Toxicology and Industrial Health

AN INTERNATIONAL JOURNAL

PROCEEDINGS OF THE CONFERENCE ON LOW-LEVEL EXPOSURE TO CHEMICALS AND NEUROBIOLOGIC SENSITIVITY

6–7 April, 1994
Baltimore, Maryland

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Sponsored by:
U.S. Department of Health and Human Services
Public Health Services
Agency for Toxic Substances and Disease Registry

Published by:
Princeton Scientific Publishing Co., Inc.
Princeton, New Jersey

NEUROBIOLOGICAL SENSITIZATION MODELS OF POST-TRAUMATIC STRESS DISORDER: THEIR POSSIBLE RELEVANCE TO MULTIPLE CHEMICAL SENSITIVITY SYNDROME

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Neurological sensitization has been proposed as a model for post–traumatic stress disorder (PTSD) (Lipper et al., 1986; van der Kolk, 1987; Friedman, 1988; Post et al., 1988, 1994; Charney et al., 1993). Laboratory paradigms in which repeated exposure to a discrete stimulus is associated with progressive intensification of a neurophysiologic, behavioral, or pharmacologic response has many parallels with the sequence of events that precipitates PTSD.

Investigators with other clinical interests have also been attracted to sensitization models. Specifically, Bell and associates (1992) have proposed that olfactory-limbic kindling is a very good model for understanding the etiology of multiple chemical sensitivity (MCS) syndrome. A number of articles in this volume have addressed the goodness-of-fit between this model and MCS.

My major assignment is to review laboratory data and clinical observations pertinent to sensitization models of PTSD. I will show that although there are intriguing parallels between the two phenomena, one must have great respect for the complexity and polymorphism of both sensitization and PTSD before grasping for simplistic theoretical conclusions. Secondly, I will address the following question; if both PTSD and MCS can be understood as sensitization phenomena, are PTSD patients at greater risk to develop MCS and vice versa? This article is divided into four sections: a) a description of three distinct sensitization phenomena; b) a description of the symptoms of PTSD; c) a review of the applicability of sensitization models to the clinical phenomenology of PTSD; and d) a review of the hypothesis that PTSD patients might be more vulnerable to MCS.

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Toxicology and Industrial Health, Vol. 10, No. 4/5, pp. 449–462
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ISSN: 0748-2337

NEUROBIOLOGICAL SENSITIZATION

It is essential to state at the outset that there are at least three sensitization phenomena that have been proposed as suitable models for PTSD: behavioral sensitization, time dependent sensitization, and kindling (Charney et al., 1993; Yehuda and Antelman, 1993; Post et al., 1994). A thorough description of each of these phenomena is far beyond the scope of this article and the reader is referred to excellent reviews of this topic (Antelman, 1988; Charney et al., 1993; Post et al., 1988, 1994). Behavioral sensitization can be produced by repeated exposure to a noxious environmental stimulus or a psychomotor stimulant such as cocaine. With repeated exposure, responses are enhanced progressively so that a stimulus that initially produced little, if any, response can subsequently produce profound effects. The outcome variable is frequently behavioral, such as locomotor activity (see Post et al., 1988) but it can also be pharmacological, such as dopamine or norepinephrine release in discrete brain areas (Anisman and Sklar, 1978; Kalivas and Duffy, 1989). Although behavioral sensitization has been studied most extensively in adrenergic and dopaminergic systems, a large number of brain structures and neurochemical systems have been implicated (Charney et al., 1993). As noted by Post et al. (1988), these are characteristics of behavioral sensitization: 1) shorter latency of response; 2) increased magnitude of response; 3) sensitized responsivity persists for weeks or months; 4) effects are dose related; 5) intermittent stimulus administration produces greater sensitization, compared with continuous administration; 6) genetic factors may influence sensitization; 7) sensitization shows environmental context dependency, i.e., it is conditionable; 8) cross-sensitization occurs with many psychomotor stimulants and dopamine agonists; 9) cross-sensitization occurs between stimulants and a variety of stressors (such as tail-pinch, shock, and starvation).

Time is a crucial factor. Behavioral sensitization does not appear immediately after exposure to the sensitizing stimulus, but only after the passage of a sufficient interval of time. The most extreme example that proves the point is the phenomenon discovered and named by Antelman (1988) as time-dependent sensitization (TDS). In TDS, behavioral sensitization can be detected following exposure to only one sensitizing stimulus provided that sufficient time has elapsed between initial exposure and subsequent testing. For purposes of discussion, I will consider TDS a special subtype of behavioral sensitization in which only one, rather than a sequence, of stimulus presentations is needed to produce a sensitized response. This distinction will be useful when we discuss the applicability of these models to PTSD.

The final sensitization model is kindling. Here the endpoint is seizure activity rather than a behavioral response, and the abnormalities preceding actual seizure induction are neurophysiologic such as increased spike magnitude. First described by Goddard et al. (1969), kindling is produced by repeated electrophysiological stimulation of a given brain area (such as the amygdala) on an intermittent basis. The stimulus is kept constant and produces no observable effects during the initial presentation. With repeated stimulation, animals exhibit a progressively widespread electrophysiological effect and marked behavioral effects until the previously ineffective stimulus precipitates a full-fledged major motor seizure. Post and

associates (1988) have produced a similar sequence of events using pharmacological rather than electrophysiological stimuli. A variety of diverse pharmacological agents can kindle seizures, including local anesthetics (lidocaine), stimulants (cocaine), cholinergic agonists (physostigmine), GABA antagonists (bicuculline), benzodiazepine inverse agonists (FG-7142), peripheral-type benzodiazepine ligands (Ro5-4864), endogenous opiates (beta-endorphin, enkephalin), and corticotropin-releasing hormone (CRH). It should be noted parenthetically that many of those substances are thought to have profound effects on the major neurobiologic systems involved in the organism's response to stress (see Friedman et al., 1995). Other important characteristics of kindling (see Post et al., 1988) are: 1) the limbic system kindles more readily than the cortex; 2) no toxic or neuropathological changes are evident: kindling is a transsynaptic process; 3) kindling persists: animals will continue to have seizures after a one-year seizure-free interval; 4) interictal spikes and spontaneous epileptiform potentials develop; 5) seizures may develop spontaneously in chronically kindled animals; and 6) the efficacy of pharmacological interventions differs as a function of the stage of kindling (i.e., developing, completed, spontaneous).

Before ending this section, it is important to note that there is some overlap between these three mechanisms of sensitization. Most notably, cocaine can produce behavioral sensitization, TDS, or kindling, depending on the experimental protocol in which it is administered. Furthermore, there may be overlapping synaptic, transsynaptic, and genomic mechanisms by which each is produced. (See Post et al., 1995, for a full discussion of these issues.) Finally, TDS can be considered a special subtype of behavioral sensitization. There are also important differences. TDS alone can produce sensitization after only one exposure to the stimulus. Only kindling can result in spontaneous effects after stimulus-induced seizures have become well established. These facts all have important implications for the applicability of sensitization models to PTSD.

POST–TRAUMATIC STRESS DISORDER

Post–Traumatic Stress Disorder (PTSD) is a psychiatric syndrome that develops when people are exposed to catastrophic stressors such as war, torture, rape, genocide, nuclear attack, natural or industrial disasters, and airplane or motor vehicle accidents. Such events are considered qualitatively and quantitatively different from the painful stressors that constitute the normal vicissitudes of life such as divorce, failure, rejection, serious illness, financial reverses and the like. Diagnostic criteria for PTSD were first proposed in 1980 in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III). They have been revised twice, most recently in the DSM-IV (American Psychiatric Association, 1994). As shown in Table 1, DSM-IV criteria for PTSD consist of exposure to a traumatic event, intrusive recollections of the event, trauma-related avoidant/numbing symptoms, hyperarousal symptoms, a minimum duration of disturbance and significant functional impairment.

The prominence of traumatic stress as an etiological factor distinguishes PTSD from most other psychiatric disorders. In their review of animal literature pertinent to PTSD, Foa and colleagues (1992) have proposed that, in contrast to a normal stressor, a traumatic stressor is one which is both uncontrollable and unpredictable. Indeed, the PTSD syndrome is based on an explicit stimulus-response causal relationship between traumatic exposure and subsequent psychopathology. This is best illustrated by the "B," or intrusive recollection, cluster of symptoms. For individuals with PTSD, the traumatic experience is an overwhelming event that retains its power to evoke panic, terror, dread, grief, or despair, as manifested in daytime fantasies, traumatic nightmares, and psychotic reenactments known as PTSD flashbacks. Traumamimetic stimuli that trigger recollections of the original event have the power to evoke mental images, emotional responses, and psychological reactions associated with the trauma. Researchers taking advantage of this phenomenon can reproduce PTSD symptoms in the laboratory by exposing affected individuals to auditory or visual traumamimetic stimuli (Keane et al., 1987). Indeed, as shown in Table 1, intrusive recollections may occur in response to such stimulation (symptoms B_4 and B_5) or they may occur spontaneously (symptoms B_1-B_3). PTSD patients often feel that their intrusive recollections have a life of their own and that they appear with or without exposure to traumamimetic stimuli. In this regard they resemble the relentless bombardment of obsessional thoughts experienced by individuals with obsessive-compulsive disorder.

The "C," or avoidant/numbing, criterion includes symptoms that reflect behavioral, cognitive, or emotional strategies by which PTSD patients attempt to avoid exposing themselves to disturbing traumamimetic stimuli, or if exposed, strategies by which they attempt to minimize the impact of such exposure. PTSD patients often feel powerless to master trauma-related thoughts, feelings, and actions that they experience as unwanted and intolerable.

The "D," or hyperarousal, criterion includes symptoms seen in other anxiety disorders such as insomnia and irritability, as well as symptoms such as hypervigilence and startle which are more specific to PTSD. The hypervigilence in PTSD may sometimes be so extreme that it appears to be paranoid behavior. The startle response has a unique neurobiological substrate and may be one of the most pathognomonic PTSD symptoms. Animal and human studies with fear-potentiated startle paradigms have suggested that this may be a very useful animal model for PTSD (Davis, 1990). Other criteria concerning duration of symptoms and functional impairment are as specified in Table 1.

APPLICABILITY OF SENSITIZATION MODELS TO PTSD

Post and Kopanda (1976; Post, 1977) were the first to propose that a kindling mechanism might produce a psychiatric disorder. Extrapolating from research with cocaine, they suggested that neuroanatomic structures in the limbic system might become increasingly sensitized following repeated stimulation with cocaine-like drugs, thereby producing

Table 1. DSM-IV Criteria for PTSD

A. The person has been exposed to a traumatic event in which both of the following have been present:
   1. the person has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others.
   2. the person's response involved intense fear, helplessness, or horror. Note: in children, it may be expressed instead by disorganized or agitated behavior

B. The traumatic event is persistently reexperienced in at least one of the following ways:
   1. recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. Note: in young children, repetitive play may occur in which themes or aspects of the trauma are expressed
   2. recurrent distressing dreams of the event. Note: in children, there may be frightening dreams without recognizable content
   3. acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when in toxicated). Note: in young children, trauma-specific reenactment may occur
   4. intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
   5. physiologic reactivity upon exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by at least three of the following:
   1. efforts to avoid thoughts, feelings, or conversations associated with the trauma
   2. efforts to avoid activities, places, or people that arouse recollections of the trauma
   3. inability to recall an important aspect of the trauma
   4. markedly diminshed interest or participation in significant activities
   5. feeling of detachment or estrangement from others
   6. restricted range of affect (e.g., unable to have loving feeelings)
   7. sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)

D. Persistent symptoms of increasing arousal (not present before the trauma), indicated by at least two of the following:
   1. difficulty falling or staying asleep
   2. irritability or outbursts of anger
   3. difficuly concentrating
   4. hypervigilance
   5. exaggerated startle response

E. Duration of the disturbance (symptoms in B, C, and D) is more than one month.

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

   Specify if: **Acute:** if duration of symptoms is less than three months
   Chronic: if duration of symptoms is three months or more

   Specify if: **With delayed onset:** onset of symptoms at least six months after the stressor

behavioral abnormalities resulting in psychopathology. These observations were extended to consider a similar paradigm in which limbic stimulation by endogenous dopamine (rather than by exogenous cocaine) might, under certain conditions, produce a psychotic state that could be reactivated subsequently by an excessive burst of dopaminergic stimulation. This model was applied to recurrent psychotic disorders and generated great excitement when it was shown that carbamazepine, an anti-convulsant with an anti-kindling action, could produce symptom reduction in bipolar manic patients who had previously failed to respond to lithium treatment.

Several investigators (Lipper et al., 1986; van der Kolk, 1987; Friedman, 1988; Yehuda and Antelman, 1993, Post et al., 1995) have suggested that a similar mechanism might occur in PTSD and have therefore proposed a sensitization model for this disorder. Specifically, they hypothesize that chronic central catecholaminergic arousal in PTSD, mediated by input to the locus ceruleus, sensitizes limbic nuclei, thereby producing a stable neurobiological abnormality. Table 2 lists fourteen characteristics of PTSD and shows how consistent they are with each of the three sensitization models discussed previously.

Table 2. Similarities Between Characteristics of PTSD and Those of Behavioral Sensitization, Time-Dependent Sensitization, and Kindling

Characteristis of PTSD	Behavioral Sensitization	Time-Dependent Sensitization	Kindling
1. May develop after a single exposure to a traumatic or sensitizing stimulus		X	
2. Develops after repeated exposure to a sequence of traumatic/sensitizing stimuli	X		X
3. Increased amplitude and duration of response	X	X	X
4. Increased responsivity is persistent	X	X	X
5. Effects are dose-related	X	X	X
6. Effects are behavioral	X	X	
7. Prior traumatization/sensitization enhances subsequent response	X	X	X
8. Responses initially elicited by stimulation may become spontaneous over time			X
9. Context independent			X
10. Context dependent and conditionable	X	X	
11. Cross-sensitization with stress	X	X	
12. Cross-sensitization with psychomotor stimulants	X	X	X
13. Mediation by limbic system	X	X	X
14. Efficacy of anti-kindling agents			X

First, PTSD may develop after a single exposure to an overwhelming event that involves actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others. Only TDS provides a neurobiologic model for this clinical scenario. What most clinicians believe to be a more common sequence of events is the second characteristic, the

development of PTSD following repeated exposure to traumatic stimuli. Examples of this include repeated physical or sexual assault in the context of child abuse, domestic violence, or political incarceration, repeated exposure to war trauma as a combatant or survivor, and repeated exposure to privation, violence, or atrocities as a political refugee during a genocidal war. Behavioral sensitization and kindling are obviously better suited to model this factor. Admittedly, one cannot draw this parallel too tightly, since it is much more difficult to define a single traumatic event than it is to define the parameters of a single stimulus used in a behavioral sensitization or kindling experiment. However, one might argue that the psychological representation of such a traumatic event (i.e., an intrusive recollection such as a traumamimetic nightmare) might itself serve as a sensitizing stimulus that continues to promote the sensitization process.

Third, patients with PTSD appear to exhibit increased amplitude and duration of response following subsequent exposure to traumatic stimuli. Stimuli with which they could previously cope evoke a more intense and sometimes intolerable response subsequently. An example is Solomon and colleagues' (1987) observation that some Israeli veterans who had apparently coped with the trauma of the 1967 Yom Kippur War became distraught and incapacitated by PTSD symptoms when redeployed for combat duty during the 1982 war in Lebanon.

Fourth, PTSD symptoms are persistent, and when untreated the syndrome may last for decades or a lifetime (Archibald and Tuddenham, 1965; Schnurr, 1991). Fifth, there appears to be a dose-response relationship between the severity (intensity and frequency) of traumatic exposure and the risk of developing PTSD (Pynoos et al., 1987; McFarlane, 1988; Kulka et al., 1990). Both persistence and dose-response characteristics are included in all three sensitization models.

Sixth, PTSD is a psychiatric disorder with behavioral symptoms and it does not include major motor seizures as one of its diagnostic criteria. Strictly speaking, we must certainly rule out kindling as a suitable model for PTSD from this perspective. Post and associates (1988, 1995) have argued, however, that although we should only use the term kindling to describe processes that result in seizures, it is important to recognize that there are kindling-like processes that stop short of full-blown classical kindling. They involve potentially relevant electrophysiological and behavioral abnormalities.

Seventh, prior traumatization and sensitization enhances sensitivity to subsequent exposure. By definition, this characteristic applies to all three sensitization models. A number of studies suggest that adults who have been exposed to sexual or physical abuse during childhood are more likely to develop PTSD following exposure to trauma than traumatized adults who were not abused during childhood (Davidson, 1993).

Eighth, responses initially elicited by stimulation may become spontaneous over time. PTSD patients may have spontaneous recollections of the traumatic event that are not triggered by environmental stimuli. Ninth, intrusive recollections, traumatic nightmares, and PTSD

flashbacks sometimes appear to have a life of their own that is completely independent of the situational context in which the patient finds him or herself. My clinical impression is that context-independent spontaneous symptoms are most often found in patients with the most severe cases of PTSD. Post et al. (1988, 1995) have argued that kindling may be the best model for patients who exhibit such a clinical pattern since neither behavioral sensitization nor TDS can account for context independent or spontaneous symptoms.

Tenth, PTSD is often context-specific and conditionable. Indeed, classic behavioral models of fear conditioning and failure of extinction have been proposed as models for PTSD (see Charney et al., 1993). Keane et al. (1985) have reinvoked Mowrer's two-factor theory of classical fear conditioning and operant escape conditioning as a suitable learning model for PTSD. Likewise, Foa et al. (1992) have reviewed inescapable vs. escapable stress paradigms as they relate to PTSD. Finally, cognitive-behavioral treatment of rape victims with PTSD that is predicated on such conditioning models has proven effective (see review by Foa et al., 1995). Behavioral sensitization and TDS but not kindling are pertinent in this regard.

Eleventh, psychological factors such as stress and context can exacerbate both behavioral sensitization, TDS, and PTSD. Several studies have shown cross-sensitization between different classes of sensitizing and laboratory-induced stress. This is consistent with the well known clinical observation that PTSD patients often become more symptomatic when forced to deal with ordinary (nontraumamimetic) environmental stressors. Relatively mild family, social, vocational, or other challenges can exacerbate PTSD symptoms in patients who had been well stabilized before being forced to confront such situations.

Twelfth, psychomotor stimulants acting on catecholaminergic systems can elicit PTSD symptoms as well as behavioral sensitization and TDS effects (Charney et al., 1993; Post et al., 1988, 1995). A large literature has emerged regarding catecholaminergic — both adrenergic and dopaminergic — mechanisms in PTSD (Ende et al., 1990; Friedman, 1991; Jensen et al., 1991; Charney et al., 1993; Murburg, 1994). Perhaps the most dramatic and convincing example is that administration of yohimbine, a centrally acting alpha-2 adrenergic antagonist that disinhibits central adrenergic mechanisms, can elicit panic attacks and trauma-related flashbacks in Vietnam veterans with PTSD, but not in control subjects (Southwick et al., 1993). It is important to remember in this regard that psychostimulants such as cocaine can induce kindling as well as behavioral sensitization and TDS.

Thirteenth, limbic structures appear to mediate the development and persistence of PTSD symptoms as well as the effects of behavioral sensitization, TDS, or kindling. As shown in Table 1, the DSM-IV definition of a traumatic event includes the subjective emotional response of the exposed individual. Therefore, exposure to a catastrophic stressor is only traumatic if the subjective response involved "intense fear, helplessness, or horror."

Finally, anticonvulsant drugs that reverse the effects of kindling have reportedly produced symptom reduction in PTSD patients. There are three published open trials in which

antikindling agents produced reduction of symptoms in Vietnam veterans with PTSD. In one study, carbamazepine reduced the intensity and frequency of traumatic nightmares, flashbacks, and intrusive recollections (Lipper et al., 1986). In a second report, carbamazepine reduced impulsivity, irritability, and violent behavior in PTSD patients (Wolfe et al., 1988). Finally, valproate treatment resulted in significant improvement in both hyperarousal and avoidant/numbing symptoms among Vietnam veterans with PTSD (Fesler, 1991).

Taken together, these fourteen observations suggest that sensitization models may have heuristic value in furthering our understanding of PTSD. They are hardly conclusive, but they do suggest a number of laboratory experiments that might strengthen our confidence in this conceptual approach. For example, what will happen when a PTSD laboratory paradigm such as inescapable stress is augmented by a behavioral sensitization or kindling paradigm? Will animals exposed to both conditions be more affected than those exposed to either paradigm alone? Will there be cross-sensitization? Will the end result be context-dependent or context-interdependent? Can the process be accelerated by certain drugs (such as psychostimulants and kindling agents) and prevented by others (such as antiadrenergic drugs or antikindling agents?) Will the augmenting effects of behavioral sensitization, TDS, and kindling be comparable in this regard, or is one process more likely to augment the effects of inescapable stress than the others? Clearly, data from experiments of this nature would give us a better basis for evaluating the attractiveness of sensitization models of PTSD.

SOME QUESTIONS ABOUT THE MODEL

Although there are a number of ways in which a sensitization model is consistent with some of the known phenomenology and pathophysiology of PTSD, the goodness-of-fit between model and syndrome is not consistent in all respects.

First, there are many varied experiential roads to PTSD. In some cases the trauma can be a single terrifying event such as a brutal rape or physical assault, while in other cases traumatic exposure may consist of chronic violence measured in months or years, such as incarceration in a Nazi death camp or captivity and torture as a political prisoner. In other words, the magnitude and frequency of traumatic events that lead to PTSD may vary greatly from one patient to another. Furthermore, in addition to such quantitative differences, there may also be critical qualitative differences in the neurobiological processing of different traumatic experiences (e.g., between rape and motor vehicle accidents).

Second, any model of PTSD must address the fact that PTSD is not a unidirectional process in which patients become progressively worse over time. Indeed some patients improve and even recover subsequently. It is possible that number, frequency, and intensity of prior traumatic exposures may hold the key to predicting PTSD recovery or chronicity, but that hypothesis needs to be confirmed empirically.

Third, any model of PTSD must address the fact that traumatic exposure is only a necessary but not a sufficient condition for the later development of PTSD. Clearly, there are individual differences in vulnerability to developing PTSD. This criticism is probably the easiest to handle since, extrapolating from Post et al. (1995), the sensitization model predicts that traumatic exposure initially induces immediate early gene expression which in turn triggers a cascade of subsequent intermediate and late gene expression involved in coding long-lasting changes in synaptic excitability and microstructure. Individual differences in this regard might explain relative vulnerability or resistance to developing PTSD.

ARE PTSD PATIENTS AT GREATER RISK FOR MCS?

Proponents of the MCS syndrome propose that this is a chronic polysymptomatic condition that affects individuals who become sensitized to low levels of common indoor and outdoor environmental chemicals such as pesticides and solvents (Bell et al., 1992). MCS is a rare, poorly understood, and controversial disorder that is often associated with psychiatric conditions. Since most people exposed to low-level chemical stimulation do not develop MCS symptoms, it appears that this disorder results only when susceptible individuals encounter such low-level stimulation. Therefore, it is also important to identify those factors that might make certain individuals more vulnerable than others to develop MCS.

There are two reasons why PTSD might be a risk factor for MCS. First of all, PTSD patients may be more susceptible to a wide variety of medical problems than non-PTSD patients. Secondly, a sensitization model predicts that PTSD patients will be especially vulnerable to MCS.

In a recent review of the trauma and health literature, Friedman and Schnurr (1995) concluded that PTSD patients are at greater risk for adverse health outcomes. This was a consistent finding, whether such health outcomes were indicated by self-reports of somatic symptoms, by medical problems confirmed by a physician's examination, by increased utilization of inpatient or outpatient medical resources, or by mortality data. Friedman and Schnurr suggested that adverse health outcomes among PTSD patients might be explained by pathophysiological and behavioral abnormalities associated with PTSD. The former include dysregulated physiological, neurotransmitter, endocrine, and immunologic systems that are essential to maintain health. The latter include smoking, drinking, immoderate dietary habits, sexual promiscuity, and other behaviors that increase the risk of adverse health outcomes. From this perspective, MCS is one of many medical problems for which PTSD patients are at greater risk than others.

A sensitization model of PTSD proposes a mechanism by which PTSD patients might be specifically vulnerable to MCS. Bell and associates (1992) have suggested that MCS itself might be best understood as a sensitized endpoint following exposure to low-level environmental chemicals such as pesticides and solvents. In their comprehensive review of

this literature, they cite numerous experiments in which repeated exposure to previously undetected olfactory stimuli produced a progressive sensitivity and intolerance of such stimulation. Furthermore, Bell et al. propose that the time pattern of MCS initiation resembles that of kindling or partial kindling. As in other sensitization phenomena, individuals with MCS appear to exhibit cross-sensitization to other stimuli that cause limbic kindling. In contrast to MCS patients whose sensitization is presumably caused by environmental chemicals, it is hypothesized that PTSD patients are sensitized by exposure to traumatic stimuli. Therefore, it is proposed that two very different classes of stimuli, environmental chemicals on the one hand, and psychological trauma-related stimuli on the other, both access the same final common pathway through which they cause limbic sensitization. It is further proposed that under these conditions, there would be cross-sensitization between chemical and traumamimetic stimulation. It follows from the above argument, if sensitization is indeed an important mechanism for both MCS and PTSD, that PTSD patients should be especially susceptible to develop this disorder.

HOW CAN WE TEST THIS HYPOTHESIS?

First we need more conclusive evidence that sensitization models are applicable to both PTSD and MCS. Secondly, we need to know whether behavioral sensitization, TDS, or kindling is the best model in this regard. On the other hand, this might not be the right question to ask given the complexity and polymorphism of both sensitization and clinical phenomena. A better question to ask might be whether certain expressions of PTSD and MCS are better understood as TDS (in the case of a single exposure) as kindling (in the case of symptoms that are spontaneous rather than stimulus-induced) or as behavioral sensitization. In any case, much more basic research is needed.

Assuming satisfactory data supporting sensitization models of both PTSD and MCS, it would be useful to test for cross-sensitization. For example, what will happen following concurrent exposure to a PTSD laboratory paradigm (such as inescapable stress) and a chemical stimulus? Is the sensitization produced by simultaneous exposure to both stimuli greater than the sensitization produced by exposure to either the stressful or chemical stimulus alone? Are these changes context dependent or independent? Can these effects be modified by drugs affecting catecholaminergic systems or kindling mechanisms?

Some less conclusive but suggestive clinical studies might also be undertaken that would be consistent with the hypothesis of sensitization in both PTSD and MCS. If, as I have proposed, there is cross-sensitization in both PTSD and MCS, so that both chemical and traumamimetic stimuli access the same final pathway, it follows that PTSD patients should be at greater risk for MCS and vice versa. A cohort in which individuals were at risk to develop PTSD, MCS, or both disorders would provide an excellent opportunity to test this prediction. Such a cohort has been described by Wolfe et al., (1993, 1994). It consists of American participants in the

Persian Gulf War who have already been assessed and followed longitudinally for PTSD symptoms. A sensitization model of both disorders would predict that, given equal exposure to environmental chemicals, Persian Gulf returnees with PTSD are more likely to develop MCS than those without PTSD.

Another suggestive clinical study might involve neuropsychological testing of PTSD and MCS patients. A number of neuropsychological tests for attention, concentration, and memory have been utilized in the assessment of MCS patients (Bell, et al., 1992; Fiedler et al., 1992; Simon et al., 1993). As proposed by Wolfe (personal communication), it would be of great interest to compare a neuropsychological performance of MCS patients with and without PTSD, PTSD patients without MCS, psychiatric controls, and normal subjects to see whether there are any similarities in cognitive patterns or deficits between these different groups. Similarities between MCS and PTSD patients would also suggest the possibility of a final common pathway for sensitization in both disorders.

Finally, assuming the applicability of a kindling (rather than a behavioral sensitization or TDS) model to both MCS and PTSD, MCS patients would be expected to exhibit symptomatic improvement when treated with antikindling agents such as carbamazepine or valproate. Furthermore, it would be predicted that these drugs should ameliorate symptoms of both PTSD and MCS in patients who are simultaneously afflicted with both disorders. It should be noted, however, that MCS patients often cannot tolerate therapeutic doses of many medications. Therefore, it remains to be seen whether this experiment is feasible.

SUMMARY

The implications of three sensitization models of PTSD have been reviewed. It appears that such a conceptual approach may have great heuristic value in furthering our understanding of PTSD. We must be cautious. The goodness-of-fit between PTSD and sensitization varies with the clinical phenomenology of the patient in question. In general, behavioral sensitization seems to be the best overall model. For PTSD following a single exposure to trauma, time-dependent sensitization seems best and for PTSD with spontaneously occurring intrusive recollections, kindling may be the best.

If MCS can also be understood as a disorder resulting from neurobiological sensitization, it is proposed that there is cross-sensitization between psychological (traumamimetic) stimuli that elicit PTSD symptoms and environmental chemical stimuli that elicit MCS. Assuming that this is indeed the case, it is further proposed that PTSD patients are at greater risk to develop MCS and vice versa.

Several experiments are proposed to test these speculations.

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