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10

Central side-effects of therapies based on CB_1 cannabinoid receptor agonists and antagonists: focus on anxiety and depression

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Both agonists (e.g. Δ^9-tetrahydrocannabinol, nabilone) and antagonists (e.g. rimonabant, taranabant) of the cannabinoid type-1 (CB_1) receptor have been explored as therapeutic agents in diverse fields of medicine such as pain management and obesity with associated metabolic dysregulation, respectively. CB_1 receptors are widely distributed in the central nervous system and are involved in the modulation of emotion, stress and habituation responses, behaviours that are thought to be dysregulated in human psychiatric disorders. Accordingly, CB_1 receptor activation may, in some cases, precipitate episodes of psychosis and panic, while its inhibition may lead to behaviours reminiscent of depression and anxiety-related disorders. The present review discusses these side-effects, which have to be taken into account in the therapeutic exploitation of the endocannabinoid system.

Cannabis and the endocannabinoid system

The herb *Cannabis sativa* (marijuana) has been used for centuries against maladies as diverse as pain, nausea or seizures. Its mechanisms of action have only partly been elucidated.[1–3] In 1964, Δ^9-tetrahydrocannabinol (Δ^9-THC) was characterized as the main active constituent of cannabis. Twenty-five years later, a specific receptor for Δ^9-THC – termed cannabinoid type 1 (CB_1) receptor – was identified in the brain, enabling the identification of the endogenous ligands in mammals, called endocannabinoids: anandamide and 2-arachidonoyl glycerol (2-AG).[3] Several new therapeutic applications have emerged based on the discovery of this novel signalling system.[4] However, possible

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side-effects of cannabinoid-based therapies in humans have also become apparent, some of which have not appeared unexpectedly, as numerous investigations evidenced a role for endocannabinoids in anxiety- and depression-related behaviours in rodents. This review aims at exposing the main side-effects of CB_1 receptor-based therapies, focusing on anxiety and depression. The potential mechanisms will be discussed on the basis of the functional characteristics of the endocannabinoid system.

CB_1 receptors are widely distributed in the central nervous system, located mainly in presynaptic terminals of neurons.[5] They are expressed in comparatively low densities in brain structures responsible for the control of respiratory and cardiovascular functions, which might explain why cannabinoids do not significantly suppress these vital physiological functions. Brain regions with high CB_1 receptor expression include the hippocampus, amygdala, prefrontal cortex, hypothalamus and basal ganglia.[5] The presence of CB_1 receptors in these structures explains why cannabis induces effects such as motor impairment, amnesia, and changes in mood and anxiety.

Endocannabinoids are synthesized 'on demand' at post-synaptic sites of neurons after increase in neural activity and calcium ion influx, and are then released into the synaptic cleft. Their main function appears to be the suppression of neurotransmitter release from the presynapse.[3] Thus, endocannabinoids act as retrograde neurotransmitters, modulating other neurotransmitter systems. To terminate the signal at the synapse, endocannabinoids are taken up by the cell, followed by hydrolysis with the enzymes fatty acid amide hydrolase (FAAH) and monoacyl glycerol lipase (MAGL), inactivating anandamide and 2-AG, respectively.[6]

There is ample anatomical, neurochemical and functional evidence that CB_1 receptor activation restrains neuronal activity by inhibiting the release of neurotransmitters relevant for anxiety and depression, such as glutamate and γ-aminobutyric acid (GABA).[7] This chapter will discuss possible mechanisms by which CB_1 receptors may interfere with emotional states, and would like to set the basis for discussing the clinical side-effects of compounds that modulate the activity of CB_1 receptors.

Possible roles for the endocannabinoid system in the modulation of mood and anxiety

Cannabis use may induce significant changes in mood and anxiety. It is often reported to elicit a rewarding feeling described as a 'high', as well as a state of relaxation and increased sociability.[8] This is in accordance with the presence of CB_1 receptors in brain regions implicated in the modulation of emotional responses related to mood and anxiety, such as prefrontal cortex, amygdala, periaqueductal grey and hippocampus. Neuroimaging studies have revealed that these structures are indeed active in individuals who smoked cannabis.[9] This notion is further supported by experiments detecting molecular correlates of neural activity (e.g. c-fos expression) in cannabinoid-treated laboratory animals.[10] In addition, techniques of intracranial injections of cannabinoids in rats revealed that activation of CB_1 receptors specifically in some of the structures mentioned above is involved in inducing anxiolytic- or antidepressant-like effects.[11–14]

However, besides its rewarding effects, cannabis may also induce aversive states in some smokers, precipitating anxiety and panic attacks.[8] Furthermore, Δ^9-THC administration may result in psychotic-like states.[15] These bidirectional effects of cannabinoids observed in humans can be mimicked in laboratory animals. Generally, in models predictive of anxiolytic-like activity, low doses of CB_1 agonists tend to be anxiolytic and high doses tend to increase aversion and anxiety-related behaviours.[16]

These data about the application of exogenous cannabinoids in humans or experimental animals are in agreement with what we know about the function of endocannabinoids in a model of aversive learning. Endocannabinoids are released in the amygdala when an animal encounters conditioned fear stimuli, such as a tone previously paired with a foot-shock. Thus, CB_1 receptor activation at this site promotes fear extinction.[17] This study also showed that CB_1 receptor blockade impairs fear extinction, indicating a potential side-effect of CB_1 receptor antagonists. In fact, other investigations have also revealed that CB_1 receptor antagonists increase anxiety-related behaviours in the elevated plus maze[18] and that genetic deficiency in CB_1 receptor leads to impair stress coping behaviour in the forced swim test.[19]

Thus, stimulation of CB_1 receptor or blockade of endocannabinoid uptake or degradation may attenuate while blockade of CB_1 receptor may increase anxiety-related behaviours. On the other hand, higher levels of stimulation of the system can increase anxiety. Endocannabinoid signalling was

proposed to protect against the consequences of stress in a certain dose range. However, above certain limits, enhancing CB_1 receptor signalling may actually be aversive rather that rewarding.[20]

This apparently contradictory feature might origin from several interesting attributes of the endocannabinoid system. First of all, as mentioned above, CB_1 receptor is expressed in diverse brain structures relevant for psychiatric disorders.[5,21] In these structures, CB_1 receptor is mainly located presynaptically where it can suppress the release of other neurotransmitters.[7] The nature of neurons expressing CB_1 receptors is diverse. Studies were able to detect it in terminals that release the main inhibitory neurotransmitter GABA, the main excitatory neurotransmitter glutamate, as well as acetylcholine, noradrenaline or serotonin.[22–26] Interestingly, CB_1 receptors have a very high expression level in GABAergic interneurons, while only a low to moderate expression level in glutamatergic neurons.

Another important characteristic of the endocannabinoid system is its on-demand activity: i.e., neuronal activity triggers the synthesis and release of endocannabinoids into the synaptic cleft. Consequently, in a physiological situation, endocannabinoid synthesis, and thus CB_1 receptor activation, will occur in particular activated neuronal circuits. This is a notable difference as compared to pharmacological treatments with receptor agonists, when the agent will activate all CB_1 receptors in the brain regardless of their specific involvement in a particular physiological process. The diversity of endocannabinoid ligands with their multiple synthetic and degradation pathways adds a further level of complexity to the endocannabinoid system.[6] Currently, our knowledge is relatively limited as to exactly how the different endocannabinoids are implicated in various (patho)physiological processes, as most members of the enzymatic machinery have been identified only recently. Most probably, however, substances targeting these enzymes will soon become available in increasing numbers, making it possible to provide more sophisticated modulations of the activity of the endocannabinoid system.

Side-effects of CB_1 receptor agonists and antagonists: anxiety and depression

CB_1 receptor agonists

Studies in laboratory animals

Cannabis extracts have been used therapeutically for alleviating pain for centuries, and a large amount of data in diverse animal models has confirmed their analgesic properties, which are achieved by both peripheral and central mechanisms.[27–29] Cannabinoids are also effective in models of nausea and vomiting[30,31] and in the stimulation of appetite and food intake.[32] As it will be discussed below, cannabinoids are already in clinical use for these purposes, and thus it is important to consider side-effect profiles.

When applied to laboratory rodents, cannabinoids induce a myriad of effects which can be measured, at least in part, by specific behavioural tests. Particularly useful for the characterization of the activity of cannabinoids is the so-called tetrad assay, which is based on the properties of these compounds to induce hypolocomotion, catalepsy, hypothermia and analgesia, typically at a Δ^9-THC concentration of 3–10 mg/kg body weight in rodents.[33,34]

CB_1 receptor agonists at low doses are able to induce anxiolytic- and antidepressant-like effects. In animal models of anxiety, Δ^9-THC and synthetic cannabinoids reduce aversive responses similarly to the clinically used anxiolytic drug diazepam.[18,35] CB_1 receptor agonists have antidepressant-like properties too[11,36], and they are able to promote the proliferation of neural precursors in the adult hippocampus[37], a process which appears to be important for responsiveness to antidepressants.

However, at high doses, these compounds may induce opposite effects, producing aversive states. Thus, some authors have reported an anxiogenic-like effect of Δ^9-THC or its synthetic analogues.[18,38] In addition, other researchers have found that cannabinoids may induce conditioned aversion, when rodents are placed in an environment previously associated with this drug treatment.[39]

Two recent studies were able to give new insights into the commonly observed biphasic effects of cannabinoids, where a low dose is anxiolytic and a high dose is anxiogenic.[14,40] The metabolically stable anandamide derivative, methanandamide, was applied by stereotactic injections into the prefrontal cortex, and rats were analysed in anxiety tests. Low doses induced anxiolytic effects, while high doses induced anxiogenic effects. Blocking experiments revealed that the anxiolytic effects are CB_1 receptor-mediated, while the anxiogenic effects were mediated by TRPV1 (transient receptor

potential vanilloid type 1 channel).[14] Another study applied the dual FAAH/VRPV1 blocker *N*-arachidonoyl-serotonin (AA-5-HT) systemically at a low dose in rats and also observed anxiolytic effects.[40] These effects were blocked by application of the CB_1 receptor antagonist AM251 and the TRPV1 agonist olvanil. Altogether, these studies indicate that CB_1 receptor activation by anandamide promote anxiolytic-like behaviours, while TRPV1 activation by anandamide leads to anxiety-like states. This notion is consistent with the analysis of knock-out mice with deficiencies in CB_1 receptor[41,42] and TRPV1[43], respectively. However, as Δ^9-THC does not bind to TRPV1, the mechanisms underlying the biphasic effects of Δ^9-THC still remain to be unravelled. In particular, these biphasic effects might be explained by the feature that CB_1 receptors are expressed at low levels on glutamatergic neurons, while on GABAergic interneurons CB_1 receptors are expressed at high levels. However, further investigations will be needed to substantiate such a hypothesis.

The anandamide-hydrolysing enzyme FAAH has emerged as a potentially interesting pharmacological target for the treatment of anxiety. Inhibitors of this enzyme (e.g. URB597) can induce anxiolytic-like effects, as shown by different studies.[18,44,45] URB597 has also antidepressant-like properties and prevents the behavioural consequences of stressful stimuli.[46,47] Contrary to direct CB_1 receptor agonists, in these studies FAAH inhibitors do not evoke effects in a biphasic manner. However, in a recent investigation, URB597 was injected specifically into the prefrontal cortex. A low URB597 dose induced anxiolytic effects, while a high URB597 dose had no effect or even provoked a tendency towards anxiety.[14] Nevertheless, the dose finding for systemically applied URB597 appears to be easier than for 'classical' cannabinoids, where biphasic effects are most commonly observed.[16] FAAH inhibitor treatment may also circumvent other problems associated with CB_1 receptor agonists, the effects of which may depend on the emotional states of the organisms in such a way that even low doses may interact with stressful stimuli and increase anxiety.[48] Remarkably, other phytocannabinoids, such as cannabidiol (CBD), while not CB_1 receptor agonists themselves, also induce anxiolytic-like effects and prevent the aversive responses induced by CB_1 receptor activation.[38,49,50] The underlying mechanisms of the CBD effects, however, remain to be further elucidated, but CBD appears to contain antagonistic activity on agonist-activated CB_1 receptors, or is an enhancer of adenosine signalling.[51]

Although animal models have provided important insights into the pharmacology of cannabinoids and the endocannabinoid system, several limitations are worth discussing. First, one has always to consider to what extent the dose administered to animals can be extrapolated to humans. Second, the route of administration and pharmacokinetics may be important factors hindering the drawing of conclusions from animal experiments. Finally, although many experiments investigate the effects of a single cannabinoid compound, cannabis extracts contain a complex mixture of numerous different and related compounds. Therefore, Δ^9-THC and cannabis administration might lead to subtle differences in effects.

Observations in humans

The popularity of cannabis as a medicine has fluctuated quite a lot over time, but the identification of Δ^9-THC and later the discovery of cannabinoid receptors greatly strengthened the interest in possible therapeutic applications of cannabinoids.[2,4,52,53] They have been used mainly for the symptomatic treatment of multiple sclerosis and neuropathic pain, and as an anti-emetic and appetite stimulant.

Δ^9-THC (dronabinol) and nabilone, a synthetic derivative of Δ^9-THC, are used clinically for chemotherapy- and cancer-related nausea and vomiting, and for the stimulation of appetite in AIDS patients. Although not first-choice medications, generally cannabinoids are well tolerated after oral administration.[54] Some aversive effects that may result from cannabis smoking, such as anxiety and panic,[8,52,53,55] are rarely observed after oral administration of Δ^9-THC and nabilone.[56–58] Actually, orally administered nabilone may even alleviate pain-associated anxiety in patients suffering from fibromyalgia.[58]

The different routes of administration are important parameters leading to some diversity of the effects induced by cannabinoids. For instance, oral Δ^9-THC can have a profile characteristic of an anxiolytic compound[59], supporting data from animal models. Functional magnetic resonance imaging (fMRI) revealed that Δ^9-THC reduces amygdala reactivity in healthy volunteers exposed to social signals of threat[59], an effect similar to anxiolytic drugs such as benzodiazepines. Thus, this study provides direct evidence, in humans, of the potential anxiolytic properties of orally administered Δ^9-THC. On the other hand, intravenous administration in healthy individuals was reported to induce

psychotic-like reactions and anxiety.[15] Accordingly, a comparative study revealed that oral Δ^9-THC induces less negative mood states than smoked marijuana.[60] The oral pathway may avoid the high peak serum concentration that occurs after cannabis smoking[61], possibly helping to avoid aversive emotions which may result from high levels of CB_1 receptor activation.

In addition to the route of administration, cannabis may differ from pure Δ^9-THC due to the presence of other components in the plant. The substance mostly investigated is CBD. Whereas the latter may induce psychotropic effects, CBD has properties similar to antipsychotic and anxiolytic drugs and may thereby prevent the aversive effects of Δ^9-THC.[62] Unfortunately, the precise mechanisms for the anxiolytic and antipsychotic action of CBD have remained poorly defined. Contrary to Δ^9-THC, it does not activate CB_1 receptors, rather it may act as a CB_1 receptor antagonist.[51] In any case, therapies based on the combination of Δ^9-THC and CBD have been developed to relieve spasticity and pain in patients suffering from multiple sclerosis. Both compounds may contribute to the analgesic effects of the mixture, while CBD might mask possible aversive and anxiogenic effects of Δ^9-THC.[62] The first large multicenter randomized placebo-controlled trial of cannabinoid therapy in multiple sclerosis comparing oral Δ^9-THC and cannabis extract (containing mainly Δ^9-THC and CBD) showed no significant improvement on spasticity, although there were benefits in secondary outcome measures. There was a reduction in the subjective perception of symptoms such as pain and spasticity.[63] No major or unexpected adverse events were observed. Some patients had an increase in appetite, dizziness and dry mouth, but no side-effects related to anxiety and depression were reported.[63]

An oromucosal spray containing a combination of Δ^9-THC and CBD in the ratio 1:1 (Sativex®; GW Pharmaceuticals) was shown to be effective against neuropathic pain with no significant psychiatric side-effects.[64] Nurmikko et al[65] conducted a randomized, double-blinded, placebo-controlled clinical trial for the treatment of neuropathic pain and did not find significant changes in anxiety- or depression-related measures. Another study aimed at investigating the effects on spasticity caused by multiple sclerosis further supported the good tolerability of Sativex.[66] Finally, a clinical trial evaluated the efficacy and safety of Sativex, with favourable therapeutic outcomes, and also checked the effects of sudden interruption, concluding that no withdrawal syndrome occurred.[67] Nevertheless, more studies are needed to address this issue, since withdrawal symptoms of cannabis smoking are reported to occur[68], but withdrawal symptoms are not necessarily included as a criteria for cannabis dependence.[69,70]

Generally, all these clinical studies report mild side-effects related to anxiety and depression. Thus, in contrast to cannabis smoking, which can induce anxiety and panic attacks in some subjects[8], oral or oromucosal cannabinoids apparently do not tend to induce significant psychiatric side-effects. Nonetheless, other alternatives should be considered and further explored. CB_1 receptor agonists can induce a bell-shaped dose–response curve in measures of anxiety and, in this regard, drugs that enhance the levels of endocannabinoids could be an alternative. Inhibitors of the anandamide-hydrolysing enzyme FAAH and the 2-AG degrading enzyme monoacyl glycerol lipase (MAGL) may increase CB_1 receptor signalling on demand, avoiding the aversive effects that result from massive activation of CB_1 receptors.[20] As discussed above, endocannabinoid degradation inhibitors have anxiolytic- and antidepressant-like properties without the problematic sedative and addictive potential of CB_1 receptor agonists at low and intermediate doses. They may also have an anti-emetic activity[31] and should be further investigated in other models of diseases, comparing the effects with those evoked by CB_1 receptor agonists.

CB_1 receptor inverse agonists/antagonists

Studies in laboratory animals

CB_1 receptor inverse agonists/antagonists have been investigated for the last 15 years in an effort to elucidate the physiological and pathophysiologial roles of the endocannabinoid system. These compounds, however, have also emerged as potential drugs in the treatment of obesity and associated metabolic dysregulation, including impaired insulin sensitivity and dyslipidaemia.[32,71] In addition, there is evidence that CB_1 receptor antagonism might also be a valuable strategy for treating substance-abuse disorders, such as tobacco smoking.[72] Rimonabant (also called SR141716; originally developed by Sanofi-Synthélabo, now Sanofi-Aventis) is the pioneering compound and has been most extensively investigated. AM251 is another antagonist widely employed in laboratory studies. Both compounds are

proposed to have inverse agonist properties, as evaluated by in-vitro pharmacological experiments.[73] However, how these properties relate to the pharmacological effects of these compounds in vivo remains to be understood in detail. Therefore, for simplicity these compounds will be described hereafter as 'antagonists'.

As discussed above, several lines of evidence indicate that low doses of CB_1 receptor agonists or FAAH inhibitors induce anxiolytic- and antidepressant-like effects.[11,18,36,44,45] In accordance with these results, studies with CB_1 receptor antagonists have uncovered a possible tonic role for the endocannabinoid system in the modulation of aversive-type reactions. Impairment of endocannabinoid signalling may induce behavioural changes that resemble signs and symptoms of psychiatric disorders. Animals acutely treated with the CB_1 antagonist rimonabant and AM251, or mice with genetic deletion of the CB_1 receptor, have an increase in aversive behaviours relevant to generalized anxiety disorder in several animal models.[18,41,42,74,75] In addition, both pharmacological antagonism and genetic inactivation of CB_1 receptors impair extinction of conditioned fear memories.[17] Recent interpretations of these effects propose that the endocannabinoid system is involved in the habituation to homotypic stress.[76,77] This is a potential mechanism protective against the later consequences of aversive encounters, whose impairment could be relevant for the development of post-traumatic stress disorder and depression.

In line with the evidence that endocannabinoids tonically inhibit stress reactions, mice lacking CB_1 receptor have an increased basal activity of the hypothalamic–pituitary–adrenocortical (HPA) axis.[19,78] Acute injections of rimonabant or AM251 also increase both basal and stress-induced serum corticosterone levels.[19,79] Furthermore, mice lacking CB_1 receptors are impaired in actively coping with stress in a model predictive for antidepressant-like activity.[19] Depressive disorders are also proposed to emerge from an impaired habituation to chronic stress. In this line, CB_1 receptor blockade impairs habituation in rodents exposed to restraint stress.[80] Finally, CB_1 receptor deletion promotes changes in hippocampal processes that are believed to be involved in depression. CB_1 receptor knock-out mice have impaired proliferation of adult neural progenitor cells[37,81] and brain-derived neurotrophic factor (BDNF) expression in this brain region.[82] Indeed, Hill and Gorzalka[83] pointed out several similarities between behavioural changes in CB_1 receptor knock-out mice and symptoms of melancholic depression, such as anhedonia, reduced eating, weight loss, heightened anxiety, increased HPA axis activity and hippocampal atrophy.

Interestingly, however, using the behavioural paradigms of forced swim and tail suspension tests and neurochemical experiments, it was also reported that chronic, subchronic and acute CB_1 receptor antagonist treatments in rodents are able to induce behaviours and neurotransmitter changes that are predictive for the action of antidepressants[84–87], suggesting that despite unfavourable neuroendocrine effects on corticosterone release, CB_1 receptor antagonism may have some antidepressant-like potential.[88] However, the mechanisms underlying these apparent antidepressant-like effects remain to be explored in more detail at the mechanistic level: for example, it is not known which neurotransmitter systems are involved in these effects. It cannot be excluded that these effects induced by CB_1 receptor antagonisms may have to be considered as a 'false-positive' signal in these commonly used behavioural assays testing the activity of potential antidepressant-like compounds.

In summary, there are several pieces of evidence that CB_1 receptor antagonism can increase aversive responses in animal models of psychiatric disorders, such as anxiety and depression.[16,20,83] It has been hypothesized that CB_1 receptor antagonism may interfere with the set point in which the endocannabinoid system keeps rewarding and aversive emotions equilibrated, by shifting it toward aversion.[20] Thus, preclinical studies indicate possible side-effects which have to be taken into consideration in clinical trials with CB_1 receptor antagonists.

Observations in humans

Based on the involvement of the endocannabinoid system in the control of food intake and energy balance, and in reward behaviours, CB_1 receptor antagonists have recently attracted considerable attention as a promising medicine against obesity and associated metabolic dysregulation (such as metabolic syndrome and diabetes type 2) and for supporting tobacco-smoking cessation.

An initial study with healthy men revealed that acute administration of the CB_1 receptor antagonist rimonabant (doses up to 90 mg/day) could prevent the effects of cannabis smoking without inducing significant physiological or psychological effects when given alone.[89]

Rimonabant – under the trade name of Acomplia® (Sanofi-Aventis) – has been approved in several countries for the treatment of obesity with associated metabolic dysregulation. This drug was first investigated in four multicenter randomized clinical trials, the Rimonabant in Obesity (RIO) studies, in which significant improvements in weight loss and in metabolic parameters were reported.[90–93] First, the RIO-Europe study followed up obese patients and found that rimonabant 20 mg/day induced a significant reduction in body weight after 1 year of treatment compared to placebo. However, rimonabant-treated subjects more often reported depressed mood and anxiety-like states than placebo control groups.[94] Similarly, in the RIO-Lipids study, which evaluated the effect of rimonabant on overweight patients with dyslipidaemia, depression- and anxiety-like states led patients to drop out from the study more frequently than in the placebo groups.[91] Both the efficacy and the side-effects were confirmed in the RIO-North America study.[92] Finally, the RIO-Diabetes study reported that overweight patients with diabetes type 2 receiving rimonabant developed depressed mood states that led them to stop their participation in the clinical trial more frequently than people in the placebo groups.[93] Thus, studies with different groups revealed the potential of rimonabant to induce anxiety- and depression-like states in obese subjects. Van Gaal et al[94] pooled the 1-year data of the RIO studies and again confirmed that the side-effects leading to the discontinuation of rimonabant–treated subjects were depressive disorders, nausea, mood alterations with depressive symptoms, anxiety, and dizziness. The authors pointed out that the total incidence remained low, and that most of the events were of mild or moderate intensity and were reversible after discontinuation of rimonabant.[94]

Although not adding any more insights into the side-effects of rimonabant, a recent meta-analysis of the four RIO studies confirmed the psychiatric side-effects as observed in the RIO Studies.[95] Participants who received rimonabant 20 mg daily were 2.5 and 3.0 times more likely to discontinue the treatment because of depression or depressive symptoms and because of anxiety, respectively. This meta-analysis also showed that, on the Hospital Anxiety and Depression Scale, rimonabant was associated with significant increases in anxiety. Since the RIO studies were conducted with psychiatric disorders as exclusion criteria, these data on the side-effects will have to be taken seriously into account when rimonabant is used by general practitioners.

STRADIVARIUS (the Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant – The Intravascular Ultrasound Study) is a recently published randomized controlled clinical trial.[96] It showed a significant effect of rimonabant on weight loss, but no significant effect on primary endpoint (i.e. percent atheroma volume), but reported a beneficial effect in the secondary endpoint (i.e. normalized percent atheroma volume). A particular feature of this study was that, contrary to the RIO studies, it did not exclude patients with psychiatric disorders and, thus, detected a higher incidence of side-effects. Thus, STRADIVARIUS may reflect more accurately the potential effects to be found in routine clinical practice.

Another compound, taranabant (developed by Merck), a CB_1 receptor inverse agonist/antagonist similar to rimonabant, has been tested for the same application profile.[97–99] Having similar mechanisms, one may expect that it would induce effects similar to those of rimonabant. Accordingly, the data available to date show that taranabant reduces body weight and associated metabolic dysregulation in obese subjects, but also it induces adverse psychiatric side-effects. More taranabant-treated patients experiencing psychiatric adverse effects, mainly anxiety, dropped out from the study as compared to placebo controls[99], which may raise the same concerns as seen in studies with rimonabant. A single oral dose study in healthy volunteers also reported anxiety and mood changes as adverse experiences.[97] Another study with multiple administrations also detected a dose-related increase in psychiatric side-effects.[98]

Thus, CB_1 receptor antagonism may induce psychiatric side-effects in humans, mainly anxiety- and depression-like states, being in accordance with the notion that the endocannabinoid system acts to keep a set point counteracting aversive emotions.[20] Obese patients already suffer from anxiety or depression more frequently than non-obese subjects.[100] Consequently, patients planned to receive CB_1 receptor antagonism treatment should be screened for possible depression-like behaviours prior to medication, and, if positive, should be excluded from the treatment. This might be a valid and efficient strategy for avoiding the reported side-effects, but still gives the benefits of CB_1 receptor antagonism to patients with obesity and associated metabolic dysregulation. In addition, continuous monitoring of treated patients with regard to anxiety- and depression-like states is also advisable, in particular in the first few months of treatment.

Conclusions

The ancient medical use of cannabis extracts has gained a new momentum after the recent mechanistic insights into the physiological and pathophysiological roles of the endocannabinoid system.[4] Furthermore, the pharmacological inhibition of endocannabinoid signalling, in particular via CB_1 receptors, has been intensively investigated as a target for new therapeutic strategies against obesity and associated metabolic dysregulation.[71] As commonly observed for any therapeutic treatment in humans, agonists and antagonists at the CB_1 receptors can elicit beneficial effects, but also side-effects.

CB_1 receptor agonists have been shown to be useful in the treatment of nausea and vomiting related to cancer chemotherapy, in neuropathic pain, and in symptom management of multiple sclerosis. The side-effects observed depend on the dose, the route of administration, and the exact composition of the cannabinoid components. Anxiogenic- and depression-like effects were reported, but in general these side-effects were rather mild.

CB_1 receptor antagonists have been investigated mainly in the treatment of obesity and associated metabolic dysregulation. Rimonabant, the first-discovered CB_1 receptor antagonist, has already been approved in several countries. There is emerging evidence of the long-term efficacy of this drug, but on the other hand the clinical studies available to date showed specific psychiatric side-effects – mainly anxiety- and depression-like states – which appear to be reversible after cessation of the drug.

Considering that psychiatric disorders have been exclusion criteria in some clinical trials with CB_1 receptor agonist or antagonists, the current estimations on the incidence of the side-effects might be too conservative. Thus, special care has to be taken when selecting patients who will receive endocannabinoid system-modulating drugs. Subjects already showing mood disorders or mild depression-like states are likely to be particularly vulnerable to the depressive and anxiogenic effects of these drugs, in particular in the case of CB_1 receptor antagonists as treatment of obesity, as obesity may already be associated with depression.

In conclusion, the recent clinical trials with drugs modulating endocannabinoid signalling reflect, from a clinical perspective, the fact that CB_1 receptor antagonism may increase anxiety and depression, and indicates that the usefulness of these drugs must be monitored critically. From a theoretical point of view, these results support preclinical data pointing to a protective function of the endocannabinoid system in coping with emotionally aversive situations.

Summary

CB_1 receptor agonists are useful therapeutic agents against emesis, vomiting and pain, although they may induce side-effects such as psychosis and panic. Drugs that act as antagonists at this receptor have also been developed as therapeutic agents in diverse fields of medicine. Clinical studies have reported that CB_1 receptor antagonism may lead to symptoms reminiscent of depression and anxiety-related disorder. Further understanding the functioning of the endocannabinoid system will hopefully provide new therapeutic avenues that may avoid these psychiatric side-effects.

Practice points

- the endocannabinoid system has been widely investigated as a therapeutic target for diverse pathologies; however, this system seems to play a major role in the modulation of emotional states
- CB_1 receptor agonists have been employed in clinics for the treatment of nausea, pain and multiple sclerosis, while antagonists have been approved for the treatment of obesity with associated metabolic dysregulation
- CB_1 receptor agonists may induce episodes of psychosis and panic reactions in some subjects, leading to discontinuation of the treatment
- clinical trials with CB_1 receptor antagonists have evidenced symptoms reminiscent of depression and anxiety as major side-effects; these drugs are contraindicated for patients

suffering from mild mood disorders and of psychiatric disorders such as depression. Before treatment starts, a questionnaire regarding mood disorders should be used to detect such disorders
- during the first 2–3 months of CB_1 receptor antagonist treatment of subjects that have not initially shown symptoms of mood disorders, doctors should still give special attention to symptoms related to mood changes and anxiety-related emotions; treatment should be immediately discontinued if any of these side-effects occurs

Research agenda

- the effects of synthetic CB_1 receptor agonists and phytocannabinoids should be further investigated and compared with those of Δ^9-THC and standardized cannabis extracts in order to identify possible advantages of such new substances or substance combinations
- it is advantageous to develop therapies based on enhancement of endocannabinoid activity (e.g. FAAH and MAGL inhibitors) rather than on direct CB_1 receptor activation; this could avoid psychotropic side-effects
- CB_1 receptor antagonists have been investigated for the treatment of obesity with associated metabolic dysregulation and smoking cessation; psychiatric side-effects should be carefully investigated, leading hopefully to more detailed insights into the aetiology of these side-effects
- preclinical studies are able to predict the potential of new drugs to induce anxiogenic- and depressive-like effects. Thus, new candidate drugs should be tested in animal models and checked for their propensity to induce side-effects
- since CB_1 receptor antagonists have already been approved in some countries, or will be approved in the near future, follow-up clinical investigations should be conducted to evaluate the adverse effects of such a medication in detail; in addition, practitioners should carefully monitor and document the side-effects
- the development of CB_1 receptor agonists and antagonists which do not cross the blood–brain barrier might not induce central nervous system-mediated side-effects, but may still retain beneficial therapeutic effects; this is particularly interesting for CB_1 receptor antagonists, as their beneficial effects on metabolic dysregulation are mediated, at least to a considerable extent, by peripheral organs

Conflict of interest

F.A.M. and M.G. declare no conflict of interest. B.L. attended advisory board meetings and gave educational talks on the endocannabinoid system for Sanofi-Aventis.

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