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Perspective

The endocannabinoid system and Post Traumatic Stress Disorder (PTSD): From preclinical findings to innovative therapeutic approaches in clinical settings

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ABSTRACT

Post-Traumatic Stress Disorder (PTSD) is a psychiatric chronic disease developing in individuals after the experience of an intense and life-threatening traumatic event. The post-traumatic symptomatology encompasses alterations in memory processes, mood, anxiety and arousal. There is now consensus in considering the disease as an aberrant adaptation to traumatic stress. Pharmacological research, aimed at the discovery of new potential effective treatments, has lately directed its attention towards the "so-called" cognitive enhancers. This class of substances, by modulating cognitive processes involved in the development and/or persistence of the post-traumatic symptomatology, could be of great help in improving the outcome of psychotherapies and patients' prognosis. In this perspective, drugs acting on the endocannabinoid system are receiving great attention due to their dual ability to modulate memory processes on one hand, and to reduce anxiety and depression on the other. The purpose of the present review is to offer a thorough overview of both animal and human studies investigating the effects of cannabinoids on memory processes. First, we will briefly describe the characteristics of the endocannabinoid system and the most commonly used animal models of learning and memory. Then, studies investigating cannabinoid modulatory influences on memory consolidation, retrieval and extinction will be separately presented, and the potential benefits associated with each approach will be discussed. In the final section, we will review literature data reporting beneficial effects of cannabinoid drugs in PTSD patients.

1. Introduction

Post-Traumatic Stress Disorder (PTSD) is a chronic psychiatric disease characterized by marked alterations in cognition, mood, emotion and social abilities, developing in individuals after the experience of a traumatic and/or life-threatening event. In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) PTSD has been included in the new category of "trauma and stressor-related disorders", where the abnormal adaptation to a traumatic experience is considered as a specific pathogenetic starting point [1]. Among the different characteristics of PTSD, much attention has been lately given to the study of abnormalities in fear memory elaboration, which are thought to be causally linked to symptoms such as spontaneous recollections, flashbacks, enhanced reactivity to trauma-related cues, dissociative amnesia [2–4]. One of the reasons that makes PTSD so persistent and resistant to pharmacological interventions is the substantial lack of treatments targeting memory alterations [5,6]. The inability to extinguish learned fear responses [7], to suppress episodic traumatic retrieval [8], to acquire safety signals [9] or to dampen the over-consolidation process taking place right after re-experiencing symptoms [10], may account for the great stability of PTSD symptomatology over time, thus PTSD can hardly be affected by traditional antidepressant and anxiolytic medications [5]. Non-pharmacological treatments such as Cognitive Behavioral Therapy (CBT) and Eye Movement Desensitization and Reprocessing (EMDR) seem to be more effective in the treatment of PTSD [11,12], but the high drop-out rates observed in *meta*-analysis studies suggest that their procedures may need further refinements [13,14]. The limitations in PTSD treatment make it urgent the discovery of new drugs with the ability to diminish the expression of the multifaceted nature of the post-traumatic symptomatol-

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ogy. Much attention has been lately directed to cannabinoid drugs because of their dual ability to modulate memory processes for emotional experiences on one hand [5,6,15] and to reduce anxiety on the other [5,6,16,17]. Moreover, literature evidence demonstrating alterations of the endocannabinoid system in PTSD patients is continuously increasing [18–22]. The modalities through which cannabinoid compounds could exert beneficial effects on PTSD are various. First, cannabinoid administration in the immediate aftermath of a trauma could reduce the impact of the subsequent traumatic memory by interfering with the memory consolidation process (i.e. that process taking place in a limited time window starting immediately after an experience and that allows an initially labile memory trace to be stabilized into a form of long term memory) [23–26]. Secondly, cannabinoids could reduce traumatic memory by interfering with the memory retrieval process (also named recollection, recall or reactivation, i.e. that process that brings out stored information from the long-term memory into consciousness) [15,27]. After a memory trace has been reactivated, it becomes labile again requiring a new wave of consolidation (or re-consolidation) to get updated in the long term memory [26,28,29]. And a poorly retrieved memory is less prone to be reconsolidated. Finally, yet importantly, cannabinoids could enhance extinction learning (i.e. the form of learning that allows a stimulus previously paired with a negatively valenced emotional experience that trigger fear and anxiety responses, to become non-threated again) [30]. The potentiation of extinction learning is probably the most promising perspective in the application of cannabinoid drugs for the treatment of PTSD since extinction mechanisms are thought to be engaged in exposure-based psychotherapies [31]. Enhancing the efficacy of exposure therapy by means of cannabinoids and other substances represents a new intriguing therapeutic opportunity attracting the attention of clinicians and scientists [6,32]. In this review, we will first briefly describe the endocannabinoid system and the most commonly used animal models for learning and memory testing. Subsequently, we will review experimental data from both human and animal studies describing therapeutic properties of cannabinoid drugs on PTSD, with a particular focus on the target of each of the aforementioned memory phases. In the final section, we will review studies examining the ameliorative effects of cannabinoids on PTSD-affected populations not strictly related to memory modulation.

2. The endocannabinoid system

The discovery of the endocannabinoid system followed the identification in the early Sixties of the major psychoactive constituent of *Cannabis* namely Delta-9-tetrahydrocannabinol (THC) [33,34]. This lipophilic compound binds and activates a particular class of G-protein coupled metabotropic receptor, called cannabinoid-receptor type 1 (CB1) [35]. The discovery of the cannabinoid-receptor type 2 (CB2), through homology cloning [36], completed the picture of cannabinoid receptors identification. In the following years, the two major endogenous cannabinoids were also identified: the N-arachidonoyl ethanolamine (anandamide) [37], which acts as a partial agonist of both receptors [38], and the 2-arachidonoyl glycerol (2-AG) [39], which acts as a full agonist of both receptors [40]. Endocannabinoids are synthesized from lipidic membrane precursors [41–43] and released "on demand" by the post-synaptic terminals in an activity-dependent fashion. From the synaptic cleft they travel retrogradely to activate receptors presinaptically located [44]. Once the receptors have been activated, endocannabinoids are recaptured into neurons by still poorly identified mechanisms [45–47], where they undergo enzymatic degradation. The principal degrading enzymes for endocannabinoids are the fatty acid amide hydrolase (FAAH) [48] and the monoacylglycerol lipase (MAGL) [49,50] for anandamide and 2-AG, respectively. The CB1 receptor is the most abundant G-protein coupled metabotropic receptor in the mammalian brain [51], it is widely expressed in the prefrontal-limbic system including areas such as the amygdala, hippocampus and prefrontal cortex [52], and it is the principal mediator of the psychoactive effects of THC and of the many behavior-altering effects observed in experimental studies (see below). In contrast, the CB2 receptor is mainly expressed in peripheral immunological tissue [36], although its presence in the central nervous system has been also recently documented in regions such as the amygdala, hippocampus, striatum, substantia nigra and cortex [53]. Both the cannabinoid receptors are coupled to $G_{i/o}$ proteins which inhibit adenylate cyclase and voltage-gathed calcium channels, activate mitogen-activate protein kinases (MAPK) and inward rectifying potassium channels [54,55]. These molecular events usually result in a general inhibition of neurotransmitters release from pre-synaptic terminals of neurons where cannabinoid receptors are expressed. These include GABAergic interneurons within the limbic system [56] as well as glutammatergic [57], serotoninergic [58,59], noradrenergic [60] and dopaminergic [58] neurons.

3. Commonly used rodent models of learning and memory

Over several decades, many different preclinical models have been developed in order to deepen our knowledge of the biological, neurochemical and neurophysiological correlates of mammalian memory functions. In this section, we will briefly describe the most relevant behavioral paradigms for memory processes that can also be useful to mimic some of the PTSD symptoms. It is worth noting that given the high complexity of psychiatric disorders such as PTSD, animal models can only reproduce some aspects of the pathology. Therefore, the translation of conclusions coming from animal studies to humans should be always made by keeping in mind their suggestive rather than deterministic value.

3.1. Fear conditioning and extinction

A typical fear conditioning protocol, involves the simple pavlovian association between a neutral stimulus (context, sound, light, odor) and an aversive stimulus (footshock, predator scent). Following one or more pairings of the neutral stimulus with the aversive unconditioned stimulus (US) carried out during the training or conditioning session, the animal will learn the association between the two stimuli. As a result, the animal will begin to express the freezing response at the delayed presentation of the neutral stimulus only (now conditioned stimulus, CS) during the test or retention session. The total freezing response duration expressed by the animal during the retention session is the test variable, with longer durations interpreted as indicative of stronger memory traces [61]. A protocol of extinction involves the new learning that the CS no longer predicts the aversive US. In other words, the rodent will learn to suppress his fear responses elicited by a CS, when the CS is repeatedly presented in the absence of the following US [62]. It is now widely accepted that extinction does not represent an erasure of the previous CS-US association [30]. Indeed, the previous fear association can re-emerge spontaneously after a certain time (spontaneous recovery), after a change in the context (renewal), after the exposure to the US (reinstatement), and it is rapidly re-acquired after the exposure to a new CS-US pairing (rapid re-acquisition) [63].

3.2. Inhibitory (passive) avoidance

The inhibitory or passive avoidance test involves the natural aversion of rats and mice for bright spaces. Indeed, in a typical step-through inhibitory avoidance protocol a rat is introduced into

a bright context connected to a darker context by a guillotine door. After a fixed amount of time, the door is opened and the rat is allowed to freely move into the dark compartment of the apparatus. Once in the dark context, the door is closed and a single footshock is delivered (training session). After a fixed retention interval, the rat is again placed in to the bright context with the door opened, and the latency to step through the door is recorded (test session). A longer latency to step into the dark compartment is interpreted as a stronger memory [64]. In another version of the task, namely the step-down inhibitory avoidance, the rat is placed on an elevated platform, the shock is delivered once the rat steps down from the platform and the test variable consists in the latency to step down the platform [65].

3.3. Fear-Potentiated startle

The fear-potentiated startle paradigm involves the conditioning of the rodent to a light cue (CS) and a footshock (US) delivered in a particular apparatus connected to a platform sensitive to rodents' movements. Once the conditioning has been established and following a certain retention interval, the animal, placed back into the apparatus, will receive sudden unpredicted loud noise bursts. The noise bursts are delivered both in the presence (light-noise trials) and in the absence of the CS (noise-alone trials), and the startle reactions of the animals are recorded. The mean startle amplitudes for light-noise trials and noise-alone trials are then averaged across trials. Significant greater amplitudes for the light-noise trials versus the noise-alone trials will indicate a successful memory retention [66]. The relevance of behavioral paradigms involving the startle response in PTSD studies comes from enhanced startle reactions on human subjects suffering for PTSD and other anxiety disorders [67,68].

3.4. Morris water maze

Differently from the paradigms described so far, the Morris Water Maze test does not involve fear learning. Rather, it involves spatial learning under the aversive/stressful condition represented by being placed into water without escaping possibilities. In this test, a rodent placed into a water-filled swimming arena is trained under multitrial sessions to find a hidden platform. After the training phase, in the retention (probe) trial the platform is removed and the latency to reach the position, the time spent in the quadrant (target), the numbers of crossing of the area where the platform was located together with other possible measures are recorded. A shorter latency to reach the platform position, a greater time spent in the target quadrant and a greater number of crossings are interpreted as a measure of increased memory [69].

3.5. Novel object recognition

The Novel Object Recognition test is a learning task involving neither aversive stimuli nor highly stressful conditions. It is based on the rodent natural tendency to explore environmental elements that they had never encountered before. In the training trial a rodent, placed into an arena with two identical objects, is free to explore them for a fixed time interval. After a certain retention interval, the rodent is placed back into the arena where one of the objects is replaced by a novel never-encountered object. The time the subject spends in the exploration of the two objects is recorded, and a significantly longer exploration of the novel object over the familiar one is indicative of a better memory retention [70].

3.6. Radial maze

The radial maze test is an appetitively motivated learning task where rodents are trained to remember the arms of an asterisk-shaped 8-arm maze where they will find a food reward. During the retention session, the entries of the animals into arms that have never been rewarded is interpreted as a memory error, therefore the memory index is represented by the percentage of correct entries (i.e. entries in the rewarded arms) over the total number of entries in a fixed amount of time [71].

4. Early intervention in the aftermath of a trauma: effects of cannabinoids on consolidation of stressful experiences

The use of cannabinoid preparations in the immediate aftermath of a trauma is probably the most controversial and less promising approach in terms of efficacy in the treatment and prevention of PTSD after exposure to a traumatic event, for a number of reasons. The first is related to the unpredictable and devastating nature of a traumatic experience, which does not easily allow the clinician to organize for a well-designed therapeutic approach. Elements such as the informed consensus, patient's anamnesis and medical history, a standardized time interval to perform drug administrations, might be difficult to obtain in an emergency situation (see below a for discussion on anesthetics in intensive care units, ICUs). Another, and perhaps most important reason, as stated by Vermetten and colleagues [26], is that only a small subgroup of people exposed to a trauma ultimately develops PTSD and it is currently impossible in such an early stage to distinguish a person needing treatment from those who do not. The third reason is related to the effects of cannabinoids on memory consolidation themselves. Indeed, conflicting and often opposite effects of cannabinoid agonists/antagonists administrations have been reported in animal studies investigating memory consolidation, depending on factors such as the tested brain area, doses used and/or the behavioral paradigms especially when involving different levels of stress and/or emotional arousal (see Ref. [15] for an updated review).

4.1. Animal studies

As stated literature data regarding cannabinoid effects on memory consolidation are controversial.

4.1.1. Agonists

In the contextual fear conditioning paradigm, the CB1 receptor agonist HU-210 was found to impair consolidation when systemically administered in rats [72]. In the inhibitory avoidance test, the non-selective CB1/CB2 agonist WIN55,212-2 was found to impair consolidation when infused into hippocampal CA1 area [73–77] and central amygdala [78] but the same drug on the same task was found to enhance consolidation when infused into basolateral amygdala [79]. Also the endocannabinoid anandamide when infused into hippocampal CA1 immediately after Inhibitory Avoidance training enhanced the consolidation of the task [80]. However, when systemically administered, anandamide impaired consolidation of Inhibitory Avoidance training [81–83]. In a fear-potentiated startle experiment, WIN55,212-2 infused into basolateral amygdala, but not into medial prefrontal cortex, impaired the consolidation of the test [84]. Systemic WIN55,212-2 also showed biphasical opposite effects on short-term memory retention of rats performing a Novel Object Recognition test when administered post-training in two different conditions [85]. In particular, the drug impaired 1-h retention of rats trained under high arousal (no prior habituation to the test apparatus) while it enhanced 1-h retention performance of rats trained under low arousal conditions (extensive prior habituation to the apparatus)

[85]. Interestingly, the same dose that impaired 1-h retention on non-habituated rats, enhanced memory consolidation in rats trained under the same arousal condition as assessed by a 24-h retention session [85]. URB597 elevates anandamide levels at active synapses through inhibition of its principal degrading enzyme FAAH [86]. We have recently demonstrated that this drug enhances consolidation of Inhibitory Avoidance training when infused into basolateral amygdala, hippocampus and prefrontal cortex, through indirect activation of cannabinoid receptors [87]. The anesthetic drug propofol, apart of its GABAergic action [88], is an inhibitor of the FAAH enzyme [89], thus inducing similar central effects of those induced by URB597 in terms of activation of the endocannabinoid system. Interestingly, we observed enhanced consolidation of Inhibitory Avoidance training in rats systemically administered with anesthetic doses of propofol; the effects were mediated by indirect cannabinoid receptor activation, and not related to GABA activity [90].

4.1.2. Antagonists

A few studies investigated the effects of cannabinoid antagonists on memory consolidation. One of these studies showed that the CB1 antagonist AM251 impaired Inhibitory Avoidance consolidation when either infused in hippocampal CA1 region [91], and another study observed the same effect when AM251 was infused into basolateral amygdala [79]. Basolateral amygdala-infused AM251 also impaired consolidation of contextual fear conditioning in rats [92].

4.1.3. PTSD models

The studies above described can account for the effects of cannabinoids on the consolidation for aversive experiences, partly modeling the memory consolidation of a traumatic event, but failing to provide useful information on the stress-related trauma-induced alterations in behavior. To address this issue, studies involving validated preclinical model of PTSD are more informative. Unfortunately, to date only a few studies examined the effect of post-stress cannabinoid administration specifically in PTSD models. In one of these studies, rats were exposed to the single-prolonged stress model [93] that involves a series of subsequent discrete stressor able to induce in exposed rats long-term behavioral alterations such as: enhanced Inhibitory Avoidance conditioning, impaired Inhibitory Avoidance extinction, potentiation of acoustic startle response, inhibition of the hypothalamic-pituitary-adrenal (HPA) axis and increased anxiety [94]. The administration of the synthetic cannabinoid agonist WIN55,212-2, 24 h after the Single Prolonged Stress procedure, was found to prevent the observed alterations in Inhibitory Avoidance conditioning and extinction, acoustic startle response potentiation and HPA inhibition [94]. Interestingly, alterations in Inhibitory Avoidance and acoustic startle response were prevented also when WIN55,212-2 was infused into the basolateral amygdala, an effect that was blocked by co-administration with the cannabinoid antagonist AM251 [94]. The same authors further investigating this subject in another study where post-stress WIN55,212-2 successfully blocked the Single Prolonged Stress-induced alterations also when infused into hippocampus but not in the prefrontal cortex [95]. In addition, the observed ameliorative effects of WIN55,212-2 where blocked by inhibition of glucocorticoid receptors in the basolateral amygdala and hippocampus [95]. In another study, rats were exposed to a single footshock with a classical Inhibitory Avoidance training, followed by situational reminder on subsequent days, which consisted in placing the animals in the light compartment without access to the dark conditioned compartment in order to avoid extinction [96]. In this experiment, animals exposed to shock and to situational reminders on later days, differently from animals exposed to shock only, showed impaired extinction, enhanced startle latency, altered hippocampus-accumbens pathway plasticity, altered CB1 and glucocorticoid receptors expression in prefrontal cortex, hippocampal CA1 and basolateral amygdala [96]. Much of these effects were prevented by post-training systemic injection of WIN55,212-2, and co-administration with AM251 blocked the ameliorative effects of WIN55,212-2 [96].

These studies seem to prove a certain efficacy of post-stress administration of cannabinoid agonists in preventing the stress-induced alterations on behavior. However, contrasting findings were reported in a recent study that examined the effects of systemic injections of the CB1/CB2 agonist THC, the principal active constituent of cannabis plant, and the CB1 antagonist AM251 [97]. In particular, when THC was given to rats immediately after exposure to predator scent stress, it was able to reduce anxiety measured in the acoustic startle and elevated plus maze tests only in the short-term, with no effects on the long-term neither on anxiety nor on contextual freezing [97]. Conversely, the CB1 antagonist AM251 reduced both anxiety levels and contextual freezing in the long-term showing PTSD-preventing properties [97]. To conclude, given the impossibility to know in advance if someone will develop PTSD after the exposure to a traumatic experience, and given the contrasting results arising from animal studies discussed so far, further studies are needed to clearly demonstrate the utility to administer cannabinoid drugs in the aftermath of a trauma.

4.2. Human studies

Human data concerning cannabinoids effects on consolidation of traumatic experiences are hard to collect and few studies are available in the literature. However, there are cases of patients treated with anesthetic drugs in ICUs after accidents and other situations requiring emergency surgery. In such cases, anesthetics are often administered during the time window where memory consolidation occurs, in close proximity to the traumatic experience. Two different studies, which examined different cohorts of ICU patients treated with propofol in the aftermath of a traumatic experience, reported correlative data between propofol use and the enhanced risk to develop PTSD and PTSD symptoms severity [98,99]. In particular, the retrospective cohort study by Usuki and coworkers (2012), examined a cohort of 300 motor vehicle accident survivors who were treated with propofol within 72 h from the trauma. They controlled for confounding factors such as alcohol consumption, use of midazolam, ketamine or morphine within 72 h from the accident and history for psychiatric illness [99]. PTSD diagnosis and symptoms severity were formulated through the administration of the Clinician-Administered PTSD Scale (CAPS) at 1 and 6 months from the accident [99]. The results showed that patients treated with propofol, had an enhanced risk for full or partial PTSD at 1 month and 6 months from the accident [99]. Moreover, propofol-treated patients also showed increased PTSD symptoms severity (i.e. higher scores at the items of the CAPS scale) at 6 but not 1 months from the accident [99]. Although the limitations of a retrospective study has to be taken into account, taken together these data suggest that the use of propofol after accidents and other traumatic experiences should be avoided since it might enhance the risk of subsequent PTSD development [100]. Nevertheless, what all of this has to do with cannabinoids? The anesthetic properties of propofol, like many other related anesthetics, are mediated by the facilitation of GABA-mediated inhibitory transmission and a specific propofol binding side on mammalian GABA-A receptor has been identified [88]. The sedative, hypnotic and amnesic actions as well as its pharmacokinetic properties, make propofol a very versatile and widely used anesthetic in the clinical practice [100]. However, propofol, as stated above, also inhibits the FAAH enzyme causing an increase of anandamide levels and this property differentiates proprofol from all the other clinically used anesthetics [89]. The authors of the reported study

speculate, also on the basis of preclinical data obtained by our group in rats [90] that the observed enhanced risk of PTSD development, linked to propofol use, might be mediated by the enhanced endocannabinoid transmission through anandamide levels elevation [99] and thus by the facilitation of traumatic memory consolidation [100]. To conclude, the mixed results of cannabinoids effects on consolidation do not seem to point out with certainty that post-trauma administrations of cannabinoids could be beneficial or even detrimental for later PTSD symptoms development.

5. "Reducing the re-experiencing of traumatic memories": the effects of cannabinoids on memory retrieval

Differently from memory consolidation studies, much consensus exists in the literature regarding the effects of cannabinoids on memory retrieval. Indeed, data from different research groups all seem to point out to an impairing effect on memory retrieval induced by cannabinoid agonists [15]. Given this, and the possible clinical applications involved, the paucity of studies examining this issue on preclinical PTSD models and on clinical trials with PTSD patients appears surprising. Indeed, by attenuating the retrieval of traumatic memories it should be theoretically possible to reduce re-experiencing symptoms thus reducing the subsequent over-consolidation which characterize PTSD patients, thus also leading to a reduced impact that those memories have on anxiety and mood. Besides, the update of the original memory trace occurring after its reactivation, known as re-consolidation, could weaken the trace making it less persistent [101]. Interestingly, this approach has already proven to be helpful in reducing phobic fear, when glucocorticoids (which share with cannabinoids the ability to impair memory retrieval) were administered to phobic patients 1 h before retrieval of fearful information [102].

5.1. Animal studies

All animal studies investigating cannabinoid effects on retrieval reported impairing effects of agonists. For example, systemic THC was found to impair retrieval of the Inhibitory Avoidance task [103]. The same treatment along with exposure to marijuana smoke, were also found to impair retrieval of Morris Water Maze task [104] and these effects were blocked by the CB1 antagonist rimonabant [104]. Morris Water Maze retrieval was also impaired by systemic treatment with administration of the cannabinoid agonist CP-55,940 [105]. A recent study, performed by our group, showed an interesting results pattern in rats performing the Morris Water Maze task under two stress conditions: a more stressful condition due to exposure to colder water (19 °C) and a less stressful condition due to the exposure to warmer water (26 °C) [106]. Our results showed that the injection of WIN55,212-2 and JZL184 (a MAGL enzyme inhibitor which elevates endogenous 2-AG levels) into the hippocampus impaired the recall of the platform location position in rats trained under the higher stressful condition only [106]. Systemic THC administration prior to retrieval, impaired rats performance in a radial maze task in two different studies [103,107] and the cannabinoid antagonist rimonabant reverted those effects [103,107]. In addition, intra-hippocampal administration of CP-55,940 induced a deficit in radial maze retrieval reverted by pretreatment with the antagonist rimonabant [107]. A deficit in radial maze retrieval was also observed when the CB1/CB2 agonist WIN55,212-2 was injected systemically or into the dorsal hippocampus [108]. The same compound also induced impaired retention of contextual fear conditioning when infused into hippocampal CA1 (an effect reverted by prior hippocampal β-adrenoceptors blockade) [109] and when infused into ventral subiculum [110]. Moreover, intracerebroventricular administration [111] or intra-CA1 injection [75,76,112] of WIN55,212-2 also impaired retrieval of step-down Inhibitory Avoidance. Systemic WIN55,212-2 was also able to impair retrieval of an object recognition task and of a radial water maze test, and both the effects were blocked through pre-treatment with rimonabant [113]. In another study that evaluated the effects of WIN55,212-2 micro-infusions in different brain regions in the fear-potentiated startle paradigm, the drug was found to impair the retrieval of the task when infused into basolateral amygdala and medial prefrontal cortex [84].

5.2. Human studies

Studies investigating cannabinoids effects on memory retrieval are scarce and clinical experimental trials on psychiatric patients are, at least to our knowledge, completely absent in literature. In addition, results from studies examining human retrieval performance in long-term learning task with administered THC or marijuana are mixed, in striking contrast to the well known impairing retrieval effects in short-term/working memory tasks [114]. However, when interpreting experimental data in humans, it must be considered that the test material in memory tasks is usually composed by lists of words/digits, prose material, visuo-spatial items, semantic knowledge, knowledge of common fact, which all share really few features in common with traumatic events in PTSD, especially regarding the stress and emotional arousal levels involved. In a study by Miller and co-workers (1977), smoking marijuana before a retrieval test for prose material learned 24 h before and under drug-free conditions, significantly reduced the performance of the task [115]. Moreover, in a study which assessed college student's ability to recall a series of common facts from long-term memory, acute administration of marijuana (calibrated to 0.3 mg/kg of THC) did impair the performance [116]. When examining marijuana effects on semantic memory retrieval of simple category items, Block and Wittenborn (1984) reported only an increase in reaction times but no effects on error rates in treated subjects in comparison to placebo-treated ones [117]. In a similar study, where subject were asked to retrieve as many instances of a certain category as they could in 2 min, the same authors found that marijuana did not alter subjects' performance but only produced a shift of the responses towards more uncommon instances [118]. Another study examined subjects' performance on a series of cognitive tasks at different time points after acute THC administration. In relation to semantic retrieval, measured by means of a verbal fluency task, 6 h after THC administration the subjects receiving the higher dose of THC (15 mg) produced significantly more words than subjects receiving the lower dose (7.5 mg) but no differences were observed in comparison to placebo [119]. In conclusion, more data on cannabinoids effects on human memory retrieval need to be collected, and preferably from clinical trials, in order to consider them as of potential benefit for PTSD treatment.

6. Potentiating the efficacy of exposure therapy through cannabinoid-mediated enhancement of extinction

The pharmacological enhancement of extinction learning is one of the most prolific fields in the study of preclinical models of stress and fear-related disorders for a two-fold reason. First, the cognitive-behavioral exposure-based therapy engages extinction mechanisms [12] and extinction enhancer compounds can either increase the efficacy itself and/or reduce the duration of psychological intervention. Secondly, extinction has to be considered not as an erasure of the original traumatic memory, rather as a new inhibitory learning able to reduce the conditioned anxiety/fear responses elicited by the exposure to trauma-related reminders [120–122]. The possibility to retain the memory for the trauma,

but without the negative devastating consequences of an established PTSD, is of great advantage in comparison to the complete erasure of the trauma traumatic memory. Indeed, in this case, a subject can use previously learned experience to afford analogue future situations (e.g. soldiers in war).

Many are the extinction enhancer compounds under investigation in PTSD field (see Refs. [6,123–126] for review). In the present review we will focus on cannabinoid compounds.

6.1. Animal studies

6.1.1. Agonists

Systemic administration of the non-selective agonist WIN55,212-2 or the indirect agonist AM404 was found to enhance extinction of contextual fear conditioning for both recent (24 h old) and remote (30 days old) memory [127]. The same treatments also facilitated contextual fear conditioning extinction with a single extended extinction session of 30 min [128]. AM404, the phytocannabinoid cannabidiol and WIN55,212-2 enhanced contextual fear conditioning extinction when intracereboventricularly infused [129,130]. Cannabidiol promoted contextual fear conditioning extinction also when infused into the infra-limbic region of medial prefrontal cortex, an effect blocked by systemic administration of rimonabant [131]. In addition, WIN55,212-2 and AM404 facilitated extinction of Inhibitory Avoidance when micro-infused into CA1 region of the hippocampus [132]. Systemic AM404 also enhanced extinction of fear-potentiated startle, an effect that was blocked by co-administration of the CB1 antagonist rimonabant [133], as well as micro-infusion of WIN55,212-2 into infra-limbic cortex [134]. Another study showed that the FAAH inhibitor URB597 facilitated short-term (but not long-term) extinction of contextual fear conditioning in mice. However, when mice where additionally stressed with a repeated social defeat procedure, URB597 also enhanced long-term contextual fear conditioning extinction [135]. Systemic URB597 enhanced extinction of auditory fear conditioning as well [136]. Moreover, the FAAH inhibitor AM3506 enhanced auditory fear conditioning extinction when systemically or intra-amygdala administered; the effect was mediated by anandamide activation of cannabinoid receptors [137]. Intra-CA1 injection of anandamide enhanced extinction of contextual fear conditioning, but co-administration with a non-altering dose of the CB1 antagonist AM251 blocked the enhancing effects thus again demonstrating the important role of cannabinoid receptor activation in facilitating memory extinction [91]. Finally, the FAAH inhibitor OL-135 showed extinction enhancing properties when systemically administered in a Morris Water Maze task, an effect blocked by administration of the cannabinoid receptor antagonist rimonabant [138].

6.1.2. Antagonists

Regarding cannabinoid antagonists and extinction of memory for emotional events, different studies showed that systemic administrations of the CB1 antagonists rimonabant and AM251 impaired extinction of cued fear conditioning [136,139–142] as well as contextual fear conditioning [127,128,143,144]. Systemic antagonism of CB1 receptors also impaired extinction of fear-potentiated startle [133,145] and the same effect was observed when CB1 were blocked selectively into prefrontal cortex [84,134]. Also in the paradigm of Inhibitory Avoidance, CB1 antagonists produced an impairment in extinction learning when given either systemically [146], into the basolateral amygdala [147] or into the CA1 region of the hippocampus [132]. In addition, intra-CA1 infusion of AM251 also impaired extinction of contextual fear conditioning [91]. Systemic administration of rimonabant also produced an impairment of extinction in the Morris Water Maze task [148]. All these studies seem to point out to a strong enhancing effect of cannabinoid agonists on extinction processes which appears to be mediated by CB1 receptors, however evidence for the ameliorating effects on preclinical PTSD models are still lacking.

6.2. Human studies

Regarding extinction processes few more data are available on cannabinoid effects in comparison with retrieval evidence, thus also indicating the great success that this field of study has been receiving. For instance, Rabinak and colleagues (2013) conditioned healthy volunteers to a sound burst after the presentation of 2 different visual conditioned stimuli on a monitor [149]. They recorded the skin conductance responses, a physiological index of emotional reactivity, immediately after the conditioned stimuli onset. On the subsequent day, one of the two conditioned stimuli was extinguished with an extinction procedure carried 120 min after subjects' ingestion of 7.5 mg of THC or placebo [149]. On the following day, participants were subjected to an extinction memory recall test. Results showed that, even if no differences on skin conductance responses were found during the acquisition phase, on the recall test THC-treated group showed significantly lower skin conductance responses at the presentation of the extinguished CS in comparison to the unextinguished one, differently from the placebo-treated group. As a result, a difference between THC and placebo-treated subjects was also found in the mean difference of skin conductance responses on extinguished minus unextinguished CS trials [149]. The same group extended these results by replicating the experiment during functional magnetic resonance (fMRI) imaging scanning [150]. The authors found that subjects who received THC prior to extinction, exhibited greater ventromedial prefrontal cortex and hippocampal activation to the extinguished CS presentation during recall, when compared to placebo-treated subjects [150]. Another study involved a human version of fear conditioning using brief electric shocks as unconditioned stimuli [151]. In this study 32 mg of cannabidiol were administered by inhalation prior or immediately after the CS extinction procedure in order to target the acquisition or the consolidation of extinction respectively. While no differences were observed in skin conductance responses during extinction, the authors found a reduction of subjective shock expectancy ratings at the presentation of extinguished CS in the recall test carried 48 h after extinction in the group treated with cannabidiol after extinction but not in the other groups [151]. Moreover, when they reinstated the extinguished association through the presentation of another brief shock, they found a lower increase of the skin conductance responses on both groups that had received cannabidiol in comparison to the placebo group, thus showing that the learned extinction on these groups was more resistant to reinstatement [151]. Conversely, another human study involving a fear conditioning plus fear-potentiated startle procedure reported only a transient reduction of skin conductance responses during extinction training on THC-treated subjects compared to placebo-treated ones [152]. Indeed, this effect was not retained during the recall test conducted 48 h later and no effects of THC were observed in the fear-potentiated startle [152]. An interesting study investigated if a genetic variation at the level of regions of the genome encoding for CB1 receptors, could impact on extinction performance in human healthy volunteers. To this aim, the authors genotyped 150 subjects that underwent a procedure of fear-potentiated startle in a virtual reality environment [153]. They found that subjects homozygotes for a particular polymorphism located within the promoter region of the CB1 receptor gene, failed to extinguish fear thus displaying significantly higher levels of fear-potentiated startle at the end of extinction training, when compared to other groups [153].

To summarize, preclinical evidence points to cannabinoid agonists as potential candidates for extinction enhancement during

exposure therapy, thus soliciting more research on human subjects. As an example, clinical effects of cannabinoid agonists might be tested in PTSD patients with drugs given immediately after a series of exposure therapy sessions, with a placebo-controlled design. Scores to standardized tools for the assessment of PTSD symptomatology (e.g. CAPS) could then be compared in each patient with measures taken before the treatment, right after the treatment and after a defined follow-up interval (e.g. 3 or 6 months). In addition, for each treatment group, a direct comparison between each interval could be also performed.

7. Ameliorative effects of cannabinoid drugs on PTSD symptomatology

Although this is a recent area of research, some studied reporting beneficial effects of cannabinoid drugs in PTSD patients are appearing in the literature. Passie and co-workers (2012) reported a case of a 19-year-old male patient with a severe abuse-related PTSD symptomatology also including dissociative states and self-mutilation behaviors triggered by flashbacks [154]. When found positive to THC in toxicological testing, he declared to clinicians that he discovered that smoking cannabis when he first felt reactivation and intensification of the traumatic memories could prevent him to enter in the dissociative state increasing his ability to maintain cognitive control on the situation [154]. In addition, he also experienced a reduced need for self-mutilation. The improvement in self-control and stability was also noted by his therapist, not aware of the use of cannabis as self-medication [154]. Interestingly, it has been also recently published a study reporting the results of an open label clinical trial with the synthetic cannabinoid agonist nabilone given orally (0.5 mg per die, 1 h before bedtime) to 47 PTSD patients [155]. Thirty-four of the treated patients (representing the 72% of the sample) experienced the total cessation of nightmares or lessening of their severity and in some cases an improvement of daytime flashbacks as well [155]. Another study examined a cohort of 101 patients from a hybrid mental health and correctional institute with various psychiatric conditions, who received off-label nabilone for 4–5 years based on its known effectiveness in chronic pain reduction and on its potential effects on PTSD insomnia and nightmare amelioration [156]. The results showed: i) a significant increase in the average numbers of hours slept, ii) a significant reduction in the number of nightmare experiences, iii) a significant increase in global functioning as assessed by the Global Assessment of Functioning (GAF), and iv) most importantly (on the subgroup of patients (n = 58) with diagnosed PTSD) a significant decrease of average PTSD symptoms severity as assessed by the Post traumatic Checklist-Civilian version (PCL-C) [156]. A reduction of PTSD symptom severity was also reported in another study that compared pre-treatment and post-treatment CAPS scores of 80 PTSD patients who began to take medical cannabis in New Mexico in 2009, when cannabis use for PTSD was approved [157]. In particular, the symptom severity reduction was statistically significant for all the different symptom clusters examined by the CAPS: total score, criterion B (re-experiencing symptoms), criterion C (numbing and avoidance) and criterion D (hyperarousal) [157]. Other studies reported that the association between PTSD and cannabis use is usually motivated by the search for its sleep-promoting effects and a general help in coping and managing the symptomatology [158,159]. Last but not least, worth of note is a study investigating the effects of nabilone specifically on PTSD-associated nightmares, in a double-blind placebo-controlled cross-over design on 10 PTSD patients [160]. Nabilone was administered daily 1 h before bedtime, for 7 consecutive weeks which were followed by 2 weeks of wash-out before the start of the other treatment period (7 weeks long). 70% of the subjects reported symptom improvement after nabilone treatment, while only a 22% of subjects reported improvement in the placebo treated group [160]. The primary improvement in the nabilone treated group was registered for the CAPS Recurring and Distressing Dream Scores which were significantly reduced on both frequency and intensity. Other improvements were observed on the Clinical Global Impression of Change (CGI-C) and the General Well Being Questionnaire [160]. In addition, at the end of the nabilone treatment period, 44% of subjects reported no distressing dreams in the last week of treatment compared to the 0% of the placebo group. Conversely, none of the subjects in the nabilone treatment period reported daily distressing dreams, while the 50% of subjects in the placebo treatment period experienced distressing dreams [160].

Taken together, these studies seem to indicate that cannabinoids could exert positive effects on an already established PTSD syndrome. Even though the design of these studies does not allow to clearly identify the nature of the cannabinoid-mediated improvements of the symptomatology, the reduction of nightmares and the general sleep quality promotion is frequently reported by PTSD patients who began either to consume or to be treated with cannabis derivatives. It is worth noting that it is now widely accepted that consolidation and reorganization of different kinds of memory occur during sleep [161–163]. It is tentative to speculate that cannabinoid stimulation during sleep may affect the reorganization of the traumatic memory, reducing trauma-related nightmares and possibly gradually reducing the distressing impact that traumatic memory exerts on behavior and mood. If future research will confirm this hypothesis, it will be possible that the administration of cannabinoids in PTSD patients, by enhancing the extinction and/or attenuating the retrieval of traumatic memories, could not only reduce post-traumatic symptomatology but could also lead the patient towards a complete recovery from the disease.

8. Conclusions

In the present paper we reviewed data from both animal and human studies showing the modulatory effects of cannabinoids on different memory phases. Even though the most of the presented data come from animal studies, and therefore conclusions on their translational value need to be taken with a word of caution, we evaluated these results in the view of a future application of cannabinoid drugs in the treatment of PTSD. Indeed, by targeting a particular stage of the traumatic memory processing at the right time, the intensity of the post-traumatic symptomatology could be drastically reduced and the efficacy of the available exposure-based psychotherapies improved. Among the memory phases taken into account, cannabinoid treatments targeting the consolidation stage of the trauma, might be the less promising in terms of efficacy. Moreover, administrating a drug in the immediate aftermath of a trauma might not be always easily achievable in the clinical practice and is not devoid of ethic concerns. Targeting the retrieval of the traumatic memory with cannabinoid agonists might exert more promising effects by reducing the vividness and persistence of the memory trace and consequently the occurrence of related symptoms. However, to date only few preclinical studies investigated cannabinoids effects on retrieval, and human studies involving fear-related tasks or clinical trials are practically absent in literature. Finally, the enhancement of extinction learning is, above the others, the most promising effect that could find a recent future application in the treatment of PTSD and other stress-related disorders. Indeed, by potentiating extinction learning processes, cannabinoid agonists could reduce the conditioned fear and anxiety responses triggered by trauma reminders, increasing patients general ability to actively cope with the trauma without affecting the original memory trace. Moreover, the use of

cannabinoids in conjunction with exposure therapy could increase its efficacy and reduce the duration of the psychological intervention. In the last section, we reviewed data on PTSD patients who already benefited or are still benefiting from treatments with medical cannabinoids thus showing how cannabinoids efficacy in PTSD treatment is far from being a mere speculation derived from animal studies. Still, more studies are needed to better characterize the quality of cannabinoid-mediated improvements and the exact way in which they could be safely used.

Conflict of interest

The authors declare no conflict of interest.

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