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Current evidence of cannabinoid-based analgesia obtained in preclinical and human experimental settings

J. Lötsch[1,2], I. Weyer-Menkhoff[1], I. Tegeder[1]

1 Institute of Clinical Pharmacology, Goethe – University, Frankfurt am Main, Germany
2 Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Project Group Translational Medicine and Pharmacology TMP, Frankfurt am Main, Germany

Correspondence
Jörn Lötsch
E-mail: j.loetsch@em.uni-frankfurt.de

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Abstract

Cannabinoids have a long record of recreational and medical use and become increasingly approved for pain therapy. This development is based on preclinical and human experimental research summarized in this review. Cannabinoid CB_1 receptors are widely expressed throughout the nociceptive system. Their activation by endogenous or exogenous cannabinoids modulates the release of neurotransmitters. This is reflected in antinociceptive effects of cannabinoids in preclinical models of inflammatory, cancer and neuropathic pain, and by nociceptive hypersensitivity of cannabinoid receptor-deficient mice. Cannabis-based medications available for humans mainly comprise Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD) and nabilone. During the last 10 years, six controlled studies assessing analgesic effects of cannabinoid-based drugs in human experimental settings were reported. An effect on nociceptive processing could be translated to the human setting in functional magnetic resonance imaging studies that pointed at a reduced connectivity within the pain matrix of the brain. However, cannabinoid-based drugs heterogeneously influenced the perception of experimentally induced pain including a reduction in only the affective but not the sensory perception of pain, only moderate analgesic effects, or occasional hyperalgesic effects. This extends to the clinical setting. While controlled studies showed a lack of robust analgesic effects, cannabis was nearly always associated with analgesia in open-label or retrospective reports, possibly indicating an effect on well-being or mood, rather than on sensory pain. Thus, while preclinical evidence supports cannabinoid-based analgesics, human evidence presently provides only reluctant support for a broad clinical use of cannabinoid-based medications in pain therapy.

Significance: Cannabinoids consistently produced antinociceptive effects in preclinical models, whereas they heterogeneously influenced the perception of experimentally induced pain in humans and did not provide robust clinical analgesia, which jeopardizes the translation of preclinical research on cannabinoid-mediated antinociception into the human setting.

1. Introduction

Cannabinoids (Fig. 1) have been consumed for their psychoactive effects for centuries. The typical marijuana-like effects consist of euphoria and relaxation, increased feeling of pleasure, getting 'high', feeling more emotions, relief of dysphoria, relief of

boredom, reduced anxiety and feeling good about oneself (Dekker et al., 2009). Numerous self-reports of patients suggested also a use of cannabis for pain relief (Ogborne et al., 2000) supported by results of some controlled clinical trials, mostly in patients with intractable neuropathic pain or pain in neurologic diseases (Berman et al., 2004; Wissel et al., 2006; Abrams et al., 2007; Wilsey et al., 2008; Ellis et al., 2009; Selvarajah et al., 2010; Wallace et al., 2015; Whiting et al., 2015). This agrees with results from preclinical research indicating an efficiency of cannabinoids in various animal pain models (Chesher et al., 1973; Sofia et al., 1975; Bensemana and Gascon, 1978). To this add observations that cannabinoids promote extinction of aversive memories of noxious stimuli through inhibition of GABAergic inhibitory circuits in the amygdala (Marsicano et al., 2002; Azad et al., 2004; Moise et al., 2008). This has been translated into human experimental settings, where functional magnetic resonance imaging (fMRI) studies have pointed at alteration of the brains function and structure (Batalla et al., 2013; Brumback et al., 2016) in general, and specifically at inhibitory effects of cannabis-based medications on the connectivity (Lee et al., 2013; Walter et al., 2016) within the so-called pain matrix of the brain (Tracey and Johns, 2010; Mouraux et al., 2011). Hence, preclinical and human experimental evidence have provided a basis for the increasing approval of drugs containing exogenous cannabinoids for the treatment of pain. Therefore, mechanistic evidence of a role of the cannabinoid system in nociceptive signalling and processing and its translation to the human experimental setting

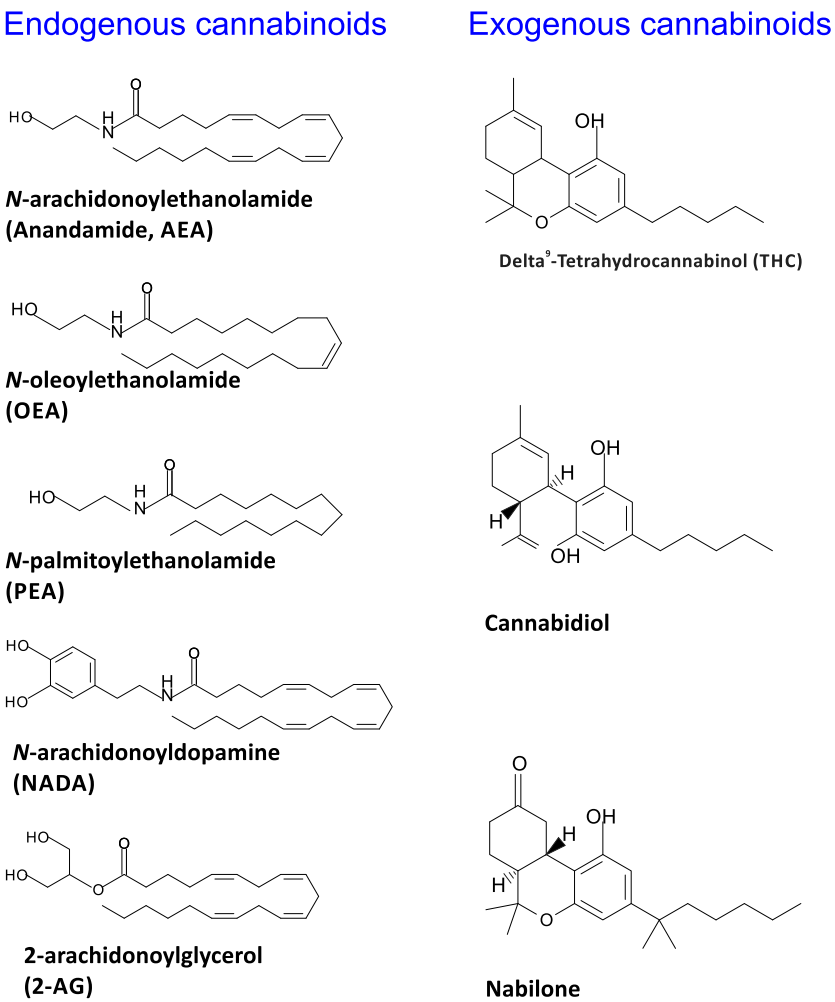

Figure 1 Chemical structures of endogenous cannabinoids (left) and of those exogenous cannabinoid-based medications that had been included in human experimental studies on the effects of cannabinoids on pain.

will be summarized in the following review, accompanying a separate overview on the clinical evidence published in temporal vicinity in this Journal.

2. Cannabinoid signalling in the nociceptive system

Cannabinoid-mediated activation of CB_1 receptors (Box 1) reduces the release of neurotransmitters from the presynaptic terminal (Piomelli, 2003; Gulyas et al., 2004; Kofalvi et al., 2007; Kano et al., 2009). This results in an inhibition of glutamatergic excitatory and GABAergic inhibitory systems (Chevaleyre et al., 2006; Lovinger, 2008; Heifets and Castillo, 2009; Kano et al., 2009) in brain and spinal cord. It is believed that endocannabinoids released from the post-synaptic neuron stimulate CB_1 receptors of the presynaptic neuron and inhibit thereby further release of neurotransmitters, which may result in inhibition or disinhibition depending on the type of synapse (Wilson and Nicoll, 2002; Lovinger, 2008). For the antinociceptive effects, inhibition of glutamate release from primary and secondary nociceptive neurons and pain-associated regions is probably the main mechanism (Wilson and Nicoll, 2002; Domenici et al., 2006). Inhibition of inhibitory GABAergic circuits contributes to cannabinoid-mediated effects in the hippocampus (Kim and Alger, 2010) and its effects on cognition (Carter and Wang, 2007). Disinhibition of inhibitory circuits may also account for cannabinoid-mediated extinction of aversive memories and fear (Marsicano et al., 2002; Azad et al., 2004) and suppression of anxiety in response to stress of social threat (Moise et al., 2008; Phan et al., 2008), which have been attributed to the fine-tuning of local inhibitory circuits in the amygdala (Marsicano et al., 2002; Azad et al., 2004; Moise et al., 2008).

In addition, cannabinoids acting at peripheral and central CB_1 receptor reduce the stress response through inhibition of noradrenaline release from presynaptic terminals, which may impact on the ability to cope with pain-evoked stress and hence alter pain-evoked affective responses in rodent models (Racz et al., 2015; Busquets-Garcia et al., 2016). Analgesia provided by cannabinoids further involves direct agonistic stimulation of glycine receptors

Box 1 Components of the cannabinoid system

Cannabinoid receptors: Cannabinoid-based drugs exert their main pharmacodynamic effects via activation of cannabinoid CB_1 and CB_2 receptors (Devane et al., 1988; Matsuda et al., 1990). These are G-protein-coupled receptors signalling via cyclic adenosine monophosphate as first messenger (Galve-Roperh et al., 2002). The typical marijuana-like effects are regarded as mainly mediated via CB_1 receptors. The expression pattern of CB_1 receptors includes the brain, spinal cord, peripheral nervous system and peripheral tissue including muscle, skin and liver.

In contrast to the nervous system dominance of CB_1 receptors, CB_2 receptors are found not only in cells of the immune system but also in the brain (Pertwee, 2005) and may contribute to signalling of pain relief by modulation of dopamine release in reward centres (Zhang et al., 2014). Nevertheless, typical marijuana-like psychoactive effects are regarded as mainly mediated via CB_1 receptors, whereas metabolic, anti-cancer and anti-inflammatory effects likely also involve nuclear receptors and orphan G-protein-coupled receptors.

Endocannabinoids: The endogenous ligands (Fig. 1) at cannabinoid receptors comprise the so-called endocannabinoids, a class of lipid mediators synthetized from arachidonic acid. Major members of this group comprise arachidonoyl ethanolamide (anandamide or AEA) and 2-arachidonoylglycerol (2-AG; Rodriguez de Fonseca et al., 2005).

Structurally related eicosanoid lipid mediators such as palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) also belong to endocannabinoids, but they are no direct agonists at the classical CB_1/CB_2 receptors (Porter et al., 2002) and interact with nuclear receptors including PPARs, TRP channels like TRPV1 (Thabuis et al., 2008) and G-coupled orphan receptors GPR55, GPR92, GPR18 and GPR119 (Godlewski et al., 2009).

These lipid mediators are involved in several physiological systems including behaviour, pain, memory, appetite, female reproduction, the gastrointestinal, immune and cardiovascular system (Rodriguez de Fonseca et al., 2005). In the nervous system, endocannabinoids contribute to the suppression of the release of excitatory and inhibitory neurotransmitters (Heifets and Castillo, 2009).

modulating thereby NMDA receptor responses (Xiong et al., 2012) and CB_2-mediated immune control (Ibrahim et al., 2006; Kinsey et al., 2011; Burston et al., 2013; Li et al., 2017). Via peripheral CB_2, cannabinoids increase the release of endogenous opioids from keratinocytes and immune cells, which in turn reduce nociceptor activation (Ibrahim et al., 2005). In addition, it is increasingly recognized that CB_2 is located in neuronal circuits in the brain relevant for pain control (Elmes et al., 2004; Beltramo et al., 2006; Shang and Tang, 2016) and dopamine mediated reward (Nader et al., 2014; Zhang et al., 2014, 2017). Pain, cognition and anxiety may be differentially modulated by the two major endocannabinoids, anandamide and 2-arachidonoylglycerol (Busquets-Garcia et al., 2011) and hence, drugs inhibiting degradation of one (Jayamanne et al., 2006; Ahn et al., 2009) or the other (Chanda et al., 2010) may be differentially useful as analgesics.

3. Preclinical evidence of antinociceptive effects of cannabinoids

3.1 Effects of cannabinoids in animals with intact cannabinoid system

Cannabinoids showed efficacy in numerous acute rodent pain models such as formalin test, hot plate and tail flick (Chesher et al., 1973; Sofia et al., 1975; Bensemana and Gascon, 1978) and in multiple models of chronic inflammatory and neuropathic pain (Jaggar et al., 1998; Clayton et al., 2002; Elmes et al., 2004; Dyson et al., 2005; Cheng and Hitchcock, 2007). There is vast evidence for antinociceptive effects of cannabinoid receptor agonists both for dual CB_1/CB_2 agonists (Rice et al., 2002; Johanek and Simone, 2004; Papanastassiou et al., 2004; Scott et al., 2004; Jeske et al., 2006; Patwardhan et al., 2006; Hasanein and Teimuri Far, 2015), specific CB_1 (Clayton et al., 2002) or specific CB_2 agonists (Ibrahim et al., 2005, 2006), the latter mainly reducing the neuroinflammatory component of neuropathic pain (Racz et al., 2008; Romero-Sandoval et al., 2008; Correa et al., 2009). However, recent evidence supports the presence of neuronal CB_2 in pain relevant circuits (Elmes et al., 2004; Beltramo et al., 2006; Shang and Tang, 2016). In particular, midbrain CB_2 stimulation increases dopamine release from neurons of the ventral tegmental area (Xi et al., 2011; Zhang et al., 2014, 2017), a mechanism contributing to pain relief and placebo effects and descending pain control (Navratilova et al., 2012, 2015).

Importantly, peripherally acting compounds reduce pain without causing the typical cannabinoid-associated behavioural side effects in rodents (Richardson et al., 1998; Johanek and Simone, 2004). Efficacy was also demonstrated with substances inhibiting the re-uptake of endocannabinoids (Costa et al., 2006), hence increasing the synaptic endocannabinoid content, or by inhibition of the degradation of the two major endocannabinoids anandamide or 2-arachidonoylglycerol (Jayamanne et al., 2006; Desroches et al., 2008; Kinsey et al., 2009; Long et al., 2009). Overall, there is stronger evidence for antinociceptive effects of inhibitors of fatty acid amide hydrolase (FAAH) (Jayamanne et al., 2006; Ahn et al., 2009; Pecina et al., 2014), the enzyme degrading anandamide, than for monoacylglycerol lipase (MAGL) (Comelli et al., 2007; Guindon et al., 2011) degrading 2-AG, likely because 2-AG may result in opposite pain-sustaining effects on long-term use (Schlosburg et al., 2010). Apart from the classical $CB_{1/2}$ agonists, some related endocannabinoids, which do not act as direct agonists of the classical CB_1 or CB_2 receptors, provide pain relief in rodent models of visceral, inflammatory and neuropathic pain such as oleoylethanolamide (Suardiaz et al., 2007) and palmitoylethanolamide (Jaggar et al., 1998; Costa et al., 2008; Luongo et al., 2013), possibly via PPARs (O'Sullivan, 2007; Costa et al., 2008), inhibition of TRPV1 channels (Costa et al., 2008), downregulation of FAAH and actions on non-neuronal cells (Bettoni et al., 2013).

Among the non-CB activating exogenous cannabis constituents (reviewed in), cannabidiol, which possesses antagonist activity at $CB_{1/2}$ (Thomas et al., 2007) and also inhibits FAAH in rat brain membranes with a median effective concentration of 8.6 ± 0.2 μmol/L (Leweke et al., 2012) has been extensively studied (Straus, 2000) and reviewed elsewhere (Izzo et al., 2009; Campos et al., 2012; McPartland et al., 2015). It provided anti-inflammatory and antinociceptive effects not only in classical nociceptive models (Malfait et al., 2000; Costa et al., 2004), but also in models of visceral pain and multiple sclerosis (Mecha et al., 2013) or in patients with Parkinson's-associated pain (Chagas et al., 2014) and intractable cancer pain (Johnson et al., 2010). The mechanisms may involve activation of nuclear receptors (O'Sullivan, 2007), antagonism of atypical cannabinoid receptors such as GPR55 (Johns et al., 2007; Ryberg et al., 2007), modulation of calcium fluxes via TRP channels (Campos et al., 2012; Iannotti et al., 2014), some neuroprotective effects found in models of epilepsy and cerebral ischaemia

(Do Val-da Silva et al., 2017; Khaksar and Bigdeli, 2017) and stimulation of neurogenesis (Esposito et al., 2011). The full spectrum and underlying mechanisms of beneficial effects of cannabidiol is still not completely understood. Further agonists of some cannabinoid-sensitive 'orphan' G-protein-coupled receptors may modify nociception and inflammation in specific models (Walker et al., 2005; Suardiaz et al., 2007; Bradshaw et al., 2009; Sharir and Abood, 2010). Tolerance towards the cannabinoid agonists does occur in rodent models (Gardell et al., 2002; Tappe-Theodor et al., 2007; Schlosburg et al., 2010) owing to a downregulation or internalization of CB_1 receptors (Hsieh et al., 1999; Rubino et al., 2006; McKinney et al., 2008; Wu et al., 2008). However, tolerance, withdrawal symptoms (Valverde et al., 2000) and agonist-evoked hypersensitivity (Pernia-Andrade et al., 2009; Kato et al., 2012) appear to be less pronounced than with opioids in rodents, possibly due to counterbalancing effects of transient receptor potential channel activation (Horvath et al., 2008; Chavez et al., 2010; Di Marzo and De Petrocellis, 2010) or positive modulation of dopaminergic 'pain-relief-reward' circuits (Pecina et al., 2014).

3.2 Effect of cannabinoids on nociception in genetic mouse models

The results obtained with cannabinoid receptor agonists were corroborated with genetic models of cannabinoid receptor deficient mice. General deletion of CB_1 (Racz et al., 2015) but also exclusive CB_1 deletion in peripheral nociceptive neurons causes nociceptive hypersensitivity in models of acute, inflammatory and neuropathic pain (Agarwal et al., 2007; Clapper et al., 2010), whereas FAAH knockout mice are protected from nociceptive hypersensitivity in models of inflammatory and neuropathic pain and acute heat- or formalin-evoked nociception (Cravatt et al., 2001; Lichtman et al., 2004), and they showed reduced signs of stress or sleep disturbances (Huitron-Resendiz et al., 2004; Hill et al., 2013), which may occur as sequelae of chronic pain.

Nociceptive hypersensitivity was also observed in CB_2 knockout mice (Yamamoto et al., 2008), but they are more affected by metabolic dysfunctions and obesity, particularly at old age (Agudo et al., 2010; Schmitz et al., 2015), which is associated with a premature decline of thermal sensitivity, possibly masking the expected nociceptive hypersensitivity (Schmitz et al., 2015). The evidence for a contribution of CB_2 for pain control mainly relies on studies with specific agonists (Yao et al., 2009; Gutierrez et al., 2011; Kinsey et al., 2011; Vincenzi et al., 2013), or maintenance of antinociceptive effects of CB_1/CB_2-agonists in CB_1-deficient mice (Sain et al., 2009; Deng et al., 2015). The double knockouts primarily suffer from increased allergy (Karsak et al., 2007), likely primarily a function of missing CB_2 (Agudelo et al., 2008; Haruna et al., 2015), and they mimic the general CB_1 knockouts in terms of nociception. GPR55 knockouts also show some nociceptive phenotype (Staton et al., 2008), but overall, rodent models suggest that the primary cannabinoid target for inhibition of pain-like behaviours are peripheral and central CB_1 receptors, whereas CB_2 receptors, although expressed in some neurons (Van Sickle et al., 2005; Wotherspoon et al., 2005), mainly act by inhibiting pro-inflammatory responses of immune cells and microglia (Romero-Sandoval et al., 2008) and contribute thereby to pain inhibition (Romero-Sandoval et al., 2008). However, recent data suggest that CB_2-mediated enhancement of dopamine release in the midbrain (Zhang et al., 2014) may contribute to descending pain control and pain relief (Navratilova et al., 2015).

4. Human experimental evidence of analgesic effects of cannabinoid-based drugs

Cannabinoid-related drugs qualifying for pain treatment (Box 2) are most frequently exogenous ligands of cannabinoid receptors mimicking the action of the endogenous ligands. Cannabinoid active substances are mainly found in the plant *Cannabis sativa* and its major active ingredient, Δ^9-tetrahydrocannabinol (THC; Fig. 1), has been the lead compound for the development of exogenous cannabinoids as drugs for medical use. The common exogenous cannabinoids are available as (1) herbal cannabis, i.e. medical marijuana, which contains a specific percentage of **THC**, followed by cannabidiol (CBD) and other compounds (Thomas et al., 2007), (2) isolated oral THC, called **dronabinol**, (3) a synthetic derivate of THC that acts also as CB_1/CB_2 receptor agonist, called **nabilone**, or as (4) an oromucosal spray, which is a whole-plant extract containing a mixture of THC and CBD, called **nabiximols** (Pertwee, 2010).

A PubMed database search (https://www.ncbi.nlm.nih.gov/pubmed) on November 21st, 2016, for "(-cannabis and pain) AND (Clinical Trial[ptyp] AND full text[sb] AND Humans[Mesh]) and healthy" OR "(cannabinoids and pain) AND (Clinical Trial[ptyp] AND full text[sb] AND Humans[Mesh]) healthy"

obtained 31 hits. Comparative studies, reviews and papers with a focus on economic aspects were excluded. In addition, only those studies were kept that had been performed in healthy volunteers and were published within the last 10 years. These criteria were met by six study reports (Table 1) consisting

Box 2 Exogenous cannabinoids contained in cannabinoid-based medications.

Delta^9-tetrahydrocannabinol (THC, Fig. 1) is a major ingredient of Cannabis sativa (Mechoulam and Gaoni, 1965). It mimics the effects of anandamide and 2-arachidonoylglycerol (2-AG) on neuronal signalling (Rodriguez de Fonseca et al., 2005). Hence, THC interacts with several endocannabinoid-based mechanisms and affects social behaviour, pain, memory, appetite, female reproduction, gastrointestinal, immune and cardiovascular functions (Rodriguez de Fonseca et al., 2005). In addition, THC competes with the natural ligands for the specific receptor binding sites interfering with endogenous feedback mechanisms, which after oral administration leads to a decrease in endocannabinoid plasma concentrations (Walter et al., 2013). Depending on the model, THC acts as full or partial agonist of CB_1 receptors (Shen and Thayer, 1999; Roloff and Thayer, 2009; Laaris et al., 2010; Paronis et al., 2012).

Cannabidiol (CBD, Fig. 1) is a further major constituent of Cannabis sativa (Thomas et al., 2007). It has been proposed as a non-psychoactive isomer of THC (Bakas et al., 2017). Unlike THC, it acts as a negative allosteric modulator (NAM) of CB_1 receptors and reduces the potencies of 2-AG and the exogenous agonist, THC. Furthermore, it also acts as a non-competitive CB_2 receptor inverse agonist (Thomas et al., 2007), i.e. CBD exhibits CB_2 receptor antagonism (Thomas et al., 2007). Furthermore, CBD has been shown to inhibit the fatty acid amide hydrolase (FAAH), an enzyme involved in the metabolism of AEA, leading to increased brain anandamide concentrations in rats (Kathuria et al., 2003). However, an inhibitory effect of CBD on human FAAH was not found (Elmes et al., 2015).

Nabilone (Fig. 1) is a synthetic derivate of THC that acts also as non-selective CB_1 and CB_2 agonist (Pertwee, 2010). In animal studies nabilone had similar behavioural and physiological effects as THC (Lile et al., 2011). In humans, subjects treated with nabilone reported less euphoria than when taking THC (Lemberger et al., 1982). In addition, reinforcement effects were lower than those of oral THC and smoked cannabis, suggesting a reduced abuse potential (Lile et al., 2010).

Table 1 Human experimental studies of the analgesic effects of cannabinoid-based drugs reported during the last 10 years.

Substance	Dose	No. Subjects (men)	Pain model	Analgesic effect	Reference
Cannabis (smoked)	0, 2, 4, 8%	15 (11)	Intradermal capsaicin, heat, electrical and mechanical stimuli	Modest analgesia with the medium dose, hyperalgesic effects of the high dose	Wallace et al. (2007)
Cannabis extract calibrated on THC (oral)	20 mg	18 (0)	UV-B, heat, electrical and mechanical pain stimuli	No analgesic effect in all models; hyperalgesic effects in the electrical pain model	Kraft et al. (2008)
Nabilone (oral)	0.5, 1 mg	17 (7)	Tonic heat pain and contralateral cold water immersion	No analgesic effects and no interaction with descending noxious inhibitory control	
Dronabinol (oral)	15 mg	12 (12)	Topical capsaicin punctate pressure	Reduction in the unpleasantness but not of the intensity of mechanical stimuli, inhibitory effect on pain matrix brain connectivity	Lee et al. (2013)
Dronabinol (oral)	20 mg	30 (15)[a]	Electrical stimuli	Hyperalgesic effects	Walter et al. (2016, 2015)
		15 (8)[a]	Intranasal gaseous CO_2-stimuli	No significant analgesia, inhibitory effect on pain matrix brain connectivity	
Cannabis (smoked)	0, 3.5, 5.6%	42 (21)	Cold-pressor test	Analgesic effects only in men	

[a]Experiments from the same study; a chemical pain model was used only in a subgroup of subjects who underwent a separately reported fMRI assessment.

in results of a cumulative count of 138 healthy volunteers.

4.1 Effects of THC on human brain activity in the pain matrix

In general, several human fMRI studies with cannabis treatment showed to have an effect on the brain structure and function (Batalla et al., 2013; Brumback et al., 2016). In particular, two studies using different experimental pain models could localize the effects of THC on pain-related human brain activations within the so-called pain matrix (Lee et al., 2013; Walter et al., 2014), which comprises a complex network of brain structures regarded to be involved in the processing and perception of pain (Tracey and Mantyh, 2007; Garcia-Larrea and Peyron, 2013).

In a first placebo-controlled study enroling 12 healthy men, the effects of 15 mg oral dronabinol on the perception of cutaneous ongoing pain and hyperalgesia temporarily induced by capsaicin were studied employing functional magnetic resonance imaging (fMRI; Lee et al., 2013). As a main result, THC reduced the reported unpleasantness, but not the intensity of ongoing pain and hyperalgesia. The THC-induced reduction in the unpleasantness of hyperalgesia was positively correlated with right amygdala activity. Using psychophysiological interaction (PPI) analysis, which model the response in one cortical area as the influence of another region and its interaction with an experimental treatment (sensory stimulus; Friston et al., 1997), THC was also found to reduce the functional connectivity between the amygdala and primary sensorimotor areas during the ongoing-pain state. The reduction in sensory-limbic functional connectivity was positively correlated with the difference in drug effects on the unpleasantness and the intensity of ongoing pain. This finding was interpreted in the sense that THC predominantly affects the limbic rather than the sensory processing of nociceptive information. However, the PPI method cannot specify the direction of the influence.

In a second placebo-controlled study enroling 15 healthy volunteers (eight men, a separately reported additional experiment performed in a subset of a study cohort reported in), the effects of 20 mg oral THC on chemically induced pain evoked by delivering short pulses (500 ms) of gaseous CO_2 to the subjects' nasal mucosa were assessed by means of fMRI (Walter et al., 2016). Following THC administration, reduced pain-associated activations were found in the hippocampus and in the anterior insular cortex. Using both, psychophysical interaction analysis and dynamic causal modelling detected that the effects of THC consisted firstly in a weakening of the interaction between the thalamus and the secondary somatosensory cortex. Only secondary to that, the activations in the hippocampus and the anterior insula were attenuated. From this it was concluded that THC does not selectively affect limbic regions, but rather interferes with sensory processing, which in turn reduces sensory-limbic connectivity, leading to deactivation of affective regions and suggesting that the reduced activations in these regions are secondary to a reduction in the connectivity that arises from somatosensory regions (Walter et al., 2016).

4.2 Effects of exogenous cannabinoids on psychophysics of experimentally induced pain

Randomized controlled human experimental studies about the effects of cannabinoids on pain (Table 1) provided heterogeneous outcomes. Observations of cannabinoid effects include (1) an increase in pain, i.e. hyperalgesic effects, (2) a lack of any analgesic effects and (3) moderate analgesia.

An unexpected observation in a human investigation on cannabis effects on pain perception was the induction of hyperalgesia to experimental electrical pain stimuli following administration of a single oral dose of 15 mg THC to 18 healthy young women (Kraft et al., 2008). This finding was independently reproduced in a cohort of 30 healthy young men or women who had received oral doses of either 20 mg THC or placebo. In this study, pain tolerance to nociceptive electrical stimuli decreased from 3.7 ± 2.1 mA to 2.5 ± 1.3 mA following THC administration, while it remained fairly stable after placebo (Walter et al., 2015). As in both studies, electrical noxious stimuli were involved, the particular pain model may play a role in the unexpected outcomes that were not reported with other pain models. However, the hyperalgesic effects in the electrical pain model of THC have not been assessed further, leaving explanations such as a co-activation of pain-enhancing TRPV1 channels by cannabis at higher doses (Chavez et al., 2010) or partial antagonist effects at CB_1 receptors (Roloff and Thayer, 2009; Paronis et al., 2012) hypothetical. It is unknown if local THC concentrations are sufficient for TRP channel activation. A limited therapeutic window for cannabis was also suggested by the findings with the capsaicin pain model (intradermal injection) where higher doses increased pain (Wallace et al., 2007), hence, the

hyperalgesic effects seem not to be restricted to electrical noxious stimuli.

Absent effects on pain perception seem to be a common finding in experimental human studies on capsaicin analgesia. Specifically, 20 mg orally administered THC did not affect heat pain thresholds in the UV-B irradiation pain, and did not alter the area of secondary hyperalgesia, flare and spontaneous pain evoked by intradermal injection of capsaicin in 18 healthy women (Kraft et al., 2008). In one of the above-mentioned fMRI studies (Lee et al., 2013), THC (15 mg administered orally) failed to reduce the intensity of ongoing pain and mechanical hyperalgesia (punctate pressure pain) induced by topical local capsaicin application and was only able to reduce the unpleasantness of the stimuli. Similarly, in the second above-mentioned fMRI study studying THC effects (20 mg administered orally) on nociceptive brain activations, the medication had no statistically significant effects on the intensity of chemically induced pain in 15 healthy men and women (Walter et al., 2016). Cannabis lacked effects on experimentally induced pain in a further study in 17 subjects who had received 0.5 or 1 mg nabilone. In that study, pain intensity of a continuous heat pulse was studied before and after the subject's contralateral arm was immersed in cold water for 2 min. Nabilone neither reduced the heat pain intensity nor did it potentiate the strength of the descending inhibitory control. Only in women but not in men, the highest dose dampened the temporal summation during the tonic heat stimulation.

Moderate analgesic effects of cannabinoids were reported from a study employing smoked cannabis at low and medium doses (3.56–5.6%). The drug produced a decrease in pain sensitivity and an increase in pain tolerance in a cold water immersion pain model. However, analgesic effects were observed only in men, who represented half of the study cohort of 42 volunteers. Finally, in a study in 15 healthy volunteers, testing low-, medium- and high-dose smoked cannabis (2%, 4% and 8% THC, respectively), the medium dose resulted in a significant decrease in pain produced by intradermal capsaicin injection, whereas the high dose increased pain as mentioned above (Wallace et al., 2007).

4.3 Side effects reported from the human experimental setting

Of note, while producing no or small effects on experimentally induced pain, most of the human laboratory studies reported cannabinoid-related side effects in the volunteers. Moderate to mild psychotropic effects were reported (Kraft et al., 2008; Redmond et al., 2008) including a dose-dependent feeling of 'high' (Wallace et al., 2007) and a slower reaction-time (Lee et al., 2013). Inhaled THC is almost instantaneously absorbed quickly reaching high plasma concentrations that drop immediately after smoking has been stopped (Wall and Perez-Reyes, 1981). A feeling of 'high' reached its maximum at 30–90 min following THC smoking. By contrast, the time to reach peak plasma concentrations after administration of oral THC or nabilone has been reported to be 2–3 h, and concentrations remain high for up to 6 h (Wall and Perez-Reyes, 1981; Lemberger et al., 1982). Consequently, the feeling of 'high' after oral administration of THC starts at 30–120 min after administration and reaches a maximum at 150–180 min (Wall and Perez-Reyes, 1981).

5. Discussion

Molecular and preclinical evidence supports the development of cannabinoid-based medications for the treatment of pain. This is based on important modulatory roles of cannabinoid signalling in the nociceptive system and multiple studies showing antinociceptive behaviours in rodents CB_1 and CB_2 agonists and FAAH inhibitors. However, the translation of these findings into the human experimental setting was only partly successful. While THC was reproducibly shown to reduce the functional connectivity between brain areas within the pain matrix, cannabinoid-based medications often lacked effects on the sensory perception of pain evoked by stimuli in experimental settings. This picture does not change when including studies older than the 10-year windows analysed in this review. For example, in 13 healthy subjects 5 mg of oral THC reduced only the affective rating of heat stimuli, and this only in combination with morphine (Roberts et al., 2006). Similarly, in 12 healthy subjects, 20 mg THC failed to produce analgesic effects in heat, cold and electrical pain models, and only in combination with morphine a synergist effect was observed on electrical pain (Naef et al., 2003).

Thus, the analysis of experimental human pain studies published during the last 10 years allows only for a reluctant advice of a clinical use of cannabis-based medications for pain treatment. Recent analytical reviews of human experimental pain models (Oertel and Lotsch, 2013; Lotsch et al., 2014) indicated an overally satisfactory prediction

of analgesic drug effects in clinical settings. A confined set of experimental human pain models including chemical hyperalgesia produced by capsaicin, chemical pain evoked using intranasal CO_2 or UV-B irradiation-based hyperalgesia, appears to be sufficient to correctly predict the analgesic drug efficacy for a set of clinical pain settings (Lotsch et al., 2014). These models had been included in human experimental studies of the analgesic effects of cannabinoid-based drugs. Hence, unsuitability of experimental pain models for the prediction of clinical analgesia does not provide a comprehensive explanation of the modest effects. By contrast, the lack of clear analgesic effects of cannabinoids in human pain raises the question whether and to what extent results obtained in molecular research and animal-models are relevant for the clinics, a criticism that has been raised previously (Mogil, 2009).

The heterogeneous effects of cannabinoids on pain observed in the human experimental settings appear to translate to the clinical setting. In support of this judgement, a PubMed database search on 21 November 2016 retrieved 23 clinical trials reporting mixed effects of cannabinoid-based medications on various settings of clinical pain in a total of 1998 patients with persistent pain (GW Pharma, Ltd, 2000; Wissel et al., 2006; Abrams et al., 2007, 2011; Nurmikko et al., 2007; Frank et al., 2008; Narang et al., 2008; Skrabek et al., 2008; Wilsey et al., 2008, 2013; Ellis et al., 2009; Johnson et al., 2010; Selvarajah et al., 2010; Ware et al., 2010; Bestard and Toth, 2011; Corey-Bloom et al., 2012; Portenoy et al., 2012; Toth et al., 2012; Langford et al., 2013; Lynch et al., 2014; Serpell et al., 2014; Turcotte et al., 2015; Wallace et al., 2015). A summarizing analysis of this evidence suggested that (1) no clear clinical setting could be found where cannabinoids produced robust analgesic effects, (2) half of the patients (n = 973) had participated in negative studies with respect to cannabis-induced analgesia and (3) all studies reported a large inter-individual variability. By contrast, cannabis was nearly always associated with analgesia in open-label studies or retrospective analyses (details not reported), possibly indicating an overall increase in well-being, sleep or mood leading to relief of intractable pain, reduction in fear and improvement of quality of life rather than measurable changes of nociceptive thresholds. This conclusion is supported by a number of meta-analyses addressing the usefulness of medicinal cannabis for the treatment of chronic pain conditions including neuropathic pain, pain in rheumatoid diseases, fibromyalgia or neurologic diseases (Centonze et al., 2009; Martin-Sanchez et al., 2009; Andreae et al., 2015; Whiting et al., 2015; Walitt et al., 2016).

6. Conclusions

While preclinical evidence clearly supports antinociceptive effects of cannabinoids, human experimental evidence draws a more heterogeneous picture. While exogenous cannabinoids modulate functional connections within the pain matrix of the brain, they influence experimentally induced pain in a heterogeneous manner, reaching from hyperalgesia to moderate analgesic effects. This evidence provides only reluctant support for a broad clinical use of cannabinoid-based medications in pain therapy. However, it has to be considered that opioids may also produce hyperalgesia (Eisenberg et al., 2015). Nevertheless, cannabis-based drugs may still be useful for pain relief of intractable pain and in some neurological diseases involving either strong neuroinflammation such as multiple sclerosis and Huntington's disease and/or muscle spasms and stiffness (Wissel et al., 2006; Zajicek et al., 2012) or deregulation of dopamine-cannabinoid reward signalling (Koppel et al., 2014).

Author contributions

JL - Concept and writing of the manuscript, revision of the manuscript, critical revision of the manuscript for important intellectual content IMW - Literature seach, writing of the manuscript, revision of manuscript IT - Writing of the manuscript, critical revision of the manuscript for important intellectual content.

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