Cannabidiol, cannabinol and their combinations act as peripheral analgesics in a rat model of myofascial pain

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ABSTRACT

Objective: This study investigated whether local intramuscular injection of non-psychoactive cannabinoids, cannabidiol (CBD), cannabinol (CBN), cannabichromene (CBC) and their combinations can decrease nerve growth factor (NGF)-induced masticatory muscle sensitization in female rats.

Design: In awake rats, changes in mechanical sensitivity induced by intramuscular injection of NGF and cannabinoids were measured by applying an electronic von Frey hair over the masseter muscle to measure the withdrawal response. The effect of CBD (5 mg/ml) and CBN (1 mg/ml) or their combinations CBD/CBN (1:1 mg/ml or 5:1 mg/ml) were assessed. To confirm a peripheral action, electrophysiological experiments were undertaken in anesthetized rats to examine whether intramuscular injections of CBD (5 mg/ml) and CBN (1 mg/ml) altered the mechanical threshold of masticatory muscle mechanoreceptors.

Results: In behavioral experiments, CBD (5 mg/ml) or CBN (1 mg/ml) decreased NGF-induced mechanical sensitization. Combinations of CBD/CBN induced a longer-lasting reduction of mechanical sensitization than either compound alone. No significant change in mechanical withdrawal threshold was observed in the contralateral masseter muscles and no impairment of motor function was found with the inverted screen test after any of the treatments. Consistent with behavioral results, CBD (5 mg/ml), CBN (1 mg/ml) and the combination of CBD/CBN (1:1 mg/ml) increased the mechanical threshold of masseter muscle mechanoreceptors. However, combining CBD/CBN (5:1 mg/ml) at a higher ratio reduced the duration of this effect. This may indicate an inhibitory effect of higher concentrations of CBD on CBN.

Conclusions: These results suggest that peripheral application of these non-psychoactive cannabinoids may provide analgesic relief for chronic muscle pain disorders such as temporomandibular disorders and fibromyalgia without central side effects.

1. Introduction

Cannabis has been used as an analgesic for centuries, but its use is controversial due to its psychoactive effects (Maione, Costa, & Di Marzo, 2013; Robson, 2014). Advances in our knowledge of the endocannabinoid system, in particular the discovery that the psychoactive effects of cannabis are primarily due to delta-9-tetrahydrocannabinol (THC), renewed interest in cannabis-based analgesics (Maione et al., 2013; Robson, 2014). There are over 100 chemical compounds in the cannabis plant, and the clinical utility of many of these compounds remains unknown (Ulugol, 2014). For example, another cannabinoid found in the cannabis plant, cannabidiol (CBD), possesses minimal psychotropic effects but has anti-inflammatory and anti-nociceptive properties (Amar, 2006; Izzo, Borrelli, Capasso, Di Marzo, & Mechoulam, 2009; Maione et al., 2013; Pertwee, 2005; Philpott, O’Brien, & McDougall, 2017). The only cannabis-based product approved for pain treatment currently on the market is SATIVEX® (GW Pharma Ltd. Wiltshire, UK), which is formulated as a buccal spray containing approximate 1-to-1 THC and CBD for the relief of muscle spasticity in multiple sclerosis and neuropathic pain. Although it is generally well tolerated, many patients discontinued its use due to adverse central nervous system effects, such as dizziness (Etges et al., 2016; Moreno Torres, Sanchez, & Garcia-Merino, 2014).

Overproduction of nerve growth factor (NGF) has been proposed to mediate muscle sensitization, while intramuscular injection of NGF has been shown to mimic the tender points observed in the craniofacial...
regions of fibromyalgia and myofascial temporomandibular disorders (TMD) patients (Clauw, 2014; Rahman, Underwood, & Carnes, 2014; Wong, Dong, & Cairns, 2014). Both disorders show a marked sex-related difference with greater prevalence in women than in men (Cairns, 2007). In a previous study, we investigated whether intramuscularly injected THC reverse NGF-induced mechanical sensitization in female rats. We found that cannabinoid receptor type 1 and 2 (CB1 and CB2) are expressed by trigeminal ganglion neurons that innervate the rat masseter muscle, and that intramuscular injection of THC alleviates NGF-induced mechanical sensitization by activating CB1 receptors (Wong, Hossain, & Cairns, 2017). We also found that intramuscular injection of NGF reduced the expression of CB1 and CB2 receptors on nociceptive trigeminal ganglion neurons, suggesting NGF may induce sensitization by a reduction in peripheral inhibitory input (Wong et al., 2017). These results suggest that peripheral cannabinoid receptors may be a target for cannabinoid-based analgesics to treat muscle pain disorders.

In the present study, we investigated whether local intramuscular injection of non-psychoactive cannabinoids including CBD, cannabinol (CBN), and cannabichromene (CBC) or their combinations could reduce NGF-induced masseter muscle sensitization in female rats. To investigate whether these cannabinoids were acting peripherally, masticatory muscleafferent fiber recordings were subsequently undertaken for each cannabinoid or combination shown to be effective in the behavioral studies. The overall goal was to determine if there is a potential for non-psychoactive cannabinoids as novel peripherally active analgesics.

2. Materials and methods

2.1. Animals

Female (225–350 g, n = 54) Sprague–Dawley rats were used for all experiments. Animals were housed in groups of two with a 12-h light/dark cycle. Food and water were given ad libitum. All animal procedures were reviewed and approved by the University of British Columbia Animal Care Committee and complied with the guidelines of the Canadian Council on Animal Care.

2.2. Drugs

CBD, CBN, and CBC were purchased from Cayman Chemicals (Ann Arbor, USA). CBD was dissolved in acetonitrile, while CBN and CBC were dissolved in methanol, all to a concentration of 10 mg/ml in a stock solution. Appropriate volumes of each solution were evaporated under nitrogen gas, and subsequently re-solubilized with 4% Tween 80 in isotonic saline to final concentrations used for injection. The following treatment groups were tested: CBD (1 and 5 mg/ml), CBN (1 mg/ml), CBC (1 mg/ml) and CBD/CBN combination (1:1 or 5:1 mg/ml). A volume of 10 μl was injected intramuscularly for all treatment groups, resulting in a dose of 10 μg (0.030-0.045 mg/kg) cannabinoids injected at a concentration of 1 mg/ml and 50 μg (0.145-0.225 mg/kg) cannabinoid injected at a concentration of 5 mg/ml. For the CBD/CBN combination group, 10 or 50 μg CBD and 10 μg CBN were injected together.

3. Behavioral experiments

3.1. Administration of NGF and cannabinoids

Rats received an injection of NGF (25 μg/ml, 10 μl, Sigma, St. Louis, MO) or vehicle (phosphate buffered saline, PBS, 10 μl) into the belly of the left and right masseter muscles, respectively, under brief isoflurane anesthesia (See Fig. 1 for experimental timeline). NGF has been shown to induce local mechanical sensitization at the site of injection which lasts approximately 5 days after injection in female rats (Wong et al., 2014, Wong, Kang et al., 2014). The masseter muscle region was shaved prior to injection and the injection sites were marked with a permanent marker for subsequent identification. The concentration of NGF was selected based on the concentration used in previous human and rat experimental studies (Mann, Dong, Svensson, & Cairns, 2006; Svensson, Cairns, Wang, & Arendt-Nielsen, 2003; Svensson, Wang, Arendt-Nielsen, & Cairns, 2008; Svensson, Wang, Dong, Kumar, & Cairns, 2010; Wong, Dong et al., 2014) Three days after NGF injection, a post-NGF injection baseline (NGF baseline) was assessed. Subsequently, either CBD, CBN, CBC, CBD/CBN or vehicle were injected into the left (NGF-injected) masseter muscle of rats under brief isoflurane anesthesia to determine the effects of peripheral application of cannabinoids on NGF-induced sensitization. Vehicle group results have been previously published (Wong et al., 2017). This study was part of the same project as the previous study and was performed over the same time period, therefore a separate vehicle group was not tested. The investigator was blinded to the identity of the treatment groups until after all data was collected and analyzed.

3.2. Mechanical withdrawal threshold

Mechanical withdrawal threshold was assessed with a rigid electronic von Frey hair (IITC Life Science, Woodland Hills, CA). Before NGF injection, rats were habituated to restraint in a towel and mechanical withdrawal assessments made. The electronic von Frey hair was applied perpendicularly to the masseter muscle at the site of NGF injection previously marked with a permanent marker and the force was gradually increased until the animal moved its head away from the stimulus (~ 5 s duration). The mechanical test stimulus was applied at 1 min intervals for 5 min and the average was calculated for further analysis. Mechanical withdrawal threshold was measured daily for 5 days prior to the start of the experiment to determine that measurements were stable. Mechanical withdrawal threshold readings recorded the day prior to NGF injection were used as naïve baseline. After induction of the NGF-induced sensitization, behavioral testing was performed to evaluate the antinociceptive effects of CBD, CBN, CBC and CBD/CBN, and the vehicle control groups (n = 6/group) at 3 days after NGF injection. On the test day, a post-NGF injection baseline (NGF baseline) was recorded before injection of cannabinoids. After treatment injections, mechanical withdrawal threshold was measured at 10, 30, 60, and 120 min after injection.

3.3. Inverted screen test

A modified version of the inverted screen test was performed to evaluate impaired motor function in rats (Coughenour, McLean, & Parker, 1977; Maxwell, Brecht, Doctor, & Wolfe, 1993). Rats were trained how to perform the test daily for three days before they were tested. Rats were placed on a screen (185 mm × 290 mm) with 5 mm diameter holes and the screen was slowly inverted 180 degrees until the rats were suspended upside down on the bottom of the screen. The animals were observed for their ability to climb to the top of the screen in the next 60 s and were assigned to a score: (0) animals successfully climbed to the top the screen; (1) held on the screen upside down; (2) or fell from the screen. Baselines were measured prior to treatment and the animals were re-tested at 10, 30, 60 and 120 min after treatment.
administration. For the CBD and CBN groups, a separate group of female rats (n = 4/group) were used. For the CBC and the CBD/CBN groups, rats were tested following each behavioral mechanical withdrawal threshold time point (n = 6).

3.4. In vivo electrophysiology

In vivo electrophysiology recordings of single ganglion neurons that innervate the craniofacial muscles were performed to investigate the mechanism of action of peripherally injected cannabinoids. Rats (n = 6/group except CBD/CBN (1:1) with n = 4 and CBD/CBN (5:1) with n = 5) from the behavioral experiments were used for subsequent in vivo electrophysiological experiments. Recordings were performed at least 7 days after the behavioral experiments and experiments were conducted on the PBS-injected masseter muscles (right side) of the rats to minimize potential residual effects of the previous cannabinoid treatments.

Rats were anesthetized with isoflurane (2–2.5% in oxygen 97–98%; AErrane; Baxter) and surgically prepared for electrophysiological recording. Heart rate, blood pressure and body temperature were monitored and a trachea tube was inserted for ventilation throughout the experiment. The hair of the face was shaved and the animal’s head was positioned in a stereotaxic frame. A parylene-coated tungsten micro-electrode (0.10", 2 MΩ, A–M Systems Inc.) was lowered into the trigeminal ganglion through the brain via a small trephination in the skull. An incision was made over the neck to expose the brain stem, and the dura was removed to allow access for a stimulating electrode to contact the caudal brain stem. Mechanoreceptors innervating craniofacial muscles (masseter and temporalis) were identified by mechanical probing using a fine-tipped cotton swab. Antidromic collisions were performed to confirm projection of the muscle primary afferent nerve fiber to the caudal brain stem (Cairns, 2007; Wong, Dong et al., 2014). A stimulating electrode (parylene-coated tungsten micro-electrode, 0.10", 2 MΩ, A–M Systems Inc.) was lowered into the ipsilateral caudal brainstem and constant-current electrical stimuli (100 μs biphasic pulse, 10–90 μA, 0.5 Hz) were applied to evoke antidromic action potentials. Orthodromic action potentials were evoked by mechanical stimulation of the tissue. Collision was demonstrated by disappearance of the antidromic spike. The straight line distance between the stimulating and recording electrodes was divided by the latency of the antidromic action potential to estimate conduction velocity. Mechanical threshold was assessed with an electronic von Frey hair (IITC Life Science) by applying mechanical stimuli at 1 min intervals for 10 min to obtain baseline threshold. After baseline measurement, treatment was administered and mechanical threshold was reassessed at 10, 30, 60, and 120 min thereafter. At the end of the experiments, animals were euthanized with pentobarbital (Nembutal 100 mg/kg, Abbott Laboratories, Chicago, IL).

3.5. Data analysis

For the behavioral experiments, mechanical withdrawal threshold from NGF and vehicle-injected sides was analyzed with a two-way repeated measures analysis of variance (ANOVA) with time and treatment as factors. For electrophysiology experiments, mechanical withdrawal threshold was also assessed with a two-way repeated measures analysis of variance (ANOVA) with time and treatment as factors. Relative mechanical threshold was calculated as post-treatment threshold /baseline threshold. Post hoc Holm Sidak’s multiple comparison tests were used to compare post injection mechanical thresholds between treatment groups at each time point. One-way repeated measures ANOVA on ranks was used to test the hypothesis that there was a trend in the data. Probability level of 0.05 was considered significant for all tests. Error bars represented standard error of the mean.

Fig. 2. The line and scatter plots show the mean (± SE) relative mechanical withdrawal threshold of 6 female rats per treatment group following intramuscular injections of (A) CBD (1 and 5 mg/ml), (B) CBN (1 mg/ml) and (C) CBC (1 mg/ml) in behavioral experiments. Significant differences were observed for CBD (5 mg/ml) and CBN compared to vehicle by 2-way repeated measures ANOVA. The asterisks (*) indicate significant differences compared with the vehicle group and pound signs (#) indicate a significant difference compared to the NGF baseline within the treatment group (Holm Sidak multiple comparison test, p < 0.05).
4. Results

4.1. Effect of intramuscular injections of cannabinoids on NGF-induced sensitization

In the behavioral studies, intramuscular injection of NGF decreased masseter muscle relative mechanical threshold at 3 days after injection by 31%, consistent with earlier studies (Fig. 2; (Wong, Dong et al., 2014, Wong, Kang et al., 2014). A dose dependent effect was observed with CBD on NGF-induced mechanical sensitization. CBD (1 mg/ml) had no effect, but a higher concentration of CBD (5 mg/ml) significantly reversed NGF-induced mechanical sensitization at 10 and 30 min after injection (Fig. 2A). CBN (1 mg/ml) significantly reversed NGF-induced mechanical sensitization at 10 min post injection (Fig. 2B). No effect on mechanical withdrawal threshold was observed following intramuscular injection of CBC (1 mg/ml) (Fig. 2C). Intramuscular injection of CBD/CBN (1:1) had a longer lasting effect when compared to the individual cannabinoids at the same concentration with significant increases in mechanical withdrawal threshold at 10 and 30 min after injection (Fig. 3A). CBD/CBN (5:1) had a similar effect on mechanical sensitization as CBD/CBN (1:1; Fig. 3B). No effect of any injection was observed on the mechanical withdrawal threshold of contralateral masseter muscles for all treatment groups (Fig. 4). No impairment of motor functions was found in the inverted screen tests after intramuscular injections of CBD, CBN and CBD/CBN treatments (median score for all treatments was 0).

4.2. Effect of intramuscular injections of cannabinoids on masseter muscle mechanoreceptors

Recordings from 33 masticatory muscle mechanoreceptors were undertaken. The median conduction velocity was 9.9 m/s and the median mechanical threshold was 30.6 g. The population consisted of 79% Aδ fibers (2–12 m/s) and 21% Aβ fibers (> 12 m/s). The results from the electrophysiology experiments for CBD and CBN paralleled the results from the behavioral experiments. CBD 5 mg/ml, but not 1 mg/ml, significantly increased relative mechanical threshold, 30 min after injection (Fig. 5A). CBN 1 mg/ml significantly increased relative mechanical threshold at 30 and 60 min after its injection (Fig. 5B). CBC had no effect on behavioral mechanical withdrawal threshold, therefore its effect on individual mechanoreceptors was not assessed. Intramuscular injection of CBD/CBN (1:1) significantly increased the relative mechanical threshold of masseter muscle mechanoreceptors at 10, 30 and 60 min after injection (Fig. 6A) while CBD/CBN (5:1) significantly increased relative mechanical threshold at 10 min after injection, however, the effect was shorter lasting with relative mechanical threshold returning to baseline values at 30 and 60 min after injection (Fig. 6B).

5. Discussion

In a previous study, a single intramuscular injection of THC, the
primary psychoactive substance in the cannabis plant, was found to alleviate NGF-induced sensitization in the masseter muscle by activating CB1 receptors expressed by nociceptive fibers innervating this muscle (Wong et al., 2017). This effect was not accompanied by evidence of central nervous system effects. It was proposed that peripheral cannabinoid receptors may be a potential target for analgesia without central adverse effects. Although this result was encouraging, repeated peripheral applications of THC may still induce significant undesirable central effects that limit the use of many of the current cannabinoid preparations for chronic pain treatment including Sativex, which is a combination of THC and CBD (Etges et al., 2016; Moreno Torres et al., 2014; Romero-Sandoval, Asbill, Paige, & Byrd-Glover, 2015). Therefore, in this study, we investigated whether intramuscular injections of other non-psychoactive cannabinoids alone (CBD, CBN, CBC) and in combination could provide similar relief in the rat NGF-induced muscle sensitization model while further minimizing the potential for limiting central adverse effects. The inverted screen test was used to evaluate effects on central motor function. While no impairments were found in any of the treatment groups, which suggests minimal motor effects, a more comprehensive battery of tests may be needed to evaluate the full effects of CBD, CBN and CBC on central functions.

It was found that the non-psychoactive cannabinoids CBD, CBN and CBC were less efficacious than THC at the same concentration (1 mg/ml) in reducing NGF-induced muscle sensitization in both behavioral and electrophysiological studies (Wong et al., 2017). This is not surprising as these cannabinoids have weaker binding affinity for the CB1 receptors when compared to THC: CBN (˜1/10th), CBC (˜1/20th) and CBD (˜1/100th) (Pertwee, 2008; Rosenthaler et al., 2014), and we have previously demonstrated that CB1 receptor activation is responsible for the local analgesic effect of THC (Wong et al., 2017). This result is also consistent with earlier studies showing similar ranking in effectiveness of these cannabinoids when administered systemically in different pain models (Sofia, Vassar, & Knobloch, 1975; Welburn, Starmer, Chesher, & Jackson, 1976). Interestingly, CBD at a higher concentration of 5 mg/ml significantly reduced NGF-induced mechanical sensitization in both combination of THC and CBD (Etges et al., 2016; Moreno Torres et al., 2014; Romero-Sandoval, Asbill, Paige, & Byrd-Glover, 2015). Therefore, in this study, we investigated whether intramuscular injections of other non-psychoactive cannabinoids alone (CBD, CBN, CBC) and in combination could provide similar relief in the rat NGF-induced muscle sensitization model while further minimizing the potential for limiting central adverse effects. The inverted screen test was used to evaluate effects on central motor function. While no impairments were found in any of the treatment groups, which suggests minimal motor effects, a more comprehensive battery of tests may be needed to evaluate the full effects of CBD, CBN and CBC on central functions. It was found that the non-psychoactive cannabinoids CBD, CBN and CBC were less efficacious than THC at the same concentration (1 mg/ml) in reducing NGF-induced muscle sensitization in both behavioral and electrophysiological studies (Wong et al., 2017). This is not surprising as these cannabinoids have weaker binding affinity for the CB1 receptors when compared to THC: CBN (1/10th), CBC (1/20th) and CBD (1/100th) (Pertwee, 2008; Rosenthaler et al., 2014), and we have previously demonstrated that CB1 receptor activation is responsible for the local analgesic effect of THC (Wong et al., 2017). This result is also consistent with earlier studies showing similar ranking in effectiveness of these cannabinoids when administered systemically in different pain models (Sofia, Vassar, & Knobloch, 1975; Welburn, Starmer, Chesher, & Jackson, 1976). Interestingly, CBD at a higher concentration of 5 mg/ml significantly reduced NGF-induced mechanical sensitization in both combination of THC and CBD (Etges et al., 2016; Moreno Torres et al., 2014; Romero-Sandoval, Asbill, Paige, & Byrd-Glover, 2015). Therefore, in this study, we investigated whether intramuscular injections of other non-psychoactive cannabinoids alone (CBD, CBN, CBC) and in combination could provide similar relief in the rat NGF-induced muscle sensitization model while further minimizing the potential for limiting central adverse effects. The inverted screen test was used to evaluate effects on central motor function. While no impairments were found in any of the treatment groups, which suggests minimal motor effects, a more comprehensive battery of tests may be needed to evaluate the full effects of CBD, CBN and CBC on central functions. It was found that the non-psychoactive cannabinoids CBD, CBN and CBC were less efficacious than THC at the same concentration (1 mg/ml) in reducing NGF-induced muscle sensitization in both behavioral and electrophysiological studies (Wong et al., 2017). This is not surprising as these cannabinoids have weaker binding affinity for the CB1 receptors when compared to THC: CBN (1/10th), CBC (1/20th) and CBD (1/100th) (Pertwee, 2008; Rosenthaler et al., 2014), and we have previously demonstrated that CB1 receptor activation is responsible for the local analgesic effect of THC (Wong et al., 2017). This result is also consistent with earlier studies showing similar ranking in effectiveness of these cannabinoids when administered systemically in different pain models (Sofia, Vassar, & Knobloch, 1975; Welburn, Starmer, Chesher, & Jackson, 1976). Interestingly, CBD at a higher concentration of 5 mg/ml significantly reduced NGF-induced mechanical sensitization in both
behavioral and electrophysiological experiments. This concentration is much less than would be expected based on the binding affinity of these two compounds for the CB1 receptor, where CBD is ~100x less potent than THC (Pertwee, 2008). It is, therefore, possible that CBD may have effects on receptors other than CB1 when administered peripherally at higher concentrations (Petrosino, Ligresti, & Di Marzo, 2009). For example, recent studies suggest that CBD may have effects on the orphan G-protein coupled receptors (GPR3, GPR6, GPR12 and GPR55 (Laun, Shadrer, Brown, & Song, 2019; Ryberg et al., 2007). These receptors have no confirmed endogenous ligands and are phylogenetically closely related to the cannabinoid receptors (Laun et al., 2019; Ryberg et al., 2007). GPR55 is predominantly expressed in the brain but is also found in many tissues and organs (Shore & Reggio, 2015). Lyso phosphatidylinositol has been proposed as its endogenous ligand, but many cannabinoids have also been found to bind to it (Ryberg et al., 2007; Shore & Reggio, 2015). The physiological function of GPR55 is unclear but it has been proposed to play a role in regulation of energy intake, bone resorption, cancer and pain (Marichal-Cancino, Fajardo-Valdez, Ruiz-Contreras, Mendez-Diaz, & Prospero-Garcia, 2017; Shore & Reggio, 2015). Further studies are needed to elucidate the receptor mechanisms which underlie CBD’s effects on peripheral mechanoreceptors.

Many cannabinoid compounds have been found to have synergistic or antagonistic effects on THC (Schoedel & Harrison, 2012). In one study, CBD enhanced the effects of THC in a chemotherapy-induced neuropathic pain model (King et al., 2017). In another study, CBD was found to antagonize the effects of THC and CB1 agonists in mouse whole membranes (Pertwee, 2008). CBD has also been found in clinical studies to reduce unwanted THC-related cognitive deficits when combined with THC (Schoedel & Harrison, 2012). In this study, we investigated whether CBD at 2 different concentrations (1 and 5 mg/ml) has additive effects with CBN (1 mg/ml). Unexpectedly, in the electrophysiology experiments, low concentration CBD (1 mg/ml) enhanced the ability of CBN to reverse NGF-mechanical sensitization, whereas the higher concentration of CBD (5 mg/ml) appeared to decrease the effectiveness of CBN. CBN may exert its effects through CB1 receptors, due to its similarity to THC (Pertwee, 2008). It has been proposed that CBD may act as an inverse agonist on CB1 receptors (Pertwee, 2008; Thomas et al., 2007). Our results suggest that if it acts as an inverse agonist, this effect may be dose dependent. An alternative explanation could be that CBD activates a different receptor that negatively impacts on the CB1 receptor signaling pathway at the higher concentrations. CBD has been suggested to have effects on other receptors as mentioned above. This concentration-related additive/inhibitory effect of CBD on CBN was less pronounced in the behavioral experiments, with CBD/CBN (1:1) and CBD/CBN (5:1) showing similar efficacy. This may be due to the higher variability in the behavioral experiments and a larger number of animals in each group may be required to have the necessary statistical power to show this difference. Further studies are needed to elucidate the mechanism of CBD in this regard.

6. Conclusions

In this study, intramuscular injections of non-psychoactive cannabinoids CBD, CBN and their combinations reversed NGF-induced sensitization in behavioral and electrophysiology experiments. Although their effects were less robust when compared to THC, they could be advantageous since they have minimal psychotropic effects; an important limitation of THC use for analgesia (Amar, 2006; Izzo et al., 2009; Pertwee, 2005). There is an increasing interest in cannabinoid-based medicine for treating chronic pain. However, current controlled clinical studies with cannabinoid-based drugs only showed moderate analgesic effects (Lotsch, Weyer-Menkhoff, & Tegeder, 2018). Exploration of the peripheral effects of non-psychoactive cannabinoids may provide a strategy for more effective and robust analgesia with less adverse effects.

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Declarations of interest

None.

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