The psychobiology and psychopharmacology of PTSD

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This paper reviews the currently available knowledge about the psychobiology and psychopharmacology of post-traumatic stress disorder (PTSD). It also reviews the various studies that have elucidated changes in brain function and structure in PTSD populations, including positron emission tomography (PET), single photon emission computed tomography (SPECT), and event-related potential (ERP) studies. It then reviews the literature on catecholamine and hypothalamic-pituitary-adrenal (HPA) axis abnormalities in PTSD, and finally reviews the literature available on the psychopharmacology of PTSD. It discusses how the pathophysiology of PTSD determines the nature of psychopharmacological interventions. Psychopharmacological interventions in PTSD are largely limited to good studies on the effects of the selective serotonin reuptake inhibitors (SSRIs). In order to effectively intervene in PTSD, studies of other psychopharmacological agents are necessary, specifically of agents which affect limbic activation, decreased frontal lobe functioning, altered HPA activity, and other biological features of PTSD. Copyright © 2001 John Wiley & Sons, Ltd.

**key words—**PTSD; psychopharmacology; SSRIs; psychobiology; brain lateralization; amygdala; hippocampus

**BACKGROUND**

When Abram Kardiner (1941) first defined what is now called post-traumatic stress disorder (PTSD), he called it a ‘physioneurosis’ in which patients developed ‘an enduring vigilance for and sensitivity to environmental threat.’ Kardiner described that physiological hyperarousal occurs not only in response to auditory stimuli: some patients suffered from sensitivity to temperature, pain, and sudden tactile stimuli, as well. ‘These patients cannot stand being slapped on the back abruptly; they cannot tolerate a misstep or a stumble. From a physiologic point of view there exists a lowering of the threshold of stimulation; and, from a psychological point of view, a state of readiness for fright reactions’ (p. 95). He claimed that these patients remained on constant alert for return of the trauma. Trauma disrupts and reorganizes homeostatic controls.

The organism receives information from the environment via its sensory input. A large variety of brain structures analyze this input, utilizing both innate and acquired knowledge about the body, the brain itself, and the environment. The basic biological regulation mediated by the hypothalamus and brain stem is complemented by controls by higher brain functions. These are extraordinarily complex and multifaceted. Since people with PTSD not only suffer from intrusive memories, numbing, and hyperarousal, but also have a great deal of trouble carrying out a host of discriminatory functions, it is not surprising that research on PTSD patients has implicated virtually every one of the following systems: brain stem, amygdala, hippocampus, anterior cingulate, corpus callosum, orbitofrontal cortex, and prefrontal cortex.

Several brain structures, in particular, have been implicated in the pathophysiology of PTSD: (1) the parietal lobes, which are thought to integrate information between different cortical association areas (Damasio, 1989); (2) the amygdala, which evaluates incoming information for emotional significance and which has been shown to be activated when people are exposed to reminders of their trauma (Rauch et al., 1996); (3) the hippocampus, which is thought to create a cognitive map that allows the categorization of experience, and which has been shown to be decreased in size in a variety of traumatized populations (Bremner et al., 1995); (4) the corpus callosum, which allows for the transfer of information by both hemispheres (Joseph, 1988), integrating emotional and cognitive aspects of the experience and which has been shown to be decreased in size in adults who were abused as children (Teicher, 1997); (5) the

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cingulate gyrus, which is thought to play a role of both an amplifier and a filter, that helps integrate the emotional and cognitive components of the mind (Devinsky et al., 1995) and which is activated following effective treatment for PTSD (van der Kolk, 1997); and (6) the prefrontal cortex, which is involved in problem solving, learning, and complex stimulus discriminations, and which has been shown to be less activated when people with PTSD are exposed to reminders of their trauma, and to have increased activation, relative to pretreatment, after people are effectively treated for PTSD.

THE SYMPTOMATOLOGY OF PTSD

Starting with Kardiner (1941) and closely followed by Lindemann (1994), a vast amount of literature on combat trauma, crimes, rape, kidnapping, natural disasters, accidents, and imprisonment demonstrated that the trauma response is complex: hypermnnesia, hyperreactivity to stimuli and traumatic reexperiencing coexist with psychic numbing, avoidance, amnesia, and anhedonia (Horowitz, 1978; APA, 1987, 1994).

Over time, we have come to understand that PTSD is only one manifestation of psychological distress to trauma and that the development of a chronic trauma-based disorder is qualitatively different from a simple exaggeration of the normal stress response. In affected individuals, a cascade of biobehavioral changes occurs that results in the eventual development of what we call PTSD. It also is clear that we are not dealing with simple conditioning: many people who do not suffer from PTSD, but who have been exposed to an extreme stressor, will again become distressed when they are once again confronted with the tragedy. Pitman et al. (1993) have pointed out that the critical issue in PTSD is that the stimuli that cause people to overreact may not be conditional enough: a variety of triggers not directly related to the traumatic experience may come to precipitate extreme reactions.

After being exposed to extreme stress, almost everyone develops intrusive symptoms, but only a certain proportion of exposed people also develop avoidance and hyperarousal. It is thought that the persistence of intrusive and repetitious thoughts, by means of the process of kindling, sets up a chronically disordered pattern of arousal. The patient is victimized by having memories of the event, not by the event itself (McFarlane, 1988).

In an apparent attempt to compensate for their chronic hyperarousal, traumatized people seem to shut down: on a behavioral level, by avoiding stimuli that remind them of the trauma; on a psychobiological level, by emotional numbing, which extends to both trauma-related and everyday experiences. Over time, people with chronic PTSD come to suffer from numbing of responsiveness to the environment, punctuated by intermittent hyperarousal in response to emotionally arousing stimuli. Thus, they come to suffer both from generalized hyperarousal and from physiological emergency reactions to specific reminders.

PSYCHOPHYSIOLOGICAL EFFECTS OF TRAUMA

Abnormal psychophysiological reactions in PTSD occur on two very different levels: (1) in response to specific reminders of the trauma; and (2) in response to intense but neutral stimuli, such as loud noises, signifying a loss of stimulus discrimination (Table 1).

Conditional responses to specific stimuli

This paradigm implies that people with PTSD suffer from heightened physiological arousal in response to sounds, images, and thoughts related to specific traumatic incidents. A large number of studies have confirmed that people with PTSD, but not episode controls who did not develop PTSD, respond to such reminders with significant increases in heart rate, skin conductance, and blood pressure (Starkman et al., 1992). The highly elevated autonomic responses to reminders of traumatic experiences that happened years ago illustrate the intensity and timeless quality of which these memories continue to affect current experience.

Research has shown that medications that stimulate autonomic arousal may precipitate visual images and affect states associated with prior traumatic experiences in people with PTSD, but not in controls. In patients with PTSD, the injection of drugs such as lactate (Rainey et al., 1987) and yohimbine (Southwick et al., 1997) tends to precipitate panic attacks, flashbacks (exact reliving experiences) of earlier trauma, or both. In our own laboratory, approximately 20% of PTSD subjects responded with a flashback of a traumatic experience when they were presented with acoustic startle stimuli (van der Kolk et al., 1985).

Hyperarousal to intense, but neutral stimuli.
Loss of stimulus discrimination

Excessive stimulation of the CNS at the time of the trauma may result in permanent neuronal changes that have a negative effect on learning, habituation, and
stimulus discrimination. These neuronal changes would not depend on actual exposure to reminders of the trauma for expression. The abnormal startle response, a sequence of muscular and autonomic responses elicited by sudden and intense stimuli, characteristic of PTSD, is one example of this phenomenon (Shalev and Rogel-Fuchs, 1993).

Another example of this phenomenon is recorded in traumatized people’s cortical event-related potentials (ERPs) in response to noises. Using ERPs, McFarlane et al. (1993) found that people with PTSD (1) were unable to differentiate relevant from irrelevant stimuli, (2) attended less to affectively neutral, but existentially relevant events, and (3) as a consequence of this relative lack of responsiveness they needed to apply more effort than nontraumatized people to respond to current experience (as reflected in delayed reaction time). These studies suggest that people with PTSD have difficulty neutralizing stimuli in their environment in order to attend to relevant tasks. To compensate, they tend to shut down. However, the price for shutting down is decreased involvement in ordinary, everyday life.

Table 1. Biological abnormalities in PTSD

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THE HORMONAL RESPONSE IN PTSD

Background

PTSD develops following exposure to events that are intensely distressing. Intense stress is accompanied by the release of endogenous, stress-responsive neurohormones, such as cortisol, epinephrine and norepinephrine (NE), vasopressin, oxytocin, and endogenous opioids. These stress hormones help the organism mobilize the required energy to deal with the stress, ranging from increased glucose release to enhanced immune function. In a well-functioning organism, stress produces rapid and pronounced hormonal responses. However, chronic and persistent stress inhibits the effectiveness of stress response and induces desensitization.

Since there is an extensive animal literature on the effects of inescapable stress on the biological stress response of other species, such as monkeys and rats, much of the biological research on people with PTSD has focused on testing the applicability of those research findings to people with PTSD (Krystal et al., 1989; van der Kolk and Fisler, 1989; Foa et al., 1992). People with PTSD, like chronically and inescapably shocked animals, seem to suffer from a persistent activation of the biological stress response upon exposure to stimuli reminiscent of the trauma. The most thoroughly studied systems are: catecholamines, corticosteroids, serotonin, and endogenous opioids.

Catecholamines. Neuroendocrine studies of Vietnam veterans with PTSD have found good evidence for chronically increased sympathetic nervous system activity in PTSD. One study (Kosten et al., 1987) found elevated 24-hour excretion of urinary NE and epinephrine in PTSD combat veterans compared with patients with other psychiatric diagnoses. While Pitman and Orr (1990) did not replicate these findings in 20 veterans and 15 combat controls, the mean urinary NE excretion values in their combat controls (58.0 µg/day) were substantially higher than those previously reported in normal populations. The expected compensatory downregulation of adrenergic receptors in response to increased levels of norepinephrine was confirmed by a study that found decreased platelet α2 adrenergic receptors in combat veterans with PTSD, compared with normal controls (Perry et al., 1987). In another study, Southwick et al. (1998) used injections of yohimbine (0.4 mg/kg), which activates neuroadrenergic neurons by blocking the α2 receptor, to study noradrenergic neuronal dysregulation in Vietnam veterans with PTSD.

Yohimbine precipitated panic attacks in 70% of subjects and flashbacks in 40%. Subjects responded with larger increases in plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) than controls. Yohimbine precipitated significant increases in all PTSD symptoms.

The locus coeruleus may serve as an alarm center which is poorly regulated and perhaps overresponsive in people with chronic PTSD.

Increased corticotropin releasing factor (CRF). Increased CRF has been demonstrated in PTSD and may be of particular significance because of its central role in regulating the global human stress response. CRF release can stimulate a cascade of corticosteroid and noradrenergic release and the release of other neurohormones. No specific PTSD-related CRF abnormalities have, to date, been identified. Investigations are currently underway to explore the use of medications which affect CRF in patients with PTSD.

Corticosteroids. Studies have shown that veterans with PTSD have low urinary cortisol excretion, even when they have comorbid major depressive disorder (Yehuda et al., 1990). Studies also have found increased numbers of lymphocyte glucocorticoid receptors in Vietnam veterans with PTSD (Yehuda et al., 1990, 1991). The number of glucocorticoid receptors was proportional to the severity of PTSD symptoms. Resnick et al. (1995) studied the acute cortisol response to trauma from blood samples from 20 acute rape victims. Three months later, a prior trauma history was taken, and the subjects were evaluated for the presence of PTSD. Victims with a prior history of sexual abuse were significantly more likely to have developed PTSD 3 months following the rape victims who did not develop PTSD. Cortisol levels shortly after the rape were correlated with histories of prior assaults: the mean initial cortisol level of individuals with a prior assault history was 15 µg/dL compared with 30 µg/dL in individuals without. These findings can be interpreted to mean either that prior exposure to traumatic events results in a blunted cortisol response to subsequent trauma, or in a quicker return of cortisol to baseline following stress. The fact that Yehuda et al. (1995) also found subjects with PTSD to be hyperresponsive to low doses of dexamethasone argues for an enhanced sensitivity of the hypothalamic-pituitary-adrenal (HPA) feedback in traumatized patients.

Serotonin. While the role of serotonin in PTSD has received less systematic attention than the corticoster-
oids, the potential importance of serotonin in PTSD is illustrated both by the fact that inescapably shocked animals are found to have decreased CNS serotonin levels (Valzelli et al., 1982), and that serotonin reuptake blockers are singularly effective pharmacological agents in the treatment of PTSD. Decreased serotonin in humans has repeatedly been correlated with impulsivity and aggression (Brown Coccaro et al., 1979; Mellman and Byers, 1998). The literature tends to readily assume that these relationships are based on genetic traits. However, studies of impulsive, aggressive, and suicidal patients seem to find at least as robust an association between those behaviors and histories of childhood trauma (Green, 1978; Lewis, 1990; van der Kolk and van der Hart, 1991). It is likely that both temperament and experience affect relative CNS serotonin levels (van der Kolk, 1987).

In order to test serotonergic contributions to trauma-related symptomatology, Southwick et al. (1997) administered 1 mg/kg meta-chlorophenylpiperazine (MCPP), a 5-hydroxytryptamine (5-HT) agonist, to 26 Vietnam veterans with PTSD. Thirty-one percent of the subjects experienced a panic attack, and 27% a flashback. These figures are comparable to the effects of the injection of yohimbine, which acts solely on the noradrenergic system. There was almost no overlap between the subjects who had these reactions to MCP and those who had reactions to yohimbine. This suggests that multiple neurotransmitters are involved in these complex PTSD symptoms.

Endogenous opioids. Stress-induced analgesia (SIA) has been described in experimental animals following a variety of inescapable stressors such as electric shock, fighting, starvation, and cold water swimming (Ademac et al., 1980). In severely stressed animals, opiate withdrawal symptoms can be produced both by termination of the stressful stimulus or by naloxone injections. Stimulated by the findings that fear activates the secretion of endogenous opioid peptides, and that SIA can become conditioned to subsequent stressors and to previously neutral events associated with the noxious stimulus, we tested the hypothesis that in people with PTSD, re-exposure to a stimulus resembling the original trauma will cause an endogenous opioid response that can be indirectly measured as naloxone-reversible analgesia (Pitman and Orr, 1990). We found that two decades after the original trauma, people with PTSD developed opioid-mediated analgesia in response to a stimulus resembling the traumatic stressor, which we correlated with a secretion of endogenous opioids equivalent to 8 mg of morphine. Self-reports of emotional responses suggested that endogenous opioids were responsible for a relative blunting of the emotional response to the traumatic stimulus.

TRAUMA AND THE LIMBIC SYSTEM

The limbic system is thought to be the part of the CNS that maintains and guides the emotions and behavior necessary for self-preservation and survival of the species (Maclean, 1985). During both waking and sleeping states, signals from the sensory organs continuously travel to the thalamus whence they are distributed to the cortex (where they affect thinking), to the basal ganglia (where they affect movement), and to the limbic system (where they affect memories and emotions) that determine the emotional significance of the sensory input. Most processing of sensory input occurs outside of conscious awareness, and only novel, significant, or threatening information is selectively passed on to the neocortex for further attention.

People with PTSD tend to overinterpret sensory input as a recurrence of past trauma. Both the previously discussed ERP studies and the recent studies that have shown limbic system abnormalities in brain-imaging studies of patients with PTSD (Saxe et al., 1992; Bremner et al., 1995) may begin to shed light on these attentional problems in people with PTSD. Two particular areas of the limbic system have been implicated in the processing of emotionally charged memories: the amygdala and the hippocampus. Before discussing their possible involvement in the pathophysiology of PTSD, it might be useful to crudely review their functions.

The amygdala

Of all areas in the CNS, the amygdala is most clearly implicated in the evaluation of the emotional meaning of incoming stimuli (LeDoux, 1986). Several investigators have proposed that the amygdala assigns free-floating feelings of significance to sensory input, which the neocortex then further elaborates and imbues with personal meaning (O’Keefe and Bouma, 1969; MacLean, 1985; LeDoux, 1986; Ademac, 1991). Moreover, the amygdala is thought to integrate internal representations of the external world in the form of memory images with emotional experiences associated with those memories (Calvin, 1990). After assigning meaning to sensory information, the amygdala guides emotional behavior by projections to the hypothalamus, hippocampus, and basal forebrain.
Emotional memories are forever

In animals, high-level stimulation of the amygdala interferes with hippocampal functioning (Ademac, 1991). This implies that intense emotions may inhibit the proper evaluation and categorization of experience. In mature animals, one-off intense stimulation of the amygdala will produce lasting changes in neuronal excitability and enduring behavioral changes in the direction of either fight or flight (LeDoux, 1991).

In kindling experiments with animals, Ademac et al. (1980) showed that, following growth in amplitude of amygdala and hippocampal seizure activity, permanent changes in limbic physiology cause lasting changes in defensiveness and predatory aggression. Preexisting ‘personality’ played a significant role in the behavioral effects of amygdala stimulation in cats: animals that are temperamentally insensitive to threat and prone to attack tend to become more aggressive, while in highly defensive animals different pathways were activated, increasing behavioral inhibition (Ademac et al., 1980).

In a series of experiments, LeDoux (1991) has utilized repeated electrical stimulation of the amygdala to produce conditioned fear responses. He found that cortical lesions prevent their extinction. This led him to conclude that, once formed, the subcortical traces of the conditioned fear response are indelible, and that ‘emotional memory may be forever’. LeDoux proposed that intense stimulation of the amygdala could uncouple emotional responses to particular stimuli from the subjective perceptions, and that intense affective stimulation may thus inhibit proper evaluation and categorization of experience. This is in line with the clinical observation that patients with PTSD suffer from impaired cortical control over subcortical areas responsible for learning, habituation, and stimulus discrimination. Decreased inhibitory control may occur under a variety of circumstances: under the influence of drugs and alcohol, during sleep (as in nightmares), with aging, and after exposure to strong reminders of the traumatic past. It is conceivable that traumatic sensations could then be revived, not in the distorted fashion of ordinary recall, but as affect states, somatic sensations, or as visual images (nightmares or flashbacks) that are timeless and unmodified by further experience. The concept of indelible subcortical emotional responses, held in check in varying degrees by cortical and septo-hippocampal activity, has led to speculation that delayed onset PTSD may be the expression of subcortically mediated emotional responses that escape cortical, and possibly hippocampal, inhibitory control (van der Kolk and van der Kolk, 1992).

The hippocampal system

The hippocampal system, which anatomically is adjacent to the amygdala, is thought to record in memory the spatial and temporal dimensions of experience. It plays an important role in the categorization and storage of incoming stimuli in memory. The hippocampus is especially vital to short-term memory, the holding in mind of a piece of information for a few moments, after which it either comes to reside in more permanent memory or is immediately forgotten. Proper functioning of the hippocampus is necessary for explicit or declarative memory (Squire and Zola-Morgan, 1991). Being able to learn from experience depends, at least in part, on smoothly functioning short-term memory processes.

The hippocampus is involved in the evaluation of how incoming input is spatially and temporally related to each other, and with previously stored information. It determines whether and how they are associated with each other, and whether the new stimuli involve reward, punishment, novelty, or non-reward (Gray, 1987; Ademac, 1991). Decreased hippocampal functioning causes behavioral disinhibition and hyperresponsiveness to environmental stimuli (Altman et al., 1973; Shestatzky et al., 1988). The neurotransmitter serotonin plays a crucial role in the capacity of the septo-hippocampal system to activate inhibitory pathways that prevent the initiation of emergency responses until it is clear that they will be of use (Gray, 1987).

In animals, stress-induced corticosterone (Pfaff et al., 1971) decreases hippocampal activity. High levels of circulating glucocorticoids have a significant negative effect on memory, which is thought to be a function of the fact that sustained activation of the glucocorticoid system under conditions of prolonged stress eventually leads to cell death in the hippocampus (Sapolsky et al., 1990; McEwen et al., 1992). This phenomenon has been well demonstrated in patients with Cushing’s disease, a hormonal condition in which tumors in the adrenal or pituitary glands, or corticosteroid drugs used for a prolonged time, cause the adrenal glands to secrete high levels of ACTH and cortisol (Bleuler, 1911). These patients suffer from serious short-term memory problems. MRI studies of patients with Cushing’s disease have shown atrophy and shrinkage of the hippocampus; cortisol levels were proportional to the level of shrinkage (Starkman et al., 1992).
The hippocampus in PTSD

A recent series of studies indicates that people with PTSD have decreased hippocampal volume. Bremner et al. at Yale found that Vietnam combat veterans with PTSD had an 8% reduction in the volume of their right hippocampus, compared with veterans who suffered no such symptoms (Bremner et al., 1995). Stein et al. (1994) found a 7% reduction in hippocampal volume in women with PTSD who had suffered repeated childhood sexual abuse, while Gurvitz and Pitman of Harvard found that Vietnam veterans with PTSD had an 8% reduction in the volume of their right hippocampus, compared with veterans who saw combat but had no symptoms (Gurvitz et al., 1995).

Shrinkage in the hippocampus suggests a loss of cell mass. Whether the loss is due to the atrophy of dendrites or actual cell death is not yet known. On a test of verbal memory, Bremner’s veterans performed 40% worse than did people of comparable age and education. Exposure to trauma is not the only explanation for these findings: it is conceivable that people with a smaller hippocampus are most vulnerable to developing PTSD. However, a more likely explanation is that the shrinkage in the hippocampus is due to the effects of heightened levels of cortisol which is known to be toxic to the hippocampus.

The amygdala in PTSD

We recently collaborated in a positron emission tomography (PET) study of patients with PTSD in which they were exposed to vivid, detailed narratives of their own traumatic experiences (Rauch et al., 1996). We read the narratives we collected from these subjects with PTSD back to them, which precipitated marked autonomic responses and triggered flashbacks. When this occurred a scan was made. For comparison, the subjects also wrote narratives that invoked a neutral scene. During exposure to the script of their traumatic experiences, these subjects demonstrated heightened activity only in the right hemisphere: in the paralimbic belt, parts of the limbic system connected with the amygdala. Most active were the amygdala, the insular cortex, the posterior orbitofrontal cortex, the anterior cingulate cortex, and the anterior temporal cortex. Activation of these structures was accompanied by heightened activity in the right visual cortex, reflecting the visual re-experiencing of the trauma that these patients reported. Perhaps most significantly, Broca’s area ‘turned off.’ We believe that this reflects those patients’ tendency to experience emotions as physical states rather than as verbally encoded experiences. This seems to indicate that the difficulties of patients with PTSD in putting feelings into words is mirrored by actual changes in brain activity.

Lateralization

Striking in this study was the marked lateralization towards the right hemisphere, which is thought to be related to evaluating the emotional significance of incoming information and in regulating autonomic and hormonal responses to these incoming stimuli. In contrast, Broca’s area, the part of the left hemisphere responsible for translating personal experiences into communicable language, had a significant decrease in oxygen utilization during exposure to traumatic reminders. This probably means that during activation of the traumatic memory, the brain is ‘having’ its experience: the person may feel, see, or hear the sensory elements of the traumatic experience. He or she may be physiologically impaired from being able to translate this experience into communicable language: when they are having their traumatic recall, victims may suffer from speechless terror in which they may be literally ‘out of touch with their feelings.’

Our data revealed a marked asymmetry in lateralization in the direction of the right hemisphere while the traumatic memories were activated. The ability of trauma to disrupt the functional integration of these widespread cortical and subcortical regions is supported by the findings of Teicher’s EEG study of sexually abused children (Teicher et al., 1997). In these children, there was a loss of the normal synchronization between the electrical activity of the different cortical areas. This indicates a loss of function associated with the integration of distributed cortical activity. There is some evidence to suggest that the dominant hemisphere is more sensitive to cortico-cortical uncoupling. Thatcher et al. (1987) and Teicher et al. (1997) found that EEG disruption was particularly prominent in the left hemisphere. It is generally understood that, while the left hemisphere is specialized in cognitive analysis and language production, the right hemisphere plays a central role in the perception and expression of emotion, particularly of negative emotion (Ross and Mesulam, 1979; Silberman and Weingartner, 1986; Tomarken et al., 1992). The right hemisphere is thought to be able to maintain a social-emotional system that can independently recall and act on certain memories and perceptions without
the active participation of the left hemisphere (Joseph, 1988). Our data provide a possible neurobiological underpinning of our (van der Kolk and Ducey, 1989) comments on the psychological processing in men with PTSD: ‘these patients are unable to integrate the immediate affective experience with the cognitive structuring of experience. Lack of integration resulted in extreme reactivity to the environment without intervening reflection’ (p. 272). This finding mirrors the clinical observation that abused children have significant problems in the dominant hemisphere function of language development. The problems that abused children have as adults recalling historical information is probably another clinical correlate of this problem (van der Kolk and Fisler, 1995).

The twice replicated finding that people with chronic PTSD have decreased hippocampal volume might explain some of the behavioral abnormalities seen in people with chronic PTSD. It is likely that the decreased size of the hippocampus in PTSD is a long-term effect of intrusive reliving of the trauma in the body and mind, and that this decreased volume may, at least in part, be responsible for the ongoing dissociation and misinterpretation of information in the direction of threat, as has been noted in patients with PTSD. In animals, decreased hippocampal functioning has been shown to cause behavioral disinhibition (Gray, 1987). It is thought that this plays a role in helping the animal define incoming stimuli in the direction of emergency (fight/flight) responses. If the same is true for people, this might explain why patients with PTSD have difficulties ‘taking in’ and processing arousing information, and to learn from such experiences. Their altered biology would make them vulnerable to react to newly arousing stimuli as a threat, and to react with aggression, or withdrawal, depending on their premorbid personality (Ademac, 1991).

Aside from the putative relationship between chronically high levels of cortisol and neurotoxicity to hippocampal cells, research has shown that high levels of stimulation of the amygdala can also interfere with hippocampal functioning (Ademac, 1991; Squire and Zola-Morgan, 1991). Thus, high levels of emotional arousal may prevent the proper evaluation and categorization of experience by interfering with hippocampal function. I have previously hypothesized that, when this occurs, sensory imprints of experience are stored in memory, but because the hippocampus is prevented from fulfilling its integrative function, these various imprints are not united into a unified whole (van der Kolk, 1994). The experience is laid down, and later retrieved, as isolated images, bodily sensations, smells, and sounds that feel alien, and separate from other life experiences. Some integrative function seems to break down. The interferes with the localization of incoming information in time and space. It is possible that a less functional hippocampus plays a role in the continued fragmentation of experience in PTSD.

**Hemispheric lateralization**

The finding of marked hemispheric lateralization in subjects exposed to their personalized trauma scripts indicates that there is differential hemispheric involvement in the processing of traumatic memories. This finding has major implications for understanding the nature of PTSD. The right hemisphere, which developmentally seems to come ‘on-line’ earlier than the left hemisphere, is involved in the expression and comprehension of global nonverbal emotional communication (tone of voice, facial expression, visual/spatial communication). The early maturation of the right hemisphere is consistent with the importance of emotional communication early in life. The right hemisphere has a diffuse representational format, which allows for a dynamic and holistic integration across sensory modalities (Davidson and Tomarken 1989). While this hemisphere may be exquisitely sensitive to emotional nuances, it has, at best, a rudimentary capacity to think or communicate analytically, to employ syntax, or to reason.

In contrast, the left hemisphere is thought to organize problem-solving tasks into a well-ordered set of operations and to process information in a sequential fashion. It is involved in perceiving and in the generation of symbolic representation by breaking down a stimulus into categorical elements and combining them into novel images: it manipulates words and symbols that transcribe personal experience into culturally shared meaning. The labeling of perceptions is a left hemisphere function (Davidson and Tomarken 1989). It is in the area of categorization and labeling of internal states that people with PTSD seem to have particular problems (Krystal, 1978; van der Kolk and McFarlane, 1996).

It is conceivable that failure of left hemisphere function during states of extreme arousal is responsible for the derealization and depersonalization reported in acute PTSD (Marmar et al., 1996; Shalev et al., 1996). In our brain scans we saw that, during exposure to a traumatic script, there was decreased functioning of Broca’s area. This would make it difficult for a traumatized individual to ‘understand’ what is going on: they experience intense emotions without
being able to label their feelings. Their bodies are aroused, and fragments of memories may be activated, but they often are unable to communicate what they are experiencing. A relative decrease in left hemispheric representation provides an explanation of why traumatic memories are experienced as timeless and ego-alien: the part of the brain necessary for generating sequences and for the cognitive categorization of experience is not functioning properly. Our research (Rauch et al., 1996) indicates that during activation of the traumatic memory, the brain is ‘having’ its experience. The person may feel, see, or hear the sensory elements of the traumatic experience, but he or she may be physiologically prevented from being able to translate this experience into communicable language: when they are having their traumatic recall, victims may suffer from speechless terror in which they may be literally ‘out of touch with their feelings.’ Physiologically, they may respond as if they are being traumatized again, but this may be dissociated from subjective experience. If the victim experiences depersonalization and derealization he cannot ‘own’ what is happening, and thus cannot take steps to do anything about it.

Psychopharmacological interventions in PTSD

Given the recognition that PTSD is a ‘physioneurosis,’ a disorder which patients themselves tend to experience as a disruption of their physical equilibrium and well-being, it is not surprising that people with PTSD have extensively used both medication and illegal substances to reduce their distress. In an apparent effort to regulate their hyperarousal and other PTSD-related problems, these patients have high rates of self-medicating: among treatment-seeking patients, 60–80% suffer from alcohol or drug abuse and dependency (Keane et al., 1988). Opioids, alcohol, and benzodiazepines tend to be preferred as the drugs of choice (Bleuler, 1911).

Just about every group of psychotropic agents has been claimed to be effective for the treatment of some aspect of PTSD symptomatology. However, there have been very few basic studies that can help us understand how various pharmacological agents might be effective in the treatment of PTSD. For example, to date, there exist no neuroimages to demonstrate how various agents act on the limbic system. Thus, while the serotonin reuptake blockers are frequently found to be effective in the treatment of PTSD, we have no notion whether their positive effects are, at least in part, due to an inhibition of amygdala activation in response to traumatic reminders.

Only very few agents have been systematically studied. Most studies have been on male combat veterans who suffered from chronic PTSD which they first developed as adults. One of our studies (van der Kolk et al., 1994) showed a marked difference in responsiveness to fluoxetine between a combat veteran population and a sample of nonveterans with PTSD. That study raised serious concerns that the studies of the effects of medication in combat veterans may not be generalizable to nonveteran populations.

Since double-blind studies are enormously expensive in terms of time and money, only a few drugs have been exhaustively studied. Which drug is selected is often not primarily a function of clinical promise, but of availability of funding and interest by investigators. The fact that a particular drug has been proven to be effective in a double-blind study only means that it is more effective than placebo in a particular patient population, within which some patients are likely to have responded better than others. The fact that a particular drug’s efficacy has been demonstrated in a controlled study does not mean that that drug is necessarily more effective than the ones that have not been tested.

RATIONALE: THE PURPOSE OF MEDICATION IN PTSD

Since PTSD is a complex disorder, with a host of symptoms, some of which are included within the core definition (intrusions, numbing/avoidance/arousal), and others, which almost invariably occur in the same patients (depression, aggression against self or others), somewhat arbitrarily defined as ‘comorbid’ conditions, patients with this disorder may have a great diversity of target symptoms:

(1) intrusive symptoms;
(2) tendency to interpret incoming stimuli as recurrences of the trauma;
(3) generalized hyperarousal;
(4) conditioned hyperarousal to stimuli reminiscent of the trauma;
(5) depressed mood, numbing, and demotivation;
(6) avoidance behavior;
(7) dissociative symptomatology; and
(8) impulsive aggression against self and others.

Intrusive reexperiencing

Intrusion of the trauma is manifested as flashbacks, affective states, somatic sensations, nightmares, and
interpersonal re-enactments. Autonomic arousal can, in state-dependent fashion, precipitate flashback phenomena (Rainey et al., 1987; Southwick et al., 1991). Drugs that decrease autonomic arousal, including the benzodiazepines, β-adrenergic blockers, and clonidine are generally thought to be effective for these symptoms. The only empirical study in which acutely traumatized people were medicated with benzodiazepines in order to prevent kindling from chronic trauma-induced hyperarousal had negative results: Shalev and his colleagues gave alprazolam to a group of acutely traumatized patients and compared them with an unmedicated control group. The alprazolam group had more PTSD symptomatology at 6 months’ follow-up (Shalev, personal communication, 1995).

Reducing the tendency to interpret incoming stimuli as recurrences of the trauma
Clinical experience and psychological testing show that traumatized individuals tend to overinterpret incoming stimuli as reminders of the trauma. It is as if their trauma-related associative networks are extraordinarily sensitive to be activated by even the slightest trigger that matches an element of the trauma. Fluoxetine has been shown to be able to significantly decrease people’s propensity to interpret sensory stimuli as a recurrence of the trauma and to increase their capacity to use cognitive functions to interpret affectively laden issues (van der Kolk, 1994).

Reducing generalized arousal
Autonomic arousal, which serves the essential function of alerting the organism to potential danger, loses that function in people with PTSD: the easy triggering of somatic stress reactions causes them to react to any number of sensory stimuli as an impending threat. This loss of neuromodulation leads to loss of affect regulation. Traumatized people tend to experience intense fear, anxiety, anger, and panic in response to even minor stimuli. This makes them either overreact and intimidate others, or to shut down and freeze. Both adults and children with such hyperarousal are vulnerable to experiencing sleep problems, both because they are unable to calm themselves sufficiently to go to sleep, and because they may be fearful to having traumatic nightmares. In clinical practice, the serotonin re-uptake blockers seem to be quite effective in helping people with PTSD deal with these symptoms. The benzodiazepines are also widely used in clinical practice, even though they have not been proven to be effective in reducing PTSD symptomatology.

Reducing conditioned arousal
People with PTSD tend to deal with their environment by emotional constriction. Over time, numbing may become the most troublesome symptom of PTSD, a symptom that often is confused with depression. However, clinical studies have shown that PTSD-related numbing and depression appear to be different psychopathological entities: while the dexamethasone test shows a blunted cortisol response, their physiological responses are conditioned to react to reminders of the trauma as an emergency. Reminders of the trauma may activate autonomic arousal, while, conversely, arousal itself may trigger memories of traumatic experiences. Excessive reactions that are irrelevant to present demands probably play a major role in making PTSD patients avoid reminders of the trauma and consequently constrict their involvement in their surroundings. Hyperarousal interferes with the capacity to put experience into words, and is likely to result in the discharge of emotional tensions, or in self-medication with drugs or alcohol. Benzodiazepines, as well as alcohol, have been shown to decrease conditioned arousal in both animals and humans.

Depression and numbing
Most people with PTSD also meet diagnostic criteria for depression (Davidson et al., 1985). However, the depression associated with PTSD appears to be psychologically and biologically distinct from major depression occurring without PTSD and is more resistant to standard antidepressant agents (Southwick et al., 1991). One recent study (van der Kolk, 1994) showed that depression and numbing show a differential treatment response: even when depression was effectively treated with fluoxetine, numbing persisted.

Numbing is one of the most intractable PTSD symptoms – many people who stop suffering from intrusions of the trauma continue to feel unmotivated and ‘dead to the world.’ In contrast with the intrusive PTSD symptoms, which occur in response to outside stimuli, numbing is part of these patients’ baseline functioning. Emotional numbness also gets in the way of resolving the trauma in psychotherapy, since the inability to imagine a future impairs the capacity to look for new solutions.
Avoidance behavior
The emotional and cognitive constriction seen in PTSD cuts off the individual’s access to an inner world of fantasy and symbols. Avoidance behavior is likely to lift once people with PTSD become aware that they are less sensitive to environmental triggers. After effective treatment for generalized and specific hyperarousal, the focus of treatment may require shifting to any remaining phobic avoidance.

Reduction in dissociative symptoms
Intrusive re-experiences, particularly in patients who are victims of childhood trauma, and who continue to dissociate, may be so vivid that patients are unable to distinguish them from reality. They are, however, different from psychotic symptoms in a classical sense, because these patients seem to be re-experiencing actual traumatic events. The hallucinations and delusions seen in flashbacks may be better conceptualized as dissociative phenomena. This raises intriguing questions about the possibility of differentiating between schizophrenic hallucinations and dissociative symptoms in patients with chronic mental illness with severe childhood abuse experiences. For example, in light of our new understanding of flashbacks of childhood traumatic experiences, it might be useful to re-evaluate the meaning and treatment of the following observation by Bleuler (1911): ‘Among schizophrenic body hallucinations, the sexual ones are by far the most frequent and the most important. All the raptures and joys of normal and abnormal sexual satisfaction are experienced by these patients, but even more frequently every obscene and disgusting practice which the most extravagant fantasy can conjure up. Male patients have their semen drawn off; painful erections are stimulated. The women patients are raped and injured in the most devilish ways . . . in spite of the symbolic meaning of many such hallucinations, the majority correspond to real sensations’ (p. 102).

Patients who have learned to dissociate in response to trauma are likely to continue to utilize dissociative defenses when exposed to new stresses. They develop amnesia for some experiences, and tend to react with fight or flight responses to feeling threatened, neither of which may be consciously remembered afterwards. People who suffer from dissociative disorders are both a clinical and a research challenge. Traditionally, these symptoms were thought to respond poorly to antipsychotic medication (Loewenstein et al., 1988; Putnam 1989). However, we have had some good results with the newer antipsychotic agents, such as risperidone and zyprexa.

Reducing impulsive aggressive behavior against self and others
Numerous studies have demonstrated that both adults and children who have been traumatized are likely to turn their aggression against others or themselves. Problems with aggression against others have been particularly well documented in war veterans, traumatized children, and in prisoners with histories of early trauma (Lewis, 1990, 1992). Because self-destructive behavior is associated with decreased serotonin function (Brown et al., 1979; Coccaro et al., 1989), fluoxetine and other serotonergic agonists should theoretically be effective. This has not as yet been documented. Carbamazepine has been shown to be effective for treatment of self-destructive behaviors in patients with borderline personality disorder (Cowdry and Gardner, 1998). One study showed that lithium carbonate can be helpful (Wickman and Reed, 1987), while opiate receptor blockers have been found to decrease self-destructive behaviors in other populations (Herman et al., 1987).

Efficacy of drug groups
Only a few psychotropic drug categories have been systematically evaluated in PTSD. Several reasons may explain this finding including firstly the question of nosology. As we have already seen in the introduction, the clinical description of the so-called PTSD is not recent. However, the first clear-cut definition of the disorder, from a nosological point of view, was made less than 20 years ago in DSM III. It is even more recently, in DSM IV, that Acute stress disorder was first isolated as a relevant diagnosis. As a consequence, in the group of antidepressants, there are fewer studies with older antidepressants, such as monoamine oxidase inhibitors (MAOIs) or tricyclics than with more recent drugs, such as selective serotonin reuptake inhibitors (SSRIs). Most of these studies have not been controlled and were conducted with war veterans, who may respond differently to medications than other traumatized populations. The medications most closely examined have been the MAOIs, tricyclics, SSRIs, and, to a lesser extent, anticonvulsants, β-blockers, and α2-adrenergic agonists.

MAO inhibitors
Historically, the MAOIs were the first to be studied in detail. However, few clinicians these days use
traditional MAOIs anymore. There have been two double-blind trials of MAOIs, by Kosten et al. (1991) and Shestatsky et al (1988). In the first study, MAOIs produced approximately a 50% reduction in intrusive and avoidance symptoms in a relatively short period of time. The second study of phenelzine produced negative results. Available research suggests that phenelzine probably is more effective than imipramine (Kosten et al., 1991).

**Tricyclic drugs**

There have now been three double-blind trials with tricyclic antidepressants: amitriptyline (Davidson et al., 1990, 1993), imipramine (Kosten et al., 1991), and desipramine (Reist et al., 1989). All these studies were conducted in male combat veterans, with the amitriptyline study being conducted in a mixed inpatient and outpatient population. Amitriptyline was more effective than placebo on a variety of measures, including PTSD, depression, and anxiety. It appears that the drug effects were most significant in less severely ill patients: impaired concentration, somatic anxiety, and guilt feelings all predicted a poorer response to amitriptyline. A study of desipramine by Reist et al. (1989) showed no efficacy.

**Selective serotonin reuptake inhibitors (SSRI)**

Fluoxetine has been reported to reduce symptoms of PTSD in a number of open studies (Davidson et al., 1991; Nagy et al., 1993). Van der Kolk et al. (1994) have published a double-blind fluoxetine vs placebo study of subjects drawn both from a Veterans Administration (VA) clinic and a civilian outpatient Trauma Clinic (TC). This was a 5-week trial, using maximum doses of 60 mg fluoxetine, although this dose was only needed in some instances. Twelve males and 21 females were recruited through the Trauma Clinic, while 30 male war veterans and one female war veteran came from the Veterans Administration Clinic. Fluoxetine significantly decreased overall PTSD symptomatology, though site (Trauma Clinic vs VA) made a more significant difference than did administration of the drug. Basically, the fluoxetine failed to work in the VA group, while the Trauma Clinic group proved to be very responsive to being in the study, with both the placebo and the fluoxetine group improving significantly. However, fluoxetine was significantly more effective in that population than was placebo. The PTSD symptoms of numbing and arousal were most affected by fluoxetine.

Interestingly, while fluoxetine was a very effective antidepressant, improvement in depression did not predict improvement in PTSD score, not even in numbing. While there was substantial improvement in depression in the VA sample, there was no meaningful change in numbing symptoms. Conversely, while the TC sample had a more modest improvement in depression, it had a substantial improvement in numbing symptoms. When numbing symptoms were separated from the avoidance, fluoxetine turned out to only affect numbing. It is likely that 5 weeks of improvement of PTSD symptomatology is insufficient for people to realize that exposure to stimuli reminiscent of the trauma will not lead to overwhelming distress. A longer trial might demonstrate whether, over time, patients feel better able to face trauma-related stressors, and thus develop a decrease in avoidant symptoms, as well.

Since most previous controlled studies were done on veterans, it is difficult to generalize from this study about the overall superiority of one drug over another. The civilian TC sample improved more in 5 weeks on fluoxetine than any of the veteran groups who had been studied on any of the other drugs over a longer period of time. However, the veterans on weeks of fluoxetine did not nearly have the same beneficial effects as the veterans in other studies who had been maintained on imipramine, amitriptyline, or phenelzine over longer periods of time. Whether a longer trial on fluoxetine would have allowed the veterans to catch up with the TC civilians, or with the veterans in others studies clearly would be an important issue to investigate further.

This study showed that numbing and depression do not measure overlapping psychological categories: while the VA sample became much less depressed on fluoxetine, there was no meaningful change in numbing symptoms. In contrast, the TC sample showed substantial improvement in both numbing and depression. Thus, the beneficial effect of fluoxetine on PTSD is not necessarily a function of its antidepressant effects.

Recent open-label studies of sertraline in rape victims (Rothbaum et al., 1996), fluvoxamine in combat veterans (Marmar et al., 1996), paroxetine in a mixture of rape, assaults and motor vehicle accidents (Marshall et al., 1996) demonstrated a positive impact on PTSD symptoms by these drugs. A recent study by Klein (1994) suggests that sertraline also is of benefit in PTSD. Other serotonergic agents, nefazodone (an SSRI plus 5-HT2 antagonist) (Hertzberg et al., 1998), and trazodone (also an SSRI plus 5-HT2 antagonist) (Hertzberg et al., 1996), have
been shown to have some benefits in open-label studies.

**Anticonvulsants**

A variety of anticonvulsant agents have been studied in open-label studies. In five studies, carbamazepine produced reductions in re-experiencing and arousal symptoms, while in three studies, valproate reduced numbing and arousal, but not re-experiencing. Studies by Lipper et al. (1986) and Wolf et al. (1988) both suggest that carbamazepine may have beneficial effects in chronic PTSD. Fesler (1991) found similar results with valproate. No double-blind trials of anticonvulsants have, as yet, been conducted in PTSD. These drugs, including the new anticonvulsant gabapentin, deserve further close attention for the treatment of chronic PTSD and dissociative disorders.

**Benzodiazepines**

While there are only three publications on benzodiazepine treatment for PTSD, none of which demonstrated improvement in PTSD symptomatology, benzodiazepines are widely used in clinical practice. In open trials utilizing alprazolam and clonazepam, patients reported improvement in their sleep, and a reduction in anxiety and irritability. However, in people with acute stress disorder, Mellman et al. (1998) found that benzodiazepine treatment had markedly positive effects on the development of PTSD symptomatology. It is worthy of note that Vargas et al. (1992) showed that acute administration of adinazolam and alprazolam leads to a decrease in locus coeruleus CRF concentrations. This supports the use of benzodiazepines to suppress kindling. The use of benzodiazepines in PTSD is further supported by two open studies of alprazolam (Dunner et al., 1985) and clonazepam (Loewenstein et al., 1988).

**β-Blockers**

Propranolol has been found to be effective in two open studies for PTSD. Kolb et al. (1984) used 20–160 mg per day in 12 Vietnam combat veterans with positive results. Improvement was noted in intrusive recollections, nightmares, sleep impairment, hyperalertness, explosiveness, and startle symptoms. Depression, poor memory, tiredness, Bradycardia, lowering of blood pressure, impaired sexual functioning, and confusion have been reported as side effects. Famularo et al. (1988) used propranolol in children with acute PTSD following physical or sexual abuse. Propranolol was reported to improve hyperarousal in these children.

**Antipsychotics**

Two open studies have explored clozapine (Hamner, 1996) and thioridazine (Dillard et al., 1993) for treatment-resistant PTSD patients. Clinical experience has shown that severe dissociative symptoms may respond well to a low dose of the newer neuroleptics, such as risperidone, zyprexa, or seroquel.

**CONCLUSIONS**

Over the last 10 years there has been growing interest in the neurobiology and psychopharmacological treatment of PTSD. Different models which have been advanced to explain the mechanisms of PTSDs also lend themselves to understanding how certain medications may work, as well as serving to guide possible treatment selection according to symptomatology. At the present time, it appears that acute trauma is best treated with any of the drugs that decrease autonomic arousal, including benzodiazepines or clonidine. In this population, it is probably critical to provide a way to avoid nightmares and other intrusive symptoms, in order to prevent kindling of the trauma. Theoretically, anticonvulsants might also be of use, but these have not been tried.

Once people have developed PTSD, one would initially select either an SSRI or a tricyclic drug, with a willingness to introduce a second drug, either an anticonvulsant, mood stabilizer, or benzodiazepine after a few weeks if response is only partial. Choice of the second drug would be guided largely by the symptom profile. In chronic PTSD, in which patients tend to have complex symptom profiles, it is useful to keep abreast of emerging studies of symptoms such as aggression, impulsivity, and self-destructive behavior. At this point, there is no evidence that any drug is particularly effective in the treatment of dissociative phenomena.
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