

The use of cannabinoids in animals and therapeutic implications for veterinary medicine: a review

L. LANDA¹, A. SULCOVA², P. GBELEC³

¹Faculty of Medicine, Masaryk University, Brno, Czech Republic

²Central European Institute of Technology, Masaryk University, Brno, Czech Republic

³Veterinary Hospital and Ambulance AA Vet, Prague, Czech Republic

ABSTRACT: Cannabinoids/medical marijuana and their possible therapeutic use have received increased attention in human medicine during the last years. This increased attention is also an issue for veterinarians because particularly companion animal owners now show an increased interest in the use of these compounds in veterinary medicine. This review sets out to comprehensively summarise well known facts concerning properties of cannabinoids, their mechanisms of action, role of cannabinoid receptors and their classification. It outlines the main pharmacological effects of cannabinoids in laboratory rodents and it also discusses examples of possible beneficial use in other animal species (ferrets, cats, dogs, monkeys) that have been reported in the scientific literature. Finally, the article deals with the prospective use of cannabinoids in veterinary medicine. We have not intended to review the topic of cannabinoids in an exhaustive manner; rather, our aim was to provide both the scientific community and clinical veterinarians with a brief, concise and understandable overview of the use of cannabinoids in veterinary medicine.

Keywords: cannabinoids; medical marijuana; laboratory animals; companion animals; veterinary medicine

Abbreviations

AEA = anandamide (N-arachidonylethanolamine, CB_{1,2} receptor agonist), **2-AG** = 2-arachidonoylglycerol (CB₁ receptor agonist), **2-AGE** = 2-arachidonyl glyceryl ether (noladin ether, CB₁ receptor agonist), **AM 251** = N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (synthetic CB₁ receptor antagonist/inverse agonist), **CB₁** = cannabinoid receptor type 1, **CB₂** = cannabinoid receptor type 2, **CP-55,940** = (–)-cis-3-[2-Hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol (mixed CB_{1,2} receptor agonist), **FAAH** = fatty acid amide hydrolase, **GABA** = gamma-amino butyric acid, **GPR18** = G-protein coupled receptor 18, **GPR55** = G protein-coupled receptor 55, **GPR119** = G protein-coupled receptor 119, **HU-210** = (6aR)-trans-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol (synthetic mixed CB_{1,2} receptor agonist), **HU-308** = [(1R,2R,5R)-2-[2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl]-7,7-dimethyl-4-bicyclo[3.1.1]hept-3-enyl] methanol (highly selective CB₂ receptor agonist), **IgE** = immunoglobulin E, **MGL** = monoacylglycerol lipase, **NADA** = N-arachidonoyl dopamine (CB₁ receptor agonist), **PEA** = palmitoylethanolamide, **SR144528** = N-[(1S)-endo-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-[(4-methylphenyl)methyl]-1H-pyrazole-3-carboxamide (CB₂ receptor antagonist/inverse agonist), **THC** = delta-9-tetrahydrocannabinol (mixed CB_{1,2} receptor agonist), **TRPV1** = transient receptor potential cation channel subfamily V member 1, **WIN 55,212-2** = (R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone (synthetic CB_{1,2} receptor agonist)

This work was supported by the project CEITEC – Central European Institute of Technology, from European Regional Development Fund (Grant No. CZ.1.05/1.1.00/02.0068).

Contents

1. Introduction
2. The endocannabinoid system and classification of cannabinoids
3. The use of cannabinoids in animals
4. Prospective veterinary use of cannabinoids
5. Conclusions
6. References

1. Introduction

Cannabinoids have been used in traditional medicine for thousands of years. There are reports going back to ancient China (Unschuld 1986; Zuardi 2006), medieval Persia (Gorji and Ghadiri 2002) or in Europe to the 19th century (following the Napoleonic invasion of Egypt) (Kalant 2001). It is important to emphasise that the use of cannabinoids in ancient or medieval cultures was not only because of the psychoactive effects of these substances; treatment was largely aimed at various somatic disorders including headache, fever, bacterial infections, diarrhoea, rheumatic pain or malaria (Kalant et al. 2001; Gorji and Ghadiri 2002; Zuardi 2006). Despite this fact, the use of cannabinoids is still illegal in many countries due to their psychoactive effects and addictive potential. Attempts by pharmaceutical companies in the sixth decade of the twentieth century to produce cannabinoids with pharmacological effects and without psychotropic activity were not successful (Fisar 2009; Pertwee 2009), although cannabinoids with very weak or no psychotropic activity are known (e.g. cannabidiol, cannabigerol, cannabichromene) (Izzo et al. 2009; Hayakawa et al. 2010).

Although cannabinoids have been attracting attention for many years, the last four decades have brought completely new and scientifically well-founded insights into their therapeutic potential. Since 1975 more than 100 controlled clinical trials with cannabinoids (or whole-plant preparations) for several indications have been carried out and the results of these studies have led to the approval of cannabis-based medicine in various countries (Grotenhermen and Muller-Vahl 2012). Consequently, there is increasing interest, particularly in companion animal owners, regarding the possible use of cannabinoids in veterinary medicine.

In order to cover this broad theme in a concise manner the text will first be focused on the classification of cannabinoids and cannabinoid receptors.

Attention will then be turned to the therapeutic potential of cannabinoids with regard to veterinary medicine.

2. The endocannabinoid system and classification of cannabinoids

The endocannabinoid system consists of several subtypes of cannabinoid receptors (the best characterised are subtypes CB₁ and CB₂), endocannabinoids (endogenous substances that bind to the receptors) and enzymes involved in endocannabinoid biosynthesis through phospholipases or degradation: post-synaptically by FAAH (fatty acid amide hydrolase) and pre-synaptically by MGL (monoacylglycerol lipase) (Pertwee 2005; Muccioli 2010; Battista et al. 2012). This system represents a ubiquitous lipid signalling system (that appeared early in evolution), which plays important regulatory roles throughout the body in all vertebrates (De Fonseca et al. 2005). Below, we will focus on the cannabinoid receptors and their ligands (cannabinoids) because of their principal therapeutic significance.

Cannabinoids are chemical substances which act primarily on specific cannabinoid receptors and are basically divided into three groups; beside endogenous cannabinoids (endocannabinoids) also herbal cannabinoids (phytocannabinoids) and synthetic cannabinoids have been described (Fisar 2009).

Endocannabinoids are endogenously formed from membrane phospholipids in response to increases in intracellular calcium; they are immediately released and act as ligands of cannabinoid receptors (Miller and Devi 2011). The first endogenous ligand, *N*-arachidonylethanolamine, was identified in 1992 from porcine brain (Devane et al. 1992). It was named anandamide (AEA) based on the Sanskrit word 'ananda' which means 'internal bliss'. Other endogenous cannabinoids include 2-arachidonoylglycerol (2-AG), 2-arachidonylglyceryl ether (2-AGE, noladin ether) (Hanus et al.

doi: 10.17221/8762-VETMED

2001), O-arachidonoyl ethanolamine (virhodamine) (Porter et al. 2002) and N-arachidonoyl dopamine (NADA) (Bisogno et al. 2000; Gaffuri et al. 2012; Mechoulam et al. 2014). Within the nervous system endocannabinoids are released from post-synaptic neurons (retrograde neurotransmission) and they bind to presynaptic CB₁ receptors (see below) which results particularly in inhibition of GABA or glutamate release (Heifets and Castillo 2009). In neuron-astrocyte signalling cannabinoids released from post-synaptic neurons stimulate astrocytic CB₁ receptors, thereby triggering glutamatergic gliotransmission (Castillo et al. 2012).

Phytocannabinoids are chemicals produced especially by female plants of *Cannabis sativa* and are present in the resin of the herb. It has been found that these plants contain over 100 phytocannabinoids (Hill et al. 2012). The most studied cannabinoids from *Cannabis sativa* include e.g. delta-9-tetrahydrocannabinol (THC), cannabidiol, tetrahydrocannabivarin, tetrahydrocannabiorcol, cannabichromene and cannabigerol (Maione et al. 2013). THC was first isolated in 1964 (Gaoni and Mechoulam 1964) and the majority of the herbal cannabinoids soon after.

Synthetic cannabinoids are manufactured compounds which bind to cannabinoid receptors (with either agonistic or antagonistic activity) and many of them were originally synthesised for research purposes in University scientific departments or pharmaceutical companies. The most frequently reported series are represented by JWH (John W. Huffman, Clemson University), CP (Pfizer), HU (Hebrew University), AM (Alexandros Makriyannis, Northeastern University), WIN (Sterling Winthrop) and RCS (Research Chemical Supply) (Presley et al. 2013). Both phytocannabinoids and synthetic cannabinoids mimic the effects of endocannabinoids (Grotenhermen 2006).

Two cannabinoid receptors were initially recognised, CB₁ and CB₂. Both these subtypes belong to the large family of receptors that are coupled to G proteins (Svizenska et al. 2008). Cannabinoid CB₁ receptors are among the most plentiful and widely distributed receptors coupled to G proteins in the brain (Grotenhermen 2006). The CB₁ receptor was cloned in 1990 (Matsuda et al. 1990) and CB₂ in 1993 (Munro et al. 1993). CB₁ receptors are present primarily in the central nervous system in regions of the brain that are responsible for pain modulation (certain parts of the spinal cord, periaqueduct-

al grey), movement (basal ganglia, cerebellum) or memory processing (hippocampus, cerebral cortex) (Grotenhermen 2006). To a lesser extent, they can also be found in some peripheral tissues such as pituitary gland, immune cells, reproductive tissues, gastrointestinal tissues, sympathetic ganglia, heart, lung, urinary bladder and adrenal gland (Pertwee 1997).

CB₂ receptors are particularly expressed in the periphery, in the highest density on immune cells, especially B-cells and natural killer cells (Pertwee 1997) and also in tonsils or spleen (Galiegue et al. 1995); nevertheless, their presence has also been described in the CNS (Van Sickle et al. 2005). The frequently discussed psychotropic effects of cannabinoids are mediated only by the activation of CB₁ receptors and not of CB₂ receptors (Grotenhermen and Muller-Vahl 2012).

Endocannabinoids have also been shown to act on TRPV1 receptors (transient receptor potential cation channels subfamily V member 1, also known as the “capsaicin receptor” and “vanilloid receptor” 1) (Ross 2003). The existence of other G-protein cannabinoid receptors has also been suggested. These proposed receptors (also called putative or non-classical cannabinoid receptors) include GPR18, GPR55 and GPR119 that have structural similarity to CB₁ and CB₂ (Alexander et al. 2013; Zubrzycki et al. 2014).

3. The use of cannabinoids in animals

It has been shown that the mechanism of action of cannabinoids is very complex. The activation of cannabinoid CB₁ receptors results in retrograde inhibition of the neuronal release of acetylcholine, dopamine, GABA, histamine, serotonin, glutamate, cholecystokinin, D-aspartate, glycine and noradrenaline (Grotenhermen and Muller-Vahl 2012). CB₂ receptors localised mainly in cells associated with the immune system are involved in the control of inflammatory processes. Their activation results in, among other effects, inhibition of pro-inflammatory cytokine production and increased release of anti-inflammatory cytokines (Zubrzycki et al. 2014). In addition, some cannabinoids were shown to act not only at cannabinoid receptors but also at vanilloid or serotonin 5-HT₃ receptors (Contassot et al. 2004; Grotenhermen and Muller-Vahl 2012). This complexity of interactions explains both the

large number of physiological effects of cannabinoids and the pharmacological influences of cannabinoid preparations (Grotenhermen and Muller-Vahl 2012).

There are a huge number of reports on the possible beneficial effects of cannabinoids in human medicine. Their therapeutic potential has been demonstrated in the treatment of many disorders including pain, inflammation, cancer, asthma, glaucoma, spinal cord injury, epilepsy, hypertension, myocardial infarction, arrhythmia, rheumatoid arthritis, diabetes, multiple sclerosis, Parkinson's disease, Alzheimer's disease, depression or feeding-related disorders, and many others (e.g. Porcella et al. 2001; Robson 2001; Rog et al. 2005; Blake et al. 2006; Pacher et al. 2006; Russo 2008; Scheen and Paquot 2009; Karst et al. 2010; Lynch and Campbell 2011; Caffarel et al. 2012; Grotenhermen and Muller-Vahl 2012; Hill et al. 2012; Maione et al. 2013; Lynch et al. 2014; Serpell et al. 2014; Lynch and Ware 2015).

Information concerning the effects of cannabinoid on animals can be found on the experimental level and were obtained during the pre-clinical testing of individual substances in mice, rats and guinea pigs (i.e. laboratory rodents). Beneficial effects of cannabinoids in these animals have been reported e.g. for disorders of the cardiovascular system, cancer treatment, pain treatment, disorders of the respiratory system or metabolic disorders, and suggest the usefulness of further research in this direction. Examples are summarised in Table 1.

For many further examples see the following reviews: Croxford (2003), Guzman (2003), Croxford and Yamamura (2005), Mendizabal and Adler-Graschinsky (2007), Sarfaraz et al. (2008), Nagarkatti et al. (2009), Steffens and Pacher (2012), Velasco et al. (2012), Han et al. (2013), Massi (2013), Stanley et al. (2013), Kucerova et al. (2014), Pertwee (2014), Kluger et al. (2015).

Compared to reports from laboratory rodents, there are a much smaller number of published papers dealing with pre-clinical testing of cannabinoids in other species (rabbits, ferrets, cats, dogs), and an even smaller number of reliable sources are available to date concerning the clinical use of cannabinoids in veterinary medicine for both companion and large animals. Indeed, the majority of articles concerns actually marijuana poisoning and its treatment rather than therapeutic applications (Girling and Fraser 2011; Meola et al. 2012; Fitzgerald et al. 2013).

It is therefore interesting that Mechoulam (2005) reported the use of cannabinoid acids (which are

precursors of the neutral cannabinoids, such as THC and cannabidiol) for veterinary purposes in Czechoslovakia already in the 1950s because of their antibiotic properties. The use of cannabinoids as antibiotic drugs, however, was not further investigated, although it has been shown that cannabinoids exert antibacterial activity (Appendino et al. 2008; Izzo et al. 2009).

The most frequently reported use of cannabinoids in companion animals (on a pre-clinical basis) is in association with the topical treatment of glaucoma. Pate et al. (1998) administered AEA, its R-alpha-isopropyl analogue, and the non-classical cannabinoid CP-55,940 into the eyes of normotensive rabbits. These substances were dissolved in an aqueous 10–20% 2-hydroxypropyl-beta-cyclodextrin solution (containing 3% polyvinyl alcohol). The doses were 25.0 µg for CP-55,940 and 62.5 µg for AEA and R-alpha-isopropyl anandamide. The low solubility of the cannabinoids in water was modified with cyclodextrins. It was shown that CP-55,940 had considerable ocular hypotensive effects, R-alpha-isopropyl anandamide exerted these effects to a smaller extent and AEA caused a typical bi-phasic initial hypertension and subsequent decrease in intraocular pressure (Pate et al. 1998). Song and Slowey (2000) administered the substance WIN 55212-2 (CB_{1,2} receptor agonist) topically into the eyes of healthy rabbits at doses of 4, 20 and 100 µg. WIN 55212-2 at a dose of 100 mg significantly reduced intraocular pressure at 1, 2, and 3 h after application. The effects of the substance peaked between 1 and 2 h after administration and intraocular pressure returned to control levels at 4 h after application. The effects of WIN 55212-2 on intraocular pressure were dose-dependent. Twenty mg of the substance produced a smaller effect than 100 mg and 4 mg of the drug elicited non-significant lowering effects (Song and Slowey 2000). Fischer et al. (2013) tested the effects of topical administration of an ophthalmic solution containing THC (2%) on aqueous humour flow rate and intraocular pressure in 21 clinically normal dogs. Topical administration of THC ophthalmic solution led to a moderate reduction in mean intraocular pressure in these animals. Chien et al. (2003) used cannabinoids in both normotensive and glaucomatous monkeys (*Macaca cynomolgus*). WIN 55212-2 (CB_{1,2} receptor agonist) dissolved in 45% 2-hydroxypropyl-β-cyclodextrin was administered at concentrations of 0.07%, 0.2%, and 0.5%

doi: 10.17221/8762-VETMED

Table 1. Examples of cannabinoid use in rodent models

Cardiovascular disorders	Slavic et al. (2013) – blockade of CB ₁ receptor with rimonabant (CB ₁ receptor antagonist/inverse agonist) improved cardiac functions after myocardial infarction and reduced cardiac remodelling
	Di Filippo et al. (2004) – administration of WIN 55,212-2 (synthetic CB _{1,2} receptor agonist) significantly decreased the extent of infarct size in the area at risk in a model of mouse myocardial ischaemia/reperfusion
	Batkai et al. (2004) – endocannabinoids tonically suppressed cardiac contractility in hypertension in rats
	Mukhopadhyay et al. (2007) – treatment with rimonabant significantly improved cardiac dysfunction and protected against doxorubicin-induced cardiotoxicity in mice
	Steffens et al. (2005) – oral administration of THC (CB _{1,2} receptor agonist) inhibited atherosclerosis in mice
Cancer	Grimaldi et al. (2006) – metabolically stable anandamide analogue, 2-methyl-2V-F-anandamide (CB ₁ receptor agonist) significantly reduced the number and dimension of metastatic nodes in mice
	Guzman (2003) – <i>in vivo</i> experiments revealed that cannabinoid treatment of mice slowed down the growth of various tumour xenografts, including lung carcinomas, gliomas, thyroid epitheliomas, skin carcinomas and lymphomas
Pain	Luongo et al. (2013) – chronic treatment with palmitoylethanolamide (endogenous cannabinoid-like compound in the central nervous system) significantly reduced mechanical allodynia and thermal hyperalgesia
	Pascual et al. (2005) – WIN 55,212-2 (synthetic CB _{1,2} receptor agonist) reduced neuropathic nociception induced by paclitaxel in rats
	Hanus et al. (1999) – HU-308 (highly selective CB ₂ receptor agonist) elicited anti-inflammatory and peripheral analgesic activity
	Xiong et al. (2012) – administration of cannabidiol (indirect antagonist of CB ₁ and CB ₂ receptor agonists) significantly suppressed chronic inflammatory and neuropathic pain in rodents
Asthma	Jan et al. (2003) – THC and cannabiniol exhibited potential therapeutic utility in the treatment of allergic airway disease by inhibiting the expression of critical T cell cytokines and the associated inflammatory response in an animal model of mice sensitised with ovalbumin
	Giannini et al. (2008) – CP-55,940 (CB _{1,2} receptor agonist) showed positive effects on antigen-induced asthma-like reaction in sensitised guinea pigs and conversely, both SR144528 (CB ₂ receptor antagonist/inverse agonist) and AM 251 (CB ₁ receptor antagonist/inverse agonist) reverted these protective effects
Vomiting	Darmani et al. (2001a) – THC and CP-55,940 (synthetic agonist at CB ₁ and CB ₂ receptors) prevented emesis produced by SR 141716A (CB ₁ receptor antagonist/inverse agonist) in the least shrew (<i>Cryptotis parva</i>)
	Darmani (2001b) – THC reduced the percentage of animals vomiting and the frequency of vomits provoked by cisplatin in the same animal species
	Parker et al. (2004) – THC and cannabidiol (indirect antagonist of CB ₁ and CB ₂ receptor agonists) reduced lithium-induced vomiting in the house musk shrew (<i>Suncus murinus</i>)
Diabetes	El-Remessy et al. (2006) – cannabidiol (indirect antagonist of CB ₁ and CB ₂ receptor agonists) reduced neurotoxicity, inflammation, and blood-retinal barrier breakdown in streptozotocin-induced diabetic rats
	Weiss et al. (2006) – cannabidiol significantly reduced the incidence of diabetes in young non-obese diabetes-prone female mice
	Weiss et al. (2008) – cannabidiol ameliorated the manifestations of diabetes in non-obese diabetes-prone female which were either in a latent diabetes stage or with initial symptoms of the disease
Retinitis pigmentosa	Lax et al. (2014) – HU-210 (CB _{1,2} receptor agonist) preserved cone and rod structure and function, thus showing neuroprotective effects on retinal degeneration in a rat model for autosomal dominant retinitis pigmentosa
Food intake, body weight	Hildebrandt et al. (2003) – AM 251 (CB ₁ receptor antagonist/inverse agonist) reduced inguinal subcutaneous, retroperitoneal and mesenteric adipose tissue mass in Western diet-induced obese mice. Anorectic effects of AM 251 were also reported by e.g. Slais et al. (2003), Chambers et al. (2006) and Tallett et al. (2007)

Five normal monkeys received 50 µl (2 × 25 µl) of WIN 55212-2 to the right eye, and an equal volume of the vehicle to the left eye. In glaucomatous monkeys, 50 µl of WIN 55212-2 was administered to the glaucomatous eye only. Moreover, a multiple-dose study was carried out in 8 monkeys with unilateral glaucoma. WIN 55212-2 (0.5%) was administered to the glaucomatous eye twice daily at 9:30 AM and 3:30 PM for five consecutive days. It was shown that in the five normal monkeys unilateral application of the substance significantly decreased intraocular pressure for up to 4, 5, and 6 h following administration of the 0.07%, 0.2%, and 0.5% concentrations, respectively. The maximum changes in intraocular pressure were found at 3 h after drug application. In the eight glaucomatous monkeys the administration of WIN 55212-2 also resulted in a significant decrease in intraocular pressure (Chien et al. 2003).

Other potential and promising indications for cannabinoid use in veterinary medicine include inflammation and pain treatment as well as possible applications in dermatology and oncology. With respect to inflammation and pain, Re et al. (2007) authored a review in which they focused on the role of an endogenous fatty acid amide analogue of the endocannabinoid AEA – termed palmitoylethanolamide (PEA) – in tissue protection. PEA does not bind to CB₁ and CB₂ receptors but has affinity for the cannabinoid-like G-coupled receptors GPR55 and GPR119. It acts as a modulator of glia and mast cells (Keppel Hesselink 2012), and has been shown to enhance AEA activity through a so-called “entourage effect” (Mechoulam et al. 1998). Re et al. (2007) concluded that the use of natural compounds such as PEA influences endogenous protective mechanisms and can represent an advantageous and beneficial novel therapeutic approach in veterinary medicine. Regarding dermatology, Scarampella et al. (2001) administered the substance PLR 120 (an analogue of PEA) to 15 cats with eosinophilic granulomas or eosinophilic plaques. Clinical improvements of signs and lesions were evident in 10 out of 15 cats, suggesting that PLR-120 could be a useful drug for the treatment of these disorders (Scarampella et al. 2001). Similarly, Cerrato et al. (2010) isolated mast cells from the skin biopsies of 18 dogs, incubated these cells with IgE-rich serum and challenged them with anti-canine IgE. Subsequently, histamine, prostaglandin D₂ and tumour necrosis factor-alpha release was measured in the presence and absence of increasing concentrations of palmitoylethanolamide.

The authors found that histamine, prostaglandin D₂ and tumour necrosis factor-alpha release induced by canine anti-IgE were significantly inhibited in the presence of PEA. Thus, it can be concluded that PEA has therapeutic potential in the treatment of dermatological disorders involving mast cell hyperactivity (Cerrato et al. 2010). Moreover, Cerrato et al. (2012) evaluated the effects of PEA on the cutaneous allergic inflammatory reaction induced by different immunological and non-immunological stimuli in six spontaneously *Ascaris*-hypersensitive Beagle dogs. These dogs were challenged by intradermal injections of *Ascaris suum* extract, substance P and anti-canine IgE, before and after PEA application (orally at doses of 3, 10 and 30 mg/kg). The results have shown that PEA was effective in reducing immediate skin reaction in these dogs with skin allergy (Cerrato et al. 2012). With respect to oncology, Figueiredo et al. (2013) found that the synthetic cannabinoid agonist WIN-55,212-2 was effective as a potential inhibitor of angiogenesis in a canine osteosarcoma cell line. Although further *in vivo* research is certainly required, the results thus far indicate that the use of cannabinoid receptor agonists as potential adjuvants to chemotherapeutics in the treatment of canine cancers could be a promising therapeutic strategy. Looney (2010) reported the use of cannabinoids for palliative care in animals suffering from oncological disease to stimulate eating habits. Finally, McCarthy and Borison (1981) reported antiemetic activity of nabilone (synthetic CB_{1,2} agonist) in cats after cisplatin (anti-cancer drug) treatment and similarly Van Sickle et al. (2003) reported that THC (0.05–1 mg/kg *i.p.*) reduced the emetic effects of cisplatin in ferrets.

4. Prospective veterinary use of cannabinoids

As can be seen from the above instances, cannabinoids have a myriad of pharmacological effects and the beneficial impact of different cannabinoids has been proven and documented many times in various laboratory/companion animals. It has been shown that the same cannabinoid drug can elicit divergent responses in humans and animals. For example, Jones (2002) reported increased heart rate and slightly increased supine blood pressure after THC administration in humans, whereas the cardiovascular effects in animals were different, with bradycardia and hypotension (Jones 2002). Thus, a definite advantage of the use of cannabinoids in

doi: 10.17221/8762-VETMED

animals is that the research and pre-clinical testing was carried out on various animal species and these categories can now represent target species in the case of veterinary use. In other words, the risk of divergent responses to the same drug, which has been described for humans and animals, is much lower.

It should also be taken into account that the majority of cannabinoids possess psychotropic properties which may change the behaviour of animals (e.g. locomotion) and that these substances have addictive potential (Fattore et al. 2008; Landa et al. 2014a; Landa et al. 2014b). On the other hand, other drug classes with even stronger effects on the CNS and addictive properties have been used therapeutically in both humans and veterinary medicine for centuries (e.g. opioids) because their benefit outweighs the risks.

Cannabis-based medical products were introduced to human medicine in the last years in many countries (among others Austria, Canada, Czech Republic, Finland, Germany, Israel, Italy). Preparations approved for use in human medicine include Cesamet, Dronabinol, Sativex, Bedrocan, Bedrobinol, Bediol, Bedica or Bedrolite. For dogs and cats, the veterinarian-recommended, ready-made hemp based supplement Canna-Pet is presently available (containing non-psychoactive cannabidiol). PEA can at present be used to restore skin reactivity in animals in a veterinary medication sold under the trade name Redonyl (LoVerme et al. 2005). It is therefore not surprising that owners of animals are also exhibiting increasing interest in the possible use of cannabinoids/medical marijuana in veterinary medicine as can be seen by the number of internet forums concerned with this issue (e.g. dvm360 magazine, Cannabis Financial Network or Medical Daily). In the Journal of the American Veterinary Medical Association, Nolen (2013) reported anecdotal evidence from pet owners describing beneficial effects of marijuana use in dogs, cats and horses and, moreover, also the opinions of professionals who believe in the potential usefulness of cannabis use in veterinary medicine. The reluctant attitude of veterinarians towards the use of cannabinoids/medical marijuana in animals could be associated with the risk that owners will make attempts to treat their animals using cannabis-based products, which can lead to intoxication. In the article by Nolen (2013), Dr. Dawn Boothe (Clinical Pharmacology Laboratory at Auburn University College of Veterinary Medicine) concluded that

veterinarians should be part of the debate about the use of cannabinoids/medical marijuana, e.g. by means of a controlled clinical trial dealing with the use of marijuana to treat cancer pain in animals.

5. Conclusions

The isolation of THC in 1964 represented a breakthrough in research progress concerning cannabinoids. The discovery of the cannabinoid receptors and their endogenous ligands, definition of the endocannabinoid system and description of other cannabinoid substances elicited increased interest in this research and in the possible therapeutic potential in animal models. The results from this basic research finally led to the addition of cannabinoids/medical marijuana to the spectrum of therapeutic possibilities for various disorders in humans. The therapeutic effects of cannabinoids/medical marijuana on companion animals are now the subject of discussion in numerous internet forums and such debate could result in attempts at treatment using cannabinoids without the necessary safety precautions. Thus, the prospective use of cannabinoids for veterinary purposes needs to be taken seriously; this could decrease the risk of attempts at unauthorised and non-professional treatment by animal owners. Legislative regulations may differ in various countries and the use of cannabinoids/medical marijuana must be in accordance with the respective rules.

6. REFERENCES

- Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL, Spedding M, Peters JA, Harmar AJ, CGTP Collaborators (2013): The concise guide to pharmacology 2013/14: G protein-coupled receptors. *British Journal of Pharmacology* 170, 1459–1581.
- Appendino G, Gibbons S, Giana A, Pagani A, Grassi G, Stavri M, Smith E, Rahman MM (2008): Antibacterial cannabinoids from *Cannabis sativa*: A structure-activity study. *Journal of Natural Products* 71, 1427–1430.
- Batkai S, Pacher P, Osei-Hyiaman D, Radaeva S, Liu J, Harvey-White J, Offertaler L, Mackie K, Rudd MA, Bukoski RD, Kunos G (2004): Endocannabinoids acting at cannabinoid-1 receptors regulate cardiovascular function in hypertension. *Circulation* 110, 1996–2002.

- Battista N, Di Tommaso M, Bari M, Maccarrone M (2012): The endocannabinoid system: an overview. *Frontiers in Behavioral Neuroscience*, 6, DOI: 10.3389/fnbeh.2012.00009.
- Bisogno T, Melck D, Bobrov MYu, Gretskaya NM, Bezuglov VV, De Petrocellis L, Di Marzo V (2000): N-acyl-dopamines: novel synthetic CB(1) cannabinoid-receptor ligands and inhibitors of anandamide inactivation with cannabimimetic activity in vitro and in vivo. *The Biochemical Journal* 351, 817–824.
- Blake DR, Robson P, Ho M, Jubb RW, McCabe CS (2006): Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology* 45, 50–52.
- Caffarel MM, Andradas C, Perez-Gomez E, Guzman M, Sanchez C (2012): Cannabinoids: A new hope for breast cancer therapy? *Cancer Treatment Reviews* 38, 911–918.
- Castillo PE, Younts TJ, Chavez AE, Hashimoto Y (2012): Endocannabinoid signaling and synaptic function. *Neuron* 76, 70–81.
- Cerrato S, Brazis P, della Valle ME, Miolo A, Puigdemont A (2010): Effects of palmitoylethanolamide on immunologically induced histamine, PGD2 and TNF α release from canine skin mast cells. *Veterinary Immunology and Immunopathology* 133, 9–15.
- Cerrato S, Brazis P, della Valle ME, Miolo A, Petrosino S, Di Marzo V, Puigdemont A (2012): Effects of palmitoylethanolamide on the cutaneous allergic inflammatory response in *Ascaris* hypersensitive Beagle dogs. *The Veterinary Journal* 191, 377–382.
- Chambers AP, Koopmans HS, Pittman QJ, Sharkley KA (2006): AM 251 produces sustained reductions in food intake and body weight that are resistant to tolerance and conditioned taste aversion. *British Journal of Pharmacology* 147, 109–116.
- Chien FY, Wang RF, Mittag TW, Podos SM (2003): Effect of WIN 55212-2, a cannabinoid receptor agonist, on aqueous humor dynamics in monkeys. *Archives of Ophthalmology* 121, 87–90.
- Contassot E, Willemotte R, Tenan M, Belkouch MC, Schnuriger V, de Tribolet N, Burkhardt K, Dietrich PY (2004): Arachidonylethanolamide induces apoptosis of human glioma cells through vanilloid receptor-1. *Journal of Neuropathology and Experimental Neurology* 63, 956–963.
- Croxford JL (2003): Therapeutic potential of cannabinoids in CNS disease. *CNS Drugs* 17, 179–202.
- Croxford JL, Yamamura T (2005): Cannabinoids and the immune system: Potential for the treatment of inflammatory diseases? *Journal of Neuroimmunology* 166, 3–18.
- Darmani NA (2001a): Δ 9-tetrahydrocannabinol and synthetic cannabinoids prevent emesis produced by the cannabinoid CB1 receptor antagonist/inverse agonist SR 141716A. *Neuropsychopharmacology* 24, 198–203.
- Darmani NA (2001b): Delta-9-tetrahydrocannabinol differentially suppresses cisplatin-induced emesis and indices of motor function via cannabinoid CB1 receptors in the least shrew. *Pharmacology Biochemistry and Behavior* 69, 239–249.
- De Fonseca FR, Del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M (2005): The endocannabinoid system: physiology and pharmacology. *Alcohol and Alcoholism* 40, 2–14.
- Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R (1992): Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 258, 1946–1949.
- Di Filippo C, Rossi F, Rossi S, D'Amico M (2004): Cannabinoid CB2 receptor activation reduces mouse myocardial ischemia-reperfusion injury: involvement of cytokine/chemokines and PMN. *Journal of Leukocyte Biology* 75, 453–459.
- El-Remessy AB, Al-Shabrawey M, Khalifa Y, Tsai NT, Caldwell RB, Liou GI (2006): Neuroprotective and blood-retinal barrier-preserving effects of cannabidiol in experimental diabetes. *American Journal of Pathology* 168, 235–244.
- Fattore L, Fadda P, Spano MS, Pistis M, Fratta W (2008): Neurobiological mechanisms of cannabinoid addiction. *Molecular and Cellular Endocrinology* 286S, S97–S107.
- Figueiredo AS, Garcia-Crescioni HJ, Bulla SC, Ross MK, McIntosh C, Lunsford K, Bulla C (2013): Suppression of vascular endothelial growth factor expression by cannabinoids in a canine osteosarcoma cell line. *Veterinary Medicine: Research and Reports* 4, 31–34.
- Fisar Z (2009): Phytocannabinoids and endocannabinoids. *Current Drug Abuse Reviews* 2, 51–75.
- Fischer KM, Ward DA, Hendrix DVH (2013): Effects of a topically applied 2% delta-9-tetrahydrocannabinol ophthalmic solution on intraocular pressure and aqueous humor flow rate in clinically normal dogs. *American Journal of Veterinary Research* 74, 275–280.
- Fitzgerald KT, Bronstein AC, Newquist KL (2013): Marijuana poisoning. *Topics in Companion Animal Medicine* 28, 8–12.
- Gaffuri AL, Ladarre D, Lenkei Z (2012): Type-1 cannabinoid receptor signaling in neuronal development. *Pharmacology* 90, 19–39.
- Galiegue S, Mary S, Marchand J, Dussosoy D, Carriere D, Carayon P, Bouaboula M, Shire D, Le Fur G, Casellas P

doi: 10.17221/8762-VETMED

- (1995): Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *European Journal of Biochemistry* 232, 54–61.
- Gaoni Y, Mechoulam R (1964): Isolation, structure, and partial synthesis of an active constituent of hashish. *Journal of the American Chemical Society* 86, 1646–1647.
- Giannini L, Nistri S, Mastroianni R, Cinci L, Vannacci A, Mariottini C, Passani MB, Mannaioni PF, Bani D, Masini E (2008): Activation of cannabinoid receptors prevents antigen-induced asthma-like reaction in guinea pigs. *Journal of Cellular and Molecular Medicine* 12, 2381–2394.
- Girling SJ, Fraser MA (2011): Cannabis intoxication in three Green iguanas (*Iguana iguana*). *Journal of Small Animal Practice* 52, 113–116.
- Grimaldi C, Pisanti S, Laezza C, Malfitano AM, Santoro A, Vitale M, Caruso MG, Notarnicola M, Iacuzzo I, Portella G, Di Marzo V, Bifulco M (2006): Anandamide inhibits adhesion and migration of breast cancer cells. *Experimental Cell Research* 312, 363–373.
- Gorji A, Ghadiri MK (2002): History of headache in medieval Persian medicine. *Lancet Neurology* 1, 510–515.
- Grotenhermen F (2006): Cannabinoids and the endocannabinoid system. *Cannabinoids* 1, 10–14.
- Grotenhermen F, Muller-Vahl K (2012): The therapeutic potential of cannabis and cannabinoids. *Deutsches Arzteblatt International* 109, 495–501.
- Guzman M (2003): Cannabinoids: potential anticancer agents. *Nature Reviews Cancer* 3, 745–755.
- Han S, Thatte J, Buzard DJ, Jones RM (2013): Therapeutic utility of cannabinoid receptor type 2 (CB₂) selective agonists. *Journal of Medical Chemistry* 56, 8224–8256.
- Hanus L, Breuer A, Tchilibon S, Shiloah S, Goldenberg D, Horowitz M, Pertwee RG, Ross RA, Mechoulam R, Frid E (1999): HU-308: A specific agonist for CB₂, a peripheral cannabinoid receptor. *Proceedings of the National Academy of Sciences of the United States of America* 96, 14228–14233.
- Hanus L, Abu-Lafi S, Fride E, Breuer A, Vogel Z, Shalev DE, Kustanovich I, Mechoulam R (2001): 2-Arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB₁ receptor. *Proceedings of the National Academy of Sciences of the United States of America* 98, 3662–3665.
- Hayakawa K, Mishima K, Fujiwara M (2010): Therapeutic potential of non-psychotropic cannabidiol in ischemic stroke. *Pharmaceuticals* 3, 2197–2212.
- Heifets BD, Castillo PE (2009): Endocannabinoid signaling and long-term synaptic plasticity. *Annual Review of Physiology* 71, 283–306.
- Hildebrandt AL, Kelly-Sullivan DM, Black SC (2003): Antiobesity effects of chronic cannabinoid CB₁ receptor antagonist treatment in diet-induced obese mice. *European Journal of Pharmacology* 462, 125–132.
- Hill AJ, Williams CM, Whalley BJ, Stephens GJ (2012): Phytocannabinoids as novel therapeutic agents in CNS disorders. *Pharmacology and Therapeutics* 133, 79–97.
- Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R (2009): Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends in Pharmacological Sciences* 30, 515–527.
- Jan TR, Farraj AK, Harkema JR, Kaminski NE (2003): Attenuation of the ovalbumin-induced allergic airway response by cannabinoid treatment in A/J mice. *Toxicology and Applied Pharmacology* 188, 24–35.
- Jones RT (2002): Cardiovascular system effects of marijuana. *The Journal of Clinical Pharmacology* 42, 58S–63S.
- Kalant H (2001): Medicinal use of cannabis. *Pain Research and Management* 6, 80–91.
- Karst M, Wippermann S, Ahrens J (2010): Role of cannabinoids in the treatment of pain and (painful) spasticity. *Drugs* 70, 2409–2438.
- Keppel Hesselink JM (2012): New targets in pain, non-neuronal cells, and the role of palmitoylethanolamide. *The Open Pain Journal* 5, 12–23.
- Kluger B, Triolo P, Jones W, Jankovic J (2015): The therapeutic potential of cannabinoids for movement disorders. *Movement Disorders* 30, 313–327.
- Kucerova J, Tabiova K, Drago F, Micala V (2014): Therapeutic potential of cannabinoids in schizophrenia. *Recent Patents on CNS Drug Discovery* 9, 13–25.
- Landa L, Slais K, Machalova A, Sulcova A (2014a): The effect of cannabinoid CB₁ receptor agonist arachidonylcyclopropylamide (ACPA) on behavioural sensitisation to methamphetamine in mice. *Veterinarni Medicina* 59, 88–94.
- Landa L, Slais K, Machalova A, Sulcova A (2014b): Interaction of CB₁ receptor agonist arachidonylcyclopropylamide with behavioural sensitisation to morphine in mice. *Veterinarni Medicina* 59, 307–314.
- Lax P, Esquivia G, Altavilla C, Cuenca N (2014): Neuroprotective effects of the cannabinoid agonist HU210 on retinal degeneration. *Experimental Eye Research* 120, 175–185.
- Looney A (2010): Oncology pain in veterinary patients. *Topics in Companion Animal Medicine* 25, 32–44.
- LoVerme J, La Rana G, Russo R, Calignano A, Piomelli D (2005): The search for the palmitoylethanolamide receptor. *Life Sciences* 77, 1685–1698.
- Luongo L, Guida F, Boccella S, Bellini G, Gatta L, Rossi F, de Novellis V, Maione S (2013): Palmitoylethanolamide reduces formalin-induced neuropathic-like behaviour through spinal glial/microglial phenotypical changes in mice. *CNS and Neurological Disorders – Drug Targets* 12, 45–54.

- Lynch ME, Campbell F (2011): Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. *British Journal of Clinical Pharmacology* 72, 735–744.
- Lynch ME, Ware MA (2015): Cannabinoids for the treatment of chronic non-cancer pain: An updated systematic review of randomized controlled trials. *Journal of Neuroimmune Pharmacology* 10, 293–301.
- Lynch ME, Cesar-Rittenberg P, Hohmann AG (2014): A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. *Journal of Pain and Symptom Management* 47, 166–173.
- Maione S, Costa B, Di Marzo V (2013): Endocannabinoids: A unique opportunity to develop multitarget analgesics. *Pain* 154, S87–S93.
- Massi P, Solinas M, Cinquina V, Parolaro D (2013): Cannabidiol as potential anticancer drug. *British Journal of Clinical Pharmacology* 75, 303–312.
- Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI (1990): Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 346, 561–564.
- McCarthy LE, Borison HL (1981): Antiemetic activity of N-methyllevonantradol and nabilone in cisplatin-treated cats. *Journal of Clinical Pharmacology* 21, 30S–37S.
- Mechoulam R. (2005): Plant cannabinoids: a neglected pharmacological treasure trove. *British Journal of Pharmacology* 146, 913–915.
- Mechoulam R, Fride E, Di Marzo V (1998): Endocannabinoids. *European Journal of Pharmacology*, 359, 1–18.
- Mechoulam R, Hanus LO, Pertwee R, Howlett AC (2014): Early phytocannabinoid chemistry to endocannabinoids and beyond. *Nature Reviews Neuroscience* 15, 757–764.
- Mendizabal VE, Adler-Graschinsky E (2007): Cannabinoids as therapeutic agents in cardiovascular disease: a tale of passions and illusions. *British Journal of Pharmacology*, 151, 427–440.
- Meola SD, Tearney CC, Haas SA, Hackett TB, Mazzaferro EM (2012): Evaluation of trends in marijuana toxicosis in dogs living in a state with legalized medical marijuana: 125 dogs (2005–2010). *Journal of Veterinary Emergency and Critical Care* 22, 690–696.
- Miller LK, Devi LA (2011): The highs and lows of cannabinoid receptor expression in disease: mechanisms and their therapeutic implications. *Pharmacological Reviews* 63, 461–470.
- Muccioli GG (2010): Endocannabinoid biosynthesis and inactivation, from simple to complex. *Drug Discovery Today* 15, 474–483.
- Mukhopadhyay P, Batkai S, Rajesh M, Czifra N, Harvey-White J, Hasko G, Zsengeller Z, Gerard NP, Liaudet L, Kunos G, Pacher P (2007): Pharmacological inhibition of CB1 cannabinoid receptor protects against doxorubicin-induced cardiotoxicity. *Journal of the American College of Cardiology* 50, 528–536.
- Munro S, Thomas KL, Abu-Shaar M (1993): Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 365, 61–65.
- Nagarkatti P, Pandey R, Rieder SA, Hegde VL, Nagarkatti M (2009): Cannabinoids as novel anti-inflammatory drugs. *Future Medicinal Chemistry* 1, 1333–1349.
- Nolen RS (2013): With pet owners already using the drug as medicine, veterinarians need to join the debate. *Journal of the American Veterinary Medical Association* 242, 1604–1609.
- Pacher P, Batkai S, Kunos G (2006): The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacological Reviews* 58, 389–462.
- Parker LA, Kwiatkowska M, Burton P, Mechoulam R (2004): Effect of cannabinoids on lithium-induced vomiting in the *Suncus murinus* (house musk shrew). *Psychopharmacology* 171, 156–161.
- Pascual D, Goicoechea C, Suardiaz M, Martin MI (2005): A cannabinoid agonist, WIN 55,212-2, reduces neuropathic nociception induced by paclitaxel in rats. *Pain* 118, 23–34.
- Pate DW, Jarvinen K, Urtti A, Mahadevan V, Jarvinen T (1998): Effect of the CB1 receptor antagonist, SR141716A, on cannabinoid-induced ocular hypotension in normotensive rabbits. *Life Sciences* 63, 2181–2188.
- Pertwee RG (1997): Pharmacology of cannabinoid CB1 and CB2 receptors. *Pharmacology and Therapeutics* 74, 129–180.
- Pertwee RG (2005): The therapeutic potential of drugs that target cannabinoid receptors or modulate the tissue levels or actions of endocannabinoids. *The AAPS Journal* 7, E625–E654.
- Pertwee RG (2009): Emerging strategies for exploiting cannabinoid receptor agonists as medicines. *British Journal of Pharmacology* 156, 397–411.
- Pertwee RG (2014): Elevating endocannabinoid levels: pharmacological strategies and potential therapeutic applications. *Proceedings of the Nutrition Society* 73, 96–105.
- Porcella A, Maxia C, Gessa GL, Pani L (2001): The synthetic cannabinoid WIN55212-2 decreases the intraocular pressure in human glaucoma resistant to conventional therapies. *European Journal of Neuroscience* 13, 409–412.
- Porter AC, Sauer JM, Knierman MD, Becker GW, Berna MJ, Bao J, Nomikos GG, Carter P, Bymaster FP, Leese AB, Felder CC (2002): Characterization of a novel endocan-

doi: 10.17221/8762-VETMED

- nabinoid, virodhamine, with antagonist activity at the CB1 receptor. *The Journal of Pharmacology and Experimental Therapeutics* 301, 1020–1024.
- Presley BC, Jansen-Varnum SA, Logan BK (2013): Analysis of synthetic cannabinoids in botanical material: A review of analytical methods and findings. *Forensic Science Review* 25, 27–46.
- Re G, Barbero R, Miolo A, Di Marzo V (2007): Palmitoylethanolamide, endocannabinoids and related cannabimimetic compounds in protection against tissue inflammation and pain: Potential use in companion animals. *The Veterinary Journal* 173, 21–30.
- Robson P (2001): Therapeutic aspects of cannabis and cannabinoids. *The British Journal of Psychiatry* 178, 107–115.
- Rog DJ, Nurmikko TJ, Friede T, Young CA (2005): Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 65, 812–819.
- Ross RA (2003): Anandamide and vanilloid TRPV1 receptors. *British Journal of Pharmacology* 140, 790–801.
- Russo EB (2008): Cannabinoids in the management of difficult to treat pain. *Therapeutics and Clinical Risk Management* 4, 245–259.
- Sarfraz S, Adhami VM, Syed DN, Afaq F, Mukhtar H (2008): Cannabinoids for cancer treatment: progress and promise. *Cancer Research* 15, 339–342.
- Scarampella F, Abramo F, Noli C (2001): Clinical and histological evaluation of an analogue of palmitoylethanolamide, PLR 120 (comiconized Palmidrol INN) in cats with eosinophilic granuloma and eosinophilic plaque: a pilot study. *Veterinary Dermatology* 12, 29–39.
- Scheen AJ, Paquot N (2009): Use of cannabinoid CB1 receptor antagonists for the treatment of metabolic disorders. *Best Practice and Research Clinical Endocrinology and Metabolism* 23, 103–116.
- Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, Ehler E (2014): A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *European Journal of Pain* 18, 999–1012.
- Slais K, Landa L, Sulcova A (2003): The effects of cannabinoid CB1 receptor antagonist AM 251 on locomotor/exploratory behaviour and body weight in mice. *European Neuropsychopharmacology* 13 (Suppl. 4), 417.
- Slavic S, Lauer D, Sommerfeld M, Kemnitz UR, Grzesiak A, Trappiel M, Thone-Reineke C, Baulmann J, Paulis L, Kappert K, Kintscher U, Unger T, Kaschina E (2013): Cannabinoid receptor 1 inhibition improves cardiac function and remodelling after myocardial infarction and in experimental metabolic syndrome. *Journal of Molecular Medicine* 91, 811–823.
- Song ZH, Slowey CA (2000): Involvement of cannabinoid receptors in the intraocular pressure-lowering effects of WIN55212-2. *Journal of Pharmacology and Experimental Therapeutics* 292, 136–139.
- Stanley CP, Hind WH, O'Sullivan SE (2013): Is the cardiovascular system a therapeutic target for cannabidiol? *British Journal of Clinical Pharmacology* 75, 313–322.
- Steffens S, Pacher P (2012): Targeting cannabinoid receptor CB(2) in cardiovascular disorders: promises and controversies. *British Journal of Pharmacology* 167, 313–323.
- Steffens S, Veillard NR, Arnaud C, Pelli G, Burger F, Staub C, Zimmer A, Frossard JL, Mach F (2005): Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice. *Nature* 434, 782–786.
- Svizenska I, Dubovy P, Sulcova A (2008): Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures – A short review. *Pharmacology Biochemistry and Behavior* 90, 501–511.
- Tallett AJ, Blundell JE, Rodgers RJ (2007): Acute anorectic response to cannabinoid receptor antagonist/inverse agonist AM 251 in rat: indirect behavioural mediation. *Behavioural Pharmacology* 18, 591–600.
- Unschuld PU (1986): *Medicine in China. A History of Pharmacology*. University of California Press, Berkeley and Los Angeles. 167 pp.
- Van Sickle MD, Oland LD, Mackie K, Davison JS, Sharkey KA (2003): Delta9-tetrahydrocannabinol selectively acts on CB1 receptors in specific regions of dorsal vagal complex to inhibit emesis in ferrets. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 285, 566–576.
- Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, Stella N, Makriyannis A, Piomelli D, Davison JS, Marnett LJ, Di Marzo V, Pittman QJ, Patel KD, Sharkey KA (2005): Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science* 310, 329–332.
- Velasco G, Sanchez C, Guzman M (2012): Towards the use of cannabinoids as antitumour agents. *Nature Reviews Cancer* 12, 436–444.
- Weiss L, Zeira M, Reich S, Har-Noy M, Mechoulam R, Slavin S, Gallily R (2006): Cannabidiol lowers incidence of diabetes in non-obese diabetic mice. *Autoimmunity* 39, 143–151.
- Weiss L, Zeira M, Reich S, Slavin S, Raz I, Mechoulam R, Gallily R (2008): Cannabidiol arrests onset of autoimmune diabetes in NOD mice. *Neuropharmacology* 54, 244–249.
- Xiong W, Cui T, Cheng K, Yang F, Chen SR, Willenbring D, Guan Y, Pan HL, Ren K, Xu Y, Zhang L (2012): Cannabinoids suppress inflammatory and neuropathic pain by

doi: 10.17221/8762-VETMED

targeting $\alpha 3$ glycine receptors. *Journal of Experimental Medicine* 209, 1121–1134.
Zuardi AW (2006): History of cannabis as a medicine: a review. *The Revista Brasileira de Psiquiatria* 28, 153–157.
Zubrzycki M, Liebold A, Janecka A, Zubrzycka M (2014): A new face of endocannabinoids in pharmacotherapy.

Part I: Protective role of endocannabinoids in hypertension and myocardial infarction. *Journal of Physiology and Pharmacology* 65, 171–181.

Received: 2015–11–13

Accepted after corrections: 2016–02–05

Corresponding Author:

Alexandra Sulcova, CEITEC Masaryk University, Kamenice 5/A19, 625 00 Brno, Czech Republic
E-mail: sulcova@med.muni.cz
