Diverse therapeutic developments for Post-Traumatic Stress Disorder (PTSD) indicate common mechanisms of memory modulation

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Abstract

Post-traumatic stress disorder (PTSD), characterized by abnormally persistent and distressing memories, is a chronic debilitating condition in need of new treatment options. Current treatment guidelines recommend psychotherapy as first line management with only two drugs, sertraline and paroxetine, approved by U.S. Food and Drug Administration (FDA) for treatment of PTSD. These drugs have limited efficacy as they only reduce symptoms related to depression and anxiety without producing permanent remission. PTSD remains a significant public health problem with high morbidity and mortality requiring major advances in therapeutics. Early evidence has emerged for the beneficial effects of psychedelics particularly in combination with psychotherapy for management of PTSD, including psilocybin, MDMA, LSD, cannabinoids, ayahuasca and ketamine. MDMA and psilocybin reduce barrier to therapy by increasing trust between therapist and patient, thus allowing for modification of trauma related memories. Furthermore, research into the memory reconsolidation mechanisms has allowed for identification of various pharmacological targets to disrupt abnormally persistent memories. A number of pre-clinical and clinical studies have investigated novel and re-purposed pharmacological agents to disrupt fear memory in PTSD. Novel therapeutic approaches like neuropeptide Y, oxytocin, cannabinoids and neuroactive steroids have also shown potential for PTSD treatment. Here, we focus on the role of fear memory in the pathophysiology of PTSD and propose that many of these new therapeutic strategies produce benefits through the effect on fear memory. Evaluation of recent research findings suggests that while a number of drugs have shown promising results in preclinical studies and pilot clinical trials, the evidence from large scale clinical trials would be needed for these drugs to be incorporated in clinical practice.

Keywords: psychedelics; MDMA; psilocybin; reconsolidation; fear; ketamine

Abbreviations

PTSD, Post-traumatic stress disorder; APA, American Psychological Association; VA, Department of Veteran Affairs USA; mPFC, Medial prefrontal cortex; LC, Locus coeruleus; ACC; Anterior cingulate cortex; MRI, Magnetic Resonance Imaging; SSRI, Selective serotonin reuptake inhibitors; SNRI, Serotonin-norepinephrine reuptake inhibitors; CBT, Cognitive-behavioral therapy; CB, Cannabinoid; EMDR, Eye movement Desensitization and Reprocessing therapy; LSD, Lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; THC, Δ^9-tetra-hydrocannabinol; DMT, Dimethyltryptamine; DCS, D-cycloserine; NPY, Neuropeptide Y; DMN, Default mode network; CAPS, Clinician-Administered PTSD Scale; IES-R, Impact of Event Scale-Revised; PCL-S, PTSD Checklist–Specific; SERT, Serotonin transporter; NET, Norepinephrine transporter; DAT, Dopamine transporter; VMAT, Vesicular monoamine transporter; NMDAR, N-methyl-D-aspartate receptor; β-AR, β Adrenergic receptor; mGluR, Metabotropic glutamate receptor; cAMP, cyclic AMP; AC, Adenylyl cyclase; PKA, Protein kinase A; PKC, Protein kinase C; MEK, Mitogen-activated protein kinase kinase; ERK, Extracellular signal-regulated kinase; PI3K, Phosphoinositide 3-kinase; mTOR, Mammalian target of rapamycin; p70S6K, Ribosomal protein S6 kinase; CREB, cAMP response element-binding protein; CRE, cAMP response elements; Zif268, Zinc finger 268; CRH, Corticotrophin-releasing hormone; AM, Adrenal medulla; AC, Adrenal cortex; IL-1, Interleukin-1; IL-6, Interleukin-6; TNF-α, Tumour necrosis factor-α.

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Acknowledgements

References

1. Introduction

Post-traumatic stress disorder (PTSD) is an acquired mental health condition following exposure to trauma resulting in lasting changes to behaviour (Kirkpatrick & Heller, 2014). These changes include core symptoms of intrusive mental imagery, avoidance of reminders, negative mood and cognition, and hyperarousal of stress reactivity (Kirkpatrick & Heller, 2014). Following trauma emotional memories are formed. In the short term the significant emotional competent can be extinguished, however, in some people this does not occur, and a diagnosis of PTSD may be made after one month of exposure to the trauma (Careaga, Girardi, & Suchecki, 2016). Unlike non-pathological traumatic memories, in patients with PTSD, memories are much more vivid, easily triggered by matching cues and more distressing (Ehlers, 2010). PTSD involves both remembering and reacting to a new traumatic event and a failure to extinguish and reacting to those events, it is a disorder of involving memory pathology.

The initial association of traumatic events with previously neutral stimuli – for example, memory of a specific location or smell associated with a traumatic episode – has behavioural and neural properties predicted by classical (or Pavlovian) fear conditioning (L. Johnson, J. McGuire, R. Lazarus, & A. A. Palmer, 2012; Yehuda & LeDoux, 2007). Evidence suggests both classical fear conditioning and PTSD involve amygdala-based associative memory and prefrontal cortex mediation of extinction of associative fear memories (L. Johnson, et al., 2012; Nader, Schafe, & LeDoux, 2000). PTSD memory deficits include reduced extinction of fear memory or overgeneralization of fear response to safe context (Parsons & Ressler, 2013).

Current mainstay treatments for PTSD are psychotherapy with cognitive behavioural therapy, cognitive processing therapy, prolonged exposure therapy and pharmacotherapy with

selective serotonin reuptake inhibitors (SSRI) (APA, 2017; Phoenix, 2020). Evidence is accumulating suggesting that alternative pharmacological treatments, most notably psychedelic drugs, and other non-conventional substances, especially when combined with psychotherapies, could offer new hope to better and long-term treatment success for PTSD (Mitchell, et al., 2021; Scheeringa & Weems, 2014; Sessa, 2017; Yatzkar & Klein, 2010). Current thinking and developments of new pharmacological and therapeutic approaches amount to a paradigm shift for modern psychiatry.

2. Epidemiology

Data indicates that the overall lifetime risk of exposure to trauma such as physical or sexual abuse, wars, accidents, torture, natural disaster at least once is high. In a large national survey of the US, Kessler and colleagues (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995) found that most people will be exposed to at least one traumatic event during their lifetime. The exposure rate to trauma in women is high with data from Resnick and colleagues (Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993) indicating 70% of women will be exposed to trauma in their lifetime. Stemming from these high rates of trauma exposure is an overall PTSD incidence of around 1% in the population (Jacques, et al., 2019; Yehuda, et al., 2015). This places PTSD on a similar level with other major mental illnesses for example schizophrenia (1% of population) with different types of occupation, country of residence and types of trauma exposure affording increased risk (Yehuda, et al., 2015). In military populations where exposure to combat related trauma is higher, higher rates of PTSD are reported including chronic PTSD (Yehuda, et al., 2015). Higher rates of PTSD are also reported in health care workers and refugees. Moreover, PTSD is often associated with comorbidities

like substance abuse, major depressive disorder and other anxiety disorders (Brady, Killeen, Brewerton, & Lucerini, 2000). It presents a significant financial and emotional burden for patient, families, and health care systems (Sareen, 2014). In summary, PTSD is a major neuropsychiatric disorder affecting a large numbers of people.

3. Pathophysiology

Dysregulation of fear memory is central to the development of PTSD (fig 1) (Bergstrom, McDonald, Dey, Fernandez, & Johnson, 2013; Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Debiec & Ledoux, 2004). Most individuals who undergo a traumatic experience recover from it, while some develop significant psychopathology (Careaga, et al., 2016). Amongst the mechanisms underlying the development of PTSD are increased encoding, decreased extinction and overgeneralization of fear memory. Furthermore, alterations in brain circuitry and neurotransmitters contribute to memory dysfunction observed in PTSD.

Structural and functional abnormalities in brain areas such as the hippocampus, amygdala and medial prefrontal cortex increase the individual's vulnerability for developing PTSD (Bremner, Elzinga, Schmahl, & Vermetten, 2008; Milad, et al., 2009; Shin, Rauch, & Pitman, 2006). Recent genetic studies highlight possible genetic contributions to hyperarousal among those with PTSD and the identification of chromosomal regions associated with basal ganglia medium spiny neurons (Gelernter, et al., 2019; Sheerin, Lind, Bountress, Nugent, & Amstadter, 2017). The neural circuits formed by interconnection of neurons from these areas govern stress response and encode traumatic memories. Alteration in these circuits is postulated to be associated with higher risk of PTSD, with one area of focus being the hippocampus (Chaaya, Battle, & Johnson, 2018). Magnetic Resonance Imaging (MRI) studies in PTSD patients have

revealed reduced hippocampal volume when compared with control subjects (Bremner, et al., 1995; Gurvits, et al., 1996). Hippocampal volume reduction seen in these patients has been linked with increased glucocorticoid receptor sensitivity despite low glucocorticoid levels (Szeszko, Lehrner, & Yehuda, 2018). Additionally, a study has shown that there may be pre-existing hippocampal volume reduction before the development of PTSD (M. W. Gilbertson, et al., 2002). In a study with monozygotic twins, the severity of PTSD was inversely correlated with the hippocampal volume in PTSD patients and patients' trauma-unexposed identical co-twins (M. W. Gilbertson, et al., 2002). This suggest that reduced hippocampal volume was present prior to trauma. When exposed to trauma, these individuals may have an increased risk for developing PTSD. The hippocampus is implicated in storage of declarative memory as well as contextual aspects of fear memory (Fuchs & Gould, 2000). Pre-existing volume reduction might be responsible for impaired extinction of fear memories which can account for the inability of these individuals to recover from traumatic experiences (M. W. Gilbertson, et al., 2002).

Hyperreactivity of the amygdala is a prominent feature consistently shown to be associated of PTSD (Shin, et al., 2006). Functional MRI studies have shown that PTSD patients have a hyperresponsive amygdala compared to controls when presented with a stressful reminder (Shin, et al., 2006). The amygdala is also found to be hyperreactive during fear acquisition in PTSD patients, suggesting that it may be responsible for enhanced encoding of fear memories (Bremner, et al., 2005). The acquisition of conditioned fear, known as 'fear load', was shown to be facilitated in individuals with PTSD when compared with control subjects (Norrholm et al., 2011), supporting the notion of intrinsic enhancement of conditioned fear memory. This finding is linked to amygdala-dependent physiological processes and neuronal overactivity within the amygdala (Johnson et al., 2012b, McGuire et al., 2013).

The medial prefrontal cortex (mPFC) has a modulatory control over amygdala and hippocampus (Shin, et al., 2006). It inhibits fear acquisition and enhances extinction of fear memories. A reduction of mPFC volume has been reported in PTSD patients, but this reduction may be secondary to PTSD and not necessarily a pre-existing risk factor (Rauch, et al., 2003). Furthermore, alteration have been found in neural circuits between the mPFC and other brain regions, such as the amygdala and hippocampus, which may predispose individuals to increased encoding of traumatic memories leading to PTSD (Shin, et al., 2004). Moreover, changes in brain connectivity involving frontoparietal executive control circuits have recently been reported in PTSD and have been linked to behavioural treatment responsivity, highlighting the importance of prefrontal cortex and its connectivity in PTSD (Korgaonkar, et al., 2020). Differences in the functional connectome have been found for PTSD compared to controls (Breukelaar, Bryant, & Korgaonkar, 2021), including reduced connectivity between regions part of the default mode and executive control network, whereas increased connectivity was found between regions involved in emotional and arousal response such as subcortical and limbic areas.

The medial prefrontal cortex can be divided into a dorsal and ventral part. The dorsal anterior cingulate cortex (dACC) is involved in emotion processing, such as the appraisal of fearful situations and expressions of negative emotions. Prelimbic (PL) division of the mPFC in rodents, homologous to human dACC, was shown to be involved in expression of conditioned fear (Corcoran & Quirk, 2007). Microstimulation of PL cortex led to increase in conditioned response whereas its inactivation reduced fear response (Vidal-Gonzalez, Vidal-Gonzalez, Rauch, & Quirk, 2006). PL cortex modulates expression of fear in rodents by sending excitatory signals to BLA (Brinley-Reed, Mascagni, & McDonald, 1995). In clinical studies, greater fMRI activation in the dACC during a cognitive interference task has been found for

veterans diagnosed with PTSD compared to veterans without PTSD (Lisa M. Shin, et al., 2011). This greater activity was related to worser symptom severity, which may be the result of interpreting more situations as fearful due to the overactivity in the dACC. However, in this twin study, the non-affected co-twin of veterans with PTSD also showed increased activity in this region, suggesting that this increased activity may be a familial risk factor. Similarly, alterations have been found during resting state fMRI. Chen et al. (Chen, et al., 2019) compared patients with PTSD to trauma-exposed controls and healthy controls. Patients with PTSD had higher functional connectivity between the dACC with regions in the sensorimotor network in comparison to trauma-exposed and healthy controls, which may be related to preparing for the fight or flight response. On the other hand, patients with PTSD showed decreased functional connectivity between the dACC with the bilateral middle frontal gyrus and inferior frontal gyrus – areas important for response inhibition (Dossi, Delvecchio, Prunas, Soares, & Brambilla, 2020) – compared to individuals who were also exposed to trauma but did not develop PTSD. In addition, decreased functional connectivity between the dACC with the right hippocampus was found for both trauma-exposed groups but was more severe in the PTSD group. This finding may be related to declarative memory, e.g., difficulties of remembering specifics about the traumatic event (Acheson, Gresack, & Risbrough, 2012).

The ventral areas of the mPFC are involved in generating an emotional response as well as the inhibition of conditioned fear (Etkin, Egner, & Kalisch, 2011) and extinction of the fear response by moderating the response of the amygdala and hippocampus (Alexandra Kredlow, Fenster, Laurent, Ressler, & Phelps, 2022; Etkin, et al., 2011). The vmPFC regions including the rostral ACC and orbitofrontal cortex play a role in regulating emotions by inhibiting the amygdala (Andrewes & Jenkins, 2019), as well as other functions, such as processing information related to our self and evaluating rewards (Andrewes & Jenkins, 2019). In rodents,

infralimbic (IL) cortex, homologous to human (vmPFC), has been shown to inhibit conditioned fear expression (Thompson, et al., 2010). Microstimulation of IL cortex led to reduced fear response in rats (Vidal-Gonzalez, et al., 2006). IL cortex modulated the fear response by sending projections to GABAergic interneurons in intercalated cell masses (ITCs) surrounding BLA ultimately reducing the central amygdala (CeA) output (Ehrlich, et al., 2009). In PTSD patients, reduced volumes of the rACC in the vmPFC have been linked to more severe symptoms. Previous studies have shown hypoactivity of the vmPFC and hyperactivity of the salience network (including the amygdala) in people with PTSD (Koenigs & Grafman, 2009), together with reduced integrity of the white matter pathway between the vmPFC and amygdala. These findings have been thought to relate to excessive emotional reactivity to context associated with the traumatic events and persistence of the conditioned fear response, reinforcing fear memories. The reduced connectivity between the vmPFC with the hippocampus (Jin & Maren, 2015b) may relate to the failure of retrieving context-specific information about fear memories, important for generating a context-appropriate behavioural response.

To conclude, alterations in brain circuitry involving the mPFC, amygdala and hippocampus, together with their changes in brain volume and activation may be related to increased encoding of fear memories in PTSD patients. These changes in brain function highlight the importance that overactive fear memory plays in the pathophysiology of PTSD. Therefore, disrupting maladaptive fear memories become a key strategy in the treatment of PTSD.

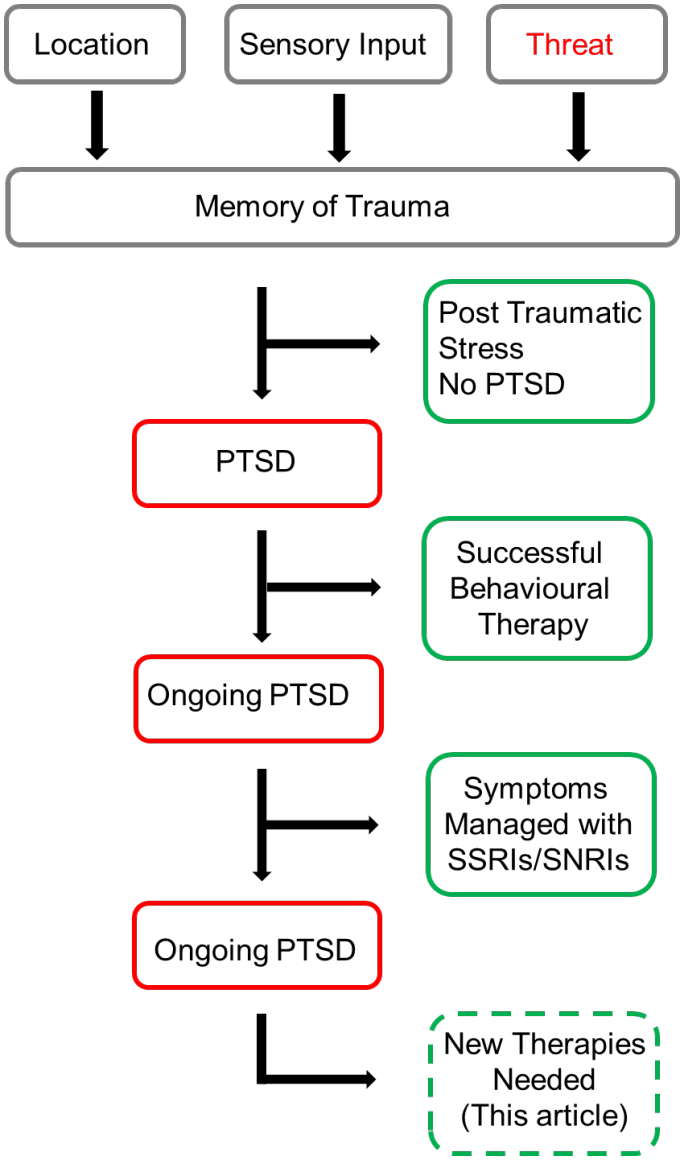

Fig. 1. Formation of post-traumatic stress disorder (PTSD) associated memories, typical outcomes and need for new treatments. PTSD can occur following exposure to a life-threatening event and emotional memories are formed often including elements of the contextual location, specific sensory inputs (e.g. sounds, sights and smells) and the memory of threat to life. Most people exposed to a traumatic event do not develop PTSD (No PTSD) however after one month some people are diagnosed with PTSD. Current therapies include behavioural therapies (Behavioural Therapy) as well as pharmacotherapies (SSRIs/SNRIs). Despite these treatment options some people have ongoing PTSD and need new treatment options. In this review we focus on recent developments in pharmacotherapy for PTSD which target emotional memories.

4. Current treatment approaches

Current treatment guidelines for PTSD list treatments ranging from strongly recommended to conditionally recommended (as listed by the American Psychological Association; APA, Phoenix Australia, and Department of Veteran Affairs (VA) USA) (fig 2). Treatment guidelines take into consideration the evidence for a treatment, the risks along with the potential benefits, as well as the application of the intervention across treatment settings of patient subgroups (APA) (Ursano, et al., 2004). Strongly recommended treatments listed are psychological interventions focused on the trauma, including trauma-focused cognitive processing therapy, cognitive therapy, cognitive-behavioral therapy (CBT), and prolonged exposure therapy (VA, APA, Phoenix) (APA, 2017; Card, 2017; Phoenix, 2020). The VA in addition also recommends Brief Eclectic Psychotherapy (APA, strongly recommended by VA), Eye movement Desensitization and Reprocessing (EMDR) therapy (APA, Phoenix, strongly recommended by VA), Narrative Exposure therapy (APA, Phoenix, strongly recommended by VA), and written narrative exposure. These therapies with components of exposure to trauma-related stimuli and cognitive restructuring (Watkins, Sprang, & Rothbaum, 2018) are seen as the first line of treatment for individuals diagnosed with PTSD (VA, Phoenix, APA). However, when trauma-focused psychotherapy is not readily available or not preferred by the patient, conditionally recommended treatments are suggested as first-line treatment (VA, Phoenix). Conditionally recommended treatment approaches are those with weaker evidence and/or potential for more severe side effects, such as present-centered therapy (Phoenix, evidence weak according to VA), stress inoculation training (Phoenix, VA) and pharmacological treatment (VA, APA, Phoenix). The four pharmacological treatments conditionally recommended for PTSD are selective serotonin reuptake inhibitors (SSRIs)

sertraline, paroxetine, and fluoxetine, as well as serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (APA, Phoenix, VA).

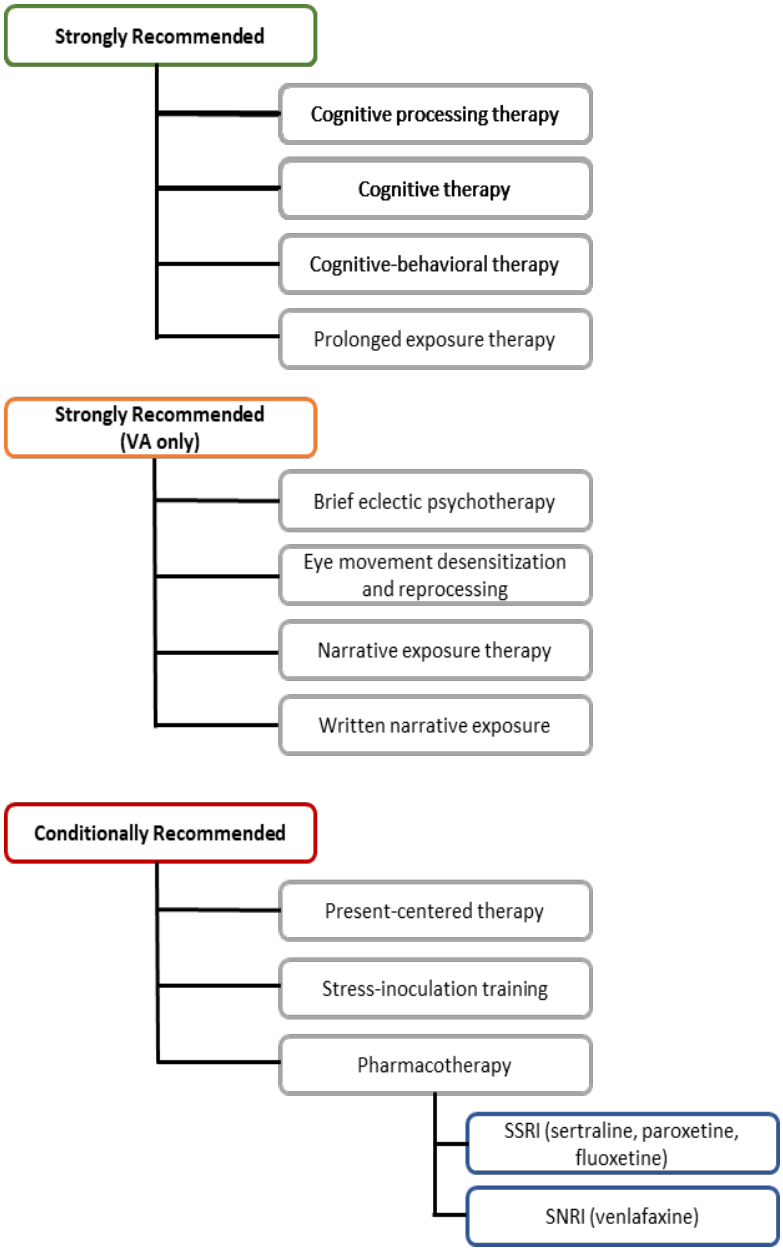

Fig. 2. Treatment recommendations for PTSD by APA, Phoenix and VA. Psychotherapies like cognitive processing therapy, cognitive therapy, cognitive-behavioral therapy, and prolonged exposure therapy are strongly recommended by all the PTSD treatment guidelines, while present-centered therapy, stress inoculation training and pharmacological treatment are recommended as second line treatments.

With regard to treatment efficacy, several meta-analyses (Coventry, et al., 2020; Karatzias, et al., 2019; Lewis, Roberts, Andrew, Starling, & Bisson, 2020; Turrini, et al., 2019) have shown the effectiveness of trauma-focused cognitive therapies and EMDR for reducing PTSD symptoms, with sustained effects at several months post follow-up (Mavranezouli, et al., 2020). In addition, Coventry et al. (2020) also found interpersonal therapy (based on two studies) to be as effective in reducing PTSD symptoms (related to emotional dysregulation) and depressive and anxiety symptoms and improving sleep quality. There is less agreement with regard to non-trauma focused interventions, however. Some have found non-trauma focused interventions to be not effective (small and non-significant effect) (Coventry, et al., 2020) whereas others found some support for an effect (Lewis, et al., 2020), e.g., non-trauma focused CBT. In addition, several studies have examined the effectiveness of pharmacological interventions in comparison to usual care and/or psychological interventions. SSRIs sertraline, paroxetine, and fluoxetine as well as SNRI venlafaxine have been found to be effective in reducing PTSD symptoms (Friedman & Bernardy, 2017; Hoskins, et al., 2015; Huang, et al., 2020). When compared to psychological interventions, pharmacological interventions with SSRIs (Mavranezouli, et al., 2020), antipsychotics (Coventry, et al., 2020) and prazosin (Coventry, et al., 2020) showed a smaller effect compared to psychological interventions in reducing PTSD symptoms (Coventry, et al., 2020; Mavranezouli, et al., 2020). In addition, SSRIs appear to be mostly effective for treating symptoms related to mood but not as much for specific PTSD symptoms (Alexander, 2012; Bryant, 2019). Nevertheless, despite a smaller effect, the clinical importance of pharmacological interventions should not be underestimated (Cipriani, et al., 2018), in particular for individuals who have no access to, are not willing to undertake or are not ready (yet) for psychological interventions.

Both psychological and pharmacological interventions come with several limitations. First, the efficacy rate for psychological and pharmacological interventions shows that not all individuals with PTSD benefit (as much) from a treatment. For example, 41-95% of individuals lost their PTSD diagnosis after prolonged exposure therapy (Watkins, et al., 2018), 30-97% after cognitive processing therapy (Watkins, et al., 2018), and 61-82.4% after CBT. As described by Berger et al. (2009), approximately 60% of individuals experience a reduction in PTSD symptoms after SSRI treatment and 20-30% lost their diagnosis. Likewise, 78% of those treated with venlafaxine showed reductions in symptoms, and 40.4% lost their diagnosis after treatment (Berger, et al., 2009). Also, the drop-out rate and risk of relapse are of concern. For example, drop-outs for sertraline and paroxetine were higher than placebo (Cipriani, et al., 2018). Similarly, the more effective trauma-focused psychological interventions have also shown higher dropout rates in comparison to non-trauma focused interventions, with approximately one third of individuals dropping out of treatment, with a large proportion (16%) of patients dropping out prior to attending the first treatment session and the majority dropping out within their first half of treatment (Gutner, Gallagher, Baker, Sloan, & Resick, 2016). In addition, not all patient groups benefit equally from the interventions. For example, it has been found that sertraline (SSRI) is not as effective in males than in females (John H. Krystal, et al., 2017), and appears to be not (or not as) effective in combat veterans (John H. Krystal, et al., 2017). Likewise, psychotherapy has found to be not as effective in military populations (Haagen, Smid, Knipscheer, & Kleber, 2015).

Treatment guidelines may benefit from considering individual differences. On average, individuals with moderate levels of PTSD symptom severity showed better treatment response than those with low or high severity levels as examined in a military population (Haagen, et al., 2015). It has also been proposed that individuals with PTSD may benefit from

different treatments depending on their clinical profile (Friedman, 2016; Friedman & Bernardy, 2017). For example, Friedman proposes that individuals with PTSD dysphoria type may respond better to SSRIs and SNRIs in comparison to those with dissociative symptoms (Friedman & Bernardy, 2017). Further, individuals with PTSD often have comorbidities, including cardiovascular, respiratory, gastrointestinal, inflammatory and autoimmune disease (Neigh & Ali, 2016), as well as psychiatric conditions. Approximately 59% of men and 44% of women diagnosed with PTSD meet the criteria for three or more other psychiatric conditions, such as major depressive disorder, anxiety disorder and substance use disorder (Brady, et al., 2000). These comorbidities along with their treatment may interfere with treatments for PTSD. Variability in treatment efficacy may also relate to the timing of the treatment since exposure to the trauma. Some studies have shown reduced treatment response for those with longer time between the trauma and treatment (cognitive therapy) (Ehlers, et al., 2013), whereas another study showed an increased treatment response (SSRI) for those with longer time since the trauma (Nøhr, et al., 2021). Understanding the factors contributing to treatment success is vital for the exploration of new treatments and more detailed guidelines for current approved treatments.

Current treatment approaches have been expanded on with the aim to improve treatment success. For example, combining treatments such as SSRI and mirtazapine (Schneier, et al., 2015) has shown better outcomes than SSRI combined with placebo, i.e., greater remission rate and reduced depressive symptoms. Likewise, combining pharmacological with psychological interventions has been explored. For example, combining SSRI with prolonged exposure therapy (Rauch, et al., 2019). However, no additional improvements were found for the group with the combined intervention, compared to SSRI or prolonged exposure therapy alone. The option of SSRI after non-responsiveness to CBT, or vice versa (Friedman & Bernardy,

2017) has also been explored, whereas others have examined whether pharmacological treatment before CBT intervention can enhance psychological interventions, but results have been mixed. These findings have confirmed the need for novel strategies, including better-targeted pharmacological treatment.

5. Psychedelics and substance assisted psychotherapy

Fueling what could be considered as a paradigm shift for modern psychiatric, evidence is accumulating suggesting that alternative pharmacological treatments, most notably psychedelic drugs and other non-conventional substances, could hold significant therapeutic benefits in mental health disorders. A renaissance of research into compounds such as psilocybin, lysergic acid diethylamide (LSD), cannabinoids, ketamine and 3,4-methylenedioxymethamphetamine (MDMA), most notably into their application to assist with psychotherapy for mental health conditions, including PTSD, has begun to unlock their distinct potential. However, their use is still limited by considerable legal obstacles and lack of social acceptance, problems that are exacerbated by near absent funding for research into their medical use. Despite these limitations, recent clinical trials support the application of psychedelic drugs for the treatment of anxiety (Griffiths, et al., 2016), depression (Davis, et al., 2021) and PTSD (Mithoefer, et al., 2019). There are different classes of drugs that share the ability to induce profounds alterations in consciousness as well as significant somatic, perceptual, cognitive and emotional changes, and do so via diverse neuropharmacological mechanisms of action that need to be considered (Garcia-Romeu, Kersgaard, & Addy, 2016). These include classic psychedelics, such as LSD, psilocybin and dimethyltryptamine (DMT), which are partial or full agonists at serotonergic 5-HT2A receptors, empathogens/entactogens, such as MDMA, whose main mechanism of action is to increase

release and/or block the reuptake of monoamines, and dissociative drugs, such as ketamine, which are mainly antagonists at the NMDA receptor (fig 3).

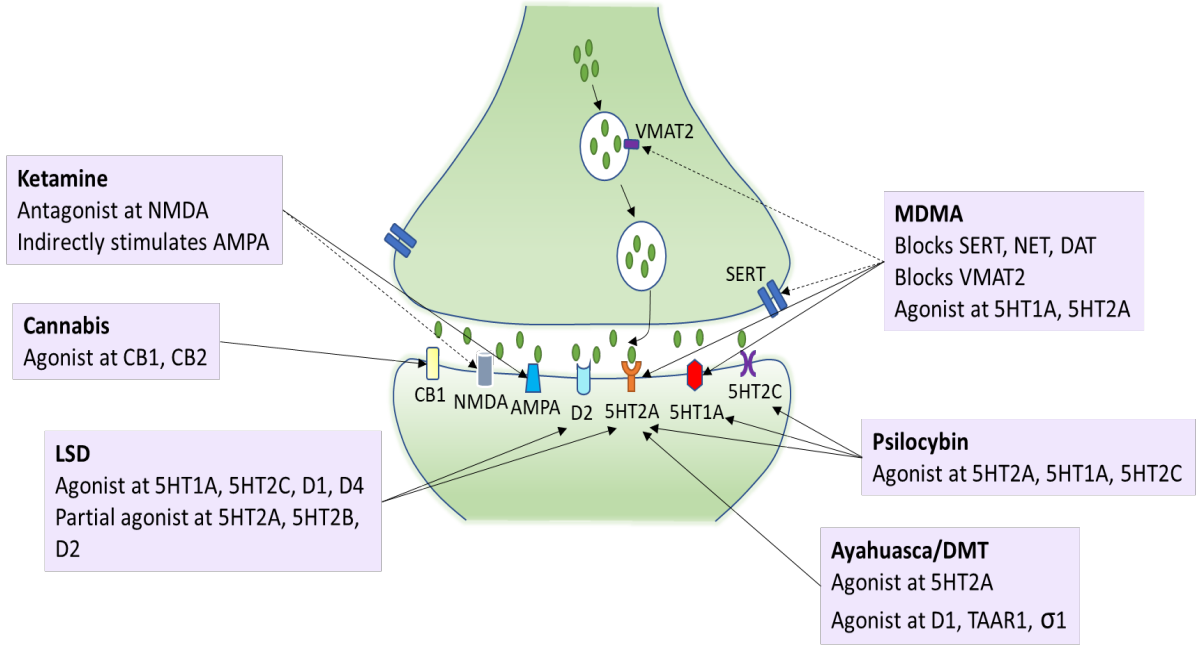

Fig. 3. Schematic diagram depicting the main actions of Psilocybin, LSD, Ketamine, cannabis, Ayahuasca, and MDMA at different synaptic receptors. Psychedelics like psilocybin, ayahuasca and LSD act mainly by agonism at 5HT2A receptors. MDMA acts at both pre and post synaptic sites to stimulate monoaminergic neurotransmission. Ketamine mainly acts as NMDA antagonist but also stimulates synaptic plasticity by agonism at AMPA receptors. Cannabis mainly acts as agonist at CB1 receptors. Abbreviation: LSD, Lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; DMT-Dimethyltryptamine); SERT, Serotonin transporter; NET, Norepinephrine transporter; DAT, Dopamine transporter; VMAT, Vesicular monoamine transporter; NMDA, N-methyl-D-

5.1 Psilocybin

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a prodrug that is metabolized in the liver into the 5-HT2A, 5-HT1A and 5-HT2C receptor agonist, psilocin. As a classic tryptamine-related drug, psilocybin induces strong perceptual alterations and a wide range of subjective

and neurophysiological effects. Psilocybin seems to have the ability to modulate bottom-up emotional reactivity, with effects that include reduced sensitivity to aversive stimulation and positively modulation of affect (Carhart-Harris, et al., 2012; Kraehenmann, et al., 2015). Psilocybin has been shown to reduce avoidance and increase acceptance and connectedness (Watts, Day, Krzanowski, Nutt, & Carhart-Harris, 2017) which may reduce PTSD patient's resistance to trauma focused psychological interventions. Other broader mental health benefits which may contribute the therapeutic actions of psilocybin include increase in emotional empathy (Pokorny, Preller, Kometer, Dziobek, & Vollenweider, 2017) and insightfulness (Kometer, Pokorny, Seifritz, & Volleinweider, 2015). Psilocybin induced a mystical-type experience (Griffiths, et al., 2011) which may mediate its improvement in patients with depression (Roseman, Nutt, & Carhart-Harris, 2017) and reduction of depression and anxiety in patients with life threatening cancer (Ross, et al., 2016). To what extent this would contribute to its therapeutic action in PTSD is not fully known.

There is evidence that psilocybin elicits changes in default mode network (DMN) connectivity (Smigielski, Scheidegger, Kometer, & Vollenweider, 2019), disruption of which, through developmental trauma, has been linked to the pathogenesis of PTSD (Daniels, Frewen, McKinnon, & Lanius, 2011). DMN is composed of aspects of medial prefrontal cortex (mPFC), posterior cingulate cortex, precuneus, medial temporal lobe, and medial and lateral parietal cortices (Buckner, Andrews-Hanna, & Schacter, 2008). Research suggests that long term trauma is associated with disruption in DMN connectivity (Akiki, et al., 2018) and contributes to PTSD symptoms such as hyperarousal and depersonalization/derealization (Tursich, et al., 2015). Moreover, whilst the amygdala is not normally linked with the DMN state, patients with PTSD experiencing hyperarousal and hypervigilance exhibit alterations in DMN functional connectivity that include the amygdala (Akiki, Averill, & Abdallah, 2017; Sripada, et

al., 2012). In a clinical study in 19 patients with depression, psilocybin administration was associated with reduced amygdala blood flow and increased connectivity in DMN network (Carhart-Harris, et al., 2017). In another study on 23 healthy human volunteer, psilocybin increased connectivity in sensory regions like bilateral occipital cortex, right superior temporal gyrus, precuneus and the left postcentral gyrus (Preller, et al., 2020). Thus, the ability of psilocybin to regulate DMN activity could provide a top-down mechanism for the modulation of negative affect in PTSD.

Psilocybin has been shown to increase neural plasticity by increasing neurogenesis, spinogenesis, and synaptogenesis in both in vivo and vitro models (Ly, et al., 2018). The increase in synaptic plasticity may enhance memory extinction as low dose of psilocybin increased hippocampal neurogenesis and facilitated extinction of cued fear conditioning in mice (Catlow, Song, Paredes, Kirstein, & Sanchez-Ramos, 2013). Moreover, increase in synaptic plasticity may reverse the stress induced changes in prefrontal cortex and contribute to the antidepressant action of psilocybin in PTSD (Arnsten, 2009). Further, psilocybin decreased (Kraehenmann, et al., 2015) the amygdala hyperreactivity seen in patients with PTSD (Francati, Vermetten, & Bremner, 2007). Although current studies are very limited in scope, these preliminary observations support the potential application of psilocybin in the treatment of PTSD.

5.2 LSD

LSD is a semi-synthetic product of lysergic acid that exhibits complex pharmacology including agonism at serotonergic systems, particularly at 5-HT_{2A} receptors, as well as actions at dopaminergic and adrenergic receptor sites (Halberstadt, 2015; Passie, Halpern, Stichtenoth,

Emrich, & Hintzen, 2008; Titeler, Lyon, & Glennon, 1988). LSD increased neuroplasticity in in vivo and in vitro preclinical models (Ly, et al., 2018) as well as increased blood plasma BDNF levels in humans (Hutten, et al., 2021). Whether this enhanced neuroplasticity contributes to increase fear extinction in LSD assisted psychotherapy need to be evaluated in PTSD patients. The predominant effects induced by LSD include visual hallucinations, audiovisual synesthesia, altered sensorimotor gating, positively experienced derealisation and MDMA-like empathogenic effects that could prove useful in clinical settings (Schmid, et al., 2015). Despite promising research in the 1950s and 1960s examining the efficacy of LSD in the treatment of a myriad of conditions, including addictive disorders (Smart, Storm, Baker, & Solursh, 1966) and cancer-related anxiety (Grof, Goodman, Richards, & Kurland, 1973), clinical research into the therapeutic applications of LSD virtually dried up in the ensuing years. In more recent times, however, additional studies have again yielded encouraging results, with a double-blind, randomised, active placebo-controlled pilot study evaluating the effects of LSD-assisted psychotherapy in 12 patients with anxiety associated with life-threatening diseases. The results showed reductions in both state and trait anxiety at the 2-month follow-up (Gasser, et al., 2014). At the 12-month follow-up, these authors reported enhanced perceived quality of life in such patients and a persistent decrease in anxiety measures which may have been facilitated by better access to, and confrontation of, the patient's emotions and understanding of their personal situation (Gasser, Kirchner, & Passie, 2015). Although no studies have investigated the potential of LSD for the treatment of PTSD, recent studies warrant further investigation into such potential. Mueller et al. (2017) used fMRI to measure the brain activity in response to fearful stimuli in 20 healthy individuals after taking 100 micrograms of LSD. LSD administration led to reduced reactivity of the left amygdala and the right medial prefrontal cortex relative to placebo during the presentation of fearful faces

(Mueller, et al., 2017). Further, a recent study suggested that a low dose of LSD increased amygdala connectivity with the right angular gyrus, right middle frontal gyrus, and cerebellum, with this increase in amygdala-middle frontal gyrus connectivity strength being positively correlated with positive mood after taking the drug (Bershad, et al., 2020). These data suggest that LSD has the ability to dampen amygdala reactivity and alter corticolimbic connectivity, which could facilitate improved emotional regulation in PTSD.

5.3 Ayahuasca

Ayahuasca is a hallucinogenic decoction that has been used for millennia both socially and as ceremonial spiritual medicine in several Amazonian regions. Ayahuasca is traditionally prepared using two plants referred to as *Banisteriopsis caapi*, which contains monoamine oxidase inhibitors, and *Psychotria viridis*, which contains its main hallucinogenic-inducing ingredient, N,N-dimethyltryptamine (DMT). DMT is a high affinity serotonergic agonist, with actions at multiple 5-HT receptor sites including what appears to be its primary target, the 5-HT_{2A} receptor (Keiser, et al., 2009). However, DMT also exerts agonist effects at the trace amine-associated receptor 1 (TAAR1) (Burchett & Hicks, 2006) and the sigma-1 receptor (Carbonaro & Gatch, 2016). Experimental data in rats revealed that chronic, intermittent, low doses of DMT produced an antidepressant-like phenotype and enhanced fear extinction learning, whilst having no effect on cued or contextual fear memory (Cameron, Benson, DeFelice, Fiehn, & Olson, 2019). DMT has been shown to enhance plasticity by increasing dendritic arbor complexity, promote dendritic spine growth, and stimulate synapse formation (Ly, et al., 2018). This enhanced neuroplasticity in prefrontal cortex may reduce symptoms of depression in PTSD patients. Specific evidence supporting the beneficial effects ayahuasca

and DMT in the treatment of trauma-related conditions in humans has shown promise. A recent retrospective survey of a clinical population of U.S. Special Operations Forces Veterans who completed a specific psychedelic treatment program involving ibogaine (a psychoactive indole alkaloid which is extracted from the *Tabernanthe iboga* rainforest shrub)- and DMT-assisted psychotherapy over three days, indicated large reductions in retrospective report of suicidal ideation, cognitive impairment, and symptoms of PTSD and anxiety (Davis, Averill, Sepeda, Barsuglia, & Amoroso, 2020). Although the study was based on self-reports and lacked randomisation and blinding and therefore the results can only be considered as preliminary, this research clearly warrants further investigation. Ayahuasca administration increased mindfulness-related capacities such as reduction in judgmental processing of experiences and in inner reactivity (Soler, et al., 2016). Further, ayahuasca increased psychological flexibility by enhancing creative divergent thinking and reducing convergent thinking, which may facilitate psychotherapeutic interventions in PTSD (Kuypers, et al., 2016). Ayahuasca consumption was associated with increased introspection, the ability to process unconscious psychological material, and emotional catharsis (Loizaga-Velder, 2013) which has been proposed to reduce avoidance to psychotherapeutic interventions and increased extinction of conditioned fear memory (Luciano, et al., 2013). It has been argued that ayahuasca/DMT exposure may facilitate retrieval and destabilisation of traumatic memories that would otherwise be repressed. In turn, the reprocessing of such traumatic events through drug-induced mystical experiences may contribute to the update of the memory, which would be subsequently loaded and stored with new affective significance, thus triggering emotional stabilisation (Inserra, 2018). This hypothesis, which requires further investigation, suggests that ayahuasca/DMT, and potentially other psychedelic drugs, may

exert neuropharmacological actions that align with the principles of memory consolidation and reconsolidation theory (Yehuda and LeDoux, 2007; Johnson et al, 2009).

5.4 Cannabis

Another psychoactive substance of interest as a candidate for the treatment of PTSD is Δ^9-tetra-hydrocannabinol (THC), the cannabinoid primarily responsible for the effects of cannabis. *Cannabis sativa* (cannabis) is among the oldest of cultivated plants known to mankind for its medicinal properties and significant role in the religious and ceremonial activities of many cultures. The CB1 receptor, a G-protein coupled receptor, is the primary target of THC in the nervous system. Downregulation of the CB1 receptor has been associated with exposure to chronic stress (Morena, Patel, Bains, & Hill, 2016) and several lines of evidence suggest that activation of the CB1 receptor modulates fear memories in humans and experimental animals and could therefore provide relief for the symptoms of PTSD. Indeed, experimental models have shown that CB1 receptor activation modulates the reconsolidation of fear memory traces. THC, alone and combined with cannabidiol, disrupted the reconsolidation of a contextual fear memory in rats, resulting in reduced long-term conditioned freezing expression (Stern, et al., 2015). Moreover, infusions of the CB1 agonist, WIN55212-2, into the amygdala after memory reactivation blocked reconsolidation of fear memory, with this effect being blocked by AM251, a specific CB1 receptor antagonist (Lin, Mao, & Gean, 2006).

A possible additional role of the CB1 receptor is to facilitate fear extinction processes. Injections of WIN55212-2 into the nucleus accumbens (Korem, Lange, Hillard, & Akirav, 2017), of CP55940 into the retrospenial cortex (Sachser, Crestani, Quillfeldt, Mello, & de Oliveira Alvares, 2015), and of cannabidiol into the infralimbic cortex (Do Monte, Souza, Bitencourt, Kroon, & Takahashi, 2013), all facilitated fear extinction in rodents whereas administration of CB1 antagonist rimonabant disrupted extinction learning in mice (Niyuhire, et al., 2007). Similarly, in humans, exposure to THC and other related cannabinoids produced effects that are consistent with an effective modulation of fear and trauma-related memories. Rabinak et al. (2013) used a randomised, double-blind, placebo-controlled study involving a Pavlovian fear extinction paradigm to test the effects of oral dronabinol (synthetic THC), showing that dronabinol prevented the recovery of fear when tested 24 h after extinction (Rabinak, et al., 2013). Similarly, administration of D9-tetrahydrocannabinol (THC) in PTSD patients enhanced extinction of memories induced by Pavlovian fear learning paradigm. PTSD patients who received THC showed significantly lower skin conductance response when exposed to conditioned stimulus (Rabinak, et al., 2018). An open labelled study on 150 PTSD patients showed that patients using dispensary obtained cannabis were 2.57 times more likely to no longer meet DSM-5 criteria for PTSD at the end one year study period compared to patients who did not use cannabis (Bonn-Miller, et al., 2020).

Further, fMRI studies have demonstrated reduced activation of the amygdala in response to social threats following treatment with THC (Phan, et al., 2008). It is important to note that neuroimaging studies have also revealed differences in the density of CB1 receptors and anandamide signalling in PTSD patients (Hauer, et al., 2013; Neumeister, et al., 2013) and,

critically, that cannabinoids can indeed reduce the symptomatology of PTSD, including overall symptom severity, sleep quality, treatment-resistant nightmares, and hyperarousal symptoms (Fraser, 2009; Greer, Grob, & Halberstadt, 2014; Roitman, Mechoulam, Cooper-Kazaz, & Shalev, 2014). The subtype of cannabinoid receptors CB2 has been linked to neuroinflammation which is another mechanism interfering with fear memory extinction. This has been discussed in subsequent sections. Taken together, data from both animal and human studies strongly support the candidacy of cannabinoids for the treatment of PTSD.

5.5 Ketamine

Ketamine, an N-methyl-D-aspartate-receptor receptor antagonist, is commonly used as anaesthetic. Recent evidence suggests that ketamine can have a rapid and robust antidepressant effect in patients with treatment-resistant depression (Fond, et al., 2014; Wilkinson, et al., 2018). Intranasal esketamine was recently (March 5, 2019) approved by the FDA for treatment-resistant depression.

There has been a significant increase in effort globally on the development of ketamine for PTSD treatment. It has been studied as both monotherapy and in combination with psychotherapy. In a randomised double blind clinical trial, a single IV infusion of ketamine significantly reduced the symptoms of PTSD after 24 hours when compared with IV midazolam (Feder, et al., 2014). As with depression single dose administration of ketamine lead to short-term improvement. However, in an open label trial, repeated infusion of IV ketamine (six doses over 12 days) rapidly improved the symptoms of PTSD, and the effect was maintained up to 41 days (Albott, et al., 2018). When combined with a mindfulness-based cognitive therapy, single IV infusion of 0.5 mg/kg ketamine produced a significantly more

sustained response in reduction of CAPS-IV PTSD symptoms compared to therapy alone in patients with refractory PTSD (Pradhan, et al., 2017). Patients were asked to recall the traumatic memories which was followed by ketamine infusion. Mindfulness exercise was practiced during the infusion to enhance trauma memory extinction and incorporate calming memories through reconsolidation.

The mechanisms by which ketamine benefits PTSD patients are still being explored. One possible explanation is the disruption of trauma associated memory. Like disorders of addiction (Lee, Milton, & Everitt, 2006a) PTSD could be thought of a disorder of memory. Experimental data in human subjects suggest that individuals with PTSD have an exaggerated acquisition of conditioned fear, known as 'fear load', compared to control subjects (S. D. Norrholm, et al., 2011), suggesting an intrinsic facilitation of conditioned fear memory. This increased fear encoding is linked to amygdala-dependent physiological processes and neuronal overactivity within the amygdala (L. R. Johnson, J. McGuire, R. Lazarus, & A. A. Palmer, 2012; McGuire, et al., 2013). Ketamine was shown to rapidly increase synaptic and neuronal plasticity (Ly, et al., 2018) and increase extinction of fear memory by increasing mTORC1 signalling in rats (Girgenti, Ghosal, LoPresto, Taylor, & Duman, 2017). Ketamine rapidly reversed the decrease in synaptic proteins expression, spine number and excitatory postsynaptic currents in layer V pyramidal neurons in the prefrontal cortex caused by chronic unpredictable stress in rats (Li, et al., 2011). It has been proposed that PTSD might be a synaptic disconnection syndrome and ketamine may work in PTSD by restoring synaptic connectivity (J. H. Krystal, et al., 2017). Furthermore, evidence suggests retrieval of a long-term memory can cause reactivation of memory trace and induce a state of instability requiring restabilization through reconsolidation (Nader, Schafe, & Le Doux, 2000; Przybyslawski, Roullet, & Sara, 1999). Research in our lab and others have shown that

pharmacological treatments can impair the reconsolidation of emotional memories when given in conjunction with the recall of events related to a trauma (Bergstrom, et al., 2013; Duclot, Perez-Taboada, Wright, & Kabbaj, 2016; Parsons & Ressler, 2013; Ratano, Everitt, & Milton, 2014). Moreover, fear memory reconsolidation has been shown to depend upon NMDA receptor activation. In preclinical studies, systemic injection of ketamine has been shown to disrupt contextual fear memory reconsolidation (Duclot, et al., 2016). Similarly in addiction models, intraperitoneal administration of ketamine, after re-exposure to a drug-paired context, disrupted reconsolidation of appetitive memory (Zhai, et al., 2008). Thus, addition of ketamine in subanesthetic dosage to trauma-focused psychotherapy has been proposed to offer a long term solution for PTSD by virtue of its action on trauma related memories (Veen, Jacobs, Philippens, & Vermetten, 2018).

At a behavioural level, psychoactive effects of ketamine especially when given in combination with psychotherapy may explain its benefits in PTSD patients. Ketamine can cause hallucinations and sensory distortions to change concept of self and attitude towards self and others (Krupitsky & Grinenko, 1997). This may lead to an increase in capacity to process emotions during therapy. The recall of traumatic experience during therapy sessions could be challenging for PTSD patients. The difficulty with reexperiencing of trauma may lead to reduced efficacy or treatment dropout for some PTSD patients. Addition of ketamine to psychotherapy may be able to increase the receptivity of patients to face these challenges.

Dissociative symptoms are the most frequently observed side effects with ketamine; however, these may be contributing to the effect of ketamine particularly when ketamine is used in combination with psychotherapy (Krupitsky & Grinenko, 1997; Pradhan, et al., 2017). Other side effects like transient increase in anxiety and increase in blood pressure and heart rate

(Feder, et al., 2014) are short lived and can be managed with supportive treatment and therefore require ketamine to be administered strictly under clinical supervision.

5.6 MDMA

3-4 methylenedioxymethamphetamine (MDMA) is a methamphetamine like synthetic compound first developed as a haemostatic agent. It was used as an adjunct to therapy in 1970s due to its psychoactive properties. However, after widespread abuse as a party drug, US DEA placed it under schedule 1 of controlled substance act and its therapeutic use declined. In the last two decades there has been a resurgence in interest to develop MDMA as aid to psychotherapy. A recent systematic review of clinical trials of MDMA assisted psychotherapy has shown moderate evidence for its use in treatment resistant PTSD (Varker, Watson, Gibson, Forbes, & O'Donnell, 2020). Due to such promising results, US FDA has given breakthrough therapy designation to MDMA-assisted psychotherapy.

Unlike ketamine, MDMA has been exclusively studied in conjunction with therapy. The first study after 2000 was conducted in six women with chronic PTSD secondary to sexual assault (Bouso, Doblin, Farré, Alcázar, & Gómez-Jarabo, 2008). Although this study could not reach its desirable sample size, it showed that a low dose of MDMA (50 or 75 mg) combined with psychotherapy sessions was physically and psychologically safe in PTSD patients. A randomized placebo-controlled trial comparing two sessions of psychotherapy with MDMA (125 mg plus 62.5 mg optional booster) or placebo showed significant reduction in CAPS scores from baseline in MDMA group (Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2011). In MDMA group 10 of 12(83%) responded to treatment compared to 2 of 8 (25%) in placebo group. A further analysis showed that this treatment effect was maintained over 3.5

years (Mithoefer, et al., 2013). In another RCT, 26 veterans and first-responders with PTSD underwent two sessions of psychotherapy with three different doses of MDMA [30 mg (7), 75 mg (7) or 125 mg (12)] (Mithoefer, et al., 2018). Patients in the 75 mg and 125 mg groups showed significant reduction in PTSD symptom severity compared to patients in the 30 mg group. When patients in the 30 mg and 75 mg groups were administered 100-125 MG MDMA in combination with three therapy sessions, the group that received 30 mg MDMA showed significant reduction in PTSD symptom severity. These effects were maintained during the 12 months follow-up period. A pooled analysis of six RCTs with 105 patients showed that patients in MDMA group had significant reduction in PTSD symptom severity compared to the control group (Mithoefer, et al., 2019). Recently, Mitchell and colleagues' (2021) conducted a phase 3 randomized clinical trial to test efficacy and safety of MDMA-assisted therapy (n=46) compared to placebo with therapy (n=44) in chronic PTSD patients. In MDMA-assisted therapy group, 67% patients no longer met the diagnostic criteria for PTSD whereas on 32% responded in placebo group at the end of treatment period. MDMA-assisted therapy also reduced symptoms of depression in PTSD patients (Mitchell, et al., 2021).

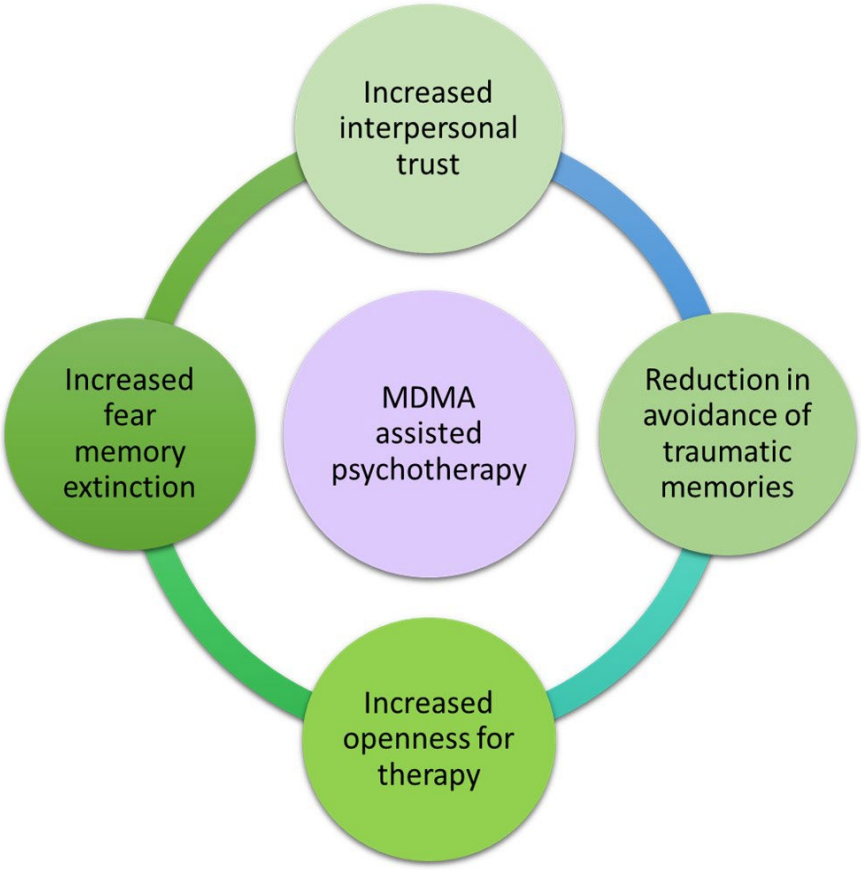

Fig. 4. Therapeutic rationale for the use of psychedelics assisted psychotherapy in PTSD. This figure illustrates four mechanisms through which MDMA can enhance psychotherapy.

The neurobiological mechanisms of MDMA involve increase in the level of serotonin in synapse. Serotonin has been found to reduce fear response during the recall of traumatic memories and thus increase the effectiveness of psychotherapy by increasing patients' openness to the intervention (Sessa, 2017) (fig 4). MDMA is also short acting compared to other psychedelics and does not interfere with cognitive and perceptual abilities of patients which helps in retaining the memories of therapy experience (Sessa, 2017). Apart from its indirect impact on trauma memory modification through increase in acceptance of therapy, MDMA also affects memory directly. MDMA has been shown to enhance fear memory extinction through activation of 5HT2A receptors in mice (Young, et al., 2017). Furthermore, it has been proposed that MDMA might be acting through modulation of memory

reconsolidation during the therapy session (Feduccia & Mithoefer, 2018). PTSD is associated with increased amygdala reactivity and reduced activation of prefrontal cortex (Dahlgren, et al., 2018; Francati, et al., 2007). MDMA administration attenuated the increased amygdala reactivity and enhanced the activation of frontal cortex (Carhart-Harris, et al., 2015; Gamma, Buck, Berthold, Liechti, & Vollenweider, 2000). A pooled analysis of eight studies in healthy human subjects showed that MDMA administration significantly increased plasma oxytocin levels (Vizeli & Liechti, 2018) which may mediate its prosocial effects (Thompson, Callaghan, Hunt, Cornish, & McGregor, 2007).

The use of MDMA in psychotherapeutic settings has not been associated with serious adverse events. In phase 3 clinical trial, MDMA was associated mild to moderate side effects which included muscle tightness, decreased appetite, nausea, hyperhidrosis and feeling cold (Mitchell, et al., 2021). With respect to cardiovascular safety, MDMA caused a transient increase in blood pressure and heart rate. MDMA also cause a slight increase in anxiety in some patients however this could be managed by therapist support (Mithoefer, et al., 2018).

6. Fear memory reconsolidation

The reinvigoration of research into memory reconsolidation from the late 1990s and 2000s (Nader, Schafe, & Le Doux, 2000; Przybyslawski & Sara, 1997), which has identified theoretical and practical strategies for the modification memories, has raised hope for the development of new treatments that target pathological memories in PTSD. Memory reconsolidation hypothesis states that remembering an event can trigger the associated memory trace to transfer from a stable into a destabilized state. Once destabilized, the trace can be altered pharmacologically before its restabilization through memory reconsolidation (Przybyslawski,

et al., 1999). In the past couple of decades, a number of preclinical and clinical studies have demonstrated the potential of drugs to disrupt fear memory reconsolidation (Kelly, Laroche, & Davis, 2003; Ratano, et al., 2014; Walker, Brakefield, Hobson, & Stickgold, 2003; Walsh, Das, Saladin, & Kamboj, 2018).

Recent evidence suggests that memory is a dynamic process, involving both increases in strength of memory and updating of its content with new experiences (Fig 5) (Nader, Schafe, & LeDoux, 2000; Przybyslawski & Sara, 1997). Retrieval of a long term memory can cause reactivation of the memory trace, and this reactivation involves destabilizing the memory whereby new protein synthesis is required in order to restabilize the memory through reconsolidation (Nader, Schafe, & Le Doux, 2000; Przybyslawski, et al., 1999). One explanation for memory reconsolidation is that it likely evolved to allow the incorporation of new information into long-term memory. The exploitation of the reconsolidation process could have enormous implications for treatment of anxiety associated disorders as it may allow for the disruption of the old, well-established maladaptive memories that contribute to the persistence of fear memory related disorders (Debiec & Ledoux, 2004).

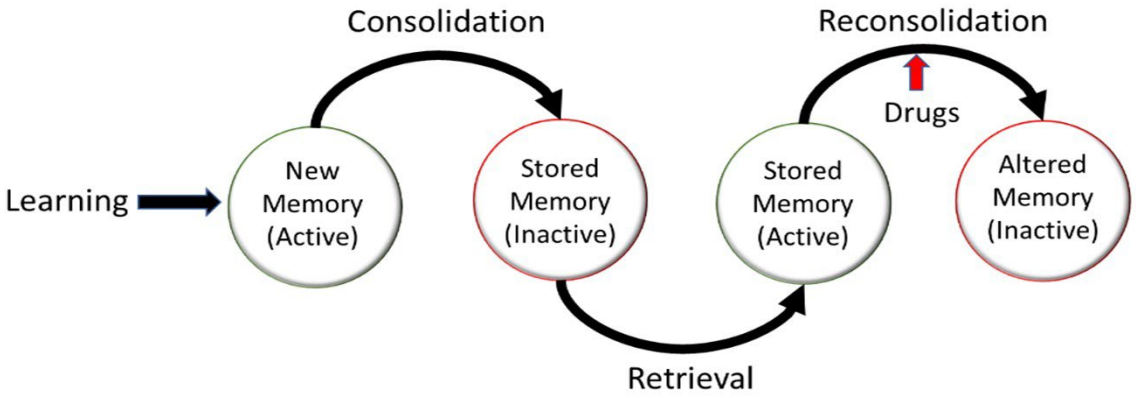

Fig. 5. Schematic model of memory re-storage and its inhibition by potential PTSD drugs during reconsolidation phase.

Molecular mechanisms for fear memory reconsolidation involve protein synthesis through activation of receptors and intracellular signalling mechanisms (fig 6). Fear memory reconsolidation requires activation of various receptors followed by activation of protein kinases and transcription factors and ultimately protein synthesis. The two most studied receptors in this context are the beta-adrenergic (Debiec & Ledoux, 2004; Huang, Zhu, Zhou, Liu, & Ma, 2017; Przybyslawski, et al., 1999) and NMDA receptors (Lee, Milton, & Everitt, 2006b), although other receptors such as glucocorticoids (Nikzad, Vafaei, Rashidy-Pour, & Haghighi, 2011), GABA (Espejo, Ortiz, Martijena, & Molina, 2017), cannabinoid CB1 (Ratano, et al., 2014) and serotonin (Schmidt, et al., 2017) receptors have also been implicated.

Receptor activation leads to phosphorylation of various protein kinases such as extracellular signal-related kinase (ERK/MAPK) (Cestari, Costanzi, Castellano, & Rossi-Arnaud, 2006), protein kinase A (PKA) (Tronson, Wiseman, Olausson, & Taylor, 2006) and mammalian target of rapamycin (mTOR) (Blundell, Kouser, & Powell, 2008). In turn, protein kinases produce downstream activation of transcription factors such as cAMP response element binding (CREB) protein (Tronson, et al., 2012), NF-kB (de la Fuente, Freudenthal, & Romano, 2011), and Zinc

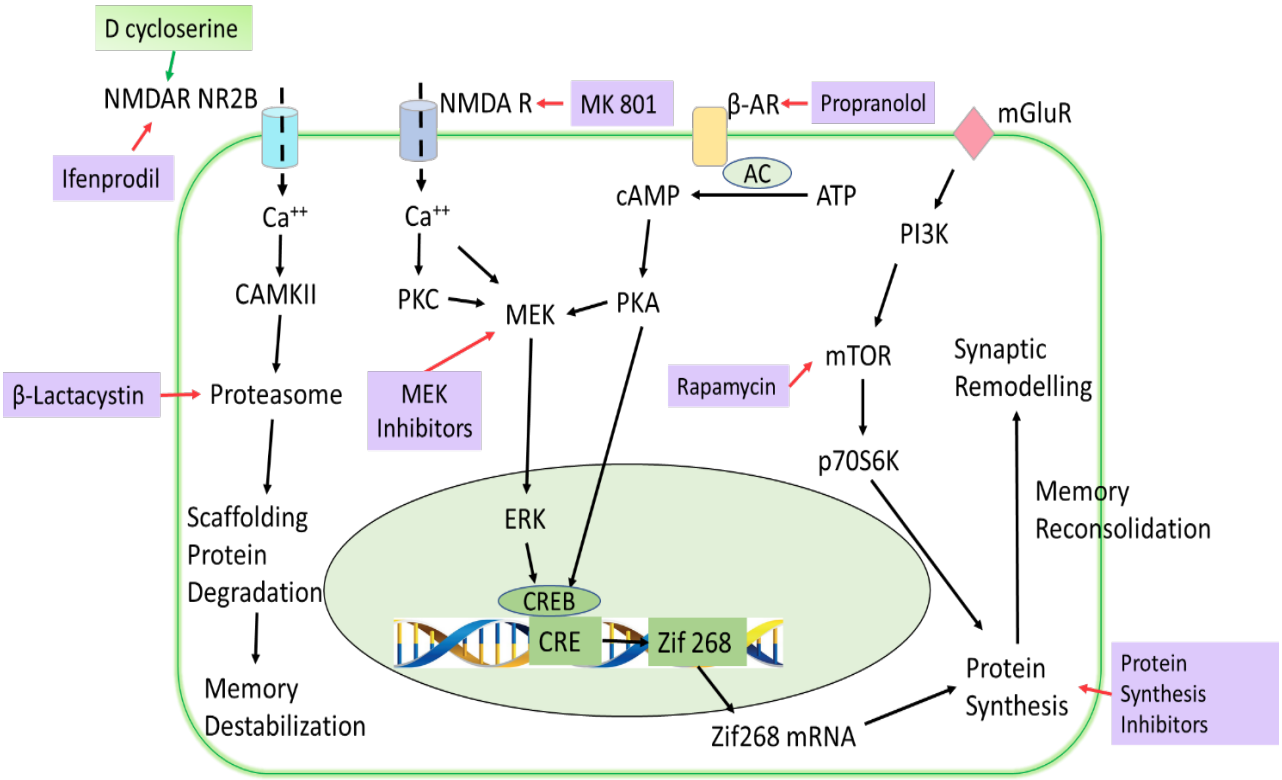

Fig. 6. Molecular mechanisms of memory destabilization/reconsolidation and potential drug targets for PTSD. Molecular pathways (black arrows), pharmacological inhibition (red arrows), pharmacological stimulation (green arrow).

Finger Transcription Factor (Zif 268) (Lee & Hynds, 2013). Transcription of these genes leads to protein synthesis required for fear memory reconsolidation (Nader, Schafe, & Le Doux, 2000). Delineation of molecular mechanisms has helped to identify various targets to disrupt the restabilization of fear memory and hence alter the reconsolidation process. Current evidence for drugs acting on these pharmacological targets to disrupt memory reconsolidation has been described below (Table 1 and 2).

6.1 β Adrenergic Receptors (β-AR)

Hyperactivity of sympathetic nervous system is one of the characteristic symptoms of PTSD (Strawn & Geracioti, 2008). PTSD patients have increased cerebrospinal fluid (CSF)

noradrenaline level compared with healthy subjects (Geracioti, et al., 2001). Noradrenergic neurons in the locus coeruleus (LC) projecting to the amygdala, prefrontal cortex, hippocampus, hypothalamus and thalamus, mediate sympathetic response to stress (Berridge, Schmeichel, & Espana, 2012). Increased input from LC neurons to the amygdala appears to be responsible for enhanced encoding of traumatic memories in PTSD patients (Giustino & Maren, 2018).

Noradrenaline is the main catecholamine neurotransmitter involved in autonomic nervous system response to stress and the beta sub-receptors (β-ARs) play a key role in increasing strength of memories caused by activation of sympathetic nervous system during traumatic event (J. L. McGaugh, 2013). The β-AR antagonist, propranolol, has been shown to consistently block fear memories in various animal models, including passive avoidance, contextual fear and auditory fear conditioning(Debiec & Ledoux, 2004; Przybyslawski, et al., 1999; Taherian, et al., 2014). Propranolol disrupted both recent (1 day) and old memories (36 days) as well as weak (2 foot shock) and relatively strong (5 foot shock) memories (Debiec & Ledoux, 2004; Taherian, et al., 2014). Moreover, amnesia caused by propranolol was maintained 16 days after the injection (Debiec & Ledoux, 2004). However, in another study propranolol disrupted both cued and contextual fear conditioning but had no effect on reconsolidation of inhibitory avoidance memory (Muravieva & Alberini, 2010). To account for this differential effect, the researchers suggested that the amygdala could play a key role in storage of fear conditioning memories but only modulate the strength of avoidance memory. These findings suggest that propranolol might have a limited effect on the reconsolidation of certain types of fear memories, such as inhibitory avoidance.

Propranolol has been the most commonly used drug for clinical studies using memory reconsolidation protocols in both healthy human volunteers and PTSD patients (Brunet, et al., 2008; Brunet, et al., 2018; Kindt, Soeter, & Vervliet, 2009; Schwabe, Nader, Wolf, Beaudry, & Pruessner, 2012). Because of its relative safety and extensive testing for cardiovascular indications, it was the first drug to be tested for memory reconsolidation therapy. In healthy human volunteers, propranolol erased the expression of fear memory while leaving the declarative memory about the association of cue and aversive stimulus intact (Kindt, et al., 2009) and this effect persisted even at one month follow up (Soeter & Kindt, 2010). Moreover, disruption of reconsolidation by propranolol prevented the generalization of fear, which is a key feature observed in PTSD (Soeter & Kindt, 2011). These results suggest that we can target a specific emotional memory while avoiding generalized amnestic effects on other important memories.

Emotionally arousing stimuli activate the noradrenergic system and hence have a higher chance of being stored in long term memory. The enhance encoding of traumatic memories can often lead to psychopathologies like PTSD (James L. McGaugh, 2013). Propranolol was effective in disrupting reconsolidation of memories enhanced by noradrenergic stimulation (Soeter & Kindt, 2012). It disrupted emotional memory more than a neutral memory (Schwabe, Nader, & Pruessner, 2013) and was associated with significantly higher activity in the amygdala and hippocampus during recall (Schwabe, et al., 2012), suggesting that these brain areas are involved in its effect on reconsolidation.

In a randomized double-blind study involving PTSD patients, propranolol reduced physiological responding monitored using heart rate, skin conductance, and left corrugator electromyogram during script driven recall compared to placebo (Brunet, et al., 2008). In

another randomized clinical trial, propranolol significantly reduced the PTSD symptoms when compared with placebo, evaluated using the Clinician-Administered PTSD Scale (CAPS) and the patient-rated PTSD Checklist-Specific (PCL-S) (Brunet, et al., 2018). In a pilot fMRI study on patients with PTSD, propranolol given prior to traumatic memory reactivation elicited decreased activation of amygdala and thalamus following the presentation of a threatening stimuli (Mahabir, Tucholka, Shin, Etienne, & Brunet, 2015).

However, the efficacy of propranolol has not been straightforward in all the studies. Importantly, propranolol administered with memory reactivation did not improve symptoms in PTSD patients (Roullet, et al., 2021; Wood, et al., 2015). Propranolol did not prevent the return of the fear response after re-exposure to threatening stimuli in healthy female volunteers (Thome, et al., 2016). It failed to disrupt reconsolidation when the strength of the conditioned stimuli (CS) was enhanced (Spring, et al., 2015) or if the memory was reactivated seven days after the initial encoding (Tollenaar, Elzinga, Spinhoven, & Everaerd, 2009b). Propranolol was less effective in disrupting memories in individuals with high trait anxiety (Soeter & Kindt, 2013) and when no new information was presented during retrieval, and it only disrupted the memory when the outcome of the retrieval cue was not fully predictable (Sevenster, Beckers, & Kindt, 2012a). These data suggest that certain boundary conditions must be met before the memory can be disrupted using propranolol. Moreover, it has been proposed that memory may not enter a labile state if no new information is presented at the time of retrieval (Sevenster, et al., 2012a). More work is needed to elucidate how much influence the boundary conditions such as age and strength of memory and the predictability of the information during retrieval, have on the effects of propranolol on memory reconsolidation.

6.2 NMDA Receptors

Exposure to trauma activates glutamatergic neurons (Chambers, et al., 1999; Hegoburu, Parrot, Ferreira, & Mouly, 2014). Glutamate mediates synaptic plasticity by stimulating NMDA receptors in the brain (Bailey, Cordell, Sobin, & Neumeister, 2013; Blair, Schafe, Bauer, Rodrigues, & LeDoux, 2001). Evidence has shown that increased glutamate input to the amygdala contributes to the enhanced encoding of traumatic memories seen in PTSD (Arco & Mora, 2009; Lee & Kim, 1998).

Blockade of NMDAR has been consistently shown to disrupt fear memory reconsolidation. The NMDAR antagonist, MK-801, disrupted the reconsolidation of contextual fear, inhibitory avoidance, auditory fear memory and conditioned food aversion (Charlier & Tirelli, 2011; Einarsson & Nader, 2012; Flint, Noble, & Ulmen, 2013; Lee, et al., 2006b; Nikitin, Solntseva, Kozyrev, Nikitin, & Shevelkin, 2018). Moreover, post-reactivation inhalation of Xenon impaired both contextual and cued fear memory reconsolidation, which was ascribe to antagonism of NMDARs in the hippocampus and amygdala by Xenon (Meloni, Gillis, Manoukian, & Kaufman, 2014). Similarly, Duclot and collaborators showed that NMDAR antagonist, ketamine, disrupted contextual fear reconsolidation (Duclot, et al., 2016). In a pilot clinical study, ketamine was recently shown to reduce harmful drinking by disrupting the reconsolidation of appetitive memories (Das, et al., 2019). It would be interesting to see if ketamine has similar effects on fear memory reconsolidation in PTSD patients. Some researchers have proposed using subanaesthetic dose of ketamine to disrupt fear memories in PTSD patients (Veen, et al., 2018). However, it should be noted that ketamine is associated

with side effects such as hallucinations, psychosis, and delirium, which might limit its clinical application.

Evidence suggests that NMDA N2A receptor subtype is required for restabilization of fear memory. Intra-BLA administration of NMDA N2A antagonist NVP-AAM077 before reactivation of memory reduced the freezing on test day while it did not affect the amnesia caused by anisomycin suggesting it did not have an effect on memory destabilization but disrupted the restabilization of reconsolidating memory (Milton, et al., 2013). Furthermore, administration of NMDA N2A antagonist TCN-201 in nucleus reuniens of thalamus after memory reactivation disrupted the reconsolidation of fear memory (Troyner & Bertoglio, 2021). This suggests that nonselective NMDA receptor antagonists disrupt fear memory reconsolidation mainly through their action on NMDA N2A receptors.

6.3 Glucocorticoid Receptors

The hypothalamic-pituitary-adrenal (HPA) axis is a major component of neuroendocrine response to stress (Prager & Johnson, 2009). In patients with PTSD, some evidence suggests there may be dysregulation of the HPA axis in mediating the stress response (Aerni, et al., 2004; Yehuda, 2006; Yehuda, McFarlane, & Shalev, 1998). Studies carried out in emergency room immediately after trauma exposure suggest that those who have low levels of cortisol in their blood at the time of the traumatic event are more likely to develop PTSD as compared to those who do not (Yehuda, et al., 1998). The downregulation of corticotropin-releasing hormone (CRH) receptor leading to decrease in adrenocorticotropin (ACTH) release from the

pituitary gland might contribute to hypocortisolism seen in PTSD patients (Yehuda, 2006). Indeed, administration of cortisol has been shown to reduce symptoms in patients with PTSD (Aerni, et al., 2004). However, the relationship between cortisol levels and PTSD is still poorly understood as other studies have found increased plasma and urinary cortisol in PTSD patients (Delahanty, Nugent, Christopher, & Walsh, 2005; Inslicht, et al., 2006).

The uncertainty surrounding the underlying pathophysiology of PTSD is also reflected in different preclinical studies in which both an agonist and an antagonist at glucocorticoid receptor were shown to disrupt fear memory reconsolidation. Injection of GR antagonist, RU486, in the basolateral nucleus of amygdala impaired the reconsolidation of auditory fear memory (Jin, Lu, Yang, Ma, & Li, 2007) and the blockade of GR with systemic and intra-hippocampal injections of RU38486 impaired reconsolidation of memory in an inhibitory avoidance task (Nikzad, et al., 2011). In contrast, other studies have shown that postretrieval activation of GR with corticosterone impairs contextual fear memory (Abrari, Rashidy-Pour, Semnanian, & Fathollahi, 2008; Cai, Blundell, Han, Greene, & Powell, 2006).

In clinical studies, cortisol, but not propranolol, given before the memory reactivation impaired the subsequent recall of both emotional and neutral information (Tollenaar, Elzinga, Spinhoven, & Everaerd, 2009a). However, subsequent studies showed that cortisol did not have any effect on fear memory reconsolidation in women (Meir Drexler, Merz, Hamacher-Dang, & Wolf, 2016) and even enhanced traumatic memories in men (Drexler, Merz, Hamacher-Dang, Tegenthoff, & Wolf, 2015). The conflicting findings of agonist and antagonist at glucocorticoid receptors seen in reconsolidation research are similar to previous research on memory consolidation (Conrad, et al., 2004; Roozendaal, 2002). Various explanations have been offered for these discrepancies. For example, in study by Cai et al., the amnesia caused

by corticosterone was not permanent, that is, it was amenable to reinstatement (Cai, et al., 2006). This suggests that corticosterone may increase extinction of fear memory rather than impair memory reconsolidation. Another explanation is that stress caused by drug infusion might increase cortisol levels and act as a confounding factor (Meir Drexler & Wolf, 2017). Differences in treatment effects seen in clinical studies for men versus women have been related to alternating levels of sex hormones in women depending on different phases of the menstrual cycle or oral contraceptive use, both of which are known to affect fear memory (Meir Drexler & Wolf, 2017; Milad, et al., 2006).

6.4 GABA Receptors

GABAergic neurons form the main inhibitory pathways in the brain. γ-Aminobutyric acid (GABA) inhibits noradrenergic signalling involved in the stress response. SPECT and PET studies in patients with PTSD have shown decreased binding of ligands to GABAA receptors in hippocampus, thalamus and cortex (Bremner, et al., 2000; Geuze, et al., 2008). These findings suggests that decreased GABAA receptor affinity may be responsible for reduced inhibitory control in PTSD patients.

In a series of studies, Bustos and colleagues explored the role of the GABA agonist, midazolam, on fear memory reconsolidation (Bustos, Giachero, Maldonado, & Molina, 2010; Bustos, Maldonado, & Molina, 2006, 2009). Midazolam was able to disrupt reconsolidation of fear memory (Bustos, et al., 2006), however, a higher dose of midazolam was needed to disrupt older memories characteristic in patients with PTSD (Bustos, et al., 2009). Researchers also found that combining D-cycloserine with midazolam labilized previously resistant memory in stressed animals making it susceptible to the effect of midazolam (Bustos, et al., 2010; Espejo,

Ortiz, Martijena, & Molina, 2016). A similar study exploring the role of D-cycloserine and midazolam on contextual fear memory reconsolidation in ethanol withdrawn rats did not yield positive results (Ortiz, Giachero, Espejo, Molina, & Martijena, 2015). However, this finding could have been due to decreased expression of the α1 GABAA-R subunit in basolateral amygdala following ethanol consumption/withdrawal (Ortiz, et al., 2015). Overall, these results suggest that GABA receptors could be important drug targets for future clinical studies.

6.5 Serotonin Receptors

Serotonin (5-Hydroxytriptamine, 5-HT) is recognized as an important neuromodulator of learning and memory processes (Ogren, et al., 2008) in addition to being a strong regulator of mood. The role of 5-HT in learning and memory is complex and depends on the receptor targeted. This complexity is linked to the large family of 5-HT receptors (Hoyer, Hannon, & Martin, 2002) and the interactions of 5-HT with other neurotransmitter systems. Acute tryptophan depletion, which reduces brain 5-HT, has been shown to impair memory consolidation (Mendelsohn, Riedel, & Sambeth, 2009).

Recently, the role of 5-HT in memory reconsolidation has also been examined, with direction and effectiveness of modulation depending on the receptor subtype being targeted. Serotonin receptor modulators were shown to disrupt reconsolidation of contextual fear, object recognition and conditioned food aversion memories (Balaban, Vinarskaya, Zuzina, Ierusalimsky, & Malyshev, 2016; Deryabina, Muranova, Andrianov, & Gainutdinov, 2018; Morici, et al., 2018; Nikitin, et al., 2018; Schmidt, et al., 2017). A 5-HT5A antagonist and a 5-HT6 agonist disrupted contextual fear memory reconsolidation while a 5-HT7 antagonist enhanced it (Schmidt, et al., 2017). In another experiment, depletion of serotonergic neurons

with the neurotoxin, 5,7-DHT (5,7-dihydroxytryptamine), and nonselective serotonin receptor blockade with mianserin both prevented the reconsolidation of context memory (Balaban, et al., 2016). 5-HT2aR antagonist infusions into the mPFC disrupted object recognition memory (Morici, et al., 2018) whereas intrahippocampal administration of a 5-HT5A antagonist impaired contextual fear memory in Wistar rats (Schmidt, et al., 2017). Researchers used the terrestrial snail, Helix locorum, to study the effect of impairment of serotonergic transmission of memory reconsolidation. Intracoelomic injections of serotonin synthesis blocker, para-chlorophenylalanine or the 5-HT receptor antagonist, methiothepin, blocked reconsolidation of contextual fear and conditioned food aversion memories, respectively (Deryabina, et al., 2018; Nikitin, et al., 2018). These results suggest that although the effect on fear memory could be receptor specific, the generalised blockade of serotonergic transmission seems to disrupt memory reconsolidation.

6.6 Endocannabinoid receptors

The endocannabinoid signalling system plays a crucial role in the consolidation of fear memory (P. Campolongo, et al., 2009; Hauer, et al., 2011). Endocannabinoids increase glucocorticoid mediated consolidation of memory in rat basolateral amygdala (Patrizia Campolongo, et al., 2009). Moreover, increased CB1 receptor expression in amygdala was shown to potentiate fear conditioning in rats (P. Campolongo, et al., 2009).

The involvement endocannabinoid system in fear memory reconsolidation is complex with both agonists and antagonists at endocannabinoid receptors (CB) disrupting fear memory (de Oliveira Alvares, Pasqualini Genro, Diehl, Molina, & Quillfeldt, 2008; Ratano, et al., 2014). Lin et al. showed that intra-amygdala administration of CB1 agonists blocked the reconsolidation

of fear-potentiated startle, while the CB1 antagonist, AM251, prevented this effect in a dose-dependent manner (Lin, et al., 2006). Similarly, infusion of the CB1 agonist, anandamide, into the dorsal hippocampus blocked contextual fear memory while AM251 prevented it (de Oliveira Alvares, et al., 2008). In another study, intra-hippocampal administration of the cannabinoid agonist, CP55,940, disrupted the reconsolidation of contextual fear memory (Santana, et al., 2016). In contrast, oral administration of cannabidiol, a non-competitive antagonist CB1 and CB2 receptors, impaired reconsolidation of fear memory in rats whereas Δ9-Tetrahydrocannabinol, a CB1 receptor agonist, did not have any effect in the same study (Murkar, et al., 2019). In addition, AM251 impaired reconsolidation of auditory fear memory when administered in rat basolateral amygdala (Ratano, et al., 2014). The difference in route of administration (Lin, et al., 2006; Murkar, et al., 2019) and dose of the antagonist, AM251(Lin, et al., 2006; Ratano, et al., 2014), might account for this variation, however more research is needed to establish the clear role for the endocannabinoid system in fear memory reconsolidation.

In addition to the neurotransmitter receptor systems discussed above, various intracellular signalling systems, including various protein kinases and transcription factors, have been shown to modulate the reconsolidation of fear memories.

6.7 ERK/MAP Kinase

Pharmacological and molecular studies have shown the necessity of ERK/MAPK for consolidation of memory (Schafe, et al., 2000; Selcher, Atkins, Trzaskos, Paylor, & Sweatt, 1999). Phosphorylation of MAPK following NMDA receptor stimulation leads to activation of transcription factors like CREB and subsequent protein synthesis essential for synaptic

plasticity and memory formation (Davis & Laroche, 2006). Previous research from our laboratory has shown that increased expression of pMAPK in lateral amygdala is associated with an increase in plasticity for fear memory (Coyner, et al., 2014). Moreover, mice which showed high fear behaviour had more pMAPK expressing neurons in the lateral amygdala as compared to mice with low fear behaviour (Coyner, et al., 2014). Using design-based stereology we showed identical number of neurons in lateral amygdala expressing pMAPK are involved in fear memory consolidation and reconsolidation which suggest that original fear memory underwent reconsolidation after reactivation by CS (Bergstrom, et al., 2013).

Various studies have demonstrated the role of MAPK in the reconsolidation of fear memories (Cestari, et al., 2006; Duvarci, Nader, & LeDoux, 2005; Kelly, et al., 2003). Direct administration of MEK inhibitors in specific brain areas (intra-BLA, intra-hippocampal) disrupted the reconsolidation in a model of auditory fear conditioning and inhibitory avoidance (Duvarci, et al., 2005; Krawczyk, et al., 2015). Furthermore, systemic administration of the MEK inhibitor, SL327, dose-dependently reduced the reconsolidation of fear memories in C57BL/6 and ERK1 mutant mice (Cestari, et al., 2006). However, despite the early preclinical success of MEK inhibitors, these compounds have not been tested clinically in PTSD patients. This could be due to low blood brain barrier penetration of currently approved MEK inhibitors (Vaidhyanathan, Mittapalli, Sarkaria, & Elmquist, 2014) or apprehension about risk versus benefit of using anticancer drugs for psychiatric indications (Heinzerling, et al., 2019).

6.8 Protein Kinase A (PKA)

PKA is an important molecular substrate of neuroplasticity. β-AR stimulation increases cAMP and further activates cAMP-dependent PKA (Lim, et al., 2018). Blockade of PKA

disrupted the consolidation of both context and cued fear memory (Schafe, Nadel, Sullivan, Harris, & LeDoux, 1999) whereas its activation enhanced the memory (Jentsch, Olausson, Nestler, & Taylor, 2002). Similarly, activation of PKA by intra-amygdala infusion of a PKA activator increased fear memory expression while PKA inhibitors disrupted the reconsolidation of fear memory (Tronson, et al., 2006). These findings suggest that both enhancement and impairment of fear memory reconsolidation can be achieved through modulation of PKA.

6.9 Mammalian target of rapamycin (mTOR)

The mammalian target of rapamycin (mTOR) kinase mediates synaptic plasticity and memory storage by regulating protein translation (Hoeffer & Klann, 2010). Modulation of mTOR pathway has been shown to regulate multiple elements of fear memory in preclinical studies and in addition has shown treatment efficacy for PTSD. Multiple studies have revealed that mTOR inhibitors disrupt the reconsolidation of inhibitory avoidance, contextual fear and auditory fear memory (Blundell, et al., 2008; Gafford, Parsons, & Helmstetter, 2011; Jobim, et al., 2012; Mac Callum, Hebert, Adamec, & Blundell, 2014). Rapamycin was most commonly administered as mTOR inhibitor either intracerebrally (Gafford, et al., 2011; Jobim, et al., 2012) or through systemic route (Blundell, et al., 2008; Mac Callum, et al., 2014). Infusion of rapamycin in the dorsal hippocampus immediately after reactivation disrupted reconsolidation of contextual fear memory (Gafford, et al., 2011) while infusions into the BLA and dorsal hippocampus inhibited reconsolidation of inhibitory avoidance memory (Jobim, et al., 2012). Systemic administration of rapamycin impaired auditory fear memory reconsolidation (Mac Callum, et al., 2014) and contextual fear memory (Blundell, et al., 2008).

However, systemic administration of rapamycin was only able to disrupt reconsolidation of contextual, but not auditory fear memory which might limit the clinical utility of mTOR inhibitors in PTSD (Glover, Ressler, & Davis, 2010).

In a double-blind, placebo-controlled pilot study, rapamycin was tested in veterans with PTSD (Suris, Smith, Powell, & North, 2013). Although there was no overall difference between groups on PTSD symptoms, data showed that in veterans who had more recent combat trauma rapamycin significantly improved symptoms as compared to control group (Suris, et al., 2013). This suggest that recent traumatic memories may be more amenable to disruption by rapamycin.

6.10 Transcription factors

Amongst the transcription factors, cAMP response element-binding protein (CREB) and nuclear factor kappa B (NF-kB) inhibit fear memory reconsolidation. Most of the kinases discussed above act on these transcription factors to induce protein transcription. Phosphorylation of PKA leads to the activation of downstream CREB. While CREB levels are increased after reactivation of memory (Han, et al., 2008), its inhibition was shown to impair auditory fear memory reconsolidation (Tronson, et al., 2012). Intrahippocampal administration of NF-kB inhibitor disrupted the reconsolidation of inhibitory avoidance memory (Boccia, et al., 2007) and also contextual fear memory (de la Fuente, et al., 2011). Si and colleagues (2012) also explored the role of NF-kB in auditory fear memory reconsolidation. Intra-BLA administration of sulfasalazine, an inhibitor of IκB kinase that activates NF-κB and SN50, a direct inhibitor of the NF-κB DNA-binding complex, impaired auditory fear memory reconsolidation (Si, et al., 2012). Researchers also found that sodium butyrate, a histone deacetylase inhibitor, given prior to NF-kB inhibition, prevented the disruption of auditory

fear memory reconsolidation, suggesting that the interaction between histone deacetylation and NF-κB in regulating transcription of protein is required for memory storage (Si, et al., 2012).

6.11 Protein synthesis and protein degradation

Memory formation is associated with a change in synaptic strength which requires new protein synthesis (Huang, Martin, & Kandel, 2000; Mayford, Siegelbaum, & Kandel, 2012). Protein synthesis inhibitors have been known to disrupt the consolidation of memory (Barondes & Cohen, 1966; Flexner, Flexner, & Roberts, 1966; Schafe, et al., 1999). They were amongst the first class of drugs shown to disrupt fear memory reconsolidation. In a seminal paper, Nader and colleagues demonstrated that anisomycin, a protein synthesis inhibitor when given after reactivation of memory in rats was able to disrupt auditory fear memory (Nader, Schafe, & Le Doux, 2000). Since then protein synthesis inhibitors were shown to inhibit contextual fear memory and inhibitory avoidance memory reconsolidation (Debiec, LeDoux, & Nader, 2002; Einarsson & Nader, 2012; Pedroso, et al., 2013). Moreover, even extinguished memories were susceptible to disruption by protein synthesis inhibitors (Duvarci, Mamou, & Nader, 2006).

The disruption of fear memory reconsolidation with protein synthesis inhibitors is not always replicable. For example, anisomycin when injected into the hippocampus either failed to disrupt memory reconsolidation (Power, Berlau, McGaugh, & Steward, 2006) or the memory returned after 21 days (Lattal & Abel, 2004). These results highlight the role of boundary conditions such as adequate labilization of memory, and the dose and route of the drug administered. Anisomycin when administered into the hippocampus did not inhibit reconsolidation of inhibitory avoidance memory but in the same study the systemic injection

of anisomycin was able to (Taubenfeld, Milekic, Monti, & Alberini, 2001). Inhibition of protein synthesis is an ultimate step underlying the effect of all the previously mentioned drugs on memory reconsolidation. However, protein synthesis inhibitors like anisomycin are unlikely to be tested clinically in PTSD patients due to their toxicity.

Recent evidence suggests that apart from protein synthesis, protein degradation which requires the ubiquitin-proteasome system is involved in fear memory reconsolidation. Administration of proteasome inhibitor (β lactacystin) which inhibits protein degradation in amygdala, impaired the consolidation of auditory and contextual fear memories (Jarome, Werner, Kwapis, & Helmstetter, 2011) and its administration in hippocampus was shown to inhibit reconsolidation of contextual fear memories (J. Lee, 2010). Furthermore, protein degradation increased following memory retrieval and administration of inhibitor of protein degradation with anisomycin after retrieval of auditory and contextual fear memories prevented the memory disruption caused by anisomycin (Jarome, et al., 2011; S.-H. Lee, et al., 2008) which suggests the protein degradation controls destabilization of fear memories. Lastly, it was shown that protein degradation caused by memory retrieval is influenced by NMDA receptor activity as administration of NMDAR NR2B inhibitor, ifenprodil, following fear memory retrieval significantly reduced protein degradation in amygdala (Jarome, et al., 2011). This suggests that both protein synthesis and protein degradation mediate fear memory reconsolidation and are regulated upstream via NMDA receptor activity.

Table 1: Summary of preclinical studies on pharmacological disruption of memory reconsolidation

Molecular Target	**Behavioural Paradigm**	**Drug used**	**Mech. of action**	**Route of administration**	**Effect**	**Reference**
NMDA Receptors	Contextual fear memory	MK801	Antagonist	Systemic	+	(Charlier & Tirelli, 2011)
		Xenon	Antagonist	Inhalation	+	(Meloni, et al., 2014)
		Ketamine	Antagonist	Systemic	+	(Duclot, et al., 2016)
	Auditory fear memory	MK801	Antagonist	Systemic	+	(Lee, et al., 2006b)
		Xenon	Antagonist	Inhalation	+	(Meloni, et al., 2014)
	Inhibitory avoidance	MK801	Antagonist	Systemic	+	(Flint, et al., 2013)
β Adrenergic Receptors	Contextual fear memory	Propranolol	Antagonist	Systemic	+	(Taherian, et al., 2014)
		Propranolol	Antagonist	Systemic	+	(Muravieva & Alberini, 2010)
	Auditory fear memory	Propranolol	Antagonist	Systemic	+	(Debiec & Ledoux, 2004)

		Propranolol	Antagonist	Systemic	+	(Muravieva & Alberini, 2010)
	Inhibitory avoidance	Propranolol	Antagonist	Systemic	+	(Przybyslawski, et al., 1999)
		Propranolol	Antagonist	Systemic	-	(Muravieva & Alberini, 2010)
Glucocorticoids Receptors	Contextual fear memory	Corticosterone	Agonist	Systemic	+	(Abrari, et al., 2008; Cai, et al., 2006)
	Auditory fear memory	RU486	Antagonist	Intra-BLA	+	(Jin, et al., 2007)
	Inhibitory avoidance	RU38486	Antagonist	Systemic and Inta-hippocampal	+	(Nikzad, et al., 2011)
GABA Receptors	Contextual fear memory	Midazolam	Antagonist	Systemic	+	(Bustos, et al., 2006, 2009)
		DCS+ Midazolam	NR2B agonist +	Systemic	+	(Bustos, et al., 2010)

		DCS+ Midazolam	GABA antagonist	Systemic	-	(Ortiz, et al., 2015)
Serotonin Receptors	Contextual fear memory	SB-699551	5-HT5A receptor antagonist	Intra-hippocampal	+	(Schmidt, et al., 2017)
		WAY-208466	5-HT6 receptor agonist	Intra-hippocampal	+	
		Mianserin, Methioptin	Nonselective 5HT receptor antagonist	Intracoelomic injection in snail	+	(Balaban, et al., 2016; Nikitin, et al., 2018)
		P-Chlorphenylalanine	5HT synthesis blocker	Intracoelomic injection in snail	+	(Deryabina, et al., 2018)
Endocannabinoid receptors	Contextual fear memory	Anandamide	CB1 agonist	Intra-hippocampal	+	(de Oliveira Alvares, et al., 2008)
		CP55,940	CB1 agonist	Intra-hippocampal	+	(Santana, et al., 2016)
	Auditory fear memory	Anandamide	CB1 agonist	Intra-BLA	+	(Lin, et al., 2006)

		AM251	CB1 antagonist	Intra-BLA	+	(Ratano, et al., 2014)
ERK/MAP Kinase	Auditory fear memory	SL327	MEK inhibitor	Systemic	+	(Cestari, et al., 2006)
		U0126	MEK inhibitor	Intra-BLA	+	(Duvarci, et al., 2005)
	Inhibitory avoidance	PD098059	MEK inhibitor	Intra-hippocampal	+	(Krawczyk, et al., 2015)
Protein Kinase A	Auditory fear memory	Rp-cAMPS	Inhibitor	Intra-BLA	+	(Tronson, et al., 2006)
mTOR	Contextual fear memory	Rapamycin	Inhibitor	Systemic	+	(Blundell, et al., 2008)
		Rapamycin	Inhibitor	Systemic	+	(Glover, et al., 2010)
		Rapamycin	Inhibitor	Intra-hippocampal	+	(Gafford, et al., 2011)
	Auditory fear memory	Rapamycin	Inhibitor	Systemic	+	(Mac Callum, et al., 2014)
		Rapamycin	Inhibitor	Systemic	-	(Glover, et al., 2010)
	Inhibitory avoidance	Rapamycin	Inhibitor	Intra-BLA and Intra-hippocampal	+	(Jobim, et al., 2012)

Transcription factor	Contextual fear memory	NF-κB decoy oligonucleotide	NF-κB inhibitor	Intra-hippocampal	+	(de la Fuente, et al., 2011)
	Auditory fear memory	SN50	NF-κB inhibitor	Intra-BLA	+	(Si, et al., 2012)
		HSV-mCREB	Viral vector to block CREB	Intra-BLA	+	(Tronson, et al., 2012)
	Inhibitory avoidance	NF-κB decoy oligonucleotide	NF-κB inhibitor	Intra-hippocampal	+	(Boccia, et al., 2007)
Protein synthesis	Contextual fear memory	Anisomycin	Inhibitor	Intra-hippocampal	+	(Debiec, et al., 2002)
		Anisomycin	Inhibitor	Intra-ACC infusions	+	(Einarsson & Nader, 2012)
	Auditory fear memory	Anisomycin	Inhibitor	Intra-BLA	+	(Nader, Schafe, & Le Doux, 2000)
		Anisomycin	Inhibitor	Intra-BLA	+	(Duvarci, et al., 2006)
	Inhibitory avoidance	Cycloheximide	Inhibitor	Intra-BLA	+	(Pedroso, et al., 2013)
		Anisomycin	Inhibitor	Intra-hippocampal	-	(Power, et al., 2006)

Table 2: Summary of clinical studies on pharmacological disruption of memory reconsolidation

Molecular Target	Study Participants	Sample Size (n)	Treatment	Effect	Remarks	Reference
β Adrenergic Receptors	Healthy volunteers	20	Propranolol 40 mg	+	• Reduced eyeblink startle reflex following treatment	(Kindt, et al., 2009)
	Healthy male volunteers	26	Propranolol 80 mg	-	• No effect on of emotional and neutral memory	(Tollenaar, et al., 2009a)
	Healthy volunteers	20	Propranolol 40 mg	+	• Reduced eyeblink startle reflex following treatment • Effect maintained after 1 month • No change in declarative memory	(Soeter & Kindt, 2010)
	Healthy volunteers	20	Propranolol 40 mg	+	• Reduced eyeblink startle reflex following treatment • Reduced fear generalization	(Soeter & Kindt, 2011)

	Healthy volunteers	20	Yohimibine 20 mg before acquisition, Propranolol 40 mg	+	• Reduced eyeblink startle reflex following treatment	(Soeter & Kindt, 2012)
	Healthy volunteers	12	Propranolol 40 mg	+	• Reduced recall of emotional stimuli compared to neutral stimuli • Increased activity in amygdala and hippocampus	(Schwabe, et al., 2012)
	Healthy volunteers	18	Propranolol 40 mg	+	• No effect on memory without prediction error during retrieval • Reduced memory recall if prediction error during retrieval	(Sevenster, et al., 2012a)
	Healthy volunteers	12	Propranolol 40 mg	+	• Reduced recall of emotional stimuli compared to neutral stimuli	(Schwabe, et al., 2013)

	Healthy volunteers	24	Propranolol 40 mg	-	• No effect on skin conductance rate following recall of negative stimuli	(Spring, et al., 2015)
	Healthy female volunteers	20	Propranolol 40 mg	-	• No effect on skin conductance rate following recall of negative stimuli	(Thome, et al., 2016)
	Chronic PTSD patients	9	Propranolol 60 mg	+	• Reduced physiologic responses during mental imagery of personal traumatic events	(Brunet, et al., 2008)
	Chronic PTSD patients	7	Propranolol 1 mg/kg	+	• Reduction in CAPS score and IES-R score pre vs. posttreatment • Reduced activation of amygdala and thalamus	(Mahabir, et al., 2015)
	Chronic PTSD patients	30	Propranolol 1 mg/kg	+	• Reduced CAPS and PCL-S score when compared with placebo	(Brunet, et al., 2018)

	Veterans with PTSD	10	Propranolol 1 mg/kg	-	• No effect on IES-R and CAPS score when compared with placebo	(Wood, et al., 2015)
	Chronic PTSD patients	33	Propranolol 1 mg/kg	-	• No effect PCL-S score when compared with placebo	(Roullet, et al., 2021)
Glucocorticoid Receptors	Healthy male volunteers	26	Cortisol 35 mg	+	• Reduced recall of emotional and neutral memory	(Tollenaar, et al., 2009a)
	Healthy male volunteers	14	Cortisol 30 mg	-	• Cortisol enhanced reconsolidation of the reactivated memory	(Drexler, et al., 2015)
	Healthy female volunteers	26	Cortisol 30 mg	-	• No effect on reconsolidation of the reactivated memory	(Meir Drexler, et al., 2016)
mTOR	Veterans with PTSD	27	Rapamycin 15 mg	-	• No effect on CAPS and PCL score when compared with placebo	(Suris, et al., 2013)

7. Fear memory destabilization following recall

One of the important functions of fear memory is to help the animal avoid situations or behaviour that resulted in harm in the past (Dickinson, 2012; Zentall, 2013). However, long term memories need to be updated to maintain their significance in the face of changing environment. Memory reconsolidation is proposed to be an important mechanism responsible for integration of new information in the original memory trace (De Oliveira Alvares, et al., 2013; J. L. Lee, 2010). Recall of memory results in plastic labile state (destabilization) which allows for incorporation of new information in the long-term memory through reconsolidation (Lee, Nader, & Schiller, 2017). However, in the absence of new information at the time of recall, memory does not enter in an active labile state (Bustos, et al., 2009; Exton-McGuinness, Lee, & Reichelt, 2015; Pedreira, Pérez-Cuesta, & Maldonado, 2004; Sevenster, et al., 2012a; Sinclair & Barense, 2018).

Recent research suggests that a mismatch between what happens at the time of recall from what is expected (prediction error) is required for memory destabilization (Popik, Amorim, Amaral, & De Oliveira Alvares, 2020; Sevenster, Beckers, & Kindt, 2013). Both preclinical and clinical studies have shown that the reconsolidation interventions failed in the absence of prediction error while the incorporation of prediction error at the time of memory retrieval resulted in successful disruption of memory by drugs inhibiting reconsolidation (Bustos, et al., 2009; Exton-McGuinness, et al., 2015; Pedreira, et al., 2004; Sevenster, Beckers, & Kindt, 2012b; Sinclair & Barense, 2018). Dopaminergic projection from ventral tegmental area (VTA) have been proposed to mediate prediction error signalling (Exton-McGuinness, et al., 2015). Dopaminergic system plays a key role in expectation of outcome (Schultz, Dayan, & Montague,

1997) and administration dopamine D2 receptor antagonist sulpiride in VTA prevents the appetitive memory destabilization (Reichelt, Exton-McGuinness, & Lee, 2013). However, the role dopamine in fear memory destabilization is still not clearly understood. Blockade of memory destabilization with intra-BLA administration of D1 receptor antagonist SCH-23390 did not affect retrieval-extinction induced attenuation of cued fear memory in rats (Cahill, Wood, Everitt, & Milton, 2019). This suggests that D1 receptors signalling in amygdala is not sufficient condition for memory destabilization as D1 receptor agonist SKF38393 alone did not have an impact but mediated the effect of nootropic nefiracetam on memory destabilization (Flavell & Lee, 2019b). The role of dopaminergic system in fear memory destabilization needs to be explored further.

Molecular mechanisms of memory destabilization involve activation of NMDA NR2B receptors (Milton, et al., 2013). Einarrson and Nader explored the role of NMDAR N2B in anterior cingulate cortex (ACC) on reconsolidation of contextual fear memory. NMDAR N2B antagonist RO25-6981 administration in ACC impaired contextual fear memory (Einarsson & Nader, 2012). Similarly, administration of the NMDA N2B antagonist, ifenprodil, blocked the amnesia caused by the protein synthesis inhibitor, anisomycin, suggesting that ifenprodil prevented the destabilization of memory required for anisomycin to have an effect (Mamou, Gamache, & Nader, 2006). Conversely, administration of D-cycloserine, a partial agonist at the NMDA receptor, increased the labilization of old traumatic memories (Bustos, et al., 2010).

Activation of L-type voltage-gated calcium channels and GluA1-containing AMPA receptor which results in increased entry of calcium intracellularly have also been shown to be involved in memory destabilization. Administration of nimodipine, a L-type voltage-gated calcium channel blocker, prior to reactivation of memory resulted in failure of memory updating

(Suzuki, Mukawa, Tsukagoshi, Frankland, & Kida, 2008). Similarly, blockade of GluA1-containing AMPA receptor in hippocampus prevented the fear memory update (Torquatto, Menegolla, Popik, Casagrande, & de Oliveira Alvares, 2019). Increased calcium entry by activation of these receptors activate protein kinase CAMKII and ubiquitin-proteasome system (UPS) which results in synaptic scaffolding protein degradation and memory destabilization (Jarome, et al., 2011; S. H. Lee, et al., 2008). Inhibition of CAMKII by myristoylated autocamtide-2 related inhibitory peptide and UPS by β lactacystin prevents destabilization of memory and blocks the effect of protein synthesis inhibitor anisomycin on memory reconsolidation (Jarome, Ferrara, Kwapis, & Helmstetter, 2016; Jarome, et al., 2011; S. H. Lee, et al., 2008).

The translational applicability of reconsolidation interventions is sometimes limited because traumatic memories that lead to PTSD may be too old or strong to be destabilized (Nader, Schafe, & LeDoux, 2000). These potential 'boundary conditions' interfere with labilization of memory. However, interventions that results in memory destabilization have shown promise to overcome these boundary conditions. D-cycloserine administered prior to reactivation rendered long-term fear memory vulnerable to post-reactivation reconsolidation blockade with the GABA agonist, midazolam (Bustos, et al., 2010). Similarly, D-cycloserine also attenuated the stress-induced resistance to the fear memory labilization and enabled the disruption of strong fear memory by midazolam (Espejo, et al., 2016). Old traumatic memories between three to forty years have shown resistance to reconsolidation intervention in previous clinical trials (Suris, et al., 2013). The incorporation of prediction error and NMDA N2B receptor agonists to destabilize the strong and old traumatic memory needs to be explored further in clinical studies in PTSD patients.

8. Fear memory extinction

Pharmacological interventions targeting fear memory extinction have been primarily used as adjunct to psychotherapies like prolonged exposure therapy (Carpenter, Pinaire, & Hofmann, 2019; Litz, et al., 2012; Singewald, Schmuckermair, Whittle, Holmes, & Ressler, 2015). Prolonged exposure therapy which works by enhancing extinction is one of the first line treatments for PTSD (APA, 2017; Card, 2017; Phoenix, 2020). However, it requires multiple sessions for full beneficial effect and is associated with significant dropout rates. Therefore, any drug which can reduce the duration of exposure therapy and enhance its efficacy will have significant impact on reduction of PTSD morbidity. We have discussed above how the pharmacological targeting of memory reconsolidation can disrupt fear memory; however, memory can also be modified by another means i.e. by enhancing extinction (Bouton, 1993). In this section we will briefly discuss key molecular mechanisms and neural circuits involved in fear memory extinction and recent landmark studies on pharmacological interventions to enhance memory extinction in PTSD patients. Effects of Cannabis, MDMA, ketamine, psilocybin, D-cycloserine, neuropeptide Y and oxytocin on fear memory extinction in PTSD have been described elsewhere in this review (see section 3 and 9). Some of the other key pharmacological interventions used to enhance fear memory extinction in PTSD include SSRIs, L-DOPA, yohimbine, cannabinoids, and glucocorticoids are discussed here. In this section we first discuss extinction mechanism and then pharmacological modulation of extinction.

Fear memory undergoes extinction if multiple presentations of previously learned CS are not followed by similar outcome (Merlo, Milton, Goozée, Theobald, & Everitt, 2014). This leads to reduction in response to stimuli which previously reminded the person of trauma (Quirk & Mueller, 2008). Evidence suggests that extinction involves new learning that CS is not

followed by US and therefore it is more than just forgetting (Bouton, 2004; Dunsmoor, Niv, Daw, & Phelps, 2015; Maren & Quirk, 2004). This is supported by the fact that extinguished memories recover spontaneously with passage of time or after the reminder to the original traumatic incidence (Bouton, Westbrook, Corcoran, & Maren, 2006; Rescorla, 2004).

The molecular mechanisms of fear memory extinction are similar in many ways to those involved in memory reconsolidation. Like reconsolidation, NMDA receptor activation is critical for memory extinction (Kwapis, Jarome, Lee, Gilmartin, & Helmstetter, 2014). Stimulation of β-adrenergic receptors by noradrenaline is known to potentiate fear memory extinction (Berlau & McGaugh, 2006; Mueller, Porter, & Quirk, 2008), while their inhibition by propranolol impairs it (Mueller, et al., 2008). In contrast to β-adrenergic receptors, administration of GABA-A agonist impairs fear memory extinction (Hart, Harris, & Westbrook, 2009), while GABA-A antagonists facilitates it (Berlau & McGaugh, 2006). Endocannabinoid system also plays a key role in fear memory extinction where administration of CB1 receptor agonists facilitates memory extinction (de Oliveira Alvares, et al., 2008; Segev, et al., 2018), while injection of CB1 receptor antagonists or CB1 knockout mice show impairment in memory extinction (Marsicano, et al., 2002; Varvel, Anum, & Lichtman, 2005). Similar to fear memory reconsolidation, extinction also requires activation of intracellular signalling like ERK/MAPK (Herry, Trifilieff, Micheau, Lüthi, & Mons, 2006) and other intracellular pathways (Kritman & Maroun, 2013) leading to protein synthesis and further synaptic remodelling (Lai, Franke, & Gan, 2012).

It is important to understand the neural circuits involved in fear memory extinction as this allows for better targeting of pharmacological interventions aimed to enhance fear memory extinction in PTSD patients. Rodent studies with brain lesion and pharmacological or

optogenetic manipulations has allowed us to understand the key role discrete brain regions like BLA, mPFC, hippocampus, nucleus reuniens and their interconnections play in fear memory extinctions. Due to its involvement in fear learning it is long known that BLA is involved in fear memory extinction (Maren, Aharonov, Stote, & Fanselow, 1996; Zimmerman & Maren, 2010); however, it has been shown recently that distinct population of BLA neurons mediate fear conditioning and fear extinction (Herry, et al., 2008). While the neurons involved in fear conditioning project from BLA to prelimbic (PL) subregion of mPFC, the neurons mediating fear extinction project for BLA to infralimbic (IL) subregion of mPFC (Senn, et al., 2014). The optogenetic activation of BLA-IL pathway neurons has been shown to facilitate fear memory extinction (Senn, et al., 2014) while lesion to infralimbic cortex impaired extinction (Bravo-Rivera, Roman-Ortiz, Brignoni-Perez, Sotres-Bayon, & Quirk, 2014; Do-Monte, Manzano-Nieves, Quiñones-Laracuente, Ramos-Medina, & Quirk, 2015). Thus, a co-ordinated activity between BLA and mPFC is required for fear memory extinction.

Recently, it was also shown that the role of prelimbic cortex is not restricted to fear learning but activation of intra-cortical glutamatergic projections from PL to IL subregion of mPFC facilitates fear memory extinction (Marek, Xu, Sullivan, & Sah, 2018). Future studies are needed to elucidate a more nuanced understanding of role of mPFC in fear memory extinction is required. Apart from their role in reward memories, projections from BLA to nucleus accumbens has also been demonstrated to be involved in fear memory extinction (Correia, McGrath, Lee, Graybiel, & Goosens, 2016). Furthermore, hippocampus plays a key role in extinction of context dependent fear memories (Kubie, Levy, & Fenton, 2020). Wang et al. (Wang, Yuan, Keinath, Álvarez, & Muzzio, 2015) have shown that there is a remapping of place cells in dorsal hippocampus during extinction of contextual fear memories. Recently, it was shown that fear memory extinction requires the suppression of a specific population of

neurons recruited during fear memory acquisition and activation of different subset of neurons in dorsal hippocampus (Lacagnina, et al., 2019). Furthermore, projections from ventral hippocampus to BLA and IL subregion of mPFC play a key role in extinction of fear memories (Jin & Maren, 2015a; Vasquez, et al., 2019). Lastly, nucleus reuniens in thalamus and its connections with hippocampus and mPFC are known to regulate the contextual information of fear memory extinction (Varela, Kumar, Yang, & Wilson, 2014). Thus, extinction of fear memory is often context dependent and therefore susceptible for recovery if the CS is presented in the different context from the extinction training and thus needs to be addressed to improve outcomes for treatments targeting extinction.

Selective serotonin reuptake inhibitors (SSRIs) are the preferred pharmacological treatment in PTSD. Their mechanism of action in PTSD has traditionally been thought to be their antidepressant action; however, evidence suggests that SSRIs also have an effect on memory extinction. Chronic administration of fluoxetine before (Deschaux, Spennato, Moreau, & Garcia, 2011) and after (Deschaux, et al., 2013) extinction in rats prevented the return of extinguished fear memory when exposed to reminder of stressful event. Combination of fluoxetine administration and extinction training in mice produced a more enduring loss of conditioned fear memory compared to fluoxetine or extinction training alone (Karpova, et al., 2011). Fluoxetine increases the synaptic plasticity and cause the memory to become more malleable to extinction induced synaptic remodelling (Karpova, et al., 2011). This suggests that combining pharmacotherapy with exposure therapy can have synergistic effect mediated by their action on memory extinction.

Yohimbine, an α-2 adrenergic receptor antagonist, acts by enhancing the release of norepinephrine in amygdala, hippocampus and prefrontal cortex (Cain, Blouin, & Barad, 2004).

Yohimbine has been demonstrated to enhance fear memory extinction in rodents (Cain, et al., 2004; Holmes & Quirk, 2010). Importantly, a recent randomized placebo-controlled trial in PTSD patients has shown that combining yohimbine with prolonged exposure therapy led significantly reduced trauma induced heart rate reactivity and rapid improvement in depression but not PTSD symptoms (Tuerk, et al., 2018).

Recent research has highlighted the critical role of dopaminergic system in fear memory extinction. Dopamine neurons from ventral tegmental area (VTA) project to amygdala and mPFC mediate the effect of drugs acting on dopaminergic system on fear memory extinction (Lee, Lee, & Kim, 2017; Weele, Siciliano, & Tye, 2019). Systemic administration of L-DOPA, a dopamine precursor, after contextual fear memory extinction training enhanced the retention of fear extinction and made the memory context independent (Haaker, et al., 2013). Similarly, L-dopa administration rescued deficient fear extinction in 129S1/SvImJ mice, which show impaired fear extinction (Whittle, et al., 2016). Systemic administration of dopamine D1/5 receptors agonist SKF 81297 facilitated both cued and contextual fear memory extinction (Abraham et al., 2016) (Abraham, Neve, & Lattal, 2016). In a clinical study on 45 male participants, enhancing dopaminergic activity by administration of L-DOPA during extinction consolidation increased the vmPFC activity and improved retrieval of extinction memory retrieval (Gerlicher, Tüscher, & Kalisch, 2018); however, further study showed that this extinction enhancement was dependant on successful extinction learning (Gerlicher, Tüscher, & Kalisch, 2019). Importantly, administration of L-DOPA in a randomized placebo controlled clinical trial boosted the reactivation of amygdala extinction encodings and reduced reinstatement of conditioned fear memory but did not improve extinction recall in women with PTSD (Cisler, et al., 2020). Future research could explore the effect of combination of L-DOPA with prolonged exposure therapy in patients with PTSD.

Glucocorticoids apart from their anti-inflammatory action have been shown to enhance fear memory. Corticosterone administration after extinction training was shown to facilitated extinction in BALB/C mice (Brinks, de Kloet, & Oitzl, 2009). In rats, administration dexamethasone, a glucocorticoid agonist enhanced while, metyrapone, glucocorticoid synthesis inhibitor disrupted the extinction of fear memory (Yang, Chao, Ro, Wo, & Lu, 2007). Combination of subthreshold dose of DCS and dexamethasone enhanced extinction synergistically (Yang, et al., 2007). Importantly, hydrocortisone, a synthetic form of cortisol, enhanced extinction learning in PTSD patients. Patients in hydrocortisone group showed significantly lower differential skin conductance response (SCR) compared to placebo (Inslicht, et al., 2021). This suggests that glucocorticoid could be acting in PTSD by facilitation of fear memory extinction. In summary, drugs like DCS, Yohimbine and L-DOPA could be used in combination with prolonged exposure therapy to facilitate fear memory extinction or enhancement of memory extinction could contribute to the effect of SSRIs, cannabinoids, and glucocorticoids in PTSD.

9. Fear memory generalization

Memory generalization occurs when experience of fear associated with a specific traumatic event is transferred to safe event resembling the original trauma (American Psychiatric Association & Association, 2013). Unlike healthy individuals who can discriminate between the current non-threatening situation from previous traumatic event and respond accordingly, patients with PTSD show hyperarousal to the situations resembling even remotely to the original traumatic event (Kaczkurkin, et al., 2017). Recent evidence suggests that besides strong fear encoding (Orr, et al., 2000) and impaired fear memory extinction (Jovanovic &

Ressler, 2010), overgeneralization of fear is an important mechanism responsible for PTSD (Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015). Fear overgeneralization increases the number of cues in the patient's environment that remind them of initial trauma thus contribution to significantly to the morbidity of PTSD (Dunsmoor & Paz, 2015).

Hippocampus plays a key role in discrimination between two different sensory stimuli by pattern separation (McTighe, Mar, Romberg, Bussey, & Saksida, 2009; Talpos, McTighe, Dias, Saksida, & Bussey, 2010), apart from its involvement in contextual fear memory consolidation and reconsolidation (Debiec, et al., 2002; Gafford, et al., 2011). Fear memory generalisation could be mediated by impairment in hippocampus mediated pattern separation to discriminate between two different contexts (Kheirbek, Klemenhagen, Sahay, & Hen, 2012). In a study by McHugh et al. (McHugh, et al., 2007), mice which lacked the essential subunit of the NMDAR NR1 in dentate gyrus granule cells of hippocampus could not discriminate between two similar contexts despite performing normally in contextual fear conditioning. It is suggested that reduction in hippocampal volume seen in PTSD patients may underlie their vulnerability to overgeneralization of fear response (Mark W Gilbertson, et al., 2002; Levy-Gigi, Szabo, Richter-Levin, & Kéri, 2015).

A reduction in mPFC inputs to BLA which is thought to be responsible for impaired fear memory extinction in PTSD (Seth D Norrholm, et al., 2011), has also been suggested to be responsible for fear memory generalization (Lopresto, Schipper, & Homberg, 2016). In a study by Likhtik et al. (Likhtik, Stujenske, Topiwala, Harris, & Gordon, 2014), mice which showed good discrimination between averseness and safety had increased number of theta oscillations between the mPFC and BLA. In another study by Sangha et al. (Sangha, et al., 2009), mice which lacked 65 kDa isoform of glutamic acid decarboxylase responsible for

increase in GABA levels, showed increased theta frequency synchronicity between hippocampus and amygdala and increased fear generalization and impaired extinction. Increased theta frequency synchronization between hippocampus and amygdala has also been observed in fear memory consolidation (Seidenbecher, Laxmi, Stork, & Pape, 2003) and reconsolidation (Narayanan, Seidenbecher, Sangha, Stork, & Pape, 2007). This suggests that fear memory generalization share common neural mechanisms with fear memory consolidation, reconsolidation, and extinction.

Fear memory generalization is susceptible to pharmacological interventions. Pedraza et.al. (Pedraza, et al., 2016)showed that strong footshock training (4 × 1.0 mA) in contextual fear conditioning led to more fear generalization compared to low intensity footshock training (4 × 0.4 mA) and this could be prevented by administration of metyrapone (cortisol steroidogenesis blocker) or propranolol (β-adrenergic antagonist). This suggests that highly stressful events can lead to fear memory generalization mediated by increased glucocorticoid and noradrenaline system activation caused by such situations. In another study, administration of α2-adrenoceptor antagonist yohimbine immediately after contextual fear conditioning led to more generalized fear memory which were also resistant to reconsolidation intervention by α2-adrenoceptor agonist clonidine or phytocannabinoid cannabidiol (Gazarini, Stern, Piornedo, Takahashi, & Bertoglio, 2015). However, this resistance to reconsolidation disruption by clonidine and cannabidiol in generalised fear memories was overcome by administration of NMDA agonist D-cycloserine before retrieval to increase memory labilization (Gazarini, et al., 2015). Further, chronic administration of SSRI fluoxetine was shown to reduce fear memory generalization and increase memory precision by remodelling of dendritic spines in hippocampus (Pedraza, et al., 2019). Subanaesthetic dose of ketamine reduced fear memory generalization mice (Asim, et al., 2020).

Administration of NMDA N2B antagonist ifenprodil or BDNF receptor TrkB antagonist ANA-12 in infralimbic cortex reversed this effect which suggests that ketamine prevented fear memory generalization via the action on GluN2B-BDNF Signalling (Asim, et al., 2020). These studies suggest that fear memory overgeneralization could be targeted therapeutically in PTSD patients. Moreover, pharmacological intervention to prevent fear memory overgeneralization could increase the effectiveness of current PTSD treatment.

10. Fear memory modification protocols

Given that there is some overlap with respect to underlying neural mechanisms, procedures to test pharmacological interventions and interpretation of finding with respect to fear memory reconsolidation, extinction, and generalization, we have described below the typical protocols to evaluate the effect of pharmacological interventions on each of the memory processes.

Pavlovian fear conditioning is the most commonly used behavioural paradigm study the effect of drugs on fear memory in PTSD (Bergstrom, et al., 2013; Blundell, et al., 2008; Bustos, et al., 2006; Davis, 1992; Debiec & Ledoux, 2004; Jacques, et al., 2019; Nader, Schafe, & Le Doux, 2000). In this model a neutral conditioned stimulus (CS) such as tone, light or context is paired with aversive unconditional stimulus (US) such as foot shock. This results in formation of associative fear memory so that presentation of CS leads to behaviour linked to memory of US. In contextual fear conditioning the memory storage requires hippocampus and amygdala whereas cued fear conditioning is mediated only by amygdala and do not involve hippocampal activity. The testing of retrieval of fear memory presenting CS without the US. Percentage freezing is the most commonly used behaviour response as a measure of fear.

10.1 Fear memory reconsolidation protocol

To evaluate the effect of drugs on fear memory reconsolidation using cued fear conditioning paradigm, the experimental procedure is carried out in 2 different chambers. Rodents are trained in conditioning chamber A wherein a single conditioned stimulus (CS; tone) is paired with an unconditioned stimulus (US; footshock) (Bergstrom, et al., 2013; Nader, Schafe, & Le Doux, 2000). Twenty-four hours following training, rodents are re-exposed to CS in a different Chamber B. Chamber B has a different flooring, appearance, and scent to reactivate only the cued fear memory. Study drugs are administered immediately after the memory reactivation. Memory is tested 24 hrs later by presenting CS without the US in chamber B. Freezing behaviour (defined as complete lack of movement, except for respiration) is measured as a marker for fear and recorded with camera. Percentage of time mice spent freezing when presented with the CS is used as the dependent measure and can be analysed manually or with software.

The test whether the fear memory disruption is specifically due to blockade of reconsolidation, in a separate group of animals, a similar protocol to that is described above is followed except study drugs are administered on day 2 without the reactivation of memory.

Several factors affect when the study drug should be administered with memory reactivation. It has been observed that memory is most susceptible to disruption 1 – 2 hours after reactivation (Nader, Schafe, & Le Doux, 2000; Przybyslawski, et al., 1999). To achieve the peak concentration of the drug at this time several factors including route of administration, pharmacokinetics and drug site of action need to be considered. For example, it has been shown that propranolol which has the t_{max} (time required to reach maximum plasma concentration) of 1-2 hour disrupted the fear memory if given 1 hour after the memory

reactivation and but had no effect if given 2 hours after memory reactivation (Kindt & Soeter, 2018). Similarly, agonists of NMDA receptors such as D-cycloserine needs to be given before memory reactivation to increase memory labilization as administration after reactivation will enhance extinction and interfere with amnestic effect of drug on reconsolidation and NMDAR antagonists like MK801 should be adminstered after memory reactivation as administration before reactivation can lead to failure of memory labilization (Lee, et al., 2006b).

10.2 Fear memory destabilization protocol

Animals are trained wherein a single conditioned stimulus (CS; 30 sec tone) is paired with an unconditioned stimulus (US; foot shock) in chamber A. Twenty-four hours after the training, effect of study drugs on memory destabilization in the context of reconsolidation is tested by administration of the D cycloserine (NMDA NR2B agonist) before memory reactivation to destabilize the memory. One hour after the D-cycloserine injection rodents will undergo reactivation session wherein they are exposed to the CS without the US in chamber B (Bustos, et al., 2010). Alternatively, memory could be destabilized by introduction of temporal prediction error for example by re-exposing the animals to a 60 sec tone CS instead of 30 sec without the US (Flavell & Lee, 2019a) at the time of memory reactivation. Immediately after memory reactivation, a blocker of memory reconsolidation like anisomycin, midazolam or another drug is administered. Animals could be divided in three groups (Group 1: Vehicle control, Group 2: memory reconsolidation blocker, Group 3: D-cycloserine + memory reconsolidation blocker). Twenty-four hours after the reactivation session memory is tested by presenting CS without the US in chamber B. Freezing time is recorded using camera and can be analyzed manually or with software. To test whether boundary conditions like strength and age of memory affect memory destabilization, memory strength could be increased

during conditioning by increasing the number of tone-foot shock pairings or memory reactivation could be done 28 days after initial training.

10.3 Fear memory extinction protocol

Fear condition in fear extinction experiments is done similar to training in fear memory reconsolidation. Animals are habituated to conditioning chamber A following which they are subjected to a mild shock paired with a tone. The tone is played for 30 seconds the shock is delivered during last second of the tone. Study drugs are administered 2.5 hours before the extinction session on day 2. Twenty-four hours after training, rodents are placed in different chamber B and exposed to 10 CS (tone) presentations without the US (foot shock) (Merlo, et al., 2014). On day 3, animals are placed in chamber B and a single CS is presented. Freezing behaviour is recorded and percentage freezing time is taken as measure of fear memory.

Evidence suggests that reconsolidation and extinction are two distinct processes in which fear memory transitions from maintenance to inhibition with increase in extent of retrieval (Suzuki, et al., 2004). To delineate the fate of memory from reconsolidation to extinction, Merlo et.al (Merlo, et al., 2014) tested the effect of 1, 4, 7 and 10 CS presentation during memory reactivation on day 2. Animals showed significantly increased freezing in groups which received 1 and 4 CS compared to 7 and 10 CS. This transition from reconsolidation to extinction was associated with increase in calcineurin levels in BLA from 1 to 10 CS group with significantly higher levels in 10 CS group compared to other groups while ERK/MAPK levels remained equal between groups. This suggests that gradually increasing extent of retrieval leads to transition from reconsolidation to extinction and the two distinct processes are mediated by change in concentration of calcineurin which regulates key proteins involved in synaptic transmission and neuronal excitability in BLA. This transition from reconsolidation to

extinction also changes the effect of pharmacological interventions on fear memory. NMDAR NR2B agonist D-cycloserine administered with 1 CS presentation resulted in increase in freezing while when given with 10 CS led to reduced freezing on test day. In contrast, NMDAR antagonist MK801 given with 1 CS presentation reduced freezing but when administered with 10 CS increased freezing (Lee, et al., 2006b; Merlo, et al., 2014). Thus, modulation of NMDA receptors can have different effect on fear memory depending on extent of memory reactivation and whether they are affecting reconsolidation or extinction.

10.4 Fear memory generalization protocol

The experimental procedure to test the effect of drugs on fear memory generalization using cued fear conditioning paradigm is carried out in 2 different chambers. On day 1, animals are habituated to chamber A and 5 presentations of two different tones (eg. CS+ a continuous sound at 1 kHz; and CS- 5 kHz clicks) (Asim, et al., 2020). Immediately after habituation, fear conditioning is done in which one of the two sounds (CS+) is paired with strong foot shock (1.2 mA for 1 s). Study drugs are administered 22 hours after conditioning. Two hours after study drug administration, fear memory is tested by playing 5 presentations of CS+ and CS- each. Freezing levels for the 2 tones are recorded separately by measuring average freezing levels of all CS+ and CS- presentations. The ratio of average freezing response to CS– to the average freezing response to CS+ is taken as a measure of fear memory generalization.

11. Other pharmacological interventions and drug targets

11.1 D-cycloserine (DCS)

D-cycloserine (DCS) is an antibiotic and approved for use in tuberculosis. DCS and has been studied extensively as an adjunct with exposure therapy for treatment of generalised anxiety disorder, obsessive compulsive disorder, and phobia (Norberg, Krystal, & Tolin, 2008). DCS is a full agonist at NMDA GluN2C receptor and a partial agonist at NMDA GluN2A, GluN2B, and GluN2D receptors (Sheinin, Shavit, & Benveniste, 2001). NMDA receptors are critical for formation of memory and fear memory extinction. The distribution of the different NMDA receptor subtypes in the CNS contributes to formation of fear responses and results in fear extinction. Blockade of NMDA receptors in animal models impairs memory extinction, whereas their stimulation leads to enhancement of memory extinction (Dalton, Wu, Wang, Floresco, & Phillips, 2012; Ogden, Khatri, Traynelis, & Heldt, 2014). DCS has been shown to increase fear extinction consistently in number of animal studies (Ledgerwood, Richardson, & Cranney, 2003, 2004; Walker, Ressler, Lu, & Davis, 2002). Similarly, DCS has been shown to enhance fear extinction when combined with exposure therapy for in patients with phobia and panic disorder (Davis, 2011). Furthermore, stimulation of NMDA GluN2B receptors with DCS has been shown to increase labilization of memory during reconsolidation making it more prone to disruption. This raises the possibility of potential use of DCS in PTSD.

The evidence for use of DCS assisted therapy in PTSD is variable. In a pilot randomized placebo controlled clinical trial conducted on 11 chronic PTSD patients, DCS was similar to placebo in reducing PTSD symptoms when used as an adjunct to psychotropic medications (Heresco-Levy, et al., 2002). Similarly, in a clinical trial comparing DCS with placebo in 76 chronic combat-related PTSD patients, DCS did not influence the frequency or severity of PTSD symptoms (Attari, Rajabi, & Maracy, 2014). However, DCS decreased intensity of avoidance and numbing symptoms. De Kliene et al (2012) compared DCS augmented exposure therapy with placebo plus exposure therapy in PTSD patients. The effect of DCS on CAPS score was

comparable to placebo, but it did show stronger treatment response and a greater reduction on PTSD symptoms in patients with severe PTSD (de Kleine, Hendriks, Kusters, Broekman, & van Minnen, 2012). In contrast, in a randomized clinical trial (RCT) in veterans with combat related PTSD, there was significantly less reduction in PTSD symptoms in DCS plus exposure therapy group compared to placebo plus exposure therapy (Litz, et al., 2012). However, Difede et al (2014) showed DCS combined with virtual reality exposure therapy significantly reduced CAPS scores post treatment and at six months follow up compared to placebo (Difede, et al., 2014). These findings could not be replicated in Iraq and Afghanistan war veterans with PTSD where DCS with virtual reality exposure therapy showed similar effects compared to placebo with virtual reality exposure therapy (Rothbaum, et al., 2014). Similarly, in children with PTSD, DCS combined with CBT showed no benefit over placebo with CBT in reducing PTSD symptoms (Scheeringa & Weems, 2014). Peskin et al (2019) showed reduction in posttraumatic and depressive symptoms with virtual reality exposure therapy which was strengthened by DCS (Peskin, et al., 2019). Differences in the methodology with respect to amount and timing of DCS administration may have produced inconsistent results (de Kleine, et al., 2012; Litz, et al., 2012).

In view of the mixed results observed in clinical trials, many factors in clinical trial design need to be addressed before DCS assisted therapy could be incorporated in PTSD treatment. The dose and the treatment regimen of DCS, type of psychotherapy, number of therapy sessions and pharmacokinetic parameters to optimize the level of DCS in CSF at the time of therapy need to be addressed in future clinical trials.

11.2 Neuropeptide Y (NPY)

Neuropeptide Y (NPY), a 36 amino-acid neuropeptide, is the most abundant peptide in the human brain. It is highly expressed in amygdala, hippocampus, hypothalamus, and cortex and involved in regulation of many systems relevant to pathophysiology of PTSD including regulation of anxiety and stress, fear learning and memory, and control of sympathetic activity (Adrian, et al., 1983; Eaton, Sallee, & Sah, 2007; Redrobe, Dumont, St-Pierre, & Quirion, 1999; Zukowska-Grojec, 1995).

Regulation of anxiety and stress is perhaps the most important mechanism through which NPY is beneficial in PTSD. NPY knockout mice show exaggerated anxiogenic response (Bannon, et al., 2000) while overexpression of NPY produce anxiolytic response in rodent models of anxiety (Primeaux, Wilson, Cusick, York, & Wilson, 2005). Similarly, administration of NPY or NPY receptor agonist produced an anti-anxiety effect in rodents (Kask, et al., 2002). NPY injection in amygdala increased long-term resilience to stress-induced reductions in social responses in rats (Sajdyk, et al., 2008). In humans, high levels of plasma NPY is shown to increase resilience to extreme psychological stress in military survival training soldiers (Morgan, et al., 2000) whereas low CSF NPY levels have been observed in patients with PTSD (Sah, Ekhator, Jefferson-Wilson, Horn, & Geracioti, 2014).

In addition to its role in regulation of anxiety and stress, NPY is also involved in fear conditioning and extinction. Intracerebroventricular administration of NPY reduced context and cued freezing in mice (Karlsson, Holmes, Heilig, & Crawley, 2005) while administration of NPY in hippocampus attenuated trauma associated fear memory (Cohen, et al., 2012). Similarly, reduced level of NPY was associated with increased fear reinstatement in chronic variable stress in rats (McGuire, Herman, Horn, Sallee, & Sah, 2010). In humans, reduced CSF

NPY levels significantly correlated with increased PTSD symptoms and more specifically with presence of intrusive traumatic memory (Sah, et al., 2014).

Only one clinical trial has examined the efficacy of NPY in individuals with PTSD till date. In a randomized and crossover dose-ranging study of NPY to evaluate its safety and anxiolytic efficacy in 26 PTSD patients, intranasal administration of NPY was well tolerated up to the highest dose of 9.6 mg (Sayed, et al., 2017). Moreover, higher doses of NPY showed more reduction in anxiety compared to placebo on Beck Anxiety Inventory score although the effect was not statistically significant. Results from the study show that NPY could be developed for treatment of PTSD however, clinical trials with larger sample size and incorporating specific measures for PTSD (CAPS, PCL) are needed.

11.3 Oxytocin

The neuropeptide oxytocin is a promising candidate albeit with modest evidence in the treatment of PTSD. Unlike its obstetrics use where it is administered intravenously to induce labour, intranasal oxytocin has been studied in psychiatry for anxiety, depression and PTSD (De Cagna, et al., 2019). Oxytocin is known to enhance the prosocial behaviour and reduce avoidance to recall of traumatic memories during psychotherapeutic session thus improving the therapeutic alliance and allowing for modification of those memories. It is postulated that prosocial effects of MDMA are mediated through release of oxytocin (Dumont, et al., 2009). Administration of single dose of oxytocin to PTSD patients reduced anxiety, irritability and intensity of intrusive thoughts while improving mood and desire for social interaction (Yatzkar & Klein, 2010). Oxytocin has been shown to increase fear extinction by modulation of central amygdala output in rats (Roozendaal, et al., 1992; Viviani, et al., 2011). Furthermore,

intranasal oxytocin facilitated fear extinction in human volunteer (Acheson, et al., 2013; Eckstein, et al., 2015). Thus, intranasal oxytocin could also be developed as adjunctive treatment to psychotherapy such as prolonged exposure therapy which is based on fear extinction (Olff, Langeland, Witteveen, & Denys, 2010).

In a RCT on 35 female PTSD patients, a single dose of oxytocin significantly reduced responses to Script-Driven Imagery and attenuated PTSD symptoms compared to placebo (Sack, et al., 2017). In another study on 37 police personnel with PTSD, intranasal oxytocin reduced subjective anxiety and nervousness in PTSD patients (Koch, et al., 2016). Flanagan and colleagues conducted a RCT to evaluate eight sessions of prolonged exposure therapy with oxytocin or placebo in PTSD patients (Flanagan, Sippel, Wahlquist, Moran-Santa Maria, & Back, 2018). Their results suggest that oxytocin lowered PTSD and depression symptoms and increased working alliance compared to placebo, however these differences did not reach statistical significance. These preliminary findings suggests that oxytocin could be potentially developed for treatment of PTSD, however, several issues with respect to sample size, dosing, psychotherapy selection, clinical assessment, and follow-up need to be addressed in scientifically designed RCTs.

11.4 Neuroactive steroids

Recent evidence suggests that neuroactive steroids could play an important role in pathophysiology and treatment of PTSD. They are involved in stress adaptation through modulation of neuronal signalling. Stress leads to increased synthesis of neuroactive steroid like allopregnanolone which reduce neuronal excitability by acting on $GABA_A$ receptors (Purdy, Morrow, Moore, & Paul, 1991). However, severe stress and prolonged isolation were both

associated with reduction in allopregnanolone levels and increase in fear conditioning, resistance to extinction, anxiety and depression in rodents (Dong, et al., 2001; Zhang, et al., 2014). Mice deficient in allopregnanolone showed slow extinction and spontaneous recovery of fear after extinction as compared to mice with normal allopregnanolone levels (Pibiri, Nelson, Guidotti, Costa, & Pinna, 2008). Whereas administration of allopregnanolone was shown to have anxiolytic, antidepressant, and neurotrophic properties and enhance fear memory extinction(Dong, et al., 2001; Eser, Baghai, Schüle, Nothdurfter, & Rupprecht, 2008; Pinna & Rasmusson, 2014).

Studies have shown that serum allopregnanolone levels are significantly lower in PTSD patients compared to control population (Rasmusson, 2016; Rasmusson, et al., 2006). Low CSF allopregnanolone in women with PTSD was associated with PTSD re-experiencing and depressive symptoms (Rasmusson, 2016). Furthermore, exogenous administration of ganxolone, a synthetic form of allopregnanolone, facilitated fear extinction and prevented spontaneous recover of fear (Pinna & Rasmusson, 2014). In a clinical trial, administration of pregnanolone, a precursor of allopregnanolone, reduced PTSD symptoms in patients with mild traumatic brain injury (NCT00623506). Clinical trials to evaluate the efficacy of pregnanolone in individuals with PTSD are underway (NCT03799562).

11.5 Neuroinflammation

A growing body of evidence has demonstrated the critical role played by immune system in pathophysiology of PTSD. Several basic and clinical studies have explored the mechanisms by which increased inflammation contributes to the development of PTSD. Studies in animals have shown that chronic stress such as seen in many PTSD patients is associated with increase

in inflammation possibly through dysregulation of hypothalamic–pituitary–adrenal (HPA) axis and activation of sympathetic nervous system (Daskalakis, et al., 2016; Hendrickson & Raskind, 2016). Increased secretion of corticotropin-releasing hormone (CRH) following stress leads to activation of sympathetic nervous system and release of norepinephrine which in turn may lead to increased production inflammatory cytokines such as IL-1 and IL-6 (Bierhaus, et al., 2003). Activation of microglia in the brain following stress leads to increased IL-6, TNF-α, and IL-1β which modulate synaptic plasticity and learning and memory processes (Levin & Godukhin, 2017; Réus, et al., 2015). Increased neuroinflammation has been shown to impair fear memory extinction and thus leading to persistence of fear memory (Quiñones, Maldonado, Velazquez, & Porter, 2016; Young, et al., 2018; Yu, et al., 2017). In clinical studies, increased inflammation was associated with greater activation of amygdala when presented with threatening stimuli (Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012; Swartz, Prather, & Hariri, 2017).

Recent evidence suggests a link between inflammatory pathophysiology and miRNA deregulation (Gupta, Guleria, & Szabo, 2021). Increased blood levels of proinflammatory cytokines were associated with reduced expression of miRNAs in veteran with PTSD (Zhou, et al., 2014). Furthermore, preclinical and clinical evidence suggests increased levels of glucocorticoid receptors (GR) - FKBP5 proteins complex which prevents GR phosphorylation in PTSD (Li, et al., 2020). A peptide which blocks the glucocorticoid receptors (GR) - FKBP5 was shown to reduce freezing time and in GR phosphorylation in fear conditioned mice (Li, et al., 2020).

PTSD patients have significantly higher risk of being diagnosed with comorbidities which involve dysregulation of immune system like ischemic heart disease, autoimmune diseases,

and metabolic syndrome (Edmondson, Kronish, Shaffer, Falzon, & Burg, 2013; Mellon, Gautam, Hammamieh, Jett, & Wolkowitz, 2018; O'Donovan, et al., 2015). Multiple studies have shown that PTSD patients have significantly higher presence of proinflammatory markers like IL-6, IL-1β, TNF-α and C-reactive protein in their blood compared to healthy controls (de Oliveira, et al., 2018; Imai, et al., 2018; Lindqvist, et al., 2017; Passos, et al., 2015). In line with this, several studies have explored the therapeutic potential of targeting neuroinflammation as well as the possibility of proinflammatory markers as diagnostic and prognostic biomarkers for PTSD (Aerni, et al., 2004; Lee, et al., 2016; Quiñones, et al., 2016).

Several drugs with anti-inflammatory properties have been investigated for their therapeutic potential in PTSD (fig 7). Systemic administration of ibuprofen, a non-steroidal anti-

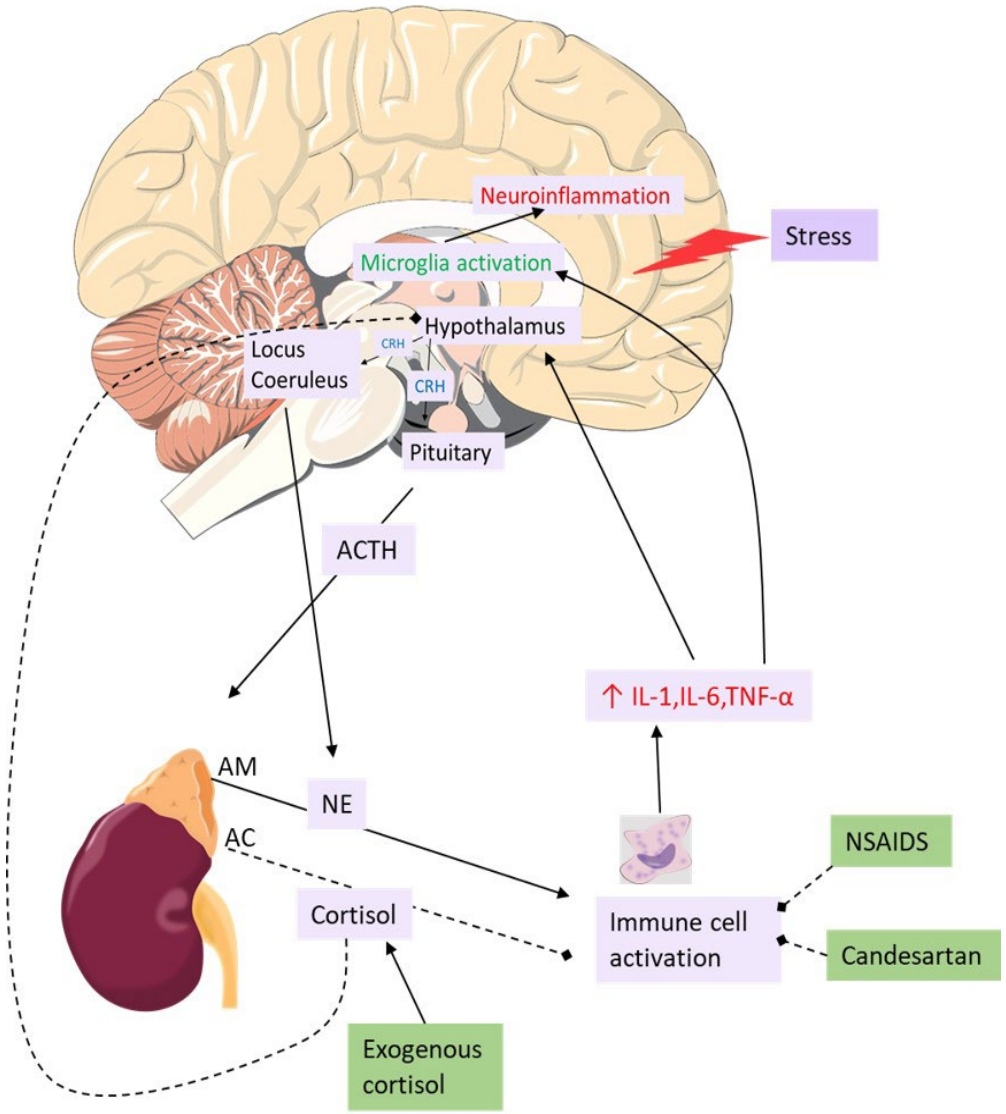

Fig. 7. Drugs targeting neuroinflammation mechanism in PTSD. PTSD is associated with dysregulation of HPA axis and activation of sympathetic nervous system leading to increased release of pro-inflammatory cytokines. Increased cytokines in the periphery cross the blood brain barrier and cause microglia activation and further neuroinflammation. This may lead to greater activation of amygdala and impairment of fear memory extinction in PTSD. NSAID, candesartan and cortisol act by reducing immune cell activation and release of cytokines. Solid line indicates stimulation, dotted line indicates inhibition. Abbreviations: CRH, Corticotrophin-releasing hormone; ACTH, adrenocorticotropic hormone; NE, norepinephrine; AM, Adrenal medulla; AC, Adrenal cortex; IL-1, Interleukin-1; IL-6, Interleukin-6; TNF-α, Tumour necrosis factor-α.

inflammatory drug (NSAID) which act by inhibiting cyclooxygenase 2 (COX-2), was shown to reduce cytokine levels and reduce anxiety in rat model of PTSD (Lee, et al., 2016). Candesartan, an angiotensin receptor blocker, attenuated impaired fear extinction caused by lipopolysaccharide induced immune activation (Quiñones, et al., 2016). Studies have shown that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have distinct anti-inflammatory properties apart from their antihypertensive action (Clancy, Koblar, & Golledge, 2014; Kortekaas, et al., 2014). In humans, a cross-sectional study has shown the correlation between the use of ACE inhibitors and ARBs and reduced PTSD symptoms in highly traumatized civilian medical population (Khoury, et al., 2012). SSRIs, which are the only approved drugs for PTSD, are postulated to have anti-inflammatory properties (Gałecki, Mossakowska-Wójcik, & Talarowska, 2018; Walker, 2013). However, the extent to which the anti-inflammatory action contributes to their therapeutic effect in PTSD is still unknown. Finally, the strong anti-inflammatory effect might contribute to the action of glucocorticoids in PTSD apart from their effect on memory reconsolidation discussed earlier. In a pilot study, low dose cortisol treatment orally for one month reduced PTSD symptom severity (Aerni, et al., 2004). A single dose of hydrocortisone in individuals with full or subsyndromal PTSD enhanced fear extinction learning (Inslicht, et al., 2021).

Evidence suggests that beneficial effects of drugs acting on endocannabinoid signalling in PTSD (Cameron, Watson, & Robinson, 2014; Fraser, 2009; Jetly, Heber, Fraser, & Boisvert, 2015) are partly mediated by their actions on neuroinflammation. Cannabinoid CB2 receptor is the target site for modulation of the neuroinflammatory responses (Turcotte, Blanchet, Laviolette, & Flamand, 2016). CB2 receptor stimulation leads to suppression of inflammatory processes by inhibiting release of pro-inflammatory cytokines (such as TNF-a, IL-1b, and IL-6), reduced expression of adhesion molecules inhibition of leukocyte migration, decreased

oxidative stress and suppressing NFkB-mediated gene transcription (Boorman, Zajkowska, Ahmed, Pariante, & Zunszain, 2016; Chiurchiù, Leuti, & Maccarrone, 2015; McCoy, 2016; Rom & Persidsky, 2013) and release cytokines on activation (Atwood & Mackie, 2010). Microglial CB2 receptor activation also promoted release of anti-inflammatory cytokines (Lin, et al., 2017; Mecha, et al., 2015). Zoppi S et al (Zoppi, et al., 2014) have reported that endocannabinoid signalling at CB2 receptors limits the neuroinflammatory responses caused due to exposure to stress. CB2 receptor activation appears to be an additional mechanism by which cannabinoids offer protection in PTSD.

12. Conclusion

An extensive range of pharmacological targets and drugs affecting them have been explored to address the core pathophysiology of PTSD. These developments are a result of our continued struggle to find definitive solutions for PTSD given the limitations of current medical and behavioural approaches (Watts, et al., 2013). Considering the fact that the current pharmacological treatments like SSRIs and SNRIs focus mainly on elevation of patient's mood rather than treating underlying pathophysiology, new treatments which target pathological recurrence of traumatic memories are needed.

The renaissance in research on psychedelics and their combination with psychotherapy has shown much promise. Diverse mechanisms for their therapeutic benefits have been proposed from reducing the barriers to psychotherapy to direct impact on fear memory. MDMA and psilocybin were used mostly in combination with therapy while ketamine showed rapid

benefits as monotherapy. It is important that more data is generated to evaluate the efficacy and safety of psychedelics and to develop standardized protocols for the therapeutic settings in which these drugs are administered.

Identification of molecular mechanisms of reconsolidation led to development of pharmacological strategies to disrupt the fear memories. Despite robust evidence from animal studies, clinical trials for pharmacological intervention in PTSD have yielded mixed results. While receptor modulation with propranolol and cortisol have not unequivocally produced positive results, it would be of interest to see if inhibiting intracellular mechanisms using drugs such as MEK inhibitors can improve the treatment outcomes. Despite increasing interest in research targeting reconsolidation process in last two decades, no effective memory reconsolidation based pharmacological therapy is yet in use for PTSD patients. This suggests that more research is needed, to identify strategies to destabilize the memories and clinical studies on different molecular targets, before this approach is to be adopted broadly.

New exciting strategies like neuropeptide Y, oxytocin, cannabinoids and neuroactive steroids seem to offer novel ways to reduce PTSD symptoms. Drugs targeting HPA axis and neuroinflammation have also shown promise for PTSD treatment. Major challenges still remain with respect to designing of clinical trials for psychedelics, recruitment of adequate PTSD patients to meet sample sizes for large scale RCTs, and patients' reluctance to recall traumatic experiences in clinical trials. However, notwithstanding these hurdles, the recent developments in the PTSD therapeutics suggest that the field is on the cusp of a revolution.

Conflict of Interest

The authors declare no conflict of interest.

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