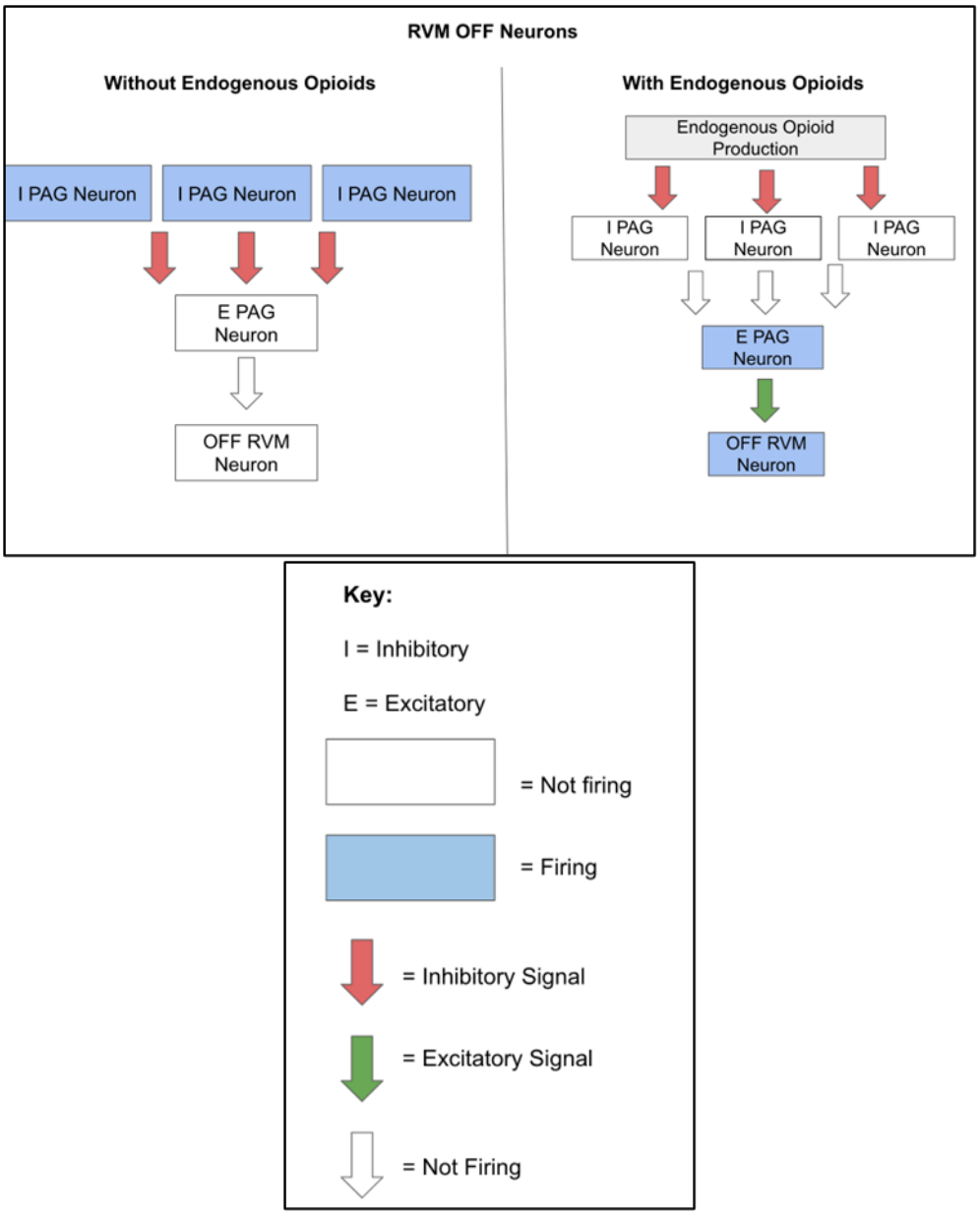

Figure 2. A simplified, diagrammatic representation of the PAG-RVM OFF Neuron Circuit based on Bagley and Ingram (2020).

The RVM neurons project to the spinal cord to influence nociceptive perception, particularly the dorsal horn [DH], which has also been linked to opioid activity [61][62]. Aside from the indirect effects of opioids on the RVM detailed above, the structure is also heavily associated with opioid receptors in both serotonergic and non-serotonergic neurons, and a subset are enkephalinergic, KOR-expressing, and dynorphin-expressing, although the role of these neurons in pain management is less-known [63]. It is also important to note that specifically, the two outlined PAG-RVM circuits are based on research with rodents, while this paper aims to illustrate the effect of music on analgesia in humans. However, human tractography studies show that while some cortical connectivity differs between humans and rodents, midbrain and hindbrain connectivity remains similar regarding the DPMC [61]. Furthermore, numerous studies involving human subjects corroborate the involvement of the PAG-RVM circuit in opioid production [64][65][61].

Anti-inflammation

Inflammation was previously listed as a cause of chronic pain, and a potential mechanism by which music creates analgesia could be through the anti-inflammatory characteristics of endogenous opioids. While chronic pain is often associated with persistence after physical inflammation is attenuated, it has been suggested that neuroinflammation is responsible for and mediates the chronification of pain [66]. Such inflammation also causes central sensitization, a hyper-sensitivity to noxious stimuli that is also common to chronic pain [67]. Both effects are largely mediated by cytokines, a type of regulatory protein involved in the immune system that regulates inflammation [68]. Pro-inflammatory cytokines promote inflammation and exacerbate pain, while anti-inflammatory cytokines attenuate such responses.

Endogenous opioids have been found to reduce inflammation by affecting cytokine production. Specifically, β - endorphins reduce the production of IL-2 and interferon IFN-γ, both of which are pro-inflammatory while increasing the quantity of IL-4, a notably anti-inflammatory cytokine through MOR interactions [69]. Through the same MOR affinity, other studies have found that β - endorphins created by immune cells produce IL-18, IL-10, and IFN-γ, all of which are anti-inflammatory [70]. Aside from cytokines, β - endorphins also prevent splenocyte proliferation and the vesicular release of noradrenaline and substance P, all of which are involved in inflammatory responses [69][71]. An important factor to consider is that some of these endogenous opioids affect and are created in the immune system, while those produced following exposure to pleasurable stimuli are neuronal. Opioid receptors are expressed by immune cells and are the same or similar to the neuronal type, and MOR mRNA and protein have been identified in immune cells in the central nervous system, as microglia and astrocytes regulate neurological cytokine upregulation [72][73]. Furthermore, the NOP receptor levels in immune cells are near those seen in the central nervous system in humans [74]. This suggests that neuronal opioids could still influence immune cell responses.

Psychological factors

Psychosomatic chronic pain is, instead of a physical tissue injury, caused or magnified by psychological factors like affective disorders and stress. Given that endogenous opioids act as both mood and pain regulators, low opioid levels due to psychological conditions that are largely dependent on experiencing pleasure could affect the body's ability to produce analgesia.

Pertaining through stress, increased cortisol production through the Hypothalamus–pituitary–adrenal [HPA] axis has been linked to the presentation of chronic pain due to increased pain sensitivity [75]. Cortisol production can also augment symptoms of chronic pain, including cognitive challenges and

fatigue, which could potentially lead to declines in positive mood, creating a cycle that further exacerbates the perception of chronic pain. Furthermore, changes in cortisol levels following sleep disturbance are related to changes in pro-inflammatory cytokine production, increasing pain intensity through heightened inflammation. However, all of these processes are not so linear and involve numerous mediating factors including endogenous opioids that ultimately affect chronic pain. Opioids and cortisol have been previously found to have an inversely proportional relationship, as opioids cause an inhibition of ACTH, which regulates cortisol production, and cortisol levels in humans [76]. It may be significant that females have cortisol responses that are more heavily influenced by endogenous opioids than males since women are also at higher risk of experiencing chronic pain [77]. Increased opioid levels after listening to music could produce analgesia by either attenuating the stress itself or by restoring depleted opioid levels caused by stress [78].

A wide array of psychological conditions are equally linked to psychogenic chronic pain, as anxiety and depression have been found to lower pain thresholds, and traumatic experiences in childhood influence chronic pain development in adulthood [79] [80]. They are also heavily associated with the endogenous opioid system, with its dysregulation linked to depression and stress-induced psychiatric disorders, specifically involving beta-endorphins [81][82]. Therefore, interest has shifted towards affecting the opioid system to treat such conditions, which is an example of how music can influence chronic pain by first attenuating the intensity of the disorders [83]. The interconnected role of opioids in nociception signaling and such disorders has been researched and proven, more so than that with cortisol.

Long-Term Effects

Research on endogenous opioids and their role in analgesia typically highlights their short-term effects, which tend to fade soon after the stimulus that triggers opioid production is no longer present. However, it is important to note that opioids also have long-term effects, which are particularly relevant to chronic pain, a condition characterized by its prolonged nature.

The anti-inflammatory effects of opioids extend beyond the immediate period during which opioids are active. By reducing inflammation, opioids can potentially lessen pain associated with an injury on a more permanent basis. This is because decreased inflammation can lead to long-term reductions in pain, even after these opioids are no longer present or functional in the body.

Furthermore, endogenous opioids have been shown to cause hyperalgesia, which paradoxically increases one's pain sensitivity [84]. This effect characteristically develops over time and reflects the complex, sometimes counterproductive, role of opioids in pain management. Exogenous opioids, which are designed to produce a more potent response than their endogenous counterparts, have been more extensively studied concerning hyperalgesia [85]. While the development of hyperalgesia following exogenous opioid use is not definitive, the existing evidence suggests that endogenous opioids could have similar prolonged influences.

A less-explored effect of opioids is their role in promoting neuroplasticity [86]. Beta-endorphins, a type of endogenous opioid, have been found to enhance neurogenesis, the process by which new neurons are formed. This suggests that opioids might influence the neural networks involved in pain perception and management. If these networks are altered due to opioid release, it could lead to long-term changes in how pain is processed and experienced, which could be a potential area of further research.

Conclusion

This review paper illustrates the role endogenous opioids play in music-induced analgesia in patients with chronic pain. While such a relationship was established, there were numerous limitations to the research, as sections outlining the role of endogenous opioids in anti-inflammatory actions and the DPMC occasionally detailed research in which rodents were the subjects instead of humans. Also, some relationships in Section 1 lacked direct links to endogenous opioid production. Further empirical research is necessary to bridge the two sections outlined in this report, along with a stronger emphasis on endogenous-opioid analgesia in chronic pain with psychological causes and the long-term effects of opioids. Developing musical pieces specifically designed to elicit analgesia based on qualities attributed to positive emotions is a promising field for future clinical research to explore.

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Conflict of Interest

The author declares that there is no conflict of interest.

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