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Neuropathic orofacial pain: Cannabinoids as a therapeutic avenue

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ABSTRACT

Neuropathic orofacial pain (NOP) exists in several forms including pathologies such as burning mouth syndrome (BMS), persistent idiopathic facial pain (PIFP), trigeminal neuralgia (TN) and postherpetic neuralgia (PHN). BMS and PIFP are classically diagnosed by excluding other facial pain syndromes. TN and PHN are most often diagnosed based on a typical history and presenting pain characteristics. The pathophysiology of some of these conditions is still unclear and hence treatment options tend to vary and include a wide variety of treatments including cognitive behaviour therapy, anti-depressants, anti-convulsants and opioids; however such treatments often have limited efficacy with a great amount of inter-patient variability and poorly tolerated side effects. Analgesia is one the principal therapeutic targets of the cannabinoid system and many studies have demonstrated the efficacy of cannabinoid compounds in the treatment of neuropathic pain. This review will investigate the potential use of cannabinoids in the treatment of symptoms associated with NOP.

1. Introduction

According to the International Association for the Study of Pain (IASP), neuropathic pain is "pain caused by a lesion or disease of the somatosensory nervous system", and unlike nociceptive and inflammatory pain is associated with noxious impulses originating from abnormalities in neural structures (for review see (Klasser and Gremillion, 2012)). Neuropathic orofacial pain (NOP) is a chronic pain condition involving the head, face, and(or) neck and is associated with dysfunction or primary lesion in the nervous system. Although the precise underlying cause of NOP has not been fully elucidated, both human and animal studies suggest that a number of intricate peripheral and central mechanisms are involved, including metabolic disorder, mechanical trauma, bacterial/viral/fungal infection and tumour growth (Klasser and Gremillion, 2012). These conditions represent a clinical challenge as pain can arise from many sources in the orofacial region, and overall NOP disorders represent a major health concern due to the impact on quality of life and extensive usage of health care facilities (McDermott et al., 2006). Furthermore, several medical disciplines may be involved in NOP disorder diagnoses as patients afflicted with such disorders often present with additional unexplained extraoral comorbidities (Mignogna et al., 2011). NOP preferentially affects women in the fifth decade of life (Rodriguez-Lozano et al., 2010) and the exact prevalence is unknown, with studies reporting prevalence rates ranging from 0.03 to 0.5%, depending on the specific disorder (Berger et al., 2004, Mueller et al., 2011). In addition, the etiology of NOP remains largely unclear, and is linked with central nervous system (CNS) pathologies, systemic disease and traumatic neuropathies associated with dental procedures (Rasmussen et al., 2004) such as endodontic treatment, implant placement, tooth extraction and direct needle trauma (Campbell et al., 1990; Lynch and Elgeneidy, 1996).

Although a number of major pain classification systems of relevance to NOP exist, including IASP, the International Headache Society classification system, and the Research Diagnostic Criteria for Temporomandibular Disorders (Zakrzewska, 2004), NOP may be broadly divided into three broad categories: episodic, continuous and combination. Episodic NOP (often referred to as paroxysmal neuralgia) includes pathologies such as trigeminal neuralgia (TN) which is characterized by unilateral short episodes

Abbreviations: 2-AG, 2-arachidonoylglycerol; 5-HT, 5-hydroxytryptamine anandamide N-arachidonoylethanolamide; BMS, burning mouth syndrome; CB, cannabinoid receptor; CBT, cognitive behavioural therapy; CNS, central nervous system; GABA, γ-Aminobutyric acid; HZ, herpes zoster; IL, interleukin; mGluR, metabotrophic glutamate receptor; MS, Multiple Sclerosis; NO, nitric oxide; NOP, neuropathic orofacial pain; PAG, periaqueductal grey; PET, positron emission tomography; PHN, postherpetic neuralgia; PIFP, persistent idiopathic facial pain; PK, protein kinase; PPAR, peroxisome proliferator-activated receptor; RVM, rostral ventromedial medulla; THC, tetrahydrocannabinol; TN, trigeminal neuralgia; TRPV1, vanilloid channel type 1; Vc, trigeminal nucleus caudalis.

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of intense sharp paroxysmal pain, which may be triggered by a stimulus and presents most commonly in the two lower branches (maxillary V2, mandibular V3) of the trigeminal nerve. Continuous NOP (often referred to as atypical odontalgia, atypical facial pain, persistent idiopathic facial pain and phantom tooth syndrome) is often described as a persistent burning or tingling sensation, similar to those symptoms associated with burning mouth syndrome (BMS) and persistent idiopathic facial pain (PIFP). BMS may be idiopathic (primary) or secondary to local/systemic factors and herein we will focus on the idiopathic variant. BMS is most commonly associated with bilateral, continuous pain commonly affecting the tongue, lower lip and hard palate predominantly in postmenopausal women. BMS is considered neuropathic in origin, with neurodegenerative (Nasri-Heir et al., 2011) and neuroinflammatory processes thought to contribute to the disease (Pezelj-Ribaric et al., 2013). PIFP is associated with continuous unilateral, dull, burning pain localized above the neck, in front of the ear, and most often in the zygomaticomaxillary complex. Limited evidence links PIFP with isolated neurophysiological dysfunction and psychological mechanisms. Combination NOP has been described as aching, continuous burning pain with episodes of intense lancinating pain, which is commonly seen in postherpetic neuralgia (PHN), a condition associated with herpes zoster (HZ) infection. PHN is diagnosed if the pain associated with HZ persists for 3 months post-healing of the vesicular skin lesions related to the condition, with pain localized to the same dermatomes as the HZ rash (Rasmussen et al., 2004).

Patients with NOP disorders often present to their dental practitioners with a variety of symptoms including allodynia (pain resulting from a stimulus that does not normally cause pain), burning and altered sensation due to the impact of these disorders. They present a difficult diagnostic challenge as NOPs can often mimic common pathologies of the oral cavity and the adjacent structures such as temporomandibular disorders and myofascial pain syndrome (Dworkin and LeResche, 1992). Inevitably, many patients undergo costly radiological investigations, unnecessary dental procedures and the prescription of medications with poorly tolerated side effects. The pathophysiology of these conditions is unclear and therefore treatment options are variable and include cognitive behavioural therapy (CBT) or pharmaceuticals such as anti-depressants, anti-convulsants and opioids. However, such therapy is not always successful and a body of literature has suggested possible novel cellular/molecular therapies for NOP disorders, including local injection of autologous mesenchymal stem cells (Vickers et al., 2014), regulation of satellite glial cells (Jasmin et al., 2010) and delivery of substance P (Mustafa et al., 2013), endomorphin (Makuch et al., 2013) and cannabinoids (Liang et al., 2007). Here we will focus on cannabinoids, reviewing the potential of the cannabinoid system as an alternative therapy in such debilitating conditions.

2. Pathogenesis

2.1. NOP: mechanisms for initiation

Pain in the orofacial region is most often odontogenic in origin and is commonly associated with infection or traumatic injury (Klasser and Gremillion, 2012). Other sources of pain including neuropathic pain can be diagnostically challenging and may be treated incorrectly as dental pain. Typically neuropathic pain persists following treatment. The underlying mechanisms for such NOP remain unclear, with NOP often presenting idiopathically without any recognizable lesion to the facial structures. Indeed, evidence indicates that tissue damage may not be directly linked to pain-modulating pathways in the CNS (Okeson and de Kanter, 1996). However, nerve injury is strongly linked with pain or neuropathic manifestations. Unfortunately the cellular mechanisms underlying NOP are poorly understood and several pathophysiological mechanisms have been suggested (Table 1).

2.1.1. BMS pathophysiology

BMS is a complex disease which may be of neuropathic etiology, with reduced pain and sensory thresholds. Using human studies alterations in salivary flow, salivary steroid (dehydroepiandrosterone) (Dias Fernandes et al., 2009) and vasodilator (calcitonin gene-related peptide) (Zidverc-Trajkovic et al., 2009) levels have been demonstrated in BMS patients. Interestingly, positron emission tomography (PET) studies have demonstrated altered dopamine D1 and D2 receptor expression in the putamen of BMS patients (Hagelberg et al., 2003b) while Borsani et al. (2014) have recently demonstrated altered expression profiles of the transient receptor potential vanilloid channel type 1 (TRPV1) and cannabinoid receptor (CB) type 1 and type 2 in human tongue epithelial cells. Nasri-Heir et al. (2011) suggest a neurodegenerative component to BMS, with chorda tympani nerve hypofunction associated with the disorder. Interestingly, polymorphism in pro-inflammatory interleukin (IL)-1β has been shown in BMS patients, suggesting that IL-1β regulation may be a therapeutic target in BMS patient cytokine pain management (Guimaraes et al., 2006). Indeed recent evidence in support of this indicates that pro-inflammatory cytokines such as IL-6 are increased in the saliva of patients with BMS, suggesting neuroinflammatory processes underlie the disease (Pezelj-Ribaric et al., 2013).

2.1.2. PIFP pathophysiology

The pathophysiology of PIFP is poorly understood, with patients often presenting with oral and(or) other psychogenic-related complaints. Indeed, some patients may respond to CBT and(or) tricyclic anti-depressants. PET studies in patients have more recently shown that alterations in blood flow occurs in the anterior cingulum and prefrontal cortex (Derbyshire et al., 1994) and alteration in the expression of D2 receptors in the putamen (Hagelberg et al., 2003a). Overall, various neuropathic mechanisms appear to be operating in PIFP, involving peripheral nerve pathology (Forssell et al., 2007), somatosensory dysfunction and changes in the excitability of primary nociceptive afferents (Koltzenburg et al., 1994).

2.1.3. TN pathophysiology

TN may be classified as idiopathic (no clinically obvious neurological cause) or secondary (underlying pathology present). Secondary TN is commonly caused by compression of the trigeminal root by a blood vessel, or by demyelination of the nerve in conditions such as Multiple Sclerosis (MS). The exact mechanism for pain production in TN remains uncertain. Using a rodent model of NOP Sugiyama et al. (2013) demonstrated the role of neuronal nitric oxide (NO) signalling in regulating neural excitability of the trigeminal ganglion following inferior alveolar nerve lesion. Elsewhere, several studies indicate specific receptor involvement in animal models of TN. Indeed, metabotrophic glutamate receptor (mGluR) 5 pathways in the trigeminal nucleus caudalis (Vc) and cervical spine mediate inflammatory tongue pain (Liu et al., 2012). In support of receptor-mediated signalling, nerve injury-induced TN is mediated by receptor tyrosine kinase ErbB3/ErbB2 heterodimers in rats (Ma et al., 2012), while distinct alterations in μ-opioid receptor expression in the nucleus accumbens has been determined in TN patients using PET, suggesting that alterations in the endogenous μ-opioid system may be linked with TN (DosSantos et al., 2012). Similarly, using a rat model of V2 injury, Okubo et al. (2013) demonstrate a clear role of serotonergic 5-hydroxytryptamine (5-HT) receptors in the Vc in hyperalgesia, while roles for voltage-gated sodium channels (Eriksson et al., 2005) in trigeminal NOP models has been suggested. Using an *in vitro* approach, Kuroda et al.

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