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Review

DBS in treatment of post-traumatic stress disorder

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Abstract: Background: Post-traumatic stress disorder (PTSD) is a common debilitating psychiatric condition for which pharmacological therapy is not always solvable. Various treatments have been suggested for these patients. Deep brain stimulation (DBS) is currently under investigation for patients affected by PTSD. 2) Methods: We review the neurocircuitry and up to date clinical concepts that may be of relevance for the implementation of DBS in posttraumatic stress disorder (PTSD). 3) Results: The role of DBS in treatment-refractory PTSD patients has been investigated relying on both preclinical and clinical studies. 4) Conclusions: DBS for PTSD is in its preliminary phases and likely to provide hope to patients with medical refractory PTSD following the results of randomized controlled studies.

Keywords: posttraumatic stress disorder; deep brain stimulation; fear extinction; amygdala; prefrontal cortex

1. Introduction

After the inclusion of posttraumatic stress disorder (PTSD) in the DSM-III in 1980 as a fear and anxiety disorder, in the DSM-V [1] PTSD is described not only as a feeling of fear and helplessness but also as a disorder including negative cognitions, negative emotional states and reactivity symptoms. Victims of sexual assault, serious accidents, sudden death of a loved one or the military personnel deployed to war zones are exposed to a broad array of traumatic events and are at risk for PTSD and other readjustment problems. Posttraumatic stress disorder can be debilitating, especially when complicated by comorbid depression and substance use [2]. To make a diagnosis of PTSD, the patient must report the symptoms mentioned above for over one month following the traumatic event so much to complain an impairment in day-to day functioning. PTSD is a significant health and economic problem with an estimated prevalence in the United States around 5-8% and a greater tendency in the female sex [3]. The risk of suicide attempt or ideation is also associated to PTSD [4]. Other risk factors involved in the biological pathophysiology of PTSD include genetic polymorphism [5], endocrine dysregulation [6], reduced levels of neurotrophic factors [7] as well as abnormal monoamine [8] and neuropeptide levels [9].

2. Materials and Methods

The anatomical structures involved in the neurocircuitry of fear conditioning are the amygdala, prefrontal cortex and the hippocampus. The main receiver of the considerable sensory afferences that reach the amygdala is the basolateral complex (BLA), consisting of the lateral nucleus (LA), the basal nucleus (BA) and the accessory basal nucleus. These afferences come from two sources: the thalamus sensory nuclei and the primary sensory areas of the cerebral cortex. For many types of emotions, and especially for fear, the amygdala is of great importance, and valuable information retransmitted through this path reaches the amygdala more rapidly than sensory information

retransmitted by the cortex. For example, lesions of the basolateral complex abolish the classic fear conditioning [10]. Other nuclei of amygdala are the cortical nucleus, the central nucleus (CE), intercalated cell clusters (ITC). The LA receives sensory fibers including auditory, visual and somatic, conveying a fast signal for danger [11,12]. From the LA the stimulus is propagated to the CE, which in turn projects to multiple brainstem and hypothalamic areas, that are responsible for autonomic responses associated with fear [13]. Neurocircuitry of fear extinction is a little different from that of fear conditioning. It involves the ventromedial prefrontal cortex (vmPFC), BLA, ITC of the amygdala and the hippocampus. Recent studies using lesion, infusion, and unit-recording techniques suggest that the infralimbic (IL) subregion of medial prefrontal cortex (mPFC) is necessary for the inhibition of conditioned fear following extinction [14]. Whereas the amygdala is important for extinction learning, the vmPFC is a site of neural plasticity that allows for the inhibition of fear during extinction recall [15]. In addition, animal models suggest that extinction depends, at least in part, on an increased inhibition of fear output CEm neurons. This increased inhibition is caused by an enhanced recruitment of GABAergic ITC cells by BLA inputs. Moreover, these changes require infralimbic activity during extinction training, suggesting that the infralimbic cortex drives extinction-related plasticity in the amygdala [16]. ITC neurons constitute probable mediators of extinction because they receive information about the conditioned stimulus from the basolateral amygdala (BLA), and contribute inhibitory projections to the CE, the main output station of the amygdala for conditioned fear responses [17]. Functional neuroimaging studies in PTSD include a number of different imaging modalities including single-photon emission tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) [18]. The target of study are the amygdala, hippocampus and prefrontal cortex. Studies found that PTSD patients exhibite increased cerebral blood perfusion in limbic regions (amygdala) and decreased perfusion in the superior frontal gyrus and parietal and temporal regions in comparison with those of the normal controls during emotional processing tasks and at rest [19,20]. Moreover, The dorsal anterior cingulate cortex and insula appear to be hyper-responsive in PTSD, as well as in other anxiety disorders. The hippocampus also appears to function abnormally in PTSD, although the direction of the abnormality tends to vary depending on the methods used [21]. Hypo-activations (comparison subjects > PTSD patients) are seen specifically in the inferior occipital gyrus, ventromedial prefrontal cortex, rostral anterior cingulate cortex, para-hippocampal gyrus, lingual gyrus, dorsal amygdala and anterior hippocampus, orbitofrontal cortex, putamen, middle occipital gyrus, dorso-medial prefrontal cortex, dorsal anterior cingulate cortex, and mid-cingulate. Probably that hypo-activity is associated with greater symptom severity [22].

3. Results

Both psychotherapy and pharmacological interventions are effective for the treatment of PTSD. Effective psychotherapies included cognitive therapy, exposure therapy, and eye movement desensitization and reprocessing. Effective pharmacotherapies included paroxetine, sertraline, fluoxetine, risperidone, topiramate, and venlafaxine [23]. However, many patients do not have an adequate response to antidepressants or psychotherapies. It is unclear when a patient affected by PTSD can be considered treatment-resistant and if the coexistence of mental diseases or substance abuse are responsible for the refractoriness to conventional treatments [24]. The application of DBS in PTSD is under investigation, after that procedure has achieved promising results in the surgical treatment of other psychiatric disorders as major depression and obsessive-compulsive disorder. Targets studied in preclinical models are the basolateral amygdala, ventral striatum, hippocampus and prefrontal cortex.

3.1 Basolateral amygdala

Langevin et al presented the potential application of DBS to the treatment of PTSD through the stimulation of the BLn of the amygdala in rats, demonstrating a striking therapeutic response following the DBS treatment in a rat model. . DBS was conducted for 4 consecutive hours daily for 7 days. The settings were: monopolar, 120 ms pulse width, 160 Hz frequency and 2.5 volts [25]. In

another rat PTSD model during defensive burying, amygdala DBS was compared with paroxetine, demonstrating that DBS may attenuate hyperactive amygdala function. The settings were: monopolar, 120 ms pulse width, 160 Hz frequency, and 2.5 V [26]. However, a potential side effect in animals stimulated with high current intensities in BLA is the development of epileptiform after-discharges [27].

3.2 Ventral Striatum

The effects of ventral striatum DBS (100–200 μA, 0.1-ms pulse duration, 130 Hz) have been tested in a rodent model. They found that DBS of the VS (the VC/VS homolog in rats) during extinction training reduced fear expression and strengthened extinction memory, while facilitation of extinction was observed for a specific zone of dorso-medial VS, just above the anterior commissure; stimulation of more ventro-lateral sites in VS impaired extinction [28].

3.3 Hippocampus and prefrontal cortex

Disruptions of fear extinction-related potentiation of synaptic efficacy in the connection between the hippocampus (HPC) and the medial prefrontal cortex (mPFC) have been shown to impair the recall of extinction memory [29]. Instead, low-frequency hippocampal stimulation at 2 Hz delivered after extinction impaired extinction learning and the development of hippocampal-PFC plasticity [30].

The only clinical use of DBS in human patients affected by PTSD is represented by Langevin's study of 2014 where six combat veterans were treated with BLA DBS (the study has been registered at www.clinicaltrials.gov (PCC# 121657) [31]. Eligible subjects signed informed consent. After this, they underwent baseline evaluations spaced over a six-week period, including neuropsychological testing and a baseline 18FDG PET scan. Patients were reassessed with the Clinician Administered PTSD Rating Scale (CAPS) at the end of this baseline period, and only those who maintained a total CAPS score ≥85 and other inclusion and exclusion criteria could be kept in the study. An additional baseline evaluation was stipulated by California Law referring to 'Psychosurgery' (WIC Sec 5326.6): an independent team, consisting of neurosurgeons and psychiatrists uninvolved in the treatment or the study protocol, examined all the potential subjects, to ascertain capacity to consent, severity of illness, and inadequacy of response to standard treatments. The intracranial leads (two/subject) (Medtronic, model 3387) were implanted bilaterally in the BLA following a traditional transfrontal trajectory, a well-documented procedure traditionally used for stereotactic amygdalotomy. Stimulation initiated at that 4-week postoperative time point or after an additional 2 months randomly. During the telemetry session, the electrodes were initially stimulated at 2.5 V, 120-μsec pulse width, and 160-Hz frequency. The amplitude was progressively increased slowly to a maximum of 7 V. The pulse width was increased to a maximum of 210 μsec. Finally, the frequency was increased to a maximum of 200 Hz [32,33]. A clinical response will be defined as a 30% reduction in CAPS [34] from baseline and a CGI-I [35] score of 1 (very much improved) or 2 (much improved), but this study is still actively recruiting patients.

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4. Conclusions

Treatment-resistant PTSD is a serious condition associated with substantial morbidity and likely early mortality. The application of DBS for PTSD is still strictly investigational. Preclinical models suggest that stimulation at high frequency delivered to the amygdala, ventral striatum, hippocampus and prefrontal cortex may facilitate fear extinction and improve anxiety-like behavior. Neuroimaging studies indicate that PTSD patients have alterations in cerebral perfusion of limbic regions and the frontal and temporal cortex without re-exposure to accident-related stimuli. This finding supports the hypothesis of the involvement of limbic regions, which might be associated with the regulation of emotion and memory, in the pathophysiology of PTSD. In the only clinical report available DBS of the bilateral BLA in treatment-refractory combat veterans has been proposed. The main concern is that the potential benefit of BLA DBS comes with the risks of any DBS

neurosurgical procedure, as well as risks associated with long-term neuromodulation or risks of seizures. As PTSD is a multi-symptomatic disorder, patients included in investigational studies should ideally be treated and managed by multidisciplinary teams, including psychiatrists, psychologists, and neurosurgeons. Informed consent has to be carefully obtained, taking into account the competency of the patient, the coexistence of psychiatric illnesses and personality disorders, that represent an exclusion criteria for most of DBS trials. Optimal stimulation parameters, targets, mechanisms of action, and the kinetics of stimulation will also need to be characterized prior to the launch of larger scale studies.

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Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "X.X. and Y.Y. conceived and designed the experiments; X.X. performed the experiments; X.X. and Y.Y. analyzed the data; W.W. contributed reagents/materials/analysis tools; Y.Y. wrote the paper." Authorship must be limited to those who have contributed substantially to the work reported.

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