PUBLISHER NOTE

After 7½ years of educating and entertaining us with text and creative icon figures about psychopharmacology, Dr. Stahl is taking some time off from BRAINSTORMS. We wish him the best in all of his undertakings and will welcome him back in the future. —*J.S.S. and J.B.*

Is Psychopharmacologic "Inoculation" Effective in Preventing Posttraumatic Stress Disorder?

Stephen M. Stahl, M.D., Ph.D.

Issue: *Early treatment following exposure to traumatic stress may prevent the development of posttraumatic stress disorder (PTSD).*

Who gets PTSD and who doesn't? Perhaps half of all adult Americans will experience a traumatic event at some time in their lives, but studies estimate that only 25% of such individuals will develop PTSD, resulting in a lifetime prevalence rate of about 8%.[1] Now it may be possible not only to identify those at high risk for developing PTSD but also to treat them before they get PTSD, and thus, in concept, to prevent them from getting PTSD.

Vulnerable or Resilient?

The best predictor of who will eventually develop PTSD after a catastrophe is the way an individual immediately reacts to it. Those who develop panic, terror, and horror (i.e., peritraumatic distress) and/or a sense of unreality, like what is happening is not real but is like being in a dream or a movie (i.e., dissociation), do the worst.[2,3] Whether or not one develops a high-risk immediate reaction—or ultimately PTSD itself—seems to be the product of both "nature" and "nurture." In terms of nature, specific genes seem to endow one with either vulnerability or resilience to stress and its consequences such as PTSD.[4] In terms of nurture, prior exposure to trauma is also a strong predictor of PTSD, since repeated stress sensitizes the nervous system to subsequent traumatic stressors, with some individuals developing PTSD and others developing depression.[5,6]

The genes that regulate the serotonin transporter may be one example of nature's biasing the central nervous system toward vulnerability or resilience to developing either depression or PTSD after multiple life stressors.[4,7,8] Other genes that are prime candidates for influencing reactions to stress include those that regulate the neurohormone and neurotransmitter corticotropin-releasing factor (CRF), as well as those that regulate the key brain neurotrophic factor known as BDNF (brain derived neurotrophic factor).[4,5]

Women are at twice the risk of men for PTSD,[1] and exposure to traumatic events in childhood, especially sexual and physical abuse in women, may trigger a persistent hyperactivity of the nervous system that sets the individual up for PTSD upon exposure to another traumatic event in adulthood.[4–6] Thus, it is now possible to identify high-risk individuals *before* they develop PTSD, such as women with a history of abuse and who dissociate and experience peritraumatic distress following exposure to a catastrophic event. The big question is what happens to such high-risk individuals if we intervene at the time of acute symptoms? Can we now envision the possibility of preventing the development of PTSD?

Diabolical Learning

To prevent the emergence of PTSD after a traumatic stressor, it is necessary to interrupt the neuronal events that establish and perpetuate the symptoms of PTSD. Following a catastrophic stressor, the nervous system not only mediates acute symptoms of peritraumatic distress, but also "learns" to react with reexperiencing these same symptoms more and more frequently over time.[4–6] This phenomenon—called fear conditioning—is a type of learning that causes vivid recall of memories of traumatic events, autonomic hyperarousal, and flash-

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From the Neuroscience Education Institute in Carlsbad, Calif., and the Department of Psychiatry at the University of California San Diego.

Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, Neuroscience Education Institute, 5857 Owens Street, Ste. 102, Carlsbad, CA 92009.

backs with exposure to sensory and cognitive memories associated with prior traumas.[4] Diabolically, the nervous system simultaneously engages in a form of molecular mischief called "reconsolidation" in which old memories undergo another round of consolidation that causes them to be reactivated by cues associated with the original trauma.[4] This reconsolidation serves to strengthen and facilitate long-term memory of the event, as well as the reexperiencing of the emotional symptoms attached to that memory. Each time a traumatic memory is recalled, it becomes easier and easier to retrieve it along with its emotional baggage and symptoms. Eventually symptoms can even become spontaneous. Can fear conditioning and reconsolidation be prevented or intercepted?

Psychopharmacologic Inoculation

Some of the neuronal mechanisms that mediate fear conditioning and reconsolidation are beginning to be understood,[4,5] leading to the hypothesis that disrupting such mechanisms after exposure to an acute trauma would sabotage the development of PTSD.[4,9–12] Indeed, 2 studies suggest that PTSD might be prevented if the β-adrenergic blocker propranolol is given to individuals after a traumatic event.[10,11] Since epinephrine strengthens memory consolidation and fear conditioning after a learning task, perhaps as a way of facilitating the remembrance of significant experiences, excessive release of epinephrine in reaction to a highly traumatic event may lead to overly strong emotional memory and fear consolidation.[4,10,11] This may involve actions of epinephrine within the amygdala and its interconnecting pathways.[4,13] Blocking the molecular mischief mediated by excessive adrenergic actions of epinephrine might disrupt fear conditioning and account for the preliminary observations of reduced PTSD after treatment with propranolol.

Take-Home Points

- Genetic make-up, prior exposure to stressors, and the type of acute reaction one has after exposure to a traumatic stressor may all be important risk factors that determine who is vulnerable to developing posttraumatic stress disorder (PTSD).
- The nervous systems of those who do develop PTSD may become engaged in a perverse form of learning, which may entrench their symptoms within their circuits and make their PTSD progressively more difficult to treat over time.
- Psychopharmacologic treatments aimed at interrupting not only acute symptoms after a traumatic event but also the molecular mischief associated with the brain's reaction to traumatic stress may arrest the progression to PTSD.

Similar findings have been reported for the use of benzodiazepines in preclinical models.[12] Given the association of the serotonin transporter with stress vulnerability and amygdalar activation,[7,8] it would not be surprising if early use of selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) might also be useful in preventing the march of acute symptoms to PTSD.

Other studies are in hot pursuit of still other molecular mechanisms to prevent the relentless progression from acute exposure to PTSD in vulnerable individuals. One idea is to block excessive CRF actions with antagonists of the CRF 1 receptor.[4,5] Another is to quell excessively activated fear circuits with $\alpha_2\delta$ ligands such as pregabalin.[14] It is too early to tell which, if any, of these potential pharmacologic interventions may develop into effective "inoculation" against PTSD, but the possibility that chronic suffering after exposure to a catastrophic stressor could be reduced is certainly worth pursuing.

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