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Diclofenac and dexamethasone modulate the effect of cannabidiol on the rat colon motility *ex vivo*

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Abstract

Introduction: Due to the growing interest in the use of cannabinoids in supportive therapies, they are increasingly used together with anti-inflammatory drugs. Cannabinoids inhibit gastrointestinal motility, while steroidal and nonsteroidal anti-inflammatory drugs influence motility in other ways. The aim of the research was to study the interactions between cannabidiol (CBD) and these two classes of anti-inflammatory drugs in the context of gastrointestinal motility. Dexamethasone (DEX) was selected as a steroidal drug and diclofenac (DCF) as a nonsteroidal counterpart. **Material and Methods:** The experiments were performed on isolated rat colon strips in isometric conditions. The contractile response to acetylcholine (ACh) (1 μM) was measured with no substance applied as a control value and was measured after application of CBD (80 μM), DEX (100 μM), DCF (100 μM), or a combination of these substances. **Results:** Cannabidiol strongly inhibited intestinal motility mediated by ACh application, DCF inhibited it non-significantly, while DEX intensified it. When CBD was co-administered with DEX, the combination inhibited intestinal motility non-significantly relative to the ACh-only control. Co-administration of CBD with DCF inhibited motility more than when these substances were administered separately. **Conclusion:** Inhibition of the intestinal response to ACh is likely due to the synergistic effect of CBD and endogenous cannabinoids. Dexamethasone lessened the inhibitory effect of CBD, likely because of diminished availability of the arachidonic acid necessary for endogenous cannabinoid synthesis. However, diclofenac may increase endogenous cannabinoid synthesis, because of the greater availability of arachidonic acid caused by DCF blocking the cyclooxygenation pathway.

Keywords: cannabidiol, additive synergism, intestinal motility, isolated rat colon strips.

Introduction

Phytocannabinoids are secondary metabolites of *Cannabis sativa*. Plant-derived cannabinoids are compounds with terpenophenolic properties and are found in the plant in the form of carboxylic acids. Depending on the hemp variety, cannabidiol (CBD) is the most or second most abundant phytocannabinoid in the tissues of *Cannabis sativa*. Cannabidiol is an increasingly widely used substance in the treatment of many diseases and ailments, but importantly – unlike tetrahydrocannabinol (THC) – it is devoid of psychoactive properties (27). In companion animal veterinary medicine, CBD has found application in the treatment of osteoarthritis, epilepsy, anxiety and aggression, and pruritus in skin atopy, primarily in dogs (25). The use of non-psychoactive cannabinoids has been the subject of many studies so far. The therapeutic potential of this group is very high, due to the possibility of using many different substances with varying degrees of affinity for cannabinoid (CB) receptors, and also due to the importance of the cannabinoid system in regulating many biological processes. Data regarding the role of CB receptors in the regulation of gastrointestinal motility suggest that cannabinoids could successfully be used as drugs in the symptomatic therapy of diseases accompanied by diarrhoea, including inflammatory diseases. It has been shown that CB1 agonists inhibit gastrointestinal tract motility (4, 5). This effect is likely in large part due to inhibition of presynaptic acetylcholine (ACh) release (18), in which small-conductance calcium-activated

potassium (SK) channels play a large role (10). It has also been shown that CB2 receptor stimulation inhibits gastrointestinal hypermotility in the course of inflammation induced by lipopolysaccharide administration (15). In addition, it has been noted that in a model of inflammation of the murine small intestine, inflammation is associated with an increase in gastrointestinal tract CB1 receptor expression, as well as increased anandamide (endogenous cannabinoid) concentration in the intestinal lumen (9). The agonists of the CB1 receptor also increase tolerance of pain induced by mechanical dilation of the colon in rats with experimentally induced colonic inflammation (19). Nabilone (a synthetic cannabinoid) has been found to be effective in the therapy of treatment-resistant diarrhoea in humans (17). Zemrani *et al.* (26) have described a case in which cannabinoids had a positive therapeutic effect in chronic intestinal pseudo-obstructive disease. Cannabidiol is one of the most studied and used cannabinoids and is the main cannabinoid in many commercially available *Cannabis sativa*-derived products not containing THC. Because of changes in the law, the availability of cannabis is growing, and presently CBD can be found in veterinary preparations (mainly in the form of oils), food supplements and feeds recommended for use in inflammation and pain. These products are often used outside the control of veterinarians to bolster conventional therapy. Similarly, non-steroidal anti-inflammatory drugs (NSAIDs) are a group of drugs also used for this purpose, often outside of medical supervision. These circumstances create a significant chance that CBD and anti-inflammatory drugs will be taken together. Therefore, studying the interaction between CBD and NSAIDs is important. Published articles (1, 2, 4, 5, 9, 16) suggest opposing effects, in which cannabinoids inhibit and NSAIDs promote gastrointestinal tract motility. The interaction is also interesting in light of the strong connection of the NSAID and cannabinoid mechanisms of action with the arachidonic acid metabolism, and given arachidonic acid's direct involvement in the synthesis of endogenous cannabinoids and prostaglandins. Considering the interaction at the level of arachidonic acid metabolism, it is worth noting the effects of glucocorticoids used in the treatment of inflammation. Glucocorticoids not only limit the availability of arachidonic acid for further synthesis of inflammatory mediators, but also modulate basal intracellular calcium levels in smooth muscles (23) and may exert a spasmolytic effect (8, 22, 24). For these reasons, the study of interactions between glucocorticoids and CBD in terms of the effect on gastrointestinal motility is also interesting. Works published on the role of the cannabinoid system in the regulation of gastrointestinal motility usually use xenobiotics with varying degrees of CB receptor affinity (4, 5, 9, 10, 11, 15, 18, 19). It is difficult to assess the overall involvement of endogenous cannabinoids in the regulation of gastrointestinal motility with the published data; however, it is known that stimulation of CB1 or CB2 receptors has an inhibitory effect (4, 5, 14). Because endogenous cannabinoids are arachidonic acid derivatives, it was decided to study the interactions between CBD and two classes of anti-inflammatory drugs in the context of gastrointestinal motility in *ex vivo* conditions. Steroidal anti-inflammatory drugs were represented by dexamethasone (DEX) and their nonsteroidal counterparts were represented by diclofenac (DCF).

Material and Methods

Chemicals and media. The following reagents were used for conducting the experiments: phytocannabinoid extract as Rich Hemp Oil/THC-free with CBD content of 887.17 mg/g/ (residual phytocannabinoids: CBG < 0.3 mg/g, CBN < 0.3 mg/g, CBC < 0.3 mg/g and CBD-A < 0.3 mg/g - Folium Biosciences, Weesp, the Netherlands); acetylcholine chloride, water soluble dexamethasone and diclofenac sodium salt (Sigma Chemicals Co, St. Louis, MO, USA); $CaCl_2$, (Merck, Darmstadt, Germany); NaH_2PO_4 (Fluka Chemie, Buchs, Switzerland); and NaCl, KCl, $MgSO_4$, $NaHCO_3$ and glucose (Avantor, Gliwice, Poland). The incubation of the strips was conducted in modified Krebs–Henseleit Solution (MK-HS) containing NaCl (123.76 mM), KCl (5 mM), $CaCl_2$ (2.5 mM), $MgSO_4$ (1.156 mM), $NaHCO_3$ (14.5 mM), KH_2PO_4 (2.75 mM) and glucose (12.5 mM) at 37°C and in a constant pH range (7.35–7.45) maintained by carbogen bubbling (95% O_2 + 5% CO_2). The CBD was dissolved in dimethyl sulfoxide and used at a solvent concentration which did not influence the spontaneous activity and reactivity of the strips (0.5%).

Animals and preparation of the intestinal strips. The tissues were isolated from male Wistar rats weighing approximately 250 g obtained from the Center for Experimental Medicine of the Medical University of Białystok, a registered laboratory animal breeder. The animals were euthanised using sedation by gradual introduction of carbon dioxide into the animal holding chamber and cervical dislocation. The procedure was carried out according to the current regulations and guidelines of the National Ethics Committee and complied with Annex IV to Directive 2010/63/EU on the protection of animals used for scientific purposes. Since all research activities were carried out post mortem, no Local Ethics Committee approval was required for the experiment.

Directly after opening the abdominal cavity, fragments of the descending colon were excised and placed in MK-HS at 37°C. After removing the digestive content by gentle washing of the intestinal lumen, the surrounding tissues were dissected. Next the strips were prepared in such a way as to be approximately 15 mm long and in the physiological tubular shape.

Registration of muscle activity. The colon preparations were incubated in the chambers of a Schuler Organ Bath set (Hugo-Sachs Elektronik Harvard Apparatus, March-Hugstetten, Germany) in isometric conditions under a load of 0.01 N. The registration of the data was performed through a force transducer and bridge amplifier (DBA, F30 type 372, Hugo-Sachs Elektronik) and PowerLab data acquisition system (ADInstruments, Dunedin, New Zealand). The graphical records were analysed in the Chart v7.0 and LabChart Reader v8.1.1 programmes (ADInstruments) and Excel for Windows XP (Microsoft, Redmond, WA, USA).

Design of experiments. After placing the colon strips in the organ bath chambers, they were preincubated for 90 min to stabilise muscle activity in *ex vivo* conditions. At the beginning of each experiment, the preparations were exposed to ACh (1 µM) to evaluate their reactivity before administration of CBD and anti-inflammatories and thereby establish a control baseline. After flushing with MK-HS and returning spontaneous activity to the muscle, the strips were treated with the solutions of test substances according to three schemes. The first treatment scheme was incubation of colon strips in a CBD solution at a concentration of 25 µg/mL for 15 min and their re-exposure (without flushing) to ACh. The second scheme was exposure of strips to a DEX solution at a concentration of 100 µM for 60 min and after this time their re-exposure to ACh. The flushed colon strips were again exposed to DEX and subsequently to CBD (25 µg/mL) for 15 min. The last step was treatment of the strips (without flushing) using ACh. The final scheme was exposure of strips to DCF at a concentration of 100 µM for 20 min and treatment with ACh. After MK-HS flushing, the strips were re-exposed to DCF and subsequently to CBD (25 µg/mL) for 15 min. After this time, ACh was added to the incubation solution. Each experiment was performed in five replicates.

Data analysis and statistics. The reaction of colon strips to ACh was established as the change of muscle tension from its state before to its state after application of the substances. The strength of the muscle contraction produced by ACh in the presence of CBD, DCF, DEX and a combination of CBD and DEX or DCF was related to the muscle reaction to ACh acting alone (this control being defined as 100%). The obtained graphical data were calculated as area under the curve. The data are expressed as mean values (n = 5) ± standard deviation. In the statistical analysis, a one-way analysis of variance with post-hoc Tukey's test was used to compare the mean values between the investigated groups and one sample *t*-test to compare the mean value of an investigated group with a control hypothetical mean (100%). Values of $P \leq 0.05$ were considered to be significant. Data were analysed using STATISTICA version 12 (StatSoft, now TIBCO, Palo Alto, CA, USA).

Results

The effect of CBD on intestinal motility. Before starting the planned experiment, the effective concentration of all tested substances was determined in separate preliminary experiments in which the dose–effect relationship was tested in terms of the effect on intestinal motility. The effective concentrations were as follows: ACh 1 µM, CBD 80 µM, DCF 100 µM and DEX 100 µM.

When administered at the beginning of the experiment proper, acetylcholine caused a strong intestinal contraction. After changing the buffer solution in the incubation chamber (flushing), the intestine displayed spontaneous contractile activity. Applying CBD followed by ACh caused a statistically significantly weaker contraction than that observed at the start of the incubation. The area under the curve for the intestinal contraction in the presence of CBD was 26.5 ± 8.6% of the contraction at the beginning of the incubation. Fig. 1 shows an example of intestinal motility changes observed after administration of ACh and CBD.

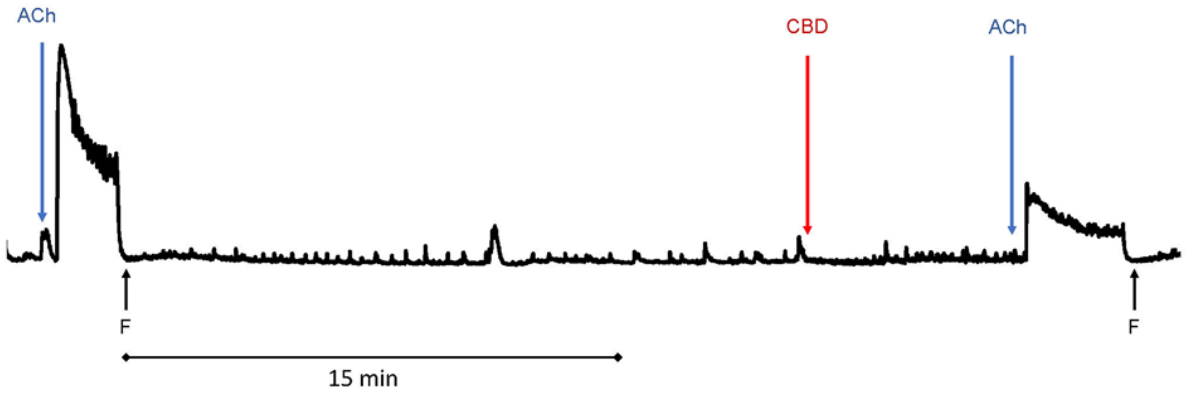

Fig. 1. Example recording of a rat distal colon strip's reactivity to acetylcholine (ACh) in the presence of modified Krebs–Henseleit solution (control reaction) and cannabidiol (CBD). F – flushing

The effect of CBD and DCF on intestinal motility. Diclofenac slightly attenuated the contractile response of the intestine to ACh administration. The area under the curve for the intestinal contraction caused by ACh in the presence of DCF was 80 ± 17.6% of the response observed at the start of the incubation, which did not differ statistically significantly from the area under the curve of contraction caused by the administration of ACh alone. Administration of CBD and DCF in the second phase of the third treatment scheme almost completely suppressed the contractile response to ACh. The area under the curve for this contraction was 5.1 ± 11% of the response observed at the start of the incubation. Fig. 2 shows an example of changes in spontaneous intestinal contractility after administration of DCF and CBD.

The effect of CBD and DEX on intestinal motility. When administered at the beginning of the incubation, ACh caused a strong intestinal contraction. After changing the buffer solution and administering DEX, the intestine displayed spontaneous contractile activity, which intensified throughout the time of incubation. Administration of ACh in the presence of DEX caused a statistically significantly larger contraction than that observed at the beginning of the incubation. The area under the curve for this contraction is 121.9 ± 18.7% of the initial contraction. After changing the medium and administering DEX and CBD, the ACh-induced contraction was statistically significantly smaller than the initial contraction, being 67.6 ± 16.8% of that. Fig. 3 shows representative changes in intestinal motility after administering DEX and CBD.

Comparison of the effect of CBD in the presence of DCF and in the presence of DEX. Diclofenac inhibited and DEX stimulated ACh-induced intestinal contractions to respective 80.0 ± 17.6% and 121.9 ± 18.7% of the control baseline level (Fig. 4 a). The presence of CBD in the incubation buffer solution always diminished the intestinal contractile response to ACh. Independent administration of CBD caused intestinal contractile response to drop to 26.5 + 8.6% of the contraction induced by ACh alone. In the presence of DCF, CBD caused the strongest inhibition of intestinal contractile response to ACh. In this case the contraction was only 5.1 ± 11.3% of the control value. In the presence of CBD and DEX, ACh caused contractions of 67.6 ± 16.8% of the ACh-only contraction. This inhibition was significantly smaller than the inhibition caused by CBD alone. Fig. 4 b compares the intestinal response to administration of CBD, CBD + DCF and CBD + DEX.

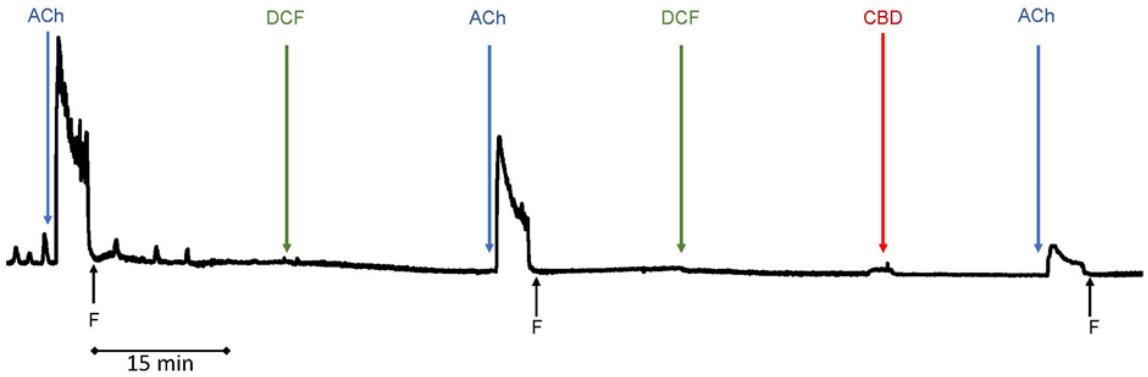

Fig. 2. Example recording of a rat distal colon strip's reactivity to acetylcholine (Ach) in the presence of modified Krebs–Hanseleit solution (control reaction), diclofenac (DCF) and DCF with cannabidiol (CBD). F – flushing

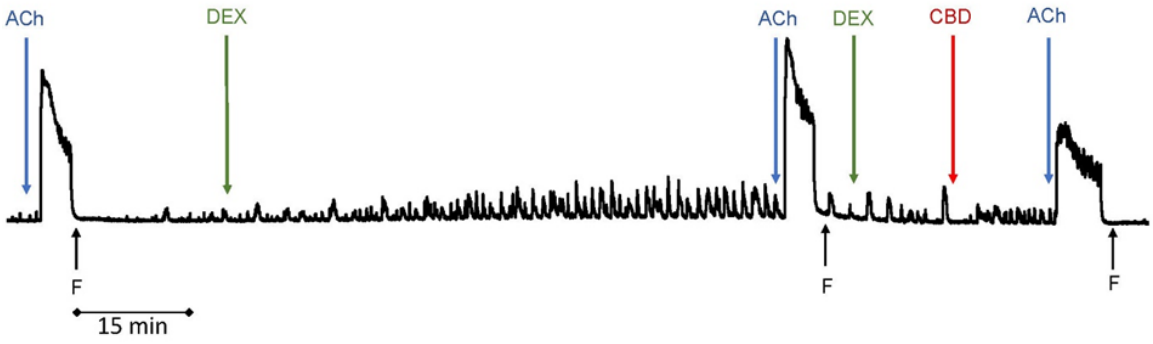

Fig. 3. Example recording of a rat distal colon strip's reactivity to acetylcholine (Ach) in the presence of modified Krebs–Hanseleit solution (control reaction), dexamethasone (DEX) and DEX with cannabidiol (CBD). F – flushing

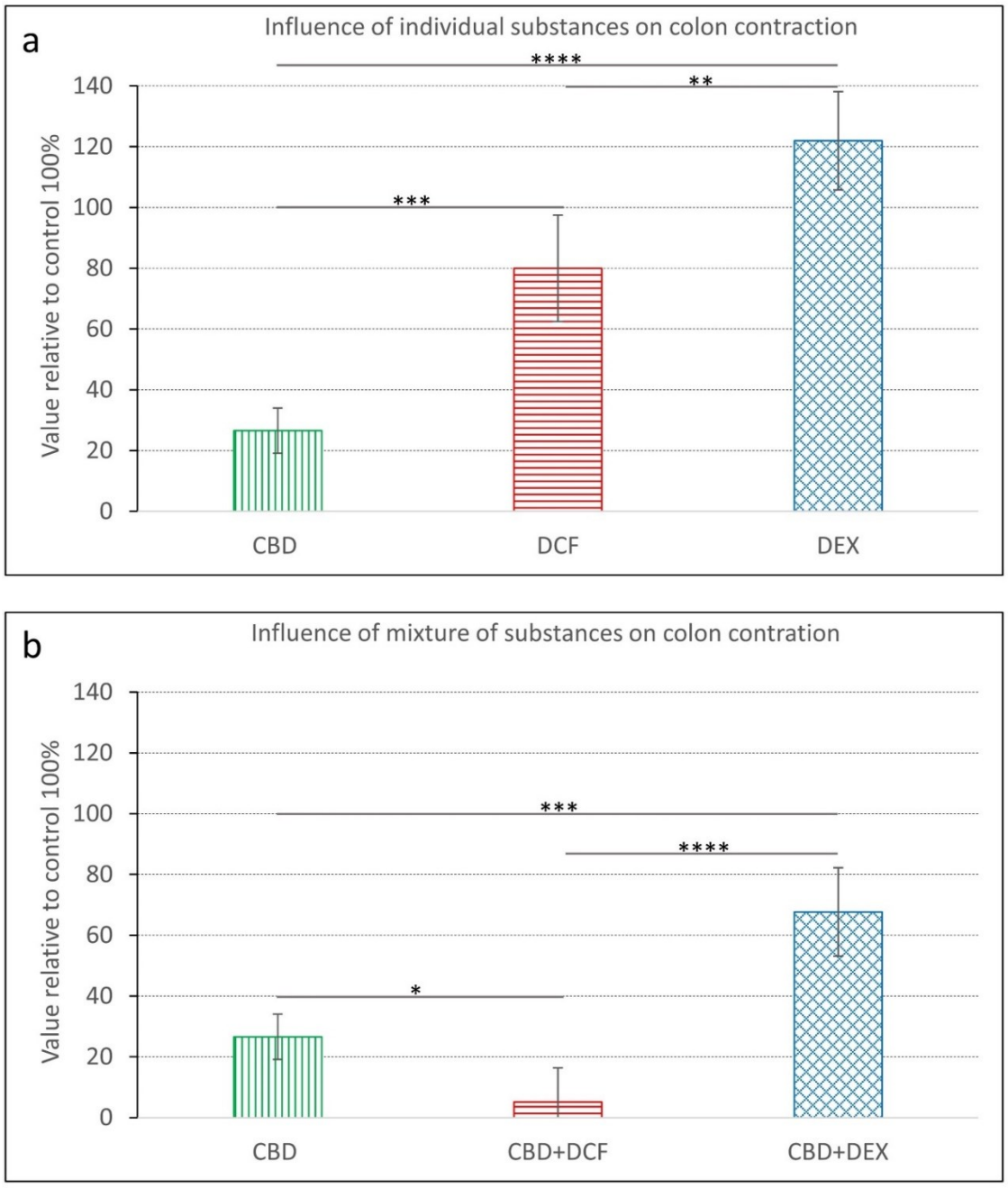

Fig. 4. Comparison of the effects of tested substances on rat colon contractility relative to control acetylcholine administration; (a) Cannabidiol (CBD), diclofenac (DCF) and dexamethasone (DEX) administered alone; (b) CBD, DCF and DEX administered in combinations. Data are expressed as the mean of independent experiments; n = 5, ± standard deviation. Asterisks indicate a statistically significant difference at the level of $P \leq 0.05$ (*), $P<0.01$ (**), $P \leq 0.001$ (***) or $P \leq 0.0001$ (****)

Discussion

Despite the interest in cannabinoids, knowledge of how they influence the gastrointestinal tract is still incomplete. More and more evidence suggests that the endocannabinoid system is crucial in modulating gastrointestinal physiology, influencing satiety, immune function, secular secretion, visceral sensation, vomiting (inhibitively), mucosal integrity and gastrointestinal motility (11). Due to the increasing availability of cannabis products, including high-purity CBD oils, CBD is becoming commonly used for the purposes of reducing anxiety, pain and inflammation. A group of drugs with a similar use exploiting their analgaesic and anti-inflammatory properties are NSAIDs. Both CBD and NSAIDs are often used outside of medical supervision, which may make their concurrent usage likely. Simultaneous use of CBD and steroid drugs is also probable. The potential for indiscriminate use of these therapeutics in combination makes it important to understand the interactions of CBD with these two classes of anti-inflammatory drugs. Commonly used examples of steroidal and nonsteroidal preparations were selected for study.

Cannabidiol inhibited spontaneous intestinal motor activity and attenuated the intestinal response to ACh to 26.6% of the control value. This finding is consistent with the research by Layman and Milton, which described an attenuation of intestinal response to acetylcholine in the guinea pig colon after administration of CBD (3). Izzo *et al.* (9) showed that the inhibitory effect of CBD on the gastrointestinal tract may be due to CB1 receptor stimulation. Such a mechanism cannot be ruled out in this experiment. However, their hypothesis that intestinal motility is inhibited by CB agonists because of stimulation of presynaptic CB1 receptors on cholinergic neurons does not explain the results of this experiment, as CBD blocked the effect of exogenous ACh on the intestine.

In this study it was observed that DEX enhanced spontaneous intestinal motor activity and strengthened ACh-induced colonic contraction. The short duration of the experiment and rapid effect make the assumption safe that that the mechanism of action of DEX was not related to transcription-level events characteristic of glucocorticoids. The observed effect must stem from transcription-independent mechanisms. The rapid nongenomic effects of glucocorticoids may be connected to the activation of the protein kinase C and phosphoinositide signalling system (21), their effect on calcium availability for contractile proteins (13), and many other mechanisms, including the activation of mitogen-activated protein kinase and adenyl cyclase (12). Many fast-acting effects of glucocorticoids are related to the limiting of cytokine activity (6). Enhanced contractility may be due to an increase of calcium-sensitivity of contraction (14). The above mechanisms cannot be ruled out as causes for the increased intestinal motility in the experiment.

Interestingly, the rapid onset of action of glucocorticoids can also be explained by their inhibition of cytosol phospholipase A2 and subsequent diminished arachidonic acid release (6). Such a mechanism is very probable in this experiment, because enhancement of intestinal contractile activity due to increased calcium-sensitivity of contraction is much faster than the gradual process which was observed after administration of DEX. On the basis of these data, it might be suggested that the inhibition of arachidonic acid release by DEX blocks the synthesis of endogenous cannabinoids. Thus, the component inhibiting intestinal motility is switched off. When DEX is co-administered with CBD, this component is bolstered by CBD.

The presented experiment did not find any significant changes in spontaneous intestinal contractility after the administration of DCF; however, it clearly attenuated intestinal response to ACh and enhanced the inhibitory effect of CBD. The mechanism underlying this phenomenon is difficult to explain. As an NSAID, DCF works through inhibiting cyclooxygenase (COX) activity, thereby decreasing prostaglandin concentrations. In humans, it has been observed that DCF does not affect upper gastrointestinal tract motility (1). Likewise, indomethacin (a drug from the NSAID group) does not affect gastric emptying in humans (2). Contrasting observations in dogs suggest that indomethacin may stimulate intestinal motility and delay gastric emptying. This effect was not observed with meloxicam (also a drug from the NSAID group) (16). Based on their observations, Gustafsson *et al.* (7) claimed that indomethacin increased intestinal motility independently of COX inhibition.

In the experiment described in this article, DCF was not found to enhance intestinal contractility, and in fact was found to decrease the contractile response to ACh. This suggests that changes in intestinal motility induced by NSAIDs may be varied and contingent on many factors, such as the basal activity of prostaglandin cocktails, and may exert a multitude of effects on the organism. It can be assumed that the mechanism of action of DCF in this experiment is related to COX inhibition and lowered concentrations of prostaglandins stimulating gastrointestinal motility. It is worth noting that COX inhibition causes a decrease in arachidonic acid utilisation for prostaglandin synthesis, thus making more acid available for the synthesis of leukotrienes or endogenous cannabinoids. Since leukotrienes are associated with smooth muscle contractions (20), it can be surmised that the presence of DCF mainly causes an increase in endogenous cannabinoid synthesis, which has an inhibitory effect on gastrointestinal tract contractility. It is also worth noting that in this experiment, intestinal motility inhibition after co-administration of CBD and DCF (a lowering of contractile activity by 95% of the control value) was equal to the sum of inhibition produced by CBD (a 74% drop relative to the control value) and DCF (a 20% drop relative to the control value). This is an example of additive synergism, which is most often observed in co-administration of drugs with identical mechanisms of action. Because CBD's mode of action originates in the stimulation of transmission specific to endogenous cannabinoids (CB receptor agonism), DCF's mechanism of action should be similar.

The obtained results indicate that DCF enhances the inhibitory effect of CBD on gastrointestinal tract motility. This could imply that most NSAIDs will exert a similar effect. The interaction discovered is significant for the practical therapeutic use of CBD and NSAIDs, because strong inhibition of gastrointestinal motility is usually deleterious to the organism. It suggests that the observed interactions are related to the synthesis of endogenous cannabinoids, which must play a significant role in the regulation of colonic motility in the rat.

Conflicts of Interest Statement: The authors declare that there is no confict of interests regarding the publication of this article.

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