Unravelling the pathophysiology of delirium: A focus on the role of aberrant stress responses

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Abstract

Delirium is a common and serious acute neuropsychiatric syndrome with core features of inattention and cognitive impairment, and associated features including changes in arousal, altered sleep–wake cycle, and other changes in mental status. The main risk factors are old age, cognitive impairment, and other comorbidities. Though delirium has consistent core clinical features, it has a very wide range of precipitating factors, including acute illness, surgery, trauma, and drugs. The molecular mechanisms by which these precipitating factors lead to delirium are largely obscure. In this article, we attempt to narrow down some specific causal pathways. We propose a basic classification for the etiological factors: (a) direct brain insults and (b) aberrant stress responses. Direct brain insults are largely indiscriminate and include general and regional energy deprivation (e.g., hypoxia, hypoglycaemia, stroke), metabolic abnormalities (e.g., hyponatraemia, hypercalcaemia), and the effects of drugs. Aberrant stress responses are conceptually and mechanistically distinct in that they constitute adverse effects of stress–response pathways, which, in health, are adaptive. Ageing and central nervous system disease, two major predisposing factors for delirium, are associated with alterations in the magnitude or duration of stress and sickness behavior responses and increased vulnerability to the effects of these responses. We discuss in detail two stress response systems that are likely to be involved in the pathophysiology of delirium: inflammation and the sickness behavior response, and activity of the limbic–hypothalamic–pituitary–adrenal axis. We conclude by discussing the implications for future research and the development of new therapies for delirium.

Keywords: Cortisol; Delirium; Glucocorticoids; Inflammation; Sickness behavior; Stress

Introduction

Delirium is a syndrome of acutely altered mental status that has the core elements of inattention and fluctuating course and multiple associated features including altered arousal, disorganized thinking, perceptual disturbances, psychosis, and sleep–wake cycle disturbance [1,2]. Delirium occurs in patients of all ages, but the highest incidence is in older people with a background of chronic central nervous system (CNS) disease. It affects 20–30% of acutely admitted older general hospital inpatients and is associated with adverse outcomes, including functional decline, permanent decrements in cognition, and mortality [2]. In the last two decades, there has been a large rise in published studies of delirium, mainly focusing on clinical manifestations, risk factors, and outcomes, and prevention and treatment of delirium by specific programmes of enhanced clinical care and drug treatment [1,3–10]. These studies have led to a greatly increased knowledge of many fundamental features of delirium. However, there has been comparatively little
work on the pathophysiology of delirium, which remains poorly understood. Published reviews give comprehensive overviews of the literature on delirium pathophysiology [11,12], and here, we do not aim to provide such broad coverage. Rather, we take an exploratory approach. Our focus is on two areas of stress biology that appear highly relevant to delirium: the inflammatory response and the activity of the limbic–hypothalamic–pituitary–adrenal (LHPA) axis. We go on to discuss how direct brain insults and aberrant stress responses might lead to delirium and conclude by discussing the implications for future research and the development of new therapies.

**Actiologies of delirium**

There is a great diversity of precipitating factors of delirium [11,12]. Some of these factors manifestly result in brain injury and dysfunction, for example, haemorrhage or prolonged hypoglycaemia. However, the mechanisms of delirium in other clinical scenarios, such as that caused by mild urinary tract infection or psychological stress, are unclear. Understanding the physiological and molecular pathways from these diverse factors to the core features of delirium, such as inattention, is a fundamental issue in research on the mechanisms of delirium.

To help to identify these mechanisms, we suggest that delirium aetiologies can be classified into two major categories: (a) direct brain insults, for example, hypotension, hypoxia, hypercapnia, infarcts, brain haemorrhage, trauma, and drugs and (b) aberrant stress responses, induced by aberrations in the normally adaptive systemic and CNS responses to stressors such as infection, surgical trauma, anxiety, and so forth. Although not an obvious binary classification, this proposal, which we clarify below, provides a conceptual framework by which we may be able to make predictions about the convergent and divergent clinical features of delirium and in which we may find commonalities in mechanisms. We will discuss direct brain insults only insofar as to justify this grouping, and we will focus on aberrant stress responses.

**Direct brain insults and delirium**

For the purposes of this article, the term *direct brain insults* includes acute processes that compromise brain function by causing energy deprivation, metabolic abnormalities, trauma, haemorrhage, or direct changes in neurotransmitter levels by drugs. Examples illustrating the breadth of this classification are provided in Table 1.

Hypoxaemia and systemic hypoglycaemia self-evidently cause acute brain dysfunction in multiple regions. This may lead to impairments in attention and cognition that meet criteria for delirium. Whether there are brain regions essential for attention that are particularly vulnerable to these general effects or whether attention is affected simply because it requires the dynamic integration of many brain systems and connections [13,14] is uncertain. Localized energy deprivation, for example, by thrombosis or haemorrhage of brain regions critical to attentional processes such as the caudate nucleus or frontal cholinergic pathways, may also cause attentional deficits and delirium [15–17]. The basal ganglia may be particularly vulnerable because their vascular supply arises from small perforating vessels, rendering them susceptible to the effects of cerebral small vessel occlusion by mechanisms including lipohyalinosis (connective tissue deposits in small vessel walls), microembolism, and, putatively, vasospasm [18]. Another common clinical scenario in which delirium is frequently present is septic shock. A recent study has demonstrated extensive white matter damage following this condition, perhaps secondary to reduced cerebral perfusion or increased blood–brain barrier permeability [19]. Primary CNS pathologies, such as meningitis or encephalitis, are associated with acute mental status change and at least part of this is due to direct damage to the brain [20]. These and other forms of direct brain insult involve energy deprivation, metabolic disturbance, or direct damage to the brain parenchyma, with secondary effects on neurotransmitters such as acetylcholine [11]. Thus, there is no single mechanism, though certain mechanisms may occur more commonly because of increased vulnerability.

Drugs are another important cause of delirium, and drug-induced delirium can be seen as a pharmacological direct brain insult. The triggering of delirium by drugs has been well described and indeed has been very informative in that it has highlighted some of the neurotransmitter systems that may be implicated. For example, anticholinergic drugs used to treat detrusor instability and many other frequently prescribed drugs impair central cholinergic transmission [21]. Similarly, drugs increasing dopaminergic tone, for example, levodopa, used in the treatment of Parkinson’s

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**Table 1**

<table>
<thead>
<tr>
<th>Examples of direct brain insults</th>
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<tr>
<td><strong>Process</strong></td>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td>Energy deprivation</td>
<td>Hypoxia (systemic)</td>
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<td></td>
<td>Hypoglycaemia</td>
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<td></td>
<td>Hypotension</td>
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<td>Cerebral thrombosis/infarction</td>
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<td>Metabolic derangement</td>
<td>Hypo/hypercapnia</td>
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<td></td>
<td>Hypercalcaemia</td>
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<td></td>
<td>Hyperammonaemia</td>
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<td></td>
<td>Hyperglycaemia</td>
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<tr>
<td>CNS trauma</td>
<td>Diffuse axonal injury</td>
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<td></td>
<td>Haemorrhage</td>
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<tr>
<td></td>
<td>Penetrating injury</td>
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<tr>
<td>Infection</td>
<td>Haematogenous invasion of CNS</td>
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<tr>
<td>Neoplasm</td>
<td>Primary CNS tumors</td>
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<tr>
<td></td>
<td>Metastases</td>
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<tr>
<td>Drug toxicity</td>
<td>Cholinergic antagonists</td>
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<td></td>
<td>Dopamine agonists</td>
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<td>GABA agonists</td>
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<td>Opioids</td>
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disease patients, can also precipitate delirium [22]. The current consensus is that overactivity of the dopaminergic system and underactivity of the cholinergic system are prominent among the key factors in delirium [11], and any change in medication inducing significant alterations in these neurotransmitter systems may thus be thought of as a pharmacological insult.

Thus, delirium can be caused by major insults such as hypoxia, hypoglycaemia, and head injury and by certain classes of drugs. However, it can also be caused by more subtle insults, which may not be clinically apparent, on a background of preexisting pathology or age-related changes. It is established that in patients with preexisting cognitive impairment and other comorbidities, relatively mild precipitating factors can induce delirium [4,23]. How these subtle peripheral insults interact with ongoing CNS pathology and result in delirium is one of the major questions in delirium pathophysiology and is discussed below.

**Aberrant stress responses and delirium**

It has long been recognized that acute stress and non-CNS illness frequently affect attention, cognition, motivation, mood, perception, and other aspects of mental function [24–26]. These changes in mental status have evolved to be adaptive in healthy organisms. For example, acute mental stress increases vigilance at the cost of deterioration in more complex cognition, through the actions of monoamines, glucocorticoids, and other mediators [27,28] (Table 2). Similarly, systemic inflammation induces fatigue, reduced activity, anhedonia, and reduced appetite. These changes are mediated through multiple routes of communication, including by means of pro-inflammatory cytokines and prostaglandins [29] (Fig. 1). This constellation of changes, collectively termed sickness behavior [25,30], appears to be initiated to conserve energy and minimize exposure to further infection or other stressors.

In health, these responses have evolved to be adaptive. However, dysfunction of the stress response and heightened inflammatory states are common with ageing and neurodegeneration [29,31]. It is clear that prior pathology (dementia or age-related changes) and systemic insults such as stress, infection, injury, and surgery often interact to induce delirium. The cholinergic, dopaminergic, and noradrenergic

<table>
<thead>
<tr>
<th>System</th>
<th>Sample mediators</th>
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<tr>
<td>LHPA axis</td>
<td>Corticotropin-releasing hormone</td>
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<tr>
<td></td>
<td>ACTH</td>
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<td></td>
<td>Cortisol</td>
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<td>Vasopressin</td>
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<td>Sympathetic nervous system</td>
<td>Acetylcholine</td>
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<td>Noradrenaline</td>
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<td>Adrenaline</td>
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<tr>
<td>Inflammatory system</td>
<td>TNF-α</td>
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<td>IL-1β</td>
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<td>PGE2</td>
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<td>IFNα/IFNβ</td>
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TNF-α, tumor necrosis factor alpha; IL, interleukin; IFN, interferon; PGE2, prostaglandin E2.

![Fig. 1. Inflammation: routes of communication from the periphery to the CNS. This illustrates three major routes by which information on peripheral inflammation is signalled to the CNS. There are multiple other potential routes and mediators.](image)
systems, which play central roles in arousal, cognition, and attention [32–34], are highly vulnerable to Alzheimer-type and cerebrovascular pathology [34–36], thus making these systems more prone to the influences of stress and inflammation. Thus, we suggest that it is heuristically useful to class overstimulation of stress responses, or pathological reaction of target tissues to stressors, as a second major category of mechanisms of delirium. This may take two distinct forms: (a) an abnormally intense stress or inflammatory response, with increased and/or inappropriately sustained levels of signalling molecules such as cortisol or (b) an exaggerated response of the target tissue to normal levels of stress or inflammatory signals. Recent research confirms that with ageing and some forms of pathology, there are exaggerated CNS responses to stress and inflammatory insults [29,37].

These acute stress responses are mediated by humoral and neural signalling pathways, and the interactions of these signals with CNS pathology make this category mechanistically distinct from the ‘direct brain insults’ described above. This separate class of pathways to delirium is here given the general label of aberrant stress responses. In the remainder of this article, we will focus on two major types of aberrant stress responses, which can lead to attentional deficits and other forms of acute mental status change: exaggerated inflammation-induced sickness behavior and LHPA axis dysfunction.

The inflammatory response and delirium

As mentioned above, the term sickness behavior is used to describe a range of adaptive behavioral and metabolic changes occurring in animals during infection or other immune stimulation. The features of sickness behavior include general malaise, decrements in cognition, decrements in locomotor and social activity, depression of mood, increased somnolence, reduced appetite, and, in many cases, changes occurring in animals during infection or other inflammatory stimuli. The features of sickness behavior are crucial for attention, and such lesions could be susceptible to acute exacerbation [52]. There are reports of mild cognitive changes during upper respiratory tract infection [26], vaccination [53], and experimental endotoxinaemia [54,55] in humans, and these studies tend to report changes attributable to attentional deficits, including psychomotor slowing, delayed recall, and difficulties in concentration. However, it is clear that the same stimuli that induce sickness behavior and these mild cognitive deficits can induce delirium in the elderly and patients with dementia [11,56]. It has now been shown in rodents that systemic inflammation can interact with either chronic neurodegeneration (Cunningham et al., submitted for publication) or ageing [57,58] to induce acute cognitive deficits that are not induced by systemic insults in control animals. The interaction of systemic inflammation with ongoing degenerative changes is clearly key to many episodes of delirium, and the interaction between systemic inflammatory mediators and the primed microglia of preexisting CNS inflammation in areas of the brain underpinning attentional and other cognitive processes represents a strong possibility to explain such episodes. Previous authors have hypothesized that dementia and delirium feature inflammation as a common
pathological mechanism [59], but it now seems, from these animal model studies, that the inflammation induced by superimposing an acute inflammatory stimulus upon an existing low-grade microglial response is significantly more aggressive than either stimulus applied alone.

Though this evidence originates in the rodent literature, the theory is broadly consistent with several studies in humans. Beloosesky et al. [60] have shown that the extent of complications post-hip fracture surgery in elderly patients was correlated with the degree of preexisting impaired mental status. Other studies have shown that while elevation of the pro-inflammatory cytokines IL-6 and IL-8 is correlated with occurrence of delirium in acute admissions of elderly medical patients to hospital, the existence of prior cognitive impairment was a stronger predictor of delirium [56]. Thus, it seems likely that more severe systemic inflammatory responses are more likely to induce delirium, but preexisting pathology in cognitive circuitry is a stronger predictor, and thus, the interaction between these two factors is key. This represents a fundamental shift in outlook from the search for specific peripheral inflammatory markers that predict episodes of delirium [61,62] and in a sense is more in line with the idea of overlap between dementia and delirium, wherein systemic inflammation acts as a stressor that can initiate an acute exacerbation of underlying dementia.

The LHPA axis and delirium

Another hypothesis of delirium pathophysiology is that pathologically sustained high levels of cortisol occurring with acute stress can precipitate and/or sustain delirium [11,63]. This hypothetical mechanism of delirium can be categorized as an aberrant stress response alongside the inflammatory response and the sickness behavior syndrome. There is substantial indirect evidence and some direct evidence supporting this hypothesis, which will now be reviewed.

Glucocorticoids (cortisol in humans, corticosterone in rodents) are the central hormones in the mammalian stress response, and levels increase with diverse stressors, such as surgery, trauma, systemic inflammation, and pain [64,65]. Glucocorticoids act via cytoplasmic receptors and also by modulation of membrane receptors [66]. Cytoplasmic receptors are the high-affinity mineralocorticoid receptor (MR), present in only a few brain regions, and the lower-affinity glucocorticoid receptor (GR), present throughout the brain (especially hippocampus, cerebellum, and prefrontal cortex). MRs are occupied with basal levels of glucocorticoids, but

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Fig. 2. From peripheral insult to delirium: possible pathways. This figure shows some of the pathways linking peripheral inflammation and other insults to changes in the CNS occurring on a background of neurodegenerative disease. These signalling pathways are hypothesized to lead to delirium. CRH, corticotropin-releasing hormone; EP₁–₄, prostaglandin E₂ receptors; GCs, glucocorticoids; GR, glucocorticoid receptor; IFN, interferon; IL, interleukin; IL-1RI, interleukin 1RI receptor; LHPA, limbic–hypothalamic–pituitary–adrenal axis; PAMPs, pathogen-associated molecular patterns; PGE₂, prostaglandin E₂.
GRs are occupied only with stress levels of glucocorticoids and during the peak of the circadian rhythm. A prompt post-stress return of glucocorticoids to basal levels, leaving GR mostly unoccupied, is achieved through inhibitory feedback loops involving the medial prefrontal cortex, the hippocampus, and the LHPA axis [67,68]. Efficient feedback regulation is crucial, because sustained high levels of glucocorticoids, chronically activating the normally mainly unoccupied low-affinity GR, can cause several serious adverse effects on the brain and other tissues [64]. Importantly, the types of patients who are at risk of delirium, that is, older patients with baseline cognitive impairment, may develop sustained high cortisol levels after major stressors because feedback regulation of the LHPA axis is impaired [67,69–72].

The effects of glucocorticoids on cognition and other mental functions are consistent with a role for these hormones in delirium. In experimental studies, short-term (days, weeks), high doses of glucocorticoids given to healthy young adults cause impairments of attention and declarative memory [73–75]. Furthermore, glucocorticoids are widely used clinically and can cause delirium in the short term (days) and affective disorders and cognitive impairments in the medium term (weeks) [76,77]. In Cushing’s disease (sustained high cortisol due to ACTH-secreting adenoma), patients develop brain atrophy and multiple cognitive deficits and are at high risk of affective disorders and psychosis. The brain atrophy and cognitive impairments are only partially reversible with treatment [78]. Some intervention studies are supportive of the effects of glucocorticoids on cognition. In rodents, reducing neuronal exposure to glucocorticoid levels from midlife attenuates hippocampal atrophy and cognitive decline [79,80]. In humans, reducing intraneuronal cortisol by carbenoxolone inhibition of 11β-HSD1 improves performance on a test of prefrontal cortical function in healthy elderly men [81]. Blockade of GR has also been found to improve performance on prefrontal–cortical tasks in patients with bipolar illness [82]. In summary, a role for dysfunction of the LHPA in delirium is suggested by two lines of evidence: (a) sustained high cortisol levels occur in some older people, particularly those with cognitive impairment following stress, and (b) sustained high cortisol levels are known to cause cognitive impairment and other neuropsychiatric deficits, particularly in older adults.

There are some studies that have directly examined LHPA function in delirium. These studies have measured abnormalities in cortisol levels and/or LHPA axis dynamics [variations in circadian rhythm, dexamethasone suppression test (DST)] [11,63]. In a study of 80 patients aged 70–90 undergoing abdominal surgery, Kudoh et al. [83] found that patients who developed postoperative delirium (N=17) had higher postoperative plasma cortisol levels immediately after surgery and at 24 and 48 h postoperatively. They reported similar relationships between cortisol and delirium in patients with schizophrenia [84] and alcoholism [85]. In an earlier study, three of seven patients undergoing elective surgery developed delirium post-surgery and all showed prolonged high cortisol levels and loss of normal circadian rhythm in contrast to the other patients [86]. O’Keeffe and Devlin [87] studied the relationship between delirium and the DST in 16 elderly patients with lower respiratory tract infection. Seven of the nine patients with delirium and only one of the seven non-delirious patients were non-suppressors. Illness severity was not significantly different between the groups. McKeith [88] found in a study of hospitalized older adults that delirium was associated with non-suppression of cortisol in the DST in the six cases studied, and in a larger study of 178 hospitalized patients with dementia, episodes of delirium were significantly associated with non-suppression [89]. Similar results were found in stroke patients, in whom non-suppression of cortisol in the DST was also associated with a higher risk of delirium [90,91].

In conclusion, there is some evidence that dysregulation of the LHPA axis plays a role in delirium, though definitive data are still lacking. Furthermore, there are some challenges to this hypothesis. Loss of circadian rhythm and higher levels of cortisol are observed in depression [92], but most patients with depression do not suffer from delirium. However, it is possible that LHPA dysregulation in depression is less severe in depression than in delirium [87,93]. Additionally, exogenous glucocorticoid administration only results in delirium in a minority of patients [76]. However, it remains an important aspect of our hypothesis that some individuals are predisposed to severe adverse effects of glucocorticoids, due to preexisting pathology such as that present in Alzheimer’s disease.

**Interactions between inflammation and the LHPA axis**

In a simplistic view of the interaction between the stress and inflammatory responses, inflammatory mediators such as IL-6 induce activation of the LHPA axis. This then results in secretion of glucocorticoids, occupation of GR, and subsequent down-regulation of inflammatory responses via blocking of nuclear factor κB-induced transcriptional activation. There is certainly clear evidence that an acute stress response can protect against inflammatory damage in the brain [94]. Recent studies, however, show that chronic unpredictable stress can actually exacerbate inflammatory actions in the brain [95,96]. LPS induces transcription of inflammatory genes in rats, and blocking GC action using RU-486 further augments these increases. However, if the animals are exposed to chronic stress prior to LPS challenge, blocking GC action now blunts the inflammatory response [97]. It now appears that the influence of LHPA axis activation on CNS inflammation may depend on both temporal profiles and concentration of glucocorticoids [95]. Thus, stress and sickness behavior responses could conceivably interact to further exacerbate the CNS effects of systemic inflammation (Fig. 2). Psychological as well as physiological stress may also have a role to play. In one recent example, surgical stress induced changes in mood and memory and marked postsurgical impairments in memory.
could be predicted from changes in memory on the morning of surgery, before any medical intervention had taken place [98]. This suggests that the psychological stress associated with anticipation of surgery may have important effects on CNS, perhaps mediated by both inflammatory processes and glucocorticoids [99]. The stress response from the surgery itself may then compound these adverse effects. Similarly, it has been shown that the deleterious CNS effects of immunotherapy with interferon-α are exaggerated in patients with a background of psychosocial stress [100]. These intriguing findings may have important implications for delirium, but much research is required to unravel these interactions even at an experimental level, before we can evaluate their significance in patients.

**Conclusions and discussion**

A fundamental goal in delirium research is characterising the physiological and molecular pathways that lead from the wide range of precipitants to the relatively stereotyped syndrome (at least with respect to the core features) of delirium. In this article, we have suggested that the precipitants of delirium can usefully be divided into two conceptually distinct classes: (a) direct brain insults and (b) aberrant stress responses. The rationale for this classification is that these categories have different implications for research and the development of therapies. The category of direct brain insults reflects dysfunction or damage of the brain resulting from mainly indiscriminate effects such as hypoxia or metabolic disturbance. The category of aberrant stress responses is distinct in that this includes the harmful effects of acute stress responses, which, in health, are adaptive. Much evidence suggests that these adaptive processes have the potential to become deleterious when they are exaggerated or sustained or when they affect a brain already compromised by disease states.

This categorization of delirium aetiology may be of benefit in suggesting new strategies for prevention and treatment of delirium. Choice of prevention or therapy of direct brain insults clearly depends on the major processes suspected in a given clinical situation, such as perioperative hypoxia or hypotension, or the toxic effects of drugs. Broadly speaking, preventing and treating delirium here are concerned with general brain protection measures, which must apply in every clinical situation: avoiding energy deprivation, metabolic disturbance, drug toxicity, and so on. These strategies have explicitly been addressed in existing studies [8,9] and are central to optimal clinical care. However, therapies for aberrant stress responses might involve alternative and more specific strategies such as using drugs to reduce the magnitude or duration of the stress response, block signalling pathways, or reduce the neural consequences of stress responses. Behavioral interventions such as repeated orientation of patients and encouraging presence of relatives known to the patient may operate through reducing psychological stress, with concomitant effects on cortisol levels and other mediators, but this has not been examined experimentally.

Another central question in delirium pathophysiology is understanding the mechanisms underlying phenomenology. For example, given that sickness behavior involves reductions in mood, motivation, and activity, it could be predicted that delirium resulting from this pathway might be more likely to be hypoactive. A systematic categorization of sickness behavior responses in elderly patients would be extremely useful in this regard. In addition, it is likely that further investigation of delirium symptoms, such as attention and apathy, which individually would not merit a diagnosis of delirium, will increase understanding of the mechanisms through which these symptoms arise in the aged population.

The pathophysiology of delirium is under-researched and poorly understood. However, as general interest in delirium continues to grow, this situation appears likely to improve. One highly promising avenue is examining ways in which insights from research on the mechanisms of acute mental status change in relation to stress biology can inform new studies on the mechanisms of delirium.

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