A Novel Treatment of PTSD Using Dendrimers for Targeted Perineuronal Net Digestion

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## Abstract

Post-traumatic stress disorder (PTSD) is a condition afflicting survivors of devastating events, from service in active combat zones to sexual assault and natural disasters. Those affected re-experience trauma through flashbacks and exhibit hyperarousal, avoidance, or emotional withdrawal; all of these symptoms can complicate daily processes such as eating, sleeping, and maintaining relationships. Current treatments for PTSD include psychotherapy, with variable or limited effectiveness, or antidepressant and antipsychotic medications, with negligible efficacy and potentially severe side effects[1]. We posit an alternative treatment of PTSD using dendrimers as a nanoscale vehicle for effective targeted drug delivery. The encapsulated drug, the enzyme chondroitinase ABC, would degrade perineuronal nets, which have recently been shown to promote stronger experience-dependent memory formation. Their disintegration allows for the erasure of fear-dependent memories, reducing the effects of PTSD dramatically and permanently and providing a better quality of life to sufferers of PTSD.

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**Present Technology**

PTSD is a serious condition with a lifetime prevalence of 6.8% within America's adult population and about 30% among veterans[2]. It affects those who have experienced physical or psychological upheaval, often coinciding with substance abuse problems, depression and similar anxiety disorders[3]. Much remains to be done in the treatment of PTSD and its associated symptomatology; for instance, sufferers re-experience trauma through flashbacks. Symptoms of PTSD also include hyperarousal, characterized by jumpiness and irritability, or avoidance, emotional numbness and withdrawal. All can complicate daily processes such as eating, sleeping, and maintaining relationships. Uncovering ways to treat PTSD is of utmost importance, and will provide sorely needed help to its sufferers - chiefly, abuse victims and veterans, although the lives of millions[1] can be improved.

Current treatments for PTSD can be divided into two main categories - medications and psychotherapy. Pharmacological treatments for PTSD commonly include antidepressants: sertraline and paroxetine, or Zoloft and Paxil, respectively, are two approved by the FDA, while antipsychotics and benzodiazepines have frequently been prescribed to help combat PTSD. However, their side effects can include extreme adverse effects, suicidal inclinations among them[1]. Additionally, some commonly prescribed antidepressants such as Risperidone have been shown in the past to be no more effective than placebo[4]. More consistently effective in treatment of certain PTSD symptoms, like nightmares, are psychotherapy methods, such as cognitive behavioral therapy[1]. Although their success still varies widely in different instances, these methods implicate the importance of relearning behaviors or otherwise rewiring thought to

improve PTSD. As such, by finding a neural basis for learning and memory processes involved in PTSD, it may be feasible to target specific functional circuits and brain structures using nanotechnology, thereby opening up opportunities for a permanent and effective treatment of this debilitating mental health problem.

**History**

The problem of post-traumatic stress disorder, or PTSD, is anything but a recent problem. Soldiers have been described as exhibiting its symptoms in civilizations as ancient as the Greek and Roman empires. During World War I, PTSD was frequently referred to as "shell-shock" or "battle fatigue" due to its high incidence in troops, although PTSD can affect survivors of car accidents, muggings, witnesses of violent crime and people from any walk of life[7]. SSRIs, developed in the 1980s and hailed in the following decade as "miracle drugs," are the most common method used to combat them[23].

SSRIs, or selective serotonin reuptake inhibitors, work by modulating neurotransmitters, namely serotonin, which is important in regulating mood and emotion. It does this by preventing reabsorption of serotonin after an action potential, when the neuron fires, and thereby allows serotonin to stay in the body longer, improving symptoms[24]. However, the main function of SSRIs was intended for the treatment of depression, chemically and physiologically different from PTSD. In the 2000s it was shown that antidepressants could also cause violent tendencies and hallucination in children, and they have also been linked to birth defects[23].

More recently, the etiology and effects of PTSD have converged with neurobiological studies, leading to better potential treatment and more recognition of PTSD as not just a condition affecting witnesses of the ravages of war but as a formal mental disorder. As stigma continues to

fall away from this condition, its study has begun to integrate other disciplines, presenting novel treatment opportunities.

One example is a phenomenon that began to gain traction in scientific circles around the 1970s and 1980s. Neuroplasticity examines the process and methods by which neurons and neural circuits in the brain alter themselves, provoked by external factors such as growth and development, new experiences and sensory information, or damage. Current research suggests that it may allow us to reopen "critical windows" that normally occur during childhood, important periods of development that are essential for the maturation and growth of an individual[6]. Other, still-developing branches of science such as nanotechnology may facilitate in the future for an interdisciplinary approach to ending PTSD.

**Future Technology**

Our idea for the facilitated treatment of PTSD - and in time, potentially other mental health disorders - falls at the intersection of nanotechnology and neuroplasticity. Recent advances in neuroplasticity have indicated the importance of perineuronal nets, or PNNs, at the synapse, for the retention and reinforcement of memories and learning. These PNNs reside in the extracellular matrix between neurons in areas of the brain such as the amygdala, a crucial component of the mind's fear network and emotional processing. They help to stabilize memories and are thought to assist in the process of long-term potentiation, by which the brain strengthens synaptic connections and stores memories. However, in some cases, retaining memories such as those triggering PTSD may be detrimental to the individual; for this reason, compounds that have been shown to degrade PNNs may be useful in the process of "overwriting" memories that have been ingrained in fear, in a process known as erasure[8].

Thanks to recent experimental studies, one manner of negating the effects of PNNs may now be possible. PNNs are largely composed of proteoglycans, which consist of a central glycoprotein and covalently attached sugar chains[9]. Previous research has shown that chondroitin sulfate proteoglycans can be dissolved through the application of an enzyme named chondroitinase ABC; Furthermore, the dismantling of these proteoglycans and the PNNs which they form is also correlated with increased erasure of fear memories in mice models[8]. In this manner, enzymatic dissolution of PNNs can alter neural activity and allow an easier transition towards the dulling or complete fading away of traumatic memories.

Traditional delivery of compounds that would degrade PNNs would be imprecise and may lose effectiveness as it travels through the bloodstream. A mechanism is needed to ensure that the applied drug would maintain its potency as it travels through the bloodstream after injection and that it would target only specific areas of the brain associated with PTSD. Dendrimers, specifically, have shown great promise in current research in the field of host-guest chemistry. These synthetic molecules with tree-like branching structures can hold drug molecules through hydrophobic (encapsulated) or covalent (conjugated) interaction[10]. They have been shown to be great candidates for molecular-scale drug delivery systems as they can increase the solubility of drugs through strong ionic and hydrophobic forces binding the drug and dendrimer together, and drug efficacy, through controlling release rates and limiting the toxicity of the drug in the human body. In addition, the initial bioavailability (the amount of the drug that stays active as it enters the bloodstream), uptake by targeted cells, and targeting ability of the drug are improved, potentially decreasing side effects and drug resistance. Thus the potency and

the effectiveness of drugs, specifically those already with a low solubility in the human body, can be significantly improved through the use of dendrimers[11].

One example of the medical potential of dendrimers is the ability of dendrimers to aid anticancer drugs in targeting and treating cancer. In previous studies, researchers found that dendrimers as carriers of cancer drugs help to increase drug solubility, mitigate the adverse effects of the drug, and better control the release of the drug into the system. In addition, dendrimers conjugated with the compound folate show extremely high accuracy in cancer-cell targeting due to the folate receptors present in certain cancers. These characteristics ensure that anticancer drugs can locate and treat tumors with maximum effectiveness[11]. We hope that this mechanism of targeting and maximization of efficacy of a drug, as observed in previous experiments, can be utilized to treat PTSD in the future. That is, the drug should only be released in key areas of the brain pertaining to fear-based memories and should retain its full potency.

Our idea embodies these two technologies: dendrimers would encapsulate PNN-digesting enzymes for their expedited distribution within the brain. Using dendrimers to carry PNN-digesting enzymes such as chondroitinase ABC, we envision a future technology wherein dendrimer host-guest chemistry is applied to deliver targeted drug treatment to those areas of the brain, such as the amygdala or insula, which are involved in emotional regulation. Other potential biomarkers to confine the release and distribution of the drug from the dendrimers into specific target areas in the brain include some of the neurobiological products created from the stress response seen in PTSD, or certain molecular domains of PNNs[12]. By causing the denaturation of PNN proteoglycans in these select areas, the fear response of subjects can be dulled, resulting in both biochemical and behavioral effects that will create more paths to

recovery from PTSD and bolster the effectiveness and prolongation of existing psychotherapy treatments. Finally, some evidence suggests that the destruction of PNNs may help stroke victims recover[21], and although more research needs to be conducted to definitively show a link between PNNs and stroke, it is possible that our technology may potentially grow to have a larger significance than treating just PTSD.

**Breakthroughs**

Implementing our treatment requires scientific and technological progress in both neuroplasticity and nanotechnology, branches of science still in their infancy. For instance, extensive research remains to be seen regarding the study of perineuronal nets' exact roles in the central nervous system. Although PNNs have been shown to play a part in plasticity, they also have a critical role in protecting existing memories and brain regions - therefore, when using dendrimers to release pharmacological agents in the brain, it is important to refine the means of host-guest chemistry used to distribute enzymatic PNN disruptors. Uncontrolled destruction of PNNs may result in heightened memory loss, and may be associated with Alzheimer's and the etiology of other neurodegenerative diseases[13]. It is pertinent to better study the behavior of PNNs and any adverse effects that may arise from destroying even a small number.

In addition, extensive experimentation would be necessary to identify any chemical modifications to the enzyme that maximize its potency as a drug. The ability of a potential drug candidate to effectively bind to and destroy the PNN peptidoglycans as well as its bioavailability and pharmacokinetics should be taken into account when considering the identity of the drug. Afterwards, it would be necessary to synthesize an appropriate dendrimer which would contain the appropriate biomarkers to recognize sites in the brain corresponding to PTSD stress, whose

size would allow the best attachment to the PNNs, and whose chemical makeup would allow a perfect fit for the drug and the maximum electrostatic and hydrophobic attractive forces between the surface of a dendrimer branch and the drug to keep the drug bound as the dendrimer-drug complex is traveling through the bloodstream. This dendrimer design must also be suited for the human body, remaining unreactive and nontoxic. It must also be able to pass the blood-brain barrier, a requirement that researchers have found certain synthesized dendrimers to fulfill[22], although still a challenge for nanoscientists working towards optimizing dendrimer drug delivery systems today.

**Design Process**

In order to finalize a feasible idea, we researched but ultimately rejected a few other ideas due to secondary concerns. We first toyed with the idea of direct, but unregulated, injection of PNN-digesting enzymes, but soon realized that the delivery was too uncontrollable to posit. Uncontrolled degradation of PNNs can be harmful, as excessive degradation could lead to diseases such as schizophrenia[12]. PNNs also have a neuroprotective role regarding Alzheimer's and epilepsy in humans[14]. In order to prevent excessive PNN loss, we introduced the idea of host-guest chemistry using dendrimers, since previous research dictated that these nanoparticles exhibit controlled targeting. An experiment with dendrimers conjugated with folate showed high accuracy in targeting cancer cells both *in vitro* and *in vivo* due to the folate receptors in the cells, which maximizes effectiveness of identifying and treating tumors. A similar method could be employed to control the degradation of PNNs[11].

Another possible method with which PTSD could be treated involved enhancing the signaling of insulin-like growth factor 2 (IGF-2), a protein that has been recently shown to have

a major role in fear extinction. Thus, targeting and decreasing the DNA methylation that silences the gene coding for production of IGF-2 would supposedly help terminate the overexpression of fear-based memories seen in PTSD. However, overexpression of IGF-2 has been definitively linked to growth of cancerous cells[15], and we believed that this would only serve to worsen the wellbeing of PTSD patients. Potential adverse effects of degradation of PNNs are less definitive and thus our proposed technology would be better suited as a treatment for PTSD.

Finally, studies have shown that decreased rates of neurogenesis, that is, the ability of the brain to generate new neurons, is heavily linked to the depression and anxiety related to PTSD, and that certain microRNAs have been linked to the choice of neural stem cells and progenitor cells to produce new neurons. Thus, we thought that these microRNAs could help increase production of neurons to facilitate the treatment of PTSD[16]. However, we found that many current antidepressants involving selective serotonin reuptake inhibitors (SSRIs) already act through a similar pathway, promoting neurogenesis[20]. Due to the low efficacy of antidepressants in treating PTSD, it could be argued that neurogenesis does not have the potent effect on extinction of fear-based memories as previously believed. While this topic requires further research, we were more definite of the role of PNNs in directing fear-based memories and, thus, were inclined to choose degradation of PNNs as the more effective treatment for the disorder.

**Consequences**

Fine-tuning this technology would allow society to reap enormous benefits, but, as with any novel innovation, especially one wielding the power to enact change on a large scale, it comes with a set of potential positive and negative ramifications. It is first critical to

acknowledge the potential adverse effects of our proposed idea, both on medical patients and society, in order to go about developing it in a responsible manner.

These negative results may take a couple of forms. For instance, host-guest technology, while greatly improving on the precision and efficacy of drug delivery, is still far from an exact mechanism. Controlling dendrimer delivery substances and overall distribution of medication was one of the main factors dictating our design process, and may require further tweaking, as the results of improperly executed PNN digestion may lead to the onset of other neurobiological diseases according to some research, such as Alzheimer's[14]. This may actually exacerbate PTSD and lead to lower quality of life.

The ethical implications of PNN digestion should also be considered. The ability to forget memories could be distorted and used against people for malicious purposes, similarly to rohypnol, which is known for its incapacitating effects on memory, and allowing those who have consumed it to be victimized and taken advantage of[17]. It may also have unprecedented effects on other bodily or mental functions. For these health-related and moral reasons, further investigation into the exact extent and best substrates for PNN dissolution should be fully scoped out before introduction into humans.

However, the extended applications and potential benefits to civilization of this technology are just as great. Dendrimer usage can be broadened to applications in accurately pinpointing and treating cancer cells; this would provide better treatment for cancer patients, perhaps even presenting an alternative solution to current methods of chemotherapy and radiation, which are damaging not only to patients' malignant tumors but also to their overall strength. Dendrimers would potentially also be able to treat a variety of diseases, including HIV,

bacterial infections, herpes, and other pressing disorders according to current research. The effective use of these nanostructures would also open the door for nanoparticle-based medicine in general, with such technology as gold nanoparticles and carbon nanotubes waiting to be implemented for major diseases like cancer[18] and Alzheimer's[19].

In addition, PNN digestion by dendrimers may present a lasting and plausible mass-marketed solution to other mental health disorders such as anxiety disorders, commonly viewed as difficult to treat and impossible to cure. Furthermore, because of PNN relevance in other conditions such as stroke[21], this technology can be adapted to treat these other diseases, and in the long run, it can serve to improve the lives of millions more than just PTSD sufferers.

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