Chapter 4
Interactions Between Cannabinoid Signaling and Anxiety: A Comparative Analysis of Intervention Tools and Behavioral Effects

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Abstract Cannabinoid signaling is believed to decrease anxiety, albeit the conflicting nature of evidence is generally acknowledged. Here we provide a comprehensive overview of available findings by grouping them according to the tools that have been used to modulate cannabinoid signaling. The systemic administration of cannabinoid receptor agonists and antagonists led to the most conflicting findings; such treatments may increase, decrease, or leave anxiety unaffected. In addition, antagonists and agonists had similar effects in many instances including their biphasic effects. The effects of genetic manipulations, cannabinoid synthesis or reuptake inhibition as well as the effects of local brain treatments with cannabinoid ligands appear more consistent. We suggest that systemically administered receptor ligands affect cannabinoid signaling globally and as such lack the spatial and temporal specificity of endocannabinoid signaling. By contrast, gene disruption and the indirect modulation of endocannabinoid availability affect ongoing (natural) processes and lead to more specific and consistent effects. Local brain treatments whit receptor ligands are spatially restricted which increases the consistency of findings, but also reveals that cannabinoids affect anxiety in a brain area-specific manner, which further explains the inconsistency of findings with systemically injected ligands. Environmental conditions have a large impact on effects with all techniques, suggesting that endocannabinoid signaling affects coping with environmental challenges rather than unconditionally decreasing anxiety. The relationship between cannabinoid signaling, anxiety and coping styles is largely understudied, but holds great promise for understanding the roles of cannabinoids in behavioral control and may broaden their therapeutic implications.

Keywords 2-arachidonoylglycerol · Anandamide · Anxiety · Coping styles · Endocannabinoids · Rodents

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Introduction

The totality of scientific evidence obtained so far suggests that cannabinoids do play a role in the inhibitory control of anxiety, but findings are highly contradictory both within and between the techniques employed to manipulate cannabinoid signaling. Inhibition by various means (gene disruption, receptor antagonism) can increase anxiety, decrease anxiety and may be without effect, and the same applies to the enhancement of cannabinoid signaling by cannabinoid receptor agonists, reuptake blockers or by the inhibition of enzymes involved in their degradation. While there seem to be more studies attributing an anxiolytic role to cannabinoids, conflicting evidence is too many to be attributable to experimental error. Contradictions were explained in various ways, and led to several hypotheses. A thorough review of these makes it clear that theoretical approaches are based on *partial* evidence and none of them is comprehensive enough to create a consistent picture. The goal of the present chapter is to provide a full review of the evidence contained by the PubMed database and to evaluate the reasons of contradictions with the ultimate aim of disentangling the roles played by endocannabinoid signaling in anxiety. We are aware of the fact that neither goal is realistic in absolute terms, because:

- The particularities of the search engine of PubMed do not rule out that some studies remained hidden to this review. The search was performed with the search term "(cannabinoid OR endocannabinoid OR THC OR arachidonoylethanolamide OR anandamide OR AEA OR 2-arachydonoylglycerol OR 2-AG OR WIN 55, 212–2 OR HU 210 OR JWH 133 OR CP 55,940 OR URB 597 OR PF 622 OR PF 3845 OR PF 750 OR JZL 184 OR FAAH OR MAGL OR AM 404 OR AM 1172 OR VDM-11 OR rimonabant OR SR 141716 OR AM 251 OR NESS 0327 OR CB1 KO OR CB2 KO) AND (anxiety OR anxiolytic OR anxiogenic OR anxiolysis OR anxiogenesis or anxious)". This term resulted in 1017 hits out of which 186 original research studies were identified as relevant for the present study. While the overwhelming majority of studies were likely identified, the database created by this search is probably incomplete. This figure does not include studies on the phytocannabinoid cannabidiol[1].
- A full understanding of the role played by endocannabinoids in anxiety may not be achievable at present stage. Reasons are multiple and range from the variability of research techniques and conditions, through species, strain, and even individual differences in the particularities of the endocannabinoid system, to yet unraveled or poorly known epiphenomena of research tools used to manipulate endocannabinoid signaling. In addition to these primarily technical reasons, one cannot rule out that the anxiety-related effects of endocannabinoids

[1] This compound has anxiolytic properties [1–14], and as such it is highly relevant to anxiety research in general. However, cannabidiol binds to cannabinoid receptors with very low affinity [15], and its mechanisms are either indirectly related to endocannabinoid signaling [16] or involve direct effects on other neurotransmitter systems [17]. Therefore, data on cannabidiol were not reviewed here.

are reflections of more general effects on emotions, emotional responsiveness or coping styles. If this was true –and many recent findings point to this possibility–, then the anxiety-related effects of endocannabinoid signaling are inherently complex and condition-dependent, and rule out the possibility of answering simple questions of the type "does endocannabinoid signaling increase or decrease anxiety"?

The next section briefly reviews the main findings of the search described above. This section is free of interpretations or explanations which constitute the subject of the third chapter. The last, concluding section is an attempt to integrate data and views.

Findings

Systemic Effects

Decreased Endocannabinoid Activity

Decreasing endocannabinoid activity *via* the genetic disruption of the type 1 cannabinoid receptor (CB_1R) resulted in an anxious phenotype in most studies employing well-validated tests of anxiety (e.g. the elevated plus-maze, light/dark, social interaction tests [18–25]. The anxiety enhancing effect of CB_1R disruption seemed to be specific to young mice in one [26] and to aversive conditions in another study [27]. Two studies did not detect anxiety-like behavior in CB_1R knockout (KO) mice tested in the elevated plus-maze [28, 29], while others may suggest that CB_1R gene disruption decreases anxiety. For instance, CB_1 KO mice showed decreased burying in the shock-prod burying test which was interpreted as an anxiolytic effect [30]. In the cue-induced conditioned fear test, CB_1R KO mice did show increased anxiety, but this *decreased* when mice were socially stressed [29], suggesting that stress exposure paradoxically ameliorates the anxious phenotype of CB_1R KOs.

The role of other cannabinoid receptors was poorly studied by transgenic techniques. Two studies suggest that the disruption of the type 2 cannabinoid receptor (CB_2R) increases anxiety in the elevated plus-maze [31], light/dark [31] and open-field tests [32]. The disruption of the G protein-coupled receptor 55, a novel cannabinoid receptor [33–35], had no effects on anxiety in the only study available so far [36].

The down-regulation of endocannabinoid signaling by the CB_1R antagonist rimonabant (SR141716A) results in biphasic effects. Low doses (0.3–3 mg/kg) reduced anxiety in several models, e.g. the elevated plus-maze [37–39], light/dark [40] and Vogel tests [38], while higher doses (3–10 mg/kg) exerted anxiogenic effects in the elevated plus-maze [28, 41–47], light/dark [48], open-field [28], novelty induced hypophagia [49], elevated T-maze [28], defensive withdrawal [45], social interaction [50] and footshock-induced ultra sound vocalization [51] tests. Such

large doses also increased cue-induced conditioned fear after both acute [52] and chronic treatment [29]; in addition, rimonabant inhibited the extinction of this response [53–55]. Rodent findings are supported by human studies, where both acute and chronic treatment with rimonabant exerted anxiogenic effects [56–60].

This ostensibly clear picture is obscured by a large body of conflicting evidence. Firstly, rimonabant did not always produce the effects presented above. Low doses –that decreased anxiety in the aforementioned studies– were sometimes without effect [28, 38, 61, 62]. High doses –anxiogenic in the studies presented above– were anxiolytic in the shock prod-burying paradigm [30]. Effects in humans were not replicated either [63]. Secondly, the effects of other antagonists were not always in line with those obtained with rimonabant. For instance, the CB_1R blocker AM251 did not show the biphasic effect seen with rimonabant. This antagonist proved to be anxiogenic over a wide range of doses (0.3–8 mg/kg) [21, 25, 50, 64–68]. In addition, AM251 reduced urocortin1 microinjection- and nicotine abstinence-induced anxieties[69, 70]. Other antagonists (AM281, AM4113, and AVE1625) did not affect anxiety [66, 71–73].

Data on CB_2R antagonists are sparse. Acute treatment with AM630, a CB_2R antagonist, led to anxiogenic effects, while chronic treatment attenuated anxiety in the same paradigm [74].

Taken together, the findings briefly reviewed above are in line with expectations and show that the effects of inhibited endocannabinoid signaling are highly variable (for a summary see Table 4.1).

Increased Endocannabinoid Activity

Similar to the antagonist rimonabant, CB_1R agonists have biphasic effects on anxiety. Surprisingly, however, the effects are not only biphasic but entirely similar to those seen with rimonabant (but not other antagonists): low doses decrease, while high doses increase anxiety. Anxiolytic effects were shown for low doses of the phytocannabinoid Δ^9-tetrahydrocannabinol (THC; 0.075–2 mg/kg), the endocannabinoid anandamide (AEA; 0.1–1.25 mg/kg) and synthetic cannabinoids (WIN55,212–2: 0.5–3 mg/kg; CP55,940: < 0.1 mg/kg; HU210: 0.01 mg/kg) [21, 43, 53, 65, 67, 68, 75–90]. Higher doses of the same agonists (THC: 2.5–10 mg/kg; AEA: 10 mg/kg; WIN55,212–2: 3–5 mg/kg; CP55,940: > 0.1 mg/kg; HU210: 0.05–0.1 mg/kg) were anxiogenic [40, 44, 71, 78, 83, 89–104]. High doses of THC increased anxiety in humans as well [105–111].

This apparently consistent picture is blurred by a large body of conflicting evidence. Low doses of agonists –anxiolytic in the above studies– increased anxiety under specific conditions, such as repeated treatments in adults, perinatal administration and in rats that were chronically treated with vehicle before drug administration [112–115]. High doses of CB_1R agonists –anxiogenic in the above studies—decreased anxiety in cocaine-self-administering subjects, in the 3,4-methylenedioxy-N-methylamphetamine-induced anxiety model, after chronic vehicle pretreatment and in adolescent subjects [116]. The biphasic effect was also overturned by species,

Table 4.1 Effects of decreased endocannabinoid activity on anxiety

Assessment tools		Effects on anxiety (references)	Number of studies
CB_1 KO		Anxiogenesis	9
		Condition-dependent effects	2
		No effects	2
		Anxiolysis	2
CB_2 KO		Anxiogenesis	2
GPR55 KO		No effects	1
CB_1R antagonist	findings compatible with biphasic effects[a] (total No. of studies: 25)	Rimonabant	25
		AM251	0
		Other antagonists	0
	findings incompatible with biphasic effects[b] (total No. of studies: 20)	Rimonabant	6
		AM251	10
		Other antagonists	4
CB_2R antagonists		*acute*: anxiogenesis; *chronic*: anxiolysis	1

[a] the general consensus is that low doses of CB_1R antagonists decrease, while large doses increase anxiety. The dose ranges for these effects were indicated in the text

[b] the hypothesis on the biphasic nature of effects was considered challenged by studies where either the low or the large those did not produce the expected effect

strain, gender, and experimental conditions (e.g. enriched environment, treatments received in adolescence) [117]. Additionally, there is a large set of studies, in which doses that effectively altered anxiety in the above studies were without effects [54, 98, 101, 114, 118–123]. Inefficacy was sometimes seen under specific conditions, like stress-induced anxiety [124] or alcohol-withdrawal [125].

The enhancement of endocannabinoid signaling *via* the selective blockade of their degrading enzymes is a novel approach for the up-regulation of endocannabinoid activity [126–129]. Endocannabinoids are synthesized "on-demand"; therefore the blockade of their breakdown promotes ongoing signaling processes, i.e. their effects are more specific than those of agonists, which activate cannabinoid receptors throughout the brain. Both genetic and pharmacological blockade of the anandamide metabolizing enzyme, fatty acid amide hydrolase (FAAH), led to anxiolytic effects in a number of reports [43, 46, 67, 71, 86, 100, 126, 128, 130–138]. In other cases, however, no effects were seen either after genetic [139] or pharmacological blockade of FAAH activity [138–140]. FAAH inhibition was anxiogenic in one study [50]. Strong dependence on environmental conditions was reported in two studies [138, 139].

Studies on the specific role of 2-AG signaling were only recently made possible by the synthesis of the first selective, specific monoacylglycerol lipase (MAGL) blocker. This compound decreased anxiety in a number of studies [132, 134, 141,

Table 4.2 Effects of increased endocannabinoid activity on anxiety

Assessment tools	Remarks	Effect on anxiety (references)	Number of studies
CB_1R agonists	Findings compatible with biphasic effects[a]	Low doses anxiolytic, large doses anxiogenic	35
	Findings incompatible with biphasic effects[b]	Effect altered/reverted by specific experimental conditions	13
		No effects on anxiety	10
Blockade of AEA degradation		Anxiolysis	17
		Condition-dependent effects	2
		No effects	1
		Anxiogenesis	1
Blockade of 2-AG degradation		Anxiolysis	4
		Condition-dependent effects	2
Endocannabinoid reuptake inhibition		Anxiolysis	6
		no effect	2

[a] the general consensus is that low doses of CB_1R antagonists decrease, while large doses increase anxiety. The dose ranges for these effects were indicated in the text
[b] the hypothesis on the biphasic nature of effects was considered challenged by studies where either the low or the large those did not produce the expected effect

142]. A few studies suggest that these effects depend on environmental aversiveness, and HPA-axis activity [143, 144].

Endocannabinoid signaling can also be stimulated by the inhibition of endocannabinoid transport. This treatment led to anxiolytic effects in a number of reports [43, 54, 87, 145–148]; no effects were seen in two studies [71, 149].

Taken together, the effects of pharmacological enhancement of endocannabinoid activity have variable effects on anxiety-like behavior. Findings are summarized in Table 4.2.

Local Brain Treatments

Neuron Type-Specific Effects

In this type of studies, transgenic animals were used; the selective disruption of CB_1Rs in glutamatergic, dopaminergic and serotonergic neurons all increased anxiety [20, 29, 150]. The same manipulation in GABA-ergic neurons did not cause such changes [29]. One study suggests that cannabinoid signaling in serotonergic neurons ameliorates conditioned fear, despite the fact that the same transgenic

animals showed anxiety in the elevated plus-maze [29]. By contrast, dopamine neuron-specific gene disruptions had congruent effects in the social interaction test of anxiety and conditioned fear [150].

Brain Area-Specific Effects

General effects. Blockade of CB_1Rs in the brain by the intracerebroventricular injection of the CB_1R antagonist AM251 increased anxiety [151], while the enhancement of endocannabinoid activity by FAAH administered *via* the same route was anxiolytic [133]. The effects of AM251 were reversed in animals treated with corticotrophin releasing hormone and in those submitted to cocaine-withdrawal [151]. Mice expressing CB_1Rs only in the dorsal telencephalon showed reduced anxiety compared to CB_1R KO mice [152].

Prefrontal cortex. The enhancement of cannabinoid signaling by cannabinoid agonists and FAAH inhibition had biphasic effects in this brain area; small doses decreased, while large doses increased anxiety [153, 154]. The genetic over-expression of the CB_1Rs in the same area mimicked the effects of large doses, i.e. it increased anxiety [155]. Thus, the studies performed so far provide a congruent picture. Interestingly, the biphasic effects seen after systemic treatments were replicated by local agonist infusions into the prefrontal cortex. Similar biphasic effects were seldom reported in other brain regions.

Amygdala. We found only one study where local treatments were suggested to cover the whole amygdala; in this case, the cannabinoid agonist arachidonylcyclopropylamide (ACPA) reduced anxiety [156]. This effect was replicated by the infusion of agonists into the basolateral amygdala but not by local treatments targeting specifically the central amygdala. In the former region, agonists (Δ9-THC, WIN55,212–2) and N-arachidonoyl-serotonin (a combined FAAH inhibitor/TRPV1 antagonist) reduced anxiety; the effect was valid to certain doses and particular conditions only, but no anxiogenic effects were observed at any dose [153, 157]. It is worth to note that no similar effects were observed with anandamide and pure FAAH inhibitors [158, 159], while Δ9-THC administration into the central amygdala increased anxiety [160].

Cannabinoid antagonists were administered into the basolateral, central, and medial amygdala. In the basolateral amygdala, where agonists decreased anxiety, antagonists increased it [69, 159, 161]; thus, the two types of treatments led to congruent effects in this brain region. In the central amygdala, antagonists (rimonabant, AM251) increased anxiety [161], similar to the agonist Δ9-THC. Thus, in this amygdala region, findings are incongruent. One study suggests that the local disruption of CB_1R expression in the medial amygdala decreases anxiety [162].

Taken together, the studies reviewed above suggest that cannabinoid signaling in the basolateral amygdala decreases anxiety. Reports on other amygdalar subregions are disparate, but suggest that the effects of cannabinoid signaling are amygdala subarea-specific.

Hippocampus. Agonists or FAAH inhibitors were infused into the CA1 region in three studies: effects were contrasting as anxiogenic effects [163], no effects [164] or anxiolytic effects [165] were observed. CB_1R blockade in the very same brain region either decreased or increased anxiety [163, 166]. In the ventral hippocampus, the enhancement of endocannabinoid signaling by agonists (Δ9-THC, high doses), as well as by FAAH or reuptake blockade resulted in anxiogenesis [153, 167, 168], while the blockade of CB_1Rs did not affect anxiety [167]. Noteworthy, the effects of Δ^9-THC were biphasic, while the effects of reuptake blockade were reversed by stress exposure [153, 167, 168].

Periaqueductal gray. Cannabinoid receptor agonists (2-AG, AEA, ACEA), the blockade of MAGL, as well as the inhibition of cannabinoid reuptake in the dorsal and dorsolateral periaqueductal gray decreased anxiety [141, 169–172]. The CB_1R antagonist AM251 was without effect [172]. Except for this latter finding, the anxiolytic roles of cannabinoid signaling in the dorsal/dorsolateral periaqueductal gray appear well supported.

Other brain regions. The local deletion of CB_1Rs in the posterior hypothalamus, the paraventricular and supraoptic nuclei increased anxiety [162]. The microinjection of AM251 into the enteropeduncular nucleus also increased anxiety [160].

Conclusions

The number of studies on neuron type-specific and brain area-specific roles of cannabinoid signaling in anxiety are clearly insufficient to draw definite conditions. Nevertheless, the findings obtained so far suggest that cannabinoids have anxiolytic effects in most brain regions. As exception, they appear to have biphasic effects in the prefrontal cortex, and anxiogenic effects in the ventral hippocampus. Data in the dorsal hippocampus and medial amygdala are sparse. Findings appear to be rather congruent in many brain regions, and neuron types. The brain area-specific effects of cannabinoids on anxiety are summarized in Table 4.3.

Interpretation

Clearly, data on the anxiety-related effects of cannabinoids are conflicting, but the thorough overview of the available findings leads to a series of interesting conclusions:

- The less reliable findings were obtained with cannabinoid agonists and antagonists. The most blatant dissimilarities relate to the biphasic effect of such treatments. Biphasic effects are not particularly unusual in pharmacology, but in the case of cannabinoid ligands, antagonists and agonists have highly similar effect profiles: small doses of both decrease anxiety, while large doses of both increase anxiety. In addition, the largest number of conflicting findings was obtained with these experimental tools.

Table 4.3 Brain area-specific effects of cannabinoid signaling on anxiety

Brain area		Most frequently reported effect	Number of studies	
Prefrontal cortex		Biphasic (low doses are anxiolytic; high doses are anxiogenic)	Supporting	4
			Not supporting	0
			Opposite effect	0
Amygdala	Whole	Anxiolysis	Supporting	1
			Not supporting	0
			Opposite effect	0
	Basolateral nucleus	Anxiolysis	Supporting	6
			Not supporting	2
			Opposite effect	0
	Central nucleus	Anxiolysis	Supporting	2
			Not supporting	0
			Opposite effect	1
	Medial nucleus	Anxiogenesis	Supporting	1
			Not supporting	0
			Opposite effect	0
Hippocampus, dorsal		Anxiogenesis		1
		No effects		1
		Anxiolysis		1
Hippocampus, ventral		Anxiogenesis	Supporting	3
			Not supporting	1
			Opposite effect	0
Periaqueductal gray, dorsal/ dorsolateral		Anxiolysis	Supporting	6
			Not supporting	1
			Opposite effect	0
Hypothalamus		Anxiolysis	Supporting	1
			Not supporting	0
			Opposite effect	0
Enteropeduncular nucleus		Anxiolysis	Supporting	1
			Not supporting	0
			Opposite effect	0

- The selective genetic disruption of cannabinoid receptors provided more congruent findings: this procedure increased anxiety in the overwhelming majority reports. One study reported no effects, while another reported context-dependent effects which included anxiogenesis under particular conditions and no effects under other conditions. In addition, one of the reports where anxiolytic effects were observed employed the shock-prod burying paradigm, a mixed anxiety and

coping test [173]. Effects on coping will be discussed below. In conclusion, the anxiogenic effects of CB_1R disruption is contradicted by one single study, and no effects were obtained in another.

- Findings obtained with agents that indirectly modulate endocannabinoid signaling (FAAH, MAGL, and reuptake blockers) are not devoid of contradictions, but again the overwhelming majority of findings suggest that such agents decrease anxiety. This statement is supported by 27 studies. Condition-dependent effects were obtained in 4 studies (usually implicating anxiolysis under particular conditions) and no effects were obtained in 3 studies. Anxiogenic effects were obtained in one study only.
- Local brain treatments with cannabinoid agents provided the most consistent sets of data. There are virtually no contradictions in the case of certain brain areas, while opposing effects are missing in other cases (e.g. discrepancies are between effects and no effects).

The perspective summarized above raise a series of questions; the following sections are attempts to answer them.

Why are the Effects of Receptor Ligands Less Reliable than Those of Indirect Modulators?

The characteristics of endocannabinoid signaling and those of receptor ligands decrease the reliability of the latter as experimental tools. Endocannabinoids are secreted from the post-synaptic membrane and retrogradely inhibit the synaptic neurotransmission that triggered their release [174]. Although a probably low level of tonic activation cannot be excluded, the endocannabinoid signal occurs phasically i.e. when the intensity of anterograde synaptic communication reaches certain levels [175–178]. As such, the main role of endocannabinoid signaling appears to be the blockade of excessive neuronal activation [179].

Agonists overrule this finely tuned mechanism by inhibiting neurotransmission in synapses where this is not justified by its intensity, i.e. where retrograde signaling is not activated under normal conditions. As such, the effects of agonists are broader than those of endocannabinoids, and instead of mimicking natural activity they extend effects to synapses, neurons and brain areas where such activity normally does not take place.

Antagonists on their turn (especially those extensively used in anxiety research), have inverse agonist properties, by which they also overrule the above-described mechanism. Instead of inhibiting endocannabinoid signaling, their inverse agonist effects inhibit neuronal discharges in areas where endocannabinoids are normally not released. Thus, their effects are also extended to synapses, neurons and brain areas where endocannabinoids are not active.

In addition, many of the tools regularly used to affect receptor function affect both CB_1Rs and CB_2Rs. Originally, this was not perceived as a problem, but relatively recent findings demonstrate that CB_2Rs are expressed in the brain and have

roles in behavior control [180]. In addition, receptor ligands also bind to other receptors, for instance to the still poorly known "third" cannabinoid receptor as well as to the GPR55 and TRPV1 receptors [181]. Naturally, endocannabinoids also bind to these receptors non-selectively; however, they affect the function of these mechanisms in spatially and temporally selective ways, while exogenous receptor ligands act indiscriminately.

A third problem with exogenous ligands is that their brain distribution is not uniform; moreover, different receptor ligands have specific patterns of brain distribution. For instance, two times more WIN55,212–2 was found in the hypothalamus than in the amygdala after the systemic administration of the compound; by contrast, the amounts of the antagonist rimonabant (administered by the same route) were similar in these two brain regions [182]. While the issue remains understudied, the available findings strongly suggest that compound-specific brain distribution patterns constitute an additional confounding factor in the elucidation of the roles of endocannabinoids in behavioral control. Furthermore, cannabinoid receptor ligands may show species- and neuron type-specific ligand sensitivity. Electrophysiological studies showed for instance that WIN-55,212–2 preferentially affected GABA-ergic neurotransmission in mice, while the same compound appeared to affect glutamatergic neurotransmission in rats, which together with species- and neuron type-specific effects of AM251 led to large species differences in the behavioral effects of these ligands and marked differences in their interaction [23].

The use of indirect modulators circumvents most these problems. Metabolic enzyme inhibitors and reuptake blockers enhance and prolong naturally occurring endocannabinoid release. Consequently, the up-regulation of endocannabinoid signaling is restricted to synapses, neurons and brain regions where the system is activated by the behavioral paradigm investigated. The enhanced activation of natural endocannabinoid signaling also eliminates problems related to receptor specificity, brain distribution and ligand sensitivity.

Why are Gene Disruption and Local Treatments More Reliable than Receptor Ligands?

The problems related to the use of receptor ligands are also circumvented by the genetic disruption of the endocannabinoid receptor and by the local brain administration of compounds. The gene disruption technique has its own flaws, among which the development of compensatory mechanisms are believed to have the largest impact on experimental findings. At the same time, however, most of the problems raised by the use of receptor ligands are avoided by this technique. The reason is the spatio-temporal overlap of networks activated by a behavioral context and the lack of receptors in these networks. While receptors are eliminated throughout the brain, the consequences of this are manifested only at those synapses which are activated under the conditions of a particular study. The effects of gene disruption on networks that are unrelated to the context (i.e. are not "working" when a

particular behavior is expressed) remain "silent" because they do not contribute to the execution of the behavioral act. Therefore, gene disruption eliminates naturally occurring cannabinoid signaling without having effects on other mechanisms. The same holds true for selectivity: while receptor ligands act on more than one receptor, gene disruptions are selective in this respect. Finally, problems associated by ligand-specific brain distribution patterns and ligand specificity are not present in receptor knockouts, where the ligands are the natural ones, i.e. endocannabinoids.

The local application of receptor ligands involves all the problems associated with direct receptor modulation, but these are spatially restricted, and by this their consequences are minimized. In other words, nonspecific effects at the targeted brain area are not amplified by nonspecific effects at other brain sites. Moreover, local applications eliminate the problem of differential effects exerted in certain brain regions. As shown above, the local administration of cannabinoids results in anxiolysis in some but not all brain regions. Systemically administered cannabinoids activate in parallel biphasic effects in the prefrontal cortex, anxiolytic effects in the amygdala, and anxiogenic effects in the hippocampus, while local administration activate only one of these mechanisms, which leads to clearer findings.

Why are Effects Condition-Dependent?

It is a common observation that the condition of subjects and experimental conditions have a large impact on how cannabinoids affect anxiety; examples were outlined above and will not be reiterated here. One possible interpretation of such condition-dependent effects is that cannabinoids do not affect particular behaviors but affect the way in which the organism responds to challenges, i.e. they affect coping styles. We identified four papers addressing the effects of cannabinoids from this perspective [25, 183–185]. Taken together, these studies suggest that cannabinoids promote active coping, which is associated with anxiolytic-like and antidepressant-like effects in particular tests.

Active and passive coping styles are two distinct behavioral phenotypes which differ in the way challenges are dealt with, and which show a bimodal distribution [186, 187]. Behavior is internally driven and problem oriented in active copers. In contrast, passive copers are governed by environmental stimuli and tend to respond challenges by avoidant behavior. These temporally stable behavioral phenotypes have adaptive significance in animals, while in humans, active (type "A") and passive (particularly type "C") coping styles influence disease susceptibility and resilience under adverse conditions [187–189]. Moreover, coping styles are believed to reliably predict disease-induced decreases in quality of life [190, 191]. Consequently, interventions promoting active coping styles -which are associated more favorably with resilience- have been proposed as therapeutic goals for a variety of physical diseases and mental disorders [190, 192, 193]. Thus, the putative effects of endocannabinoid signaling on coping styles are highly relevant from a therapeutic point of view.

The relationships between cannabinoids and coping on one side, and cannabinoids and anxiety on the other side have not been elucidated so far. There are several scenarios that may be considered: (1) cannabinoids affect anxiety in the first place, and promote active coping by decreasing anxiety; (2) cannabinoids affect coping in the first place, and their anxiolytic effects are context-dependent consequences of the shift in coping styles; (3) effects on coping and anxiety are mediated by different cannabinoid-dependent mechanisms that interact under specific conditions.

Conclusions

Overall, the findings suggest that cannabinoid signaling decreases anxiety. The number of conflicting findings is large. A comparison of different technologies demonstrates that the reliability of findings is rather low with receptor ligands (agonists and antagonists). Considerably more consistent findings were obtained with gene knockouts, the indirect enhancement of endocannabinoid signaling (e.g. enzyme inhibitors), and local brain treatments. The anxiolytic effects of cannabinoid signaling are more robustly shown by the latter three as compared with the former approach, but notably, the effects of cannabinoids is not uniform across brain areas. In the prefrontal cortex, biphasic effects were noticed (anxiolysis at low and anxiogenesis at large doses), while in the amygdala and hippocampus cannabinoids seem to decrease and increase, respectively, anxiety-like behavior. The condition of subjects and experimental conditions have a strong impact on the effects of cannabinoids, and this seems to be independent from the technique employed to manipulate endocannabinoid signaling. Recent findings demonstrate that cannabinoids promote a shift from passive to active coping with challenges, which may explain the context-dependence of their anxiety-related effects, and may broaden their therapeutic implications. The relationship and directionality of the triple association between cannabinoid signaling, anxiety and coping styles is largely understudied, but holds great promise for the understanding of the roles of cannabinoids in behavioral control, and the therapeutic potentials of cannabinoid modulators.

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