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Pathoetiological Model of Delirium: a Comprehensive Understanding of the Neurobiology of Delirium and an Evidence-Based Approach to Prevention and Treatment

José R. Maldonado, MD, FAPM, FACFE

*Departments of Psychiatry and Medicine, Stanford University School of Medicine,
401 Quarry Road, Suite 2317, Stanford, CA 94305, USA*

“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.” (Engel and Romano, 1959)

Delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity secondary to systemic disturbances [1–3]. The literature describes the sensorium of delirious patients as “waxing and waning.” On the other hand, it is actually alertness (ie, a state of readiness of an organism to integrate stimuli enabling possible responses to stimuli) and vigilance (ie, paying attention to crucial external events) that are fluctuating. A delirious patient does indeed receive external information but integrates it incorrectly, which produces behavioral responses that are inadequate to the environment. So it is not really the attention, but the mental content that is altered and fluctuating.

The incidence of delirium is rather high in both medically and surgically ill patients [4,5], and even higher among critically ill patients (up to 80%) [6,7]. In addition to causing distress to patients, families, and medical caregivers, the development of delirium has been associated with increased

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E-mail address: jrm@stanford.edu

morbidity and mortality [8–12], increased cost of care [11,13], increased hospital-acquired complications [12], poor functional and cognitive recovery [4,10,14], decreased quality of life [12,14,15], prolonged hospital stays [6,8,10–12,14–16], and increased placement in specialized intermediate- and long-term care facilities [12,14,15]. Contrary to some definitions, delirium is unfortunately not always reversible. A study conducted at a teaching hospital suggested that once delirium occurs, only about 4% of patients experience full resolution of symptoms before discharge from the hospital [10]. In the same study, it was not until 6 months after hospital discharge that an additional 40% experienced full resolution of symptoms.

To date, no single cause of delirium has been identified. Known risk factors for delirium include advanced age, preexisting cognitive impairment, medications (especially those with high anticholinergic potential), sleep deprivation, hypoxia and anoxia, metabolic abnormalities, and a history of alcohol or drug abuse. Over time, a number of theories have been proposed in an attempt to explain the processes leading to the development of delirium. Most of these theories are complementary, rather than competing. The “oxygen deprivation hypothesis” proposes that decreased oxidative metabolism in the brain causes cerebral dysfunction because of abnormalities of various neurotransmitter systems. The “neurotransmitter hypothesis” suggests that reduced cholinergic function; excess release of dopamine, norepinephrine, and glutamate; and both decreased and increased serotonergic and gamma-aminobutyric acid activity may underlie the different symptoms and clinical presentations of delirium. The “neuronal aging hypothesis” is closely related to the changes in neurotransmitters observed in normal aging. Accordingly, this theory suggests that elderly patients are more at risk for developing delirium, likely because of age-related cerebral changes in stress-regulating neurotransmitter and intracellular signal transduction systems. The “inflammatory hypothesis” suggests that increased cerebral secretion of cytokines as a result of a wide range of physical stresses may lead to the development of delirium, probably by their effect on the activity of various neurotransmitter systems. The “physiologic stress hypothesis” suggests that trauma, severe illness, and surgery may give rise to modification of blood-brain barrier permeability, to the sick euthyroid syndrome with abnormalities of thyroid hormone concentrations, and to an increased activity of the hypothalamic-pituitary-adrenal axis. These circumstances may alter neurotransmitter synthesis and cause the release of cytokines in the brain, thus contributing to the occurrence of delirium. Finally, the “cellular-signaling hypothesis” suggests that more fundamental processes like intraneuronal signal transduction (ie, second messenger systems that at the same time use neurotransmitters as first messengers) may be disturbed, affecting therefore neurotransmitter synthesis and release. It is likely that none of these theories by themselves explain the phenomena of delirium, but rather it is more likely that two or more of these, if not all, act together to lead to the biochemical derangement we know as delirium (Table 1). At the end, it is unlikely that

Table 1
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	Chages in RBF	EEG	Mel	Inflam	Cort
Anoxia/hypoxia	↓	↑	↑	↓	↓	↓	↑?	↑	↑, ↓	⚡↑	⚡	↑	⚡	↓		↑	
Aging	↓									⚡↑	⚡		⚡	↓			
CVA		↑														⚡	↑
Hepatic Failure	↓	↑	↑	↑	↑	↓?	↑	↑			⚡	↑	⚡	↓			
Sleep deprivation			⚡								⚡			↓	⚡, ↓	⚡	↑
Trauma, Sx, and post-op	↓	↑?			↓	↑?	↓	↑	↑	↑	↑		⚡	↓	↓	↑	↑
Etoh and CNS-Dep withdrawal	↑?	↑?	↑	↓	↓, ↑	↑	↓				⚡		↔	↑	↓		↑
DA agonist		↑			↓	↑?					⚡						
Infection/Sepsis	↓?	↑?			↓		↓	↓	↓	↑	⚡		⚡			↑	↑
GABA use	↓			↑							⚡				↓		
Dehydration and electrolyte imbalance	↓?		↑							↑	⚡						
Glucocorticoids																	↑
Medical illness	↓				↓		↓	↑					⚡		↓	⚡	↑
Hypoglycemia	↓																

Abbreviations: ↑, likely to be increased or activated; ↓, likely to be decreased; ↔, no significant changes; ⚡, likely a contributor, exact mechanism is unclear; 5HT, 5-hydroxytryptamine or serotonin; ACH, acetylcholine; CNS-Dep, central nervous system depressant agent; Cort, Cortisol; CVA, cerebro-vascular accident; Cytok, cytokines; DA, dopamine; EEG, electroencephalograph; Etoh, alcohol; GABA, gamma-aminobutyric acid; GLU, glutamate; His, histamine; HPA axis, hypothalamic-pituitary-adrenocortical axis; Mel, melatonin; Inflam, inflammation; NE, norepinephrine; NMDA, N-methyl-D-aspartic acid; Phe, phenylalanine; RBF, regional blood flow; Sx, surgery; Trp, tryptophan.

we find a stringently common pathway to the development of delirium, more likely, the syndromes of delirium (ie, hyper, hypo, and mixed types) represent the common end product of one or various independent neurochemical pathways (Table 2).

This article is an attempt to understand the pathophysiological contributors to delirium and their relationship regarding basic neurotransmitter pathways and systems. The author will describe our interpretation of the cascade of processes that lead to delirium based on a comprehensive review of the literature (Fig. 1). Throughout the article we shall discuss the different neurochemical mechanisms and pathways that lead to the common features of delirium. Finally, based on those theories and understanding, we can begin postulating potential prevention methods and treatment techniques.

The neurochemical pathways of delirium

Aging: acetylcholine, vascular supply, and delirium

Human studies have revealed that the cholinergic system is widely involved in arousal, attention, memory, and rapid-eye-movement (REM) sleep. A deficiency of cholinergic function relative to that of other neurotransmitters can be expected to alter the efficiency of these mental mechanisms [17]. In fact, one leading hypothesis is that delirium results from an impairment of central cholinergic transmission [18–20]. Low levels of acetylcholine (ACh) in plasma and cerebrospinal fluid (CSF) have been described in delirious patients [18,21–28].

Studies have suggested that age is an independent predictor of transitioning to delirium. Some have demonstrated that older patients have a higher incidence of developing postoperative delirium, even after relatively simple outpatient surgery [29]. In fact, for each additional year after age 65, the probability of transitioning to delirium increased by 2% (multivariable *P* values less than .05) [30]. Studies evaluating pre- and

Table 2
Neurochemical mechanisms associated with delirium type

Delirium type	ACH	DA	GLU	GABA	5HT	NE	O2 deprivation	Sleep	Cytokines	HPA	Trp	Phe	EEG	Mel
Hypo	↓	↑	↑		↑				↑	↑	↑	↑	↓	
Hyper	↓		↑		↓	↓			↑	↑	↑	↑	↑	↓
Mixed	↓		↑			↓			↑	↑	↑	↑	↑↓	

Abbreviations: ↑, likely to be increased; ↓, likely to be decreased; ⇌, uncertain action; 5HT, 5-hydroxytryptamine or serotonin; ACH, acetylcholine; DA, dopamine; EEG, electroencephalograph; GABA, gamma-aminobutyric acid; GLU, glutamate; HPA, hypothalamic-pituitary-adrenocortical axis; Mel, melatonin; NE, norepinephrine; Phe, phenylalanine; Sx, surgery; Trp, tryptophan.

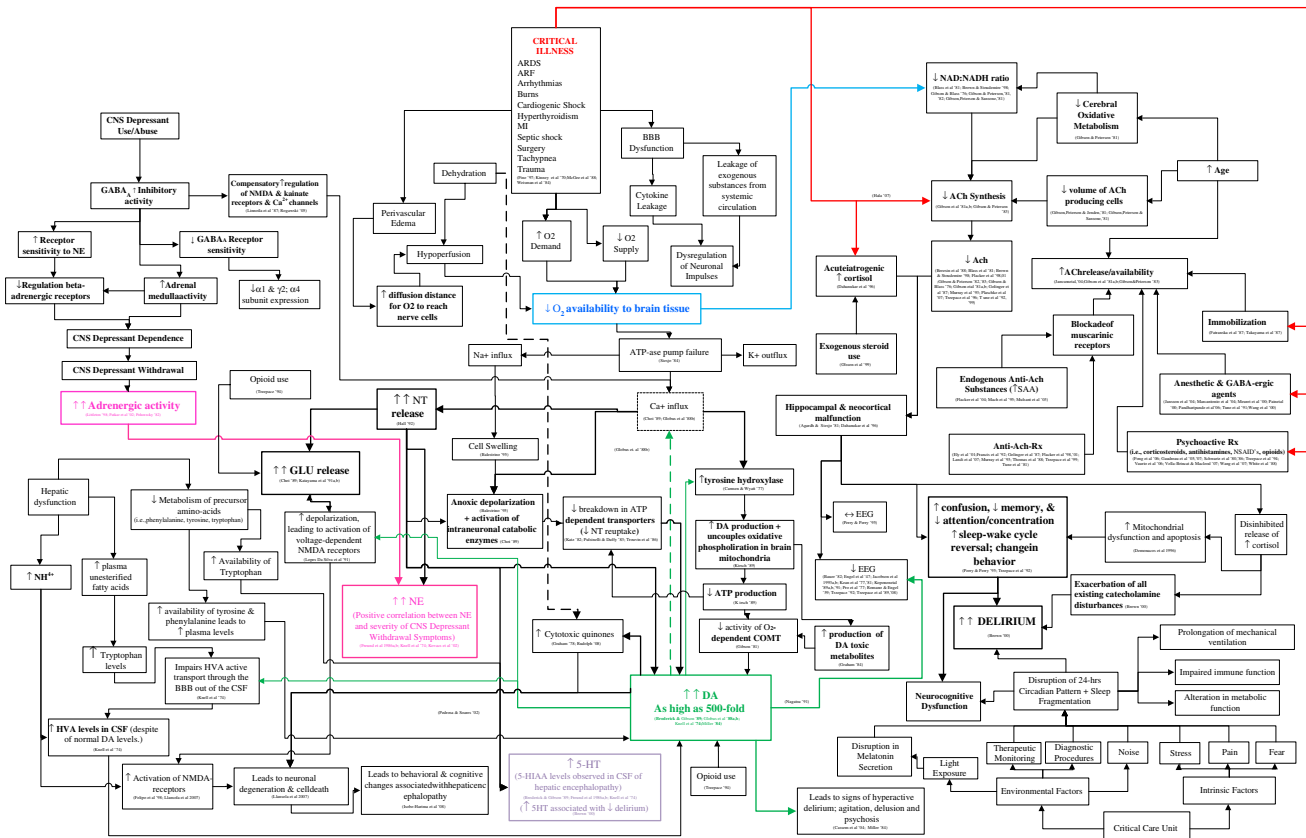


Fig. 1. A basic pathoetiological model of delirium.

postoperative neuropsychological performance in older nondemented patients after elective orthopedic surgery found that the presence of preoperative attentional deficits was closely associated with postoperative delirium [31].

The increased incidence of delirium in older patients may be associated with a decrease in the volume of ACh-producing cells occurring during the normal aging process [32]. Aging is also associated with decreased cerebral oxidative metabolism [33]. Both of these factors lead to a normal decline in ACh synthesis [32–35]. The decline in cognitive functioning associated with the normal process of aging may be aggravated by the presence of even mild hypoxia, which further inhibits ACh synthesis and its release [17,36,37]. Hypoxia leads to decreased oxygen supply to brain tissue, which leads to a decreased redox state (nicotinamide adenine dinucleotide [NAD]-oxidized: NADH-reduced), which may also result in decreased ACh production [17,33,36–39].

Similarly, studies in both the acute medical ward and surgical units suggest that the presence of baseline dementia increases the occurrence of delirium [40–42]. Alzheimer's disease, which is characterized by a loss of cholinergic neurons, carries an increased risk of delirium, particularly associated with the use of anticholinergic medication [33].

Higher levels for serum anticholinergic activity (SAA) [43] have been associated with an increased likelihood of delirium in both surgical [23,44,45] and medical [18,46] inpatients. A dose-response relationship between symptoms of delirium and SAA has also been suggested [18]. Studies have shown that SAA is significantly higher in delirious, compared with nondelirious patients, and that resolving delirium is correlated with decreasing SAA [47]. In fact, some have observed that high SAA (ie, > 20) has a predictive value for delirium (defined as confusion assessment method [CAM] positive) of 100% [48].

Most clinicians had presumed this high association between SAA and delirium to be the result of the use of exogenous anticholinergic substances. Nevertheless, studies have demonstrated that detectable SAA levels in serum have been found in delirious patients who were not exposed to pharmacologic agents with known anticholinergic activity. These findings suggest that endogenous anticholinergic substances may exist during acute illness and may be implicated in the etiology of delirium [22,47,49].

Animal studies have demonstrated the negative influence of age on prefrontal ACh release and Fos (ie, Fos protein) response in the hypothalamic paraventricular nucleus and the nucleus tractus solitarius (NTS) of rats following isoflurane anesthesia (known to decrease ACh release in most brain regions). The old rat group showed significantly greater Fos induction in the paraventricular nucleus compared with the young adult rat group ($P < .05$), indicating that the old rats when subjected to anesthesia were more profoundly affected than young adult rats with regard to reductions in acetylcholine release and stress responses [35].

In another study, injecting atropine into rat brains, researchers were able to mimic a model for delirium in humans (defined by cortical electroencephalogram [EEG] recordings, maze performance, and observation of behaviors) [50]. Using this model, researchers were able to demonstrate higher EEG amplitudes and slower frequencies (hallmarks of drowsiness and sleep) in the atropine condition. Atropine-treated rats exhibited significant elevation in their mean maze time ($P < .016$, RM analysis of variance [repeated measures ANOVA]), and similarly to what is observed in delirious human subjects, atropine-treated rats exhibited difficulty with attention and memory, sleep-wake reversal, and changes in usual behavior.

Other animal studies have revealed impairment in cholinergic neurotransmission in models of encephalopathy/delirium, hypoxia, nitrite poisoning, thiamine deficiency, hepatic failure, carbon monoxide poisoning, and hypoglycemia [21,50,51]. Animal models have also demonstrated that immobilization may cause widespread ACh reduction [52,53]. This model may mimic the decreased mobility of critically ill patients.

Changes in ACh activity may be one of the mechanisms mediating the diffuse slowing pattern often described in the electroencephalogram (EEG) of patients suffering from delirium. The most common EEG finding is that of slowing of peak and average frequencies, decreased alpha activity, and increased theta and delta waves. Studies suggest that EEG changes correlate with the degree of cognitive deficit, but not with behavior assessed solely on degree of spontaneous movements. In other words, low levels of ACh do not slow the EEG to the point of sleep or absence of motor behavior, but seem to slow cognition [2,50,54–60].

Also with aging comes a broad decline in cardiovascular and respiratory reserves. Studies suggest that by age 85, vital capacity is reduced by nearly 40% and the arterio-alveolar gradient widens. Studies have demonstrated significant decreases in alveolar volume, nitric oxide and carbon monoxide lung transfer measurements, membrane diffusion, and capillary lung volume in relation to age ($P < .05$) and continuous negative pressure induced a significant increase in all variables [61]. Oxygen delivery to the brain may then be diminished at times of metabolic stress due to reduced capacity for compensatory changes in the arterial vasculature because of vasculopathy and senile changes. The normal aging process is accompanied by a complex series of changes in the autonomic control of the cardiovascular system, favoring heightened cardiac sympathetic tone with parasympathetic withdrawal and blunted cardiovagal baroreflex sensitivity. Together these changes have the potential to further magnify the effects of concomitant cardiovascular disease [62].

Animal studies have suggested that in patients with baseline organic cerebral disorders (eg, cerebrovascular disease) who are submitted to surgery, hypoxia during anesthesia may cause tissue damage in the caudoputamen, which may be responsible for long-lasting postoperative delirium in patients with stroke and/or dementia [63].

Chronic forms of hypoperfusion may lead to subcortical ischemic vascular dementia, a relatively common form of dementia. This is more likely due to anatomic changes caused by aging in the arterial vascular system and predisposes the elderly to the effects of hypotension. Particular regions of the brain are more susceptible to ischemic hypoperfusive injury, including the periventricular white matter, basal ganglia, and hippocampus, leading to cognitive and memory problems. This may explain why older patients may be particularly sensitive to hypotension and hypoperfusion associated with orthostatic hypotension, congestive heart failure, or the changes associated with routine surgical procedures such as hip and knee replacement and coronary artery bypass graft (CABG) [64].

Similarly, increasing evidence supports the notion that chronic oxidative stress is the final pathway implicated in two major brain disorders characterized by cognitive impairment: cerebral chronic small vessel disease (microangiopathic leukoencephalopathy) and Alzheimer's disease (AD) [65]. Both disease processes seem to involve chronic hypoperfusion. The process of hypoperfusion appears to induce chronic oxidative damage in tissues and cells, largely due to the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These conditions outpace the capacity of endogenous redox systems to neutralize these toxic intermediates and may lead to a system imbalance or to a major compensatory adjustment to rebalance the system. This new redox state is generally referred to as "oxidative stress" and is associated with other age-related degenerative disorders, such as atherosclerosis, ischemia/reperfusion, and rheumatic disorders. Chronic ischemic injury can also affect differently selective areas of the brain [65] due to a well-documented variation in vulnerability of cerebral areas, with its imputability in spreading neuronal depression [66–68].

Medications and delirium

Factors associated with medication-induced delirium include the number of medications taken (generally more than 3) [69], the use of psychoactive medications [70], and the agent's anticholinergic potential [71]. There are a number of pharmacologic agents identified with an increased risk of developing delirium (Box 1). The number of agents used may be associated with pharmacokinetic or pharmacodynamic effects of the combined agents (eg, drug-drug interactions, metabolic inhibitions, additive negative effects). Similarly, studies have demonstrated a link between the use of pharmacologic agents with psychoactive effects and the occurrence of delirium in 15% to 75% of cases [15,72–77]. Certain agents with known psychoactive activity (ie, opiates, corticosteroids, benzodiazepines, nonsteroidal anti-inflammatory agents [NSAIDs], and chemotherapeutic agents) have been identified as major contributors to delirium in several studies [70]. Data suggest that a very high number of ventilated patients (more than 80%) develop delirium [6,7]. Similarly, about 90% of ventilated patients receive

Box 1. Risk of delirium with certain commonly used drugs**High risk**

- Opioid analgesics
- Antiparkinsonian agents (particularly anticholinergic agents)
- Antidepressants (particularly anticholinergic agents)
- Benzodiazepines
- Centrally acting agents
- Corticosteroids
- Lithium

Medium risk

- Alpha-blockers
- Antiarrhythmics (lidocaine [lignocaine] has the highest risk)
- Antipsychotics (particularly sedating agents)
- β -Blockers
- Digoxin
- Nonsteroidal anti-inflammatory drugs
- Postganglionic sympathetic blockers

Low risk

- ACE inhibitors
- Antiasthmatics (highest risk with aminophylline and lowest risk with inhaled agents)
- Antibacterials
- Anticonvulsants
- Calcium channel antagonists
- Diuretics
- H₂-antagonists

Data from Bowen JD, Larson EB. Drug-induced cognitive impairment. Defining the problem and finding the solutions. *Drugs Aging* 1993;3(4):349–57.

benzodiazepines, opioids, or both to facilitate their management and ease the discomfort associated with intubation [78]. The question is, how are these two factors related?

The fact is, opioid agents have been implicated in the development of delirium [79–83] and are blamed for nearly 60% of the cases of delirium in patients with advanced cancer [84]. Narcotic use has been associated with the development of delirium [85–87]. Some have suggested that opioids cause delirium via an increased activity of dopamine (DA) and glutamate (GLU), while decreasing ACh activity [20]. The association of delirium with the use of meperidine has been well documented [30,64,88–91]. Meperidine is itself metabolized to normeperidine, a potent neurotoxic metabolite with marked anticholinergic potential [88]. Both its direct neurotoxic effect,

as well as the strong anticholinergic activity, may contribute to the development of delirium. Cases of opioid toxicity have been reported in relation to fentanyl and methadone [92–94].

Increasing evidence from experimental studies and clinical observations suggest that drugs with anticholinergic properties can cause physical and mental impairment. It has long been thought that low ACh levels may be associated with the disorientation, arousal, and cognitive problems observed in delirious patients [12]. Several studies have demonstrated a relationship between a drug's anticholinergic potential, as measured by SAA and the development of delirium [18,23,28,44,69,71,91,95–99]. Tune and colleagues [28,44,71,91,99,100] conducted several studies looking at the cumulative effect of drugs with subtle anticholinergic potential and their SAA (Box 2; Table 3).

A cross-sectional study [18] of 67 acutely ill older medical inpatients demonstrated that elevated SAA was independently associated with delirium. Furthermore, multivariate logistic regression revealed that the SAA quintile remained significantly associated with delirium, even after adjusted for ADL impairment, admission diagnosis of infection, and elevated white blood cell count. Among the subjects with delirium, a greater number of delirium symptoms were associated with higher SAA. Each increase in SAA quintile was associated with a 2.38-times increase in the likelihood of delirium (Fig. 2). Similarly, a study of elderly (ie, older than 80 years) ($n = 364$) patients demonstrated that the use of anticholinergic drugs is associated with impaired physical performance and functional status (Fig. 3) [101].

Studies have measured anticholinergic activity in blood and CSF from patients admitted for urological surgery and compared peripheral (ie, blood) and central (ie, CSF probes) anticholinergic levels [24]. Anticholinergic activity was determined by competitive radioreceptor binding assay for muscarinic receptors and correlation analysis conducted for both sets of samples. The mean anticholinergic levels were 2.4 ± 1.7 in the patients' blood and 5.9 ± 2.1 pmol/mL of atropine equivalents in CSF, demonstrating that the anticholinergic activity in CSF was about 2.5-fold higher than in patients' blood. Still, there was a significant linear correlation between blood and CSF levels (Fig. 4). These studies have found that exposure to anticholinergic agents was an independent risk factor for the development of delirium, and specifically associated with a subsequent increase in delirium symptom severity.

Decreased cholinergic activity has been demonstrated in delirium and it is suggested that ACh repletion may serve as treatment of delirium [102]. In fact, physostigmine has been reported as reversing delirium when it was induced by anticholinergic agents in healthy volunteers [103], as well as delirium secondary to anticholinergic syndrome [104–108]. Conversely, studies in animals and healthy elderly adults have shown that cholinergic antagonist agents produced deficits in information processing, arousal, and attention and a reduced ability to focus [109,110].

Sleep pattern disruption and delirium

Sleep is a physiologic state that humans need to experience every day to restore physical and mental functions. Typically, humans adapt to a 24-hour circadian pattern, where they sleep at night and are awake during the day. This 24-hour internal clock (circadian pattern) is maintained by environmental factors, primarily light exposure, which affects melatonin secretion at night [111]. Conversely, sleep disruption may be another factor implicated as a mediating factor in the development of delirium, at least preponderantly in the ICU setting, if not in any hospitalized patient. Studies suggest that sleep deprivation may lead to the development of memory deficits [112–114]. Studies have shown that “chronic partial sleep deprivation” (ie, sleeping limited to 4 hours per night, for 5 consecutive nights) translates into cumulative impairment in attention, critical thinking, reaction time, and recall [115,116]. Furthermore, studies have found that sleep deprivation (even just 36-consecutive hours) may lead to symptoms of emotional imbalance (ie, short temper, mood swings, and excessive emotional response) likely due to a disconnect between the amygdala and the prefrontal cortex [117].

The above findings may contribute to many of the cognitive and behavioral changes observed in delirious patients. In fact, studies have demonstrated that sleep deprivation may lead to both psychosis [118] and delirium [51,119–121]. Mounting data suggest that cumulative sleep debt may not just be a cause of, but may aggravate or perpetuate delirium [122–127]. Using staff observations, there was a higher prevalence of delirium among sleep-deprived patients [128,129]. Overall, delirious patients were reported to have irregular patterns of melatonin release [130] and disrupted circadian rhythms, resulting in fragmented sleep/wake cycles and nighttime awakenings [131].

The amount of sleep debt associated to the critical care environment is not insignificant. Studies have found that the average ICU patient sleeps about 1 hour and 51 minutes per 24-hour period [132]. Factors associated with decreased length of sleep in the ICU include the high frequency of therapeutic interventions (eg, blood pressure monitoring, blood draws and flushing of lines, dressing changes and wound care), the nature of diagnostic procedures, pain, fear, and the noisy environment. As many as 61% of ICU patients report sleep deprivation, placing it among the most common stressors experienced during critical illness [133]. Previous studies used polysomnography (PSG) to demonstrate severe sleep fragmentation, a loss of circadian rhythm, and a decrease or absence of both slow-wave sleep and REM sleep in ICU patients [132,134,135]. In addition to causing emotional distress, sleep deprivation in the critically ill has been hypothesized to contribute to ICU delirium and neurocognitive dysfunction, prolongation of mechanical ventilation, and decreased immune function [136].

Melatonin secretion is one reflection of this internal sleep/wake mechanism. Melatonin levels are normally high during the night and low during daytime, being suppressed by bright light. Urinary excretion

Box 2. Medications with anticholinergic effects

Alprazolam
Amantadine
Amitriptyline
Ampicillin
Atropine
Azathioprine
Captopril
Cefamandole
Cefoxitin
Chlorazepate
Chlordiazepoxide
Chlorthalidone
Cimetidine
Clindamycin
Codeine
Corticosterone
Cycloserine
Cyclosporin
Desipramine
Dexamethasone
Diazepam
Digoxin
Diltiazem
Diphenhydramine
Dipyridamole
Dyazide
Flunitrazepam
Flurazepam
Furosemide
Gentamycin
Hydralazine
Hydrochlorothiazide
Hydrocortisone
Hydroxyzine
Imipramine
Isosorbide
Keflin
Lanoxin
Methyldopa
Nifedipine
Oxazepam

Oxybutynin chloride
Oxycodone
Pancuronium bromide
Phenelzine
Phenobarbital
Piperacillin
Prednisolone
Ranitidine
Theophylline
Thioridazine
Ticocillin
Tobramycin
Triamterene
Valproic acid
Vancomycin
Warfarin

Data from Tune LE, Egeli S. Acetylcholine and delirium. Dement Geriatr Cogn Disord 1999;10:342–4.

of 6-sulphatoxymelatonin (6-SMT)—the chief metabolite of melatonin—closely parallels serum melatonin concentrations. Therefore, the urinary excretion of 6-SMT can serve as a reliable measurement of serum melatonin. In a study of hospitalized, postoperative elderly patients, melatonin plasma samples were obtained every 2 hours from 19 patients without delirium and 10 with delirium after major abdominal surgery. Results demonstrated that patients without delirium showed nearly identical preoperative and postoperative melatonin secretion for 24 hours. On the other hand, patients with delirium experienced melatonin levels that were lower than preoperative values [137].

A study of medically hospitalized patients measured 6-SMT urinary levels twice: first in the acute phase of delirium (day when delirium rating scale [DRS] ≥ 14 points) and again after recovery (on the first day when DRS ≤ 6 points). The results demonstrated that among the hyperactive delirium patients, the levels of 6-SMT were lower during the acute delirium state than after recovery ($P < .001$). In contrast, among the hypoactive delirium patients, the levels of 6-SMT were higher during the acute delirium state than after recovery ($P < .01$). With the mixed patients, there was no difference in the level of 6-SMT between the two phases of delirium ($P < .45$) [138].

A study of blood and urine melatonin levels revealed an abolition of the circadian rhythm of physiologic melatonin release in deeply sedated ICU patients [139]. These findings suggest that the dyssynchronization of the melatonin secretion rhythm commonly found among critical care patients

Table 3
Anticholinergic drug used most frequently by the patients in the treatment and comparison groups

Drug	No. patients	Percentage of patients	Median (range) no. prescriptions ^a per patient	Median (range) day supply per prescription
Treated with donepezil				
Amitriptyline	18	4.3	2.0 (1–11)	30.0 (3–34)
Oxybutynin	15	3.6	5.0 (1–15)	30.0 (3–33)
Hyoscyamine	14	3.4	4.0 (1–11)	30.0 (10–30)
Diphenoxylate and atropine	12	2.9	1.0 (1–5)	5.0 (2–30)
Olanzapine	12	2.9	2.5 (1–13)	30.0 (4–30)
Hydroxyzine	11	2.6	4.0 (2–8)	30.0 (1–33)
Doxepin	11	2.6	6.0 (2–12)	30.0 (3–33)
Meclizine	9	2.2	2.0 (1–21)	8.0 (5–30)
Imipramine	7	1.7	6.0 (1–19)	30.0 (3–30)
Cyproheptadine	6	1.4	4.5 (1–11)	30.0 (2–30)
Not treated with donepezil				
Meclizine	16	3.8	1.0 (1–8)	12.0 (4–33)
Amitriptyline	14	3.4	4.5 (1–12)	30.0 (1–33)
Hyoscyamine	9	2.2	2.0 (1–11)	30.0 (1–30)
Oxybutynin	8	1.9	1.5 (1–5)	30.0 (8–33)
Hydroxyzine	8	1.9	2.0 (1–12)	30.0 (3–30)
Dicyclomine	7	1.7	2.0 (1–9)	30.0 (5–31)
Belladonna alkaloids and Phenobarbital	7	1.7	3.0 (1–11)	30.0 (2–30)
Phenylephrine/codeine/promethazine	4	1.0	1.0 (1–2)	5.0 (2–10)
Diphenoxylate and atropine	4	1.0	1.0 (1–1)	4.5 (3–6)
Orphenarine	4	1.0	3.0 (1–8)	30.0 (10–33)

^a Prescriptions for large supplies of medication were converted to 30-day equivalents (eg, a prescription for a 90-day supply of medication was counted as three prescriptions, each with a 30-day supply).

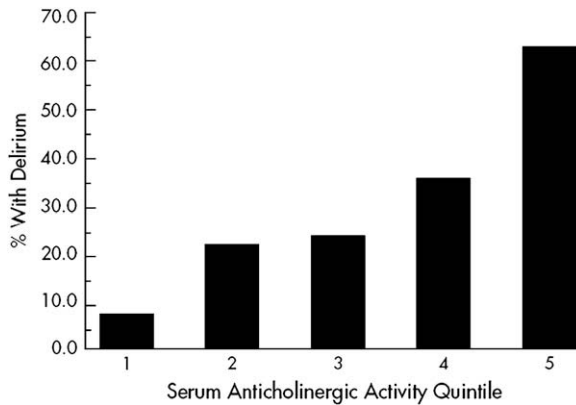


Fig. 2. Percentage of subjects with delirium by serum anticholinergic activity quintile. (From Flacker JM, Cummings V, Mach JR, et al. The association of serum anticholinergic activity with delirium in elderly medical patients. *Am J Geriatr Psychiatry* 1998;6(1):31–41; with permission.)

(possibly mediated or exacerbated by the use of sedative agents) may contribute to the development of delirium (Fig. 5). It also suggests that sedative agents may contribute to the development of delirium by more than one mechanism (ie, disruption of sleep patterns, central acetylcholine inhibition, disruption of melatonin circadian rhythm).

The immune system has long been regarded as a vulnerable target for sleep deprivation. Cytokines synthesized by the immune system may play a role in normal sleep regulation, by increasing non-REM sleep and decreasing REM sleep, and during inflammatory events, an increase in cytokine levels may intensify their effects on sleep regulation [140]. Current evidence suggests that acute and chronic sleep deprivation is associated with decreased proportions of natural killer cells [141], lower antibody titers following influenza virus immunization [142], reduced lymphokine-activated killer activity, and reduced interleukin (IL)-2 production [143]. Moreover, sleep deprivation may alter endocrine and metabolic functions, altering the normal pattern of cortisol release and contributing to alterations of “glucocorticoid feedback regulation” [144], glucose tolerance, and insulin resistance [145].

Trauma, surgery, systemic inflammation, and delirium

Delirium may represent a central nervous system (CNS) manifestation of a systemic disease state that has indeed crossed the blood brain barrier (BBB). Many of the circumstances associated with a high incidence of delirium (eg, infections, medication use, postoperative states) may be associated with BBB integrity compromise. As a response to traumatic events (including the trauma of surgery) the uniform cascade of interacting processes

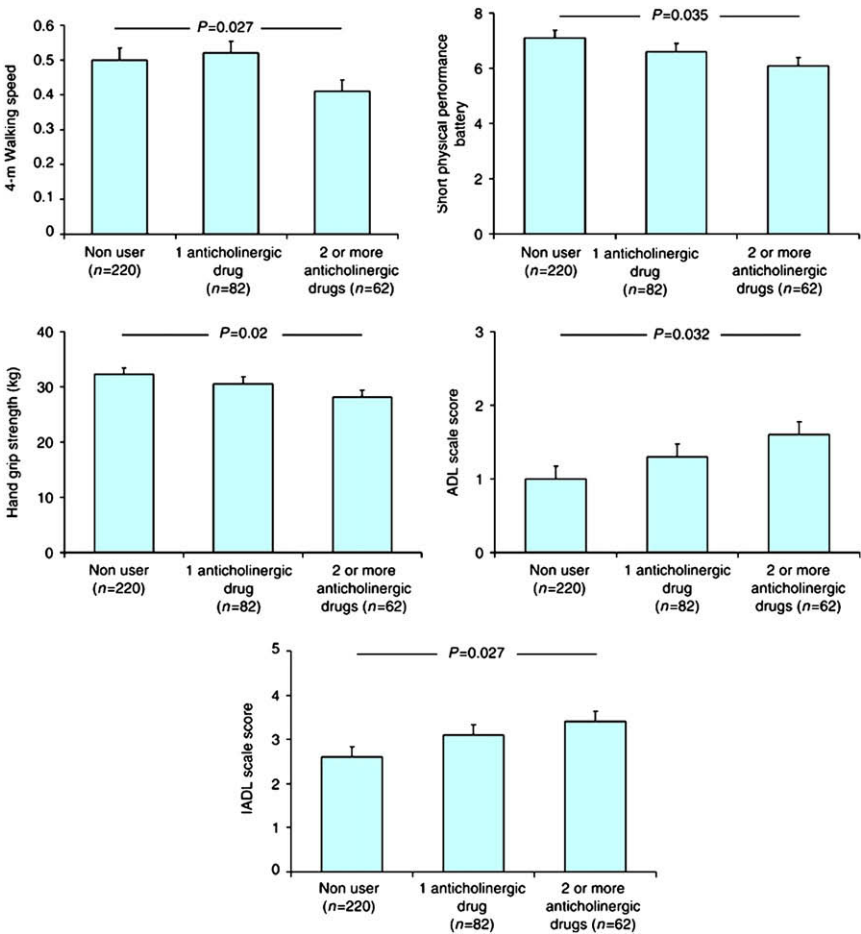


Fig. 3. Anticholinergic drugs and physical function among frail elderly population. (From Landi F, Russo A, Liperoti R, et al. Anticholinergic drugs and physical function among frail elderly population. Clin Pharmacol Ther 2007;81(2):235–41; with permission.)

known as the “systemic inflammatory response” is activated. Some surgical procedures may increase the risk of developing delirium, presumably because of the complexity of the surgical procedure, the extensive use and type of intraoperative anesthetic agents, and potential postoperative complications [146]. The more intense the primary insult is, the more pronounced is the inflammatory response. Illness processes and surgical procedures offer several triggering factors: use of anesthetic agents, extensive tissue trauma, elevated hormone levels, blood loss and anemia, blood transfusions, use of extracorporeal circulation, hypoxia, ischemia and reperfusion, formation of heparin–protamin complexes, microemboli formation and migration, and the inflammatory process. Similarly, studies have demonstrated that the

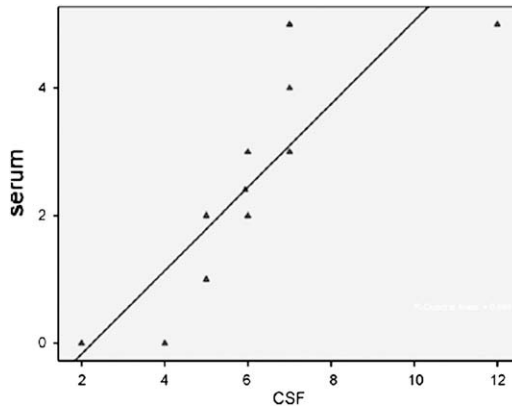


Fig. 4. Anticholinergic activity. Correlation analysis according to Pearson ($r = 0.861$; $P < .001$). The results are reported in pmol/mL of atropine equivalents. (From Plaschke K, et al. Significant correlation between plasma and CSF anticholinergic activity in presurgical patients. *Neurosci Lett* 2007;417(1):16–20; with permission.)

severity of the patient's initial injury or underlying medical problem (as measured by Acute Physiology and Chronic Health Evaluation [APACHE] scores) is significantly directly correlated with the development of delirium [14,30,147].

During or after illness processes or surgery, leukocytes adhere to endothelial cells (EC) and become activated. This leads to degranulation, which releases free oxygen radicals and enzymes, which in turn leads to EC membrane destruction, loosening of intercellular tights, extravascular fluid shift, and formation of perivascular edema, changes that are likely to occur within the brain tissue as well. Thus, systemic inflammation as a response to surgical trauma may cause diffuse microcirculatory impairment. The most relevant pathologies include leukocyte adhesion to vessel lining, endothelial cell swelling, perivascular edema, narrowing of capillary diameters, and lowered functional capillary density. These morphologic changes lead to a decrease of nutritive perfusion and to longer diffusion distance for oxygen. Because ACh synthesis is especially sensitive to low oxygen tension, decreased ACh availability and symptoms of its deficiency readily develop [148].

The magnitude of the inflammatory response after surgery or induced by medical illness has been implicated as a risk factor of neurocognitive decline, including delirium. This has been well documented after various surgical procedures [149–151]. Under normal conditions, the BBB inhibits cytokines and many medications from passing across capillaries into the brain parenchyma so the brain is relatively protected from the harmful effects of systemic inflammation [152]. Chemokines are locally acting cytokines that may enhance migration of inflammatory cells into the brain by

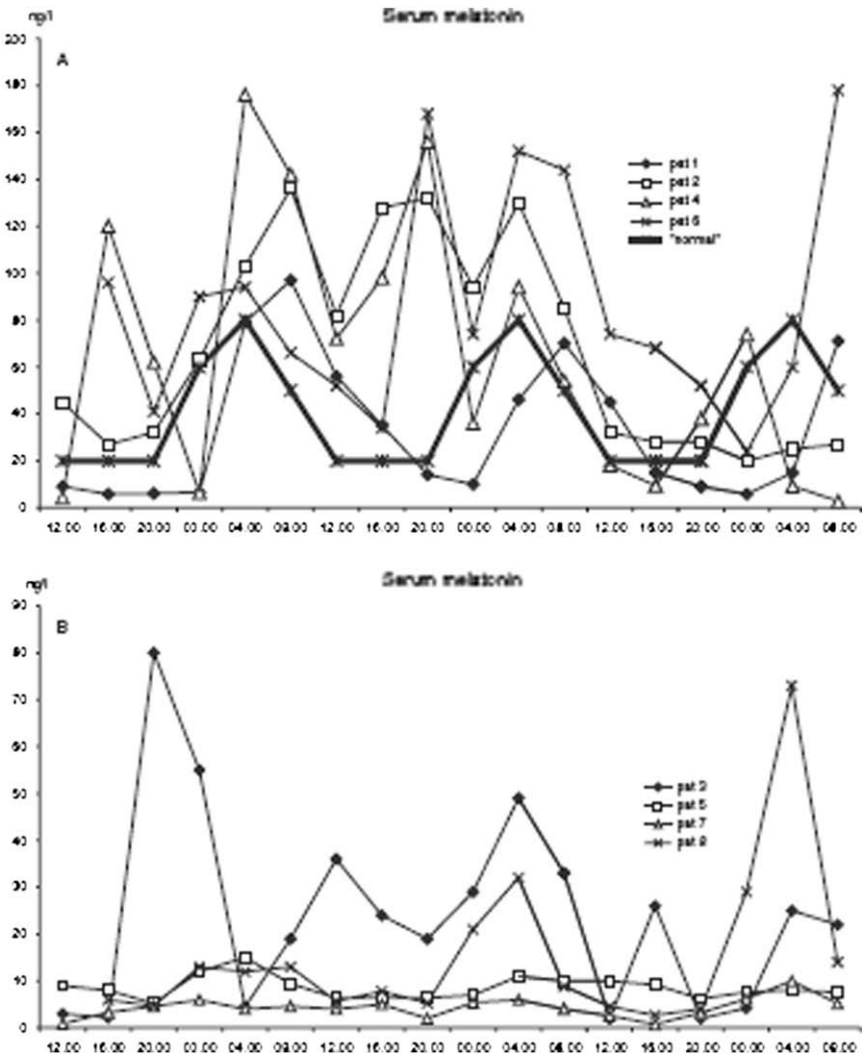


Fig. 5. Serum melatonin (ng/L) in eight critically ill subjects. The serum melatonin rhythm was found to be disturbed in all but one patient (A, B). The exception was patient 8. Her melatonin levels were low during her first day in the ICU, rising to much higher peak values on days 3 to 4. She began to recover a clear melatonin rhythm already on day 2, with a maximum at 4:00 AM. (From Olofsson K, Alling C, Lundberg D, et al. Abolished circadian rhythm of melatonin secretion in sedated and artificially ventilated intensive care patients. *Acta Anaesthesiol Scand* 2004;48(6):679–84; with permission.)

compromising the BBB integrity [153–156]. Compromise of the BBB integrity allows the brain to become more susceptible to the effects of systemic inflammation [153,157]. Transient increases in the levels of circulating inflammatory markers (10 to 100 times more than baseline) has been

hypothesized to result from tissue damage, adrenal stress response, cardiopulmonary bypass, and/or anesthesia [158,159].

A study was conducted examining the expression patterns of pro- and anti-inflammatory cytokines in acutely medically ill, hospitalized elderly patients (ages ≥ 65 ; $n = 185$) with and without delirium [160]. Patients underwent cognitive and functional examination by validated measures of delirium, memory, and executive function, and measurements of C-reactive protein (CRP) and cytokines (IL-1beta, IL-6, tumor necrosis factor [TNF]-alpha, IL-8, and IL-10). A total of 34.6% of subjects developed delirium within 48 hours after admission. Compared with patients without delirium, delirious patients were older and had experienced more frequent preexistent cognitive impairment. In patients with delirium, significantly more IL-6 levels (53% versus 31%) and IL-8 levels (45% versus 22%) were above the detection limit as compared with patients who did not have delirium, even after adjusting for infection, age, and cognitive impairment. This suggests that pro-inflammatory cytokines may contribute to the pathogenesis of delirium.

In a similar study, acutely medically ill patients ($n = 164$), 70 years or older, were studied within 3 days of hospital admission and reassessed twice weekly until discharge, to identify and follow the clinical course of delirium [161]. Patients underwent measurements of apolipoprotein-E (APOE) genotype and the level of circulating cytokines. Researchers found that delirium was significantly ($P < .05$) associated with a previous history of dementia, age, illness severity, disability, and low levels of circulating insulin-like growth factor 1 (IGF-1). Recovery was significantly ($P < .05$) associated with lack of APOE 4 allele and higher initial interferon (IFN)-gamma. It further found a positive relationship between delirium with APOE genotype, IFN-gamma, and IGF-I, but not with IL-6, IL-1, TNF-alpha, and leukemia inhibitory factor.

In a cohort of elderly hip-fracture patients ($n = 41$), serum was obtained during the first 10 hours after fracture and before surgery, 48 to 60 hours postoperative, and 7 and 30 days postoperative, measuring CRP, IL-1beta, IL-6, IL-8, TNF-alpha, IL-10, and IL-1 receptor antagonist (IL-1RA) [162]. A significant increase was found postoperatively for CRP, IL-6, TNF-alpha, IL-1RA, IL-10, and IL-8. CRP kinetics curves were higher in patients with complications as a group, and in those suffering from infections, delirium, and cardiovascular complications. Additional complications appeared in patients with impaired mental status (IMS) versus cognitively intact patients. Analyzing the interaction effect of complications and IMS on CRP and cytokine production demonstrated that the increase in CRP was independently related to complications and IMS. IL-6, IL-8, and IL-10 were higher in IMS patients but not in patients with complications without IMS. This suggests that only CRP significantly and independently increases in patients who are mentally altered and in patients with complications, whereas cytokines significantly increase only in mentally altered patients.

Similarly, a study of cardiac surgery patients ($n = 42$) measured the serum concentrations of 28 inflammatory markers [163]. Inflammatory markers were assigned to five classes of cytokines, which are capable of disrupting BBB integrity in vitro. A class z score was calculated by averaging the standardized, normalized levels of the markers in each class. Beginning on postoperative day 2, patients underwent a daily delirium assessment. The study found that patients who went on to develop delirium had higher increases of chemokines compared with matched controls. Among the five classes of cytokines, there were no other significant differences between patients with or without delirium at either the 6-hour or postoperative day 4 assessments.

Several risk factors for delirium such as severe illness, surgery, and trauma can induce immune activation and a physical stress response comprising increased activity of the limbic-hypothalamic-pituitary-adrenocortical axis, the occurrence of a low T3 syndrome, and, possibly, changes in the permeability of the BBB [164].

Furthermore, some data suggest that inflammation may enhance the detrimental effects of hypoxia in cases of brain injury and long-term cognitive dysfunction. Using a porcine model, Fries and colleagues [165] found that acute lung injury/acute respiratory distress syndrome (ALI/ARDS) was associated with significantly greater hippocampal injury and higher serum levels of protein S100b, a marker of glial injury, than seen in animals that were exposed to hypoxemia alone without ALI/ARDS. These findings suggest that systemic inflammation linked to ALI/ARDS may have contributed to the brain injury seen in this model.

Cortisol, the hypothalamic-pituitary-adrenal axis, and delirium

Glucocorticoid hormones are important for coping with stress and have significant effects on the mobilization of energy substrates and inhibition of nonvital processes [166,167]. Yet, glucocorticoid hormones may have deleterious effects on mood and memory during prolonged excessive secretion. Some have suggested that glucocorticoids may be important for the pathogenesis of delirium, especially in later life [168,169]. In fact, delirium has been reported in cases of hypercortisolism associated with surgery [169], Cushing's syndrome [51], and dementia [170]. In demented patients, significant differences were found in basal cortisol levels between groups of patients with different severities of delirium. Patients without delirium had significantly lower basal cortisol levels than patients with mild delirium and these had significantly higher basal cortisol levels than patients with moderate/severe delirium. Significant differences in post-dexamethasone suppression test (DST) cortisol levels between patients with different degrees of delirium were also found, with the highest values in the moderate/severe delirium group. An increase in the frequency of nonsuppressors with increased severity of delirium was seen (Fig. 6) [170].

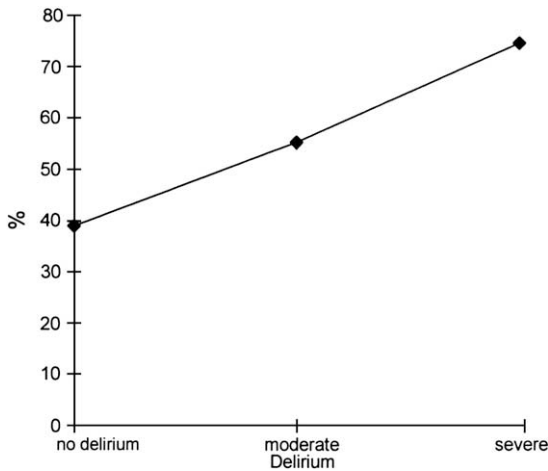


Fig. 6. Percentages of nonsuppressors in delirium. A significant difference in the occurrence of nonsuppressors was found between patients with different severity of delirium ($P = .004$). An increase in the frequency of nonsuppressors with increased severity of delirium was seen: no delirium ($n = 105$) 33%, mild delirium ($n = 47$) 51%, and moderate/severe delirium ($n = 20$) 70%, respectively. (From Robertsson B, Blennow K, Brane G, et al. Hyperactivity in the hypothalamic-pituitary-adrenal axis in demented patients with delirium. *Int Clin Psychopharmacol* 2001;16(1):39–47; with permission.)

Studies have found that, early after a stroke, delirium seems to be associated with an increased adrenocortical sensitivity to adrenocorticotrophic hormone (ACTH) stimulation and a decrease in glucocorticoid-negative feedback [171], even after controlling for possible confounding factors, including the extent of functional impairment and age. Also, increased cortisol excretion after stroke is associated with disorientation [172].

A key abnormality related to cortisol excess in delirium seems to be abnormal “shut-off” of the hypothalamic-pituitary-adrenal (HPA) axis tested by the DST. In experimental models, the hippocampal formation is of prime importance for normal HPA axis shut-off. In this brain area, a close interaction between neurotransmitters, notably acetylcholine, serotonin, and noradrenaline, and glucocorticoid receptors, is relevant for the development of delirium in elderly patients with stroke and neurodegenerative brain diseases (Fig. 7) [173].

Steroid and thyroid hormones may act on nuclear gene transcription by activating protein receptors, which in turn bind to hormone response elements (HREs). Among these cell-specific processes regulated by steroid receptors is energy metabolism through increased synthesis of respiratory enzymes. As some of these enzymes are encoded by both nuclear and mitochondrial genes, coordination of their synthesis is probable, inter alia, at the transcriptional level. Some have demonstrated a direct effect of steroid hormones on mitochondrial gene transcription, suggesting that glucocorticoid

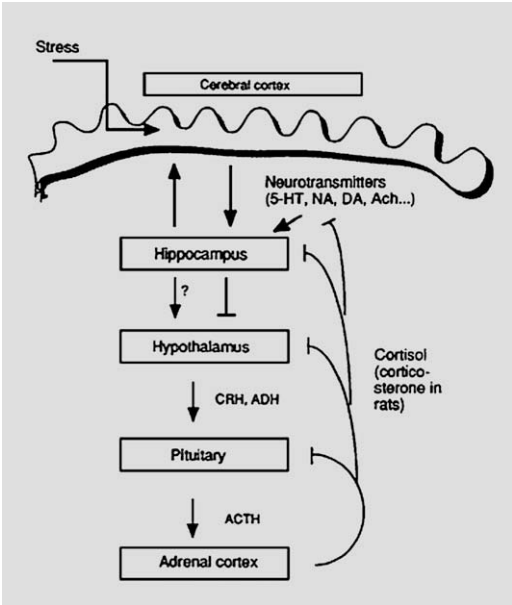


Fig. 7. Glucocorticoid-neurotransmitter interactions. Alterations in neurotransmitter input may influence glucocorticoid receptor expression in the brain, notably the hippocampus. A decrease in receptor expression may decrease feedback sensitivity inducing high circulating glucocorticoid levels, especially after stress. This may influence neurotransmitter synthesis and receptor expression and also adversely affect neuronal function, survival, and possibly the development of delirium. (From Olsson T. Activity in the hypothalamic-pituitary-adrenal axis and delirium. *Dement Geriatr Cogn Disord* 1999;10(5):345–9; with permission.)

receptors (GR) rapidly translocate from the cytoplasm into mitochondria after administration of glucocorticoids. Similar results were obtained for thyroid hormone receptor (TR alpha) localization, import, and binding to TR elements.

Excessive glucocorticoid levels seem to induce a vulnerable state in neurons. The hippocampus is a major target for these effects with its dense concentration of GR. Glucocorticoid excess may thus exacerbate cell death induced by hypoxia/ischemia, hypoglycemia, and seizures. This can be related to numerous adverse effects including inhibition of glutamate reuptake in the synaptic cleft, inhibition of calcium efflux or sequestration, exacerbation of breakdown of cytoskeletal proteins including tau, increase in reactive oxygen species, decrease in activity of antioxidant enzymes, a reduction in release of inhibitory neurotransmitters such as gamma-aminobutyric acid (GABA), and decreased production of neurotrophins, notably brain derived neurotrophic factor [30]. Finally, glucocorticoid excess may contribute to energy failure of neurons by inhibiting glucose transport into cells [173–176].

The increased cortisol availability associated with illness and trauma (eg, burns, surgery) or exogenous steroid administration may indeed be associated with disruption of hippocampal function [1]. This disruption of normal hippocampal activity will further disinhibit the release of cortisol, thus sustaining high levels of circulating cortisol. High levels of circulating cortisol may then be associated with mitochondrial dysfunction and apoptosis [177], which may lead to confusion and disturbance of attention and memory [178,179]. There is suspicion that an increase in circulating cortisol may also exacerbate the catecholamine disturbances observed in delirium. If this is true, it is possible that the stress response itself may contribute to the pathogenesis of delirium [1].

Thus, the hippocampal-adrenal circuit may contribute to the amplification of deliriogenic factors [1]. There is evidence that relatively early during the metabolic stress leading to delirium the hippocampus begins to malfunction [174,180]. This leads to some of the memory dysfunction and errors in information processing, leading to confabulation, commonly seen in delirious patients. The loss of normal inhibition of adrenal steroidogenesis results in continuous secretion of peak amounts of corticosteroids, leading to further mitochondrial dysfunction and apoptosis and further exacerbation of the catecholamine disturbances described above [181,182]. Glucocorticoids themselves can further potentiate ischemic neuronal injury in areas of high concentration (eg, hypothalamus), as well as in areas where corticosteroid receptors are low (eg, cerebral cortex).

Large neutral amino acids and delirium

Another hypothesis in the etiology of delirium is that changes in large neutral amino acids (LNAAs), which are precursors of several neurotransmitters that are involved in arousal, attention, and cognition, may play a role in delirium [183]. All LNAAs (isoleucine, leucine, methionine, phenylalanine, tryptophan, tyrosine, and valine) enter the brain by using the same saturable carrier, in competition with each other. As the concentration of one LNAA increases, CNS entry of other LNAAs declines [184]. For example, brain concentrations of serotonin may increase if the relative blood concentration of tryptophan (TRP) increases. Alternatively, serotonin concentrations may decrease if other LNAA concentrations are increased relative to TRP. Phenylalanine (PHE) has the additional interesting property of possible conversion to neurotoxic metabolites and competes with TRP for entry into the brain and subsequent metabolism [185]. Several studies have demonstrated a relationship between elevated PHE/LNAA ratios and delirium.

A study of cardiac surgery patients ($n = 296$) found that elevations of the PHE/LNAA ratio were independently associated with postoperative delirium [186]. Other studies of patients with septic encephalopathy have also reported increased levels of PHE and PHE metabolites in the plasma and

CSF of those with encephalopathy [187,188]. Furthermore, elevated levels of PHE have been associated with prolonged performance time and impaired higher integrative function in older treated patients with phenylketonuria [189,190]. Finally, studies of elderly medically ill patients suggest that an elevated plasma PHE/LNAA ratio during acute febrile illness is associated with delirium (Fig. 8) [19,191].

Serotonin (5HT) is one of the neurotransmitters that may play an important role in medical and surgical delirium. Normal 5HT synthesis and release in the human brain is, among others, dependent on the availability of its precursor tryptophan (TRP). Both increased and decreased serotonergic activity have been associated with delirium. Hepatic encephalopathy has been associated with both elevated TRP availability and increased cerebral 5HT. Excess serotonergic brain activity has been related to the development of psychosis, as well as serotonergic syndrome of which delirium is a main symptom. On the other hand, alcohol withdrawal delirium, delirium in levodopa-treated Parkinson patients, and postoperative delirium have been related to reduced cerebral TRP availability from plasma suggesting diminished serotonergic function. Sudden discontinuation of serotonin (5HT) reuptake inhibitors has been associated with a number of psychologic and neuropsychiatric syndromes, including delirium [192–194].

Hepatic dysfunction may lead to decreased metabolism of precursor amino acids (ie, phenylalanine, tyrosine, tryptophan), which leads to increases in availability of tryptophan, which leads to increases in 5HT. In fact, increased 5-hydroxyindoleacetic acid (5-HIAA) levels have been described in the CSF of subjects with hepatic encephalopathy and in patients suffering from hypoactive delirium [1,195–198]. On the contrary, some have

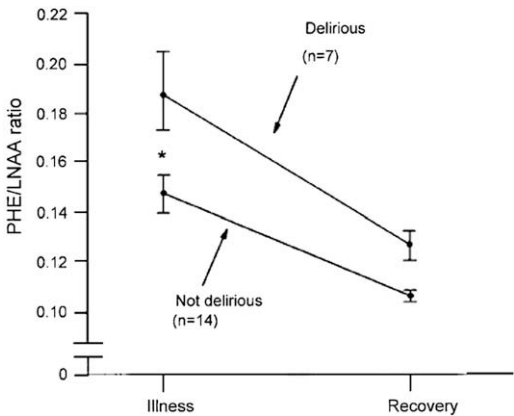


Fig. 8. PHE/LNAA ratio during illness and recovery in subjects with and without delirium. This figure demonstrates that delirious individuals had a significantly higher PHE/LNAA ratio during illness than nondelirious individuals ($P = .03$). (From Flacker JM, Lipsitz LA. Large neutral amino acid changes and delirium in febrile elderly medical patients. *J Gerontol A Biol Sci Med Sci* 2000;55(5):B249–52; discussion B253–4; with permission.)

suggested that low 5HT levels, as it occurs in hypoxia, may be associated with hyperactive delirium [199–201].

Oxidative failure due to hypoxia, anemia, hypoperfusion, or ischemia and neurotransmitter imbalances

Severe illness processes, combined with both decreased oxygen supply and/or increased oxygen demand may lead to the same common end problem, namely decreased oxygen availability to cerebral tissue. Patients in the critical care setting are particularly at risk to suffer the effects of hypoperfusion, hypoxemia, and hypoxia. There may be extrinsic factors leading to decreased oxygen exchange, such as pump failure with mild global cerebral oligemia (eg, cardiac disease, intraoperative hypotension), intrinsic lung disease (eg, pulmonary edema, pneumonia, acute respiratory failure [ARF], acquired respiratory distress syndrome [ARDS]), and anemia (eg, failure to transport a sufficient amount of O_2). There may also be sources of increased O_2 demand in medically ill individuals, including but not limited to hyperthermia (eg, an increase in O_2 consumption as represented by a rise in oxygen consumption (VO_2) by 10% to 13% for every degree centigrade in body temperature [202]), seizures, burns, hyperthyroidism, myocardial infarction, septic shock, multiorgan failure, and trauma, including the trauma of surgery [203–206].

The work of Rossen and colleagues in 1943 [207] and later Corel and colleagues in 1956 [208,209] laid the foundation of our understanding of neuronal activity and its crucial dependence on the availability of substrates for aerobic metabolism. Animal studies suggest that many factors influence the hypoxic response: environmental conditions (eg, temperature, PaO_2 also affected by atmospheric pressure), comorbidities (eg, age, general health status), patterns of the hypoxic insult (ie, continuous versus intermittent), and finally duration (ie, chronic versus acute) of the hypoxic event. In response to hypoxia, diverse reconfigurations of widespread neuronal network seem to occur. A remodeling is accomplished at all levels of the nervous system (ie, molecular, cellular, synaptic, neuronal, network): synaptic transmission is depressed through presynaptic mechanisms and excitatory/inhibitory alterations involving potassium (K^+), sodium (Na^+), and calcium (Ca^{2+}) channels [210]. More recently, Harukuni and Bhardwaj [211] revisited the process by which cerebral ischemia leads to a rapid depletion of energy stores triggering a complex cascade of cellular events, including cellular depolarization and Ca^{2+} influx, resulting in excitotoxic cell death (Fig. 9).

Inadequate oxidative metabolism may be one of the causes of the problems observed in delirium, namely, inability to maintain ionic gradients causing “spreading depression” [200,212–216]; abnormal neurotransmitter synthesis, metabolism, and release [217–225]; and a failure to effectively eliminate neurotoxic by-products (also, see Fig. 1) [218,219,223].

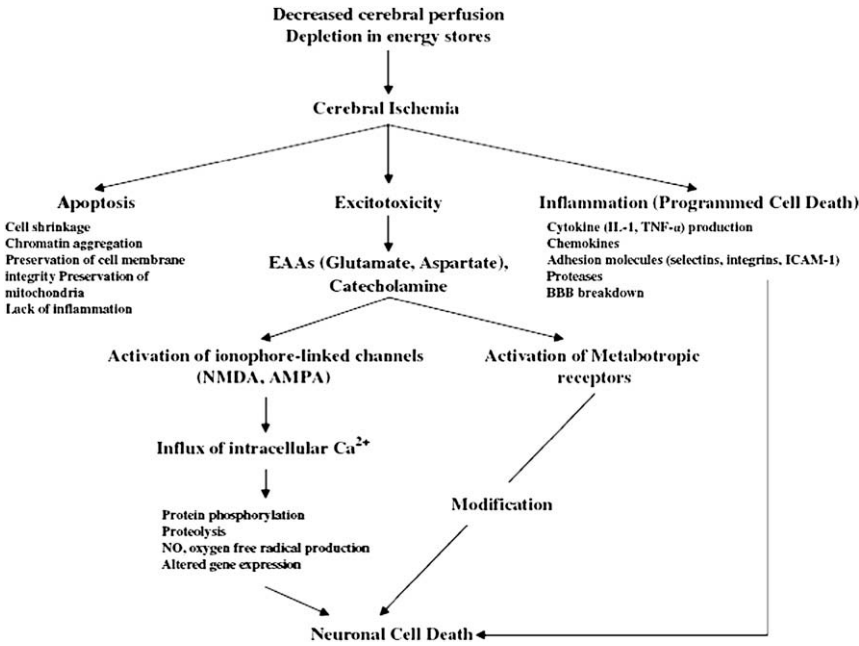


Fig. 9. Mechanisms of brain injury after global cerebral ischemia. (From Harukuni I, Bhardwaj A. Mechanisms of brain injury after global cerebral ischemia. *Neurol Clin* 2006;24:1–21; with permission.)

Indeed, decreased oxygenation causes a failure in oxidative metabolism, which leads to a failure of the ATP-ase pump system [226]. When the pump fails, the ionic gradients cannot be maintained, leading to significant influxes of Na^+ followed by Ca^{2+} , while K^+ moves out of the cell [226,227]. Some have theorized that it is the excess inward flux of Ca^{2+} that precipitates the most significant neurobehavioral disturbances observed in delirious patients [228,229]. The influx of Ca^{2+} during hypoxic conditions is associated with the dramatic release of several neurotransmitters, particularly GLU and dopamine (DA). GLU further potentiates its own release as GLU stimulates the influx of Ca^{2+} [228–230], and it accumulates in the extracellular space as its reuptake and metabolism in glial cells is impeded by the ATPase pump failure [226]. In addition, at least two factors facilitate dramatic increases in DA: first, the conversion of DA to norepinephrine (NE), which is oxygen dependent, is significantly decreased; second, the catechol-o-methyl transferase (COMT) enzymes, required for degradation of DA, get inhibited by toxic metabolites under hypoxic conditions, leading to even more amassment of DA [231]. At the same time, serotonin (5HT) levels fall moderately in the cortex, increase in the striatum, and remain stable in the brainstem (BS) [195].

Hypoxia also leads to a reduced synthesis and release of ACh, especially in the basal forebrain cholinergic centers [17]. Indeed, cholinergic neurotransmission is particularly sensitive to metabolic insults, such as diminished availability of glucose and oxygen [21]. The reason is simply that 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 [232–234].

There are definite data correlating poor oxygenation and cerebral dysfunction.

For instance, some have demonstrated that delirium can be induced in healthy control subjects by dropping PaO_2 to 35 mm Hg [33]. During cardiac arrest, there is total loss of oxygen input. From the pioneer work of Siesjo in 1978 [235], we know that once anoxia sets in, a neuron has about 12 seconds of remaining metabolic rate using its ATP, followed by 20 seconds from the ATP-reserve phosphocreatine (PCr). In the delirious critically ill patient, the problem is not total loss of oxygen input, but more a possible imbalance in supply and demand, still leading to chronic hypoxic injury. A recent prospective study of patients ($n = 101$) admitted to the ICU examined whether oxidative metabolic stress existed within the 48 hours before delirium onset. As expected, older patients experienced a higher incidence of delirium. The results further demonstrated that three measures of oxygenation (ie, hemoglobin level, hematocrit, pulse oximetry) were worse in the patients who later developed delirium. Similarly, clinical factors associated with greater oxidative stress (eg, sepsis, pneumonia) occurred more frequently among those diagnosed with delirium [236].

Studies have demonstrated a strong correlation between mental function on postoperative days (POD) 3 and 7, and the O_2 saturation on POD 0 [237]. Clinically significant cognitive impairment has been observed in patients suffering from obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) [238]. The severity of these deficits is inversely correlated with arterial oxygenation [239]. In thoracotomized patients, there is a correlation between postoperative O_2 saturations and delirium. Studies have shown that decreased postoperative O_2 saturations are associated with the development of delirium, with delirium reversal after O_2 supplementation [240]. Finally, septic patients suffer from both increased oxygen demand and decreased oxygen delivery as they are proven to have lower hemoglobin level, lower cerebral blood flow, and lower cerebral O_2 delivery compared with controls [241].

Animal studies suggest that neuronal susceptibility to ischemic injury is not uniform: particularly vulnerable are the CA1 and CA4 regions of the hippocampus, the middle laminae of the neocortex, the reticular nucleus of the thalamus, the amygdala, the cerebellar vermis, select neurons in the caudate nucleus, and certain brain stem nuclei, such as the pars reticulata of the substantia nigra [242]. This sensitivity appears to be caused by the

inherent properties of neurons in those brain regions, and not by uneven circulation. Hypotheses for the differential susceptibilities of certain brain regions to ischemia include the induction of certain enzyme systems such as heat shock proteins, or c-fos or c-jun gene products, which confer a relative sensitivity to ischemia, and nonuniform cellular energy requirements (eg, small surface neurons require less, or oxidative-enzymes-dependent circuitries) [243]. Indeed, the more membrane that a neuron has, the more ATP must be dedicated to ion pumps. Conversely, the less cytoplasm a neuron has, the fewer mitochondria will be available to supply ATP. Therefore, the SAVR (surface area to volume ratio) of a neuron helps to define how resistant a neuron may be to oxidative stress.

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 etiology [244–247]. Overall, the least susceptible neurons to oxidative stress are the small inhibitory interneurons (ie, GABAergic, glycinergic), while the most susceptible neurons are those of the ACh, DA, histamine (HA), NE, and 5HT pathways [68]. This constitutes another robust argument substantiating the neurotransmitter imbalances theories in delirium due to oxidative failure.

Besides hypoxia, a superimposed global mild ischemic injury (ie, global oligemic 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 (eg, intraoperative hypotension, cardiac failure, hypotensive anesthetic agents, diuretics, and blood pressure lowering agents).

Hypoxia, anemia, and hypoperfusion with global cerebral mild ischemia (ie, oligemia) are all common factors leading to neurotransmitter imbalances that have a well documented structural spreading to susceptible neurons in a specific order. This “spreading depression” correlates clinically with the symptoms and signs of progressing deliria [66,67,216], and makes another robust argument substantiating this coherent etiologic theory on delirium mechanisms.

The role of dopamine

Elevations of DA have long been associated with the development of delirium [19,26,248,249]. There are several additional metabolic pathways that lead to significant increases in DA under impaired oxidative conditions: first, significant amounts of DA are released and there is a failure of adequate DA reuptake. At the same time the influx of Ca^{2+} stimulates the activity of tyrosine hydroxylase (TH) [250], which converts tyrosine to 3,4-dihydroxyphenylalanine (DOPA), thus leading to increased DA production and further uncouples oxidative phosphorylation in brain mitochondria [227]. The outcome is further disruption of adenosine triphosphate (ATP) production. Decreased ATP and the increased production of toxic metabolites of DA

(formed under hypoxic conditions) inhibit the activity of the oxygen-dependent catechol-O-methyl transferase (COMT) [37,231], which is the major extracellular deactivator of DA, further leading to high levels of DA. Furthermore, an increase in the firing rates of catecholamine neurons may further induce TH synthesis, which leads to even more DA production [251].

The influx of Ca^{2+} also stimulates DA release, anoxic depolarization [252], and the activation of catabolic enzymes [229]. This is another mechanism by which impaired oxidative conditions leads to the breakdown in ATP-dependent transporters, which in turn leads to a decrease in DA reuptake [253–255]. The increases in DA can be considerable. In fact, levels as high as 500-fold increase in extracellular DA concentrations have been recorded in cases of striatal ischemia [195,198,220,221,256]. Of note, the excess in extracellular DA can in itself promote more Ca^{2+} influx, further perpetuating the problem [220]. The failure to adequately limit the production of and effectively eliminate toxic DA metabolites is a source of ongoing cellular injury during hypoxia and may contribute to some of the features of a post-delirium syndrome [1]. Figiel and colleagues [257] also found an excess of DA in association with delirium induced by electroconvulsive therapy. Similarly, studies show that DA agonists can create slower EEG in spite of motor hyperactivity [258], which represents a perfect symptomatological match to hyperactive delirium.

The dramatic increases in DA availability may lead to some of the neurobehavioral alterations observed in delirious patients—primarily the signs of hyperactive or mixed type delirium, namely increased psychomotor activity, hyperalertness, agitation, irritability, restlessness, combativeness, distractibility, and psychosis (ie, delusions and hallucinations) (see Fig. 1) [256,259,260]. In addition to generation of H_2O_2 and quinone formation, L-Dopa- and DA-induced cell death may result from induction of apoptosis, as evidenced by increases in caspase-3 activity. Also, DA per se induces apoptosis by a mechanism independent of oxidative stress [261].

Interestingly, depletion in DA by alphamethylparatyrosine actually protects neurons against hypoxic stress and injury [262,263]. Similarly, DA blockade can be used to reduce hypoxic damage in the hippocampus [264].

Hepatic dysfunction and the role of glutamate in delirium

DA may exert its deliriogenic activity by more than one mechanism. The direct activity of DA can be observed in cases of toxicity with substances known to increase DA release or availability, such as amphetamines, cocaine, and dopamine. On the other hand, DA may have a secondary activity by enhancing GLU-mediated injury.

Thus, increased GLU availability may be due to the influx of Ca^{2+} caused by a number of factors (eg, hypoxia, excess DA) best known of all is liver failure. Hepatic failure leads to hyperammonemia, which in turn leads to excessive N-methyl-D-aspartate (NMDA) receptor activation. This leads to dysfunction of the glutamate-nitric oxide-cGMP (cyclic

guanosine monophosphate) pathway, which leads to reduced cGMP and contributes to impaired cognitive function in hepatic encephalopathy.

As described above, the influx of Ca^{2+} during hypoxic conditions is associated with the release of several neurotransmitters, particularly high levels of GLU [229,230,265,266]. Hypoxic conditions may further extend GLU activity as the absence of extracellular mechanism of degradation require the functioning of ATP-dependent reuptake, which is impaired under these conditions [226]. GLU is an excitatory neurotransmitter that may lead to neuronal injury via its activation of NMDA receptors [267–271]. Nevertheless, it appears that GLU requires the presence of DA to exert some of its toxic effects, namely its Ca^{2+} -induced neuronal injury [219,221,223,228]. At high levels, DA may cause enough depolarization of neurons as to activate the voltage-dependent NMDA receptor, therefore facilitating the excitatory effect of GLU (see Fig. 1) [272].

At least in one study of high-risk adults ($n = 557$) undergoing cardiac surgery, serum concentrations of NMDA receptor antibodies, as measured by serum concentrations of (NMDA) receptor antibodies (NR2Ab) were predictive of severe neurologic adverse events (eg, delirium, transient ischemic attack, or stroke). Patients with a positive NR2Ab test (≥ 2.0 ng/mL) preoperatively were nearly 18 times more likely to experience a postoperative neurologic event than patients with a negative test (< 2.0 ng/mL) (Fig. 10) [273].

Glutamate (the principal excitatory neurotransmitter) is metabolized by glutamate decarboxylase (GAD) (using pyridoxal phosphate or vitamin B6, as a cofactor) into GABA (the principal inhibitory neurotransmitter).

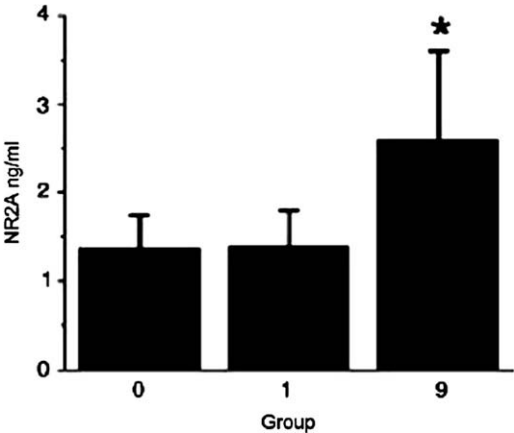


Fig. 10. Preoperative serum NR2Ab and postoperative neurologic events. The 0 indicates no neurologic event; 1, anxiety or agitation; 9, confusion/delirium, transient ischemic attack, or stroke. Patients in group 9 had significantly higher preoperative serum NR2Ab than groups 0 or 1 ($P = 0.0004$). (From Bokesch PM, et al. NMDA receptor antibodies predict adverse neurological outcome after cardiac surgery in high-risk patients. *Stroke* 2006;37(6):1432–36; with permission.)

GABA has also been implicated in the development of the delirium [274]. There is evidence to suggest that GABA activity is increased in delirium related to hepatic encephalopathy, but decreased in delirium caused by hypnotic or sedative withdrawal [275]. The precise role of GABA in hepatic encephalopathy is unclear, but at least one source found that flumazenil, a benzodiazepine antagonist, reversed coma and improved hypoactive delirium in cirrhotic patients [276]. Reduced GABA has also been implicated in delirium that results from ethanol or CNS-depressant (eg, benzodiazepines, propofol, barbiturates) withdrawal.

Excessive activation of NMDA receptors leads to neuronal degeneration and cell death. Hyperammonemia and liver failure alter the function of NMDA receptors and of some associated signal transduction pathways. Acute intoxication with large doses of ammonia (and probably acute liver failure) leads to excessive NMDA receptor activation, which is responsible for ammonia-induced death. The function of the glutamate-nitric oxide-cGMP pathway is impaired in brain in vivo in animal models of chronic liver failure or hyperammonemia and in homogenates from brains of patients who died in hepatic encephalopathy. The impairment of this pathway leads to reduced cGMP and contributes to impaired cognitive function in hepatic encephalopathy. Learning ability is reduced in animal models of chronic liver failure and hyperammonemia [277].

Hepatic dysfunction also is associated with an increase in unesterified plasma fatty acids, which leads to increased tryptophan levels, which leads to impairment in the active transport of homovanillic acid (HVA) through the BBB and out of the CSF [198]. In fact, in cases of hepatic failure, the above may lead to significant increases in CSF-HVA levels, despite initial normal DA levels. Eventually, this contributes to the excessive DA levels described above.

Finally, there is evidence that hepatic failure may be associated with a shift in the regional cerebral blood flow (rCBF) patterns and cerebral metabolic rates from cortical to more subcortical areas of the brain [278–283]. In fact, studies of end-stage liver disease using single-photon emission computed tomography (SPECT) brain scans demonstrated that their rCBF was decreased in bilateral frontotemporal and right basal ganglia regions as compared with control subjects and that impairment in cognitive tests was correlated with ratios of rCBF values [284].

Gamma-aminobutyric acid activity, central nervous system–depressant abuse, withdrawal states, and delirium

GABA has also been implicated in the development of the delirious state [274,285]. The role of GABA in hepatic encephalopathy and delirium is unclear, but at least one source found that flumazenil, a benzodiazepine antagonist, reversed coma and improved hypoactive delirium in cirrhotic patients [276,286]. GABA activity has been found to be increased in delirium related

to hepatic encephalopathy and decreased in hypnotic/sedative withdrawal [275,287–290]. Conversely, reduced GABA serum levels are found in alcohol withdrawal [291] and antibiotic-induced delirium [292]. GABA is formed by the decarboxylation of glutamate by GAD. It is of note that GAD requires B6 (pyridoxine as a cofactor), and B6 has already been implicated as a prominent player in the development of delirium [20].

Oversedation has been found to be an independent predictor of prolonged mechanical ventilation. In a prospective, controlled study ($n = 128$) of adults undergoing mechanical ventilation, subjects were randomized to either continuous sedation or daily awakenings [293]. They found that the median duration of mechanical ventilation was 4.9 days in the intervention group (ie, daily awakening), as compared with 7.3 days in the control group ($P = .004$) (Fig. 11A), and the median length of stay in the intensive care unit was 6.4 days as compared with 9.9 days, respectively ($P = .02$) (Fig. 11B).

Among the agents known to cause delirium and other cognitive impairments in the medically ill patient, GABAergic medications have been shown to be some of the most significant and frequent culprits [6,89,103,294–297]. There are several mechanisms by which sedative agents (eg, benzodiazepines, propofol) contribute to delirium: (1) interfering with physiologic sleep patterns (ie, significantly reduce slow-wave and REM sleep, increase spindles, increase cortical activity at low doses, and decrease EEG amplitude) [298–300]; (2) causing a centrally mediated acetylcholine deficient state (ie, interruption of central cholinergic muscarinic transmission at the level of the basal forebrain and hippocampus) [103,296,297]; (3) enhancing NMDA-induced neuronal damage [301]; (4) disrupting the circadian rhythm of melatonin release [139]; (5) disruption of thalamic gating function (ie, the ability of the thalamus to act as a filter, allowing only relevant information to travel to the cortex) leading to sensory overload and hyper-arousal [248]. Studies have demonstrated a direct relationship between benzodiazepine use and the development of delirium [89]. In both Surgical-ICU and Trauma-ICU the use of benzodiazepines has been identified as an independent risk factor for the development of delirium [126]. In fact, studies have demonstrated that lorazepam is an independent risk factor for daily transition to delirium (Fig. 12) [30].

Alcohol and CNS-depressant substances cause intoxication through effects on diverse ion channels and neurotransmitter receptors, including GABA_A receptors—particularly those containing δ subunits that are localized extrasynaptically and mediate tonic inhibition—and NMDA receptors. Alcohol dependence results from compensatory changes during prolonged alcohol exposure, including internalization of GABA_A receptors, which allows adaptation to these effects. The short-term effects of alcohol result from its actions on ligand-gated and voltage-gated ion channels [302,303]. Prolonged alcohol consumption leads to the development of tolerance and physical dependence, which may result from compensatory functional

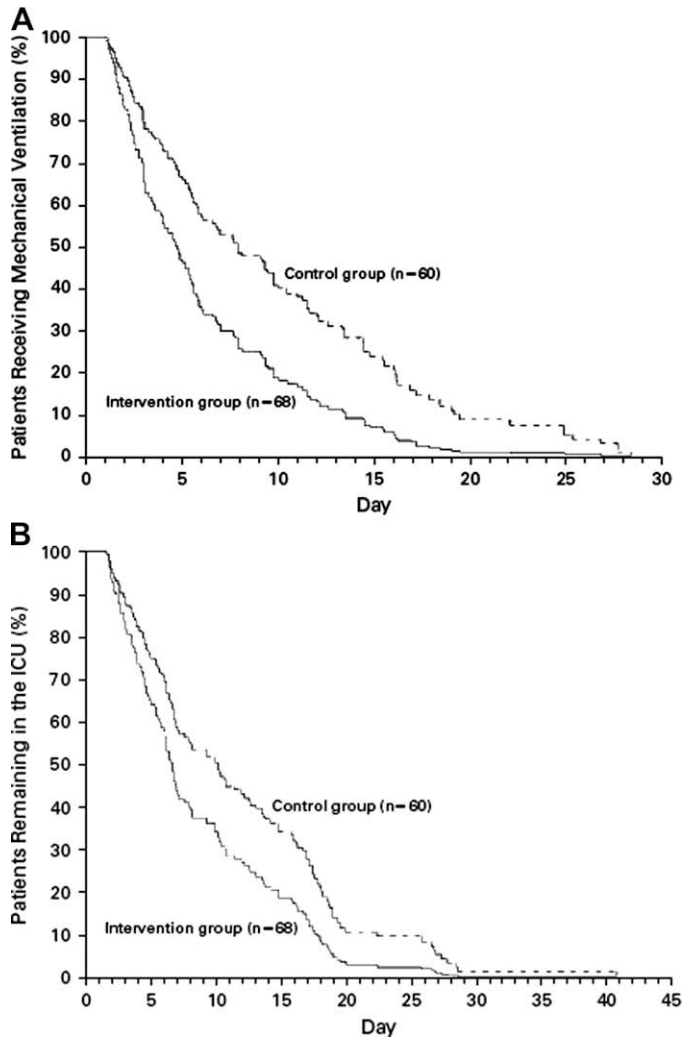


Fig. 11. (A) Analysis of the duration of mechanical ventilation, according to study group. After adjustment for base-line variables (age, sex, weight, APACHE II score, and type of respiratory failure), mechanical ventilation was discontinued earlier in the intervention group than in the control group (relative risk of extubation, 1.9; 95% confidence interval, 1.3 to 2.7; $P < .001$). (B) Analysis of the length of stay in the intensive care unit (ICU), according to study group. After adjustment for baseline variables (age, sex, weight, APACHE II score, and type of respiratory failure), discharge from the ICU occurred earlier in the intervention group than in the control group (relative risk of discharge, 1.6; 95% confidence interval, 1.1 to 2.3; $P = .02$). (From Kress JP, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000;342(20):1471–77; with permission. Copyright © 2000, Massachusetts Medical Society.)

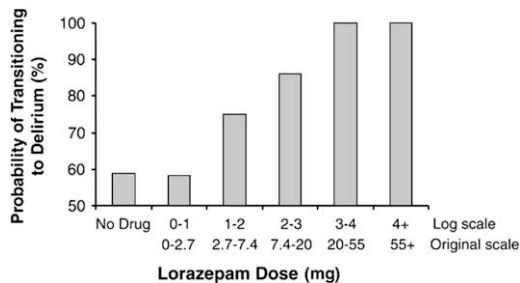


Fig. 12. Lorazepam and the probability of transitioning to delirium. Lorazepam and the probability of transitioning to delirium. The probability of transitioning to delirium increased with the dose of lorazepam administered during the previous 24 hours. This incremental risk was large at low doses and plateaued at approximately 20 mg/d. (From Girard, et al. Delirium in the intensive care unit. *Critical Care* 2008;12(Suppl 3):S3; with permission; and *Adapted from* Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006;104:21–6; with permission.)

changes in the same ion channels. Similarly, acute administration of alcohol is known to stimulate 5-HT turnover, while chronic alcohol intake is reported to decrease 5-HT synthesis and release [304]. Not surprisingly, plasma noradrenergic (NA) levels [305] and 5-HT function [306] have been found to be elevated in alcoholic patients.

Ethanol modifies the functional activity of many receptors and ion channels, including NMDA [307,308], kainate [309], serotonin 5-HT3 [310], GABA_A [311], and glycine [312] receptors as well as G protein–coupled inwardly rectifying potassium channels [313] and calcium channels [314]. GABA_A receptors containing the δ subunit, in particular $\alpha 4\beta 2\delta$ and $\alpha 6\beta 2\delta$ receptors, are exceptionally sensitive to ethanol. Brain regions that express δ subunits, including the cerebellum, cortical areas, thalamic relay nuclei, and brainstem, are among those that are recognized to mediate the intoxicating effects of alcohol [315]. The mechanisms of alcohol dependence are less well understood than are those responsible for acute intoxication. However, it now appears that compensatory adaptation of GABA_A receptors to prolonged ethanol exposure plays a critical role in alcohol dependence. Among the possible adaptive mechanisms, down-regulation of GABA_A receptors, as a result of decreases in the surface expression of $\alpha 1$ or $\gamma 2$ subunits, is emerging as an important candidate [316].

Compensatory up-regulation of NMDA and kainate receptors as well as Ca²⁺ channels follow, leading to Ca²⁺ influx and changes associated with delirium [317]; these mechanisms may also have been implicated in alcohol dependence and withdrawal seizures. For example, the inhibitory effects of ethanol on NMDA receptors leads to up-regulation in the number of NMDA receptors in many brain regions, which may be an additional factor in the susceptibility to alcohol withdrawal seizures [318–320]. The relevance

of this mechanism is highlighted by the fact that NMDA-receptor antagonists are highly effective anticonvulsants in animal models of alcohol withdrawal seizures [321].

Alcohol withdrawal is associated with reduced density of synaptic GABA_A receptors as well as alterations in GABA_A-receptor subunit composition that lead to reduced inhibitory efficacy; both effects would be expected to predispose to seizures. Indeed, susceptibility to alcohol withdrawal seizures has been associated with a loss of GABA_A-mediated inhibition [322]. Alcohol withdrawal has been linked to increased metabolism and release of NA/NE (noradrenaline or norepinephrine) [323,324], reduced $\alpha 2$ adrenoceptor function [325,326], reduced 5-HT function [327], and alterations in neuroendocrine responsiveness to challenge with NA and 5-HT agents [328]. Withdrawal seizures are believed to reflect unmasking of these changes and may also involve specific withdrawal-induced cellular events, such as rapid increases in $\alpha 4$ subunit-containing GABA_A receptors that confer reduced inhibitory function [316].

The role of histamine and delirium

Histamine receptors A1 (HA1) and A2 (HA2) are known to affect the polarity of cortical and hippocampal neurons [329,330] and pharmacologic antagonism of either receptors is sufficient to cause delirium [331]. Others have suggested that, during surgical stress and hypoxia, there may be an excessive release of HA, which may lead to delirium [332]. In these cases, blockade of either HA1 or HA2 receptors helped to limit neuronal death within the hippocampus [333,334]. So, both excess and deficiency of HA may be associated with delirium. Clinical experience has demonstrated that drugs like diphenhydramine, both anti-HA and anti-ACh, can cause delirium. Similarly, it has been reported that H2 blockers such as cimetidine and ranitidine may cause cognitive dysfunction and delirium in the elderly [1].

The role of somatostatin and endorphines in delirium

There is not a lot of data regarding somatostatin and delirium. Nevertheless, the available data on elderly delirious patients suggests that delirious patients showed significant reduction of somatostatin-like immunoreactivity (SLI) in CSF, as compared with the controls. Koponen and colleagues [335,336] also found a significant correlation between SLI levels and Mini-Mental State Examination scores. Koponen and colleagues [335,336] suggest a role for somatostatinergic dysfunction in the genesis of some symptoms of delirium, and postulate that somatostatinergic dysfunction may be linked to the long-term prognosis of delirious patients [335,336].

Other studies have demonstrated significant reductions in the β -endorphin-like immunoreactivity (BLI) values in the CSF of delirious patients ($n = 69$) compared with controls ($n = 8$). The changes in BLI had no

correlation with age or neuroleptic drug dosage, but did have a significant positive correlation with cognitive functioning as evaluated by the Mini-Mental State exam [337,338].

Electrolyte abnormalities, dehydration, and delirium

Dehydration is a reliable predictor of impaired cognitive status and delirium [15,339–341]. Objective data, using tests of cortical function, support the deterioration of mental performance in mildly dehydrated younger adults, and it would be expected the effects would be more profound in the elderly and medically ill [342]. Available evidence indicates the increased susceptibility of older adults to dehydration and the resulting complications, including delirium [343,344]. Dehydration in older adults has been shown to be a reliable predictor of increasing frailty, progressive deterioration in cognitive function, and an increased incidence in the development of delirium [340,345–349]. Studies have demonstrated a significant correlation between cognitive dysfunction and severity of dehydration, induced by a combination of fluid restriction and heat stress [350]. Subjects exhibited progressive impairment in mathematical ability, short-term memory, and visuomotor function once 2% body fluid deficit was achieved. Similarly, other studies have demonstrated impaired long-term memory following dehydration resulting from heat stress [351]. Animal studies have identified neuronal mitochondrial damage and glutamate hypertransmission in dehydrated rats. Additional studies have identified an increase in cerebral nicotinamide adenine dinucleotide phosphate-diaphorase activity (nitric oxide synthase, NOS) with dehydration. Available evidence also implicates NOS as a neurotransmitter in long-term potentiation, rendering this a critical enzyme in facilitating learning and memory. With aging, a reduction of NOS activity has been identified in the cortex and striatum of rats. The reduction of NOS activity that occurs with aging may blunt the rise that occurs with dehydration, and possibly interfere with memory processing and cognitive function [342]. Dehydration has been shown to be a reliable predictor of increasing frailty, deteriorating mental performance, and poor quality of life. In other words, dehydration may begin a cascade of events that lead to cognitive dysfunction and delirium.

There are four main pathways by which dehydration may cause cognitive dysfunction and delirium (Fig. 13) [342]: (1) dehydration may cause intracellular changes leading to increased cytokine concentrations, increased anticholinergic burden, and altered pharmacokinetics; (2) dehydration leads to intravascular volume depletion, causing cerebral hypoperfusion, thromboembolic disorders, and cardiac ischemia; (3) dehydration causes extravascular changes, leading to water and electrolyte imbalances, contraction alkalosis, and uremia secondary to acute renal failure; and (4) studies have identified neuronal mitochondrial damage and glutamate hypertransmission in dehydrated animals. Other ways in which dehydration and fluid

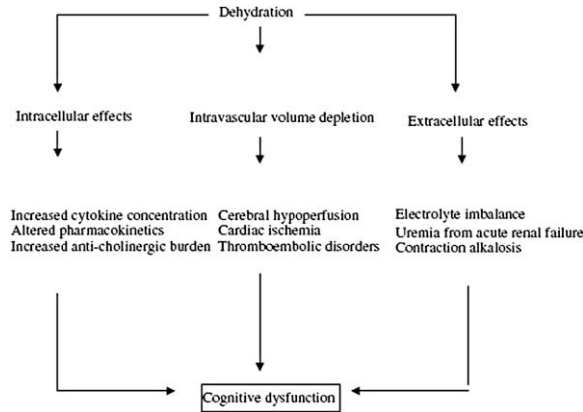


Fig. 13. Pathophysiology of cognitive dysfunction in moderate and severe dehydration. (From Wilson MM, Morley JE. Impaired cognitive function and mental performance in mild dehydration. *Eur J Clin Nutr* 2003;57(Suppl 2):S24–9; with permission.)

deficit may contribute to delirium include hypoperfusion (both cerebral and renal), increased concentration of drugs and/or their metabolites, and decreased renal elimination of drugs/metabolites and toxic by-products [340].

Similarly, it has been well documented that Na^+ abnormalities, as well as other electrolytes, can lead to mental status changes and delirium. One known mechanism is that Na^+ leads to cell swelling, which then causes anoxic depolarization [252]. Hypernatremic hyperosmolar delirium has been documented in medically ill and postoperative patients [352–354]. Yet, hyponatremia has been equally associated with the development of delirium, although the mechanism may not be so clearly understood [355–364].

Many have defined alterations of serum electrolytes, glucose, and renal function as both risk markers and causes of delirium [365]. Studies have suggested that a blood urea nitrogen (BUN)/creatinine ratio greater than 18 is an independent predisposing risk factor for delirium in general medical patients [339]. Elevations in BUN/creatinine may be indicative of dehydration, congestive heart failure, poor oral intake, or other factors that may contribute to the development of delirium. Others have similarly suggested that in the postoperative population a number of “abnormal serum chemistries” (ie, sodium <130 or >150 mEq/L; potassium <3.0 or >6.0 mEq/L; glucose <60 or >300 mg/dL) are predictable independent risk factors for postoperative delirium [366].

The EEG and delirium

Back in 1959, Engel and Romano [2] declared “*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 and at the physiologic level by the characteristic slowing of the EEG". Indeed, studies have demonstrated a very close temporal relationship between local reduction of oxygen availability and change in the EEG; the latter usually occurs 6 to 8 seconds after the local oxygen tension begins to fall [367]. In fact, both hypoxia and hypoglycemia produce slowing of the EEG [368]. These are two physiologic conditions under which it is well established that the metabolism of the brain cannot be successfully supported. EEG changes have also been described in association with anticholinergic drug-induced delirium [369].

Some have suggested that changes in EEG frequency can be demonstrated before any change in behavior or neuropsychiatric performance becomes demonstrable and well before any change in total cerebral oxygen uptake can be measured. The fundamental fact has been demonstrated that the behavioral changes correlating most precisely with the slowing of EEG frequency were those that had to do with awareness, attention, memory, and comprehension, that is, the cognitive functions [2]. Data also suggest that the significant EEG finding is *the degree of slowing rather than the absolute frequency* [370]. Thus, if the EEG initially is fast or in the upper range of normal, a significant reduction in the level of consciousness and EEG frequency may be provoked by drugs, alcohol, hypoxia, and so forth, without the EEG frequency necessarily falling below the accepted normal range. Therefore, it is therefore possible to have a "normal EEG" in the presence of an appreciable degree of cerebral insufficiency and reduction in the level of awareness, as when a person whose premorbid alpha frequency is t1 to t2 per second shows a slowing to 8 to 9 per second during a moderate delirium [371]. Findings confirming there are instances when the EEG may be read as "normal" in delirium due to a fast baseline range has been documented by others [372,373]. In these cases, a comparison with the same subject's previous EEG demonstrates the abnormality.

Others have found an association between spectral EEG changes and severity of cognitive deterioration in delirium. Spectral analysis of EEG found that delirious patients showed significant reductions of alpha percentage, increased theta and delta activity, and slowing of the peak and mean frequencies; these changes were also obvious in individual recordings. Furthermore, as previously described by Engel and Romano [2,54], the alpha percentage and various ratio parameters correlated significantly with Mini Mental State score (MMSE), and delta percentage and mean frequency with the lengths of delirium and hospitalization [55,56,374].

Similarly, serial quantitative electroencephalographic (QEEG) studies performed in elderly delirious and control subjects demonstrated that changes in scores for the relative power map and changes in relative power in the alpha band had significant associations with changes in the clinical state as measured by the MMSE [375,376]. A study of ICU patients with delirium measured the correlation between SAA (measured using a competitive radioreceptor binding assay for muscarinic receptors) and QEEG.

During this study, delirium was diagnosed using the CAM-ICU. The results show that that under comparable conditions patients in the delirium group showed a higher relative EEG theta power and a reduced alpha power than did the nondelirious patients. On the other hand, there was no significant difference in measured SAA levels [24].

In summary, studies suggest that in the right hands the EEG could be a useful tool for the diagnosis and follow-up of delirium caused by various conditions. Conventional EEG characteristics of delirium include slowing or dropout of the posterior dominant rhythm, generalized theta or delta slow-wave activity, poor organization of the background rhythm, and loss of reactivity of the EEG to eye opening and closing. As delirium progresses, generalized theta and delta slow waves appear. When the background frequency slows to 5 or 6 Hz, loss of reactivity is seen. With further progression of delirium, generalized delta slowing appears. When any of these characteristic findings is seen, an electroencephalographer may report the presence of an “encephalopathy,” which is the EEG term for global electrocerebral derangement. Sometimes triphasic waves can be seen. These are characteristic of a number of metabolic derangements (eg, hepatic failure, renal insufficiency, electrolyte abnormalities, and anoxia) [377]. These are paralleled by the QEEG findings of increased absolute and relative slow-wave (theta and delta) power, reduced ratio of fast-to-slow band power, reduced mean frequency, and reduced occipital peak frequency [56,375,376].

Finally, some have demonstrated these changes in EEG activity could be replicated by artificially increasing DA or decreasing or interfering with ACh activity, specifically in the caudate nucleus [378,379], confirming the suspicion that both decreased central cholinergic activity (either caused by hypoxia or by the use of substances with anticholinergic activity) or excess dopamine activity (caused either by hypoxia or by the exogenous use of substances) may lead to the classic behavioral manifestations of delirium and corresponding EEG changes.

Common pathways

At the end, it may very well be that all the known etiologic “factors” for the development of delirium may all act by similar mechanisms, namely causing changes to neuronal membrane function, which in turn leads to a number of neurotransmitter aberrations. Affected neurons begin to experience abnormalities of membrane function and polarization. This may lead to a domino-like effect known as “spreading depression” by which, as one neuron loses membrane integrity and stability, neighboring neurons have a more difficult time maintaining their own physiologic integrity and functioning. Some have postulated that the patterns of cerebral structure vulnerability leads to a predictable pattern of spreading neuronal depression, which causes the symptoms characteristic of delirium [1]. That progression is postulated to go from the hippocampus, to the neocortex, the subcortical

nuclei, the brain stem, gray matter, moving to the cerebellar cortex, and finally affecting the spinal cord [66,67,216].

The cholinergic and the dopaminergic systems interact not only with each other but with glutamatergic and GABA pathways. Studies suggest that excess dopamine may cause delirium and that dopaminergic antagonists are often successfully used to treat cholinergic delirium [380,381]. Furthermore, the interplay between DA and ACh in the production of delirium may be further substantiated by the fact that D2 antagonists enhance ACh release, which may be another mechanism by which they help alleviate the symptoms of delirium [382,383].

Besides the cerebral cortex, critical anatomic substrates of psychosis pathophysiology would comprise the striatum, the substantia nigra/ventral tegmental area, and the thalamus. The thalamus acts as a filter, allowing only the relevant information to travel to the cortex. Illicit drugs (eg, PCP, Ecstasy), as well as psychoactive medications frequently prescribed to hospitalized patients (eg, benzodiazepines, opioids) could compromise the thalamic gating function, leading to sensory overload and hyperarousal. Gaudreau and Gagnon [248] have proposed 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.

Which neurotransmitter (or set of neurotransmitters) is involved, and the degree to which it may be affected, may well determine the motoric subtype that the patient presents, the degree of disorientation, and the cognitive deficits that the patient may exhibit during the episode of delirium (Table 4).

Theoretic implications for prevention and treatment options

This is meant to be a theoretic treatise on the prevention and management of delirium. For a more clinical approach, please see Maldonado JR, *Delirium in the Acute Care Setting: Characteristics, Diagnosis and Treatment*, 2008 [384].

Table 4
Neuronal circuitries and their incumbent neurotransmitters for alertness, attention, and judgment

Cognitive function	Associated neuronal circuitries
Alertness	Ascending reticular activating system
Attention	Different circuitries of the brainstem
	Thalamocortical loops
	Nondominant parietal lobe
Judgment/coherence	Diffuse cortical interconnections, somewhat more in the frontal lobes

Acetylcholine

Because of the relationship between low central ACh levels, anticholinergic potential of the medications, and delirium, it would make sense to consider two approaches that will potentially help prevent and treat delirium.

The first approach is a systematic elimination of medications, either known to cause delirium or with high anticholinergic potential, to prevent delirium, if possible. Once delirium has presented, the elimination of any potential offending agent is imperative. Switch crucial medications to other agents with the same benefits but no known anticholinergic effects. Always pay special attention to hidden anticholinergic potentials and drug-drug interactions (eg, impaired metabolism or additive effect).

Second, the use of cholinesterase inhibitors as a way to prevent or treat delirium should be considered. Indeed, acetylcholinesterase inhibitors (ACI) have a well-established use in the antagonism of neuromuscular blockade and the therapy of central anticholinergic syndrome (CAS). They also have many favorable indications such as the prevention and therapy of postanesthetic shivering and the treatment of various types of intoxication. Therefore, many have suggested that they potentially play a role in delirium prevention [385]. In particular, physostigmine, a reversible acetylcholinesterase inhibitor, has been widely used as first-line treatment of the CAS, as well as a great diagnostic and therapeutic agent for medication-induced delirium [105].

The potential usefulness in prevention of delirium with the use of ACI was demonstrated in a study using the agent rivastigmine, a dual inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) [386]. The researchers followed men and women ($n = 246$) aged 68 to 85 years who were ambulatory outpatients who carried the diagnosis of vascular dementia (VaD). Patients were divided into two homogeneous groups matched for age and education levels. Group A received rivastigmine 3 to 6 mg/d, while Group B received cardioaspirin 100 mg/d. Patients receiving rivastigmine began treatment on the lower dose of 3 mg/d and were titrated to the higher dose of 6 mg/d after 16 weeks. All persons in the study group received periodical neurologic and neuropsychological examinations over a 24-month period. Both groups presented episodes of delirium, which occurred during a concomitant medical illness (eg, complications after a fall, during a sudden hospitalization, or after the patient received anesthesia). During the follow-up period, 48% of the entire population presented episodes of delirium. The mean duration of each episode was 7.45 ± 5.31 days. When considering the two groups separately, 40% of patients in Group A (rivastigmine group) presented episodes of delirium; whereas, 62% of patients in group B presented episodes of delirium ($P < .001$). Moreover, the mean duration of the delirium was shorter in Group A (mean duration 4.00 ± 1.71 days) than in Group B (7.86 ± 2.73 days; $P < .01$). Another study of dementia patients on chronic rivastigmine use found that the

rivastigmine group had a much lower incidence of delirium (45.5%), compared with the control group (88.9%) ($P < .05$) [387]. Nevertheless, there have been two significant failed prevention trials using the acetylcholinesterase agent, donepezil [388,389].

Finally, there have been at least 19 papers, mostly case reports, suggesting that acetylcholinesterase inhibitor agents (eg, donepezil, galantamine, physostigmine, rivastigmine) may be effective in the treatment of delirium [93,96,105,108,387,390–403].

Dopamine

Dopaminergic neurons are among the most susceptible to oxidative stress, which, as explained earlier, may lead to massive releases of DA. This in turn causes some of the classic behavioral symptoms of delirium, but it also leads to further neuronal injury. Administered DA agonist agents can produce slowing of the EEG in spite of motor hyperactivity [258] and excess dopamine is known to cause delirium [380,381].

Antipsychotic agents have long been used in the management of delirium. It is likely that initially its use was associated with the need for rapid tranquilization or neuroleptization of agitated patients, but over time clinicians have observed a rapid restoration of putative hippocampal functions (eg, short-term memory) and reversal of other regional brain disturbances (eg, agitation, psychosis, primitive reflexes) [1]. Data suggest that depletion in DA by alphas-methylparatyrosine actually protects neurons against hypoxic stress and injury [262,263]. Similarly, dopaminergic blockade can be used to reduce hypoxic damage in the hippocampus [264]. D2 antagonist agents also enhance ACh release, which may be another mechanism by which they help alleviate the symptoms of delirium [382,383]. Thus, antipsychotic agents are not only effective in the symptomatic management of the symptoms of delirium, but they also serve to address the underlying massive DA surge inherent to the etiopathological entity of delirium. In fact, clinical and experimental data suggest that neuroleptics may have a role even in the treatment of hypoactive delirium [404]. In acutely ill populations, limited data suggest that administration of antipsychotic agents with dopamine receptor antagonist activity may reduce the rate or severity of delirium [404,405].

The role of DA in facilitating GLU-mediated, Ca^{2+} -induced neuronal injury and functional derangement has been discussed earlier in this article. If that premise is correct, it is then possible that antipsychotics do much more than acute management of agitation. The exact mechanisms are not clear but, in the case of delirium, agents with DA-antagonist activity may block or reverse the DA-mediated, GLU-precipitated hypoxic neuronal injury [220]. Some data suggest that depletion of DA, as in cases of damage to the substantia nigra, may in fact protect neurons against subsequent hypoxic stress and injury [262,406].

A Cochrane database review study looking at the use antipsychotics for the treatment of delirium was conducted and included haloperidol and all atypical antipsychotics for which data have been published [407]. The studies included ($n = 3$) compared haloperidol with risperidone, olanzapine, and placebo in the management of delirium and in the incidence of adverse drug reactions. The authors concluded that the decreases in delirium scores were not significantly different comparing the effect of low-dose haloperidol (< 3.0 mg per day) with the atypical antipsychotics olanzapine and risperidone (odds ratio [OR] 0.63, 95% CI, 10.29–1.38; $P = .25$); and that low-dose haloperidol did not have a higher incidence of adverse effects than the atypical antipsychotics. Finally, low-dose haloperidol may be effective in decreasing the degree and duration of delirium in postoperative patients, compared with placebo.

Ozbolt and colleagues [408] conducted a search of the published literature using MEDLINE and PubMed for articles (in the format of review articles, randomized controlled trials [RCTs], clinical trials, or meta-analyses) written in English. They found that risperidone was the most thoroughly studied atypical antipsychotic for the management of delirium. In most studies, risperidone was found to be approximately 80% to 85% effective in treating the behavioral disturbances of delirium at doses of 0.5 to 4.0 mg per day. The search indicated that olanzapine was approximately 70% to 76% effective in treating the behavioral manifestations of delirium at doses of 2.5 to 11.6 mg per day. There were very few studies conducted using quetiapine; although available data suggest that it also appears to be a safe and effective alternative to high-potency antipsychotics. In the limited number of trials comparing atypical antipsychotics to haloperidol, haloperidol consistently produced a higher rate (an additional 10% to 13%) of extrapyramidal side effects.

At least in theory, dopamine-antagonist agents should be able to prevent delirium as well. One RCT addressed the issue of prophylactic haloperidol. In at-risk patients older than 70 years, oral haloperidol 0.5 mg twice a day was administered from up to 72 hours preoperatively and until the third postoperative day. This study found that prophylactic haloperidol use did not alter the incidence of postoperative delirium (15.1%) compared with placebo (16.5%) with a relative risk (RR) = 0.91 (95% CI, 0.59–1.44) [409].

Yet another study ($n = 430$) demonstrated a modest reduction in the overall incidence of postoperative delirium when haloperidol was administered prophylactically (ie, 1.5 mg/d, started preoperatively and continued for up to 3 days postoperatively), with patients in the haloperidol group having a lower incidence of delirium versus placebo (15.1% versus 16.5%) (RR 0.91 [0.6–1.3]); better DRS-R-98 scores (14.4 ± 3.4 versus 18.4 ± 4.3) (mean difference 4.0 [2.0–5.8]; $P < .001$); shorter delirium duration was (5.4 days versus 11.8 days) (mean difference 6.4 days [4.0–8.0]; $P < .001$); and shorter mean length of hospital stay (17.1 ± 11.1 versus 22.6 ± 16.7) (mean difference 5.5 days [1.4–2.3]; $P < .001$). The study found no significant haloperidol-related side effects [404].

Similarly a randomized, double-blinded, placebo-controlled trial ($n = 126$) of patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), randomly assigned patients to receive either 1 mg of risperidone or placebo sublingually upon regaining consciousness immediately postoperatively. The incidence of postoperative delirium in the risperidone group was lower than the placebo group (11.1% versus 31.7% respectively, $P = .009$, RR 0.35 [0.16–0.77]) [410]. Finally, a recently presented abstract [411] reported a significant decrease in the incidence of postoperative delirium following orthopedic joint replacement surgery ($n = 400$). The study compared olanzapine (5 mg Zydys formulation administered just preoperatively, and 5 mg administered immediately after surgery upon awakening) to placebo. Researchers found the incidence of delirium in the intervention group was 15%, compared with 41% in the placebo-controlled group ($P < .0001$).

Norepinephrine

As in the case of DA, acute NE (NA noradrenaline in Europe, NE norepinephrine in the United States) released secondary to hypoxia or ischemia leads to further neuronal injury and the development of worsening of delirium [412]. At least one randomized trial demonstrated that the selective alpha-2 agonist, dexmedetomidine (DEX), substantially decreased the incidence of postoperative delirium compared with conventional, GABAergic agents (3% versus 50%, respectively) [413]. It is theorized that the mechanism for the “delirium-sparing effect” is related to the receptor selectivity, absence of anticholinergic side effects, absence of respiratory depression, and potential neuron-protective effects. DEX has been shown to suppress the increase of circulating catecholamine concentrations found during cerebral ischemia [414]. In fact, one study found that, compared with placebo, DEX decreased plasma NE concentrations by 90% [415]. Another mechanism for possible neuroprotection involves its ultra-early modulation of the balance between pro- and anti-apoptotic proteins [416].

Serotonin

As previously discussed, 5-HT is toxic in elevated concentrations. High levels of 5-HT are found in cases of hepatic encephalopathy. Given its neuromodulatory effect, elevated 5-HT should be associated with hypoactive delirium.

At least one report suggests that the antiemetic agent ondansetron (ie, a selective serotonin 5-HT₃-type receptor antagonist) may be effective in the treatment of delirium [417]. Bayindir and colleagues [417] conducted a prospective study of patients ($n = 35$) who developed delirium in the ICU after coronary artery bypass graft surgery. The investigators developed a behavioral scoring scale, with normal scored as 0, and severe verbal and

physical agitation was scored as 4. After a subject was determined to be delirious, the patient received a single intravenous (IV) dose of ondansetron (ie, 8 mg), and was reevaluated 10 minutes later. Before the treatment, 7 (20%) patients had a score of 2; 10 (28.6%) patients had a score of 3; and 18 (51.4%) patients had a score of 4. After the treatment, 28 (80%) patients dropped their score to 0; 6 (17.1%) patients dropped to a score of 1; and 1 (2.9%) patient remained at a score of 4. The mean score dropped from 3.20 ± 1.01 to 0.29 ± 0.75 after treatment. No adverse side effects were reported.

Glutamate and NMDA receptors

Ammonia has been recognized as an important factor in the pathogenesis of hepatic encephalopathy. Some have found that acute ammonia toxicity is mediated by activation of NMDA receptors [418]. Ischemic injury is also associated with a marked increase in extracellular GLU and activation of GLU receptors, leading to additional Ca^{2+} influx. Compounds that prevent ammonia toxicity in mice (eg, carnitine) also prevent GLU toxicity in cultured neurons. These compounds do not prevent activation of NMDA receptors or the rise of Ca^{2+} . They interfered with subsequent steps in the toxic process. The protective effect of carnitine (also known as l-carnitine or levocarnitine, is a quaternary ammonium compound biosynthesized from the amino acids lysine and methionine) is mediated by activation of metabotropic GLU receptors (mGluRs). Agonists of mGluRs, especially of mGluR5, prevent GLU toxicity. Agonists of muscarinic receptors also prevent GLU toxicity and there seems to be an interplay between muscarinic and mGluRs in the protective effect. The authors suggest that GLU toxicity can be prevented at different steps or by activating receptors coupled to the transduction pathways interfering with the toxic process.

NMDA receptors modulate learning and memory, but excessive activation leads to neuronal degeneration and cell death. Hyperammonemia and liver failure alter the function of NMDA receptors and of some associated signal transduction pathways. The function of the glutamate–nitric oxide–cGMP pathway is impaired in brain *in vivo* in animal models of chronic liver failure. The impairment of this pathway leads to reduced cGMP and contributes to impaired cognitive function in hepatic encephalopathy, but there is some evidence to suggest this may be restored by pharmacologic manipulation of brain cGMP, which may be achieved by administering phosphodiesterase inhibitors (zaprinast or sildenafil) or cGMP itself [277].

The alpha-1 adrenoreceptor agonists (eg, DEX) has demonstrated a robust effect on neuroprotection modulated by GLU. The study compared DEX and the GLU receptor antagonist cis-4(phosphonomethyl)-2-piperidine carboxylic acid (CGS). The results demonstrated that DEX's neuroprotective efficacy was better than that produced by CGS [419].

Although the NMDA-receptor antagonist dizoclipine (MK801) has been shown to provide significant histologic neuroprotection in animal models of global cerebral ischemia [92,400,401], its clinical use in ischemic stroke has been shown to produce significant undesirable side effects (eg, delirium, psychosis, hallucinations) [420]. The NMDA/dopamine agonist agents amantadine and memantine have been used for the treatment of hypoactive-like symptoms associated with coma, traumatic brain injury, and stroke [421–423]. There are clinical data to suggest that their use may be indicated in cases of extreme psychomotor retardation, apathy, or catatonia.

Gamma-aminobutyric acid

As discussed above, GABAergic agents may lead to the development of delirium by various mechanisms. In fact, among the pharmacologic agents used in the general hospital and the critical care unit, benzodiazepine and other GABAergic agents (ie, propofol) are among the best predictors of delirium. Therefore, avoiding GABAergic agents is imperative. The only time GABAergic agents have a role in the treatment of delirium is when the mental status changes are presumed to be secondary to the withdrawal from a CNS-depressant agent (eg, alcohol, benzodiazepines, barbiturates). Otherwise, GABAergic agents should be avoided, if at all possible. This includes most commonly used sleeping aids. Please see the following section for alternate recommendations.

GABA levels are reported to be increased in patients suffering from hepatic encephalopathy. Correspondingly, at least one study found that flumazenil, a benzodiazepine antagonist, reversed coma and improved hypoactive delirium in cirrhotic patients [276].

Conversely, reduced GABA has been implicated in delirium that results from ethanol and CNS-depressant withdrawal, thus the treatment of choice for these conditions is the reintroduction of a benzodiazepine agent [424].

Sleep deprivation

The mechanism of action of most commonly used sedative agents includes either GABAergic activity or central anticholinergic effects (eg, benzodiazepine, barbiturates, propofol). Although the benzodiazepines decrease sleep latency and awakenings and increase sleep duration and efficiency (sleep duration/time in bed), these drugs also significantly reduce slow-wave and REM sleep, increase spindles, increase cortical activity at low doses, and decrease EEG amplitude at high doses [298–300]. Narcotics also suppress deep and REM sleep and increase arousals and stage-1 sleep [425].

Propofol (2,6-diisopropylphenol) is widely used in clinical anesthesia and for sedation in the ICU because of its rapid onset and clear emergence [426]. Propofol potentiates and directly activates the GABA_A receptor. GABA is

the major inhibitory system in the CNS, and is involved in down-regulation of neuronal activity, including sleep [427,428].

Propofol, however, is often associated with adverse cardiovascular effects, including decreases in cardiac output and arterial blood pressure [429]. Propofol seems to have a greater depressant effect on the cardiovascular system than barbiturates. The GABA_A receptor is a target of many general anesthetics, including volatile general anesthetics [430], barbiturates [431], and benzodiazepines [432], suggesting that propofol may affect the activity of the hypothalamic paraventricular nucleus.

Given the roles of melatonin in the regulation of the sleep-wake cycle, resetting of circadian rhythm disturbances and its extensive antioxidant activity have potential applications in critical care patients [433]. There are some data to suggest that exogenous melatonin supplementation may improve sleep quality and thus help prevent or alleviate delirium [121,130,139,434]. More studies are required to substantiate these claims.

DEX is a potent alpha-2 agonist agent that achieves sedation without any clinically significant respiratory depression. Thus this agent is a valuable alternative to the use of GABAergic agents (eg, benzodiazepines, propofol) to achieve adequate sedation without risk of causing or exacerbating a delirium. There are no case reports of DEX-induced delirium. On the other hand, DEX may be used to transition patients who are difficult to extubate due to agitation upon lowering of conventional sedative agents. The recommendation is to add DEX to the current sedation regimen. Once the patient has been effectively sedated for 12 to 24 hours on the combination, a slow titration of the conventional sedatives is done—the speed of this taper will depend on the sedative agent and how long has the patient been on it. This will be followed by a moderately slow titration off DEX.

Given the significant disruptions in the sleep pattern of ICU patients and the alterations in melatonin circadian rhythms, it would make sense to attempt to correct for the changes by either providing patients with sources of adequate lighting (either natural or via special lamps) or to provide melatonin supplementation. There are some, but limited data suggesting that exogenous melatonin supplementation may improve sleep quality and thus may help prevent or alleviate delirium [121,130,139,433]. More studies are needed to substantiate these claims. There are no available data on the potential use of the melatonin agonist ramelteon. As in the case of melatonin, studies are required to assess ramelteon's potential effectiveness in cases of sleep deprivation-induced delirium.

Ketamine

At least one randomized, double-blind study involving children undergoing dental repair [435] demonstrated the effectiveness of ketamine (versus placebo) for the prevention of delirium in sevoflurane-induced anesthesia using the Pediatric Anesthesia Emergence Delirium scale. The study group

exhibited a substantially lower incidence of emergence agitation (16.6%) compared with the placebo group (34.2%).

Future directions

Given the complexities already described and the multiple pathways and mechanisms that likely “go wrong together” or “cause a domino-like” effect, it would make sense to consider a treatment strategy that addresses all these factors simultaneously. Unfortunately, there are very limited data to support any of these approaches, let alone in combination. But only well-designed treatment trials will be able to determine whether the theory bears out in clinical success. The basic approach of treating delirium may consider the neurochemical underpinnings described earlier. Thus, in treating an acutely delirious individual we should consider restoring adequate function of all recognized dysfunctional pathways. How to effectively do that, to prevent neurochemical derangement or restore adequate functioning, should be the focus of future studies.

Summary

Delirium is an acute or subacute organic mental syndrome characterized by disturbance of consciousness, cognition, orientation, attention, psychomotor activity, sleep-wake cycle, and behavior. Delirium is likely to be the most common and the most serious complication in the medically ill, particularly the elderly and the critically ill. Not only does it cause distress to patients, families, and medical caregivers, but its presence is associated with increased morbidity and mortality, prolonged hospital stays, poor functional and cognitive recovery, increased placement in specialized intermediate and long-term care facilities, and increased cost of care.

It is unlikely that we will ever be able to find a single cause of delirium, or a single pathway leading to delirium. Nevertheless, the better we are able to understand how multiple clinical or environmental factors influence brain chemistry and functioning, the better we will be able to understand the complex sets of neurochemical cascades that are set in motion and that manifest themselves in the symptoms of delirium. If we truly get to understand the pathophysiological mechanisms that, working together, lead to the disordered brain function that causes delirium, we may be able to find evidence-based medication treatments or environmental manipulations that address each and every one of them to shorten the course of the syndrome. More importantly, given the recognized long-term cognitive and functional effects of delirium, we should eventually strive to find ways to prevent its development altogether. Given the complexities of the human brain and the many intricacies in the interacting pathways that likely help the brain function properly or go awry, we have a better chance of

effectively preventing and treating delirium by implementing multilevel approaches that address the many pathways described in this article.

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References

- [1] Brown T. Basic mechanisms in the pathogenesis of delirium. In: Stoudemire A, Greenberg DB, editors. *The Psychiatric Care of the Medical Patient*. 2nd edition. New York: Oxford Press; 2000. p. 571–80.
- [2] Engel GL, Romano J. Delirium, a syndrome of cerebral insufficiency. *J Chronic Dis* 1959; 9(3):260–77.
- [3] Lipowski ZJ. Update on delirium. *Psychiatr Clin North Am* 1992;15(2):335–46.
- [4] Pompei P, Foreman M, Rudberg MA, et al. Delirium in hospitalized older persons: outcomes and predictors. *J Am Geriatr Soc* 1994;42(8):809–15.
- [5] Inouye S, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113(12):941–8.
- [6] Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med* 2001;27(12):1892–900.
- [7] Inouye SK. Delirium in hospitalized older patients: recognition and risk factors. *J Geriatr Psychiatry Neurol* 1998;11(3):118–25, discussion 157–8.
- [8] Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *Jama* 2004;291(14):1753–62.
- [9] Inouye SK. Delirium in hospitalized older patients. *Clin Geriatr Med* 1998;14(4):745–64.
- [10] Levkoff SE, Evans DA, Liptzin B, et al. Delirium. The occurrence and persistence of symptoms among elderly hospitalized patients. *Arch Intern Med* 1992;152(2):334–40.
- [11] Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. *Crit Care Med* 2004;32(4):955–62.
- [12] Murray AM, Levkoff SE, Wetle TT, et al. Acute delirium and functional decline in the hospitalized elderly patient. *J Gerontol* 1993;48(5):M181–6.
- [13] Ebert AD, Walzer TA, Huth C, et al. Early neurobehavioral disorders after cardiac surgery: a comparative analysis of coronary artery bypass graft surgery and valve replacement. *J Cardiothorac Vasc Anesth* 2001;15(1):15–9.
- [14] O'Keeffe S, Lavan J. The prognostic significance of delirium in older hospital patients. *J Am Geriatr Soc* 1997;45(2):174–8.
- [15] Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. *Jama* 1990;263(8):1097–101.
- [16] Shinn JA, Maldonado JR. Performance improvement: increasing recognition and treatment of postoperative delirium. *Prog Cardiovasc Nurs* 2000;15(3):114–5.
- [17] Gibson GE, Blass JP. Impaired synthesis of acetylcholine in brain accompanying mild hypoxia and hypoglycemia. *J Neurochem* 1976;27(1):37–42.
- [18] Flacker JM, Cummings V, Mach JR Jr, et al. The association of serum anticholinergic activity with delirium in elderly medical patients. *Am J Geriatr Psychiatry* 1998;6(1):31–41.
- [19] Flacker JM, Lipsitz LA. Neural mechanisms of delirium: current hypotheses and evolving concepts. *J Gerontol A Biol Sci Med Sci* 1999;54(6):B239–46.

- [20] Trzepacz PT. The neuropathogenesis of delirium. A need to focus our research. *Psychosomatics* 1994;35(4):374–91.
- [21] Beresin EV. Delirium in the elderly. *J Geriatr Psychiatry Neurol* 1988;1(3):127–43.
- [22] Flacker JM, Wei JY. Endogenous anticholinergic substances may exist during acute illness in elderly medical patients. *J Gerontol A Biol Sci Med Sci* 2001;56(6):M353–5.
- [23] Golinger RC, Peet T, Tune LE. Association of elevated plasma anticholinergic activity with delirium in surgical patients. *Am J Psychiatry* 1987;144(9):1218–20.
- [24] Plaschke K, Thomas C, Engelhardt R, et al. Significant correlation between plasma and CSF anticholinergic activity in presurgical patients. *Neurosci Lett* 2007;417(1):16–20.
- [25] Trzepacz PT. Anticholinergic Model For Delirium. *Semin Clin Neuropsychiatry* 1996;1(4):294–303.
- [26] Trzepacz PT. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. *Semin Clin Neuropsychiatry* 2000;5(2):132–48.
- [27] Tune LE, Bylsma FW, Hilt DC. Anticholinergic delirium caused by topical homatropine ophthalmologic solution: confirmation by anticholinergic radioreceptor assay in two cases. *J Neuropsychiatry Clin Neurosci* 1992;4(2):195–7.
- [28] Tune LE, Egeli S. Acetylcholine and delirium. *Dement Geriatr Cogn Disord* 1999;10(5):342–4.
- [29] Milstein A, Pollack A, Kleinman G, et al. Confusion/delirium following cataract surgery: an incidence study of 1-year duration. *Int Psychogeriatr* 2002;14(3):301–6.
- [30] Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006;104(1):21–6.
- [31] Lowery DP, Wesnes K, Ballard CG. Subtle attentional deficits in the absence of dementia are associated with an increased risk of post-operative delirium. *Dement Geriatr Cogn Disord* 2007;23(6):390–4.
- [32] Gibson GE, Peterson C, Jenden DJ. Brain acetylcholine synthesis declines with senescence. *Science* 1981;213(4508):674–6.
- [33] Gibson GE, Peterson C. Aging decreases oxidative metabolism and the release and synthesis of acetylcholine. *J Neurochem* 1981;37(4):978–84.
- [34] Gibson GE, Peterson C. Acetylcholine and oxidative metabolism in septum and hippocampus in vitro. *J Biol Chem* 1983;258(2):1142–5.
- [35] Jansson A, Olin K, Yoshitake T, et al. Effects of isoflurane on prefrontal acetylcholine release and hypothalamic Fos response in young adult and aged rats. *Exp Neurol* 2004;190(2):535–43.
- [36] Gibson GE, Peterson C. Decreases in the release of acetylcholine in vitro with low oxygen. *Biochem Pharmacol* 1982;31(1):111–5.
- [37] Gibson GE, Peterson C, Sansone J. Decreases in amino acids and acetylcholine metabolism during hypoxia. *J Neurochem* 1981;37(1):192–201.
- [38] Blass J, Gibson G, Duffy T, et al. Cholinergic dysfunction: a common denominator in metabolic encephalopathies. In: Pepeu G, Ladinsky H, editors. *Cholinergic Mechanisms*. New York, NY: Plenum Publishing Corp.; 1981. p. 921–8.
- [39] Brown T, Stoudemire A. Antipsychotics. *Psychiatric Side Effects of Prescription and Over-the-Counter Medications*. Washington, DC: American Psychiatric Press; 1998. p. 3–33.
- [40] Bergmann K, Eastham EJ. Psychogeriatric ascertainment and assessment for treatment in an acute medical ward setting. *Age Ageing* 1974;3(3):174–88.
- [41] Wacker P, Nunes PV, Cabrita H, et al. Post-operative delirium is associated with poor cognitive outcome and dementia. *Dement Geriatr Cogn Disord* 2006;21(4):221–7.
- [42] Wahlund L, Bjorlin GA. Delirium in clinical practice: experiences from a specialized delirium ward. *Dement Geriatr Cogn Disord* 1999;10(5):389–92.
- [43] Tune L, Coyle JT. Serum levels of anticholinergic drugs in treatment of acute extrapyramidal side effects. *Arch Gen Psychiatry* 1980;37(3):293–7.
- [44] Tune LE, Damlouji NF, Holland A, et al. Association of postoperative delirium with raised serum levels of anticholinergic drugs. *Lancet* 1981;2(8248):651–3.

- [45] Thomas RI, Cameron DJ, Fahs MC. A prospective study of delirium and prolonged hospital stay. Exploratory study. *Arch Gen Psychiatry* 1988;45(10):937–40.
- [46] Mussi C, Ferrari R, Ascari S, et al. Importance of serum anticholinergic activity in the assessment of elderly patients with delirium. *J Geriatr Psychiatry Neurol* 1999;12(2):82–6.
- [47] Mach JR Jr, Dysken MW, Kuskowski M, et al. Serum anticholinergic activity in hospitalized older persons with delirium: a preliminary study. *J Am Geriatr Soc* 1995;43(5):491–5.
- [48] Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *Jama* 2001;286(21):2703–10.
- [49] Mulsant BH, Pollock BG, Kirshner M, et al. Serum anticholinergic activity in a community-based sample of older adults: relationship with cognitive performance. *Arch Gen Psychiatry* 2003;60(2):198–203.
- [50] Trzepacz PT, Leavitt M, Ciongoli K. An animal model for delirium. *Psychosomatics* 1992;33(4):404–15.
- [51] Lipowski ZJ. Delirium (acute confusional states). *Jama* 1987;258(13):1789–92.
- [52] Fatranska M, Budai D, Oprsalova Z, et al. Acetylcholine and its enzymes in some brain areas of the rat under stress. *Brain Res* 1987;424(1):109–14.
- [53] Takayama H, Mizukawa K, Ota Z, et al. Regional responses of rat brain muscarinic cholinergic receptors to immobilization stress. *Brain Res* 1987;436(2):291–5.
- [54] Engel GL, Romano J. Delirium, a syndrome of cerebral insufficiency. 1959. *J Neuropsychiatry Clin Neurosci* 2004;16(4):526–38.
- [55] Koponen H, Hurri L, Stenback U, et al. Computed tomography findings in delirium. *J Nerv Ment Dis* 1989;177(4):226–31.
- [56] Koponen H, Partanen J, Paakkonen A, et al. EEG spectral analysis in delirium. *J Neurol Neurosurg Psychiatry* 1989;52(8):980–5.
- [57] Koponen H, Stenback U, Mattila E, et al. Delirium among elderly persons admitted to a psychiatric hospital: clinical course during the acute stage and one-year follow-up. *Acta Psychiatr Scand* 1989;79(6):579–85.
- [58] Plaschke K, Hill H, Engelhardt R, et al. EEG changes and serum anticholinergic activity measured in patients with delirium in the intensive care unit. *Anaesthesia* 2007;62(12):1217–23.
- [59] Romano J, Engel G. Delirium. I. EEG data. *Arch Neurol Psychiatry* 1944;51:356–77.
- [60] Trzepacz PT, Scwabassi RJ, Van Thiel DH. Delirium: a subcortical phenomenon? *J Neuropsychiatry Clin Neurosci* 1989;1(3):283–90.
- [61] Rouatbi S, Dardouri K, Farhat Ouahchi Y, et al. [Aging of the lung parenchyma]. *Rev Mal Respir* 2006;23(5 Pt 1):445–52 [French].
- [62] Kaye DM, Esler MD. Autonomic Control of the Aging Heart. *Neuromolecular Med* 2008, in press.
- [63] Miyamoto E, Tomimoto H, Nakao Si S, et al. Caudoputamen is damaged by hypocapnia during mechanical ventilation in a rat model of chronic cerebral hypoperfusion. *Stroke* 2001;32(12):2920–5.
- [64] Roman GC. Brain hypoperfusion: a critical factor in vascular dementia. *Neurol Res* 2004;26(5):454–8.
- [65] Aliev G, Obrenovich ME, Smith MA, et al. Hypoperfusion, Mitochondria Failure, Oxidative Stress, and Alzheimer Disease. *J Biomed Biotechnol* 2003;2003(3):162–3.
- [66] Bures J, Buresova O, Krivanek J. The meaning and significance of Leao's spreading depression. *An Acad Bras Cienc* 1984;56(4):385–400.
- [67] Czéh G, Somjen GG. Hypoxic failure of synaptic transmission in the isolated spinal cord, and the effects of divalent cations. *Brain Res* 1990;527(2):224–33.
- [68] Nicoll RA, Malenka RC, Kauer JA. Functional comparison of neurotransmitter receptor subtypes in mammalian central nervous system. *Physiol Rev* 1990;70(2):513–65.
- [69] Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *Jama* 1996;275(11):852–7.

- [70] Gaudreau JD, Gagnon P, Roy MA, et al. Association between psychoactive medications and delirium in hospitalized patients: a critical review. *Psychosomatics* 2005;46(4):302–16.
- [71] Tune L, Carr S, Cooper T, et al. Association of anticholinergic activity of prescribed medications with postoperative delirium. *J Neuropsychiatry Clin Neurosci* 1993;5(2):208–10.
- [72] Brauer C, Morrison RS, Silberzweig SB, et al. The cause of delirium in patients with hip fracture. *Arch Intern Med* 2000;160(12):1856–60.
- [73] Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. *Psychosomatics* 2002;43(3):183–94.
- [74] Tuma R, DeAngelis LM. Altered mental status in patients with cancer. *Arch Neurol* 2000;57(12):1727–31.
- [75] Lawlor PG, Gagnon B, Mancini IL, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. *Arch Intern Med* 2000;160(6):786–94.
- [76] Morita T, Tei Y, Tsunoda J, Inoue S, Chihara S. Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients. *J Pain Symptom Manage* 2001;22(6):997–1006.
- [77] Olofsson SM, Weitzner MA, Valentine AD, et al. A retrospective study of the psychiatric management and outcome of delirium in the cancer patient. *Support Care Cancer* 1996;4(5):351–7.
- [78] Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *Jama* 2002;287(3):345–55.
- [79] Fong HK, Sands LP, Leung JM. The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. *Anesth Analg* 2006;102(4):1255–66.
- [80] Gaudreau JD, et al. Opioid medications and longitudinal risk of delirium in hospitalized cancer patients. *Cancer* 2007;109(11):2365–73.
- [81] Vaurio LE, Sands LP, Wang Y, et al. Postoperative delirium: the importance of pain and pain management. *Anesth Analg* 2006;102(4):1267–73.
- [82] Vella-Brincat J, Macleod AD. Adverse effects of opioids on the central nervous systems of palliative care patients. *J Pain Palliat Care Pharmacother* 2007;21(1):15–25.
- [83] Wang Y, et al. The effects of postoperative pain and its management on postoperative cognitive dysfunction. *Am J Geriatr Psychiatry* 2007;15(1):50–9.
- [84] Centeno C, Sanz A, Bruera E. Delirium in advanced cancer patients. *Palliat Med* 2004;18(3):184–94.
- [85] Dubois MJ, Bergeron N, Dumont M, et al. Delirium in an intensive care unit: a study of risk factors. *Intensive Care Med* 2001;27(8):1297–304.
- [86] Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. *Dement Geriatr Cogn Disord* 1999;10(5):393–400.
- [87] Inouye SK, Schlesinger MJ, Lydon TJ. Delirium: a symptom of how hospital care is failing older persons and a window to improve quality of hospital care. *Am J Med* 1999;106(5):565–73.
- [88] Eisendrath SJ, Goldman B, Douglas J, et al. Meperidine-induced delirium. *Am J Psychiatry* 1987;144(8):1062–5.
- [89] Marcantonio ER, et al. The relationship of postoperative delirium with psychoactive medications. *Jama* 1994;272(19):1518–22.
- [90] Stock SL, Catalano G, Catalano MC. Meperidine associated mental status changes in a patient with chronic renal failure. *J Fla Med Assoc* 1996;83(5):315–9.
- [91] Bruera E, Pereira J. Acute neuropsychiatric findings in a patient receiving fentanyl for cancer pain. *Pain* 1997;69(1-2):199–201.
- [92] Bruera E, Strasser F, Shen L, et al. The effect of donepezil on sedation and other symptoms in patients receiving opioids for cancer pain: a pilot study. *J Pain Symptom Manage* 2003;26(5):1049–54.
- [93] Vigano A, Fan D, Bruera E. Individualized use of methadone and opioid rotation in the comprehensive management of cancer pain associated with poor prognostic indicators. *Pain* 1996;67(1):115–9.

- [94] Han L, McCusker J, Cole M, et al. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. *Arch Intern Med* 2001; 161(8):1099–105.
- [95] Kobayashi K, Higashima M, Mutou K, et al. Severe delirium due to basal forebrain vascular lesion and efficacy of donepezil. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; 28(7):1189–94.
- [96] Milusheva E, Sperlagh B, Kiss B, et al. Inhibitory effect of hypoxic condition on acetylcholine release is partly due to the effect of adenosine released from the tissue. *Brain Res Bull* 1990;24(3):369–73.
- [97] Tune LE. Anticholinergic effects of medication in elderly patients. *J Clin Psychiatry* 2001; 62(Suppl. 21):11–4.
- [98] Tune L, et al. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. *Am J Psychiatry* 1992;149(10):1393–4.
- [99] Tune LE. Serum anticholinergic activity levels and delirium in the elderly. *Semin Clin Neuropsychiatry* 2000;5(2):149–53.
- [100] Tune L, Folstein MF. Post-operative delirium. *Adv Psychosom Med* 1986;15:51–68.
- [101] Landi F, Russo A, Liperoti R, et al. Anticholinergic drugs and physical function among frail elderly population. *Clin Pharmacol Ther* 2007;81(2):235–41.
- [102] Blass JP, Gibson GE. Cerebrometabolic aspects of delirium in relationship to dementia. *Dement Geriatr Cogn Disord* 1999;10(5):335–8.
- [103] Meuret P, Backman SB, Bonhomme V, et al. Physostigmine reverses propofol-induced unconsciousness and attenuation of the auditory steady state response and bispectral index in human volunteers. *Anesthesiology* 2000;93(3):708–17.
- [104] Beaver KM, Gavin TJ. Treatment of acute anticholinergic poisoning with physostigmine. *Am J Emerg Med* 1998;16(5):505–7.
- [105] Haase U, Rundshagen I. [Pharmacotherapy–physostigmine administered post-operatively]. *Anesthesiol Intensivmed Notfallmed Schmerzther* 2007;42(3):188–9 [German].
- [106] Holinger PC, Klawans HL. Reversal of tricyclic-overdosage-induced central anticholinergic syndrome by physostigmine. *Am J Psychiatry* 1976;133(9):1018–23.
- [107] Richardson WH 3rd, Williams SR, Carstairs SD. A picturesque reversal of antimuscarinic delirium. *J Emerg Med* 2004;26(4):463.
- [108] Weizberg M, Su M, Mazzola JL, et al. Altered mental status from olanzapine overdose treated with physostigmine. *Clin Toxicol (Phila)* 2006;44(3):319–25.
- [109] Francis J, Kapoor WN. Prognosis after hospital discharge of older medical patients with delirium. *J Am Geriatr Soc* 1992;40(6):601–6.
- [110] Trzepacz PT. Update on the neuropathogenesis of delirium. *Dement Geriatr Cogn Disord* 1999;10(5):330–4.
- [111] BaHammam A. Sleep in acute care units. *Sleep Breath* 2006;10(1):6–15.
- [112] Walker MP, Stickgold R. Sleep-dependent learning and memory consolidation. *Neuron* 2004;44(1):121–33.
- [113] Walker MP, Stickgold R. Sleep, memory, and plasticity. *Annu Rev Psychol* 2006;57:139–66.
- [114] Yoo SS, et al. A deficit in the ability to form new human memories without sleep. *Nat Neurosci* 2007;10(3):385–92.
- [115] Dinges DF, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep* 1997;20(4):267–77.
- [116] Dinges DF. The state of sleep deprivation: From functional biology to functional consequences. *Sleep Med Rev* 2006;10(5):303–5.
- [117] Yoo SS, Gujar N, Hu P, et al. The human emotional brain without sleep—a prefrontal amygdala disconnect. *Curr Biol* 2007;17(20):R877–8.
- [118] Berger M, Vollmann J, Hohagen F, et al. Sleep deprivation combined with consecutive sleep phase advance as a fast-acting therapy in depression: an open pilot trial in medicated and unmedicated patients. *Am J Psychiatry* 1997;154(6):870–2.

- [119] Evans JI, Lewis SA. Sleep studies in early delirium and during drug withdrawal in normal subjects and the effect of phenothiazines on such states. *Electroencephalogr Clin Neurophysiol* 1968;25(5):508–9.
- [120] Johns M, Large AA, Masterton JP, et al. Sleep and delirium after open heart surgery. *Br J Surg* 1974;61(5):377–81.
- [121] Mistraletti G, Carloni E, Cigada M, et al. Sleep and delirium in the Intensive Care Unit. *Minerva Anestesiol* 2008;74(6):329–33.
- [122] Bergamasco B, Brignolio F, Doriguzzi T, et al. [Longitudinal polygraphic study of sleep in 11 patients with delirium tremens. Physiopathological considerations on “sleep deprivation”]. *Acta Neurol (Napoli)* 1968;23(2):289–99 [Italian].
- [123] Ito H, Harada D, Hayashida K, et al. [Psychiatry and sleep disorders–delirium]. *Seishin Shinkeigaku Zasshi* 2006;108(11):1217–21 [Japanese].
- [124] Lee JW. Recurrent delirium associated with obstructive sleep apnea. *Gen Hosp Psychiatry* 1998;20(2):120–2.
- [125] Munoz X, Marti S, Sumalla J, et al. Acute delirium as a manifestation of obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 1998;158(4):1306–7.
- [126] Pandharipande P, Ely EW. Sedative and analgesic medications: risk factors for delirium and sleep disturbances in the critically ill. *Crit Care Clin* 2006;22(2):313–27, vii.
- [127] Whitney JF, Gannon DE. Obstructive sleep apnea presenting as acute delirium. *Am J Emerg Med* 1996;14(3):270–1.
- [128] Heller SS, Frank KA, Malm JR, et al. Psychiatric complications of open-heart surgery. A re-examination. *N Engl J Med* 1970;283(19):1015–20.
- [129] Helton MC, Gordon SH, Nunnery SL. The correlation between sleep deprivation and the intensive care unit syndrome. *Heart Lung* 1980;9(3):464–8.
- [130] Miyazaki T, Kuwano H, Kato H, et al. Correlation between serum melatonin circadian rhythm and intensive care unit psychosis after thoracic esophagectomy. *Surgery* 2003;133(6):662–8.
- [131] Misra S, Ganzini L. Delirium, depression, and anxiety. *Crit Care Clin* 2003;19(4):771–87, viii.
- [132] Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in 32 patients receiving postoperative care. *Br Med J (Clin Res Ed)* 1985;290(6474):1029–32.
- [133] Simini B. Patients’ perceptions of intensive care. *Lancet* 1999;354(9178):571–2.
- [134] Cooper AB, Thornley KS, Young GB, et al. Sleep in critically ill patients requiring mechanical ventilation. *Chest* 2000;117(3):809–18.
- [135] Freedman NS, Gazendam J, Levan L, et al. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *Am J Respir Crit Care Med* 2001;163(2):451–7.
- [136] Weinhouse GL, Schwab RJ. Sleep in the critically ill patient. *Sleep* 2006;29(5):707–16.
- [137] Shigeta H, Yasui A, Nimura Y, et al. Postoperative delirium and melatonin levels in elderly patients. *Am J Surg* 2001;182(5):449–54.
- [138] Balan S, Leibovitz A, Zila SO, et al. The relation between the clinical subtypes of delirium and the urinary level of 6-SMT. *J Neuropsychiatry Clin Neurosci* 2003;15(3):363–6.
- [139] Olofsson K, Alling C, Lundberg D, et al. Abolished circadian rhythm of melatonin secretion in sedated and artificially ventilated intensive care patients. *Acta Anaesthesiol Scand* 2004;48(6):679–84.
- [140] Krueger JM, Majde JA. Humoral links between sleep and the immune system: research issues. *Ann N Y Acad Sci* 2003;992:9–20.
- [141] Ozturk L, Pelin Z, Karadeniz D, et al. Effects of 48 hours sleep deprivation on human immune profile. *Sleep Res Online* 1999;2(4):107–11.
- [142] Spiegel K, Sheridan JF, Van Cauter E. Effect of sleep deprivation on response to immunization. *Jama* 2002;288(12):1471–2.

- [143] Irwin M, McClintick J, Costlow C, et al. Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. *Faseb J* 1996;10(5):643–53.
- [144] Leproult R, Copinschi G, Buxton O, et al. Sleep loss results in an elevation of cortisol levels the next evening. *Sleep* 1997;20(10):865–70.
- [145] Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;354(9188):1435–9.
- [146] Litaker D, Locala J, Franco K, et al. Preoperative risk factors for postoperative delirium. *Gen Hosp Psychiatry* 2001;23(2):84–9.
- [147] Ouimet S, Kavanagh BP, Gottfried SB, et al. Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med* 2007;33(1):66–73.
- [148] Hala M. Pathophysiology of postoperative delirium: systemic inflammation as a response to surgical trauma causes diffuse microcirculatory impairment. *Med Hypotheses* 2007;68(1):194–6.
- [149] Kalman J, Juhasz A, Bogats G, et al. Elevated levels of inflammatory biomarkers in the cerebrospinal fluid after coronary artery bypass surgery are predictors of cognitive decline. *Neurochem Int* 2006;48(3):177–80.
- [150] Ramlawi B, Rudolph JL, Mieno S, et al. Surgery. C-Reactive protein and inflammatory response associated to neurocognitive decline following cardiac surgery 2006;140(2):221–6.
- [151] Ramlawi B, Rudolph JL, Mieno S, et al. Serologic markers of brain injury and cognitive function after cardiopulmonary bypass. *Ann Surg* 2006;244(4):593–601.
- [152] Becher B, Bechmann I, Greter M. Antigen presentation in autoimmunity and CNS inflammation: how T lymphocytes recognize the brain. *J Mol Med* 2006;84(7):532–43.
- [153] Dimitrijevic OB, Stamatovic SM, Keep RF, et al. Effects of the chemokine CCL2 on blood-brain barrier permeability during ischemia-reperfusion injury. *J Cereb Blood Flow Metab* 2006;26(6):797–810.
- [154] Mahad D, Callahan MK, Williams KA, et al. Modulating CCR2 and CCL2 at the blood-brain barrier: relevance for multiple sclerosis pathogenesis. *Brain* 2006;129(Pt 1):212–23.
- [155] Ubogu EE, Callahan MK, Tucky BH, et al. CCR5 expression on monocytes and T cells: modulation by transmigration across the blood-brain barrier in vitro. *Cell Immunol* 2006;243(1):19–29.
- [156] Ubogu EE, et al. Determinants of CCL5-driven mononuclear cell migration across the blood-brain barrier. Implications for therapeutically modulating neuroinflammation. *J Neuroimmunol* 2006;179(1-2):132–44.
- [157] Jeppsson B, Freund HR, Gimmon Z, et al. Blood-brain barrier derangement in sepsis: cause of septic encephalopathy? *Am J Surg* 1981;141(1):136–42.
- [158] Holmes JH, Connolly NC, Paull DL, et al. Magnitude of the inflammatory response to cardiopulmonary bypass and its relation to adverse clinical outcomes. *Inflamm Res* 2002;51(12):579–86.
- [159] Roth-Isigkeit A, Borstel TV, Seyfarth M, et al. Perioperative serum levels of tumour-necrosis-factor alpha (TNF-alpha), IL-1 beta, IL-6, IL-10 and soluble IL-2 receptor in patients undergoing cardiac surgery with cardiopulmonary bypass without and with correction for haemodilution. *Clin Exp Immunol* 1999;118(2):242–6.
- [160] de Rooij SE, van Munster, B C, Korevaar JC, et al. Cytokines and acute phase response in delirium. *J Psychosom Res* 2007;62(5):521–5.
- [161] Adamis D, Treloar A, Martin FC, et al. Int J Geriatr Psychiatry. APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients 2007;22(7):688–94.
- [162] Beloosesky Y, Hendel D, Weiss A, et al. Cytokines and C-reactive protein production in hip-fracture-operated elderly patients. *J Gerontol A Biol Sci Med Sci* 2007;62(4):420–6.

- [163] Rudolph JL, Ramlawi B, Kuchel GA, et al. Chemokines are associated with delirium after cardiac surgery. *J Gerontol A Biol Sci Med Sci* 2008;63(2):184–9.
- [164] van der Mast RC, Fekkes D. Serotonin and amino acids: partners in delirium pathophysiology? *Semin Clin Neuropsychiatry* 2000;5(2):125–31.
- [165] Fries M, Bickenbach J, Henzler D, et al. S-100 protein and neurohistopathologic changes in a porcine model of acute lung injury. *Anesthesiology* 2005;102(4):761–7.
- [166] Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocr Rev* 1984;5(1):25–44.
- [167] Seckl JR, Olsson T. Glucocorticoid hypersecretion and the age-impaired hippocampus: cause or effect? *J Endocrinol* 1995;145(2):201–11.
- [168] Basavaraju N, Phillips SL. Cortisol deficient state. A cause of reversible cognitive impairment and delirium in the elderly. *J Am Geriatr Soc* 1989;37(1):49–51.
- [169] McIntosh TK, Bush HL, Yeston NS, et al. Beta-endorphin, cortisol and postoperative delirium: a preliminary report. *Psychoneuroendocrinology* 1985;10(3):303–13.
- [170] Robertsson B, Blennow K, Brane G, et al. Hyperactivity in the hypothalamic-pituitary-adrenal axis in demented patients with delirium. *Int Clin Psychopharmacol* 2001;16(1):39–47.
- [171] Olsson T, Marklund N, Gustafson Y, et al. Abnormalities at different levels of the hypothalamic-pituitary-adrenocortical axis early after stroke. *Stroke* 1992;23(11):1573–6.
- [172] Olsson T. Urinary free cortisol excretion shortly after ischaemic stroke. *J Intern Med* 1990;228(2):177–81.
- [173] Olsson T. Activity in the hypothalamic-pituitary-adrenal axis and delirium. *Dement Geriatr Cogn Disord* 1999;10(5):345–9.
- [174] De Kloet ER, Vreugdenhil E, Oitzl MS, et al. Brain corticosteroid receptor balance in health and disease. *Endocr Rev* 1998;19(3):269–301.
- [175] Sapolsky RM. Why stress is bad for your brain. *Science* 1996;273(5276):749–50.
- [176] Sapolsky RM, Krey LC, McEwen BS. Stress down-regulates corticosterone receptors in a site-specific manner in the brain. *Endocrinology* 1984;114(1):287–92.
- [177] Demonacos CV, Karayanni N, Hatzoglou E, et al. Mitochondrial genes as sites of primary action of steroid hormones. *Steroids* 1996;61(4):226–32.
- [178] Agardh CD, Siesjö BK. Hypoglycemic brain injury: phospholipids, free fatty acids, and cyclic nucleotides in the cerebellum of the rat after 30 and 60 minutes of severe insulin-induced hypoglycemia. *J Cereb Blood Flow Metab* 1981;1(3):267–75.
- [179] Perry EK, Perry RH. Acetylcholine and hallucinations: disease-related compared to drug-induced alterations in human consciousness. *Brain Cogn* 1995;28(3):240–58.
- [180] Jacobson L, Sapolsky R. The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocr Rev* 1991;12(2):118–34.
- [181] Fischette CT, Komisaruk BR, Edinger HM, et al. Differential fornix ablations and the circadian rhythmicity of adrenal corticosteroid secretion. *Brain Res* 1980;195(2):373–87.
- [182] Rubin RT, Mandell AJ, Crandall PH. Corticosteroid responses to limbic stimulation in man: localization of stimulus sites. *Science* 1966;153(737):767–8.
- [183] van der Mast RC, Fekkes D, Moleman P, et al. Is postoperative delirium related to reduced plasma tryptophan? *Lancet* 1991;338(8771):851–2.
- [184] Fernstrom JD, Wurtman RJ. Brain serotonin content: physiological regulation by plasma neutral amino acids. *Science* 1972;178(59):414–6.
- [185] Kaufman S. An evaluation of the possible neurotoxicity of metabolites of phenylalanine. *J Pediatr* 1989;114(5):895–900.
- [186] van der Mast RC, van den Broek WW, Fekkes D, et al. Delirium after cardiac surgery. The possible role of tryptophan in relation to the other neutral aminoacids. *Adv Exp Med Biol* 1996;398:93–6.
- [187] Mizock BA, Sabelli HC, Dubin A, et al. Septic encephalopathy. Evidence for altered phenylalanine metabolism and comparison with hepatic encephalopathy. *Arch Intern Med* 1990;150(2):443–9.

- [188] Takezawa J, Taenaka N, Nishijima MK, et al. Amino acids and thiobarbituric acid reactive substances in cerebrospinal fluid and plasma of patients with septic encephalopathy. *Crit Care Med* 1983;11(11):876–9.
- [189] Krause W, Halminski M, McDonald L, et al. Biochemical and neuropsychological effects of elevated plasma phenylalanine in patients with treated phenylketonuria. A model for the study of phenylalanine and brain function in man. *J Clin Invest* 1985;75(1):40–8.
- [190] Krause W, Epstein C, Averbook A, et al. Phenylalanine alters the mean power frequency of electroencephalograms and plasma L-dopa in treated patients with phenylketonuria. *Pediatr Res* 1986;20(11):1112–6.
- [191] Flacker JM, Lipsitz LA. Large neutral amino acid changes and delirium in febrile elderly medical patients. *J Gerontol A Biol Sci Med Sci* 2000;55(5):B249–52; discussion B253–4.
- [192] Blum D, Maldonado J, Meyer E, et al. Delirium following abrupt discontinuation of fluoxetine. *Clin Neurol Neurosurg* 2008;110(1):69–70.
- [193] Black K, Shea C, Dursun S, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: proposed diagnostic criteria. *J Psychiatry Neurosci* 2000;25(3):255–61.
- [194] Fava M, Mulroy R, Alpert J, et al. Emergence of adverse events following discontinuation of treatment with extended-release venlafaxine. *Am J Psychiatry* 1997;154(12):1760–2.
- [195] Broderick PA, Gibson GE. Dopamine and serotonin in rat striatum during in vivo hypoxic-hypoxia. *Metab Brain Dis* 1989;4(2):143–53.
- [196] Freund HR, Fischer JE. The use of branched chain amino acids (BCAA) in acute hepatic encephalopathy. *Clin Nutr* 1986;5(3):135–8.
- [197] Freund HR, Muggia-Sullam M, LaFrance R, et al. Regional brain amino acid and neurotransmitter derangements during abdominal sepsis and septic encephalopathy in the rat. The effect of amino acid infusions. *Arch Surg* 1986;121(2):209–16.
- [198] Knell AJ, Davidson AR, Williams R, et al. Dopamine and serotonin metabolism in hepatic encephalopathy. *Br Med J* 1974;1(5907):549–51.
- [199] Harrison MJ, Marsden CD, Jenner P. Effect of experimental ischemia on neurotransmitter amines in the gerbil brain. *Stroke* 1979;10(2):165–8.
- [200] Shimizu-Sasamata M, Bosque-Hamilton P, Huang PL, Moskowitz MA, E.H. Lo. Attenuated neurotransmitter release and spreading depression-like depolarizations after focal ischemia in mutant mice with disrupted type I nitric oxide synthase gene. *J Neurosci* 1998;18(22):9564–71.
- [201] Zivin JA, Stashak J. The effect of ischemia on biogenic amine concentrations in the central nervous system. *Stroke* 1983;14(4):556–62.
- [202] Beisel W, Wannemacher RW, Neufeld HA. Relation of fever to energy expenditure. In: Kinney J, Lense E, editors. *Assessment of Energy Metabolism in Health and Disease*. Columbus (OH): Ross Laboratories; 2000. p. 144–50.
- [203] Fine A, Anderson NL, Rothstein TL, et al. Fas expression in pulmonary alveolar type II cells. *Am J Physiol* 1997;273(1 Pt 1):L64–71.
- [204] Kinney JM, Duke JH Jr, Long CL, et al. Tissue fuel and weight loss after injury. *J Clin Pathol Suppl (R Coll Pathol)* 1970;4:65–72.
- [205] McGee W, Veremakis C, Wilson GL. Clinical importance of tissue oxygenation and use to the mixed venous blood gas. *Res Medica* 1988;4(2):15–24.
- [206] Weissman C, Kemper M, Damask MC, et al. Effect of routine intensive care interactions on metabolic rate. *Chest* 1984;86(6):815–8.
- [207] Rossen R, Kabat H, Anderson JP. Acute arrest of cerebral circulation in man. *Arch Neurol Psychiatry* 1943;50:510–28.
- [208] Cole SL, Corday E. Four-minute limit for cardiac resuscitation. *J Am Med Assoc* 1956;161(15):1454–8.
- [209] Corday E, Rothenberg S, Weiner SM. Cerebral vascular insufficiency; an explanation of the transient stroke. *AMA Arch Intern Med* 1956;98(6):683–90.
- [210] Pena F, Ramirez JM. Hypoxia-induced changes in neuronal network properties. *Mol Neurobiol* 2005;32(3):251–83.

- [211] Harukuni I, Bhardwaj A. Mechanisms of brain injury after global cerebral ischemia. *Neurol Clin* 2006;24(1):1–21.
- [212] Basarsky TA, Feighan D, MacVicar BA. Glutamate release through volume-activated channels during spreading depression. *J Neurosci* 1999;19(15):6439–45.
- [213] Iijima T, Shimase C, Iwao Y, et al. Relationships between glutamate release, blood flow and spreading depression: real-time monitoring using an electroenzymatic dialysis electrode. *Neurosci Res* 1998;32(3):201–7.
- [214] Moghaddam B, Schenk JO, Stewart WB, et al. Temporal relationship between neurotransmitter release and ion flux during spreading depression and anoxia. *Can J Physiol Pharmacol* 1987;65(5):1105–10.
- [215] Somjen GG, Aitken PG, Balestrino M, et al. Extracellular ions, hypoxic irreversible loss of function and delayed postischemic neuron degeneration studied in vitro. *Acta Physiol Scand Suppl* 1989;582:58.
- [216] Somjen GG, et al. Spreading depression-like depolarization and selective vulnerability of neurons. A brief review. *Stroke* 1990;21(11 Suppl):III179–83.
- [217] Busto R, Dietrich WD, Globus MY, et al. Extracellular release of serotonin following fluid-percussion brain injury in rats. *J Neurotrauma* 1997;14(1):35–42.
- [218] Busto R, Globus MY, Dietrich WD, et al. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. *Stroke* 1989;20(7):904–10.
- [219] Globus MY, Alonso O, Dietrich WD, et al. Glutamate release and free radical production following brain injury: effects of posttraumatic hypothermia. *J Neurochem* 1995;65(4):1704–11.
- [220] Globus MY, Busto R, Dietrich WD, et al. Effect of ischemia on the in vivo release of striatal dopamine, glutamate, and gamma-aminobutyric acid studied by intracerebral microdialysis. *J Neurochem* 1988;51(5):1455–64.
- [221] Globus MY, et al. Intra-ischemic extracellular release of dopamine and glutamate is associated with striatal vulnerability to ischemia. *Neurosci Lett* 1988;91(1):36–40.
- [222] Globus MY, et al. Direct evidence for acute and massive norepinephrine release in the hippocampus during transient ischemia. *J Cereb Blood Flow Metab* 1989;9(6):892–6.
- [223] Globus MY, Busto R, Martinez E, et al. Ischemia induces release of glutamate in regions spared from histopathologic damage in the rat. *Stroke* 1990;21(11 Suppl):III43–6.
- [224] Globus MY, Wester P, Busto R, et al. Ischemia-induced extracellular release of serotonin plays a role in CA1 neuronal cell death in rats. *Stroke* 1992;23(11):1595–601.
- [225] Takagi K, Ginsberg MD, Globus MY, et al. Effect of hyperthermia on glutamate release in ischemic penumbra after middle cerebral artery occlusion in rats. *Am J Physiol* 1994;(5 Pt 2):267:H1770–6.
- [226] Siesjo BK. Cerebral circulation and metabolism. *J Neurosurg* 1984;60(5):883–908.
- [227] Kirsch JR, Diringner MN, Borel CO, et al. Brain resuscitation. Medical management and innovations. *Crit Care Nurs Clin North Am* 1989;1(1):143–54.
- [228] Choi DW. Calcium-mediated neurotoxicity: relationship to specific channel types and role in ischemic damage. *Trends Neurosci* 1988;11(10):465–9.
- [229] Choi DW, Weiss JH, Koh JY, et al. Glutamate neurotoxicity, calcium, and zinc. *Ann N Y Acad Sci* 1989;568:219–24.
- [230] Katayama Y, Kawamata T, Tamura T, et al. Calcium-dependent glutamate release concomitant with massive potassium flux during cerebral ischemia in vivo. *Brain Res* 1991;558(1):136–40.
- [231] Graham DG. Catecholamine toxicity: a proposal for the molecular pathogenesis of manganese neurotoxicity and Parkinson's disease. *Neurotoxicology* 1984;5(1):83–95.
- [232] Bertrand N, Bralet J, Beley A. Post-ischemic regional changes in acetylcholine synthesis following transient forebrain ischemia in gerbils. *Neurochem Res* 1992;17(4):321–5.

- [233] Hirsch JA, Gibson GE. Selective alteration of neurotransmitter release by low oxygen in vitro. *Neurochem Res* 1984;9(8):1039–49.
- [234] Hirsch JA, Gibson GE. Thiamin antagonists and the release of acetylcholine and norepinephrine from brain slices. *Biochem Pharmacol* 1984;33(14):2325–7.
- [235] Siesjo BK. Brain energy metabolism and catecholaminergic activity in hypoxia, hypercapnia and ischemia. *J Neural Transm* 1978;14(Suppl):17–22.
- [236] Seaman JS, Schillerstrom J, Carroll D, et al. Impaired oxidative metabolism precipitates delirium: a study of 101 ICU patients. *Psychosomatics* 2006;47(1):56–61.
- [237] Rosenberg J, Kehlet H. Postoperative mental confusion—association with postoperative hypoxemia. *Surgery* 1993;114(1):76–81.
- [238] Kim HC, Young T, Matthews CG, et al. Sleep-disordered breathing and neuropsychological deficits. A population-based study. *Am J Respir Crit Care Med* 1997;156(6):1813–9.
- [239] Grant I, Heaton RK, McSweeney AJ, et al. Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. *Arch Intern Med* 1982;142(8):1470–6.
- [240] Aakerlund LP, Rosenberg J. Postoperative delirium: treatment with supplementary oxygen. *Br J Anaesth* 1994;72(3):286–90.
- [241] Maekawa T, Fujii Y, Sadamitsu D, et al. Cerebral circulation and metabolism in patients with septic encephalopathy. *Am J Emerg Med* 1991;9(2):139–43.
- [242] Blomqvist P, Wieloch T. Ischemic brain damage in rats following cardiac arrest using a long-term recovery model. *J Cereb Blood Flow Metab* 1985;5(3):420–31.
- [243] Takemoto O, Tomimoto H, Yanagihara T. Induction of c-fos and c-jun gene products and heat shock protein after brief and prolonged cerebral ischemia in gerbils. *Stroke* 1995;26(9):1639–48.
- [244] Adams J, Brierley JB, Connor RC, et al. The effects of systemic hypotension upon the human brain. Clinical and neuropathological observations in 11 cases. *Brain* 1966;89(2):235–68.
- [245] Auer R, Benveniste H. Hypoxia and related conditions. In: Graham D, Lantos PL, editors. *Greenfield's Neuropathology*. New York: Oxford University Press; 1997. p. 263–314.
- [246] Margerison JH, Corsellis JA. Epilepsy and the temporal lobes. A clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes. *Brain* 1966;89(3):499–530.
- [247] Ng T, Graham DI, Adams JH, et al. Changes in the hippocampus and the cerebellum resulting from hypoxic insults: frequency and distribution. *Acta Neuropathol* 1989;78(4):438–43.
- [248] Gaudreau JD, Gagnon P. Psychotogenic drugs and delirium pathogenesis: the central role of the thalamus. *Med Hypotheses* 2005;64(3):471–5.
- [249] Sommer BR, Wise LC, Kraemer HC. Is dopamine administration possibly a risk factor for delirium? *Crit Care Med* 2002;30(7):1508–11.
- [250] Carmen JS, Wyatt RJ. Calcium and malignant catatonias. *Lancet* 1977;2(8048):1124–5.
- [251] Nagatsu T. Genes for human catecholamine-synthesizing enzymes. *Neurosci Res* 1991;12(2):315–45.
- [252] Balestrino M. Pathophysiology of anoxic depolarization: new findings and a working hypothesis. *J Neurosci Methods* 1995;59(1):99–103.
- [253] Katz IR. Oxygen dependence of dopamine-beta-hydroxylase activity and lactate metabolism in synaptosomes from rat brain. *Brain Res* 1982;231(2):399–409.
- [254] Pulsinelli WA, Duffy TE. Regional energy balance in rat brain after transient forebrain ischemia. *J Neurochem* 1983;40(5):1500–3.
- [255] Trouvin JH, Prioux-Guyonneau M, Cohen Y, et al. Rat brain monoamine metabolism and hypobaric hypoxia: a new approach. *Gen Pharmacol* 1986;17(1):69–73.
- [256] Miller R. Major psychosis and dopamine: controversial features and some suggestions. *Psychol Med* 1984;14(4):779–89.

- [257] Figiel GS, Krishnan KR, Doraiswamy PM. Subcortical structural changes in ECT-induced delirium. *J Geriatr Psychiatry Neurol* 1990;3(3):172–6.
- [258] Ongini E, Caporali MG, Massotti M. Stimulation of dopamine D-1 receptors by SKF 38393 induces EEG desynchronization and behavioral arousal. *Life Sci* 1985;37(24):2327–33.
- [259] Cassem N, Murray GB, Lafayette JM, et al. Delirious patients. In: Stern T, Fricchione GL, Cassem NH, Jellinek MS, Rosenbaum JF, Littleton MA, editors. *Massachusetts General Handbook of General Hospital Psychiatry*. Littleton (MA): PSG Publishing Co; 2004. p. 119–34.
- [260] Liptzin B, Levkoff SE. An empirical study of delirium subtypes. *Br J Psychiatry* 1992;161:843–5.
- [261] Pedrosa R, Soares-da-Silva P. Oxidative and non-oxidative mechanisms of neuronal cell death and apoptosis by L-3,4-dihydroxyphenylalanine (L-DOPA) and dopamine. *Br J Pharmacol* 2002;137(8):1305–13.
- [262] Globus MY, Ginsberg MD, Dietrich WD, et al. Substantia nigra lesion protects against ischemic damage in the striatum. *Neurosci Lett* 1987;80(3):251–6.
- [263] Weinberger J, Nieves-Rosa J, Cohen G. Nerve terminal damage in cerebral ischemia: protective effect of alpha-methyl-para-tyrosine. *Stroke* 1985;16(5):864–70.
- [264] Globus MY. Role of dopamine in ischemic neuronal damage. *Stroke* 1989;20(6):827–8.
- [265] Katayama Y, Tamura T, Becker DP, et al. Calcium-dependent component of massive increase in extracellular potassium during cerebral ischemia as demonstrated by microdialysis in vivo. *Brain Res* 1991;567(1):57–63.
- [266] Freeman GB, Mykityn V, Gibson GE. Differential alteration of dopamine, acetylcholine, and glutamate release during anoxia and/or 3,4-diaminopyridine treatment. *Neurochem Res* 1987;12(11):1019–27.
- [267] Reid AA, Monn JA, Jacobson AE, et al. Characterization of NMDA-coupled and dopamine reuptake carrier coupled [3H]-TCP binding sites in guinea pig brain. *NIDA Res Monogr* 1989;95:530–1.
- [268] Rothman SM, Olney JW. Excitotoxicity and the NMDA receptor—still lethal after eight years. *Trends Neurosci* 1995;18(2):57–8.
- [269] Rothman SM, Yamada KA, Lancaster N. Nordihydroguaiaretic acid attenuates NMDA neurotoxicity—action beyond the receptor. *Neuropharmacology* 1993;32(11):1279–88.
- [270] Rothman S. Synaptic release of excitatory amino acid neurotransmitter mediates anoxic neuronal death. *J Neurosci* 1984;4(7):1884–91.
- [271] Yamada KA, Rothman SM. Diazoxide blocks glutamate desensitization and prolongs excitatory postsynaptic currents in rat hippocampal neurons. *J Physiol* 1992;458:409–23.
- [272] Lopes da Silva FH, Witter MP, Boeijinga PH, et al. Anatomic organization and physiology of the limbic cortex. *Physiol Rev* 1990;70(2):453–511.
- [273] Bokesch PM, Izykenova GA, Justice JB, et al. NMDA receptor antibodies predict adverse neurological outcome after cardiac surgery in high-risk patients. *Stroke* 2006;37(6):1432–6.
- [274] Huda A, Guze BH, Thomas A, et al. Clinical correlation of neuropsychological tests with 1H magnetic resonance spectroscopy in hepatic encephalopathy. *Psychosom Med* 1998;60(5):550–6.
- [275] Weinberger DR. A connectionist approach to the prefrontal cortex. *J Neuropsychiatry Clin Neurosci* 1993;5(3):241–53.
- [276] Howard CD, Seifert CF. Flumazenil in the treatment of hepatic encephalopathy. *Ann Pharmacother* 1993;27(1):46–8.
- [277] Llansola M, Rodrigo R, Monfort P, et al. NMDA receptors in hyperammonemia and hepatic encephalopathy. *Metab Brain Dis* 2007;22(3-4):321–35.
- [278] Baldy-Moulinier M, Bories P. CBF and metabolism in hepatic encephalopathy: effects of acute hyperammonemia and of L. dopa. *Acta Neurol Scand Suppl* 1977;64:348–9.

- [279] Aggarwal S, Obrist W, Yonas H, et al. Cerebral hemodynamic and metabolic profiles in fulminant hepatic failure: relationship to outcome. *Liver Transpl* 2005;11(11):1353–60.
- [280] O'Beirne JP, Chouhan M, Hughes RD. The role of infection and inflammation in the pathogenesis of hepatic encephalopathy and cerebral edema in acute liver failure. *Nat Clin Pract Gastroenterol Hepatol* 2006;3(3):118–9.
- [281] Saksena S, Rai V, Saraswat VA, et al. Cerebral diffusion tensor imaging and in vivo proton magnetic resonance spectroscopy in patients with fulminant hepatic failure. *J Gastroenterol Hepatol* 2007, in press.
- [282] Strauss GI. The effect of hyperventilation upon cerebral blood flow and metabolism in patients with fulminant hepatic failure. *Dan Med Bull* 2007;54(2):99–111.
- [283] Strauss GI, Moller K, Larsen FS, et al. Cerebral glucose and oxygen metabolism in patients with fulminant hepatic failure. *Liver Transpl* 2003;9(12):1244–52.
- [284] Trzepacz PT, Tarter RE, Shah A, et al. SPECT scan and cognitive findings in subclinical hepatic encephalopathy. *J Neuropsychiatry Clin Neurosci* 1994;6(2):170–5.
- [285] Naegele T, Grodd W, Viebahn R, et al. MR imaging and (1)H spectroscopy of brain metabolites in hepatic encephalopathy: time-course of renormalization after liver transplantation. *Radiology* 2000;216(3):683–91.
- [286] Als-Nielsen B, Gluud LL, Gluud C. Benzodiazepine receptor antagonists for hepatic encephalopathy. *Cochrane Database Syst Rev* 2004;(2):CD002798.
- [287] Basile AS, Harrison PM, Hughes RD, et al. Relationship between plasma benzodiazepine receptor ligand concentrations and severity of hepatic encephalopathy. *Hepatology* 1994;19(1):112–21.
- [288] Butterworth RF. Hepatic encephalopathy: a neuropsychiatric disorder involving multiple neurotransmitter systems. *Curr Opin Neurol* 2000;13(6):721–7.
- [289] Butterworth RF. Neurotransmitter dysfunction in hepatic encephalopathy: new approaches and new findings. *Metab Brain Dis* 2001;16(1-2):55–65.
- [290] Ferenci P, Schafer DF, Kleinberger G, et al. Serum levels of gamma-aminobutyric-acid-like activity in acute and chronic hepatocellular disease. *Lancet* 1983;2(8354):811–4.
- [291] Aliyev NA, Aliyev ZN, Aliguliyev AR. Amino acid neurotransmitters in alcohol withdrawal. *Alcohol Alcohol* 1994;29(6):643–7.
- [292] Akaike N, Shirasaki T, Yakushiji T. Quinolones and fenbufen interact with GABAA receptor in dissociated hippocampal cells of rat. *J Neurophysiol* 1991;66(2):497–504.
- [293] Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000;342(20):1471–7.
- [294] Kudoh A, Takase H, Takahira Y, et al. Postoperative confusion increases in elderly long-term benzodiazepine users. *Anesth Analg* 2004;99(6):1674–8 [table of contents].
- [295] Tune LE, Bylsma FW. Benzodiazepine-induced and anticholinergic-induced delirium in the elderly. *Int Psychogeriatr* 1991;3(2):397–408.
- [296] Pain L, Jeltsch H, Lehmann O, et al. Central cholinergic depletion induced by 192 IgG-saporin alleviates the sedative effects of propofol in rats. *Br J Anaesth* 2000;85(6):869–73.
- [297] Wang Y, Kikuchi T, Sakai M, et al. Age-related modifications of effects of ketamine and propofol on rat hippocampal acetylcholine release studied by in vivo brain microdialysis. *Acta Anaesthesiol Scand* 2000;44(1):112–7.
- [298] Achermann P, Borbely AA. *Hum Neurobiol*. Dynamics of EEG slow wave activity during physiological sleep and after administration of benzodiazepine hypnotics 1987;6(3):203–10.
- [299] Borbely AA, Mattmann P, Loepfe M, et al. Effect of benzodiazepine hypnotics on all-night sleep EEG spectra. *Hum Neurobiol* 1985;4(3):189–94.
- [300] Qureshi A, Lee-Chiong T Jr. Medications and their effects on sleep. *Med Clin North Am* 2004;88(3):751–66, x.

- [301] Zhu H, Cottrell JE, Kass IS. The effect of thiopental and propofol on NMDA- and AMPA-mediated glutamate excitotoxicity. *Anesthesiology* 1997;87(4):944–51.
- [302] Crews FT, Morrow AL, Criswell H, et al. Effects of ethanol on ion channels. *Int Rev Neurobiol* 1996;39:283–367.
- [303] Nevo I, Hamon M. Neurotransmitter and neuromodulatory mechanisms involved in alcohol abuse and alcoholism. *Neurochem Int* 1995;26(4):305–36, discussion 337–42.
- [304] Tollefson GD. Serotonin and alcohol: interrelationships. *Psychopathology* 1989; 22(Suppl. 1):37–48.
- [305] Smith AJ, Brent PJ, Henry DA, et al. Plasma noradrenaline, platelet alpha 2-adrenoceptors, and functional scores during ethanol withdrawal. *Alcohol Clin Exp Res* 1990;14(4): 497–502.
- [306] Patkar AA, Gopalakrishnan R, Naik PC, et al. Changes in plasma noradrenaline and serotonin levels and craving during alcohol withdrawal. *Alcohol Alcohol* 2003;38(3):224–31.
- [307] Lovinger DM, White G, Weight FF. Ethanol inhibits NMDA-activated ion current in hippocampal neurons. *Science* 1989;243(4899):1721–4.
- [308] Lovinger DM, White G, Weight FF. NMDA receptor-mediated synaptic excitation selectively inhibited by ethanol in hippocampal slice from adult rat. *J Neurosci* 1990;10(4):1372–9.
- [309] Carta M, Ariwodola OJ, Weiner JL, et al. Alcohol potently inhibits the kainate receptor-dependent excitatory drive of hippocampal interneurons. *Proc Natl Acad Sci U S A* 2003;100(11):6813–8.
- [310] Lovinger DM, White G. Ethanol potentiation of 5-hydroxytryptamine₃ receptor-mediated ion current in neuroblastoma cells and isolated adult mammalian neurons. *Mol Pharmacol* 1991;40(2):263–70.
- [311] Davies M. The role of GABA_A receptors in mediating the effects of alcohol in the central nervous system. *J Psychiatry Neurosci* 2003;28(4):263–74.
- [312] Mihic SJ, Ye Q, Wick MJ, et al. Sites of alcohol and volatile anaesthetic action on GABA(A) and glycine receptors. *Nature* 1997;389(6649):385–9.
- [313] Kobayashi T, Ikeda K, Kojima H, et al. Ethanol opens G-protein-activated inwardly rectifying K⁺ channels. *Nat Neurosci* 1999;2(12):1091–7.
- [314] Walter HJ, Messing RO. Regulation of neuronal voltage-gated calcium channels by ethanol. *Neurochem Int* 1999;35(2):95–101.
- [315] Pirker S, Schwarzer C, Wieselthaler A, et al. GABA(A) receptors: immunocytochemical distribution of 13 subunits in the adult rat brain. *Neuroscience* 2000;101(4):815–50.
- [316] Rogawski MA. Update on the neurobiology of alcohol withdrawal seizures. *Epilepsy Curr* 2005;5(6):225–30.
- [317] Whittington MA, Lambert JD, Little HJ. Increased NMDA receptor and calcium channel activity underlying ethanol withdrawal hyperexcitability. *Alcohol Alcohol* 1995;30(1): 105–14.
- [318] Hoffman P, Grant KA, Snell LD, et al. NMDA receptors: role in ethanol withdrawal seizures. *Ann N Y Acad Sci* 1992;654:52–60.
- [319] Grant KA, Valverius P, Hudspeth M, et al. Ethanol withdrawal seizures and the NMDA receptor complex. *Eur J Pharmacol* 1990;176(3):289–96.
- [320] Hoffman P, Rabe CS, Grant KA, et al. Ethanol and the NMDA receptor. *Alcohol* 1990; 7(3):229–31.
- [321] Grant KA, Snell LD, Rogawski MA, et al. Comparison of the effects of the uncompetitive N-methyl-D-aspartate antagonist (±)-5-aminocarbonyl-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5,10-imine (ADCI) with its structural analogs dizocilpine (MK-801) and carbamazepine on ethanol withdrawal seizures. *J Pharmacol Exp Ther* 1992; 260(3):1017–22.
- [322] Faingold C, Li Y, Evans MS. Decreased GABA and increased glutamate receptor-mediated activity on inferior colliculus neurons in vitro are associated with susceptibility to ethanol withdrawal seizures. *Brain Res* 2000;868(2):287–95.

- [323] Fujimoto A, Nagao T, Ebara T, et al. Cerebrospinal fluid monoamine metabolites during alcohol withdrawal syndrome and recovered state. *Biol Psychiatry* 1983;18(10):1141–52.
- [324] Hawley RJ, Major LF, Schulman EA, et al. Cerebrospinal fluid 3-methoxy-4-hydroxyphe-nylglycol and norepinephrine levels in alcohol withdrawal. Correlations with clinical signs. *Arch Gen Psychiatry* 1985;42(11):1056–62.
- [325] Berggren U, Fahlke C, Norrby A, et al. Subensitive alpha-2-adrenoceptor function in male alcohol-dependent individuals during 6 months of abstinence. *Drug Alcohol Depend* 2000; 57(3):255–60.
- [326] Nutt D, Glue P, Molyneux S, et al. Alpha-2-adrenoceptor function in alcohol withdrawal: a pilot study of the effects of iv. clonidine in alcoholics and normals. *Alcohol Clin Exp Res* 1988;12(1):14–8.
- [327] Ballenger JC, Goodwin FK, Major LF, et al. Alcohol and central serotonin metabolism in man. *Arch Gen Psychiatry* 1979;36(2):224–7.
- [328] Krystal JH, Webb E, Cooney NL, et al. Serotonergic and noradrenergic dysregulation in alcoholism: m-chlorophenylpiperazine and yohimbine effects in recently detoxified alco-holics and healthy comparison subjects. *Am J Psychiatry* 1996;153(1):83–92.
- [329] Schwartz JC, et al. Histamine receptors in the brain: characterization by binding studies and biochemical effects. *Adv Biochem Psychopharmacol* 1980;21:169–82.
- [330] Schwartz JC, Arrang JM, Garbarg M, et al. Properties and roles of the three subclasses of histamine receptors in brain. *J Exp Biol* 1986;124:203–24.
- [331] White JM, Rumbold GR. Behavioural effects of histamine and its antagonists: a review. *Psychopharmacology (Berl)* 1988;95(1):1–14.
- [332] Sitter H, Lorenz W, Klotter HJ, et al. Elevated plasma histamine concentration as a sensi-tive real-time parameter for distinct phases of surgical trauma: a tool for technology assess-ment. *Agents Actions* 1991;33(1-2):203–7.
- [333] Adachi N, Oishi R, Saeki K. Changes in the metabolism of histamine and monoamines after occlusion of the middle cerebral artery in rats. *J Neurochem* 1991;57(1):61–6.
- [334] Fujitani T, Adachi N, Nagaro T, et al. Histaminergic H2 action protects hippocampal CA1 neurons by prolonging the onset of the anoxic depolarization in gerbils. *J Neurochem* 1996; 67(6):2613–5.
- [335] Koponen H, Reinikainen K, Riekkinen PJ. Cerebrospinal fluid somatostatin in delirium. II. Changes at the acute stage and at one year follow-up. *Psychol Med* 1990;20(3):501–5.
- [336] Koponen HJ, Leinonen E, Lepola U, et al. A long-term follow-up study of cerebrospinal fluid somatostatin in delirium. *Acta Psychiatr Scand* 1994;89(5):329–34.
- [337] Koponen H, Stenback U, Mattila E, et al. CSF beta-endorphin-like immunoreactivity in delirium. *Biol Psychiatry* 1989;25(7):938–44.
- [338] Koponen H, Riekkinen J. A longitudinal study of cerebrospinal fluid beta-endorphin-like immunoreactivity in delirium: changes at the acute stage and at one-year follow-up. *Acta Psychiatr Scand* 1990;82(4):323–6.
- [339] Inouye S, Viscoli CM, Horwitz RI, et al. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. *Ann Intern Med* 1993;119(6): 474–81.
- [340] Lawlor PG. Delirium and dehydration: some fluid for thought? *Support Care Cancer* 2002; 10(6):445–54.
- [341] Seymour DG, Henschke PJ, Cape RD, et al. Acute confusional states and dementia in the elderly: the role of dehydration/volume depletion, physical illness and age. *Age Ageing* 1980;9(3):137–46.
- [342] Wilson MM, Morley JE. Impaired cognitive function and mental performance in mild de-hydration. *Eur J Clin Nutr* 2003;57(Suppl. 2):S24–9.
- [343] Rolls BJ, Phillips PA. Aging and disturbances of thirst and fluid balance. *Nutr Rev* 1990; 48(3):137–44.
- [344] Silver AJ. Aging and risks for dehydration. *Cleve Clin J Med* 1990;57(4):341–4.

- [345] George J, Rockwood K. Dehydration and delirium—not a simple relationship. *J Gerontol A Biol Sci Med Sci* 2004;59(8):811–2.
- [346] Reyes-Ortiz CA. Dehydration, delirium, and disability in elderly patients. *Jama* 1997; 278(4):287–8.
- [347] Stiefel F. Delirium and dehydration: inevitable companions of terminal disease? *Support Care Cancer* 2002;10(6):443–4.
- [348] Miller DK, Perry HM 3rd, Morley JE. Nestle Nutr Workshop Ser Clin Perform Programme. Associations among the Mini Nutritional Assessment instrument, dehydration, and functional status among older African Americans in St. Louis, Mo., USA. 1999;1: 79–86.
- [349] Warren JL, Bacon WE, Harris T, et al. The burden and outcomes associated with dehydration among US elderly, 1991. *Am J Public Health* 1994;84(8):1265–9.
- [350] Gopinathan PM, Pichan G, Sharma VM. Role of dehydration in heat stress-induced variations in mental performance. *Arch Environ Health* 1988;43(1):15–7.
- [351] Cian C, Barraud PA, Melin B, et al. Effects of fluid ingestion on cognitive function after heat stress or exercise-induced dehydration. *Int J Psychophysiol* 2001;42(3):243–51.
- [352] Giltay EJ, Huijskes RV, Kho KH, et al. Psychotic symptoms in patients undergoing coronary artery bypass grafting and heart valve operation. *Eur J Cardiothorac Surg* 2006;30(1): 140–7.
- [353] Hiramatsu Y, Sakakibara Y, Mitsui T, et al. [Clinical features of hypernatremic hyperosmolar delirium following open heart surgery]. *Nippon Kyobu Geka Gakkai Zasshi* 1991; 39(10):1945–8 [Japanese].
- [354] Mattle H. [Neurologic manifestations of osmolality disorders]. *Schweiz Med Wochenschr* 1985;115(26):882–9 [German].
- [355] Aldemir M, Ozen S, Kara IH, et al. Predisposing factors for delirium in the surgical intensive care unit. *Crit Care* 2001;5(5):265–70.
- [356] Bartoli E, Castello L, Sainaghi PP. [Diagnosis and therapy of hyponatremia]. *Ann Ital Med Int* 2003;18(4):193–203 [Italian].
- [357] Chuang YF, Chiu YL, Hwang TJ, et al. Delirium and multiple electrolyte abnormalities associated with high dose paroxetine exposure. *Psychiatry Clin Neurosci* 2006;60(5): 642–3.
- [358] Croxson M, Lucas J, W. Bagg. Diluting delirium. *N Z Med J* 2005;118(1222):U1661.
- [359] Gunther A, Rauch M, Krumpelmann U, et al. [Hyponatraemic delirium as an early symptom of small-cell bronchial carcinoma]. *Nervenarzt* 2003;74(11):1016–9.
- [360] Ladino M, Guardiola VD, Paniagua M. Mirtazapine-induced hyponatremia in an elderly hospice patient. *J Palliat Med* 2006;9(2):258–60.
- [361] Huguenard P. [Delirium provoked by intravenous therapy without sodium.]. *Anesth Anal* 1956;13(3):592–7 [French].
- [362] Welti W. Delirium with low serum sodium. *AMA Arch Neurol Psychiatry* 1956;76(5): 559–64.
- [363] Rai A, Whaley-Connell A, McFarlane S, et al. Hyponatremia, arginine vasopressin dysregulation, and vasopressin receptor antagonism. *Am J Nephrol* 2006;26(6):579–89.
- [364] Zaluska M, Janota B, Papierska L. [Personality and behavioural disturbances, with delusional-hallucinatory and delirium episodes in the course of hyponatremia due to paraneoplastic inappropriate vasopressin secretion (SIADH)]. *Psychiatr Pol* 2006;40(6):1149–60 [Polish].
- [365] Elie M, Cole MG, Primeau FJ, et al. Delirium risk factors in elderly hospitalized patients. *J Gen Intern Med* 1998;13(3):204–12.
- [366] Marcantonio ER, et al. A clinical prediction rule for delirium after elective noncardiac surgery. *Jama* 1994;271(2):134–9.
- [367] Meyer JS, Fang HC, Denny-Brown D. Polarographic study of cerebral collateral circulation. *AMA Arch Neurol Psychiatry* 1954;72(3):296–312.

- [368] Gibbs FA, Williams D, Gibbs EL. Modification of the Cortical Frequency Spectrum by Changes in Carbon Dioxide, Blood Sugar, and Oxygen. *J Neurophysiol* 1940;3:49.
- [369] Itil T, Fink M. Anticholinergic drug-induced delirium: experimental modification, quantitative EEG and behavioral correlations. *J Nerv Ment Dis* 1966;143(6):492–507.
- [370] Engel GL, Webb JP, Ferris EB. Quantitative Electroencephalographic Studies of Anoxia in Humans; Comparison with Acute Alcoholic Intoxication and Hypoglycemia. *J Clin Invest* 1945;24(5):691–7.
- [371] Engel GL, Romano J, Ferris EB. Variations in the Normal Electroencephalogram During a Five-Year Period. *Science* 1947;105(2736):600–1.
- [372] Pro JD, Wells CE. The use of the electroencephalogram in the diagnosis of delirium. *Dis Nerv Syst* 1977;38(10):804–8.
- [373] Trzepacz PT, Meagher DJ, Lafayette JM, et al. Neuropsychiatric aspects of delirium. In: Yudofsky SC, Hales RE, editors. *Textbook of Neuropsychiatry*. Washington, DC: American Psychiatric Press; 2008. p. 445–518.
- [374] Koponen H. Electroencephalographic indices for diagnosis of delirium. *Int Psychogeriatr* 1991;3(2):249–51.
- [375] Jacobson SA, Leuchter AF, Walter DO. Conventional and quantitative EEG in the diagnosis of delirium among the elderly. *J Neurol Neurosurg Psychiatry* 1993;56(2):153–8.
- [376] Jacobson S, Leuchter AF, Walter DO, et al. Serial quantitative EEG among elderly subjects with delirium. *Biol Psychiatry* 1993;34(3):135–40.
- [377] Jacobson S, Jerrier H. EEG in delirium. *Semin Clin Neuropsychiatry* 2000;5(2):86–92.
- [378] Keane PE, Hall RC. The effect of acetylcholine and dopamine on the caudate spindle in cats. *J Neurosci Res* 1977;3(3):209–16.
- [379] Keane PE, Neal H. The effect of injections of dopaminergic agonists into the caudate nucleus on the electrocorticogram of the rat. *J Neurosci Res* 1981;6(2):237–41.
- [380] Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry* 1996;153(2):231–7.
- [381] Platt MM, Breitbart W, Smith M, et al. Efficacy of neuroleptics for hypoactive delirium. *J Neuropsychiatry Clin Neurosci* 1994;6(1):66–7.
- [382] Ikarashi Y, Takahashi A, Ishimaru H, et al. Regulation of dopamine D1 and D2 receptors on striatal acetylcholine release in rats. *Brain Res Bull* 1997;43(1):107–15.
- [383] Ikarashi Y, Takahashi A, Ishimaru H, et al. Suppression of cholinergic activity via the dopamine D2 receptor in the rat striatum. *Neurochem Int* 1997;30(2):191–7.
- [384] Maldonado J. Delirium in the Acute Care Setting: Characteristics, Diagnosis & Treatment. *Critical Care Clinics* 2008;24:657–720.
- [385] Kleinschmidt S, Ziegeler S, Bauer C. [Cholinesterase inhibitors. Importance in anaesthesia, intensive care medicine, emergency medicine and pain therapy]. *Anaesthesist* 2005;54(8):791–9 [German].
- [386] Moretti R, Torre P, Antonello RM, et al. Cholinesterase inhibition as a possible therapy for delirium in vascular dementia: a controlled, open 24-month study of 246 patients. *Am J Alzheimer's Dis Other Demen* 2004;19(6):333–9.
- [387] Dautzenberg PL, Mulder LJ, Rikkert Olde, et al. Delirium in elderly hospitalised patients: protective effects of chronic rivastigmine usage. *Int J Geriatr Psychiatry* 2004;19(7):641–4.
- [388] Liptzin B, Laki A, Garb JL, et al. Donepezil in the prevention and treatment of post-surgical delirium. *Am J Geriatr Psychiatry* 2005;13(12):1100–6.
- [389] Sampson EL, Raven PR, Ndhlovu PN, et al. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. *Int J Geriatr Psychiatry* 2007;22(4):343–9.
- [390] Baraka A, Harik S. Reversal of central anticholinergic syndrome by galanthamine. *Jama* 1977;238(21):2293–4.

- [391] Burt T. Donepezil and related cholinesterase inhibitors as mood and behavioral controlling agents. *Curr Psychiatry Rep* 2000;2(6):473–8.
- [392] Fisher RS, Bortz JJ, Blum DE, et al. A Pilot Study of Donepezil for Memory Problems in Epilepsy. *Epilepsy Behav* 2001;2(4):330–4.
- [393] Gleason OC. Donepezil for postoperative delirium. *Psychosomatics* 2003;44(5):437–8.
- [394] Hori K, Tominaga I, Inada T, et al. Donepezil-responsive alcohol-related prolonged delirium. *Psychiatry Clin Neurosci* 2003;57(6):603–4.
- [395] Kaufer DI, Catt KE, Lopez OL, et al. Dementia with Lewy bodies: response of delirium-like features to donepezil. *Neurology* 1998;51(5):1512.
- [396] Logan CJ, Stewart JT. Treatment of post-electroconvulsive therapy delirium and agitation with donepezil. *J Ect* 2007;23(1):28–9.
- [397] Moretti R, Torre P, Antonello RM, et al. Rivastigmine in frontotemporal dementia: an open-label study. *Drugs Aging* 2004;21(14):931–7.
- [398] Noyan MA, Elbi H, Aksu H. Donepezil for anticholinergic drug intoxication: a case report. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;27(5):885–7.
- [399] Palmer TR. Donepezil in advanced dementia, or delirium? *J Am Med Dir Assoc* 2004;5(1):67.
- [400] Slatkin N, Rhiner M. Treatment of opioid-induced delirium with acetylcholinesterase inhibitors: a case report. *J Pain Symptom Manage* 2004;27(3):268–73.
- [401] Wengel SP, Burke WJ, Roccaforte WH. Donepezil for postoperative delirium associated with Alzheimer's disease. *J Am Geriatr Soc* 1999;47(3):379–80.
- [402] Wengel SP, Roccaforte WH, Burke WJ. Donepezil improves symptoms of delirium in dementia: implications for future research. *J Geriatr Psychiatry Neurol* 1998;11(3):159–61.
- [403] van den Blik BM, Maas HA. [Successful treatment of three elderly patients suffering from prolonged delirium using the cholinesterase inhibitor rivastigmine]. *Ned Tijdschr Geneesk* 2004;148(43):2149. [author reply 2149] [Dutch].
- [404] Kalisvaart K, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *J Am Geriatr Soc* 2005;53(10):1658–66.
- [405] Skrobik YK, Bergeron N, Dumont M, et al. Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive Care Med* 2004;30(3):444–9.
- [406] Globus MY, Ginsberg MD, Harik SI, et al. Role of dopamine in ischemic striatal injury: metabolic evidence. *Neurology* 1987;37(11):1712–9.
- [407] Lonergan E, Britton AM, Luxenberg J, et al. Antipsychotics for delirium. *Cochrane Database Syst Rev* 2007;(2):CD005594.
- [408] Ozbolt LB, Paniagua MA, Kaiser RM. Atypical antipsychotics for the treatment of delirious elders. *J Am Med Dir Assoc* 2008;9(1):18–28.
- [409] Schrader SL, Wellik KE, Demaerschalk BM, et al. Adjunctive haloperidol prophylaxis reduces postoperative delirium severity and duration in at-risk elderly patients. *Neurologist* 2008;14(2):134–7.
- [410] Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. *Anaesth Intensive Care* 2007;35(5):714–9.
- [411] Larsen KA, Kelly S, Stern TA. A double-blind, randomized, placebo-controlled study of peri-operative administration of olanzapine to prevent post-operative delirium in joint replacement patients. Presented at the Annual Meeting of the Academy of Psychosomatic Medicine. Amalia Island, FL: 2007.
- [412] Bhardwaj A, Brannan T, Martinez-Tica J, et al. Ischemia in the dorsal hippocampus is associated with acute extracellular release of dopamine and norepinephrine. *J Neural Transm Gen Sect* 1990;80(3):195–201.
- [413] Maldonado J, van der Starre P, Wysong A, et al. Dexmedetomidine: Can it reduce the incidence of ICU delirium in postcardiotomy patients? *Psychosomatics* 2004;45(2):173.

- [414] Engelhard K, Werner C, Kaspar S, et al. Effect of the alpha2-agonist dexmedetomidine on cerebral neurotransmitter concentrations during cerebral ischemia in rats. *Anesthesiology* 2002;96(2):450–7.
- [415] Jalonen J, Hynynen M, Kuitunen A, et al. Dexmedetomidine as an anesthetic adjunct in coronary artery bypass grafting. *Anesthesiology* 1997;86(2):331–45.
- [416] Engelhard K, Werner C, Eberspacher E, et al. The effect of the alpha 2-agonist dexmedetomidine and the N-methyl-D-aspartate antagonist S(+)-ketamine on the expression of apoptosis-regulating proteins after incomplete cerebral ischemia and reperfusion in rats. *Anesth Analg* 2003;96(2):524–31. [table of contents].
- [417] Bayindir O, Guden M, Akpinar B, et al. Ondansetron hydrochloride for the treatment of delirium after coronary artery surgery. *J Thorac Cardiovasc Surg* 2001; 121(1):176–7.
- [418] Jolipo V, Hermenegildo C, Montoliu C, et al. Neurotoxicity of ammonia and glutamate: molecular mechanisms and prevention. *Neurotoxicology* 1998;19(4-5): 675–81.
- [419] Jolkkonen J, Puurunen K, Koistinaho J, et al. Neuroprotection by the alpha2-adrenoceptor agonist, dexmedetomidine, in rat focal cerebral ischemia. *Eur J Pharmacol* 1999;372(1): 31–6.
- [420] Rossberg M, Bhardwaj A, Hurn PD, et al. Principles of cerebroprotection. In: Murray M, Coursin DB, Pearl RG, et al, editors. *Critical care medicine: perioperative management*. Philadelphia: Lipincott Williams & Williams; 2002. p. 225–35.
- [421] Chandler MC, Barnhill JL, Gualtieri CT. Amantadine for the agitated head-injury patient. *Brain Inj* 1988;2(4):309–11.
- [422] Eddy K, Larsson J, Eek M, et al. Amantadine treatment of a patient with anoxic brain injury. *Childs Nerv Syst* 1995;11(10):607–9.
- [423] Van Reekum R, Bayley M, Garner S, et al. N of 1 study: amantadine for the amotivational syndrome in a patient with traumatic brain injury. *Brain Inj* 1995;9(1):49–53.
- [424] Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. *Jama* 1997;278(2): 144–51.
- [425] Cronin AJ, Keifer JC, Davies MF, et al. Postoperative sleep disturbance: influences of opioids and pain in humans. *Sleep* 2001;24(1):39–44.
- [426] Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism—an overview. *Postgrad Med J* 1985;61(Suppl. 3):45–50.
- [427] Concas A, Santoro G, Mascia MP, et al. The general anesthetic propofol enhances the function of gamma-aminobutyric acid-coupled chloride channel in the rat cerebral cortex. *J Neurochem* 1990;55(6):2135–8.
- [428] Sanna E, Garau F, Harris RA. Novel properties of homomeric beta 1 gamma-aminobutyric acid type A receptors: actions of the anesthetics propofol and pentobarbital. *Mol Pharmacol* 1995;47(2):213–7.
- [429] Ebert TJ, Muzi M. Propofol and autonomic reflex function in humans. *Anesth Analg* 1994; 78(2):369–75.
- [430] Yang J, Isenberg KE, Zorumski CF. Volatile anesthetics gate a chloride current in postnatal rat hippocampal neurons. *FASEB J* 1992;6(3):914–8.
- [431] Nicoll RA, Wojtowicz JM. The effects of pentobarbital and related compounds on frog motoneurons. *Brain Res* 1980;191(1):225–37.
- [432] Study RE, Barker JL. Diazepam and (–)-pentobarbital: fluctuation analysis reveals different mechanisms for potentiation of gamma-aminobutyric acid responses in cultured central neurons. *Proc Natl Acad Sci U S A* 1981;78(11):7180–4.
- [433] Bourne RS, Mills GH. Melatonin: possible implications for the postoperative and critically ill patient. *Intensive Care Med* 2006;32(3):371–9.

- [434] Hanania M, Kitain E. Melatonin for treatment and prevention of postoperative delirium. *Anesth Analg* 2002;94(2):338–9. [table of contents].
- [435] Abu-Shahwan I, Chowdary K. Ketamine is effective in decreasing the incidence of emergence agitation in children undergoing dental repair under sevoflurane general anesthesia. *Paediatr Anaesth* 2007;17(9):846–50.