Pathophysiology of Delirium in the Intensive Care Unit

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The most common behavioral manifestation of acute brain dysfunction is delirium, which occurs in up to 60% to 80% of mechanically ventilated medical and surgical ICU patients and 50% to 70% of non-ventilated medical ICU patients [1–5]. Delirium is defined as an acute change or fluctuation in mental status, inattention, and disorganized thinking or an altered level of consciousness [6]. During the ICU stay, acute delirium is associated with complications of mechanical ventilation including nosocomial pneumonia, self-extubation, and reintubation [5,7]. ICU delirium predicts a 3- to 11-fold increased risk of death at 6 months even after controlling for relevant covariates such as severity of illness [8,9]. Of late, delirium has been recognized by some as a sixth vital sign [10], and it is recommended that delirium assessment be a part of routine ICU management [11]. The elderly may be at particular risk for this spectrum of delirium and dementia [12–16]. As the average age of the critically ill advances, raising awareness in the medical community regarding this syndrome is imperative.

A firm understanding of the pathophysiologic mechanisms of delirium remains elusive despite improved diagnosis and potential treatments. Several theories have been proposed to help explain the pathophysiology

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of delirium (Figs. 1 and 2). Because an exhaustive review of all of these aspects is not possible in a single manuscript, the focus herein is on the following six components (Table 1): (1) neuroimaging and neuroanatomic correlates of delirium, (2) sedatives and analgesics, (3) sepsis, (4) biomarkers and neurotransmitters, (5) surgical factors and postoperative cognitive dysfunction (POCD), and (6) future directions such as molecular genetics.

Neuroimaging and neuroanatomic correlates of delirium

To understand delirium and its long-term consequences, it is necessary to explain acute brain dysfunction at the neurologic level. Delirium research has only recently begun to employ neuroimaging. The studies described herein are beginning to provide evidence that delirium may be caused by widespread brain dysfunction rather than localized disruption [17,18]. Further evidence suggests that this may lead to cell death in the central nervous system (CNS). The few functional neuroimaging studies that have evaluated delirious patients in acute states are reviewed [19–21]. Structural imaging findings are then examined that describe neuronal atrophy that may be related to delirium [22–35].

Functional neuroimaging during acute delirium

Recent advances in functional neuroimaging have offered a much needed window into the effects of delirium on the brain. The first of these studies
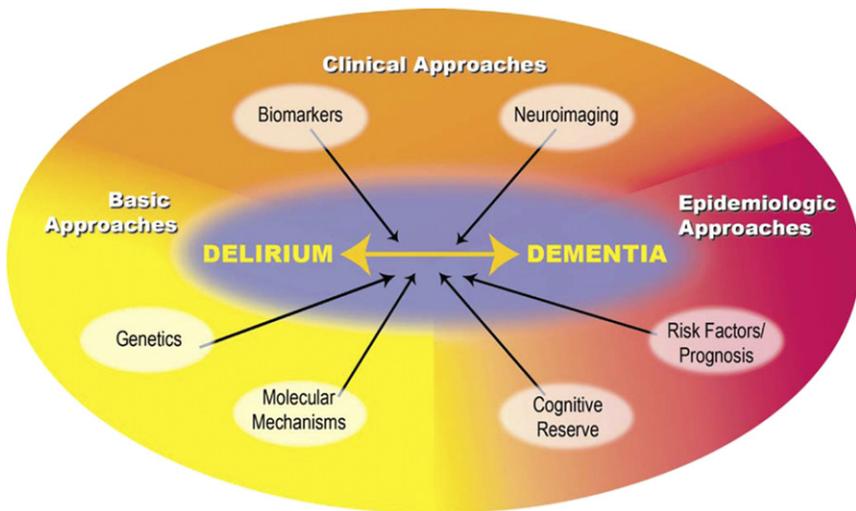

Fig. 1. Conceptual framework for exploring the interrelationship between delirium and dementia. (*From* Inouye SK, Ferrucci L. Introduction: elucidating the pathophysiology of delirium and the interrelationship of delirium and dementia. J Gerontol Biol Sci Med Sci 2006; 61A(12):1278; with permission.)
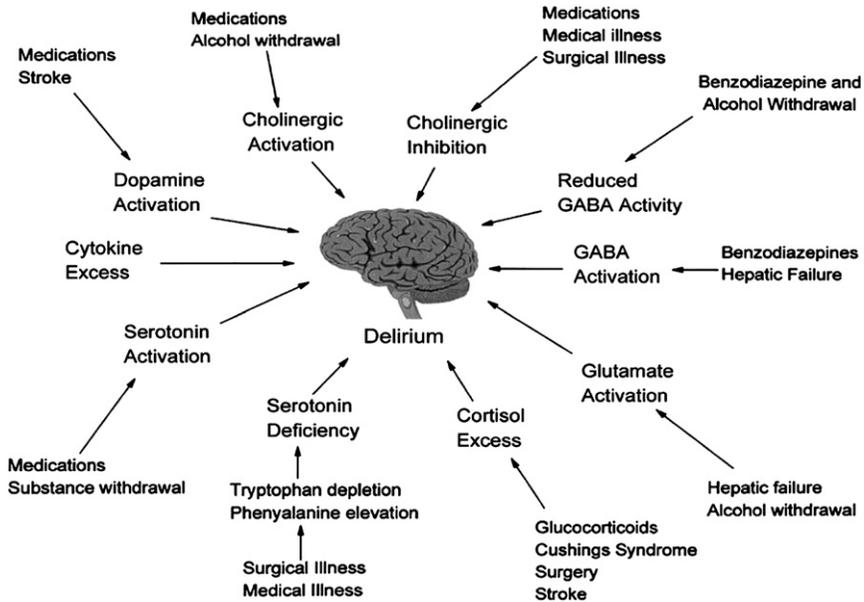
Fig. 2. Neurotransmitters and biomarkers of delirium. The evidence supports multiple mechanisms of delirium, which may pertain in different clinical situations. (*From* Flacker JM, Lipsitz LA. Neural mechanisms of delirium: current hypotheses and evolving concepts. J Gerontol Biol Sci Med Sci 1999;54A:B243; with permission.)

was reported by Yokota and colleagues [19] in 2003. Using xenon-enhanced CT during and after acute delirious states, this study [19] reported that delirious patients experienced a 42% reduction in overall cerebral blood flow (CBF). Furthermore, there were even greater CBF decreases in subcortical and occipital regions [19]. This overall decrease in CBF suggests that delirium may, indeed, manifest via widespread brain dysfunction rather than localized disruption [17,18]. Additionally, global hypoperfusion would have the potential to cause several of the long-term changes associated with prolonged delirious states, including autophagy [36,37] and long-term cognitive impairment (LTCI) [38,39]. More recently, Fong and colleagues [20] used single-photon emission computed tomography to examine geriatric patients during and after acute delirious episodes. Like the study by Yokota and colleagues [19], their results indicated wide-spread hypoperfusion with marked decreases in regional CBF in the occipital lobe and brainstem. In a recent case report, Kitabayashi and colleagues [21] scanned a patient experiencing delirium tremens. Consistent with the investigations of Fong [20] and Yokota [19], Kitabayashi and colleagues [21] described a reduction in blood flow in multiple areas of the brain.

Taken together, these studies support the notion that CNS blood flow may be disrupted during delirium. Medical conditions or sedative agents could impact brain perfusion, causing cognitive processing to fluctuate

Table 1
Evidence for and against various potential pathophysiologic mechanisms of ICU-related delirium

Pathogenic mechanism	Evidence for	Evidence against
Neuroimaging and neuroanatomic correlates of delirium	Has the potential to account parsimoniously for multiple instances of delirium [19–30,34,35].	Requires a great deal of additional empirical evidence [24,25,27,31–33].
Sedatives and analgesics	Data are accumulating in favor of support for this mechanism as a viable modifiable component of delirium in ICU settings [42–51].	Difficult to isolate such causal variables in patients with multiple comorbidities [62–67].
Sepsis	Inflammation and coagulopathy universally present in septic patients and represent a highly plausible mechanism of delirium [68–82].	Work on both the inflammatory and "flow" impairments in sepsis as related to the brain in sepsis is needed [69,73–75,77,80].
Biomarkers and neurotransmitters	Several potential links exist to important pharmacologic factors [87–89,93–98, 103,104,107–110,119,120,122,123].	Inconsistent results and methodologic problems dramatically limit current clinical application of hypotheses [92,101,107,112,113,121,129].
Surgery and POCD	Aspects of anesthetic and procedural management in the operating room seem logical as etiologies, with some supportive data [15,133–146].	Cohort studies and interventional trials to date have not supported improved outcomes. Postoperative delirium may be better accounted for by other factors such as overall severity of illness and general ICU management issues that are not specific to surgery [64,134,154,163,165–167].
Molecular genetics	Potential exists to understand molecular mechanisms of delirium and inter-individual susceptibility [130,131,171,174,175].	The research is in its infancy and requires additional data [172,174].

and manifest as acute confusion or delirium. When maintained for a sufficient length of time, changes in CNS blood flow may begin to trigger apoptotic mechanisms such as autophagy [36,37] leading to brain damage and LTCI [18]. The following section reviews neuroradiologic data that may provide clues regarding the anatomic correlates of delirium.

The neuroanatomic correlates of delirium

Several reports have documented long-term cognitive and behavioral sequelae of delirium (ie, declines in intellectual functioning) [39–41] that are presumably attributable to underlying cellular changes in the brain. Several studies have used CT or MRI to examine lesions or other structural abnormalities associated with delirium [23–35]. Frank hemorrhage or ischemia may cause delirium. In these cases [26–35], delirium is more likely to have been a result rather than a cause of stroke. In other studies, the lines of causation between delirium and structural changes may be less clear [23–25]. An early CT study reported atrophy surrounding the cerebral ventricles in elderly psychiatric patients experiencing delirium when compared with matched controls [22]. Furthermore, the degree of atrophy was related to the patients' Mini Mental-State Examination (MMSE) scores. Patients in this study [22] also displayed cerebral infarctions and hemorrhages in frontal and parietal regions. Some reports [35] have found little or no association between delirium and neuropathology, whereas others [24,25] have suggested that major neuroanatomic changes may, indeed, occur in patients experiencing prolonged delirium. For example, CT scans revealed that 61% of critically ill patients were found to have gross white and gray matter atrophy, white matter lesions with hyperintensities, cortical and subcortical lesions, or ventricular enlargement [25]. Another study [23] that examined the effects of electroconvulsive shock therapy in delirious patients found white matter abnormalities and lesions in the basal ganglia. These reports have provided essential descriptions for potential links between anatomic changes and delirium [24,25].

Sedatives and analgesics

Sedatives and analgesics currently represent the leading modifiable iatrogenic risk factors for transitioning to delirium in the ICU [42–48]. Marcantonio and colleagues [44] found an association between benzodiazepines and meperidine and delirium. Pandharipande and colleagues [49–51] recently reported that the administration of benzodiazepines was an independent risk factor for the development of delirium in surgical and trauma ICU patients. Dubois and colleagues [43] have shown that narcotics (morphine and meperidine) may be associated with delirium in medical and surgical ICUs. Inouye and colleagues [42] concluded that benzodiazepines, narcotics,

and other psychoactive drugs are associated with a 3- to 11-fold increased relative risk for delirium.

In the ICU, patients often undergo prolonged and massive exposure to potent sedatives and analgesics [42–48]. Survey data [52] suggest that delirium is frequently treated with lorazepam in excess of 50 mg/d by a significant number of ICU professionals. More than 90% of ventilated patients receive benzodiazepines and opiates [53,54] to improve oxygenation, alleviate agitation, and prevent removal of support devices. Unfortunately, the quantity and dosing intervals are largely based on clinical experience rather than evidence-based guidelines. It is common to find both young and old patients in a drug-induced delirium [55]. Considering the role of age as a susceptibility factor in the development of LTCI, it is striking that physicians rarely modify the quantity or dosing intervals of these drugs based on the patient's age. This observation flies in the face of evidence that, for many drugs, aging results in reduced or altered metabolism [56,57]. It is clear that large doses and extended use of sedatives and analgesics often result in oversedation that may be reduced but not eliminated through the use of clinical protocols [55,58–61].

Past studies of the relationship among sedatives, analgesics, and outcomes have used the total drug dose to estimate exposure [62–64]. Nevertheless, it has been recognized for over 2 decades that drug responses for essentially all medications exhibit interindividual variability, often marked, when drug dosage alone is considered. These differences exist because the associated drug level leading to a response is determined by the interaction of genetic, environmental, age, and disease factors modulating drug disposition, including the distribution to the brain and other organs. By contrast, there is frequently a better quantitative relationship between a drug's plasma concentration and its effects. In healthy volunteers and critically ill patients, a relationship exists between levels of sedation induced by short-term midazolam and morphine infusions and their plasma concentrations [65–67]. Accordingly, understanding of the association between drug exposure and LTCI may be enhanced by further examination of plasma levels of psychoactive drugs to which the patient is exposed. Sedative and analgesic medications appear to represent excellent modifiable pathophysiologic risk factors for ICU delirium.

Sepsis

Sepsis, a known or suspected infection leading to the systemic inflammatory response syndrome, frequently presents with delirium and represents perhaps the most common causal factor for ICU delirium [68–70]. Several plausible explanations suggest that sepsis may be a gateway to acute CNS dysfunction and brain damage via degradation of the blood-brain barrier and neuroinflammation [68–82]. The prevalence of coexistent delirium during sepsis ranges from 9% to 71% depending on diagnostic definitions

[71–73]. A septic inflammatory cascade has the potential to decrease essential oxygen and nutrient delivery to cells by impairing capillary blood flow [81–83]. Elevated levels of tumor necrosis factor-alpha, interleukin-1, and other cytokines and chemokines that are released in response to lipopolysaccharide can result in disseminated intravascular coagulation and promote leukocyte–vascular endothelium adhesion and induce endothelial damage [83,84]. Sharshar and colleagues [76] have suggested that sepsis-induced encephalopathy may result from degradation of the blood-brain barrier, leading to increased permeability. They recently reported that individuals who sustained septic shock exhibited abnormal MRIs with varying degrees of encephalopathy and damage to white matter tracts [76]. Moreover, in sepsis, the prolonged exposure to lipopolysaccharide may impair the synaptic transmission and neuronal excitability of pyramidal neurons of the hippocampus [85]. These indications suggest that the relationship between sepsis and delirium will continue to be a productive area of research. Regrettably, to date, few studies have specifically examined the role of sepsis in delirium [69,73–77,80]. To better understand how sepsis and other acute infections may lead to delirium, it will be necessary to develop accurate biomarkers of deliriogenic processes. Unfortunately, this has proven to be a difficult task.

Biomarkers and neurotransmitters

To adequately define a syndrome, biomarkers provide invaluable information to aid clinicians and researchers; however, in delirium, biomarkers to date have proven less than definitive. Several lines of research suggest that prolonged delirium causes brain damage [13,16,25,38,86]. If this is indeed true, to the extent that brain damage is occurring in these patients, biomarkers that are sensitive to neuronal or glial cell death should also be highly correlated with delirium. Serum markers that have been used in stroke and head trauma could potentially be employed as delirium biomarkers [87–89]. Markers such as neuron-specific enolase, S-100 beta, and neuronal tau protein have been used for this purpose and may provide clues regarding the onset of brain injury in delirium. In particular, S-100 beta could be promising because it has been linked to postoperative cognitive dysfunction [90]; however, other attempts to examine surrogates of neuronal cell death have been inconsistent at best [91,92].

The cholinergic hypothesis

Another line of investigation has suggested that acetylcholine and its precursor choline may also be linked to the pathogenesis of delirium [93–98]. Han and colleagues [98] proposed that patients with greater anticholinergic activity owing to medication side effects may be at greater risk for delirium. Case studies reported that when the administration of anticholinergic

agents was discontinued, symptoms of delirium ceased [99]; however, evidence also suggests that perturbations in the cholinergic system may occur independent of medication effects [100], and some investigators [101] have begun to question the relevance of anticholinergic activity in cognitive functioning.

Despite potential problems with the choline hypothesis, a surrogate marker dubbed ''serum anticholinergic activity'' (SAA) has been developed as a biologic indicator to detect anticholinergic processes. SAA is believed to cross the blood-brain barrier and has been linked to the depth of delirium in several studies [102–104]. The assay required to measure SAA was first developed in 1980 by Tune and Coyle [105]. Following this development, several clinical investigations found relationships between SAA levels and the development of delirium [102–104]. Thomas and colleagues [102] reported that SAA levels were higher in delirious patients when compared with non-delirious individuals in a sample of surgical patients in the ICU. Tune and colleagues [103] reported similar findings in postoperative cardiac patients whose MMSE scores were related to SAA levels (r = 0.83; $P < .001$). Flacker and colleagues [96] reported that higher levels of SAA were associated with delirium ($P = .006$) in medical inpatients aged more 75 years. Furthermore, the prevalence of delirium in this study [96] jumped from 8% to 62% when comparing patients with the highest and lowest SAA levels (top and bottom 20th percentile). Mussi and colleagues [104] also reported a link between the incidence of delirium and SAA levels ($P < .004$) while controlling for other risk factors such as the use of antipsychotics and benzodiazepine. Additionally, all of the patients who had SAA profiles greater than 20.0 pmol/mL [104] were found to be delirious as defined by the Confusion Assessment Method for the ICU [106].

When evaluating these studies, it is important to remember the inherent methodologic challenges. For example, it may be difficult to differentiate whether elevated SAA levels are causal mediators of delirium or simply associated correlates [107]. The SAA assay method involves radioactively labeling quinuclidinyl benzilate and examining the relative binding concentrations to muscarinic receptors [105]. This technique has been criticized for potentially measuring not only the quantity that is displaced by cholinergic antagonists but agonists as well [107]. Even when considering these methodologic difficulties, SAA may be related to the development of delirium and other changes in cognitive status; however, the specific nature of this association remains under investigation.

Additional delirium biomarkers

Other theories [50,108–111] have proposed that various metabolites thought to be important in brain functioning may serve as potential delirium biomarkers as well. For example, high serum levels of phenylalanine and low serum tryptophan have been associated with delirium [108,109]. Balan

and colleagues [110] examined melatonin urine metabolites and found higher levels in individuals with hypoactive delirium and lower levels in those with hyperactive delirium. One longitudinal investigation [112] assayed large neutral amino acid (LNAA) concentrations thought to impact brain serotonin levels and delirium. Although levels of large neutral amino acids were marginally related to the resolution of acute delirium [112], this finding has yet to be pursued or replicated [113]. Unfortunately, a precise understanding of the relationship between delirium and serotonin has yet to be established, with some studies reporting inconsistent findings [110,114].

Another potential marker that has been proposed is melatonin [110]. It is secreted by the pineal gland and may also be linked to sleep disturbances that are common in delirium [50,111]. Cortisol may also be linked to delirium [107] and apoptosis [115]. High stress levels related to the ICU environment may increase activation of the sympathetic nervous system and, in turn, elevate serum cortisol or other stress hormones [107]. Higher levels of catecholamines have been linked to delirium tremens, but the results are less clear regarding ICU-related delirium [114]. Most studies that have examined the relationship between cortisol and cognitive outcomes have been longitudinal [113,116–118]. Because ICU stress may be intense but shorter in duration than conditions typically linked to cortisol (eg, major depression) [116], the relationship between cortisol and cognition may be less pronounced in the ICU. Another possibility is that the association between delirium and stress hormones may only manifest at high or low levels [119]. In line with this hypothesis, O'Keeffe and Devine [120] reported that individuals who failed a dexamethasone suppression test appeared to be at increased risk for delirium. In either case, the relationship between delirium and stress hormones requires further investigation with larger samples and more rigorous controls [118,121].

Neurotransmitters and delirium

Multiple neurotransmitters are thought to be involved in delirium. Imbalances in the release, synthesis, and degradation of gamma-aminobutyric acid (GABA), glutamate, and acetylcholine, as well as all of the monoamines (serotonin, norepinephrine, and dopamine) have been hypothesized to be linked to the development of delirium and LTCI [93,122,123]. Additionally, GABA, the primary inhibitory neurotransmitter in the CNS, exerts powerful effects across the brain. Several agents commonly prescribed in the ICU (eg, benzodiazepines and propofol) have high affinity for GABAergic receptors in key areas such as the brainstem [124]. Decreasing global CNS arousal has the potential to cause unpredictable neurotransmission and brings about disruptions in cerebral functional connectivity [18]. If this state persists for a sufficient length of time, it may lead to neuronal atrophy resulting in LTCI [86,125–127].

Other key neurotransmitters may also have a role in the pathogenesis of delirium. The monoamines are thought to modulate neurotransmission, in turn, impacting behavior, cognitive function, and mood [128]. The relationship between dopamine, cognitive functioning, and behavior is complex and varies depending on the specific cerebral region of interest [129]. Additionally, optimal dopamine levels follow an inverted U-shaped curve [130,131]. Lack of dopamine results in parkinsonian symptoms and excessive levels may cause psychosis, with ideal levels observed at the top of the inverted "U" between the two extremes [132]. Further complicating matters, various receptor subtypes (eg, D2 versus D4 receptors) also appear to differentially influence behavior, because different brain regions have higher concentrations of dopaminergic ligands. Research into monoamines and other neurotransmitters has the potential to answer important questions regarding the development and treatment of delirium, in particular as they relate to pharmacologic interventions such as antipsychotics.

Surgical factors and postoperative cognitive dysfunction

Several reports suggest that delirium may be a side effect of anesthesia or surgery [15,133–148]. To date, studies examining associations between surgery and delirium have investigated microemboli migration [149–151], hypoperfusion [64,137,152–154], inflammatory responses [155–157], changes in hormone levels [158–161], and local and general anesthesia [64,133,162,163]. Gottesman and colleagues [152] hypothesized that a drop in the mean arterial pressure may put patients at risk for early cognitive dysfunction. Moreover, elderly patients are characterized by a normal ageing process with a reduction in organ function and altered pharmacokinetics and pharmacodynamics [164]. This process is supported by the finding that adverse reactions to surgery may be particularly likely in elderly individuals [64,137,153]. All of these studies support the notion that there may be a relationship between surgery and delirium.

Several etiologic factors for postoperative delirium have been described, suggesting that the pathogenesis of acute confusion is multifactorial [134,165–167]. In the studies discussed previously, it is often difficult to determine whether the factor is, indeed, the surgery or the clinical context under which the surgery takes place. Various perioperative factors may precipitate the development of postoperative delirium. For example, an impaired cerebral oxygen supply may lead to transient or irreversible neurologic changes. Perioperative hypotension and a reduced blood hemoglobin level could also have a causal role in postoperative delirium [154]. Currently, there is no definitive evidence regarding a causal link between moderate perioperative hypoxemia or hypotension and cognitive dysfunction. Relatively large clinical trials have failed to show a connection between modest hypoxemia and postoperative complications [64,168]. Bearing these considerations in mind, the link between surgery and POCD should continue to be explored

because postoperative delirium may be caused by several other factors, either drug induced or somatic, which impact the CNS during surgery [134,165–167]. In future studies of POCD, it will be important to account for the clinical context and to control for, or rule out, potentially spurious mediators to better understand the link between surgery and delirium.

Future directions: molecular genetics

Recent advances in molecular genetics have begun to bridge gaps between bench science and bedside care. The concept of "personalized medicine" suggests that it may eventually be possible to tailor health care to an individual's needs based on the patient's specific genotype and phenotype. Genetic approaches may offer several opportunities to realize this goal and may also shed light on underlying metabolic and molecular mechanisms of acute brain dysfunction. One of the first genes that drew researcher's attention was that encoding for apoliprotein E (APOE) [169]. Because of the links of delirium to dementia, this gene, which has been well studied in Alzheimer's disease, may provide clues regarding how individuals at risk for the development of early onset Alzheimer's disease could also be prone to delirium. APOE is a 299–amino acid, lipid-binding protein with three common human isoforms (APOE 2, 3, and 4). In particular, the APOE4 variant is known to be associated with a higher susceptibility for Alzheimer's disease [170] and has recently been implicated in an increased duration of delirium for ICU patients [171]. These findings are somewhat controversial [172]. Varying methodologies and patient populations may yield different results, and larger more definitive investigations are warranted.

Other genes that regulate monoamine metabolism, and therefore neurotransmission, have also been implicated in the development of delirium. Catechol-o-methyl transferase (COMT) is an essential enzyme for the synthesis and breakdown of dopamine in the prefrontal cortex [130,131]. The dopamine hypothesis of schizophrenia has been used to suggest that acute confusional status (ie, hallucinations, delusions, and, more generally, cognitive dysfunction) is related to fluctuating levels of dopamine. Several studies have shown that prefrontal and midbrain atrophy may be caused by suboptimal dopamine levels linked to certain COMT variants [130,131]; therefore, individual differences in the metabolism of dopamine may be related to differential outcomes for acute brain dysfunction, apoptosis, and cognitive impairment. Along the same lines, another monoamine regulatory polymorphism is the X-linked monoamine oxidase A (MAOA). Recent evidence [173] suggests that commonly occurring variants in this gene also appear to influence functional brain connectivity, neurocognitive functioning, and anatomic brain structure in key regions. Common genetic variants that influence levels of MAOA via enzymatic catabolism in the Xp11.23 locus have been shown to impact the function of specific brain structures, particularly in the frontal lobe and greater cingulate cortex.

Many of these regions appear to be important for behavioral inhibition and are also implicated in executive functioning ability. Examining the correlates of common MAOA variants in patients in whom delirium develops could lead to earlier interventions to halt the loss of frontal lobe–linked executive functioning and provide new opportunities for early intervention.

Another possible avenue to pursue may be genetic variants that are thought to be related to the development of delirium tremens. Although this form of delirium differs in important ways from ICU delirium, there appear to be several comparable components. First, GABA transmission is thought to be a key factor for both disorders. A recent meta-analysis by Van Munster and colleagues [174] suggested that reduced levels of GABA may mediate up-regulation of dopamine transmission in delirium tremens. They noted that polymorphisms in DRD3 and the dopamine active transporter (also known as SLC6A3) that influence both dopamine and GABA transmission are the most consistently replicated genetic variants associated with delirium tremens. Interestingly, this dopamine/GABA mechanism associated with delirium tremens has been replicated more consistently in the literature than other theoretically plausible variants thought to influence GABA transmission more directly [174]. DRD3 and the dopamine active transporter may help in advancing the understanding and treatment of both delirium tremens and ICU-related delirium via a common thread, with dopamine transmission mediated by GABA.

Another family of genes involved in neuronal growth factors may also harbor insights related to delirium and LTCI. Brain-derived neurotrophic factor (BDNF) has long been known to be critical for the growth and survival of neurons [175]. A common gene variant of BDNF appears to influence memory for events in humans by altering a growth factor in the hippocampus, a brain area known to mediate memory [176]. On average, people with a particular version of the gene that codes for BDNF perform worse on tests of episodic memory, such as on tasks recalling what happened yesterday [176]. They also demonstrate differential hippocampal activation as well as compromised overall neuronal health and interconnectivity. Other research has suggested that these effects are likely traceable to limited secretion of dopamine, which affects human hippocampal neurogenesis [177,178]. The inhibitory influence of BDNF on neuronal health and growth factors is also thought to be mediated by GABA-A receptor-linked, post-synaptic currents [175]. This influence is important for ICU patients at risk for delirium owing to the number of GABAergic sedative agents commonly prescribed in the ICU. BDNF may also have potential for advancing understanding of the pathophysiologic mechanisms of ICU-related delirium and LTCI.

The individual contribution of each of these genetic influences requires more research. This line of investigation may eventually be able to aide in the implementation of personalized medicine in the ICU. Additionally, a more refined understanding of genetic mechanisms of action has the potential to greatly expand the understanding of delirium. Ideally, this

research will eventually lead to a comprehensive view of ICU delirium at multiple levels of analysis, ranging from the molecular to the behavioral.

Summary

The current review summarizes recent research into the pathophysiology of ICU-related delirium. Although this research has generated several important hypotheses, most require further evaluation. Advances in our understanding of how sedatives and analgesics impact brain functioning appear to be particularly promising for the prevention of ICU delirium and its long-term neurologic sequelae (see Table 1). These approaches hold great potential for increasing our understanding of delirium and improving outcomes in critical illness.

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