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Treatment of trauma with lithium to forestall the development of posttraumatic stress disorder by pharmacological induction of a mild transient amnesia

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a severe anxiety disorder that develops after exposure to trauma. Symptoms include persistent reexperiencing, persistent avoidance, persistent numbing, and persistent hyperarousal. Subsequent to trauma exposure, the onset of symptoms of an acute stress reaction can typically develop over varying amounts of time from days to months. Current pharmacotherapies for PTSD are available after symptoms manifest, and primarily consist of selective serotonin reuptake inhibitor (SSRI) antidepressants. There are currently no FDA approved pharmacological interventions available for the treatment of acutely traumatized individuals to forestall the development of PTSD after trauma and prior to the onset of symptoms.

A prominent model of PTSD developed by Roger Pitman attributes the pathogenesis of PTSD to over-consolidated traumatic memories that are mediated by endogenous stress hormones released with trauma and after trauma.

The molecular processes of memory consolidation in neurons are mediated by intracellular signaling pathways. One secondary messenger signaling pathway with a putative role in long-term potentiation (LTP) is the inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) secondary messenger system.

Lithium, a treatment for bipolar disorder, and a pharmacotherapy that is associated with inducing transient impairments in cognition, memory, and learning, is an inhibitor of inositol monophosphatase (IMP), an enzyme in the IP3 and DAG secondary messenger pathway.

I am advancing the hypothesis that the administration of lithium for a brief interval to traumatized individuals at risk for PTSD within the time period after trauma and prior to the onset of symptoms could potentially forestall the development of PTSD by disrupting LTP. I am proposing that this treatment will reduce the incidence of PTSD and reduce the severity of symptoms in those who eventually develop PTSD.

Introduction

PTSD is an illness with a lifetime prevalence rate of 6.8% in the United States [1]. PTSD has a clearly defined etiology, making the onset of this condition predictable. Pretraumatic and peritraumatic factors that increase the likelihood of developing PTSD include: a history of childhood abuse, a history of psychiatric illness, younger age, female gender, the presence of violence, the intensity of trauma, a lack of social support, and life stress [2].

It has been postulated that endogenous stress hormones mediate the consolidation of memories associated with fear conditioning [3]. Investigators have focused attention on developing emergency treatments for traumatized individuals by targeting catecholamines, specifically epinephrine and norepinephrine [4]. Candidate pharmacotherapies include treatments that target the effector sites of catecholamines (e.g. propranolol – a beta adrenergic antagonist) and treatments that attenuate the release of catecholamines, including opioids, clonidine, cortisol, and guanfacine [4].

Rather than targeting stress hormones, I am predicting that directly targeting the processes of memory consolidation during the early stages of the pathogenesis of PTSD will forestall the development of PTSD.

Hypothesis

In humans, having the ability to recall harmful events clearly serves a protective function. Remembering frightening, threatening, and traumatic stimuli is important for harm avoidance. The close interactions between the amygdala and the hippocampus mediate this process [5].

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There appears to be an optimal set-point for learning and memory consolidation when a person is threatened or harmed. If humans possessed weak memory consolidation responses to harmful stimuli, they would be at risk for future harm by failing to recognize stimuli associated with risk. Conversely, excessive memory consolidation responses to minimally harmful stimuli could be equally problematic, as humans would be unable to function without becoming terrified by normal everyday events. The optimal set-point for memory consolidation appears to be altered and over-active in individuals who develop PTSD.

An analogous example to help appreciate the importance of having a proper set-point for proper functioning can be drawn from our immune system. The immune system serves a protective function when it is operating at optimal levels. When this system is compromised, individuals are at an increased risk for multiple infections, and when this system is over-active, individuals are at an increased risk for autoimmune disease. In cases of autoimmune disease, when the immune system is over-active, there are clearly identifiable risk factors, such as age, gender, genetics, a prior history of autoimmune disease, and sensitization to self-antigens, that increase the likelihood of developing an autoimmune disease, and likewise, with PTSD, there are clearly identifiable risk factors, enumerated previously, that increase the likelihood of an exaggerated stress–memory response to trauma.

The mechanisms of memory consolidation involve transcription events within neurons that can imbue permanence [6]. Undoing pathologically over-consolidated memories subsequent to the onset of PTSD with pharmacotherapies is challenging because these treatments would have to be able to reverse genetic and transcriptional events, and synaptic changes etched into neurons. There is no known drug therapy that has this capability.

This creates a compelling reason to investigate pharmacotherapies to interfere with the development of PTSD prior to and during the initial memory consolidation phase, for traumatized individuals at risk for developing PTSD. There appears to be a candidate drug, lithium, which has the potential to forestall PTSD by inducing cognitive impairments and disrupting the neuronal processes of memory consolidation prior to the point when transcription events imbue long-lasting modifications in synapses.

Memory, synaptic plasticity, and LTP

In 1894, Santiago Ramon y Cajal proposed that memory and learning are processes mediated by the growth of synaptic connections [7], a process expanded upon in the 1940's by Jerzy Konorski and Donald Hebb, and named synaptic plasticity [8,9].

Synaptic plasticity describes the capacity for neurons to modify synaptic structure in response to either use or disuse. Eric Kandel, recipient of the 2000 Nobel Prize in Physiology or Medicine for his research on the physiology of memory, described the physical changes in synaptic structure associated with synaptic plasticity as the final and most stable phase of long-term memory storage [6].

Scoville and Milner, and later, Larry Squire, identified the anatomical location for the learning of conscious events and facts (declarative learning), in the medial temporal lobe and the hippocampus [10,11]. As a framework developed for understanding memory storage, both structurally and anatomically, progress was made in elucidating the molecular events within neurons that mediate synaptic plasticity.

In 1973, Bliss and Lømo introduced the concept of long-lasting potentiation [12], later renamed long-term potentiation (LTP) by Douglas and Goddard [13], to describe the physiological enhancement of a synapse after pre-synaptic stimulation, and that lasts for a time period subsequent to stimulation, to potentiate a synapse to future excitation. LTP has been divided into two phases. The early phase LTP, lasting approximately 60 minutes, and the late phase LTP, which is the protein synthesis dependent component of LTP [14]. LTP associated changes have been detected at a synapse on both pre-synaptic and post-synaptic neurons [15].

LTP is integral to conditioning, as repeated nerve stimulation that generates and maintains LTP potentiates a neuron to re-firing [12,13]. LTP is also integral to associative learning, as input stimulation from multiple pre-synaptic inputs can have an additive effect on the generation of LTP [16].

In reviewing LTP, there are well-characterized synaptic events that have an essential role in generating LTP. There is a general consensus that the generation of LTP is mediated by the influx of calcium ions into the cytosol of post-synaptic neurons [6,14,16–18]. There is also a general consensus that calcium ion influx into the cytosol activates kinases associated with LTP, leading to transcription, protein synthesis, and neuronal remodeling [6,14,16]. The chelation of calcium ions in the cytosol of post-synaptic neurons has been shown to block the development of LTP [17,18].

The influx of calcium ions into the cytosol of post-synaptic neurons can come from two principal sources. One source is extracellular, through cell surface receptors including N-methyl-D-aspartate (NMDA) receptor gated channels located on dendrites, and the second source is from the smooth endoplasmic reticulum [19–21]. The influx of calcium ions stored in the smooth endoplasmic reticulum is modulated by two receptor types located on the surface of the smooth endoplasmic reticulum. The first type of receptor is the ryanodine receptor, and the second type is the IP3-receptor [19–21].

IP3, which binds to and opens IP3-receptors, is produced from the cell membrane phospholipid phosphatidylinositol-4,5-bisphosphate (PIP2). PIP2 is cleaved into IP3 and DAG when neurotransmitters activate metabotropic receptors (e.g. glutamate activating certain subtypes of metabotropic glutamate receptors). After PIP2 is cleaved into IP3 and DAG, IP3 diffuses through the cytosol and binds to IP3-receptors, inducing the release of calcium from the smooth endoplasmic reticulum into the cytosol [16,19–22].

Another metabotropic receptor located on hippocampal neuronal dendrites, the alpha-1 adrenergic receptor, which has a high affinity for norepinephrine, also activates the PIP2, IP3 and DAG cascade [23]. The alpha-1 adrenergic receptor blocker prazosin has been shown to improve sleep and decrease nightmares in patients with PTSD [24–27].

The relationship of IP3, the influx of calcium into the cytosol, and the induction of LTP, has been well-characterized. It has been demonstrated in pancreatic beta cells that blocking IP3 binding to IP3-receptors on the smooth endoplasmic reticulum, with heparin, an IP3-receptor blocker, inhibits the release of calcium from the smooth endoplasmic reticulum into the cytosol [28]. Blocking IP3 binding to IP3-receptors in rat sympathetic ganglion neurons with heparin, in both pre-synaptic and post-synaptic neurons, and in either pre-synaptic or post-synaptic neurons, has been shown to decrease LTP [29].

Lithium, secondary messengers, and IMP

Lithium, an FDA approved pharmacotherapy for the treatment of mood disorders, can induce transient cognitive, memory, and learning impairments in humans that are reversed when treatment is discontinued [30,31]. The lithium ion, the active principle in lithium carbonate, has a crystal ionic radius of .60 Å, similar to that of the magnesium ion at .65 Å [32]. Like magnesium, the lithium ion is positively charged, and because both molecules have similar properties, lithium can bind to and inhibit magnesium dependent molecules, including receptors and enzymes [32–35].