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Pharmacotherapeutic modulation of the endocannabinoid signalling system in psychiatric disorders: Drug-discovery strategies

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Abstract

Medicinal chemistry has produced small-molecule agents with drug-like character that potently and safely modulate the activity of discrete endocannabinoid system components as potential treatments for medical disorders, including various psychiatric conditions. Two cannabinoid (CB) receptors (CB1 and CB2) currently represent prime endocannabinoid-system therapeutic targets for ligands that either mimic endocannabinoid signalling processes and/or potentiate endocannabinoid-system activity (agonists) or attenuate pathologically heightened endocannabinoid-system transmission (antagonists). Two endocannabinoid deactivating enzymes, fatty acid amide hydrolase (FAAH) and soluble monoacylglycerol lipase (MGL), are increasingly prominent targets for inhibitors that indirectly potentiate endocannabinoid-system signalling. Continued profiling of drug candidates in relevant disease models, identification of additional cannabinoid-related therapeutic targets, and validation of new pharmacological modes of endocannabinoid system modulation will undoubtedly invite further translational efforts in the cannabinoid field for treating psychiatric disorders and other medical conditions.

Introduction

Pharmacotherapeutic tuning of endocannabinoid signalling as a means to treat psychiatric disorders is supported by several lines of evidence. Some plant cannabinoids (CBs) (phytocannabinoids) isolated from *Cannabis* sp. exert neurobiological, behavioural, and/or psychological (e.g. anxiolytic, antipsychotic) actions in experimental animals and man (Leweke & Koethe, 2008; Pertwee, 2008). Such biological effects mainly reflect the phytocannabinoid agonist (activating ligand) property at two major CB G protein-coupled receptor (GPCR) subtypes, designated CB1 and CB2 (Woelkart, Salo-Ahen, & Bauer, 2008). Endogenous CB-receptor agonists (endocannabinoids) and synthetic CB-receptor ligands influence diverse neurological, psychological, and behavioural processes in health and disease (Drago, 2007; Janero & Makriyannis, 2007; Moriera & Lutz, 2008). Endocannabinoid signalling is also intrinsically neuroprotective (Karanian et al., 2007).

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This article highlights exemplary natural and synthetic compounds that modulate prime druggable targets within the endocannabinoid system. Emphasis is placed on agents having application to psychiatric, neurobiological, and/or behavioural indications.

Phytocannabinoids

Cannabis contains some 70 unique phytocannabinoids, most prominently the ‘classical cannabinoids’ (–)-9-tetrahydrocannabinol (–9-THC), (–)-8-tetrahydrocannabinol (–8-THC), cannabidiol, and cannabinol (Thakur, Duclos, & Makriyannis, 2005; Woelkart et al., 2008) (Figure 1). The archetypal phytocannabinoid and the main psychotropic constituent of cannabis, –9-THC is a fused-ring tricyclic terpenoid derivative incorporating a polar benzopyran ring with a terminal, hydrophobic alkyl (*n*-pentyl) side-chain, a characteristic lipophilic domain, and hydrogen-bonding substituents (Thakur et al., 2005).

–9-THC can activate the CB1 receptor as a partial agonist, binding to both CB1 and CB2 receptors with low nanomolar affinity (Pertwee, 2008). Among its wide-ranging effects, –9-THC can influence brain function and neuropsychological performance and may induce some behavioural and cognitive changes reminiscent of psychiatric disorders including depression and anxiety (Gonzalez, 2007). The psychotropic effects of cannabis are believed mainly to reflect –9-THC activation of CNS presynaptic CB1 receptors (Pertwee, 2008).

–8- and –9-THC are virtually equivalent as to CB-receptor affinity and pharmacological activity, although –8-THC is the more chemically stable isomer (Charalambous et al., 1991; Thakur et al., 2005).

In contrast to THC, the phytocannabinoids cannabinol and cannabidiol display significantly lower affinity for CB receptors, modest CB2-receptor selectivity, and little or no psychotropic activity (Pertwee, 2008; Woelkart et al., 2008). Aside from its anti-inflammatory effects, cannabidiol is neuro-protective, antipsychotic, and anxiolytic, and preliminary studies show that it reduces schizophrenic symptoms in patients (Mechoulam, Peters, Murillo-Rodriguez, & Hanuš, 2007; Pertwee, 2008).

Over the past 40 years, some two dozen randomized controlled clinical trials (exclusive of studies on recreational cannabis use in humans) have been conducted with medical cannabinoid-based preparations, often containing –9-THC with or without cannabidiol. Although the principal indications addressed were non-psychiatric (e.g. pain, multiple sclerosis), the most frequently reported adverse events in medicinal cannabinoid trials were ‘nervous system’ and/or ‘altered mood’ disorders (Wang, Collet, Shapiro, & Ware, 2008). The few cannabinoid-related marketed pharmaceuticals have a direct relationship to cannabis and, hence, act as non-selective agonists at both CB1 and CB2 receptors to treat nausea and emesis (Di Marzo, Bifulco, & De Petrocellis, 2004). Regarding discrete psychiatric applications, clinical studies have recently been completed to evaluate cannabidiol as an antipsychotic agent (University of Cologne, 2006). A clinical trial is ongoing for a mixture of –9-THC and cannabidiol in bipolar affective disorder (University of British Columbia, 2006). Human trials are planned testing cannabidiol in schizophrenic cognitive dysfunction (Yale University, 2008).

Synthetic CB1/CB2-receptor agonists

In an approach towards structural simplicity and improved agonist activity as compared to Δ^9 -THC, bicyclic 'nonclassical cannabinoids' lacking the hallmark CB dihydropyran ring were first synthesized by Pfizer (Makriyannis & Rapaka, 1990). The most thoroughly studied bicyclic compound, (–)-CP-55,940, shows high affinity and efficacy at both CB1 and CB2 receptors and increased potency with reduced lipophilicity relative to Δ^9 -THC (Herkenham et al., 1990) (Figure 2). Similar to Δ^9 -THC, the C-3 alkyl side-chain and phenolic hydroxyl are pharmacophoric elements crucial to the biological activity of CP-55,940 and related open pyran ring non-classical cannabinoids (Ashton, Wright, McPartland, & Tyndall, 2008). As exemplified by CP-55,940 and HU-210 (Figure 2), a hydroxyl group at the C-9 or C-11 enhances cannabinoid affinity and potency for both CB receptors (Mechoulam et al., 1988).

Although bearing no structural relationship to cannabinoids, the aminoalkylindole WIN-55,212-2 (Figure 2) engages CB receptors (Bell et al., 1991). The aminoalkylindoles are less lipophilic than classical and non-classical CB-receptor ligands (Ashton et al., 2008). The (–) enantiomer of WIN-55,212-2 is a potent CB1 and CB2 agonist with high (nanomolar) CB-receptor affinity and moderate (~5–10-fold) preference for the human CB2 versus CB1 receptor (Ashton et al., 2008; Reggio et al., 1998). The 3-aryl moiety and the 1-chain of WIN-55,212-2 are important for its cannabinergic activity (Xie, Eissenstat, & Makriyannis, 1995).

These synthetic CB1/CB2-receptor agonists have been used experimentally to investigate how CB signalling affects learning/memory and behaviour (Bambico, Katz, Debonnel, & Gobbi, 2007) and substance abuse (Vinod et al., 2008).

Synthetic selective CB2-receptor agonists

The moderate CB2-receptor selectivity of WIN-55,212-2 and the very limited CB2 receptor expression in brain, which would be expected to render CB2-receptor agonists largely devoid of the central psychotropic effects, encouraged the rational design of highly selective CB2-receptor agonists (Malan et al., 2003). This effort first met success with AM1241 (Ibrahim et al., 2003) (Figure 3), a racemic aminoalkylindole with an *N*-methylpiperidiny-2-methyl substituent at the N-1 position and a 2-iodo-5-nitrobenzoyl group as the C-3 indole substituent. AM1241 can be crystallized and exhibits high binding potencies (i.e. low nanomolar K_i values) and selectivities of 110-fold and 34-fold for the human and rat CB2 over the CB1 receptor, respectively (Ibrahim et al., 2003; Malan et al., 2001). Preclinical data show that AM1241 exerts peripheral analgesia and potent full agonist activity *in vivo* (Malan et al., 2001).

As summarized (Marriott and Huffman, 2008), efforts to develop structure-activity relationships in the indole CB2-receptor agonist class have met with limited success. JWH-015 is an indole in which the WIN-55,212-2 morpholine ring has been replaced by a short alkyl tail (Figure 3). JWH-015 exhibits low nanomolar affinity for the CB2 receptor, 3- to 10-fold selectivity at the human CB2 versus CB1 receptor, and ~3-fold greater affinity for

the human versus rat CB2 receptor (Mukherjee et al., 2004). In laboratory animals, JWH-015 exerts anti-inflammatory, immunosuppressive, and analgesic effects without psychotropic liability or tolerance (Lombard, Nagarkatti, & Nagarkatti, 2007; Romero-Sandoval, Natile-McMenemy, & DeLeo, 2008) and shows efficacy in neurodegeneration models (Ehrhart et al., 2005).

Two novel planar ring cannabimimetics, AM1710 and AM1714, have emerged as selective CB2-receptor agonists (Khanolkar et al., 2007) (Figure 3), AM1714 displaying the greater (490-fold) selectivity and subnanomolar CB2-receptor affinity. Pronounced species-dependent affinity and selectivity favouring the rat versus the human cannabinoid CB2 receptor have been observed with AM1710 and AM1714 (Khanolkar et al., 2007; Mukherjee et al., 2004). Devoid of CB1 receptor-mediated side effects, both AM1710 and AM1714 exert peripheral analgesic activity in animal models of neuropathic pain (Khanolkar et al., 2007).

Synthetic selective CB1-receptor agonists

Cyclic variations in the C-3 alkyl side chain of classical cannabinoids led to prototypic compounds with some CB1-receptor selectivity. Of these, the synthetic adamantyl analog AM411 (Figure 4) was the first pharmacologically active classical cannabinoid to be crystallized (Lu et al., 2005). AM411 demonstrates low nanomolar affinity and ~8-fold selectivity as a CB1-receptor agonist without eliciting rapid receptor desensitization (Lu et al., 2005; Luk et al., 2004).

Another approach to CB1 receptor-selective agonists enhanced the marginal selectivity of the endocannabinoid anandamide (AEA). This approach yielded the metabolically more stable chiral AEA analog, AM356 [*R*-(+)-methanandamide] (Figure 4), which is ~50-fold selective for the CB1 versus CB2 receptor with ~4-fold greater CB1-receptor affinity than AEA itself (Abadji et al., 1994; Lin et al., 1998). A cyano analog of AM356 (O-1812), along with the readily hydrolyzable arachidonoyl-2'-chloroethylamide (ACEA) and arachidonoylcyclopropylamide (ACPA) and the putative endocannabinoid 2-arachidonoylglycerol ether (noladin ether) (Figure 4), are other AEA analogs with reasonably high (~40- to 1500-fold) CB1-receptor agonist selectivities relative to the CB2 receptor and low nM CB1-receptor affinities. In general, these CB1-receptor agonists exert cannabimimetic effects *in vivo* (Di Marzo et al., 2001; Hanuš et al., 2001; Hillard et al., 1999).

Synthetic selective CB1-receptor antagonists/inverse agonists and neutral antagonists

CB1-receptor antagonists have the potential to treat a number of persistent global healthcare problems (e.g. substance abuse disorders, overweight/obesity, metabolic syndrome) often accompanied by co-morbid psychological conditions (Jagerovic, Fernandez-Fernandez, & Goya, 2008; Janero & Makriyannis, 2007; Lange & Kruse, 2008; Vemuri, Janero, & Makriyannis, 2008). Among the first selective CB1-receptor antagonists, the diarylpyrazole analogue rimonabant (SR141716A) (Figure 5) engages the CB1 receptor with low

nanomolar affinity and ~150-fold selectivity versus the CB2 receptor (Rinaldi-Carmona et al., 1994). The C-3 piperidinylamide group, the N-1 dichlorophenyl substituent, and the C-5 phenyl ring contribute to rimonabant's high CB1-receptor affinity and selectivity (Jagerovic et al., 2008). Rimonabant's suppression of appetite leading to weight loss in adult, non-obese rats (Colombo et al., 1998) incited an intense search for other novel CB1-receptor antagonists and set rimonabant itself on the path to eventual approval outside the USA as a weight control drug. However, rimonabant has been withdrawn from some major markets due to prominent side effects including nausea and psychiatric/mood disorders, and all rimonabant clinical studies have been halted (Rumsfeld & Nallamothu, 2008; Sanofi-Aventis, 2008a, 2008b). No data have yet appeared in the referenced clinical literature as to the safety or efficacy of most other CB1-receptor antagonists (i.e. surinabant, ibipinabant, AVE1625, otenabant, rosonabant). Adverse psychological effects similar to rimonabant's have been associated with the CB1-receptor antagonist taranabant, whose development programme has been discontinued (Fulmer, 2008; Merck, 2008). A similar corporate decision was rendered for otenabant (Pfizer, 2008).

Replacement of rimonabant's 4-chloro group with a 4-iodo substituent generated AM251 (Figure 5), which exhibits improved (low nanomolar) CB1-receptor affinity and selectivity (~300-fold) with respect to the CB2 receptor (Gatley et al., 1997). A related CB1-receptor antagonist, AM281 (Figure 5), was derived by substituting the *N*-(piperidin-1-yl) moiety of rimonabant with an *N*-(morpholin-4-yl) group. AM281 has low nano-molar affinity for the CB1-receptor comparable to that of AM251, but with greater CB1-receptor (~350-fold) selectivity, oral bioavailability, and brain penetration (Gatley et al., 1998).

Rimonabant, AM251, and AM281 have served as tool compounds for investigations that have enhanced our appreciation of overactive CB1-receptor transmission in the etiology of disorders (overweight/obesity, drug addiction, substance abuse) having a reward-supported appetitive component (Muccioli, 2007).

Traditional pharmacology functionally classifies receptor ligands as either agonists, which activate receptors, or neutral antagonists, which block agonist receptor activation but do not elicit a biological response themselves. Accumulating evidence indicates that GPCRs, including the CB1 receptor, display agonist-independent constitutive activity (Canals & Milligan, 2008). In certain test systems *in vitro*, many ligands previously classified as neutral antagonists demonstrate 'negative efficacy' on constitutive GPCR activity – i.e. an 'inverse agonist' property. Biochemical profiling of rimonabant and most other CB1-receptor antagonists indicates that they act as antagonists/inverse agonists, not as truly neutral antagonists, and as such may affect constitutive endocannabinoid signalling in the absence of CB1-receptor stimulation, promoting signal transduction responses opposing those of agonists (Hodge et al., 2008; Hurst et al., 2002). Translational interest rests with the proposition that at least some untoward side effects of CB1-receptor antagonists/inverse agonists noted in clinical trials (e.g. nausea, adverse psychological responses) may reflect their functional suppression of basal CB1-receptor signalling (i.e. their inverse-agonist property) (Bergman et al., 2008). AM4113, a pyrazole analogue related to rimonabant (structure undisclosed), has emerged as the first well-characterized CB1-receptor neutral antagonist and has shown impressive preclinical effects in suppressing food intake and food-

reinforced behaviour without inducing signs of nausea or emesis (Salamone, McLaughlin, Sink, Makriyannis, & Parker, 2007; Sink et al., 2008). If CB1-receptor neutral antagonists were to suppress food intake without producing nausea and undesirable psychological side effects in humans, they would offer concrete therapeutic advantage over CB1-receptor antagonists/inverse agonists such as rimonabant and taranabant.

Restricting blood-brain barrier penetration of CB1-receptor antagonists so as to favour their peripheral action might improve their safety by reducing the opportunity for adverse, centrally mediated side effects (Kunos, Osei-Hyiaman, Bătăki, Sharkey, & Makriyannis, 2008). This approach appears from initial laboratory data potentially attractive for treating metabolic syndrome, insulin resistance/glucose intolerance, and steatosis (Osei-Hyiaman et al., 2008).

Synthetic selective CB2-receptor antagonists/inverse agonists

The best known selective CB2-receptor antagonist/inverse agonist, SR144528, was developed by Sanofi around a pyrazole moiety and displays ~700-fold selectivity and sub-nanomolar affinity for the CB2 versus CB1 receptor (Bouaboula, Dussosoy, & Casellas, 1999; Rinaldi-Carmona et al., 1998) (Figure 6). The CB2-receptor selectivity of SR144528 is partly conferred by its 4-methylbenzyl group (Rinaldi-Carmona et al., 1998). Another high-profile CB2-receptor antagonist/inverse agonist, AM630, contains a 6-iodoindole moiety and exhibits a 170-fold CB2- versus CB1-receptor selectivity (Pertwee et al., 1995) (Figure 6). Preclinical data suggest the potential therapeutic utility of CB2-receptor antagonists in inflammatory and allergic syndromes (Ashton & Glass, 2007).

Endocannabinoids

AEA and 2-arachidonoyl glycerol (2-AG) are the most extensively studied endocannabinoids (Figure 7). AEA is a partial CB1-receptor agonist with modest affinity (K_i = 61 nM (rat) and 240 nM (human)) and a relatively weak CB2-receptor ligand (K_i = 440–1930 nM for rodent and human CB2 receptors) with low overall efficacy (Lin et al., 1998; McPartland, Glass, & Pertwee, 2007). Produced in much greater amounts than AEA, 2-AG is a full agonist that binds to both CB1 and CB2 receptors with lower affinity (K_i = 472 and 1400 nM, respectively), but with greater efficacy, relative to AEA (Mechoulam et al., 1995; Thakur et al., 2005). Common structural features of both the phytocannabinoid Δ^9 -THC and the endocannabinoids AEA and 2-AG, including a polar head group and a hydrophobic chain with a terminal *n*-pentyl moiety, allow both classes of compounds to share similar CB1-receptor binding motifs (Thakur et al., 2005). Among their myriad roles, AEA and 2-AG participate in neuromodulation as retrograde synaptic messengers and immune-cell function (Di Marzo & Petrosino, 2007).

First identified decades ago (Bachur, Masek, Melmon, & Udenfriend, 1965), *N*-palmitoylethanolamide (PEA) (Figure 7) is a saturated *N*-acylamide AEA congener more abundant than AEA in most tissues that shares some actions with Δ^9 -THC (Mackie & Stella, 2006). PEA synthesis and inactivation involve metabolic routes distinct from those of 2-AG and AEA (Tsuboi et al., 2005). At physiologically relevant concentrations, PEA does not bind to rat or human CB1 and CB2 receptors (Lambert et al., 1999), whereas it activates

the GPR55 receptor in the nanomolar range (Pertwee, 2007). Nonetheless, PEA exhibits many pharmacological properties reminiscent of a CB2-receptor agonist (Lambert & Di Marzo, 1999). Synthesized in cells during tissue damage and inflammation, PEA exerts tissue-protective anti-inflammatory actions and relieves neurogenic and neuropathic pain (Lambert, Vandevoorde, Jonsson, & Fowler, 2002; Re, Barbero, Miolo, & Di Marzo, 2007). Although its mode of action is as yet undefined, PEA has been cited as the subject of clinical trials for the treatment of chronic lumbrosiatalgia and multiple sclerosis (Lambert et al., 2002). PEA may also find therapeutic use in stroke and chronic inflammatory central nervous system disorders such as Alzheimer's, Huntington's, and Parkinson's diseases (Carbonare et al., 2008; Schomacher, Müller, Sommer, Schwab, & Schäbitz, 2008).

Fatty acid amide hydrolase (FAAH) inhibitors

Given AEA's greater affinity for the CB1 versus CB2 receptor and the role of FAAH in catalytic AEA inactivation (Ahn, McKinney, & Cravatt, 2008), a FAAH inhibitor should potentiate signalling through the CB1 receptor. A major attraction of such an indirect approach for enhancing endocannabinoid activity rests with its potential to offer 'site- and event-specific' therapeutic relief in those tissues where endocannabinoids are being released as part of a physiological protective mechanism. In contrast, direct agonist activation of all accessible CB receptors indiscriminately may invite unwanted CB receptor-mediated psychotropic effects (Gonzalez, 2007; Moriera & Lutz, 2008; Pertwee, 2008).

Palmitylsulfonyl fluoride (AM374) inhibits FAAH irreversibly at low nanomolar concentrations (Figure 8). However, AM374 also acts on the CB1 receptor at micromolar concentrations as well as *E. coli* outer-membrane phospholipase A (Deutsch et al., 1997). AM374 effectively potentiates anandamide concentrations and signalling *in vitro* and *in vivo*, thereby providing neuroprotection and functional protection against excitotoxic brain injury in rats (Gifford et al., 1999; Karanian et al., 2007) and reducing hyperkinesia in a model of Huntington's disease (Lastres-Becker et al., 2003).

The carbamate ester URB597 (Figure 8) inhibits FAAH at low nanomolar concentrations (Fegley et al., 2005) as well as multiple mouse and human serine hydrolases (Ahn et al., 2008). URB597 potency for FAAH is modulated by the shape of its rigid aromatic biphenyl moiety. Carbamates such as URB597 irreversibly inactivate FAAH through carbamylation of the enzyme's active-site serine 241 residue (Alexander & Cravatt, 2005). URB597 effectively enhances endogenous brain levels of AEA (and congeners) and elicits anxiolytic, analgesic, and antinociceptive effects without inducing cardinal cannabimimetic responses (e.g., catalepsy, hypothermia, hypomotility, hyperphagia) characteristic of CB1-receptor agonists (Jayamanne et al., 2006). FAAH inhibition may thus represent an innovative approach to managing pain and mood disorders/depression. URB597 is devoid of reinforcing effects in primates, which distinguishes it from direct-acting CB agonists such as -9-THC and suggests that FAAH inhibitors might be used therapeutically without abuse liability or triggering a drug relapse in patients with a substance abuse disorder (Gaetani, Cuomo, & Piomelli, 2003). Phase-I clinical testing of URB597 has been noted (Labar & Michaux, 2007).

The heterocyclic urea compound LY2183240 (Figure 8) targets covalently mouse-brain FAAH ($IC_{50} \sim 13$ nM) and other brain serine hydrolases (Alexander & Cravatt, 2006). Analogous to the mechanism of action of URB597, LY2183240 inactivates FAAH by carbamylating a critical serine (Alexander & Cravatt, 2005). In laboratory animals, LY2183240 increases brain AEA concentrations and exerts analgesic and antinociceptive effects (Dickason-Chesterfield et al., 2006).

Monoacylglycerol lipase (MGL) inhibitors

N-Arachidonoylmaleimide (NAM) was modelled after the 2-AG substrate MGL to target MGL sulfhydryl group(s) at (or near) the enzyme's catalytic site (Saario et al., 2005) (Figure 8). NAM inhibits rat-membrane MGL with an IC_{50} of 0.14 μ M, as compared to an IC_{50} of 3.3 μ M for FAAH inhibition. NAM inhibits human MGL by alkylating cysteine residues 215 and/or 249, cysteine 249 being of paramount importance for catalysis (Zvonok et al., 2008).

LY2183240 (as a mixture of its two isomers) (Figure 8) inhibits recombinant mouse MGL in a time-dependent manner ($IC_{50} \sim 5.3$ nM) some-what more potently than it inhibits FAAH ($IC_{50} \sim 13$ nM) (Alexander & Cravatt, 2006) (*vide supra*). The 2,5-isomer (AM6701) is a more potent inhibitor of human recombinant MGL than the 1,5-isomer (AM6702) ($IC_{50} = 0.9$ versus 9.1 nM, respectively) (Zvonok et al., 2008). MGL inhibition by AM6701 involves a covalent interaction resulting in serine carbamylation in the MGL catalytic triad (Zvonok et al., 2008). *In vivo*, LY2183240 exerts antinociceptive effects (Maione et al., 2008).

Inhibitors of endocannabinoid transport

As the first novel inhibitor of endocannabinoid transport into cells, AM404 (Figure 8) inhibits cellular AEA uptake at low micromolar concentrations and increases AEA concentrations in plasma and, in some cases, select brain areas when administered to experimental animals (Bortolato et al., 2006; Giuffrida, Rodriguez de Fonseca, Nava, Loubet-Lescoulié, Piomelli, 2000). AM404 may also inhibit FAAH, bind to CB1 receptors, and interact weakly with other targets (Pertwee 2005; Rawls, Ding, & Cowan, 2006). Structural analogues of AM404 show marginal, if any, improvement in selectivity or potency (Pertwee, 2005). AM404 potentiates and prolongs many of the physiological and behavioural effects of AEA (Solinas et al., 2007) and has anxiolytic properties in rodents (Bortolato et al., 2006). Since a discrete endocannabinoid transport protein has not been isolated or expressed, the molecular mechanism underlying these effects should be approached cautiously (Fowler et al., 2004). Paracetamol (acetaminophen) may exert its analgesic (and, perhaps, anti-pyretic) effects *in vivo* by its FAAH-dependent conversion to AM404 in the nervous system (Anderson, 2008).

Discussion

- Translational mining of the endocannabinoid system is mandated by the increasing number of medical conditions considered amenable to treatment through pharmacotherapeutic modulation of endocannabinoid signalling.

- In preclinical models, modulators of the endocannabinoid system exert therapeutically relevant effects on biological and behavioural endpoints related to neurobiological/psychiatric function.
- Novel pharmacological modalities will be increasingly applied to the endocannabinoid system for potential therapeutic benefit with improved safety: e.g. neutral (Bergman et al., 2008), peripherally directed (Kunos et al., 2008), and allosteric (Ross, 2007) CB1-receptor ligands.
- Emerging targets, e.g. diacylglycerol lipase (Ortar et al., 2008), and metabolites, e.g. endocannabinoid-derived oxidation products including prostaglandin ethanolamides (Khanapure, Garvey, Janero, & Letts, 2007; Kozak & Marnett, 2002), will be studied for potential therapeutic relevance.

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Figure 1.
Structures of the principal phytocannabinoids.

Figure 3.
Structures of synthetic selective CB2-receptor agonists.

Figure 4.
Structures of synthetic selective CB1-receptor agonists.

Figure 5.
Structures of synthetic selective CB1-receptor antagonists/inverse agonists.

Figure 6.
Structures of synthetic selective CB2-receptor antagonists/inverse agonists.

Figure 7.
Structures of the principal endocannabinoids.

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