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Effects of phenytoin on memory, cognition and brain structure in post-traumatic stress disorder: a pilot study

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Abstract

Phenytoin (Dilantin®) is an anticonvulsant used in the treatment of epilepsy. It is believed to act by modulation of glutamatergic transmission. Because the neurobiology of post-traumatic stress disorder (PTSD) has been hypothesized to involve alterations in glutamatergic transmission with subsequention neurotoxicity, we assessed the effects of phenytoin on cognition and brain structure in PTSD patients. Phenytoin was administered in an open label fashion for 3 months to nine adult patients with PTSD related to a variety of traumas, including early abuse, combat and car accidents. Subjects underwent magnetic resonance imaging for measurement of whole brain and hippocampal volume, and neuropsychological testing of memory and cognition, before and after treatment. Phenytoin treatment resulted in a significant 6% increase in right brain volume ($p < 0.05$). Increased hippocampal volume was correlated with reductions in symptom severity as measured by the Clinician Administered PTSD Scale and improvements in executive function as measured by the Trails test. However, treatment associated improvements in memory and cognition did not achieve statistical significance. These findings suggest that phenytoin treatment may be associated with changes in brain structure in patients with PTSD.

Keywords

hippocampus, pharmacology, phenytoin, PTSD, stress, treatment

Introduction

Post-traumatic stress disorder (PTSD) affects 8% of Americans at some time in their lives and is associated with considerable morbidity (Kessler *et al*., 1995). Developing effective treatments for PTSD is of critical importance. Large placebo-controlled trials revealed efficacy for the selective serotonin reuptake inhibitors (SSRIs) sertraline (Brady *et al*., 2000) and paroxetine (Tucker *et al*., 2001) in PTSD, but not all patients respond optimally to SSRI treatment. Understanding the neurobiology of PTSD and the brain mechanisms involved in treatment response is critical for development of novel treatments for this disorder.

Studies in laboratory animals have revealed that stress is associated with damage to the hippocampus (McEwen *et al*., 1992;

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Sapolsky, 1996) and inhibition of neuronal growth (Gould *et al*., 1998; Malberg *et al*., 2000) with associated deficits in new learning and memory (Arbel *et al*., 1994; Luine *et al*., 1994; Pavlides *et al*., 1995; Diamond *et al*., 1996). Mechanisms that have been proposed for these effects include stress-induced elevations in glucocorticoids (cortisol) with associated glutamatergic toxicity (Sapolsky *et al*., 1990; Sapolsky, 1996), decreased brain derived neurotrophic factor (Nibuya *et al*., 1995; Smith *et al*., 1995), increased levels of excitatory amino acids such as glutamate (Moghaddam *et al*., 1997), alterations in serotonin (McEwen *et al*., 1997) and direct hippocampal effects of corticotropin releasing factor (Brunson *et al*., 2001).

Phenytoin is an anticonvulsant whose mechanism of action includes blocking cellular responses to excitatory amino acids (Wamil and Mclean, 1993; Kawano *et al*., 1994). Moreover, calcium-mediated cellular functions (protein phosphorylation, neurotransmitter release) and calcium-dependent depolarization, both associated with neuronal death, have been shown to be arrested by phenytoin (De Lorenzo, 1977; Gage *et al*., 1980). *In vivo*, phenytoin decreased the dimension of cerebral infarct in animals with bilateral or unilateral carotid occlusion (Taft *et al*., 1989; Boxer *et al*., 1990). In laboratory animal studies, phenytoin was shown to prevent stress and corticosterone-induced atrophy of CA3 pyramidal neurones (Watanabe *et al*., 1992) and to reverse stress-induced impairment of spatial learning and hippocampal atrophy (Luine *et al*., 1994).

Patients with PTSD have been reported to have smaller hippocampal volume or other hippocampal abnormalities as measured with magnetic resonance imaging (MRI) (Bremner *et al*., 1995b; Gurvits *et al*., 1996; Bremner *et al*., 1997; Stein *et al*., 1997; Freeman *et al*., 1998; Schuff *et al*., 2001; Gilbertson *et al*., 2002; Villareale *et al*., 2002; Bremner *et al*., 2003b) and deficits in hippocampal-based verbal declarative memory function (Gil *et al*., 1990; Bremner *et al*., 1993; Uddo *et al*., 1993; Bremner *et al*., 1995a; Yehuda *et al*., 1995; Barrett *et al*., 1996; Golier *et al*., 1997; Jenkins *et al*., 1998; Vasterling *et al*., 1998; Moradi *et al*., 1999; Sachinvala *et al*., 2000; Gilbertson *et al*., 2001; Roca and Freeman, 2001; Vasterling *et al*., 2002). Treatment for 1 year with the SSRI paroxetine led to a 5% increase in hippocampal volume and a 35% improvement in verbal declarative memory function in PTSD patients (Vermetten *et al*., 2003). We recently reported a significant improvement in PTSD symptoms as measured by a 27-point reduction in the Clinician Administered PTSD Scale (CAPS) (Blake *et al*., 1995) score in an open label phenytoin treatment study of PTSD (Bremner *et al*., 2004). Based on these studies, we hypothesized that phenytoin treatment would be associated with increases in hippocampal volume and improvements in memory function in PTSD patients.

Materials and methods

Subjects

Twenty-eight subjects were initially screened for participation in this study, of these, 14 were excluded because they did not meet criteria for PTSD, or they were currently treated with either a benzodiazepine or an antipsychotic drug. Fourteen subjects signed a consent form and two withdrew from the study before treatment was initiated. Of the 12 subjects who started treatment, three did not remain in the study until its conclusion (described below). Thus, nine subjects (four men and five women), who were aged 18 years or older and fulfilled criteria for PTSD, completed the study. All subjects were recruited by advertisement and provided their written informed consent for participation in the study. This study was approved by the Emory University Investigational Review Board. PTSD subjects were included with the diagnosis of PTSD based on the Structured Clinical Interview for DSM-IV (SCID) (First *et al*., 1995). PTSD patients had experienced a range of traumas including childhood abuse, motor vehicle accident, rape, assault and combat. Subjects were excluded if they presented with a history of current (past 6 months) alcohol or substance abuse or dependence, schizophrenia, or an eating disorder, as determined by the SCID, serious medical disorder as determined by laboratory tests and physical examination, organic mental disorder, neurological disorder or head trauma. Current medications were not discontinued for the purpose of participation in this study. No subjects were on another psychotropic medication during the time of the study. Study completers were not treated with psychotropic medication for the 4 weeks preceeding the start of the study.

Behavioural assessments

All subjects were evaluated with the SCID for co-morbid psychiatric diagnoses. Six out of nine PTSD subjects (66%) fulfilled criteria for a lifetime history of major depression but none for current major depression. One subject (11%) fulfilled criteria for lifetime and current history of panic disorder without agoraphobia and one (11%) for lifectime and current social phobia. None of the subjects had lifetime or current alcohol or substance abuse/dependence.

All PTSD subjects were assessed with the CAPS (Blake *et al*., 1995), a reliable and valid measure of PTSD symptom severity with subcomponents for the individual symptom clusters. Current depressive symptoms were assessed with the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960). State anxiety was measured with the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959).

Neuropsychological assessments

All subjects were assessed before and after treatment with a battery of neuropsychological assessments. Attention was assessed with the Gordon Box test. The Gordon Box is an assessment of attention that includes assessments of vigilance and distractibility. For vigilance, subjects press a button every time they see a '9' following after a '1'. For distractibility, distracting numbers are flashed lateral to the location of the target (Gordon *et al*., 1986). Executive function was assessed with the Trails Test, Parts A and B. Trails A involves connecting dot-to-dot following serial letters or numbers. Trails B involves letter-number series (e.g. A–1–B–2–, and so on. Score is related to the time required to complete the task (e.g. the

lower the score, the better the performance) (Arbuthnott and Frank, 2000). Declarative memory was assessed with the Selective Reminding Test (SRT), a validated measure of verbal and visual memory (Hannay and Levin, 1985). The SRT assesses consolidation of memory. Subjects are read a word list and asked to repeat them. Words that are missed are then repeated to the subjects, and the subjects have to remember the words that they remembered correctly in previous trials. Memory was also assessed with paragraph recall using methods similar to the Wechsler Memory Scale and methods previously described (Bremner *et al*., 2003a). Subjects were read two paragraphs with assessment of recall, both immediately and with a delay, and two different paragraphs with immediate and delayed recall after treatment. Subjects were randomized to paragraph order (i.e. half were presented paragraphs No. 1 and No. 2 pre-treatment and No. 3 and No. 4 post-treatment, while the other half were presented paragraphs No. 3 and No. 4 pre-treatment and No. 1 and No. 2 post-treatment). The number of correctly recalled elements of the paragraph were scored and scores on the two paragraphs were summed for immediate and delayed recall. Percent recall was calculated by dividing delayed recall by immediate recall (paragraph percentage retention). In situations where more elements were recalled with delayed than immediate recall, the percentage retention score was greater than 100%. In our hands, there is good test–retest reliability for paragraph recall using this test ($r = 0.64$ for delayed recall).

MRI methods

Magnetic resonance images of 1.5 mm contiguous slices were obtained with a 1.5 Tesla Philips Gyroscan Intera device. An initial sagittal localizing sequence was obtained to determine the long axis of the hippocampus. Coronal images were then acquired with a T1-weighted gradient echo three-dimensional sequence with, TR = 35 ms, TE = 12 ms, flip angle 35, NEX = 2, matrix 512 × 512, field of view = 22 cm. This protocol provides high contrast between grey and white matter regions and the smaller voxel size improves anatomical resolution. Axial sections were then obtained perpendicular and parallel, respectively, to the long axis of the hippocampus using a fast spin echo with TR = 3000, dual echo TE = 20,100, flip angle 90, 2.5 mm contiguous axial slices, 256 × 256 matrix. Images were then transferred via internet to a SunSparc Workstation (Sun Microsystems, Inc., Santa Clara, CA, USA) for image processing, with archiving on optic disk media. Volumetric measurements of the hippocampus and left and right whole brain volumes were performed independently by one rater who was blinded to subject diagnosis. Manual volumetric techniques were used because these have been shown to be reliable and valid in our hands, and to reproduce the methodology used to demonstrate smaller hippocampal volume in PTSD and an increase in volume with paroxetine treatment in our previous studies (Vermetten *et al*., 2003). MRI scans were then resliced to correct for head rotation and to create slices perpendicular to the long axis of the hippocampus using the ANALYSE program (Robb *et al*., 1989). First, corrections for head rotation were achieved using anatomical landmarks including the internal auditory canal and the seventh and eighth cranial nerve. Then, two mid-hippocampal points separated by 15 mm were selected to construct a line which defines the long axis of the hippocampus. A third mid-hippocampal point in the opposite hippocampus was then selected to define a plane parallel to the long axes of both hippocampi. A series of oblique images were constructed perpendicular to this plane to create images orthogonal to the long axis of the hippocampus. The outline of the hippocampus was then traced using a mouse-driven cursor following the method of Watson *et al*. (1992). The anterior border of the hippocampus was defined by the amygdala. The uncal recess of the temporal horn of the lateral ventricle is the most reliable way to separate the hippocampal head from the amygdala. However, in cases where the uncal recess was not clearly visible, traces were made along the alveus which connects the inferior horn of the lateral ventricle to the sulcus at the inferior margin of the semilunar gyrus (i.e. the semianular or amygdaloid sulcus). If neither the uncal recess or the alveus was clearly visible, a horizontal line connecting the plane of the inferior horn of the lateral ventricle with the surface of the uncus was used. The posterior most slice of the hippocampus was defined as the slice of the hippocampus where the pulvinar interrupts the fornix superiorly. The superior border of the hippocampus includes grey matter visible within the hippocampus, as well as the alveus and fimbriae. The inferior border of the hippocampus includes the subiculum. A straight line from the inferior subcortical white matter extending medially was used to disconnect the parahippocampal gyrus from the subiculum. Inter-rater reliability for these measurements shows an intra-class correlation of greater than 0.9 in our laboratory. Whole brain measurements were performed by manually tracing the cortical outline of the brain for left and right brain separately, including grey matter, white matter and cerebrospinal fluid, for all supratentorial structures. Reliability of these measurements in our laboratory is greater than 0.9.

Phenytoin treatment

Subjects were treated with a variable dose of phenytoin in an open label fashion for 3 months. Treatment was begun at 300 mg per day divided into three doses and increased to 400 mg/day if plasma levels were sub-therapeutic. Plasma levels of phenytoin were measured at weeks 1, 2, 3, 4, 8 and 12, and dose adjusted to be within the therapeutic range used in the treatment of epilepsy (10–20 ng/ml). Subjects were treated with folic acid to prevent folic acid deficiency secondary to phenytoin treatment. As noted above, 12 patients started the study, two patients dropped out because of side-effects and one patient was relocated out of state. Behavioural ratings of PTSD, depression and anxiety were obtained every 4 weeks.

Data analysis

A paired *t*-test was used to assess the effects of phenytoin on brain structure and cognitive outcomes. $p < 0.05$ was considered statistically significant.

Results

As reported in a companion manuscript (Bremner, 2004), PTSD patients showed a significant improvement in PTSD symptoms as measured by CAPS with phenytoin treatment. Phenytoin did not have a significant effect on depression or anxiety as measured with the HAM-D and HAM-A, respectively.

There were no significant changes in memory or cognition with phenytoin treatment as measured by neuropsychological testing (Table 1). Phenytoin administration resulted in a significant 6% increase in right whole brain volume as measured with volumetric MRI (Fig. 1; Table 2). A five percent increase in right hippocampal volume was observed that was not statistically significant. However, there were significant correlations between increases in hippocampal volume and reduction of PTSD symptoms as measured with the CAPS for the intrusion cluster for both the left

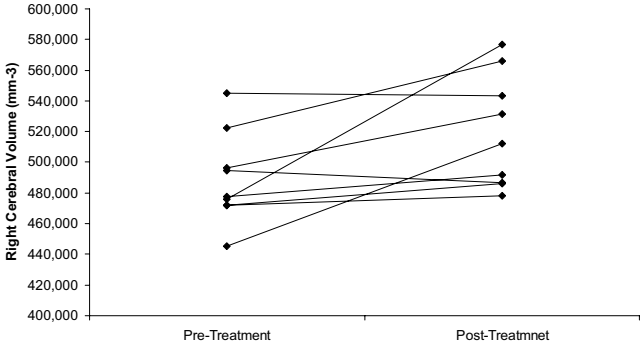

Figure 1 Effects of phenytoin on right brain volume. There was a significant 6% increase in right whole brain volume after 3 months of treatment in post-traumatic stress disorder ($p < 0.05$)

Table 1 Effects of phenytoin on memory and cognition

Test	Pre-treatment	Post-treatment	% Change	*t*-value	d.f.	*p*-value
WMSL-I	30 (13)	25 (8)	−20%	−1.18	7	0.27
WMSL-D	26 (10)	25 (10)	−4%	−0.27	7	0.79
WMSL-R	90 (25)	106 (42)	15%	1.21	7	0.26
WMSF-I	28 (5)	27 (5)	−2%	−0.27	7	0.79
WMSF-D	23 (10)	21 (7)	−10%	−0.62	7	0.55
WMSF-R	82 (24)	77 (13)	−6%	−0.69	7	0.51
SRTVe Rec	115 (12)	122 (15)	6%	1.97	7	0.09
SRTVe LTS	103 (21)	109 (26)	6%	0.91	7	0.39
SRTVe LTR	102 (21)	108 (28)	6%	0.97	7	0.36
SRTVe CLTR	91 (25)	104 (30)	12%	1.52	7	0.17
SRTVe Delay	10 (1)	10 (1)	3%	1.15	7	0.28
SRTVi Rec	132 (7)	135 (6)	2%	1.51	7	0.17
SRTVi LTS	130 (9)	134 (7)	3%	1.05	7	0.32
SRTVi LTR	129 (11)	133 (7)	3%	1.15	7	0.28
SRTVi CLT	128 (12)	132 (8)	4%	1.17	7	0.28
SRTVi Del	12 (1)	12 (1)	0%	0	7	1
Trails A	34 (13)	30 (8)	−13%	−0.81	7	0.44
Trails B	65 (14)	59 (13)	−10%	−1.16	7	0.28
Gbdis	29 (1)	29 (1)	1%	1.00	7	0.35
Gbvig	30 (1)	30 (1)	1%	−1.40	7	0.20

WMS, Wechsler Memory Scale Score; WMSL, WMS Logical (verbal) memory (paragraph recall); WMSL-I, WMSL-Immediate Recall (immediate recall of paragraph); WMSL-D, Delayed Recall (after 30 min); WMSL-R, WMSL = % retention (percentage of paragraph retained in memory after delay); WMSF, WMS Figural (visual) memory; SRT, Selective Reminding Test; SRTVe, SRT Verbal memory; SRTVi, visual memory; LTR, Long-term retrieval; LTS, long-term storage; Rec, recall; CLTR, continuous long-term retrieval. For Trails A and B, a reduction in score is related to improved performance. GB, Gordon Box (attention test); Gbdis, distractibility; Gbvig, GB vigilance.

Table 2 Effects of phenytoin on brain structure

Brain stucture	Pre-treatment	Post-treatment	% Change	*t*-value	d.f.	*p*-value
Left brain	505 178 (34 668)	516 611 (34 292)	2%	1.01	7	0.34
Right brain	488 959 (29 763)	519 193 (36 836)	6%	2.56	7	0.03
Left hippocampus	2123 (258)	2207 (318)	4%	0.76	7	0.47
Right hippocampus	2257 (285)	2363 (224)	5%	1.64	7	0.14

(r = –0.70, d.f. = 8, p = 0.037) and right (r = –0.73, d.f. = 8, p = 0.026) hippocampus, and for the hyperarousal cluster for right (r = –0.70, d.f. = 8, p = 0.048) hippocampal volume. Correlations with total CAPS score were not significant. Improvements on the Trails A (r = –0.81, d.f. = 8, p = 0.008) and Trails B (r = –0.70, d.f. = 8, p = 0.035) were correlated with increases in right hippocampal volume. There was no correlation between changes in whole brain volumes and improvements on the CAPS.

Discussion

This study suggests that phenytoin may be associated with changes in brain structure, specifically a 6% increase in right whole brain volume. Although a 5% increase in right hippocampal volume and modest improvements in cognition were not statistically significant, increases in hippocampal volume were correlated with decreases in PTSD symptom levels, as measured with the CAPS and improvements in executive function as measured by the Trails test.

One possible mechanism by which phenytoin could affect brain structure is its effect on glutamatergic function. In laboratory animal studies. phenytoin has been shown to antagonize glutamate-induced excitation of cerebrocortical neurones (Matthews and Connor, 1977) and to block the effect of glutamate at the NMDA receptor (Wamil and Mclean, 1993; Kawano *et al*., 1994). Phenytoin differs in its mechanism of action related to the glutamatergic system relative to other anti-epileptic medications such as carbamazepine (Kawano *et al*., 1994). The chronic stress of PTSD could be associated with ongoing glutamatergic toxicity that is benefited by phenytoin treatment. Kindling phenomena have been hypothesized to underlie both the pathophysiology of epilepsy, and certain mood and anxiety disorders. In kindling, repeated stimulation in the hippocampus or amygdala leads to an enhancement of the postsynaptic potential and an increased risk of seizures. Phenytoin results in a decrease in seizures in kindled animals (Rundfeldt *et al*., 1990).

The primary hypothesis of this study was that phenytoin would affect hippocampal volume. Note that the 5% increase in right hippocampal volume is equivalent to our previous study of paroxetine (Vermetten *et al*., 2003). However, we did not have adequate statistical power in the current study to show an effect due to the small sample size. However, paroxetine did not lead to a change in whole brain volume, and a larger sample might not demonstrate a significant change in hippocampal volume after phenytoin treatment. However, the correlation between symptom reduction and change in hippocampal volume suggests that there may be an effect at the level of the hippocampus. In addition, the cognitive effects of phenytoin were smaller in magnitude than that observed with paroxetine.

It is unclear why there should have been a greater effect on the right brain as opposed to the left brain. The greater contribution of the right brain to emotion and non-verbal cognitive processes is well known. A mechanism by which a greater effect on the right hemisphere as opposed to the left is obscure. There was some positive increase on both sides, and it may be that the greater effect on the right side was due to chance alone.

Some studies have provided some evidence for efficacy for phenytoin in the treatment of anxiety disorders and depression (Resnich, 1967; Jonas, 1969; Stephens and Shaffer, 1970; Gottschalk *et al*., 1973; Overall *et al*., 1973; Bremner *et al*., 2004). Phenytoin blocked the anxiety induced by the benzodiazepine antagonist Ro 5-4864 in healthy human subjects (File and Lister, 1983). Other studies have suggested efficacy in the treatment of PTSD (Bremner *et al*., 2004) anxiety (Jonas, 1969; Stephens and Shaffer, 1970) hostility (Resnich, 1967; Turner, 1967; Gottschalk *et al*., 1973) and depression (Overall *et al*., 1973).

There are several limitations of the current study. Most prominent among them is the open-label nature of the study, and the small sample size. Future studies using a double-blind, randomized, placebo-controlled design should be performed. We also used a broad number of neuropsychological tests to assess the effects of phenytoin on memory and cognition. Future studies should include neuropsychological tests with greater sensitivity for the detection of memory deficits in PTSD. Subjects were treated with folate, which has effects on the brain. We cannot exclude the possibility that brain changes were due to folate alone, apart from phenytoin. Future studies should assess the effects of phenytoin on the brain. The correlations reported in the present study should be interpreted as exploratory because multiple correlations are associated with the finding of statistically significant effects by chance alone. Brain volumetrics involved measurement of whole brain volumes, which include both grey and white matter; therefore, we cannot comment on whether the effects of phenytoin were specific to grey matter or whether there were also effects for both grey and white matter.

The results of this study suggest that phenytoin affects whole brain as well as hippocampal volume. The results provide evidence that medications used in the treatment of various neurological and psychiatric disorders have effects on the brain that were previously unanticipated, including transformation of the very structure of the brain. We do not fully understand the mechanism by which this may occur, and this remains the subject of future research.

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