Pathophysiology of Delirium

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ABSTRACT

Hypotheses about the pathophysiology of delirium are speculative and largely based on animal research. According to the neurotransmitter hypothesis, decreased oxidative metabolism in the brain causes cerebral dysfunction due to abnormalities of various neurotransmitter systems. Reduced cholinergic function, excess release of dopamine, norepinephrine, and glutamate, and both decreased and increased serotonergic and γ-aminobutyric acid activity may underlie the different symptoms and clinical presentations of delirium. According to the inflammatory hypothesis, increased cerebral secretion of cytokines due to a wide range of physically stressful events plays an important role in the occurrence of delirium. Since cytokines can influence the activity of various neurotransmitter systems, these mechanisms may interact. Also, more fundamental processes like intraneuronal signal transduction, second messenger systems that at the same time use neurotransmitters as first messengers and play an important role in their synthesis and release, may be disturbed. Furthermore, severe illness and physiologic stress may give rise to modification of blood-brain barrier permeability, the sick euthyroid syndrome with abnormalities of thyroid hormone concentrations, and increased activity of the hypothalamic-pituitary-adrenal axis. These circumstances possibly also contribute to changes in neurotransmitter synthesis and release of cytokines in the brain, and consequently to the occurrence of delirium. Elderly patients are more at risk for developing delirium,very likely due to age-related cerebral changes in stress-regulating neurotransmitter and intracellular signal transduction systems. This paper will expand upon these current theories and discuss their applicability to research and clinical work with elderly patients suffering from delirium. (*J Geriatr Psychiatry Neurol* 1998; 11:138–145).

A broad spectrum of clinical problems may contribute to the development of delirium, suggesting common metabolic and neuronal final pathways in the brain.[1] Advanced age, pre-existing cognitive impairment, severe illness and poor functional status, psychoactive medications, metabolic disturbances, infection and fever, alcohol abuse, and vision and hearing impairment are the main risk factors for delirium in surgical and nonsurgical elderly patients.[2–6] It is possible that age-related cerebral changes in stress-regulating neurotransmitter and second messenger systems contribute to the higher incidence of delirium in elderly patients.[1,7,8] Mechanisms related to Alzheimer's disease, an important risk factor for delirium, may also be involved.[1] It is also possible that disturbances associated with severe illness and surgery may exist, such as the presence of an euthyroid sick syndrome, or low T3 syndrome,[9] altered permeability of the blood-brain barrier,[10] and increased hypothalamic-pituitary-adrenal (HPA) axis activity.[2] These circumstances may be associated with changes in neurotransmission, intraneuronal signal transduction by the second messenger systems, and secretion of cytokines in the brain, directly or indirectly. Expression may take place in certain neuroanatomical areas and neurotransmitter systems that represent final common pathways for the otherwise diverse etiologies of delirium.[11,12]

The focus of this article will be to review the various cerebral metabolic and neurochemical changes that may lead to delirium. First, the effects of the diverse etiologies of delirium on brain neurochemistry will be examined. Second, the impact on delirium of the physiologic stressors associated with severe illness itself will be discussed. Third, the known age-related changes in the human brain that render the elderly more vulnerable to delirium will be described. In conclusion, an attempt will be made to use these findings to suggest areas for further clinical research.

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NEUROTRANSMITTER HYPOTHESIS OF DELIRIUM

Different neurotransmitter systems in the brain may be important in the various symptoms and clinical presentations of delirium, and more than one pathophysiologic mechanism may be involved.[8,11,13] Widespread reduction of cerebral oxidative metabolism is an important factor supposed to underlie alterations of neurotransmitter availability and function.[8] The development of delirium may be related to circumstances interfering with the cerebral oxidative metabolism and the metabolism of neurotransmitters, such as a lack of oxygen, glucose, or amino acids; altered cerebral blood flow; increased permeability of the blood-brain barrier; toxins; hyper- or hypothermia; damage of cell membranes; thiamine and niacin deficiency; and deficient synthesis and blockade of certain neurotransmitters.[7] Animal models of delirium have shown important effects of hypoxia, ischemia, hypoglycemia, and deficiencies of thiamine and niacin on the synthesis and release of several neurotransmitters.[1] The relationship of specific neurotransmitters to potential etiologies of delirium will be explored below.

Delirium and Cholinergic Dysfunction

The cholinergic neurotransmitter system is widely represented throughout the brain and is thought to be involved in several functions known to be dysregulated in delirium, such as arousal, attention, memory processes, and REM sleep.[1,7,8,13] Reduced cholinergic activity in the brain has been suggested as the "final common pathway" of delirium because the central cholinergic system is particularly vulnerable to metabolic insults such as diminished availability of glucose and oxygen.[1] It appears that the primary problem is less an overall impairment of energy production than an issue of substrate deficiency, as only small quantities of adenosine triphosphate (ATP) are needed for the synthesis of neurotransmitters.[13] The synthesis of acetylcholine is particularly at risk, as its precursor, acetyl coenzyme A, is also an important rate-limiting step in the oxygen- and glucose-demanding citric acid cycle (Fig. 1).

The acetyl group of acetyl coenzyme A and acetylcholine is derived from the oxidation of glucose and pyruvate, and carbohydrate catabolism, oxidative processes, and acetylcholine synthesis are closely linked.[1] Reduced synthesis of acetylcholine due to hypoxic hypoxia, anemic hypoxia, histotoxic hypoxia, and hypoglycemia occurs without alterations in its levels, but with a diminished release and activity of acetylcholine.[1] Thiamine deficiency negatively affects the turnover of acetylcholine and interferes with cerebral oxidative metabolism, leading to selective cell death in animals. Deficiency of choline and niacin is another cause of decreased synthesis of acetylcholine.[1,14]

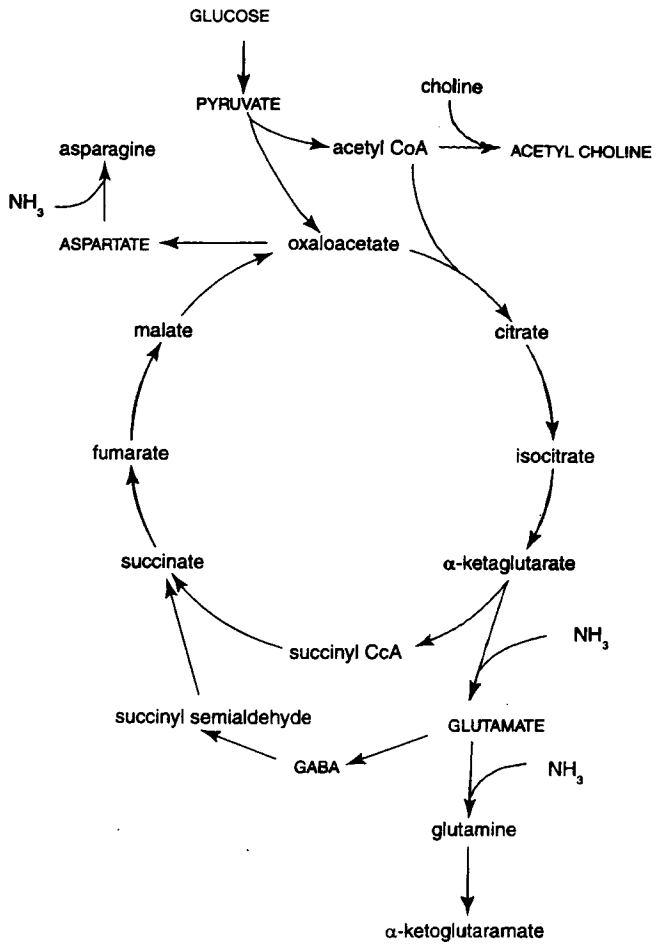

Figure 1. The citric acid cycle.

In humans, anticholinergic drugs that can cross the blood-brain barrier are well known to be able to induce delirium. A clear association has been found between elevated anticholinergic activity in serum, plasma, and cerebrospinal fluid (CSF) on the one hand and cognitive impairment and delirium on the other, especially in elderly medical patients.[1,7,8,13,15–19] Anticholinergic delirium can be reversed with physostigmine.[7]

Thus, decreased synthesis of acetylcholine and cholinergic neurotransmission due to deficiency of oxygen, glucose, acetyl coenzyme A, choline, thiamine, and niacine and blockade of acetylcholine release or postsynaptic receptors by drugs may be an important pathophysiologic mechanism contributing to the occurrence of delirium, especially in the elderly and patients with dementia whose cholinergic systems are already less functional.[1,20]

Delirium and Monaminergic Dysfunction

The principal monoamine neurotransmitters in the brain are the catecholamines dopamine and norepinephrine and the indolamine serotonin. They are all implicated in the control of the sleep-wake cycle and arousal, both of which are disturbed in delirium. Cholinergic mechanisms

subserve attention, while selectively inhibiting automatic motivational and affective responses to stimuli that are mediated by the monoaminergic arousal system.[13]

Serotonergic neurons projecting from the midbrain raphe nuclei of the brain stem to widespread areas of the cerebral cortex are involved in functions such as aggressive and impulsive behavior, mood, and motor activity that may be disturbed in delirium.[8] Serotonin has also been implied to have a role in the development of psychosis and delirium. Both dopamine and serotonin agonists can induce psychosis,[21] serotonin-blocking drugs appear to have a therapeutic effect in schizophrenia,[22] and excess serotonin in the brain has been related to the development of the serotonin syndrome.[23] Elevated serotonergic activity due to the concomitant use of selective serotonin reuptake inhibitors or tryptophan, as well as monoamine oxidase inhibitors, can produce this disorder, of which delirium is a main symptom.[23] On the other hand, postoperative delirium has been associated with reduced cerebral availability of tryptophan from plasma, suggesting reduced serotonergic function.[2,24,25]

Increased dopaminergic release and neurotransmission are known to cause psychotic disturbances, and antipsychotic medications that block dopamine receptors may relieve psychotic symptoms frequently seen in delirium.[26,27] Opiates have glutamatergic, anticholinergic, and dopaminergic properties, all of which may relate to their association with delirium.[28]

Noradrenergic neurons project from the locus ceruleus, which plays a role in the modulation of attention, anxiety, and mood, to widespread areas of the cerebral cortex, thalamus, and hypothalamus.[26,27] Although both the synthesis and degradation of monoamines require oxygen, during stress the dependency of monoamine synthesis on oxygen availability is abolished. Thus, while hypoxia itself does not greatly alter the release of noradrenaline and serotonin, it does increase extracellular dopamine. Excess extracellular dopamine may foster cell death and cause the psychotic symptoms of delirium.[1] It is postulated that an imbalance of cholinergic and noradrenergic systems underlies the delirium caused by anticholinergic drugs. This hypothesis is supported by the observation that anoxia leads to increased extracellular dopamine levels, whereas the release of acetylcholine decreases.[1]

Delirium, Cerebral γ-Aminobutyric Acid, and Glutamate

Only a small proportion of the neurons in the brain are cholinergic or monoaminergic.The most prevalent cerebral neurotransmitters are γ-aminobutyric acid (GABA), a major inhibitory neurotransmitter, and its amino acid precursor glutamate, a major excitatory neurotransmitter. GABA and glutamate, stimulating almost any neuron, are closely involved with the energy-producing citric cycle and, consequently, are very vulnerable to metabolic disturbances.[27] For example, hypoxia decreases the incorporation of glucose into glucose-derived amino acids such as glutamate and GABA, as well as acetylcholine.[1]

Glutamate has been associated with psychotic phenomena.[1,11] In the presence of glutamate, calcium channels open, calcium enters into the cell, and the neuron is prepared for neurotransmission. Processes like hypoxia and thiamine defiency that trigger excessive glutamate (*N*-methyl-D-aspartate, NMDA, subtype) activity are associated with neurodegeneration.[27] Increased glutamatergic neurotransmission induces excessive calcium flux into the cell that activates enzymes producing free radicals. These free radicals destroy other chemicals and cellular components, particularly membranes and energy-producing mitochondria. This excitotoxic mechanism may play a role in neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, stroke, and Huntington's disease,[1,27] and possibly as well in delirium. NMDA receptor antagonists, calcium channel blockers, and antioxidants may theoretically act as neuroprotective agents, but further research is necessary.[27]

Histamine and Delirium

Histamine seems to be an important neurotransmitter in normal arousal as is demonstrated by the sedative effects of H1 antagonist antihistamines.[8,28] H1 and H2 antagonists are associated with delirium, especially in the elderly, which may, however, also be due to their anticholinergic properties. The exact relevance of disturbances in histamine function to delirium is unknown.[8]

Clinical Examples of Neurotransmitter Imbalance

Hepatic Encephalopathy. Hepatic encephalopathy (HE) is a form of delirium that may be partially caused by decreased acetylcholine synthesis. Acetyl coenzyme A that is necessary for the synthesis of acetylcholine is diverted into the citric acid cycle because there is an increased conversion of α-ketoglutarate into glutamate and glutamine caused by enhanced cerebral ammonia in HE (see Fig. 1).[13] In this way, HE interferes with the citric acid cycle and affects synthesis of various neurotransmitters among which is acetylcholine.

As a consequence of impaired hepatic oxidative deamination, levels of tyrosine, phenylalanine, and tryptophan are increased, giving rise to the enhanced synthesis of, respectively, dopamine and serotonin in the brain. In addition, the excess of cerebral glutamine due to increased ammonia may further stimulate tryptophan uptake in the brain[29] and, thereby, enhance the synthesis of serotonin (see Fig. 1). The increased activity of serotonin may be partly responsible for the clinical picture of HE, which resembles the serotonin syndrome.[23] Thus, excess dopamine synthesis and dysfunction of the serotonergic system may also play a role in HE.[11,23]

Furthermore, increased GABAergic activity has been associated with the hypoalert-hypoactive clinical picture of HE.[1,8,11] GABA is produced by the gut flora and is normally prevented from reaching the brain by liver metabolism and the blood-brain barrier. In liver failure, as is the case in HE, GABA enters the systemic circulation, possibly due to increased blood-brain barrier permeability, and induces neuronal inhibition in the brain. This may result in the hypoalertness and hypoactivity seen in HE.[11,13] However, in contrast with this hypothesis, in patients with HE, normal concentrations of GABA have been found in postmortem brain tissue, as well as normal numbers of GABA-benzodiazepine-receptor complexes.[30]

Alcohol Withdrawal Delirium. Alcohol withdrawal delirium has been associated with monoaminergic dysfunction, in particular of norepinephrine and serotonin. Increased α-adrenergic receptor sensitivity and enhanced noradrenergic activity have been implicated in some of the core characteristics of alcohol withdrawal delirium such as hyperalertness, hyperactivity, and overactivity of the sympathetic nervous system.[7,8] The electrocardiographic changes observed in alcohol withdrawal delirium differ from those found in delirium due to other etiologies, suggesting different pathophysiologic mechanisms.[7,8]

Inhibited cerebral serotonergic function may play a role in alcohol withdrawal delirium, as chronic alcoholism may lead to reduced cerebral availability of its precursor tryptophan from plasma. This may be due to nutritional deficiencies and metabolic derangement, since alcohol itself enhances the metabolism of tryptophan in the liver, thereby decreasing the availability of tryptophan for the brain.[31] This process may be further stimulated by the elevated levels of corticosteroids, which can occur under stressful circumstances such as delirium.[32]

Withdrawal of alcohol (and benzodiazepines) has been related to transient reduced GABA inhibitory function as well.[27] The GABA receptor is a postsynaptic receptor complex with separate receptors for GABA, benzodiazepines, barbiturates, and perhaps alcohol.[27] Benzodiazepines, and possibly alcohol, enhance GABA inhibitory activity by increasing GABA receptor binding.[27] Withdrawal of alcohol, which may result in hyperalert-hyperactive delirium, may be associated with reduced GABAergic activity.[7,27] Thus, alcohol withdrawal delirium may be the result of imbalanced neurotransmission caused by overactivity of the noradrenergic system, decreased function of the serotonergic system, and reduced GABA inhibitory function.

Parkinson's Disease. In humans, chronic levodopa treatment for Parkinson's disease may give rise to serious sleep and psychotic disturbances. In Parkinson's patients, these disturbances are related to the dose and duration of levodopa therapy, as well as to concurrent cerebral atrophy.[7,33] Next to increased mesolimbic dopaminergic activity, altered serotonergic function may contribute to delirium, as levodopa reduces plasma and brain levels of its precursor tryptophan by competing with tryptophan for uptake from the gut and at the blood-brain barrier.[33] The initially reduced serotonergic activity would, at a later stage of the disease and duration of treatment with levodopa, be followed by sensitization and increased activity of the serotonin receptors.[33] The inconclusive results of supplementation with tryptophan and 5-hydroxytryptophan in Parkinson's patients may be explained by the different stages of the disease and the treatment duration with levodopa.[34]

Delirium and Abnormalities in Glucocorticoids and Endorphins

Cortisol is an important stress hormone that has modulating effects on both the limbic system and the immune system.[35] It also inhibits the release of thyroid stimulating hormone (TSH). Abnormalities in corticosteroids may account for a variety of alterations of behavior and cognition, including delirium, possibly due to their influence on neurotransmitter systems in the brain.[36–38]

Dysfunction of β-endorphins, which are endogenous substances having the pharmacologic properties of morphine, appears to increase susceptibility to delirium, but the evidence to date is sparse and inconsistent.[2] Plasma cortisol and β-endorphin levels have been described to become elevated after surgery in association with delirium in one preliminary study.[39]

Delirium, Second Messenger Systems, and Calcium Homeostasis

The different etiologies of delirium may affect neurotransmitter systems in a variety of ways; thus, more fundamental processes such as the intraneuronal second messenger systems are likely involved as mediators.[1,27] Neurotransmitters released in the synaptic cleft act as first messengers that give off their message to a group of specialized intracellular molecules, the second messengers, by way of the postsynaptic neurotransmitter receptor.[27] Second messengers are intracellular signal-transducing systems involving G proteins, the nucleotides adenosine monophosphate and guanosine monophosphate, phosphatidylinositol, calcium, and protein phosphorylation. They can modify the excitability of the neuron and also send their information to the nucleus of the cell and the DNA, thus influencing the synthesis of proteins.[40] Furthermore, they may impact upon the rates of synthesis of enzymes that can alter the amount of neurotransmitter available for neurotransmission.[27]

The calcium ion is an important regulator of neuronal excitability. At a normal rate, calcium flux through ion channels of the neuron modifies neuronal excitability but is not damaging to the neuron. However, due to toxins

and neurodegenerative processes such as excess glutamate and dopamine release, calcium influx may become too abundant, leading to irreversible damage and finally to cell death.[27] Cerebral calcium homeostasis is linked intimately to the activity of first and second messenger systems, and altered cellular calcium homeostasis may be important in the pathophysiology of aging and Alzheimer's disease, in which decreasing calcium transport in vitro has been found.[1,27] Furthermore, both low and high calcium levels have been associated with psychosis and delirium.[1,7] In vitro, hypoxia diminishes calcium uptake both into the cell and the mitochondria. Increases in glutamate and dopamine release induced by hypoxia and decreases in acetylcholine release are all associated with alterations in calcium metabolism.[1]

INFLAMMATORY HYPOTHESIS OF DELIRIUM

There is a strong inter-relationship between the immune system and the central nervous system (CNS).[41,42] Cytokines are polypeptides that can be secreted by macrophages. Cytokines, like the interleukins (among which IL-1, IL-2, IL-6), interferon-α (IF-α), and tumor necrosis factor (TNF), have an important role in immune activation. They are transported into the CNS, activate glia cells to produce other cytokines, and are released from activated glia cells under stressful circumstances.[41,42] In normal circumstances, the extracellular level in the CNS is low.[41,42] Cytokines may directly or indirectly influence both hormone regulation through the HPA axis and cerebral neurotransmission.They may influence the activity of catecholaminergic, serotonergic, GABAergic, and cholinergic neurotransmitters systems and cause increased release of dopamine and norepinephrine and reduced acetylcholine release.[41–43]

According to the inflammatory hypothesis, cytokines have a major role in the pathogenesis of delirium, not only from inflammatory and infectious causes but also due to surgery and other stressors.[10,28,44] Tissue injury and inflammatory responses give rise to the release of cytokines, modification of the blood-brain barrier, and interference with neurotransmitter synthesis and neurotransmission.[10,28,41–43] Interleukin-1 is involved in thermogenesis, induction of slow-wave sleep, and release of pituitary hormones such as the corticosteroids, and is released following a wide range of infectious, inflammatory, and toxic insults to the body.[13] Furthermore, treatment with cytokines like IFN-α, IL-2, and lymphokine-activated killer cells may cause dose-dependent cognitive, emotional, and behavioral disturbances, including delirium,[41,45,46] and pathophysiology of Alzheimer's disease, an important risk factor for delirium, has been associated with an increase of circulating IL-6 and immune activation.[47]

Cytokine immune regulation may also be influenced by neuronal processes. Norepinephrine has been demonstrated to stimulate activated astrocytes to produce IL-6.[41] Thus, the activation of cytokines due to diverse physiologic circumstances may be central to the underlying pathophysiologic mechanisms of delirium.

Severe Illness and Thyroid Hormone Metabolism

It is known that physiologic stressors such as severe systemic illness, starvation, major accidental and surgical trauma, and the use of certain medications may be accompanied by abnormal thyroid hormone concentrations in the absence of clinically evident thyroid illness.[9,48–50] This "euthyroid sick syndrome" is characterized by low triiodothyronine (T3) and is often accompanied by elevated levels of the inactive metabolite of thyroxine, reverse T3 (rT3), as well as normal or decreased total thyroxine (T4) and TSH levels. The degree of thyroid hormone change is dependent on the severity of disease.[48] Low levels of thyroid hormones predict poor prognosis in several illnesses and, in critically ill patients, low serum T4 correlates, with the probability that the patient will die.[48,50] During aging, the decline in serum T3 (euthyroid sick syndrome) may be more prominent due to the frequency of medical problems with advanced age and the increased use of medication in that population.[51,52]

For example, in a study performed by van der Mast among 296 patients (mean age = 63 years, age range = 26–83 years) undergoing cardiac surgery, the ratio of inactive thyroid hormone-rT3-/active thyroid hormone-T3-, a measure for physiologic stress, increased significantly for all patients, and more so for postoperatively delirious patients, who were all over 60 years of age.[2]

The diminished availability of active thyroid hormones in euthyroid sick syndrome may be seen as part of an adaptive response to stressful circumstances. Decreases in thyroid hormones reduce tissue energy expenditure, which may support healing processes.[9,48] However, euthyroid sick syndrome may also be considered as a maladaptive response-inducing hypothyroidism.[48]

The clinical consequences of the euthyroid sick syndrome for the syndrome of delirium are unclear. Under normal circumstances, T3, which is formed from T4 in the liver, is transported via the circulation to the various tissues where, in the nucleus of the cell, it affects gene expression; across the cell membrane, it enhances transport of amino acids and sugars, and, in the cell, it stimulates ATP synthesis via direct action on the mitochondria (Fig. 2). Under stressful circumstances, thyroid hormone metabolism is altered, changes possibly due to alterations in cytokines and other inflammatory mediators.[48] The conversion of thyrotropin-releasing hormone (TRH) into TSH is inhibited by dopamine and dopamine agonists, somatostatin, and cortisol, all of which are increased under stressful circumstances (see Fig. 2).

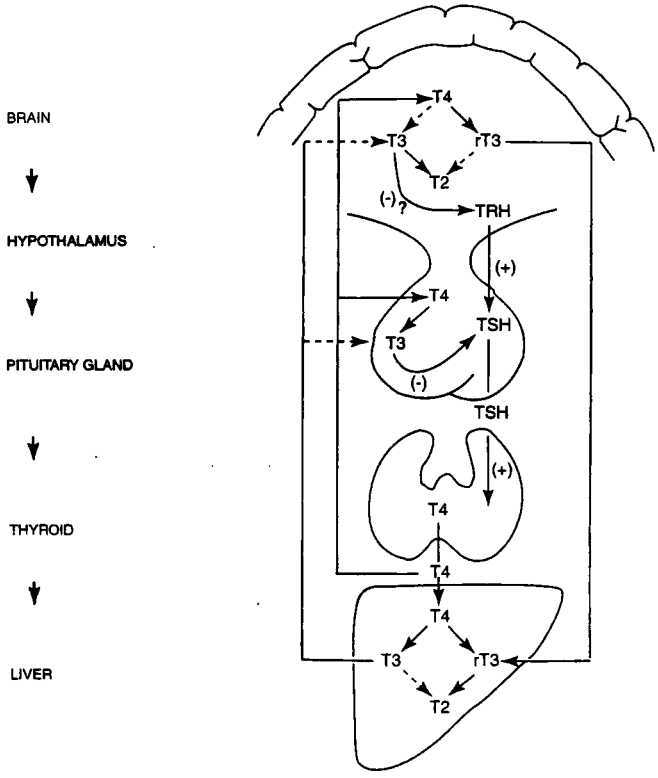

Figure 2. Regulation of thyroid hormone metabolism.

Severely ill patients who develop euthyroid sick syndrome have reduced transport of amino acids and sugars into the cell as well as reduced synthesis of ATP interfering with cell metabolism. This may lead to widespread reduction of cerebral oxidative metabolism and an imbalance of neurotransmission, considered important pathophysiologic mechanisms of delirium,[7] and may help explain the severe cerebral dysfunction of delirium.

Neurophysiology of Aging

In normal aging, many morphologic changes have been described, such as a decrease in brain volume and weight, reduced number and volume of neurons, and loss of dendrites and synapses.[20] However, the human brain has great reserve capacities.[20] The original number of neurons is very large, and function can be maintained even when the number of neurons has been greatly reduced. Also, neurons are capable of increasing their metabolism if necessary, and by producing more neurotransmitters, they may compensate for the loss of other neurons. Furthermore, nerve terminals are able to increase in size and take over the function of lost neighboring terminals. Moreover, receptors can increase their sensitivity and thus continue to respond adequately, although the release of neurotransmitters is reduced.[20] When all of these compensatory mechanisms are exhausted, symptoms of insufficiency appear such as delirium and cognitive dysfunction.[20]

Furthermore, hormonal and neurochemical changes have been described in normal aging. The activity of hypothalamic corticotropin-releasing hormone (CRH) and of the HPA axis is increased in elderly people, as in Alzheimer's disease and depression,[20] and excessive levels of plasma cortisol have been associated with cognitive impairment and delirium in old age.[13]

Aging also affects the function of neurotransmitter systems. Changes in the cholinergic system comprise selective cell loss, decreased synthetic choline acetyl transferase (CAT) activity, and synthesis of acetylcholine, but unchanged acetylcholinesterase.[1,20,27] This age-related decline in release and synthesis of acetylcholine parallels the decline seen in hypoxia and thiamine deficiency and can also be related to decreased oxidative metabolism with aging.[1] Deterioration of the cholinergic system is related to cognitive decline, especially to memory impairment, both in normal aging and in Alzheimer's disease.

In aging, loss of dopaminergic and noradrenergic neurons in the substantia nigra and locus ceruleus and reduced concentrations of dopamine and dopamine uptake sites have been reported.[1,20] However, the basal release of dopamine and glutamate, both associated with excitotoxic neuronal damage, in vivo appears to be increased.[1,27] Excitotoxic mechanisms, as described above, also may play a role in neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, stroke, and Huntington's disease, and possibly in delirium.[1,22]

Serotonin metabolism is also sensitive to aging. In certain brain regions, serotonergic neurons and concentrations of serotonin are decreased. Possibly, the turnover of serotonin is compensatorially enhanced.[20] Decline of serotonergic metabolism may also be deduced from a reduced activity of the two synthesizing enzymes of serotonin (e.g., tryptophan hydroxylase and carboxylase).[20]

Thus, age-related changes in stress management, hormonal regulation, cerebral neurotransmission, intraneuronal signal-transducing systems, and immune response are in line with pathophysiologic mechanisms supposed to underlie delirium and make elderly more vulnerable.

Summary and Conclusion

Elderly are especially prone to develop delirium, and advanced age is a major risk factor for delirium. Although the pathogenesis of delirium in the elderly does not seem to be different, the age-related morphologic, neurochemical, and metabolic changes in the brain, together with an increased susceptibility for stress, reduce the cerebral reserve capacities. As a consequence, the balance between neurotransmitter systems mutually and between neurotransmitter systems and intraneuronal second messenger systems becomes more vulnerable.

One must bear in mind that the findings presented in this review are mostly derived from animal and in vitro studies, and that further neurochemical research in dif-

ferent, homogeneous patient samples is necessary to elucidate pathophysiologic mechanisms of delirium.[11,53,54] The human brain is so extraordinarily complex that the precise mechanisms by which it malfunctions remain largely unknown, despite the enormous progress made during the last decades.

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