Neuroanatomical Changes Associated with Pharmacotherapy in Posttraumatic Stress Disorder

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ABSTRACT: Brain imaging studies have mapped out the neural circuitry of posttraumatic stress disorder (PTSD), implicating brain areas sensitive to stress such as the hippocampus. Animal studies show that antidepressants promote hippocampal neurogenesis and block the effects of stress on the hippocampus. We found that treatment of PTSD patients for a year with the serotonin reuptake inhibitor (SSRI) paroxetine resulted in a 5% increase in hippocampal volume and a 35% improvement in verbal declarative memory function. Patients subjectively reported an improvement in cognition and work performance. These studies are consistent with the idea that antidepressants have a beneficial effect on hippocampal function in PTSD patients.

KEYWORDS: PTSD; hippocampus; pharmacotherapy; stress; neurogenesis; paroxetine; depression

INTRODUCTION

Studies in animals exposed to stress showed deficits in hippocampal-based memory function[1] and alterations in hippocampal morphology.[2,3] Stress interfered with hippocampal-based mechanisms of memory function, including long-term potentiation.[1,4] A variety of mechanisms have been proposed for these findings, including elevated levels of glucocorticoids released during stress,[5,6] stress-related inhibition of brain-derived neurotrophic factor,[7,8] or changes in serotonergic function,[9] although mechanisms continue to be debated.[10] Since that time, studies have shown that stress is associated with an inhibition of neurogenesis (or the growth of new neurons)[11,12] in the hippocampus and that these effects are reversible with treatment with serotonin reuptake inhibitor (SSRI) medications[13–15] as well as other medications including tianeptine[16] and phenytoin.[17] Antidepressant-induced promotion of neurogenesis may underlie the behavioral effects of these medications,[18] although the relation between the hippocampus and depression and PTSD is still not clear.[19]

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The role of the hippocampus in learning and memory, and the wide range of memory alterations seen in PTSD patients, led to the hypothesis of hippocampal dysfunction in PTSD.[20,21] Neuroimaging studies subsequently showed alterations in the hippocampus in PTSD. Initial studies demonstrated deficits in hippocampal-based learning and memory in PTSD.[22,23] The first neuroimaging study in PTSD was performed using magnetic resonance imaging to measure the volume of the hippocampus.[24] This study showed an 8% decrease in MRI-based measurement of right hippocampal volume in patients with combat-related PTSD ($n = 26$) in comparison with matched controls ($n = 22$) ($P < .05$). Decreases in right hippocampal volume in PTSD patients were associated with deficits in short-term memory.[24] Findings of smaller hippocampal volume and/or a reduction in NAA in the hippocampus (a marker of neuronal integrity) in adults with chronic, long-standing PTSD have been replicated several times in the published literature.[25–31] One study used a specific cognitive task to probe hippocampal function and demonstrated a failure of left hippocampal activation with a memory task in women with abuse-related PTSD. This was significant after controlling for differences in hippocampal volume measured on MRI in the same subjects. Women with PTSD had smaller hippocampal volume than did both abused non-PTSD and non-abused non-PTSD women.[32] Studies in children have not shown smaller hippocampal volume in PTSD.[33–35]

Based on findings related to the effects of antidepressants on neurogenesis, we assessed the effects of the SSRI paroxetine on outcomes related to function of the hippocampus. We studied 28 patients with PTSD and treated them for up to a year with variable doses of paroxetine. Twenty-three patients completed the course of treatment, and MRI post-treatment was obtained in 20 patients. Patients who did not complete treatment stopped because of a relapse of substance abuse or were lost to followup (possibly because of a treatment nonresponse). Neuropsychological testing was used to assess hippocampal-based declarative memory function and MRI to assess hippocampal volume before and after treatment. Declarative memory was assessed with the Wechsler Memory Scale–Revised and Selective Reminding Test. Patients with PTSD showed significant improvement in PTSD symptoms with treatment. Treatment resulted in significant improvements in verbal declarative memory and a 4.6% increase in mean hippocampal volume. These findings suggest that long-term treatment with paroxetine is associated with improvement in verbal declarative memory deficits and an increase in hippocampal volume in PTSD.[36]

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