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Neuropathogenesis of Delirium: Review of Current Etiologic Theories and Common Pathways

José R. Maldonado, M.D., F.A.P.M., F.A.C.F.E.

Delirium is a neurobehavioral syndrome caused by dysregulation of neuronal activity secondary to systemic disturbances. Over time, a number of theories have been proposed in an attempt to explain the processes leading to the development of delirium. Each proposed theory has focused on a specific mechanism or pathologic process (e.g., dopamine excess or acetylcholine deficiency theories), observational and experiential evidence (e.g., sleep deprivation, aging), or empirical data (e.g., specific pharmacologic agents' association with postoperative delirium, intraoperative hypoxia). This article represents a review of published literature and summarizes the top seven proposed theories and their interrelation. This review includes the "neuroinflammatory," "neuronal aging," "oxidative stress," "neurotransmitter deficiency," "neuroendocrine," "diurnal dysregulation," and "network disconnectivity" hypotheses. Most of these theories are complementary, rather than competing, with many areas of intersection and reciprocal influence. The literature suggests that many factors or mechanisms included in these theories lead to a final common outcome associated with an alteration in neurotransmitter synthesis, function, and/or availability that mediates the complex behavioral and cognitive changes observed in delirium. In general, the most commonly described neurotransmitter changes associated with delirium include deficiencies in acetylcholine and/or melatonin availability; excess in dopamine, norepinephrine, and/or glutamate release; and variable alterations (e.g., either a decreased or increased activity, depending on delirium presentation and cause) in serotonin, histamine, and/or γ-aminobutyric acid. In the end, it is unlikely that any one of these theories is fully capable of explaining the etiology or phenomenologic manifestations of delirium but rather that two or more of these, if not all, act together to lead to the biochemical derangement and, ultimately, to the complex cognitive and behavioral changes characteristic of delirium.
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Key Words: Aging, delirium, encephalopathy, physiologic stress, neuroinflammation, large neutral amino acids, neuroendocrine, oxidative stress

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DELIRIUM: SCOPE OF THE PROBLEM

Delirium is a neurobehavioral syndrome caused by dysregulation of baseline neuronal activity secondary to systemic disturbances,[1] characterized by an alteration in the level of attention and awareness, which develops over a relative short period of time, and represents a change from the subject's baseline.[2] Clinically, delirium is an acute or subacute organic mental syndrome characterized by a disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment), cognition (e.g., memory deficit, disorientation), language, visuospatial ability, or perception that is not better explained by a preexisting, established, or other evolving neurocognitive disorder.[2–5]

A recent study at a large general hospital found that the point prevalence of delirium is one in every five inpatients, with some variation in certain medicosurgical units and populations.[6] Studies have found that between 14% and 24% of elderly patients are admitted to the hospital with delirium[7,8] and that delirium occurs in up to 50% of elderly inpatients.[9] In the emergency department, the prevalence in elderly patients is 9.6%.[10] The reported rate of postoperative delirium ranges between 10% and 74% depending on the type of surgery and population under study.[11–15] Studies have demonstrated that up to 87% of critically ill patients develop delirium during their intensive care unit (ICU) stay.[16] This is important considering that the proportion of patients in the ICU aged at least 65 years is 56%.[17] Furthermore, studies predict that by 2015 the rate of elderly aged 80 years and older admitted to the ICU will increase by 72%, representing roughly one in four admissions to the ICU.[18]

DELIRIUM CONSEQUENCES

Delirium has been reported to be one of the six leading causes of preventable conditions in hospitalized elderly patients.[19] After controlling for demographics, apparent illness severity, age, and medical comorbidities, patients who develop delirium fare much worse than their nondelirious counterparts. The mortality rate for elderly patients in acute care hospitals is much higher among those with delirium than those without delirium: 8% versus 1% in a study of 229 medically ill, hospitalized elderly patients.[20] Even years after it occurred, delirium continues to have a long-lasting impact, with a 3-year mortality of 75% for patients who had developed in-hospital delirium versus 51% for control patients (risk ratio: 2.24), even after accounting for prehospital measures of global cognition, physical functioning, and medical comorbidity.[21] The number of days of delirium older patients experience during an ICU admission is significantly associated with mortality up to 1 year after admission after controlling for severity of illness ($p = 0.001$).[22]

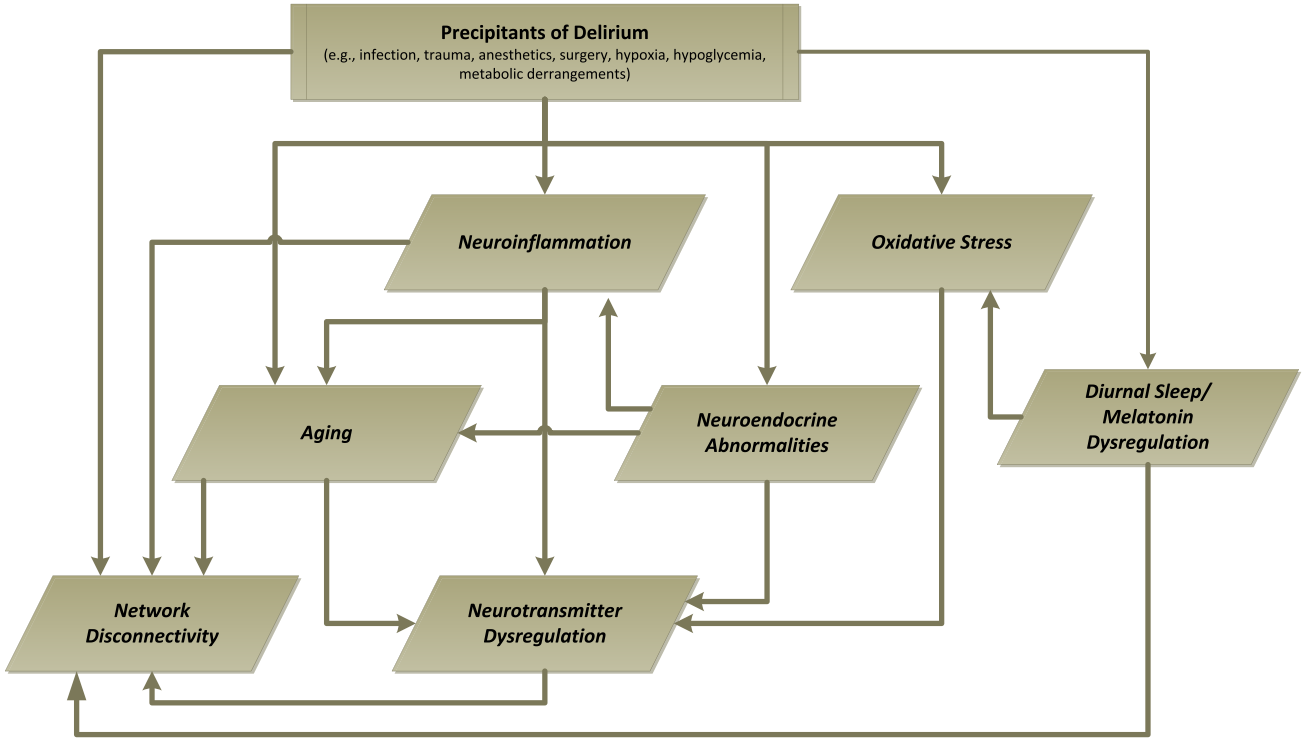
Delirious patients, when compared with patients suffering from the same medical problem who do not develop delirium, experience prolonged hospital stays, on average 5–10 days longer.[20,23–26] Among elderly medically ill inpatients incident delirium was associated with an excess stay after diagnosis of 7.78 days, even after controlling for covariates.[27] Studies have demonstrated that delirium in the emergency department was an independent predictor of prolonged hospital length of stay (i.e., twice as long) compared with nondelirious patients, even after adjusting for confounding factors.[28] Significantly more patients who develop delirium in the hospital ultimately require institutional postacute care, such as placement in a skilled nursing facility (e.g., 16% versus 3%), even after controlling for illness severity, activities of daily living status, prior cognitive impairment, and fever.[20,26]

A review of available empirical evidence suggested that a substantial proportion of patients who survive delirium were much more likely to experience long-term cognitive impairment[4,29–40] and to require institutional postacute care, such as placement in a skilled nursing facility (e.g., 16% versus 3%), even after controlling for illness severity, activities of daily living status, prior cognitive impairment, and fever.[26,41] The increased morbidity and extended hospital care associated with delirium have been associated with greater care costs.[24,42,43] The total annual direct healthcare costs attributable to delirium in the United States has been estimated to be as high as $152 billion.[44]

NEUROPATHOGENESIS OF DELIRIUM

Despite its high prevalence and high morbidity, much is not understood about delirium. Known risk

FIGURE 1. Theories on the development of delirium. Schematics of the interrelationship of current theories on the pathophysiology of delirium and how they may relate to each other. Each proposed theory has focused on a specific mechanism or pathologic process (e.g., DA excess or Ach deficiency theories), observational and experiential evidence (e.g., sleep deprivation, aging), or empirical data (e.g., specific pharmacologic agents' association with postoperative delirium, intraoperative hypoxia). Most of these theories are complementary rather than competing, with many areas of intersection and reciprocal influence. In the end, it is unlikely that any one of these theories is fully capable of explaining the etiology or phenomenologic manifestations of delirium but rather that their interaction lead to the biochemical derangement and, ultimately, to the complex cognitive and behavioral changes characteristic of delirium.



factors for delirium include advanced age, preexisting cognitive impairment (including dementia), medications (especially those with high anticholinergic potential), sleep deprivation, hypoxia and anoxia, metabolic abnormalities, and a history of alcohol or drug abuse.[4] For years it has been predicted that metabolic processes must be involved in its etiology, as described by Engel and Romano over 50 years ago: "We thus arrive at the proposition that a derangement in functional metabolism underlies all instances of delirium and that this is reflected at the clinical level by the characteristic disturbance in cognitive functions."[45 (p. 532)] Therefore, we begin with the premise that delirium is a neurobehavioral syndrome caused by the dysregulation of neuronal activity secondary to systemic disturbances.[1,45–47]

Over the years, a number of theories have been proposed in an attempt to explain the processes leading to the development of delirium.[1] Each proposed theory has focused on a specific mechanism or pathologic process (e.g., dopamine [DA] excess or acetylcholine [Ach] deficiency theories), observational and experiential evidence (e.g., sleep deprivation, aging), or empirical data (e.g., specific pharmacologic agents' association with postoperative delirium, intraoperative hypoxia). To date, however, no single unitary pathophysiologic mechanism has been identified.

This article summarizes the seven most prominent theories hypothesized to explain the phenomenon of delirium and highlights areas of commonality with the intent of increasing an appreciation of the underlying pathophysiologic mechanisms, help focus future research, and assist in developing prophylactic and treatment strategies. Most of these theories are complementary rather than competing (Fig. 1). Thus,

TABLE 1. Mechanisms Mediating Delirium and Cognitive Impairment

1. A number of factors and mechanisms leading to delirium may also directly cause CNS damage and neuronal dysfunction and thus mediate both the manifestations of delirium and long-term cognitive impairment (e.g., cytokine release and other neuroinflammatory mediators; decrease perfusion and oxygenation leading to decreased cerebral oxidative metabolism; changes in BBB permeability; hypercatabolic states; water and electrolyte imbalances; excessive GC levels and other HPA axis dysfunctions; melatonin and sleep–wake cycle abnormalities).
2. Pharmacologic agents used either to treat the underlying causes of the delirium (e.g., steroids, calcineurin inhibitors, other immunosuppressant agents, DA) or those agents used to treat delirium (e.g., DA blocking agents, benzodiazepines) may themselves lead to neuronal damage in a fragile brain.
3. Any mechanism listed above may themselves lead to alterations in neurotransmitter concentration or receptor sensitivity, which itself may underlie the different symptoms and clinical presentations of delirium and/or long-term cognitive dysfunction. Thus, the same mechanisms that cause the substrate for delirium may mediate the cognitive impairments observed after the acute presentation of delirium has resolved.
4. It is possible that instead of causing cognitive deficits or dementia, delirium (and its underlying causes) only serve as a catabolic agent leading to an acceleration of normal physiologic cerebral aging mechanisms leading to dementia.
5. It is also possible that an episode of delirium simply unmasks subtle cognitive deficits already present but not yet identified.

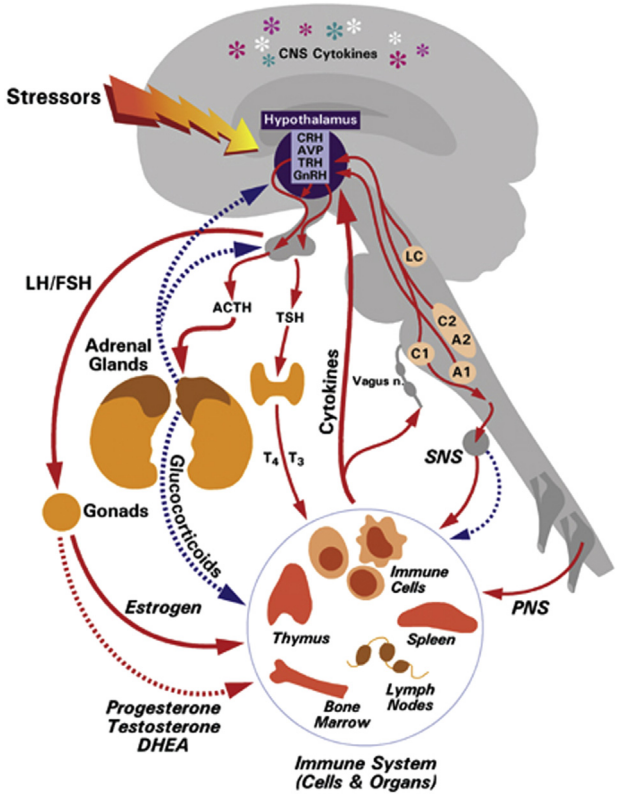
Notes: Source: Maldonado[222]

it is likely that none of these theories by themselves is fully capable of explaining the etiology or phenomenologic manifestations of delirium but rather that two or more of these, if not all, act together to lead to the biochemical derangement we know as delirium (Table 1).

NEUROINFLAMMATORY HYPOTHESIS

The Neuroinflammatory Hypothesis (NIH) proposes that acute peripheral inflammatory stimulation (from infectious, surgical, or traumatic etiologies) induces activation of brain parenchymal cells and expression of proinflammatory cytokines and inflammatory mediators in the central nervous system (CNS) that induce neuronal and synaptic dysfunction and subsequent neurobehavioral and cognitive symptoms characteristic of delirium (Fig. 2).[48–53] Others have previously demonstrated how the brain monitors the presence of peripheral inflammation and how upon exposure to infection or inflammation sick individuals develop nonspecific physiologic (e.g., fever, pain, malaise, fatigue, and anorexia) and behavioral

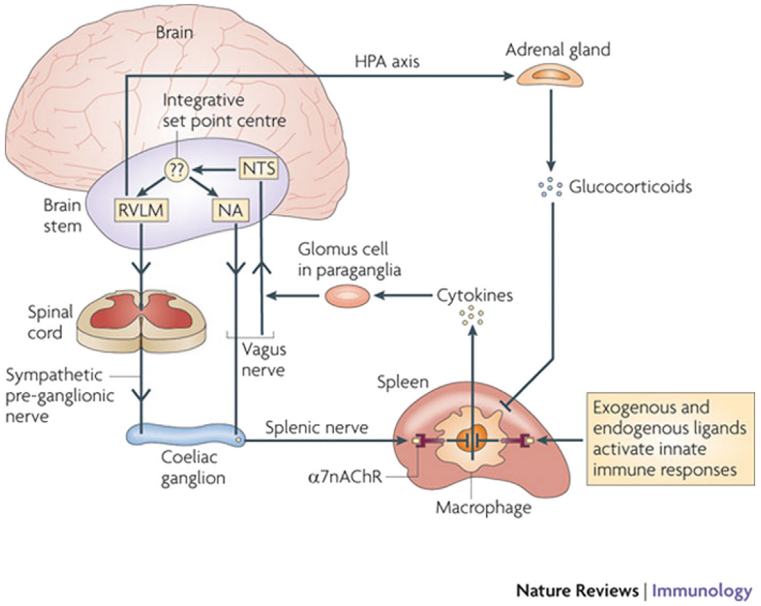
FIGURE 2. Schematic illustration of neural immune connections. Immune signaling of the CNS via systemic routes and the vagus nerve (Vagus n.) and CNS regulation of immunity via the HPA, hypothalamic–pituitary–thyroid, and hypothalamic–pituitary–gonadal axes and the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). Cytokine expression within the CNS is represented by asterisks within the brain. Dotted lines represent negative regulatory pathways, and solid lines represent positive regulatory pathways. CRH: corticotrophin-releasing hormone; AVP: arginine vasopressin; TRH: thyrotropin-releasing hormone; GnRH: gonadotropin-releasing hormone; ACTH: adrenocorticotrophin hormone; TSH: thyroid-stimulating hormone; T_4: thyroxine; T_3: triio-dothyronine; LH: luteinizing hormone; FSH: follicle-stimulating hormone; LC: locus coeruleus; Al, Cl, A2, C2: brainstem adrenergic nuclei. (From Marques-Deak et al.[377]).



(e.g., lethargy, depressed mood, social withdrawal, cognitive loss, and anhedonia) changes known as "sickness behavior."[54–59]

Thus, ultimately the NIH suggests that delirium may represent the CNS manifestation of a systemic disease state that has indeed crossed the blood–brain

FIGURE 3. **Functional anatomy of the inflammatory reflex. Afferent (sensory) neural signals to the brain stem are relayed by the vagus nerve to the nucleus of the solitary tract (nucleus tractus solitaries [NTS]). Polysynaptic relays then connect to the outflow centers of the autonomic nervous system, the rostral ventrolateral medullary (RVLM) sympathoexcitatory neurons and the vagal motor neurons in the nucleus ambiguus (NA), and the dorsal vagal motor nucleus. Outflow arrives at the coeliac ganglion from either the vagus nerve or the preganglionic efferent nerves, which originate in the sympathetic trunk. Stimulating the vagus nerve suppresses innate immune responses and down-regulates proinflammatory cytokine release in the spleen through a mechanism that depends on nicotinic Ach receptor subunit α7 (α7nAChR). Note that after the activation of the inflammatory reflex by sensory input to the brainstem, the signals are also relayed to the nuclei controlling the function of the HPA axis, which increases GC hormone release by the adrenal gland. This provides an important connection between the neural networks that can acutely provide compensatory signals to adjust immune responses and the humoral anti-inflammatory mechanisms that can more chronically modulate innate and adaptive immune responses. (From Tracey[378]).**



barrier (BBB).[1] Many of the circumstances associated with a high incidence of delirium (e.g., infections, postoperative states) may be also associated with BBB integrity compromise. It is theorized that several illness processes (i.e., trauma, infections) and surgical procedures may introduce triggering factors leading to the activation of the inflammatory cascade: use of anesthetic agents, extensive tissue trauma, presence of foreign organisms or substances, elevated hormone levels, blood loss and anemia, blood transfusions, use of extracorporeal circulation, hypoxia, ischemia and reperfusion, formation of heparin–protamine complexes, and microemboli formation and migration (reviewed by Maldonado[1]).

Others have demonstrated two pathways through which immune signals from the periphery are transduced to the brain (Fig. 3): the neural pathway and the humoral pathway.[60] In the neural pathway, peripherally produced pathogen-associated molecular patterns and cytokines activate primary afferent nerves, such as the vagus nerve. The humoral pathway involves circulating pathogen-associated molecular patterns that reach the brain at the level of the choroid plexus and the circumventricular organs where pathogen-associated molecular patterns induce the production and release of proinflammatory cytokines by macrophage-like cells expressing Toll-like receptors. Several studies have demonstrated that patients develop delirium during acute medical hospitalizations experienced elevation of C-reactive protein, interleukin (IL)-6, tumor necrosis factor-α, IL-1RA, IL-10, and IL-8 as compared with patients who did not have delirium, even after adjusting for infection, age, and cognitive impairment, suggesting an association between proinflammatory cytokines and the pathogenesis of delirium.[61–63]

A study of adult patients admitted to medicine wards showed that those who developed delirium had significantly elevated levels of IL-6 (53% versus 31%) and IL-8 (45% versus 22%) when compared with patients who did not develop delirium, even after adjusting for infection, age, and cognitive impairment.[61] This is the first study to show a relationship between peripherally measured cytokine levels and delirium as a symptom of sickness behavior in acutely admitted elderly. It also showed that cognitive function can be impaired by a systemic infection in patients with a neurodegenerative disorder such as Alzheimer disease and that this cognitive decline is preceded by raised serum levels of IL-1h. Similarly, a recent study found that high preoperative neopterin levels predicted delirium after cardiac surgery in older adults, suggesting that plasma neopterin levels may be a candidate biomarker for delirium among this patient population.[64] Neopterin is produced by human monocytes/macrophages upon stimulation with the cytokine interferon-γ and thus can serve as a maker for immune system activation.[65]

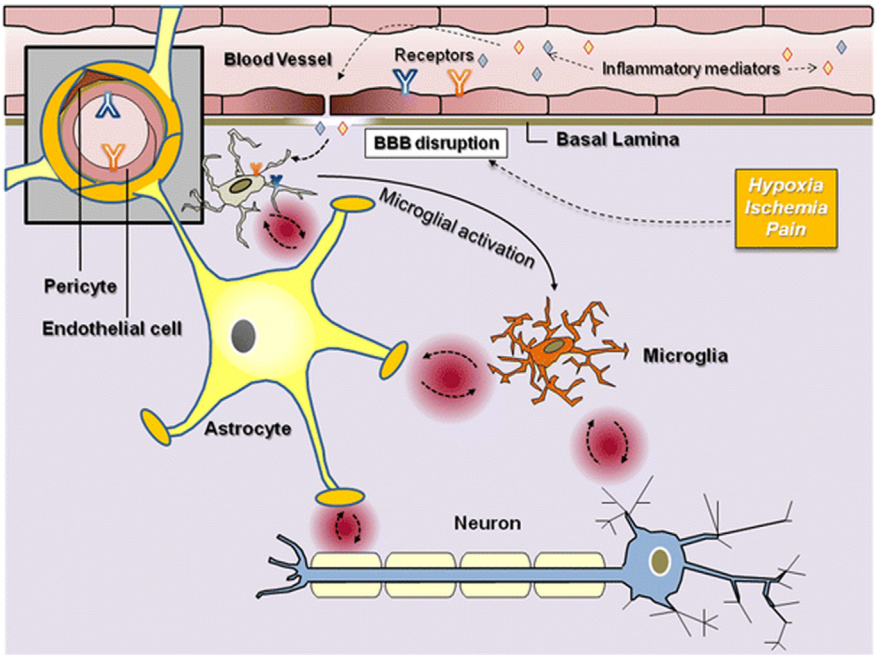
CNS resident cells react to the presence of peripheral immune signals, leading to production of cytokines and other mediators in the brain, cell proliferation, and activation of the hypothalamics–pituitary–adrenal (HPA) axis (see Neuroendocrine Hypothesis, below) through a complex system of interactions. These neuroinflammatory changes cause BBB permeability disruption (as suspected by elevations of S100 beta) and changes in synaptic transmission, neural excitability, and cerebral blood flow, leading to the neurobehavioral and cognitive symptoms characteristic of delirium (e.g., disruption in behavior and cognitive functions).[48] S100 beta is a calcium-binding protein with cytokine-like properties, secreted primarily by astrocytes under metabolic stress, and is considered a putative biomarker of CNS damage: Increased cerebrospinal fluid (CSF) and serum S100 beta are linked with adverse CNS outcomes. Several studies have reported findings of elevated S100 beta levels among patients suffering from either dementia[66–68] or delirium.[69–72] Furthermore, aging and neurodegenerative disorders exaggerate brain microglial responses after stimulation by systemic immune stimuli such as peripheral inflammation and/or infection (see Neuronal Aging Hypothesis, below).

During or after various disease processes or trauma/surgery, leukocytes adhere to endothelial cells, which make up the bulk of the blood–brain barrier and become activated, leading to degranulation and the release of free oxygen radicals and enzymes, which in turn leads to endothelial cell membrane destruction, disruption of cell–cell adhesions, and increased endothelial permeability.[73,74] This in turn causes extravascular fluid shifts and the development of perivascular edema in cerebral tissue, which leads to decreased perfusion and longer diffusion distance for oxygen.[48,75,76] These processes may lead to such extensive perfusion impairment that the blood flow in individual capillaries becomes disrupted; thus, systemic inflammation as a response to trauma or illness leads to microcirculatory impairment and subsequent ischemic injury (see Oxidative Stress Hypothesis, below). Among the pertinent neurotransmitters, Ach synthesis and release may be the most sensitive to this type of hypoxic injury and other homeostatic changes in the brain (see Neurotransmitter Hypothesis, below).[77] Similarly, neuroinflammatory injuries have also been associated with imbalances in other neurotransmitters including DA, serotonin (5HT), and norepinephrine (NE).[78]

In response to traumatic and systemic events, the systemic inflammatory response is activated, causing monocytes and macrophages to produce neopterin, cytokines, and reactive oxygen species, which can be found in the plasma, urine, and CSF of delirious patients.[1,48,63,64,79–82] In addition, disruptions of the endothelial cells (as described above) may also lead to enhanced cytokine transport across the disrupted BBB and infiltration of leukocytes and cytokines into the CNS, producing ischemia and neuronal apoptosis (Fig. 4).[48,83,84]

Systemic inflammation is common in liver failure, and its acquisition is a predictor of hepatic encephalopathy (HE) severity. Studies provide convincing evidence for a role of neuroinflammation in liver failure; this evidence includes activation of microglia, together with increased synthesis in situ of proinflammatory cytokines (i.e., TNF, IL-1β, and IL-6). The proposed "liver–brain signaling mechanisms" in liver failure include direct effects of systemic proinflammatory molecules, recruitment of monocytes after microglial activation, brain accumulation of ammonia, lactate and manganese, and altered

FIGURE 4. Effect of Inflammation on the development of delirium. Recognition and propagation of peripheral immune stimuli in the CNS. The initial interaction of circulating inflammatory mediators (e.g., cytokines and lipopolysaccharide) with the neurovascular unit occurs through a vast number of receptors and is associated with an increased paracellular permeability of the BBB. In addition to systemic inflammation, other factors affect the integrity of BBB including hypoxia, ischemia, and pain. Recognition of peripheral inflammatory stimuli in the BBB is followed by a cascade of events leading to microglia activation and subsequent modulation of adjacent cells including astrocytes and neurons (represented with dashed reciprocal arrows). (From Cerejeira et al.[48]).

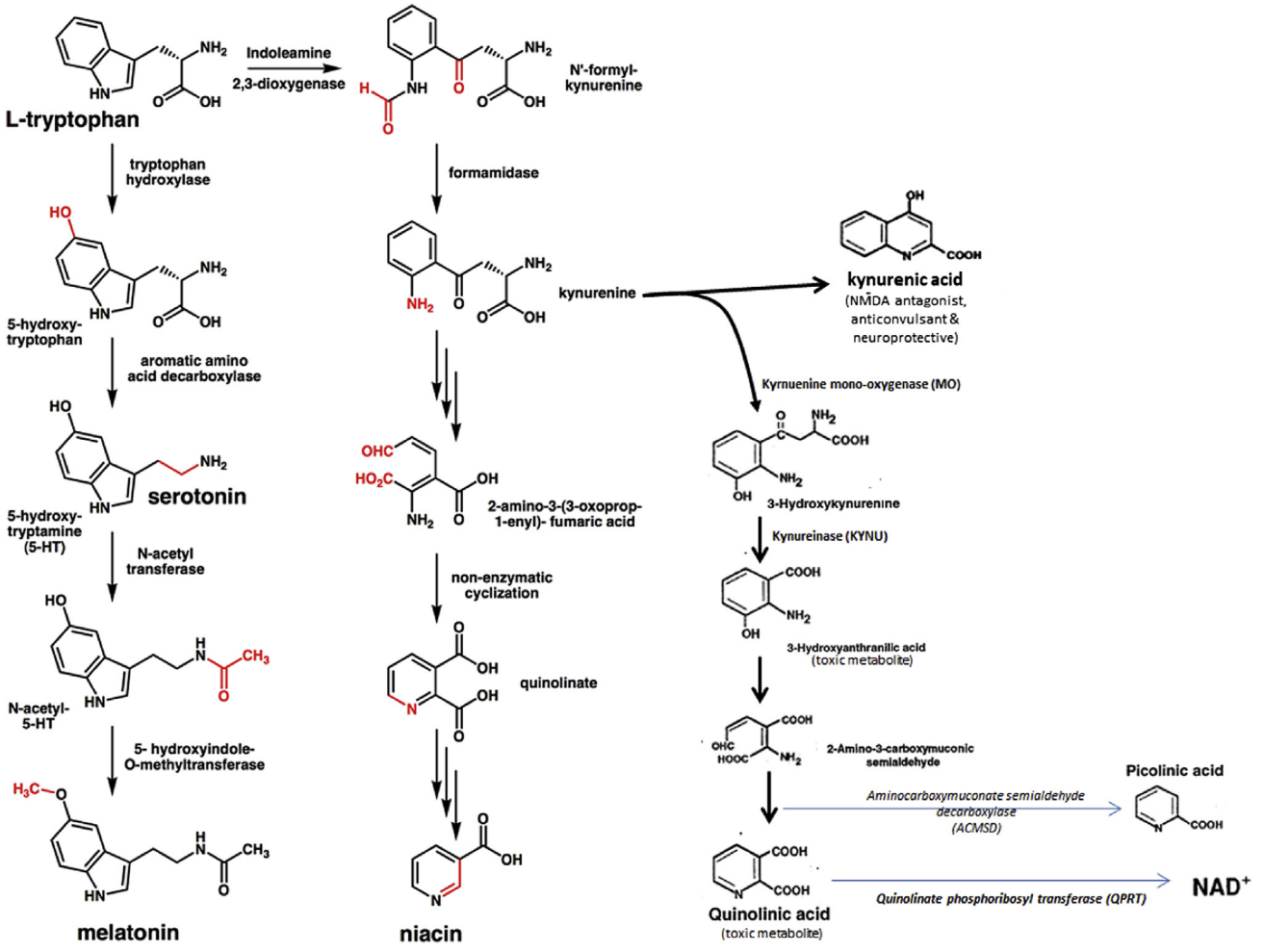


permeability of the BBB.[85,86] This provides another intersection of the NIH with the Neurotransmitter Hypothesis (NTH) as the above changes may contribute to the alteration in neurotransmitter functioning in cases of HE (e.g., increased DA, 5HT, and γ-aminobutyric acid [GABA]).

There is also mounting evidence that some proinflammatory cytokines that induce sickness behavior also enhance activity of the ubiquitous indoleamine-2,3-dioxygenase (Fig. 5).[87,88] Activation of indoleamine-2,3-dioxygenase results in decreased tryptophan (TRP) levels, thus a reduction in 5HT and melatonin production, whereas there is a shift to the production of kynurenine and other TRP-derived metabolites that have neurotoxic effects.[89–91]

Systemic inflammation, such as that caused by injury (including surgery) or infection, has long been recognized as trigger for episodes of delirium, particularly in elderly or demented patients, even though their deliriogenic effect seems to be lessened in younger and nondemented patients.[51,62,74,92–99] Yet, even in younger and nondemented adult patients, the severity of the patient's injury or underlying medical problem is significantly directly correlated with the development of delirium.[100,101] These facts suggest that either a low dose of precipitant in a vulnerable patient or a high dose in the nonvulnerable may overwhelm the system and lead to delirium. Thus, it seems likely that more severe systemic inflammatory responses are more likely to induce delirium, but pre-existing pathology in cognitive circuitry is a stronger predictor; thus, the interaction between these two factors is key.[102] The NIH intersects with the Neuronal Aging Hypothesis (NAH) because it has been shown that microglia, the major macrophage population of the brain, are primed by prior neurodegenerative pathology to respond more robustly to systemic inflammatory signals.[53,103] There is also an interaction with the HPA axis (see Neuroendocrine Hypothesis, below) as hormones help coordinate an animal's physiology and behavior to match its environment and maximize

FIGURE 5. Metabolic Pattern of TRP, 5HT, melatonin, and kynurenic and quinolinic acid. Evidence suggests that some proinflammatory cytokines cannot only induce sickness behavior but also enhance activity of the ubiquitous indoleamine-2,3-dioxygenase, leading to deficient TRP levels, thus a reduction in 5HT and melatonin production, and a shift to the production of kynurenine and other neurotoxic TRP-derived metabolites. (Adapted from Stone et al.[87] & Darlington et al.[88]).

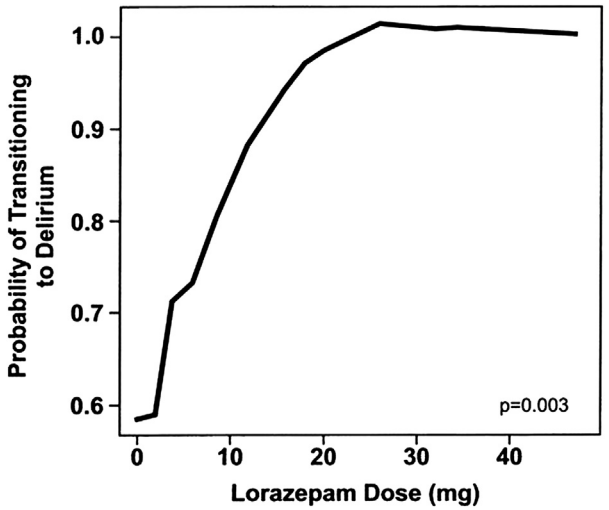


survival; among the most important processes influenced by endocrine hormones are the immunologic and behavioral responses to infection.[104,105]

NEURONAL AGING HYPOTHESIS

The NAH suggests that the aging process and accompanying physiologic changes constitute an independent risk factor for delirium. The concept of homeostenosis implies that a functional elderly person may maintain health into old age but may become increasingly vulnerable to stress and illness because of a lack of physiologic reserve.[106] Accordingly, aging is associated with age-related cerebral changes in stress-regulating neurotransmitters, brain–blood flow decline, decreased vascular density, neuron loss (particularly in locus coeruleus and substantia nigra), and intracellular signal transduction systems.[107–122] This likely explains why the aging process itself is associated with some degree of cognitive deficits and an increased risk of dementia (Table 1). The NAH may also explain why the elderly seem to experience a greater chance of developing delirium when challenged by physiologic distress that is better tolerated by younger individuals.

FIGURE 6. Age and transition to delirium. An estimation of the probability of transitioning to delirium by age indicates that the incremental risk is large for patients aged 65 years and older. The probability of transitioning to delirium increased dramatically (by 2%) for each year of life after 65 years. Adjusted odds ratio: 1.01 [(1.00, 1.02)], p = 0.03. (Pandharipande P et al.)[101]



Although the estimated annual incidence of Alzheimer disease in the population is 0.6% for persons aged 65 and older,[123] among elderly patients in the ICU, the probability of developing delirium increases by 2% per year of age for each year after age 65 (Fig. 6).[101] Other studies confirm that older age is an independent risk factor among medically ill and surgical patients, with the increase in rate per year dependent on the specific context in which incidence is measured.[124–128] The data also suggest a reciprocal relationship between delirium and cognitive decline: Dementia is the strongest risk factor for delirium among older patients,[27,92,129,130] and the development of delirium appears to increase the risk of cognitive decline, including dementia.[32]

It is well established that individuals with compromised cognitive ability preoperatively (e.g., dementia) are at greater risk of delirium.[131–134] A study of elderly subjects undergoing orthopedic surgery demonstrated that the presence of dementia increased the incidence of postoperative delirium from 32% to 100%.[33] However, evidence suggests that decrements in higher-order cognitive functions, such as executive function (e.g., problem solving, processing speed, planning, complex sequencing, and reasoning), may also predict postoperative delirium in the absence of frank cognitive impairment.[135,136] A study of nondemented elderly patients undergoing elective orthopedic surgery demonstrated that subtle preoperative attention deficits, as tested by digit vigilance and reaction time testing, were closely associated with postoperative delirium.[137] In fact, these subtle changes predicted a four- to fivefold increased risk of postoperative delirium for subjects more than one standard deviation above the sample means on these variables.

Conversely, studies have demonstrated that among elderly surgical patients, delirium is a strong independent predictor of cognitive impairment and the occurrence of severe dependency in activities of daily living. In fact, 38 months after discharge from hospital, 53.8% of surviving patients with postoperative delirium continued to experience cognitive impairment, as compared with only 4.4% of nondelirious subjects.[35] Similarly, a prospective, matched, controlled cohort study of elderly hip surgery patients demonstrated that the risk of dementia or minimal mild cognitive impairment over a 30-month follow-up almost doubled in inpatients with postoperative delirium compared with those without delirium.[36]

The data suggest that many older hospital patients do not recover from delirium and that persistence of delirium is associated with adverse outcomes. In some studies, the long-term outcomes (e.g., mortality, nursing home placement, cognition, function) of patients with persistent delirium were consistently worse than the outcomes of patients who had recovered from delirium.[138] These findings suggest that delirium does not simply persist for a certain time but also predicts a future cognitive decline with an increased risk of dementia. Table 2 provides a list of potential mechanisms associated with the increased risk of delirium in the elderly.

The observed increased levels of circulating inflammatory mediators (e.g., cytokines, acute phase proteins) suggest that chronic neurodegeneration is accompanied by an inflammatory response characterized by chronic, but selective, activation of CNS microglial cells that are "primed" to produce exaggerated inflammatory responses to immunologic challenges.[48,53] Age-related changes in the immune system, known as immunosenescence, and increased secretion of cytokines by adipose tissue represent the

TABLE 2. Potential Mechanisms Associated with the Increased Risk of Delirium in the Elderly

- Neuronal loss particularly in locus coeruleus and substantia nigra[110,111]
- Changes in various neurotransmitter systems[111]
- Age-related decline in white matter integrity, observed as increases in water diffusion and volume of hyperintense white matter lesions, intergyral spans, and reduction in fractional anisotropy of water diffusion, correlated with a decline in the global and regional cerebral glucose uptake[109]
- Age-related decline in regional cerebral blood flow, particularly in the anterior cingulate gyrus, bilateral basal ganglia, left prefrontal, left lateral frontal and left superior temporal and insular cortex, as measured by single-photon emission tomography[119]
- Age-related changes in cerebral blood flow, likely associated with brain microvascular pathologies:[112–116,118]
  - Rarefaction of the microvasculature in some regions of the brain
  - Decreased vascular density
  - Damaged microvessels, with associated microinfarcts and microhemorrhages, likely due to peripheral arterial aging leading to stiffening and dilation of the proximal aorta with transmission of flow pulsations downstream into the brain
  - Decline in cerebrovascular angiogenesis
  - Impaired cerebral blood flow due to tortuous arterioles and deposition of excessive collagen in veins and venules
- Age-related decline in cerebral metabolic rate of oxygen more markedly in bilateral putamen, left supratemporal, left infrafrontal, and left parietal cortices[121]
- Decreased oxygen supply (e.g., hypoxia) leading to a decrease in redox activity, resulting in decreased ACh production[158,194]
- Decreased cerebral oxidative metabolism[158]
- Age-related changes in brain neurochemical activity:[122]
  - There is a significant increase in soluble hexokinase activity with age, due to an increased release of mitochondrially bound hexokinase.
  - There is a negative correlation of the activity of fructose-6-hosphate kinase with age, particularly in brain cortex and putamen.
  - There is a significant decline of carbonic anhydrase (important in the regulation of the Po_2/Pco_2 ratio in the brain tissue) with increasing age. Thus, Pco_2-dependent regulation of tissue pH, ionic transport processes, and cerebral blood flow regulation have the tendency to become more and more unstable.
  - There is a progressive, age-dependent decline in cAMP-dependent activity, most significantly in brain cortex and thalamus, followed by hippocampus, amygdala, and globus pallidus.
- Age-related cerebral changes in stress-regulating neurotransmitter and intracellular signal transduction systems[53]
- Decreased ACh levels in plasma and CSF[181,185,187,192,195,196]
  - This is likely due to
    - Decreased volume of Ach-producing cells associated with normal aging (see Neurotransmitter Hypothesis)[158]
    - Decreased ACh synthesis associated with aging[158]
    - Increase in baseline levels of circulating inflammatory mediators including cytokines and acute phase proteins (see Neuroinflammatory Hypothesis)[48,52,60,61,108,191]

major causes of chronic inflammation, a phenomenon known as "inflammaging."[139] This inflammation may contribute to disease progression through the production of inflammatory mediators. The aging process is associated with a two- to fourfold increase in baseline levels of circulating inflammatory mediators, including cytokines and acute phase proteins.[52,60,61] Other factors may influence the medically ill elderly patient, such as lower cognitive reserves, lower metabolic capacity, increased sensitivity to medications, and lower threshold to a medication's anticholinergic effects. In fact, even though high levels of postoperative pain and high opioid use was found to increase the risk for postoperative delirium in all elderly patients, the highest incidence of delirium occurred among patients who had high preoperative risk for delirium (e.g., lower baseline cognitive status, comorbid psychiatric symptoms).[140]

Finally, there has been some controversy regarding the contribution of apolipoprotein E (APOE) to the development of postoperative cognitive dysfunction. Of the nine articles published to date on the topic, four found that *APOE-E4* genotype was not associated with postoperative cognitive dysfunction,[141–144] whereas five suggested a positive relationship[145–149] (Table 3). At least one study found a positive relationship between delirium with APOE genotype, interferon-γ, and insulin-like growth factor-I and that recovery was significantly associated with lack of APOE4 allele and higher initial interferon-γ.[145] The only published meta-analysis on the matter found a positive association between postoperative cognitive dysfunction and the APOEσ4 allele.[150]

OXIDATIVE STRESS HYPOTHESIS

Hypoperfusion appears to induce chronic oxidative damage in tissues and cells, largely due to the generation of reactive oxygen and reactive nitrogen species. Any condition that outpaces the capacity of endogenous redox systems to neutralize such toxic intermediates could lead to a system imbalance or to major compensatory adjustments that rebalance the system. This new redox state is generally referred to as "oxidative stress" (Fig. 7).[151] The Oxidative Stress Hypothesis (OSH), initially proposed by Engel and Romano,[45] proposes that a number of physiologic processes, such as tissue damage, hypoxia, severe illness, and infections, may give rise to increased oxygen consumption and/or decreased oxygen availability, with associated increased energy expenditure and reduced cerebral oxidative metabolism, leading to cerebral

TABLE 3. Association Between APOE genotype and POCD

Study	Population	Findings	p
Abildstrom et al., 2004[141] Prospective, N = 967	Patients aged 40 y, older undergoing noncardiac surgery	• One week after surgery, the incidence of POCD was 11.7% in patients with the ε4 allele and 9.9% in patients without the ε4 allele. • Conclusion: unable to show a significant association between APOE genotype and POCD.	0.41
Adamis et al., 2007[145] Prospective, N = 164	≥70 y/o hospitalized medically ill patients	• Recovery was significantly ($p < 0.05$) associated with lack of APOE4 allele and higher initial IFN-γ. • A model incorporating gender, APOE ε4 status, and insulin-like growth factor-I levels predicted recovery or not from delirium in 76.5% of cases, with a sensitivity of 0.77 and specificity of 0.75. • It further found a positive relationship between delirium with APOE genotype, IFN-γ, and insulin-like growth factor-I but not with IL-6, IL-1, TNF-α, and leukemia inhibitory factor.	<0.05
Leung et al., 2007[147] Prospective, N = 190	Patients aged >65 y scheduled to undergo major non-cardiac surgery requiring anesthesia	• The presence of one copy of the ε4 allele was associated with an increased risk of early postoperative delirium (28.3% vs. 11.1%; $p = 0.005$). Even after adjusting for covariates, patients with one copy of the ε4 allele were still more likely to have an increased risk of early postoperative delirium (OR: 3.64; 95% CI: 1.51−8.77) compared with those without the ε4 allele.	0.005
Tagarakis et al., 2007[143]	Elderly adults undergoing cardiac bypass surgery; excluded dementia	• Study confirmed the high incidence of cognitive decline and delirium after coronary surgery but did not support the role of the APOE ε4 allele in the occurrence of delirium.	NS
Van Munster et al., 2007[144] N = 415	Acutely admitted patients aged ≥65 y to the Department of Medicine	• The OR for carriers of an APOE ε4 allele compared with patients without an APOE ε4 allele for developing delirium was 1.17 (95% CI: 0.49−2.78) in the cognitively intact patients and 0.42 (95% CI: 0.14−1.30) in the cognitively impaired patients. No relation existed between the total number of APOE ε4 alleles and the different delirium subtypes.	0.12
Ely et al., 2007[146] N = 53	Mechanically ventilated intensive care unit patients	• Using multivariable regression analysis to adjust for age, admission diagnosis of sepsis or acute respiratory distress syndrome or pneumonia, severity of illness, and duration of coma, the presence of APOE4 allele was the strongest predictor of delirium duration (OR: 7.32; 95% CI: 1.82−29.51).	0.005
Zhang et al., 2008[149] N = 196	Elderly patients (>60 y/o) scheduled for major abdominal surgery requiring general anesthesia	The presence of the ε4 allele and low level of education were both associated with an increased risk of EA (36.9% vs. 15.8%, $p = 0.005$; 30% vs. 14.3%, $p = 0.01$). After adjustment for covariates, the patients with the copy of ε4 allele were shown to have a greater likeliness of an	0.01

(*Continued*)

TABLE 3. (*Continued*)

Study	Population	Findings	p
		increased risk of EA (OR: 4.32; 95% CI: 1.75−10.05).	
Van Munster et al., 2009[148] Meta-analysis, N = 656+	Medical Department and Orthopedic/ Traumatology Department of University Hospital from 2003 to 2007	The OR for delirium adjusted for age, cognitive, and functional impairment of σ4 carriers compared with non-σ4 carriers was 1.7 (95% CI: 1.1−2.6). Four studies were added to the meta-analysis, which included 1,099 patients in total. The OR for delirium in the meta-analysis was 1.6 (95% CI: 0.9−2.7) of σ4 carriers compared with non-σ4 carriers. This study and meta-analysis suggest an association between delirium and the APOE σ4 allele.	0.04
Bryson et al., 2011[142] N = 88	Patients ≥60 y/o undergoing open aortic repair	Delirium predicted POCD at discharge (OR: 2.86; 95% CI: 0.99−8.27) but not at 3 months. APOE ε4 genotype was not associated with either delirium or POCD after adjustment for covariates.	0.625

Source: Maldonado[222]
Notes: POCD: postoperative cognitive dysfunction; IFN-γ: interferon- γ; NS: nor significant; OR: odds ratio; CI: confidence interval.

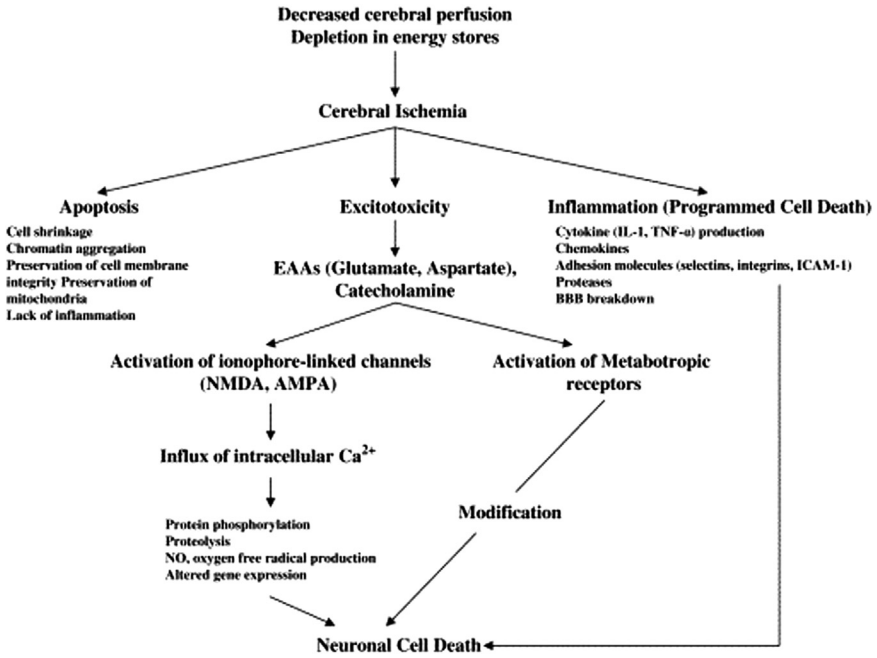
dysfunction and associated cognitive and behavioral symptoms of delirium. In other words "[delirium is] the clinical expression of a cerebral metabolic defect."[45 (p. 531)]

Some have found that oxidative stress and/or antioxidant deficiencies increase damage to cerebral tissue and lead to cognitive decline with irreversible degeneration as sequelae of delirium.[30,152−154] Among patients undergoing cardiopulmonary bypass surgery, researchers found alterations in the levels of markers of oxidative stress. In this sample, patients who developed delirium demonstrated significantly lower preoperative levels of the antioxidant enzyme catalase (normally produced by the body as the primary endogenous defense against free radical−induced injury) compared with nonpostoperative delirium patients.

Also, clinical data exist that correlate poor oxygenation and cerebral dysfunction. A study of medically ill ICU patients demonstrated that oxidative metabolic stress was present within 48 hours before the onset of delirium, as evidenced by abnormalities in three measures of oxygenation (i.e., hemoglobin, hematocrit, and pulse oximetry) among patients who developed delirium.[155] In the same sample, clinical factors associated with greater oxidative stress (e.g., sepsis, pneumonia) occurred more frequently among delirious subjects. Similarly, studies have demonstrated a strong correlation between intraoperative O_2 saturation and postoperative mental function.[156,157] Even healthy control subjects may experience delirium after dropping their Pa_{O_2} to 35 mm Hg.[158] In fact, intraoperative cerebral oxygen desaturation was found to be a significant risk factor for postoperative delirium among cardiac surgery patients.[159] In addition, operative cerebral oxygen saturation levels among patients undergoing abdominal surgery was an independent risk factor for postoperative delirium.[160] Similarly, among a group of patients undergoing cardiac surgery, those who developed postoperative delirium had lower pre- and intraoperative cerebral oxygen saturation levels, were older, and had lower preoperative hemoglobin levels compared with nonpostoperative delirium patients.[161]

Animal studies suggest that neuronal susceptibility to ischemic injury is not uniform. The basal ganglia, thalamus, Purkinje, layer 3 of the cortex, and the pyramidal neurons of the hippocampus are particularly vulnerable to hypoxia, but the degree of damage may vary depending on the cause.[162] A superimposed global mild ischemic injury is often present in critically ill patients, galvanizing the oxidative failure. Indeed, patients in the critical care setting are particularly at risk to suffer the effects of hypoperfusion resulting from a number of potentially controllable extrinsic factors (e.g., intraoperative hypotension).

FIGURE 7. **Mechanisms of brain injury after global cerebral ischemia. During cerebral ischemia, excess GLU exits into the extracellular compartment due to cellular depolarization, coupled with its impaired uptake, which results in increases in intracellular Ca^{2+}. The cascade of events responsible for GLU excitotoxicity includes three distinct processes: (1) induction, whereby extracellular GLU efflux is transduced by receptors on the neuronal membrane to cause intracellular Ca^{2+} overload, which leads to lethal intracellular derangements; (2) amplification of the derangement, with an increase in intensity and involvement of other neurons; and (3) expression of cell death triggered by cytotoxic cascades. Excess release of Ca^{2+} and its intracellular influx is thought to be the primary trigger for a variety of complex, deleterious intracellular processes that result from activation of catabolic enzymes such as phospholipases (which lead to cell membrane breakdown, arachidonic acid, and free radical formation) and endonucleases (which lead to fragmentation of genomic DNA and energy failure due to mitochondrial dysfunction). (From Harukuni & Bhardwaj[379]).**



Inadequate oxidative metabolism may be one of the underlying causes of the basic metabolic problems initiating the cascade that leads to the development of delirium, namely the inability to maintain ionic gradients causing cortical spreading depression (i.e., spreading of a self-propagating wave of cellular depolarization in the cerebral cortex);[163–168] abnormal neurotransmitter synthesis, metabolism, and release;[169–177] and a failure to effectively eliminate neurotoxic byproducts.[170,171,175]

The OSH intersects with the NTH because decreased oxygenation causes a failure in oxidative metabolism, which may be one cause of the problems observed in delirium, namely decreased oxygenation, which causes a failure in oxidative metabolism and leads to a failure of the ATPase pump system.[179] When the pump fails, the ionic gradients cannot be maintained, leading to significant influxes of sodium (Na^+) followed by calcium (Ca^{2+}), whereas potassium (K^+) moves out of the cell.[178,179] Some have theorized that it is the excess inward flux of Ca^{2+} that precipitates the most significant neurobehavioral disturbances observed in delirious patients.[232,233] The influx of Ca^{2+} during hypoxic conditions is associated with the dramatic release of several neurotransmitters, particularly glutamate (GLU) and DA.[178,179] GLU further potentiates its own release as GLU stimulates the influx of Ca^{2+}[233,234] and accumulates in the extracellular space as its reuptake and metabolism in glial cells is impeded by the ATPase pump failure.[179] In addition, at least two factors facilitate dramatic increases in DA: First, the conversion of DA to NE, which is oxygen dependent, is significantly decreased, and second, the catechol-o-methyl transferase enzymes, required for degradation of DA, get inhibited by toxic metabolites under

hypoxic conditions, leading to even greater accumulation of DA.[216] At the same time, 5HT levels fall moderately in the cortex, increase in the striatum, and remain stable in the brainstem.[235] Hypoxia also leads to a reduced synthesis and release of ACh, especially in the basal forebrain cholinergic centers.[236] Indeed, cholinergic neurotransmission is particularly sensitive to metabolic insults, such as diminished availability of glucose and oxygen.[237] ACh synthesis requires acetyl coenzyme A, which is a key intermediate linking the glycolytic pathway and the citric acid cycle. Thus, reduction in cerebral oxygen and glucose supply and deficiencies in enzyme cofactors such as thiamine may induce delirium by impairing ACh production.[77,238] These changes have been extensively reviewed and discussed elsewhere (Fig. 8).[1]

NEUROTRANSMITTER HYPOTHESIS

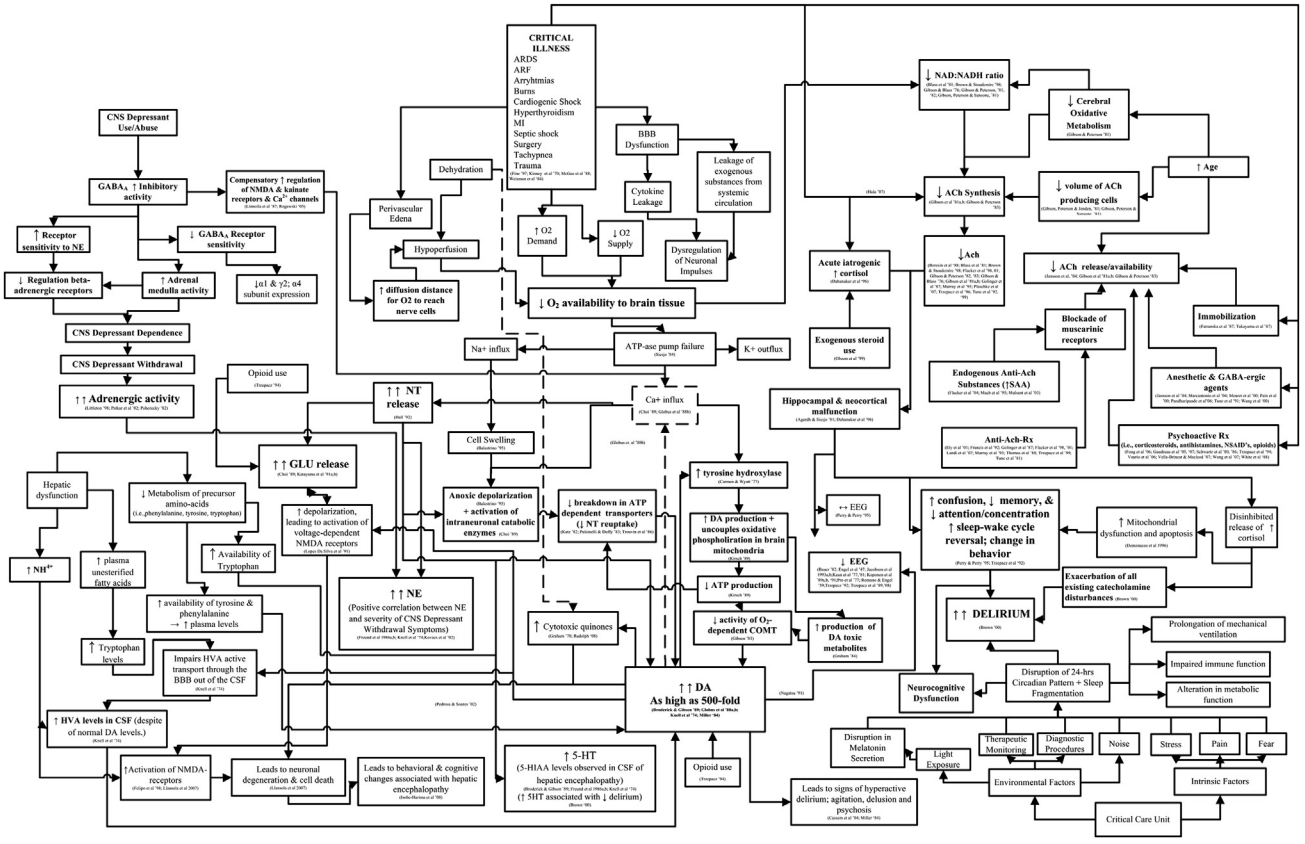
The NTH was proposed after clinical observations that delirium occurred after the use of substances (e.g., medications, toxins) that alter neurotransmitter function or availability; it was originally used to explain delirium secondary to impaired cholinergic function.[78,180–185] Some have postulated that delirium may be seen as a temporary psychiatric disorder resulting from a reduced central cholinergic transmission, combined with an increased dopaminergic transmission.[108,186,187] The NTH stresses the fact that the cholinergic and dopaminergic systems interact not only with each other but with glutamatergic and GABA pathways.[188] In fact, some pharmacologic agents (e.g., opioids) may cause delirium by increasing DA andGLU activity while decreasing Ach availability.[189] In general, the most commonly described neurotransmitter changes associated with delirium are reduced availability of Ach (↓Ach); excess release of DA (↑DA), NE (↑NE), and/or GLU (↑GLU); and alterations (e.g., both a decreased and increased activity depending on circumstances and etiological factors) in 5HT (↓↑5HT), histamine (↓↑H1 and H2), and/or GABA (↓ ↑GABA) (Table 1), as previously reviewed by others (Table 4).[1,4,108]

The cholinergic system is one of the most important modulatory neurotransmitter systems in the brain, controlling activities that depend on selective attention, which are an essential component of conscious awareness[190] (the two key components in *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, criteria for diagnosing delirium). Adequate ACh levels are also essential for the regulation of rapid-eye-movement sleep, memory, and synchronization of the electroencephalogram, among others. One of the leading hypotheses is that delirium results from an impairment of central cholinergic transmission[1,181,191–193] and is considered by some to be "a common denominator" in delirium (or toxic–metabolic encephalopaties).[194] Studies have demonstrated low levels of ACh in plasma and CSF among delirious patients.[181,185,187,192,195,196] Many have demonstrated a relationship between a drug's anticholinergic potential and its deliriogenic effects,[181,184,197–202] thus raising awareness of the potentially significant additive effect of medications commonly thought to have low ACh activity.[185,203,204]

Similarly, high levels for serum anticholinergic activity[198] have been associated with an increased likelihood of delirium among surgical[205] and medical[206] inpatients. In fact, serum anticholinergic activity levels may predict delirium,[181] and resolving delirium has been correlated to decreasing serum anticholinergic activity levels.[207] Of interest, some have found detectable serum anticholinergic activity levels in delirious patients not exposed to known anticholinergic agents, suggesting that endogenous anticholinergic substances may be produced during acute illness and could be implicated in the etiology of delirium.[195,208] In a group of hospitalized elderly patients, the Anticholinergic Risk Scale was able to predict the all-cause mortality when factored in along with baseline cognitive impairment, in-hospital delirium, place of residence (e.g., home versus nursing home), and length of hospital stay.[209]

Animal studies have revealed impairment in cholinergic neurotransmission in several models of encephalopathy and delirium, including hypoxia, nitrite poisoning, thiamine deficiency, hepatic failure, carbon monoxide poisoning, anesthesia, selective intracranial atropine injection, physical immobilization, and hypoglycemia.[186,210,211] Finally, potential animal models mimicking the decreased mobility of critically ill patients have demonstrated that immobilization may cause widespread reduction in ACh levels.[210,211] Here the NTH intersects with the NAH because aging itself is associated with age-related cerebral changes in stress-regulating hormones and

FIGURE 8. Oxidative stress and neurotransmitter theories of delirium. A basic pathoetiologic model of delirium illustrates the theorized intersections between the OSH and the NTH of the delirium, demonstrating potential common biochemical outcomes, which may explain the complex cognitive and behavioral changes characteristic of delirium. The OSH proposes that a number of physiologic processes (e.g., hypoxia, severe illness, infectious processes) may give rise to increased oxygen consumption and/or decreased oxygen availability, with associated increased energy expenditure and reduced cerebral oxidative metabolism, leading to cerebral dysfunction and associated cognitive and behavioral symptoms of delirium. The NTH was proposed after clinical observations that delirium occurred after the use of substances (e.g., medications, toxins) that alter neurotransmitter function or availability. The OSH intersects with the NTH because decreased oxygenation causes a failure in oxidative metabolism, leading to a failure of the ATPase pump system, which leads to an inability to maintain adequate ionic gradients, which in turn leads to significant electrolyte alterations (e.g., influx of Na^+ and Ca^{2+}; efflux of K^+) and subsequent alterations (e.g., excess release or decreased availability) of several neurotransmitters (e.g., GLU, DA, Ach). (From Maldonado[1]).



intracellular signal transduction systems. Aging is also associated with a decreased volume of ACh producing cells and decreased cerebral oxidative metabolism (see Oxidative Stress Hypothesis, above). Similarly, hypoxia is known to reduce the synthesis and release of ACh.[212] In addition, delirium is associated not only with an unbalanced inflammatory response but also with a dysfunctional interaction between the cholinergic and immune systems (see Neuroinflammatory Hypothesis, above).[213] In fact, acute systemic inflammation is a major trigger for cholinergic hypoactivity and is thought to be important in cognitive dysfunction during delirium.[214]

Elevations of DA have long been suspected in the development of delirium.[187,188,191] For example, studies have confirmed elevation of DA's metabolites (i.e., homovanillic acid) in the CSF of patients with fulminant HE.[215] At least two factors facilitate dramatic increases in DA. First, the conversion of DA to NE, which is oxygen dependent, is significantly decreased (allowing DA to accumulate). Second, the catechol-o-methyl transferase enzymes, required for

TABLE 4. Theorized Neurochemical Mechanisms Associated with Conditions Leading to Delirium

Delirium Source	ACH	DA	GLU	GABA	5HT	NE	Trp	Phe	His	Cytok	HPA axis	NMDA activity	Changes in RBF	EEG	Mel	Inflam	Cort
Anoxia/hypoxia	↓	↑	↑	↑	↓	↓	⇔	↑	↑,↓	⫩↑	⫩	↑	⫩	↓	↓	↑	↑
Aging	↓	↓	↓	↓	↓	↓	↓	↓	↓	⫩↑	⫩	↓	⫩	↓	↓	↑	↑
TBI	↑	↑	↑	↑	↑	↑	↑	↑	↓	↑⫩	↑	↑	↑	↓	↓	↑⫩	↑
CVA	↓	↑	↑	↑	↑	↑	↑	↑	↓	↑⫩	↑	↑	⫩	↓	↓	↑⫩	↑
Hepatic Failure (encephalopathy)	⇔	↓	↑	↑	↑	↓	↑	↑	↑	↑⫩	⫩	↑	⫩	↓	↓	↑	↑
Sleep deprivation	↓	↓	⫩	↑	↑	↑	↓	↑	↑	↑	⫩	↑	↑	↓	↓⫩	↑⫩	↑
Trauma, Sx, & Post-op	↓	↑	↑	↑	↓	↑	↓	↑	↑	↑	↑	↑	⫩	↓	↓	↑	↑
ETOH & CNS-Dep Withdrawal	↑	↑	↑	↓	↑	↑	↓	↑	↑	↑	↑⫩	↑	↓	↑	↓	↑	↑
Infection/Sepsis	↓	↓	↑	↑	↓	↓	↓	↓	↓	↑	↑⫩	↑⫩	⫩	↓	↓	↑	↑
Dehydration & Electrolyte Imbalance	⇔	↑	↑	↑	↓	↑	?	?	↑	↑	⫩	↑	↓	⫩	↓	⫩↑	↑
Medical Illness	↓	↑	↑	⫩	↓	↑	↓	↑	↑	↑	↓	↑	⫩	⫩	↓	⫩	↑

Notes: ↑ = likely to be increased or activated; ↓ = likely to be decreased or slowed; ⇔ = no significant changes; (⫩) = likely a contributor, exact mechanism is unclear; (−) = likely not to be a contributing factor; CVA = cerebro-vascular accident; Sx = surgery; ETOH = alcohol; CNS-Dep = central nervous system depressant agent; ACH = acetylcholine; DA = dopamine; GLU = glutamate; GABA = gamma-aminobutyric acid; 5HT = 5-hydroxytryptamine or serotonin; NE = norepinephrine; Trp = tryptophan; Phe = phenylalanine; His = histamine; Cytok = cytokines; HPA axis = hypothalamic-pituitary-adrenocortical axis; NMDA = N-methyl-D-aspartic acid; RBF = regional blood flow; EEG = electroencephalograph; Mel = melatonin; Inflam = inflammation; Cort = Cortisol. Source: Adapted from Maldonado, J. R. (2008). "Pathoetiological model of delirium: a comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment." *Crit Care Clin* 24(4): 789-856.

degradation of DA, get inhibited by toxic metabolites under hypoxic conditions, leading to even more amassment of DA.[216]

In delirious patients, several metabolic pathways lead to significant increases in DA under impaired oxidative conditions (reviewed elsewhere[1]). One such pathway is when significant amounts of DA are released and there is a failure of adequate DA reuptake. A second pathway is when the influx of Ca^{2+} stimulates the activity of tyrosine hydroxylase,[217] which converts tyrosine to 3,4-dihydroxyphenylalanine and leads to increased DA production and further uncouples oxidative phosphorylation in brain mitochondria.[178] The outcome is a disruption of adenosine triphospate production and the increased production of toxic metabolites of DA (formed under hypoxic conditions) that inhibit the activity of the oxygen-dependent catechol-O-methyl transferase,[212,216] the major extracellular deactivator of DA, further leading to high levels of DA. Finally, an increase in the firing rates of catecholamine neurons may further induce tyrosine hydroxylase synthesis, which leads to even more DA production.[218]

Elevation in DA availability may lead to some of the neurobehavioral alterations observed in delirious patients, via DA's direct effects and by potentiating GLU's excitotoxic effects.[1,187,216] DA may exert its deliriogenic effect by one of three mechanisms: (1) the direct excitatory activity of DA (e.g., toxicity with substances known to increase DA release or availability, such as amphetamines, cocaine, and DA); (2) DA enhances GLU-mediated injury;[216] and (3) excess DA may itself induce apoptosis by mechanisms independent of oxidative stress,[219] which may explain why DA depletion by α-methyl-paratyrosine may have a neuroprotective effect against hypoxic stress and injury[220] and why DA blockade can be used to reduce hypoxic damage in the hippocampus.[221]

It is also important to note the growing body of evidence demonstrating that antipsychotic agents are effective not only as treatment of delirium,[222–227] because a recent meta-analysis demonstrated that antipsychotic agents are one of the few pharmacologic agents demonstrated to prevent delirium.[228] A new meta-analysis revealed no significant differences in efficacy among agents.[229] Furthermore, the authors concluded that the available evidence does not indicate major differences in response rates between clinical subtypes of delirium, suggesting the potential efficacy of antipsychotic agents in the management and prevention of hypoactive delirium as well as the agitated and mixed types. Thus, it is possible that antipsychotic agents are not only effective in the symptomatic management of the symptoms of delirium, but they also address the underlying massive DA surge associated with some forms of delirium, even the hypoactive type.[4,222]

GLU is the brain's principal excitatory neurotransmitter, yet excessive activation of *N*-methyl-D-aspartate (NMDA) receptors may lead to neuronal degeneration and cell death.[230,231] In at least one study of high-risk adults undergoing cardiac surgery, serum concentrations of NMDA, as measured by serum concentrations of NMDA receptor antibodies (NR2Ab), were predictive of severe neurologic adverse events (e.g., delirium, transient ischemic attack, or stroke) postoperatively.

As in the case of DA, increased GLU availability may be due to the massive Ca^{2+} influx described above, associated with a number of physiologic conditions (e.g., hypoxia, hepatic failure), leading to GLU release. Excess GLU further stimulates Ca^{2+} influx, which releases even more GLU.[232–234] Normally, GLU is released into the synapse and then removed by astrocytes and converted into glutamine, ending its action. Under oxidative conditions, however, GLU accumulates in the extracellular space as its reuptake and metabolism in glial cells is impeded by the ATPase pump failure.[179] It appears that GLU requires the presence of DA to exert some of its toxic effects, namely Ca^{2+}-induced neuronal injury.[171] At high levels, DA may cause enough depolarization of neurons to activate the voltage-dependent NMDA receptor, therefore facilitating GLU's neurotoxic effects.[239]

It has been known for a while that high ammonia levels are a factor in the pathogenesis of delirium and HE in cirrhotic patients, but it may not be that well known that acute ammonia toxicity is mediated by the activation of NMDA receptors.[240] In fact, some have suggested that drug-induced delirium would result from such transient thalamic dysfunction caused by exposure to medications that interfere with central glutamatergic, GABAergic, dopaminergic, and cholinergic pathways at critical sites of action.[188] Furthermore, GLU is metabolized by GLU-decarboxylase into GABA, which itself has been implicated in the development of the delirium.[241]

GABA is the chief inhibitory neurotransmitter in the human CNS and plays a role in regulating neuronal excitability throughout and the regulation of muscle tone. Evidence suggests that GABA activity is increased in some types of delirium but decreased in others. For example, the "increased GABAergic tone" theory of HE, a neuropsychiatric disorder associated with liver failure, proposes the role of increased GABAergic neurotransmission in HE.[242–245] Some of the supporting evidence comes from clinical experience demonstrating that flumazenil, a highly selective benzodiazepine antagonist at the GABA receptor complex, improved electrencephalographic activity, reversed coma, and improved symptoms of hypoactive delirium in cirrhotic patients and in some HE patients.[242,246] In addition, neurosteroids, synthesized in the brain mainly by astrocytes independent of peripheral steroidal sources (i.e., adrenals and gonads), are potent positive allosteric modulators of the $GABA_A$ receptor. As such, neurosteroids stimulate inhibitory neurotransmission in the CNS by increasing GABAergic tone, a suggested pathophysiologic mechanisms in HE.[247]

Conversely, decreased GABAergic activity has been described in deliria caused by ethanol or CNS-depressant withdrawal[248] and antibiotic-induced delirium.[249] There is also mounting evidence that some GABAergic substances (e.g., benzodiazepines) may themselves induce delirium due to a variety of mechanisms, including[101,188,250–252] (1) by interfering with physiologic sleep patterns,[253] (2) by interrupting central cholinergic muscarinic transmission at the level of the basal forebrain and hippocampus,[254–258] (3) by increasing compensatory up-regulation of NMDA and kainite receptors and Ca^{2+} channels,[259] (4) by disrupting thalamic gating function,[188] (5) by causing withdrawal states upon their cessation, and (6) by disrupting the circadian rhythm of melatonin release.[260]

Acute NE release secondary to hypoxia or ischemia leads to further neuronal injury and the development or worsening of delirium.[261] Specifically, in cases of alcohol withdrawal, excess noradrenergic activity drives most of the symptoms (e.g., diaphoresis, tachycardia, increased blood pressure, restlessness, anxiety, agitation, tremors). Under normal circumstances the α_2-receptor inhibits the firing of presynaptic NE neurons. Yet, evidence suggests that during alcohol withdrawal, signaling at the α_2-receptor may be less sensitive, resulting in an inability of the noradrenergic system to regulate its firing.[262,263] In addition, alcohol withdrawal causes an up-regulation of GLU transmission in the locus coeruleus (the major noradrenergic nucleus of the brain), increasing the activity of the noradrenergic system.[264] This may contribute to the autonomic instability, behavioral agitation, and psychosis seen during alcohol withdrawal delirium.[265] Furthermore, catecholamines can enhance the activity of the bed nucleus of the stria terminalis neurons that may in turn increase the excitability of glutamatergic bed nucleus of the stria terminalis neurons that project to the ventral tegmental area.[266]

Randomized clinical trials have demonstrated that selective α_2 agonist agents (e.g., dexmedetomidine) substantially decreased the incidence of postoperative delirium compared with GABAergic agents.[4,14,267,268] Similarly, α_2 agonist agents have shown neuroprotective qualities by suppressing circulating catecholamine levels during cerebral ischemia.[269]

Alterations in 5-HT activity, both elevated and decreased, have been linked to delirium development in various clinical populations. Normal 5HT synthesis and release in the brain is dependent on the availability of its precursor TRP (Fig. 5). Reduced 5HT levels have been identified in patients suffering from hypoxia, infections and sepsis, alcohol withdrawal delirium, delirium associated with levodopamine use for the treatment of Parkinson disease, immobility, catabolic states, and postoperative delirium, among others.[191,270] Others have found an association between low 5HT levels associated with hyperactive delirium.[271] In fact, the sudden discontinuation of 5HT reuptake inhibitors has been associated with various neuropsychiatric syndromes, including delirium.[272]

Decreased TRP availability may lead to a reduction in 5HT.[270,273,274] All large neutral amino acids (i.e., phenylalanine [PHE], TRP, eucine, isoleucine, methionine, tyrosine, valine) compete to enter the brain through the same saturable carrier. Therefore, as the concentration of one increases, CNS entry of other LNAAs conversely decreases.[275] PHE has the additional interesting property of conversion to neurotoxic metabolites and competes with TRP for entry into the brain.[276] Once it enters the brain, PHE competes with TRP and tyrosine for metabolism, via hydroxylation.[270] Studies have demonstrated that elevations of the PHE/LNAA ratio are independently

associated with postoperative delirium.[274,277,278] Studies of elderly medically ill patients suggest that an elevated plasma PHE/LNAA ratio during acute febrile illness is associated with delirium.[191,277] Similarly, patients with hepatic[279] and septic[280] encephalopathy have also been found to experience increased levels of PHE and PHE metabolites in the plasma and CSF. Studies have found that an increased ratio of free-to-bound TRP enhances its availability to brain tissue, which in turn increases 5HT synthesis, thus precipitating HE.[281]

Conversely, elevated 5HT levels have been described among patients suffering from 5HT syndrome, HE, and clozapine-induced delirium.[191,215,282,283] At least two reports suggest that selective 5HT3-type receptor antagonists may be effective in the treatment of agitated postoperative delirium.[284,285] Similarly, hepatic dysfunction may lead to decreased metabolism of precursor amino acids (i.e., PHE, tyrosine), which may lead to increases in TRP availability, which leads to increases in 5HT. In fact, elevation in 5-hydroxyindoleacetic acid levels has been associated with HE and in patients suffering from hypoactive delirium.[46] Figure 5 shows the relationship between TRP, 5HT, and kynurenic acid metabolism.

Histamine receptors A1 and A2 are known to affect the polarity of cortical and hippocampal neurons[286] and that both increased and decreased histamine levels may lead to delirium. It is well known that pharmacologic antagonism of either receptor is sufficient to cause delirium.[287] Others have suggested that during surgical stress and hypoxia, there may be an excessive release of histamine, which may lead to delirium.[288]

A detailed review of the studies supporting the various neurotransmitter findings have been published elsewhere and are not repeated here.[1] The NTH intersects with the OSH because the abnormalities in neurotransmitter concentration or receptor sensitivity may underlie the different symptoms and clinical presentations of delirium that are caused by a decreased in cerebral oxidative metabolism.

NEUROENDOCRINE HYPOTHESIS

The Neuroendocrine Hypothesis suggests that delirium represents a reaction to acute stress, mediated by abnormally high glucocorticoid (GC) levels, which induce a general vulnerability in brain neurons by impairing the ability of neurons to survive after various metabolic insults.[289,290] GCs are steroid hormones that modulate metabolism, salt balance, development, reproductive processes, and immune function.[104] Although acute elevations of GCs enhance some immune functions, such as leukocyte infiltration at the sites of injury, chronic elevations induce leukocyte apoptosis, reduce proinflammatory cytokine release, and generally suppress immune activity.

Stress activates the HPA axis: Stressors (through inputs from the brainstem nuclei and the amygdala) activate the paraventricular nucleus of the hypothalamus resulting in the release of corticotrophin-releasing hormone, which (through the hypophyseal portal system) acts on the pituitary gland, inducing the release of adrenocorticotrophic hormone, which promotes GC (including cortisol) release from the adrenal cortex. Under normal circumstances, GCs act to aid the body in coping with the demands imposed by stress exposure, mobilizing energy stores, and suppressing nonvital body functions (e.g., inflammatory responses and reproduction) (Fig. 9).[81,291–293]

However, plenty of scientific evidence demonstrates that GCs, the adrenal steroids secreted during stress, can have a broad range of deleterious effects in the brain.[292] Recent data demonstrated that repeated or prolonged exposure to GCs has a negative impact on brain function and provide evidence suggesting such exposure may contribute to age-related cognitive decline.[81,294] Growing evidence suggests that GCs may have proinflammatory effects in the brain and can enhance neuroinflammation at multiple levels in the pathway that link lipopolysaccharide exposure to inflammation.[295] In fact, GCs have been shown to enhance ischemic and seizure-induced neuronal injury.[296] A number of mechanisms have been postulated to explain how excess GC release can compromise the neuron's ability to survive various neurologic insults (e.g., seizures, ischemia), which may lead to or exacerbate cell death (Table 5).

The above may explain how GCs contribute to the pathogenesis of delirium, especially in the elderly.[292,294,297] The hippocampus, derived from medial regions of the telencephalon, is part of the limbic system and plays important roles in information encoding, related to short-term and long-term memory, and spatial navigation.[298] The hippocampus also

FIGURE 9. **Neuroimmune circuits in delirium. The HPA axis and inflammation. Various stressors can activate the HPA axis. The hypothalamus is stimulated to secrete corticotrophin-releasing hormone (CRH), which leads to adrenocorticotrophic hormone (ACTH) secretion into the peripheral circulation. ACTH in turn triggers adrenal GC release and production. The CRH system is inhibited by GCs in a negative feedback loop. Tumor necrosis factor (TNF)-α and IL-1 are produced from inflammatory sites and are potent activators of the HPA axis. IL-6 acts synergistically with GCs to stimulate the hepatic secretion of acute phase proteins. Although GCs are widely known for their anti-inflammatory actions, "(−)," more recently proinflammatory effects have also repeatedly been reported, "(+)." (+): enhancing; (−): suppressing. (From Dinkel et al.[291]).**

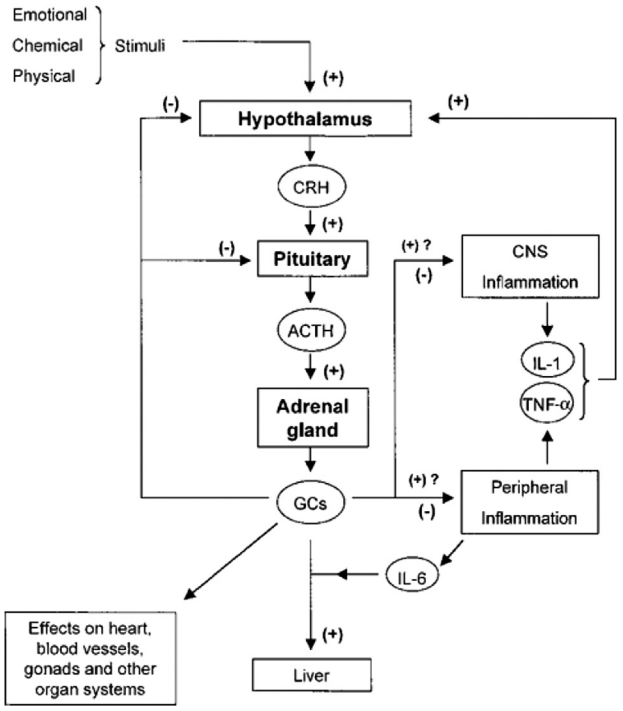


TABLE 5. **Potential Mechanisms to Explain How Excess GC Release Can Compromise Neuron's Ability to Survive Neurologic Insults that May Lead to or Exacerbate Cell Death**

- Inhibiting glucose transport into neuron, thus inducing metabolic vulnerability[292,301]
- Increase proinflammatory cell migration, cytokine production, and even transcription factor activity in the brain[81]
- Amplifying the damaging cascade of GLU excess, calcium (Ca^{2+}) mobilization, and oxygen radical generation[304,306,309,380,381]
- Inducing spine loss and dendritic atrophy, thus decreasing neuroplasticity[382]
- Enhancing oxygen radical-mediated neurotoxicity[383]
- Exacerbating the toxicity of other neurotoxins (e.g., adriamycin) whose mechanisms of action overlap GC pathways[384]
- Impairing long-term potentiation[303]
- Reducing hippocampal glial cell activation and proliferation[385]
- Altering the expression and signaling of neurotropins, particularly brain-derived neurotropic factor[302,386]
- Exacerbating the breakdown of cytoskeletal proteins (i.e., tau)[387]
- Impairing neurogenesis[388]

happens to contain the highest concentration of GC receptors of any brain region and thus may be a major target for the negative effects of excessive GC levels. Current evidence suggests that hippocampal malfunction occurs relatively early during the metabolic stress environment, leading to delirium,[102,290,291,293,299–308] and that the highly catabolic GC's induce a general metabolic vulnerability in these neurons and thus compromise their ability to survive various toxic insults.[309] Hippocampal injury may explain some of the attentional deficits and memory dysfunction and errors in information processing (leading to confabulation) commonly seen in delirious patients.

The hippocampal formation is of prime importance for normal HPA axis shut-off, and a key abnormality related to GCs excess in delirium seems to be an abnormal "shut-off" of the HPA axis as tested by the dexamethasone suppression test.[310] The loss of normal inhibition of adrenal steroidogenesis results in continuous secretion of peak amounts of corticosteroids, which causes resistance to cortisol feedback inhibition mediated by receptor loss in the hippocampus.[292,304,309] The increased GC availability associated with illness and trauma (e.g., burns, surgery) or exogenous steroid administration further disrupt hippocampal function, which in turn may further disinhibit the release of GCs, thus sustaining high levels of circulating cortisol.[46] Studies have found that patients experiencing postoperative delirium had an impaired stress regulating system with significantly elevated mean plasma cortisol levels compared with the preoperative baseline and nondelirious patients.[311] Among patients with delirium triggered by lower respiratory tract infections, 78% were found by the dexamethasone suppression test to be nonsuppressors compared with 14% of those with normal suppression responses.[290] Demented patients with delirium exhibited significant differences in basal cortisol levels compared with demented, nondelirious patients.[312] Furthermore, there was a strong linear

relationship between delirium and dexamethasone suppression test pathology irrespective of age and severity of dementia: The greater the intensity of delirium, the greater the level of nonsuppression.[312] Similarly, patients with poststroke delirium exhibited significantly greater activation of the HPA system compared with those without.[310,313]

DIURNAL DYSREGULATION OR MELATONIN DYSREGULATION HYPOTHESIS

This hypothesis suggests that disruptions to the 24-hour circadian cycle and the usual stages of sleep may lead to disturbances in the integrity of sleep and the physiologic sleep architecture.[1,222] Sleep deprivation has long been linked to the development of delirium[314] and psychosis.[315] Hospitalized patients experience severe alterations of the sleep–wake cycle with sleep loss, sleep fragmentation, and sleep–wake cycle disorganization. The 24-hour internal clock (circadian pattern) is maintained by environmental factors, primarily light exposure, which affects melatonin secretion, and its disruption may lead to the development of delirium.[316]

Others have demonstrated that sleep deprivation may lead to significant memory deficits[317] and to symptoms of emotional imbalance, likely due to disconnection between the amygdala and the prefrontal cortex.[318] Similarly, "chronic partial sleep deprivation" (i.e., sleeping limited to 4 hours per night for 5 consecutive nights) may lead to cumulative impairment in attention, critical thinking, reaction time, and recall.[319] Thus, cumulative sleep debt can cause delirium in itself and can aggravate or perpetuate delirium and its associated cognitive deficits.[320–322] Studies have found sleep deprivation to consistently precede onset of delirium in postsurgical cardiac patients[323,324] and that ICU patients with sleep deprivation were significantly more likely to develop delirium than patients without sleep deprivation.[260,325]

Melatonin plays important roles in multiple bodily functions that may have potential implications regarding the development of delirium in the medically ill: Melatonin has significant chronobiotic effect (i.e., affecting aspects of biologic time structure), has sleep–wake cycle regulatory effects, helps reset circadian rhythm disturbances, is an effective free radical scavenger with extensive antioxidant activity (particularly nuclear and mitochondrial DNA) with strong antiapoptotic signaling function, has extensive anti-inflammatory activity, and possesses some antinociceptive and analgesic effects.[326–328] In addition, melatonin reduces the affinity of GCs receptors, prevents GCs inhibition of cell proliferation, and reduces the GC-induced neurotoxicity and apoptosis.[329] These qualities may protect natural mechanisms of learning and memory.[317,326–328,330–336] Melatonin also inhibits the aggregation of the amyloid beta protein into neurotoxic microaggregates responsible for the neurofibrillary tangles characteristic of Alzheimer disease and prevents the hyperphosphorylation of the tau protein.[333,337–343] Data suggest that melatonin may have potential implications regarding the development of delirium in the medically ill and postoperative patient. Conversely, it has been theorized that the natural, age-related decline in brain melatonin may contribute to a pro-amyloidogenic microenvironment in the aging brain.[337]

Current evidence suggests that acute and chronic sleep deprivation is associated with decreased proportions of natural killer cells,[344] reduced lymphokine-activated killer activity,[345] and reduced IL-2 production.[345] Conversely, cytokines may play a role in normal sleep regulation by increasing non–rapid-eye-movement sleep and decreasing rapid-eye-movement sleep, and during inflammatory events, an increase in cytokine levels may intensify their impact on sleep regulation.[346] Moreover, sleep deprivation may alter endocrine and metabolic functions, altering the normal pattern of cortisol release and contributing to alterations of GC feedback regulation, glucose tolerance, and insulin resistance.[347] We previously described the impact of disruption of GC regulation and delirium and cognitive function (see Neuroendocrine Hypothesis, above).

Studies have demonstrated a relationship between an irregular melatonin circadian rhythm (i.e., abnormally low serum levels of melatonin) and postoperative delirium.[260,348] The administration of melatonin in ICU patients has been shown to improve quality of sleep and prolongation of sleep time,[349] whereas others demonstrated that the

prophylactic administration of low-dose exogenous melatonin may decrease the incidence of delirium.[350,351] Finally, data suggest that the use of prophylactic melatonin decreases the incidence and severity of "sundowning" and agitated behavior in elderly, demented individuals.[332]

Some have observed a relationship between the motoric delirium subtype and melatonin levels. A study of hospitalized elderly medical patients were evaluated daily using the Dementia Rating Scale and urinary measures of 6-sulphatoxymelatonin, the chief metabolite of melatonin.[352] A study found that during periods of hyperactive delirium, subjects had decreased urinary 6-sulphatoxymelatonin levels, whereas patients with hypoactive delirium had raised 6-sulphatoxymelatonin levels.[353]

NETWORK DISCONNECTIVITY HYPOTHESIS

The Network Disconnectivity Hypothesis (NDH) suggests that the heterogenicity of delirium presentations is better explained by the action of various factors (e.g., drugs or toxins) acting on specific brain neurochemical systems.[354] Thus, this hypothesis postulates that factors affecting different neurotransmitter-specific projections, whether due to aging (e.g., degeneration), disease (e.g., inflammation), or pharmacologic agents (e.g., anticholinergic substances), will lead to different types of delirium presentations (e.g., hyperactive or hypoactive) and that, depending on the degree of reversibility of those changes, the delirium episode would have short or long-term sequelae (or effects). Initially, it immediately recognized two systems as potential culprits: the cholinergic and the GABAergic systems.

The NDH highlights the role of the cortical cholinergic system and associated projections in mediating specific attentional processing (i.e., sustained, selective, and divided attention performance), arousal, and rapid-eye-movement sleep–associated dreaming[78,355] and that the selectivity of the behavioral effects of cortical ACh is based on close temporal interactions with converging sensory or associational cortical inputs.[356] In fact, increased cholinergic activity in prefrontal regions is hypothesized to contribute to the activation of the anterior attention system and associated executive functions.[355] Finally, the NDH suggests that the failure (e.g., hypo- or hyperactivity) of one system will undoubtedly affect others (i.e., the connectivity principle).

The NDH recognizes that the brain is a highly organized and interconnected structure functioning to allow complex integration of sensory information and motor responses and suggests that delirium represents a variable failure in the integration and appropriate processing of sensory information and motor responses. Thus, the NDH proposes that delirium results from an acute breakdown in network connectivity within the brain.[357]

Furthermore, the NDH suggests that two important factors determine a subject's vulnerability to delirium: (1) the baseline network connectivity (defined as the connectivity of neural networks within the brain before the precipitating insult provoking delirium), which is influenced by most recognized nonmodifiable delirium risk factors (e.g., age, baseline level of cognitive functioning), and (2) the level of inhibitory tone, which will determine the degree of change in network connectivity and is influenced by modifiable risk factors (e.g., metabolic abnormalities, sleep deprivation, infection and inflammation, medication such as benzodiazepines).[357] The model suggests that when these two factors affect separate neuronal networks, to different degrees, they produce the various motoric phenotypes described (e.g., hyperactive, hypoactive, mixed). Thus, the form of delirium that ensues will depend on how and which networks breaks down (dependent on both the individual's baseline network connectivity and the degree of change in inhibitory tone produced).

Electroencephalographic and evoked potential data may provide further support for this theory by suggesting that the pathophysiology of at least some forms of delirium may have a subcortical component.[358] More recently, a study using functional magnetic resonance imaging scans examined the correlations of blood oxygen levels between various brain regions in resting-state functional magnetic resonance imaging scans during and after the resolution of delirium. Findings demonstrated a long-lasting disruption in reciprocity of the dorsolateral prefrontal cortex with the posterior cingulate cortex and a reversible reduction of functional connectivity of subcortical regions (e.g., thalamus) with the reticular activating system and with nuclei responsible for

forebrain Ach (i.e., the midbrain nucleus basalis) and DA (i.e., the midbrain ventral tegmental area) innervation.[359] The persistence of these physiologic disruptions, beyond the resolution of acute delirious symptoms, may account for reported cognitive problems that often outlast the acute episode of delirium.

The NDH intersects with the NTH because GABAergic neurotransmission is implicated in increasing the inhibitory tone, which may contribute to the development of delirium.[357] Furthermore, GABAergic agents may further destabilize the sleep–wake cycle, as they suppress orexinergic neural firing in the perifornical nucleus.[360] Orexin (hypocretin) is a peptide produced in the lateral hypothalamus that strengthens the ascending reticular activating system, thus maintaining wakefulness and preventing inappropriate transition into sleep.[17,18,265,361] It also relates to the NIH because systemic inflammation drives an up-regulation in expression of $GABA_A$ receptors and an increased GABA synthesis[362,363] and suppresses orexinergic neuronal activity during the wakeful period.[364]

This model also intersects with the NAH because it suggests that aging is associated with gray matter volume, neurotransmission, and white matter integrity (which consists mostly of glial cells and myelinated axons that transmit signals from one region of the cerebrum to another and between the cerebrum and lower brain centers) and thus may represent an anatomic correlate of functional connectivity.[357,365,366] A study assessing white matter integrity using diffusion tensor imaging in patients who developed delirium after cardiac surgery suggested that abnormalities in the deep white matter and thalamus could have accounted for the delirious patients' vulnerability to postoperative delirium, compared with nondelirious subjects.[367] A more recent study, also conducted among elderly cardiac surgery patients, demonstrated that the prevalence of severe cerebral white matter hyperintensities on magnetic resonance imaging was significantly higher in delirious patients and similarly concluded these lesions were likely one of the most important risk factors for the development of delirium after cardiac surgery.[368]

Aging is also associated with a reduction in GABAergic tone, thus allowing for increased neuronal activity in certain brain regions, primarily the prefrontal cortex.[369] With advanced age there is a down-regulation of several subunits of the $GABA_A$ receptors (i.e., $\alpha1$, $\alpha5$, $\beta3$, $\gamma2$); therefore, a stimulus that increases the level of inhibitory tone may have a relatively greater effect and further breakdown network connectivity.[370] The aged brain also experiences reductions in orexin signaling,[371–374] which may contribute to the fluctuating arousal level seen in delirious states when exposed to various noxious stimuli (e.g., infection, GABAergic agents, sleep deprivation). Similarly, it intersects with the NTH because it specifically implicates the GABA system (e.g., benzodiazepine or HE-induced delirium) and the cholinergic system (e.g., anticholinergic delirium) as likely principal culprits.

The NDH also intersects with the NTH because data from anesthetic agent studies demonstrate that some core symptoms of delirium likely involve changes in dynamic aspects of neuronal activity affecting brain's ability to integrate information through functional disconnection between different anatomic structures.[375,376] Finally, it intersects with the NIH because acute neuroinflammatory reactions affect physiologic processes implicated in neuronal and synaptic function with consequent neurochemical disturbances and functional disconnection between different anatomic structures.[48]

CONCLUSION

Delirium is a neurobehavioral syndrome caused by the disruption of neuronal activity secondary to systemic disturbances. To date, no single unitary pathophysiologic mechanism has been identified. Most existing theories on the etiology of delirium are complementary rather than competing. Thus, it is likely that none of these theories by themselves explains the full phenomenon of delirium but rather that two or more of these, if not all, act together to lead to the biochemical derangement we know as delirium.

A review of the available literature suggests a number of factors that lead to a final common pathway associated with alterations in neurotransmitter synthesis and availability that mediates the behavioral and cognitive changes observed in delirium. These alterations in neurotransmitter synthesis appear to provide a relatively satisfactory

explanation of the complex behavioral and cognitive changes observed in delirium. These factors include a wide range of endocrinologic, immunologic, neuroinflammatory, neurologic (i.e., brain connectivity circuits), and metabolic effects (i.e., oxidative stress) described throughout the article. In addition, certain specific circumstances or phases of life may lower the threshold for such events or exaggerate the body's response, such as the presence of inflammatory or infectious processes, sleep deprivation, aging, and neurodegenerative disorders. The observed changes in neurotransmitters are not uniform. In general, the most commonly described neurotransmitter changes associated with delirium are deficiencies in Ach availability (↓Ach) and melatonin (↓MEL); excess in DA (↑DA), NE (↑NE), and/or GLU (↑GLU) release; and variable alterations (e.g., both a decreased and increased activity) in 5HT (↓↑5HT), histamine (↓↑H1 and H2), and/or GABA (↓↑GABA). Ultimately, it is likely that relative neurotransmitter alterations determine the phenotypic presentations of delirium (e.g., hyperactive, hypoactive, or mixed).

Thus, in the end, it is unlikely that a single cascade will explain the phenomena of delirium. Rather, it is more likely that a number of pathways will be shared, based on common systemic vulnerabilities and pathologic processes, yielding varying neurotransmitter deficiencies. The absence of a single common pathway or uniform neurotransmitter abnormality may explain why effective prophylaxis and treatment of delirium has proven so difficult and remained so elusive.

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