Editorial

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β-adrenergic Receptor Blocker Use for Traumatic Memory Reconsolidation in Posttraumatic Stress Disorder

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"Trauma is personal. It does not disappear if it is not validated. When it is ignored or invalidated the silent screams continue internally heard only by the one held captive. When someone enters the pain and hears the screams healing can begin."
Danielle Bernock, *Emerging with Wings*

The complexity of traumatic memories and emotional information processing highlights the fact that traumatic events have potential to cause a wide range of emotions which include physical arousal and an observable impact on emotional memory. From an evolutionary point of view, it seems logical that a confrontation with a stressful situation is better remembered than a neutral situation, resulting in more adequate reaction in a similar situation. This reasoning led to a widely accepted view that the memory for emotional information is generally recalled better than neutral information[1,2].

Noradrenaline as neurotransmitter and stress hormone in emotional memory processing

Noradrenaline (NA) containing neurons can be found throughout the nervous system and plays a prominent role for this neurotransmitter in the central nervous system. The majority of these neurons in the brain are located in the locus coeruleus of the brain stem. This nucleus is a primary source for an extensive NA network in the forebrain and takes nearly exclusive care of the NA supply of the amygdala, hippocampus, and neocortex[3]. Adrenaline and its agonists applied at encoding or immediately post-training enhance memory performance in all types of stressful tasks. In contrast, β-noradrenergic antagonists, given at these same points in time lead to decreased memory performance such as longer retention times[4].

The noradrenergic system is critical in modulating memory processes, and stimulation of β-noradrenergic receptors has been found to facilitate emotional and non-emotional memory consolidation[4,5] as well as reconsolidation6. Noradrenergic enhancement and specifically enhancement of the β-noradrenergic signaling during memory reconsolidation has been suggested to increase the strength of emotional memory, and hence has been suggested to contribute to the persistence of traumatic memories[6]. Moreover, a hyper-noradrenergic state has been implicated in the pathophysiology of PTSD[7]. In this context, the β-noradrenergic receptor antagonist propranolol has generated considerable interest as an agent for dampening emotional and traumatic memories in healthy humans and in patients with PTSD.

Key brain regions for emotional memory

The pathophysiology of PTSD implicates hyper-arousal of the sympathetic nervous system, particularly elevated noradrenergic activity[7-9] which primarily inhibits the prefrontal cortex, curtailing emotional control and extinction capacities, while stimulating the amygdala[10]. In healthy individuals, a single dose of the norepinephrine reuptake inhibitor (reboxetine) administered 2 hours before scanning pharmacologically induced right amygdala, right hippocampal, and bilateral inferior frontal gyri activation in response to fearful but not neutral stimuli[11]. In another fMRI study, an oral dose of the β-adrenergic receptor antagonist propranolol attenuated amygdala activity to neutral, positive, and aversive facial stimuli in healthy controls[12].

The specific role of the amygdala in emotional information processing has been well-reviewed and can be summarized as follows: (1) the amygdala gets activated during exposure to aversive stimuli from

a variety of sensory modalities; (2) the amygdala responds to positively valenced stimuli, but to a lesser extent than to those induced by aversive stimuli; (3) amygdala responses are modulated by the arousal level or current motivational value of stimuli; (4) emotionally valenced stimuli need not reach conscious awareness to engage amygdala processing, hence they can be presented subliminally and still activate the amygdala; (5) conscious cognitive appraisals of the emotional value of the stimuli do not require amygdala activation; (6) activation of the amygdala is associated with many other motor and autonomic functions, as well as cognitive processes including attention and memory , and (7) the extent and laterality of amygdala activations are related to factors including psychiatric condition, gender, and personality[13].

In a study14 subjects received either a β blocker or placebo and were scanned at encoding as well as at retrieval, 8 1/2 h later. They found that verbal items that evoke amygdala activation at encoding evoke greater hippocampal responses at the retrieval compared to neutral items. Administration of the β-adrenergic antagonist propranolol at encoding abolishes the enhanced amygdala encoding and hippocampal retrieval effects, despite the fact that propranolol is no longer present at retrieval. Memory-related amygdala responses at encoding and hippocampal responses at recognition of emotional items seem therefore to depend on β-adrenergic engagement at encoding. These results suggest that human emotional memory is associated with a β-adrenergic-dependent modulation of the amygdala.

In addition to amygdala, two other brain areas involved in the circuitry that determines noradrenaline effects on emotional memory are the hippocampus and the prefrontal cortex (PFC). The hippocampus, main brain region for associative memory, is strongly related to amygdala function in emotional memory and both brain structures showed to be NA dependent in this function[14]. Critical levels of catecholamine stimulation may be needed to optimize PFC cognitive function; high levels of catecholamine release during stress may serve to take the PFC 'off-line' to allow faster, more habitual responses mediated by the posterior and/or subcortical structures to regulate behavior[15].

Predominant neurobiological models have posited that hypoactive medial and lateral PFC/ and or ACC function decreases inhibitory feedback to the amygdala resulting in the exaggerated emotional responses experienced by PTSD patients[16,17]. When fearful facial expressions were presented above conscious awareness, PTSD participants exhibited diminished mPFC and ACC activity, which correlated with greater symptom severity[18-21]. Overall, these functional imaging studies support the notion that PTSD is characterized by a generalized dysfunction within the neural circuitry mediating threat detection[22], and it is likely that a sensitized amygdala has a lower activation threshold in response to both traumatic and non-traumatic emotional stimuli in this population.

Traumatic event and Development of PTSD

Although the exact mechanism of posttraumatic stress disorder (PTSD) remains elusive, accumulated evidence indicates that disrupted regulation of fear memory and enhanced amygdala activity to stress are intimately associated with the occurrence of PTSD[23,24]. Why are some individuals more likely than others to develop a PTSD in the face of similar levels of trauma exposure? Epidemiologic research has clarified risk factors that increase the likelihood of PTSD after exposure to a potentially traumatic event. PTSD is an interaction between a subject, a traumatogenic factor, and a social context. Most studies have shown that unrelated to the traumatic event, additional risk factors for developing PTSD include younger age at the time of the trauma, female gender, lower social economic status, lack of social support, premorbid personality characteristics, and preexisting anxiety or depressive disorders increase the risk of PTSD. The psychic trauma is firmly attached to the repetition and the previous traumas are as many risks of developing a subsequent PTSD in the wake of a new trauma. PTSD in adults may represent a prolonged symptomatic reaction to prior traumatic assault, child abuse, and childhood adversities. Related to the traumatic event, the organic pain, the traumatic brain injury, even the sight of blood can lead to a trauma being considered as more serious or more harmful.

Even though the majority of people with acute stress disorder subsequently develop PTSD, the current data indicate that too many people can develop PTSD without initially displaying acute stress disorder. Though peritraumatic dissociation and peritraumatic distress have emerged as the strongest predictors for PTSD and have to be treated as soon as possible with the debriefing or the pharmacology. The facts, emotions, and thoughts are not partitioned but inter-linked, thus enabling a fragmentation of the traumatic experience. In the face of the annihilation experienced, benzodiazepines are contraindicated at this stage as they promote more dissociation and concealed resurgences. On the other hand, treatment with propranolol could be proposed: a two or three week course of propranolol begun in the aftermath of a traumatic event can reduce subsequent PTSD symptoms.

PTSD occurs when a terrifying event overstimulates a sympathetic 'fight-or-flight' hormonal response, which then strengthens its memory (the conditioned fear) and later manifests as an over-reactive fearful response to reminders of the event[25,26]. An over-reactive limbic system, which includes our amygdala, is hypothesized to mediate the aberrant conditioning process in which a hormonal response is fixed to a memory[27]. Alterations to the HPA axis have also been implicated[28]. For example, heightened noradrenaline concentrations are found in the cerebrospinal fluid of patients with PTSD[29]. Dysfunction is also found in the ability of the hippocampus to regulate the recollection of fearful events. This may underlie the recurrent nature of the symptoms, especially to seemingly neutral stimuli[30].

A genetic polymorphism is evidently at work in the development of a PTSD via the regulation of the expression of genes of interest to the serotoninergic system and the adrenocorticotropic axis. The 5-HTTLPR (promoter region of SLC6A4 witch encodes the serotonin transporter) constitutes a genetic candidate region that may modulate emotional responses to traumatic events. The interaction between variation at the 5HTTLPR and stressful life events could predict PTSD and depression. Considering the dopaminergic pathway, the A1 allele coding the type 2 dopaminergic receptor is associated with a severe comorbidity of PTSD with the presence of somatic disorders, anxiety, social change, and depression. For noradrenergic neuromodulation, an interaction between the polymorphism of gene GABRA2 and the occurrence of PTSD is described whereas an interaction between the number of traumatic events and Val(158)Met polymorphism of the gene coding for catecholamine-o-methyltransferase has also been found. The role of polymorphisms in FKBP5 (a co-chaperone of hsp

90 which binds to the glucocorticoid receptor) in predicting PTSD too, with a gene-by-environment interaction. These gene-by-environment interactions are needed to focus more on distinct endophenotypes and influences from environmental factors. If several candidate genes are involved, a weighing of susceptibility to such neurological regulation system will imply various endophenotypes. According to the monoamine predominantly incriminated, PTSD can take on a more hyper-vegetative clinical expression linked with noradrenergic overuse. Differently, avoidance behavior and the depressive aspect invoke more a modification of the serotoninergic modulation whilst posttraumatic psychotic reactions question the role of dopaminergic pathways.

Propranolol for Emotional Trauma

Propranolol is a β1–β2 noradrenergic receptor blocking agent most commonly used in the treatment of hypertension, migraine headaches, essential tremor, and myocardial infarction[31]. Propranolol acts to decrease heart rate, myocardial contractility and oxygen demand, and blood pressure. It is contraindicated for patients with asthma and chronic obstructive pulmonary disease, and patients with bradycardia, heart blocks, and systolic blood pressure less than 90 mmHg. Propranolol is frequently prescribed off-label for the treatment of performance related anxiety. Propranolol easily crosses the blood brain barrier was predominantly used to explore the effect of NA on memory. One of the first human studies that changed the focus from a cognitive perspective to a more neurobiological viewpoint was of Cahill et al.'s study[32]. The participants were shown an arousal or neutral version of a picture story after receiving the betablocker propranolol (40 mg) or placebo. They found that the increase in memory for the emotional part of the story in the placebo group was blocked in the betablocker group. Participants who received propranolol remembered the emotional story completely comparable to the neutral story. This result of this study first demonstrated the role of noradrenergic receptors in emotional arousal and emotional memory. Similarly, using functional magnetic resonance imaging (fMRI), viewing emotional pictures resulted in increased amygdala activation compared to neutral pictures and this effect was enhanced in subjects with a high versus low endogenous cortisol level under placebo condition[33]. β blockade with propranolol, lowering the noradrenergic level in the amygdala, disrupted this effect and apparently the interaction with cortisol. These data supported the hypothesis that high endogenous cortisol levels at the time of encoding interact with noradrenergic activation in the amygdala in humans[33]. A comparable effect was shown during retrieval where blockade of β-adrenoceptors with propranolol prevented glucocorticoid-induced memory retrieval deficits in human subjects[34]. The subtle interplay between these two systems might also explain why the memory deficits in PTSD patients are characterized by the enhancement of unwanted memories as well as deficits in the recall of information. It is hypothesized that the intrusions, that are so characteristic for PTSD patients, are the result of peaks in noradrenaline levels in reaction to the trauma, whereas elevated cortisol levels might be related to the deficits and blackouts that are also part of the symptoms.

Some pilot studies on emergency room traumas have provided some evidence for the use of propranolol at the time of trauma in lessening the severity of PTSD[35-37]. For patients that were administered propranolol, findings were reduced physiological responses during script-guided imagery[35,37] and fewer PTSD symptoms[36]. Time of administration may be a critical component for treatment efficacy. Efficacy varied in both timing of initial medication administration and in prescribed dosage. Symptom severity and physiologic response were improved when propranolol was administered within 24 hours of trauma.

In the first study, Pitman et al.[35] administered 40 mg of propranolol within six hours of trauma. Patients were randomized to receive 40 mg of propranolol or placebo four-times daily for 10 days (followed by a 9-day taper period), starting no

longer than 6 h after the TE. Eleven propranolol patients and twenty placebo patients completed the study. The investigators found a statistically non-significant trend for the propranolol patients to have lower average Clinician-Administered PTSD Scale (CAPS) scores than the placebo patients. During script-driven imagery performed at 3 months, none of the 8 propranolol patients and 8 of 14 placebo patients showed a significantly elevated physiologic response. Vaiva et al.[36] in a non-randomized trial with 19 ED patients who had experienced a traumatic event accompanied by physiological arousal (tachycardia of at least 90 beats/min) administered 40mg of propranolol within 24 hours of trauma. Patients were not randomized and the dosing was 40mg of propranolol (n=11) three times a day for seven days, with a taper period at days 8–12 versus those patients that refused propranolol (n=8). Two months after the traumatic event, the patients who refused propranolol were significantly more likely to suffer PTSD and to experience PTSD symptoms than those who took the drug. It indicates that perhaps higher dosage and/or longer application of propranolol post-training (than a single 40 mg dosage) should be used to lead to significant effects on memory consolidation in an experimental setting. In a more recent randomized placebo controlled trial (n=41 patients), Hoge et al.[37] administered propranolol within 12 hours of trauma (n=21). Patients were administered an initial dose of either 40 mg short-acting propranolol, followed by additional dose of 60 mg long-acting propranolol if blood pressure parameters were met. Patients were then administered 120 mg of long-acting propranolol twice a day for ten days, tapered to 120 mg in the morning and 60 mg in the evening for three days, then 60 mg in the morning and 60 mg the evening for three days, followed by 60 mg in the morning for the last three days. In addition, participants were provided the opportunity to skip doses in order to prevent side effects. Although Hoge et al.[37] found that the rate of PTSD was not significantly different between the control and experimental group, results did support Pitman et al.'s[35] findings of decreased physiological response during script-driven imagery months after trauma. However, Hoge et al.[37] study's findings were only for the high medication adherence participants. Stein et al.[38] administered propranolol in a double blind randomized control trial up to 48 hours posttrauma. The trial included propranolol (n=17), gabapentin (n=14), or placebo (n=17). Medication was administered for 14 days. Propranolol was started within 48 h of injury and 40 mg was administered 3 times daily for 8 days (followed by a 4-day taper period). None of the drug cohorts in the study differed significantly from one another over time in the reduction of PTSD symptoms. Researchers acknowledged that 48 hours from the time of the trauma may be beyond the therapeutic window for propranolol to be effective in preventing PTSD.

Few functional imaging studies have applied fearful face paradigms to examine the neural correlates of recovery in PTSD patients. Felmingham, et al.[39] showed that treatment with cognitive behavioral therapy (CBT) was associated with increased rACC activation in response to fearful facial expressions in PTSD. Furthermore, even though amygdala activation did not change with treatment, greater improvements in PTSD symptoms were associated with greater decreases in amygdala activation. Aupperle, et al.[40] found that treatment with CBT was associated with increased rACC and decreased anterior insula activation in response to the anticipation of negative stimuli and decreased amygdala activation in response to viewing negative stimuli in PTSD. After prolonged exposure therapy, PTSD-remitted participants showed reduced lateral anterior insula activity when anticipating negative images, suggesting that successful symptom reduction involves the ability to interpret physiological states and regulate the aversive sensations associated with the anticipation of trauma cues during exposure-based interventions[41]. It remains plausible that in chronic PTSD, hyper-adrenergic signaling may continue to enhance the reconsolidation of traumatic memories when retrieved, such that they do not readily yield to extinction[6]. Furthermore in PTSD,

difficulties coping with trauma reminders may be an indicator of a persistent abnormality in threat evaluation extending to emotional, non-trauma related stimuli[18]. Schwabbe et al.[42] showed for the first time an effect of propranolol on the reconsolidation of episodic emotional memories. The administration of the adrenergic receptor antagonist propranolol during memory re-activation abolished the emotional enhancement of memory and made emotional memories comparable to neutral memories. Their data shed light on the neural correlates of reconsolidation impairments by propranolol in the human brain. The reactivation of the learned pictures recruited the amygdala and the hippocampus, structures that are commonly associated with the successful retrieval of emotional and neutral material. In those participants that received propranolol before memory reactivation, greater hippocampus and amygdala activity might have been required at test to successfully remember the learned material. Blockade of adrenergic receptors after memory reactivation might have reduced the strength of the (emotional) memory trace in the hippocampus or the interplay between hippocampus and amygdala that is needed to (re) build emotional memories.

A key question in the pharmacological manipulation of reconsolidation processes is the timing of the drug administration. When should the drug be administered to make sure that it affects reconsolidation processes? Peak levels of propranolol can be expected in humans at approximately 90 min after oral administration. If propranolol is administered before reactivation, it might affect the reactivation itself. If propranolol is administered after reactivation it might be that peak levels of drug activity occur outside of the reconsolidation window, which is limited to a short period after reactivation.

Combined Therapeutic Approach

The therapeutic approach traditionally combines a pharmacological and a psychotherapeutic treatment. A posttraumatic stress disorder is never just a coincidence. The different stages of the evolution and the establishment of a PTSD are the expression of an interaction between the outside and the inner self. Despite a known progression of the PTSD, this deleterious evolution is far from being a predictable conclusion. On the contrary, several levels of prevention are possible at each stage of its structuration to propose treatments to subjects who are vulnerable and/or present symptoms. A therapeutic proposal constitutes an environmental factor par excellence which can be either protective or deleterious. The advances in genetic and neuroimaging techniques are in the process of superseding psychometric studies in terms of reliability and validity; maybe we should see in this social evolution the changes of tomorrow concerning the clinical of PTSD and its treatment. The healing of the psycho-traumatized subject cannot just be established on the passive status of victim, which would be detrimental to reflection and ultimately reconstruction: the rebirth of the subject will require active commitment, which could distract from the deadly repetition. While the confrontation with death resembled nonsense, the subject will question the psychotraumatic determinants of his/ her life history to reinstate this tragic event within a search for meaning. PTSD is a pathology which interacts with the societal context: on the one hand the trauma is established on the brutal reconsideration of social values which seem immutable and on the other hand, the clinical and nosographical concept of PTSD is changing with the evolution of society. Pharmacological reconsolidation blockade might have the potential to become a novel treatment in psychiatry.

Future studies on reconsolidation need to include behavioral measures of reactivation to control for such effects. Moreover, the sample size of the studies on the consequences of reconsolidation impairments by propranolol was rather moderate. In conclusion, administration of the β blocker propranolol during memory reactivation (i.e., during reconsolidation) provides a promising opportunity to change unwanted

memories in disorders such as PTSD or drug addiction. Future studies on this topic would benefit from larger sample sizes that provide more statistical power and allow for additional analyses such as gender differences in memory processes and their underlying neural circuits. Furthermore, it would be interesting to see whether a higher dose of propranolol (e.g., 100 mg) would result in more severe reconsolidation impairments and whether the propranolol effects are limited to the reconsolidation of negative memories or whether propranolol might also affect the reconsolidation of positive memories.

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