Glutamate and cortisol—a critical confluence in PTSD?

JMHM Reul  Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, University of Bristol, Bristol, UK.
DJ Nutt  Psychopharmacology Unit, University of Bristol, Bristol, UK.

Post traumatic stress disorder (PTSD) is a unique psychiatric condition in that it is the only one which requires provocation—usually an event of great threat to the person or to their family or close friends. For this reason, there are two necessary elements for such a trauma to lead to PTSD—the experience of stress and memory of the event.

Memory is critical in that for the trauma to have impact, it must be registered in memory. Once encoded in memory, the event or elements of it, such as noises and smells, can be relived or re-experienced, for example, as flashbacks. Often, the memory is actively suppressed, which leads to the symptoms of emotional numbing and avoidance. Memory disruption at the time of the trauma, by either drugs or head injury, reduces the likelihood of PTSD development (O’Brien and Nutt, 1998; Gil, et al., 2005) and overwriting/erasing established traumatic memories is a promising new approach to treatment (Davis, et al., 2006).

The degree of stress involved in PTSD is somewhat arbitrary and under discussion by bodies concerned with diagnostic schemes. The early concept of the trauma being rare or unusual and accompanied by a sense of one’s life being threatened has already been revised. In part, this is due to the realisation from epidemiology that a large minority (perhaps even the majority) of the population will experience at least one significant trauma in their life. In part, it is due to the fact that observing others being traumatised or even listening to recounted stories of trauma of someone else can also produce symptoms of PTSD (Gershons, 2000). Moreover, not all traumatised people develop PTSD; only a minority for natural disasters, for example, earthquakes, whereas the majority for rape (Kessler, et al., 1995).

So what are the neurochemical processes that underlie PTSD and why are they expressed only in some people after certain traumas?

Traumatic memory formation

The molecular basis and brain locations of certain memories are now becoming understood. The facts of an event are most likely stored in cortex, but memory for place (topographic memory) is critically dependent on encoding within the hippocampus, whereas emotional memories require amygdala involvement. In the hippocampus and probably in most other brain regions, the key neurotransmitters in memory formation are glutamate and gamma-aminobutyric acid (GABA). Release of glutamate leads to the long-term changes in synaptic plasticity that ensure memory is encoded, whereas GABA receptor activation inhibits this—which is why benzodiazepines lead to amnesia. In most brain regions, the target receptors for glutamate to encode memory are the alpha-amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptor subtypes with activation of the latter being critical for allowing the calcium influx into the neuron that leads to the post-synaptic changes in neuron function that in turn give permanence to the memory. Other neurotransmitters, especially noradrenaline, may also play a facilitatory role, especially in traumatic memories (Nutt, 2000).

How memories of stressful life events are stored is also becoming understood and appears to involve changes in gene expression in response to the stimulus. Genes can be in a state of active transcription in open chromatin or kept in a silent state in condensed chromatin. For a gene to be “turned on”, the chromatin structure needs to be opened (remodelled) to allow the access of transcription factors and enzymes. For the chromatin to uncoil and allow transcription, the structure of histone molecules (a set of core protein constituents of chromatin) needs to be modified (Cheung, et al., 2000). Principal modifications sparking gene transcription of silent genes are the simultaneous phosphorylation at one site (serine-10) and acetylation at another site (Lysine-14) within the histone H3 molecule, which requires joint activity of two enzymes, mitogen- and stress-activated kinase (MSK) and histone acetyl transferase (e.g., CREB (cAMP responsive element-binding protein) (CBP), activated after CREB phosphorylation; Bilang-Bleuel, et al., 2002) (Reul and Chandramohan, 2007). Once this process has taken place, gene expression can be initiated leading to mRNA production. This then progresses to new protein synthesis, which results in long lasting
alterations in neuronal function and the activity of neural circuits together forming the neural basis of memory. Chromatin remodelling to allow gene transcription is, therefore, a crucial early step in the memory encoding process. Such changes in chromatin structure without altering the actual DNA template are called epigenetic mechanisms. In other systems, they have been shown to have a lasting effect on gene expression and function for a long time—months to years. If the same were true in the hippocampus, then this could explain why stress memories can stay prominent for a very protracted period.

Recently, it has been shown that NMDA receptor activation will lead to such chromatin modifications—as indicated by histone H3 phospho-acetylation—in just a small subset of neurons in the dentate gyrus of the hippocampus—less than 10,000 neurons for each memory-inducing stress event (Figure 1; Chandramohan, et al., 2007, 2008; Reul and Chandramohan, 2007). The special function of the dentate gyrus within the hippocampus structure permits the dentate neurons a prominent role in the encoding of sensory information for memory formation thereby orchestrating the outputs of the rest of the hippocampus and possibly other downstream structures.

**What about cortisol?**

Cortisol is prototypically the stress hormone as both physical and psychological stress leads to cortisol elevation in blood and then in brain (Droste, et al., 2008). Yet the relationship of cortisol to PTSD has been quite confused. Early work in people who had survived years after extensive chronic trauma in the Holocaust found that they had lower than normal cortisol levels (Yehuda, 2000). This was a paradox as traumatic stress...
elevates cortisol, but it now seems that this low level may either reflect some compensatory response to the elevated cortisol at the time of the trauma or be a phenotype that assists people in resisting the effects of stress. Studies of acute trauma show elevations of cortisol (Fukuda, et al., 2000), and that higher plasma cortisol correlates with symptoms of PTSD (Maes, et al., 1998). More recent studies in young first-time traumatised people are reporting that higher cortisol on presentation to the emergency room tends to predict later development of PTSD (De Bellis, et al., 1999; Delahanty, et al., 2005). Could cortisol, therefore, have a role in symptom production?

This possibility has become more intriguing in the light of our recent work revealing that cortisol is as necessary as NMDA receptor activation for the phospho-acetylation of histone H3 in the dentate gyrus after stressful events (Chandramohan, et al., 2007; Reul and Chandramohan, 2007). Cortisol acting through the glucocorticoid receptor (GR; Reul and De Kloet, 1985) seems to interact with the NMDA-ERK (extra-cellular signal-regulated kinase) pathway to facilitate activation of MSK (see Figure 1). Remarkably in the rodent models tested so far (forced swimming and novelty exposure), where chromatin remodelling has been identified, blockade of either NMDA receptors or GRs with selective antagonists prevents it, proving their synergistic interactions (Bilang-Bleuel, et al., 2005; Chandramohan, et al., 2007, 2008). As well, these interventions also block the memory of exposure to the stress (Bilang-Bleuel, et al., 2005; Reul and Chandramohan, 2007; Chandramohan, et al., 2008). Thus, memory formation of stressful events involves chromatin remodelling and gene transcription in dentate gyrus neurons which are brought about by signalling through both the NMDA/ERK/MSK, and the GR pathways (Figure 1).

Implications for aetiology and treatment

These new data showing synergism of two quite distinct pathways that are crucial for stress memory offers explanations of several aetiological aspects of PTSD. For instance, PTSD is rare when trauma occurs under anaesthetic probably because NMDA or upstream glutamate function is impaired. Head trauma with unconsciousness may work in the same way (O’Brien and Nutt, 1998). People with low cortisol responses will presumably be less likely to encode traumatic stress memories which may explain their relative resistance to trauma.

It also makes some predictions about risk factors—states of high NMDA and cortisol function, for example, alcohol withdrawal (Nutt, 1999) may be particularly likely to lead to memory encoding with negative therapeutic consequences. Gene variants of the GR, or NMDA receptor, or downstream elements that alter function might be predicted to alter vulnerability to PTSD, and this could be examined in some of the larger cohorts. The new finding that a polymorphism of FKBP5 (a GR chaperone protein) predicts PTSD in people with childhood trauma (Binder, et al., 2008) begins to support this view.

Moreover, this understanding offers new approaches to treatment. GR antagonists are in clinical trials for depression (Matthew, et al., 2008) but might be also of use in PTSD. NMDA antagonists or other glutamate depressing drugs, such as mgluR agonists, might have value in PTSD if initiated very soon after the trauma. We have shown in rats that lorazepam, a benzodiazepine agonist, abolishes phospho-acetylation of histone H3 in stress exposure (Papadopoulos, Chandramohan, Droste, Collins, Nutt and Reul, unpublished), which may explain why being on another GABA-A agonistic drug, alcohol, during the trauma reduces PTSD incidence (McFarlene, 2000). It also helps explain the old human data that the benzodiazepine receptor inverse agonist FG7142, and other GABA-A receptor antagonistic drugs produced severe anxiety (Nutt and Ballenger, 2003) and a PTSD-like state in humans (Kalueff and Nutt, 1996) because in rodents we found that FG7142 enhanced histone H3 phospho-acetylation in dentate neurons (Papadopoulos, et al., unpublished).

In the light of these recent developments, mapping the identity of the genes associated with stress-evoked phospho-acetylated histone H3 in dentate neurons could lead to new targets for intervention therapies.

References


