Loss of consciousness and post-traumatic stress disorder

A clue to aetiology and treatment

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Post-traumatic stress disorder (PTSD) is a condition that appears to be becoming increasingly prevalent in psychiatric and general practice. Davidson (1992) reports a lifetime prevalence of 1–9% in the community, with high levels of chronicity and comorbidity. It routinely features in the general as well as medical literature following major traumas such as the *Herald of Free Enterprise* disaster. PTSD is also growing more important in medico-legal terms, as the recent police attempt to obtain compensation for their experiences in the Hillsborough tragedy demonstrates. Despite the high profile of the condition and the repeated descriptions of its development and (partial) resolution after every major disaster, there is very little research into the most effective means of preventing or treating PTSD. The usual approach of debriefing has been shown to be without effect (Deahl *et al*, 1994) and a recent review of drug treatments revealed only a few small-scale studies, none of which would be suitable for the licensing of a drug for this disorder (Davidson, 1992). This may be because most drug treatments are initiated well after the trauma, which may be too late to prevent the laying down of immutable brain traces for the memories, behaviours and affect that trauma causes and which develop into PTSD.

The need to improve the treatment of PTSD led us to explore the published literature relating brain mechanisms to the outcome of PTSD. We found a consistent theme dating back to the original studies of Adler that suggested brain trauma might protect from PTSD. As this is a rather surprising observation we thought it important to bring it to the knowledge of psychiatric and other professionals involved in the treatment of people with PTSD. In addition, as it potentially offers a new insight into the nature and treatment of PTSD, we briefly review the brain mechanisms which may be responsible.

UNCONSCIOUSNESS AND PTSD

The literature from the 1940s and 1950s first described the post-traumatic syndrome as we recognise it (Adler, 1943). In her follow-up of patients from the Coconut Grove Disaster, she noted that:

> "of the 20 patients who did not develop psychiatric complications, 15 had lost consciousness, which with 12 of the 15 was prolonged beyond one hour. Of the 25 with psychiatric complications, 13 had lost consciousness. This however was short, below one hour in 10 of the 13 cases."

In other words, unconsciousness, especially if prolonged for more than one hour, improved outcome.

Since that time there have been only a few reports that have examined this issue. Adler herself noted in another series of patients:

> "that in only one of eight patients with a retrograde amnesia of more than an hour did psychogenic symptoms develop" (Adler, 1945*b*).

Much later, McMillan (1991) in a single case study of a road traffic accident victim suggested that PTSD can occur even where there is loss of consciousness and organic amnesia for the event and its immediate sequelae. However, the importance of coma as a protective element has been revived by the recent work by Mayou and colleagues in Oxford (Mayou *et al*, 1993). Their study on the psychiatric consequences of road traffic accidents showed that post-traumatic syndromes were strongly associated with horrific memories of the accident; they did not occur in any subject who had been unconscious and were amnesic for the accident.

Why might this be? Adler took a psychodynamic view, wondering if:

> "prolonged unconsciousness might prevent psychiatric complications following terrifying events, but not in patients in whom unresolved conflicts were to form the basis of post-traumatic difficulties" (Adler, 1945*a*).

Obviously, loss of consciousness that leads to the absence of any memory of an incident means that the patient will not have any horrific memories, flashbacks or nightmares and so will not re-experience the incident repeatedly. This may prevent the progressive activation of other brain circuits that together form the brain substrate for PTSD.

Furthermore, the lack of memory means that there is less reason to avoid the relevant cues to the event and this probably results in less avoidance.

BRAIN MECHANISMS

Unconsciousness following trauma can be the result of a number of factors. Brain trauma (concussion) is the most common, but others include: spinal trauma, hypoxia, hypovolaemia, chemical intoxicants such as noxious vapours, simple fainting and possibly dissociation. Virtually nothing is known about the brain sequelae of any of these, except concussion, which is thought to be due to the disruption of ascending pathways from brain stem to cortex due to a combination of neuron shearing and oedema-induced increases in intra-cerebral pressure. These pathways are primarily glutamatergic although ascending monoamine fibres are probably also involved. Glutamate is the primary excitatory transmitter in the brain and is intimately involved in consciousness and memory (Collingridge & Bliss, 1995). It is thought that stressors are registered and remembered when they lead to enough glutamate release to activate *N*-methyl-D-aspartate (NMDA) receptors which then produce long-term memories (Glue *et al*, 1993). Disruption of glutamate transmission will therefore prevent memory and probably the other brain changes that result from a stressor.

Unconsciousness can also be produced by increasing inhibition in the brain. The primary inhibitory transmitter in the brain is gamma-aminobutyric acid (GABA), acting through the GABA-A receptor. Activating this receptor either by the endogenous transmitter or by drugs such as the benzodiazepines, barbiturates and anaesthetics (e.g. propofol), renders people unconscious and at lower concentrations amnestic. It is not known if GABA is released in response to brain trauma, although the local nature of the GABA system means these neurons are unlikely to be damaged by trauma and

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so in the face of reduced glutamate release even normal GABA release could lead to coma.

There is now good evidence for endogenous benzodiazepine-like molecules and neurosteroids which act at modulatory sites on the GABA-receptor complex and potentiate the actions of GABA. There is evidence that these are released by stressors and have been suggested to serve a role in reducing anxiety; perhaps they also contribute to limiting memory and it may be they contribute to dissociative states (Izquierdol & Medina, 1991).

The monoamine transmitters, especially noradrenaline, are also very important in mediating the responses to stress (Glue *et al*, 1993). Noradrenaline has been shown to contribute to the processes of memory formation in the brain, probable by potentiating the actions of glutamate in the hippocampus (Harley *et al*, 1996). Switching off noradrenergic function by drugs such as clonidine reduces the level of arousal and attention and decreases anxiety; conversely increasing brain noradrenaline release activates PTSD symptoms (Southwick *et al*, 1993). Peripheral arousal can also be problematic, here beta-blockers may be helpful.

IMPLICATIONS, FOR TREATMENT

If loss of consciousness protects from PTSD by preventing the encoding of traumatic memories could this be a route to new treatments? A number of amnestic agents are currently available and some have a good track record in preventing military stress leading to breakdown and later PTSD. For some time military doctors have used heavy sedation with barbiturates, and more recently benzodiazepines, to deal with acutely 'shell-shocked' individuals. Many non-military trauma casualties have been treated in the same way, although there appears never to have been a controlled study of this sort of intervention. Moreover, the exaggerated recent concern over the perceived dangers of benzodiazepines has frightened many doctors into not using them in traumatised patients. One suspects that this makes PTSD more likely because the benzodiazepine actions to promote sleep and reduce anxiety should decrease the repeated reliving of the traumatic image and so reduce the depth to which it becomes embedded in memory. The only placebo-controlled study of a benzodiazepine (alprazolam) in PTSD showed no effect on core symptoms, though anxiety and well-being were improved (Braun *et al*, 1990). These patients all had long-standing PTSD so the benzodiazepine treatment was started far too late to test our theory.

In practice, many sufferers turn to another sedative – alcohol. This acts like a benzodiazepine to increase GABA function and also blocks some aspects of glutamate transmission (Nutt & Peters, 1994), which could suggest it would have better efficacy than the benzodiazepines, although the toxic side-effects and its short duration of action would make controlled studies difficult.

One of the critical issues is whether coma is required or just complete amnesia. The available data are too sparse to be of use; however, amnestic agents such as the benzodiazepines and barbiturates, while producing a profound anterograde amnesia (for events after they have been taken), have relatively little effect on the memory for prior events (retrograde amnesia). Indeed, there is some evidence that by blocking the formation of new memories they facilitate ones just prior to their administration. Other drugs such as hyoscine have greater anterograde effects and it might be interesting to combine these with benzodiazepines to more closely mimic the effects of coma. Similarly, a combination of clonidine and benzodiazepine could be more effective than a benzodiazepine alone.

In the light of the possibility that endogenous anxiety-producing benzodiazepines are released by trauma (Davidson *et al*, 1988), it may be that a benzodiazepine receptor antagonist such as flumazenil might be of use. This has never been tried in acute PTSD but perhaps should be as it is safe and in some patients anxiolytic in chronic PTSD (Randall *et al*, 1995; Coupland *et al*, 1997).

It is a real possibility that we can devise treatments that work through the glutamate system, as antagonists for all three main classes of glutamate receptor now exist. Some such as dizolcilpine (MK801) have been used in humans as potential anti-brain ischaemia agents and do produce a state of reduced sensory input similar to dissociation. Further work is needed to determine whether this and related compounds have anti-stress and retrograde memory blocking properties. Animal experiments such as those of Adamec (1998) have shown that NMDA antagonists can block both the behavioural and neurophysiological changes in a model of PTSD.

Finally, there is good evidence that the brain's endogenous opioid system (e.g. the endorphins) is activated by stress, and serves a compensatory role at least in terms of pain reduction. There is now preliminary evidence that supporting this system, with synthetic agonists such as buprenorphine, is therapeutically useful in PTSD (Mongan & Calloway, 1990). It is possible that a combination of opioid and amnestic agents might be especially effective.

The evidence that brain trauma and its resultant impairment of consciousness can have a paradoxical beneficial effect on the psychological recovery from trauma. This may be explained in terms of the failure of trauma memory consolidation secondary to alterations in key neurotransmitters. These observations offer the hope of new therapeutic approaches to the prevention of PTSD.

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