A review of the mechanisms behind MDMA and propranolol assisted PTSD treatment and their memory modulating qualities

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Abstract

Post-traumatic stress disorder (PTSD) significantly affects mental and physical health, imposing a substantial burden on society. Current treatments, including pharmacotherapy and cognitive-behavioral therapy (CBT), exhibit limitations such as modest and short term efficacy, tolerance buildup, and high discontinuation rates. Central in PTSD pathology is the traumatic memory, which, like all memory, can be reactivated. When reactivated, the memory is unstable and susceptible to disruptions until it is reconsolidated. This disruption offers a potential alternative to conventional treatments. Since the original memory trace is affected, successful disruption would show long term efficacy. Propranolol, a beta-adrenergic receptor blocker, has shown promise in blocking fear memory reconsolidation. Additionally, 3,4-methylenedioxymethamphetamine (MDMA) assisted psychotherapy demonstrates long term PTSD symptom reduction, possibly through the disruption of memory reconsolidation. This review aims to compare the mechanisms of propranolol and MDMA in memory alteration, contributing to a better understanding of their therapeutic effects on PTSD. Current literature shows that both MDMA and propranolol exposure therapies exhibit promise in treating PTSD, with the disruption of memory reconsolidation likely being a key mechanism, explaining their enduring effects. Propranolol's effectiveness remains debated, with challenges in replication suggesting the influence of variables like sufficient memory reactivation and drug administration timing to play important roles in enabling its efficacy in treatment. In contrast, MDMA therapy presents stronger evidence for its effectiveness in treating PTSD, although the exact role memory reconsolidation plays in this is not clear. The disruption of memory reconsolidation is shown to contribute, however fear extinction and other mechanisms cannot be ruled out as to also adding to its effectiveness.

Introduction

Post traumatic stress disorder (PTSD) has been found to have a significant influence on both mental and physical health (Watson, 2019). The DSM-5 presents PTSD as resulting from trauma exposure that leads to the person experiencing distressing memories recalling the event, flashbacks or recalling the event in dreams. Consequently, PTSD creates clinically significant stress or impairs the functioning in social, work or other crucial areas of life (5th ed.; DSM–5; American Psychiatric Association, 2014).

PTSD imposes a significant health and financial burden on society (Watson, 2019). Current treatment mostly consists of pharmacotherapy and cognitive behavioral therapy. In pharmacotherapy selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine (NE) reuptake inhibitors (SNRIs) are commonly prescribed. This is because the side effects of these medications are in general well tolerated and they are known to reduce PTSD symptoms (Shrader & Ross, 2021). However the magnitude of effect remains small and is generally not long lasting after stopping treatment (Hoskins et al., 2018). Consequently, prolonged treatment with SSRIs will lead to a tolerance buildup. This makes it hard to end treatment due to potentially severe withdrawal symptoms and can lead to long term unnecessary medication (Horowitz & Taylor., 2019).

CBT typically consists of two components. The first component, cognitive restructuring (CR), is a technique that is used to reframe patients´inaccurate beliefs. (Ezewa & Holling, 2023). The second component, exposure therapy, acts through reactivation of the traumatic memory, which is where PTSD symptoms originate from. By reactivating the traumatic memory in a safe

environment with the assistance of a therapist, fear extinction is meant to take place. Fear extinction (FE) works through creating an alternative competing memory which suppresses the original memory (Kindt & van Emmerik, 2016)(see figure 1). This leads to reduced activation of the traumatic memory after treatment. However, while effective in suppressing PTSD symptoms, the fear memory can come back in a new context in the long term (Kindt & van Emmerik, 2016). CBT is also often discontinued by a significant number of people (Gutner et al., 2015).

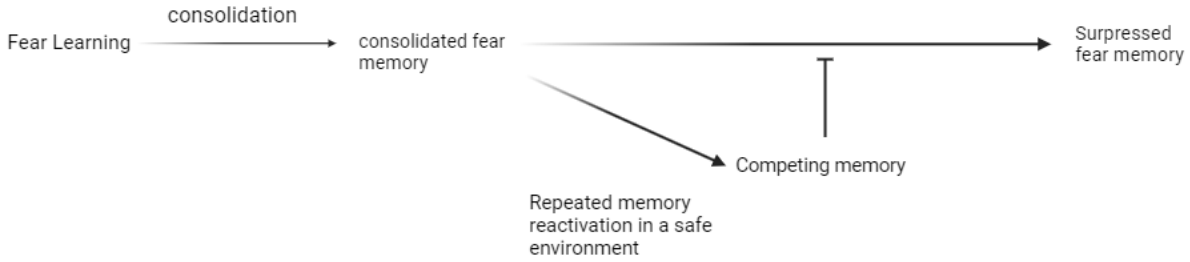

Figure 1, Fear extinction works through creating a competing memory that suppresses the fear memory.

In conclusion, CBT and pharmacotherapy are shown to be effective in treating PTSD and reducing symptoms. However they are not effective for all patients and especially in the case of pharmacotherapy are not without their drawbacks. As such the search for alternative treatments of PTSD are of interest.

As mentioned earlier, a traumatic memory is where the symptoms of PTSD originate from. After the traumatic event has occurred, it is consolidated and stored in the brain. The process of memory consolidation is an active process where protein synthesis takes place to make the neuronal connections that will form the memory, this process is called long term potentiation (LTP)(Haubrich & Nader, 2018). During consolidation a memory is known to be in a labile state by the fact that in the first hour after learning, consolidation can be disturbed by

protein synthesis inhibitors like vancomycin (Flexner et al., 1965)(see figure 2). The retrieval of memory on the other hand, used to be thought of as a passive process. However current understanding tells us that memory retrieval leads to the very active process of memory reconsolidation (Haubrich & Nader, 2018). Where before memory was thought to be fixed after consolidation, we now know that it is something that needs to be constantly maintained. After a memory is stored, it is not statically fixed but subjected to constant processes that lead to either the memory being sustained or lost (Haubrich & Nader, 2018). When the memory is retrieved, the process of memory reconsolidation is susceptible to the same disruptions as initial memory consolidation (see figure 2). This means that memory reconsolidation can also be blocked using protein synthesis inhibitors such as vancomycin (Nader et al., 2000). To what extent the memory can be altered is however reliant on how strongly the memory is consolidated and thus lessened with strong memories or memories that have been stored for a long time (Haubrich & Nader, 2018).

Fear memories, which lie at the base of PTSD, are stored through complex circuitry mainly involving the amygdala and the medial prefrontal cortex. Specifically the basal lateral amygdala (BLA) plays an important role in storing fear related memories (Duvarci et al., 2014). The BLA is made up primarily of spiny glutamatergic neurons (~80%) and GABAergic interneurons (~20%)(Duvarci et al., 2014). Glutamatergic neurons play a central role in learning and memory formation. This is shown by antagonists of glutamate receptors AMPA and NMDA impairing memory processes (Robbins & Murphy, 2006). Of note is that the presence of corticosterone and norepinephrine enhances the excitability of the glutamatergic neurons (Duvarci et al., 2014). These are present in emotionally stimulating situations and it is shown that injecting norepinephrine into the BLA, prefrontal cortex or hippocampus enhances emotional

memory consolidation (Roozendaal & Hermans, 2017). Interestingly, beta adrenergic agonists like norepinephrine enhance long term memory formation, while beta adrenergic receptor blockers disrupt memory formation (Ilhan & Kislal, 2023). Intra-amygdala injections of the beta adrenergic receptor blocker propranolol showed to block memory reconsolidation of conditioned fear response in rats (Dębiec & Ledoux, 2004)(see figure 2).

Extrapolating this to PTSD, through the process of disrupting memory reconsolidation it might be possible to alter traumatic memory, relieving PTSDsymptoms. Since the memory itself would be altered instead of being suppressed by a new memory as is the case in fear extinction, memory reconsolidation would show longer lasting effects (Kindt & van Emmerik., 2016). Interestingly 3,4-methylenedioxymethamphetamine (MDMA) assisted psychotherapy has shown strong evidence for being able to decrease PTSD symptoms sustained for a long period after treatment (Latimer et al., 2021). The underlying mechanism behind this success is debated, however some research points to the disruption of memory reconsolidation explaining these long lasting effects (Hake et al., 2019;Arluk et al., 2022). MDMA is a psychoactive substance that targets the monoamines in the brain (Green et al., 2003). It does this through attaching itself to and blocking the norepinephrine, serotonin and dopamine transporters and through enacting the efflux of serotonin and dopamine into the synapse (Latimer et al., 2021). In MDMA assisted psychotherapy the patients administered MDMA are placed in a comfortable environment with a therapist who will guide them through remembering their traumatic experiences, bringing the traumatic memory into an active state. The patients report having clearer recall of their traumatic experience and show less dissociation (Feduccia et al., 2018).

This study seeks to elucidate the underlying mechanisms inherent in psychotherapeutic interventions involving both propranolol and MDMA. The primary objective is to draw a

comparative analysis between these two treatments, laying a focus on memory formation processes. By examining the distinct roles of propranolol and MDMA in the context of memory modulation, the study aims to contribute to an understanding of the therapeutic mechanisms underlying each treatment approach.

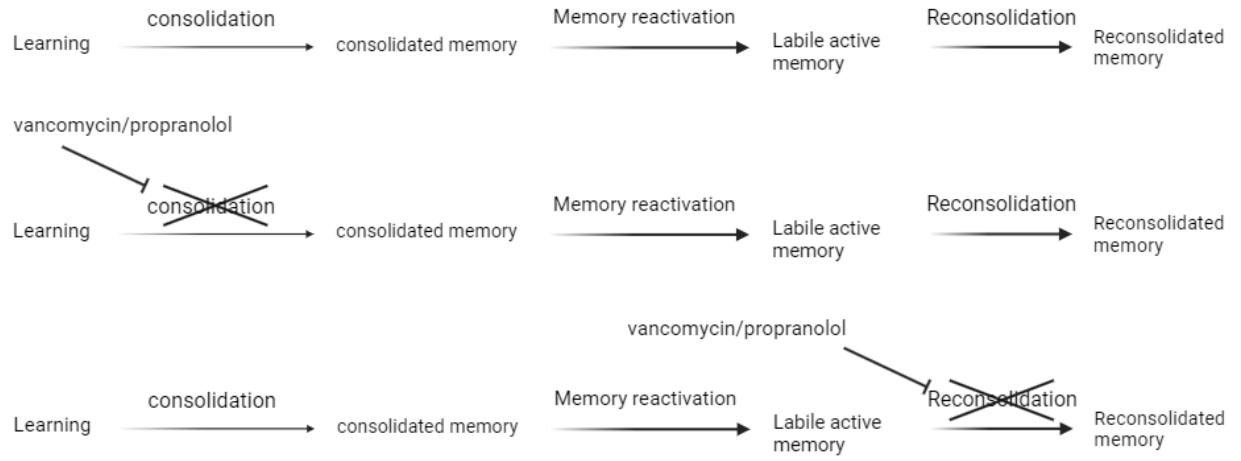

Figure 2, the process of both memory consolidation and reconsolidation can be blocked by vancomycin and propranolol intervention.

Propranolol

Propranolol has been extensively studied in both animals and humans. Some studies have shown that it alters memory consolidation and is successful in treating PTSD, while other studies have failed to show the same. So what does our current understanding tell us about the mechanisms and effectiveness behind propranolol PTSD treatment?

In the clinical trials done by Kindt & van Emmerik (2016) they showed that through treatment of PTSD with propranolol, they were able to reduce PTSD symptoms. First an intake session was conducted where the traumatic memories were identified. The treatment started with

reactivation of the traumatic memory. This was done through imaginal exposure procedures. This is a classical CBT technique where a patient is guided by a therapist into remembering and visualizing their traumatic experience (Mclean et al., 2021). As to rule out that extinction learning would take place, the memory reactivation was terminated as soon as the patient's distress reached a maximum. If memory reactivation was deemed successful, a 40 mg pill of propranolol was administered after the reactivation procedure. PTSD symptoms were assessed after the first session, 1 week, 1 month and 4 months after the procedure. In 3 out of their 4 patients they observed rapid and long term relief of their PTSD symptoms after only 1 or 2 interventions. Their fourth patient did not see improvements, the authors themselves speculate that this is likely due to the traumatic memory not reaching a labile state. PTSD memories are complex, much more complex than condition fear memory in rodents for example. As such successful reactivation appears to be more difficult to achieve. They stopped memory reactivation after the patient reached high levels of distress, their results indicate that high levels of distress do not necessarily correspond with the memory reaching an active labile state. In another clinical trial, Kindt et al (2023) again made use of propranolol, to treat war veterans that have been unresponsive to classical exposure therapy. Their treatment however also included other newer PTSD treatment techniques. Five out of seven veterans saw clear improvements in their PTSD symptoms showing that their treatment methods are promising. However they did not have a placebo group and also made use of imagery rescripting therapy which is known to be effective in treating PTSD.

In a study by Roullet et al (2021) they also aimed to showcase the effectiveness of propranolol assisted PTSD treatment. They however, unlike Kind & van Emmerik (2016) and Kindt et al (2023) did make use of a control group. They conducted a clinical trial with 66 adults

suffering from long lasting PTSD. They were randomly divided into either a traumatic memory reactivation + propranolol or traumatic memory reactivation + placebo group and assessed for either severe or moderate PTSD symptoms. Treatment consisted of administration of 1 mg/kg propranolol or a placebo, followed 90 minutes after by traumatic memory reactivation. Traumatic memory reactivation consisted of writing a one page trauma narrative paragraph, focusing on disturbing details. In subsequent follow up treatment the patient was asked to read his or her narrative to the therapist instead. This was done once a week for 6 consecutive weeks. Between week 1 and week 7, as well as after 3 months, this study failed to find a significant difference between the propranolol and placebo group and both groups showed a substantial decrease in PTSD symptoms. The authors speculate that the substantial decrease might be due to the safe environment in which reactivation took place where, although the personnel was asked not to take a therapeutic stance, they did act sympathetic towards the patients. This mimicked exposure therapy and could explain the substantial reduction in symptoms.

Roullet et al (2021) through the use of a placebo controlled group, shows the difficulty in contributing successful reductions in PTSD symptoms to propranolol only. Like in Kindt & van Emmerik (2016), they also shortened the period of traumatic memory reactivation to prevent the process of fear extinction from taking place, however likely unsuccessfully as seen by the substantial reduction of PTSD symptoms in the placebo group. Although Kindt & van Emmerik (2016) worked with a different protocol, the findings of Roulette et al (2021) do shed light on the potential role the exposure therapy itself might have played in their findings. One notable difference in protocol between the two studies is the timing of propranolol administration. Where in Kindt & van Emmerik (2016) propranolol was administered after memory reactivation, it was administered 90 minutes ahead of memory reactivation in Roullet et al (2021). They argued for

this because propranolol reaches its peak concentration only 75 minutes after administration and they wanted an optimal blood level to be achieved during reactivation. Memory reconsolidation and the labile state of the memory occurs in a specific time window and it is not clear how the different timings affected both studies.

A recent study by Santos et al (2021) aimed to clarify the mechanisms by which propranolol is able to attenuate fear. Mice were trained using a contextual fear paradigm followed by either immediate or delayed context reexposure. They were administered propranolol, either ahead or after first context reexposure. They utilized fluorescent activity-dependent tags which allowed them to map brain activity through observing neuronal activity. They then measured fear expression during second context reexposure. They found that propranolol was only effective in decreasing fear expression when administered ahead of reexposure. To what extent the timing of administration translates from mice to humans will of course vary, however, this study does indicate that timing can make the difference between successful and unsuccessful treatment. Through the fluorescent tags Santos et al (2021) were also able to observe that propranolol had an acute effect on the memory traces from the dorsal dentate gyrus and basolateral amygdala (BLA) and functional connectivity between the amygdala, hippocampus (HPC) and prefrontal cortex was observed to be decreased. The BLA plays a central role in fear memories as discussed before, and these results show again that blocking the beta adrenergic receptors lowers BLA activity. The HPC stores contextual memories, as such reduced HPC activity likely reduced the fear response to the conditioned contextual fear. The reduced activity in the before mentioned regions might be the underlying mechanisms explaining the decreased fear response during reexposure. The results found by Santos et al (2021) do however not explain the potential reconsolidation effect of propranolol since they did not show

long lasting fear reducing effects after drug washout. What they showed is that propranolol reduced retrieval of contextual fear memory. A subsequent study by Cox et al (2022) instead aimed to highlight propranolol's effect during reconsolidation.

Cox et al (2022) conducted a study with the aim of coming to a better understanding of the mechanisms behind how propranolol disrupts memory reconsolidation. To this end, they tried to develop a training paradigm that would, after reexposure and treatment with propranolol, successfully induce the expected disruption of memory reconsolidation. They were however, to their surprise, unsuccessful in this. The mice underwent contextual fear conditioning, memory reactivation and a retention test. Immediately after memory reactivation the mice received either a saline or propranolol injection. Fear behavior was analyzed during the retention test and neural activity was estimated by observing the number of c-fos cells in the hippocampal dentate gyrus. Since they were unsuccessful in showing the memory reconsolidation disrupting effects of propranolol they replaced propranolol with vancomycin, a well known reconsolidation disrupting drug. Here they however also did not show the expected disrupting effects. They suggest this may be due to their training paradigm being unsuccessful in bringing the conditioned fear stimulus memory into a sufficiently labile state. However they used different fear conditioning paradigms that have been proven effective by earlier studies. Compared to Santos et al (2021) where propranolol only successfully disrupted memory when administered ahead of memory reactivation, propranolol and vancomycin in this study were administered immediately after. Whether this played a significant role is difficult to say but could be incorporated into future research. In the previously mentioned study of Dębiec & Ledoux (2004) propranolol was injected into rats after memory reactivation. They however did find memory reconsolidation to be disrupted. In the similar study by Nader et al (2000) they infused vancomycin after memory

reactivation in rats. They also found memory reconsolidation to be disrupted. As such the timing in Cox et al (2022) shouldn't have failed in facilitating the disruption of memory reconsolidation. It could be that the ideal timing of propranolol administration differs for mice to rats, something to be considered in future studies.

The results from cox et al (2022) do not rule out the memory reconsolidation disrupting effects of propranolol. They do however highlight its complex nature. Though this disrupting effect is what the promise of effectiveness of propranolol treatment is based upon, it could also be the cause of unwanted side effects. Balbinot et al (2023) aimed to unveil the potential effect propranolol might have on non-target memories. They specifically aimed to show how recognition memory would be affected. They achieved this through the use of an object recognition (OR) test. Rats were exposed to two objects, A and B, for 10 minutes and 24 hours later reexposed to one familiar (A) and one novel object (C), followed by intra-hippocampal saline or propranolol injections (5 μg/side). 24 hours later the animals were tested using one familiar (A, B or C) and one novel object (D). They found that propranolol disrupted the consolidation of the during reexposure novel object C. Using a doubled dose of propranolol (10 μg/side), they additionally found that object B was also not retained. The authors interpret their results as indicating that OR memory reconsolidation was blocked using intra-hippocampal propranolol injections. They however did not show OR of object A to be disrupted. Since object C is a novel object during reexposure, the lack of OR after propranolol injection can also be interpreted as disrupted consolidation instead of reconsolidation. The higher dose of propranolol (10 μg/side) decreasing OR of object B, which the rats were only shown during first exposure, does indicate reconsolidation being disrupted, indicating the risk propranolol might disrupt untargeted memories.

Propranolol has shown promise in treating PTSD. However direct evidence for its effectiveness appears to be missing. Clinical trials like Kindt & van Emmerik (2016) and Kindt et al (2023) give positive results but with no control groups and small sample sizes, while a larger clinical trial using a control group like Roullet et al (2021) failed to replicate the same positive results. Studies like Santos et al (2021) do give insights into the mechanisms behind propranolol's effect on the brain, however, where the main benefit over classical therapies should come from its disrupting effect on memory reconsolidation, Cox et al (2022) failed to highlight this process. The studies where the disruption of reconsolidation is shown, Nader et al (2000) Dębiec, Ledoux (2004) and Balbinot et al (2023) all made use of rats instead of mice, as was used in Cox et al (2022) and Santos et al (2021). This might indicate propranolol enacts different effects between the two species and raises the question of which results translate better to humans. In all, the mechanisms and effectiveness of propranolol in the treatment of PTSD appears to be lacking in information and results vary. Memory reconsolidation is a complex process and successful intervention relies on effective reactivation, timing of the disruptive agent and is not yet proven to be completely reproducible through the use of propranolol. To highlight the mechanisms and prove the effectiveness, future research is needed. Propranolol is also not the only promising memory modulating agent used for PTSD treatment.

MDMA

Similar to propranolol, MDMA has recently attracted significant scientific interest regarding its potential role in enhancing the successful treatment of PTSD. Clinical trials, such as performed by Mitchell et al (2021) showcase how MDMA assisted therapy is effective in

reducing PTSD symptoms. They assessed the safety and efficacy of MDMA assisted therapy in treating individuals with PTSD. Subjects suffering from severe PTSD were selected. They first received three preparatory therapy sessions after which baseline symptoms were measured and they were randomly selected for either the placebo or MDMA group. The treatment period consisted of three 8h sessions spaced 4 weeks apart where the subjects were either administered MDMA or a placebo. 2 months after the final treatment session, PTSD symptoms were again measured and compared. They found that the MDMA group experienced a substantial greater reduction in PTSD symptoms compared to the placebo group and the MDMA group did not show any adverse symptoms (Mitchell et al., 2021).

Although studies like this highlight the effectiveness of MDMA assisted therapy, what the specific underlying mechanisms are remains a question of debate. One of the mechanisms could be that through its release of monoamines, MDMA enhances the formation of a competing memory, facilitating fear extinction learning. Young et al (2015) working with this hypothesis, aimed to prove the facilitation of fear extinction learning to be behind the success of MDMA assisted therapy. To investigate their hypothesis they conducted the following experiments. On the initial day their mice were subjected to cued fear conditioning, where a conditioning tone was linked with a footshock. Then 48 hours later on the third day, fear extinction training took place where the conditioning tone was given without footshock. Ending with extinction testing on the fourth day (or, alternatively, on the tenth day for an evaluation of long-term effects). They found that, When administered prior to extinction training, MDMA consistently enhanced fear extinction seen by reduced freezing to the conditioning stimulus. Also when the CS was delivered in a new context on day 10, the mice that received MDMA treatment showed

significant reduced fear response, highlighting a long term reduced fear response to the conditioned stimulus.

In a subsequent study conducted by the same research group, Young et al (2017) emphasis was placed on examining the influence of specific monoamines affected by MDMA on the fear extinction process. Utilizing the same protocol as in their previous study, the researchers explored the impact of MDMA on fear extinction when co-administered with a serotonin transport inhibitor, dopamine transport inhibitor, or norepinephrine transport inhibitor. The findings revealed that acute and chronic administration of serotonin transport inhibitors negated the effect of fear extinction, whereas inhibitors targeting dopamine and norepinephrine did not exhibit a similar effect. This study underscores the significance of serotonergic neurotransmission in the mechanism through which MDMA facilitates fear extinction.

The studies of young et al made use of cued fear conditioning. Persistent fear memories as seen in PTSD are however often more so linked to contextual memories of the trauma. As such Hake et al (2019) aimed to investigate whether MDMA will also enhance fear extinction learning when applied to a contextual fear conditioning paradigm. Other than enhancing fear extinction, Hake et al (2019) also aimed to investigate whether MDMA may disrupt memory reconsolidation. As mentioned before, memory reconsolidation should show longer persistence of reduced PTSD symptoms after treatment than fear extinction. This is also seen in clinical trials using MDMA assisted therapy such as in Mitchell et al (2021) mentioned earlier. To this end they developed the following protocol. Rats underwent contextual or auditory fear conditioning. The auditory fear conditioning group received a footshock paired with an auditory conditioning stimulus (CS), the contextual fear conditioning group did not receive a conditioning stimulus. Both of these processes occurred in so-called chamber A. 24 hours later, both groups received

systemic administration of saline or different doses of MDMA (ranging from 1 to 10 mg/kg). This administration occurred either 30 minutes before fear extinction training or right after a brief retrieval of fear memories, specifically during the reconsolidation phase. Retrieval of fear memories occurred for the auditory fear conditioning group, through administration of the CS in a novel chamber B. This chamber provided a novel context as the light was changed from red to white, a vanilla scent was added and the floor was changed from a shock grid floor to a smooth floor or textured floor. The contextual fear conditioning group was instead placed back in chamber A which served as their conditioning stimuli. They found that MDMA administration did not facilitate fear extinction of the contextual nor the cued stimuli. MDMA administration before fear extinction training did not cause reduced fear behavior during the fear extinction memory test compared to the control group. They did however find that when the MDMA was administered after brief retrieval of fear memories, one auditory CS instead of twenty/3 minutes in chamber A instead of 15 minutes, as was given in the fear extinction protocol, memory reconsolidation was disrupted. This showed itself in a reduced fear reaction to both the cued and contextual fear stimulus, up to a week later. As such their results implicate the disruption of memory reconsolidation, rather than a facilitation of fear extinction, to be the underlying mechanism explaining the success of MDMA assisted therapy. The results between Hake et al (2019) and young et al (2015;2017) vary widely. One possible explanation might be the difference between rats and mice. Rats have, like humans, high levels of serotonin 6 receptors for example (Ellenbroek & Youn., 2016). MDMA is active on the serotonergic system and functional differences like these could contribute to the varying results.

A recent study by Arluk et al (2022) builds on memory reconsolidation being the underlying mechanism of MDMA assisted therapy. This study aimed to further elucidate the mechanism behind PTSD. For this, like in Hake et al (2019), they made use of rats. These rats, having been exposed to predator-scent stress (PSS)(used cat litter), experienced a trauma cue (unused cat litter) 7 days thereafter shortly after receiving a single dose of MDMA (5 mg/kg). The behavioral responses were categorized based on assessments using the elevated plus maze and acoustic startle response tests on day 14. Further evaluation included measuring freezing responses to a subsequent trauma reminder on day 15 and on day 16 the rats were sacrificed and the dentate gyrus (region in the hippocampus) and BLA were examined. In a second experiment, either saline or MDMA was administered to show the potential disruptive effect of MDMA on reconsolidation. They found that MDMA administration at day 7 diminished behavioral stress responses on day 14 and 15. Dendritic trees of cells in the DG and BLA also normalized in the MDMA + trauma cue group. They also show that MDMA only diminished stress response when administered ahead of a paired trauma cue and was unable to with an unpaired trauma cue. They only made use of a short trauma cue which should not be so effective in facilitating fear extinction training but should reactivate the trauma memory. Still they were able to observe diminished stress responses indicating that MDMA disrupted memory reconsolidation. Since MDMA was only effective in the paired trauma cue experiment, it indicates that its efficacy relies on memory reactivation since without memory reactivation, as seen in the unpaired trauma cue experiment, MDMA lost its effectiveness. When the experiment was combined with either a glucocorticoid receptor (GR) antagonist, serotonin receptor 5-HT-1A or 5-HT-2A antagonist, MDMA was no longer able to diminish stress responses. In line with Young et al (2015;2017), these results show the importance of the serotonin receptors for the efficacy of MDMA while

also highlighting the importance of the glucocorticoid receptor. This is of note because MDMA also increased the corticosterone levels in the rats. Corticosteroids are involved in memory formation (Rozendaal & McGaugh, 2012) and since blocking the GR negates the efficacy of MDMA, it means corticosteroids are likely to be involved in the potential memory reconsolidation disrupting effects of MDMA. To this end they also experimented with rats, genetically modified to have lower GR expression, and also here found that MDMA loses its efficacy. Corticosteroids are however normally associated with the enhancement of emotional memory consolidation and reconsolidation (Rozendaal & McGaugh, 2012). This would mean the increase in corticosterone would enhance reconsolidation of the traumatic memory, not disrupt it. However the authors note that the effect on memory by GCs is not so clear as both antagonist and agonist have been found to disrupt reactivated memories. As such they argue that the high levels of corticosterone induced by MDMA likely disrupts memory reconsolidation explaining its long term efficacy. This theory requires further research to be proven, however, would explain the counter intuitive nature of MDMA blocking memory reconsolidation. The results of Arluk et al. (2022) do not rule out the facilitation of fear extinction, as found in the two studies from young et al (2015;2017), to also be one of the underlying mechanisms. It does however build on memory reconsolidation to be the prime mechanism and gives further understanding as to how MDMA facilitates this disruption of memory reconsolidation which was lacking in the study by Hake et al. (2019).

Interestingly, a recent study by Keller et al. (2022) aimed to find MDMA's facilitating effect on fear extinction learning in humans. In Keller et al (2022) a study was conducted with healthy adults using a randomized placebo controlled trial. They used a proven method involving fear conditioning, extinction training, and testing extinction retention. Before extinction training,

subjects would either receive MDMA (100mg) or a placebo. They found that pre extinction administration did not interfere with fear extinction training as in that both groups were able to successfully demonstrate extinction learning. Nor did they find that acute MDMA administration showed improvement within session fear extinction or fear retention. They did however find that there were significantly more people of the MDMA versus placebo group who showed retained extinction learning. This means that successful fear extinction was retained between the extinction training and extinction retention sessions. The study was inspired by the findings of young et al (2015;2017) but was unable to replicate their results in humans. Since the results of Hake et al (2019) and Arluk et al (2022) indicate memory reconsolidation to be the underlying mechanisms. It would be of interest to see a similar study as to Keller et al (2022), however replicating the setup seen in Hake et al (2019) or Arluk et al (2022), to test if their results translate to humans.

The studies evaluated indicate that memory reconsolidation is the mechanism through which MDMA facilitates its long term efficacy in the treatment of PTSD. Enhancement of fear extinction is not ruled out but the results from Young et al (2015;2017) lack reproducibility in humans and rats. Since both fear extinction and the disruption of memory reconsolidation rely on memory reactivation it is however difficult to distinguish which process acts when. Arluk et al (2022) through showing the importance of MDMA inducing corticosteroids for its efficacy, sheds light on the possible mechanism by which it impairs memory reconsolidation. Further clarification and proof is however needed to unveil the precise mechanisms behind the efficacy of MDMA assisted therapy.

Discussion

Both MDMA and propranolol exposure therapy have shown promising results in treating PTSD. Memory consolidation appears to be one of the underlying mechanisms explaining the long lasting effects of both. The effectiveness of propranolol therapy however still appears to be more debated, with some promising results failing to be successfully reproduced. This could be due to many variables, as the process of memory reactivation and the timing of propranolol administration appear to play important roles in how effective a treatment will be. MDMA exposure therapy on the other hand shows stronger evidence for its effectiveness. The process by which this occurs and specifically how large a role memory reconsolidation plays is still something yet to be fully established. Evidence does however point in the direction of memory reconsolidation being the underlying process, explaining the long lasting effectiveness of MDMA therapy.

Although promising, the studies discussed also highlight the unclear nature of memory reconsolidation. Propranolol therapy, which is based solely on the impairment of memory reconsolidation, is still proven to not always be effective in impairing memory reconsolidation, even as recently as in the study by Cox et al (2022). Early studies such as Nader et al (2000) through vancomycin and Dębiec, Ledoux (2004) through propranolol administration, show memory reconsolidation is able to be impaired. However the boundary conditions for this process to take place should be further explored. Effective retrieval of the fear memory is thought to be central for being able to disrupt memory reconsolidation. Santos et al (2021) showed that propranolol administered before memory reactivation can inhibit retrieval.

Interestingly in the study by Roullet et al (2021) where their results indicated propranolol did not block memory reconsolidation, they administered propranolol 90 minutes ahead of reactivation. Inadvertently it can be speculated that they suppressed memory retrieval this way, potentially not allowing it to reach a labile state explaining their negative results. In MDMA assisted therapy patients instead report clearer recall of their traumatic memories (Feduccia et al (2018). MDMA promotes the release of dopamine (Green et al., 2003). The administration of dopaminergic receptor antagonists into the BLA is shown to block the disruption of memory reconsolidation using vancomycin in rats (Meerlo et al., 2015). The dopaminergic receptor antagonists prevented the memory from reaching a labile state, because of which protein synthesis was not needed for the memory to persist since reconsolidation did not take place and the memory was unaffected by the vancomycin treatment (Meerlo et al., 2015). This indicates dopamine's role for facilitating memory retrieval and through the release of dopamine, MDMA likely enhances memory retrieval helping the memory to reach a more labile state. This difference between propranolol and MDMA could partially explain why MDMA assisted PTSD treatment has shown higher success. Also if MDMA facilitates memory retrieval, if then combined with propranolol treatment, it might enhance the memory reconsolidation disrupting effect.

However, it is important to note that propranolol and MDMA both come with side effects. Propranolol's effect outside of the brain is mainly the lowering of heart rate and blood pressure (NHS, 2021) while MDMA can increase heart rate and blood pressure (Abuse, N. I. on D. 2017). Combining these substances with opposing effects on the cardiovascular system could be unpredictable and potentially dangerous, through blocking the beta adrenergic system propranolol administration could lead to unopposed alpha adrenergic stimulation, which can lead to potentially dangerous increased blood pressure levels (Hysek et al., 2010). When administered

alone, common side effects of propranolol are usually mild and short lived but may include headaches, tiredness or feeling sick (NHS, 2021). The doses used in for example Kindt & van Emmerik, 2016, (40 mg) are however on the lower side. Propranolol is typically prescribed to treat heart problems and taken at home. The risks of taking propranolol under supervision of a doctor who can examine potential risk factors are relatively low. Balbinot et al (2023) has pointed to the potential disruption of untargeted memories however. To what extent well consolidated untargeted memories could be disrupted is unclear however. Balbinot et al (2023) showed that recently required recognition memory can be altered, however their findings do not necessarily indicate that well consolidated memory is at risk. This area of research is a topic for future research. Since MDMA likely also disrupts reconsolidation, a future study similar to Balbinot et al (2023) is recommended to examine if MDMA poses the same risk. MDMA also belongs to a class of drugs that releases serotonin (Malcolm & Thomas, 2021). The use of these drugs can lead to serotonin toxicity. Although serotonin toxicity is seldom fatal, it is important to evaluate the risk that comes with treatment using for example MDMA. The risk for serotonin toxicity is especially high when serotonin releasing agents such as MDMA are used in conjunction with drugs that block the metabolism of serotonin (monoamine oxidase inhibitors) (Malcolm & Thomas, 2021). The lower doses used in therapy, however, do not appear to give rise to a substantial risk for serotonin toxicity. It should be examined though whether patients are also using other drugs such as monoamine oxidase inhibitors. The clinical trials discussed in this review (Mitchell et al., 2021;Keller et al., 2022), did not report any adverse effects. Mitchell et al (2021) in particular aimed to evaluate the safety of MDMA. They tracked their patients for any adverse events. They reported that MDMA treatment did not induce adverse symptoms such as

drug abuse, suicidality or QT prolongation (cardiac health). MDMA isn't without its side effects but appears to be safe when administered in a controlled environment.

This review focused only on propranolol and MDMA assisted therapy. These two novel approaches appear to both act through disrupting memory reconsolidation. Eye Movement Desensitization and Reprocessing (EMDR) like MDMA assisted therapy has shown substantial clinical success, however its underlying mechanisms are also not yet fully understood (Landin-Romero et al., 2018). Certain eye movements (EM) reduce the anxiety related to disturbing thoughts (Landin-Romero et al., 2018). As also seen in propranolol and MDMA assisted therapy, EMDR also relies on reactivating the traumatic memory (Landin-Romero et al., 2018). After reactivation the patient is asked to follow an object (ie. a light or the finger of the therapist) in order to stimulate both brain halves (bilateral stimulation)(Landin-Romero et al., 2018). Similar to MDMA in MDMA assisted therapy, the bilateral stimulation acts to lower the experienced stress and discomfort associated with the fear memory, this way assisting in processing the trauma (Landin-Romero et al., 2018). It is hypothesized that the brain has a limited working memory capacity. Through combining memory reactivation and the EM task, the images and emotions related to the memory become dampened (Landin-Romero et al., 2018). What exactly happens to the memory trace is unclear. In a clinical trial by Jellestad et al (2021) they show that EMDR is successful in disrupting memory reconsolidation. It might be of interest for future research to compare the mechanisms underlying EMDR therapy with those of propranolol and MDMA assisted therapy. If EMDR disrupts memory reconsolidation, combined treatment of EMDR with MDMA or propranolol could enhance treatment efficacy. Unlike earlier proposed combinational therapy with MDMA and propranolol, the combination of MDMA nor propranolol with EMDR wouldn't increase the risk posed by their respective side effects.

In conclusion, the disruption of memory reconsolidation gives rise to treatments that allow for long term reduction of PTSD symptoms. How this occurs through propranolol, MDMA or even potentially EMDR requires further understanding. Future research that is able to further highlight the mechanisms behind the disruption of memory reconsolidation will not only improve clinical applications but also contribute to the ongoing research into effective PTSD treatments.

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