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Thyroid disease-related sleep disorders and its diagnostic and therapeutic recommendations: A literature review

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Highlights

- Complains of sleepless and tinnitus are common in sleep clinics, which is a different type of sleep disorder. In this article, we first summarize this disorder, which is defined as thyroid disease-related sleep disorder (TSD), and propose to categorize it as insomnia secondary to a somatic disorder.
- We have attempted to provide some preliminary diagnostic and therapeutic recommendations for TSD.
- In the treatment of TSD, we suggest relying on the theory of integrating Chinese and Western medicine, emphasizing holistic diagnosis and treatment, and precise medication.

Abstract

As perioperative medicine evolves, more hospitals are offering comfort sleep clinics. Thyroid disorders (e.g., hypothyroidism, hyperthyroidism, and thyroid cancer) affect the peripheral circadian clock. Elevated serum thyroid-stimulating hormone levels have been found to associate with the incidence of thyroid cancer in humans, but the relationship between circadian disruption and thyroid disease requires further investigation. Malignant transformation of thyroid nodules is characterized by disruption of the expression of biological clock genes. Sleep clinics often see patients complaining of sleepiness and tinnitus. These patients often have comorbid thyroid disorders and are therefore highly susceptible to misdiagnosis or underdiagnosis. In this article, we first summarize this category of disorders, which we propose to classify as insomnia secondary to somatic disease and define as thyroid disease-related sleep disorder (TSD). The primary and common clinical complaints of TSD patients are different types of sleep disorders. In addition, we attempt to provide some preliminary diagnostic and therapeutic recommendations for TSD in the hope that it may assist healthcare professionals in the early diagnosis and management of this disorder.

Keywords: Thyroid disease, sleep disorders, definition, diagnose and treatment, traditional Chinese medicine

I. Introduction

As more patients undergo surgery, the prevention of perioperative neurocognitive deficits has become a priority for patients, families, and perioperative research. As perioperative medicine evolves, more hospitals are offering comfort sleep clinics. Sleep and hypothalamic-pituitary-thyroid (HPT) axis are closely related and mutually interact with each other. Sleep quality and duration can significantly affect thyroid stimulating hormone (TSH) rhythms, which in turn cause a variety of endocrine and metabolic changes [1, 2]. Decreased sleep quality and duration can lead to decreased TSH secretion and concomitant

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sympathetic activation, which in turn increases thyroxine (T4) secretion. HPT axis activity can influence sleep quality and duration. Some studies have shown that changes in thyroid structure and function can also alter biological circadian rhythms, but the exact mechanisms are unknown [1-4].

It is well known that the HPT axis is controlled by the circadian rhythm system and plays a dominant role in the central pacemaker in the suprachiasmatic nucleus as well as in the sleep-wake cycle [3]. Thyroid disorders, such as hypothyroidism, hyperthyroidism and thyroid cancer, affect the peripheral biological clock. Thus, thyroid function and the biological clock are interrelated [4]. Generalized disruption of the endocrine system is thought to be one of the important mechanisms mediating the adverse effects of circadian dysregulation [2]. Although several studies have shown that elevated serum TSH levels are associated with the incidence of thyroid cancer in humans, the relationship between circadian disruption and thyroid cancer requires further investigation [4-6]. In contrast, disruption of oncogenes can cause dysregulation of the biological clock, and disruption of biological clock gene expression has been reported during malignant transformation of thyroid nodules [4, 5]. Since this type of sleep disorder is often overlooked and misdiagnosed, its analysis and generalization is of unique significance in the early diagnosis of thyroid nodules, especially thyroid cancer [5].

Thyroid disease-related sleep disorders (TSD), a type of secondary insomnia, is a group of somatic sleep disorders associated with thyroid disease in which sleep disturbance is the primary complaint. Patients are often first seen in sleep clinics with insidious clinical features of primary thyroid disease and a specific clinical presentation. Previously, this condition was not well understood, and affected patients often have a delayed diagnosis, which causes patient distress and exacerbates physician-patient conflicts. Therefore, in this article, we defined this clinical syndrome and provide some preliminary diagnostic and therapeutic recommendations to help health care professionals diagnose and treat this disease.

II. Thyroid Disorders and Sleep Disorders

The reciprocal relationship between sleep and the thyroid axis under normal circumstances

Physiology of the HPT axis

Thyrotropin-releasing hormone (TRH) is the central hub of the HPT axis. The circadian rhythm affects the function of the suprachiasmatic nucleus and the pineal gland to promote the secretion of TRH from the median eminence, which in turn acts on thyrotropin in the anterior pituitary and stimulates the secretion of TSH, triggering the secretion of T4 and triiodothyronine (T3). Then, the downstream signaling molecules of T4 and T3 negatively feedback to regulate TRH and TSH, thus maintaining the physiological function of the HPT axis [5, 6] (**Figure 1**).

Sleep stages and architecture

Based on sleep architecture and electroencephalogram, human physiological sleep is divided into rapid eye movement (REM) and non-rapid eye movement (NREM) [4-8]. NREM can be further divided into three distinct stages, N1, N2, and N3 [9]. REM and NREM occur alternately with an interval of 90-120 minutes each [10, 11].

Biological clocks, sleep and thyroid hormone secretion

Circadian rhythm is a natural, internal process that regulates the sleep-wake cycle and repeats approximately every 24 hours. Other physiological changes that occur according to circadian rhythms include heart rate and various cellular processes, such as oxidative stress, cellular metabolism, immune and inflammatory responses, regulation of endocrine function, and autophagy [12-14]. The supraoptic nucleus and the pineal gland are thought to be the regulatory centers for circadian rhythms. When light stimulation is received, the production of melatonin in the pineal gland is suppressed, thereby keeping people awake. Conversely, melatonin is produced, and people becomes tired [15, 16] (**Figure 1**).

Numerous studies have shown that in normal humans, the secretion of thyroid hormones (TRH, TSH, free triiodothyronine (FT3) and free thyroxine (FT4), etc.) regulated by the HPT axis has obvious circadian rhythm characteristics [17, 18]. Among them, TSH fluctuates most significantly during the day and night, making TSH the most studied target.

Studies have shown that under normal sleep conditions, TSH secretion begins to increase in the evening until it reaches its highest concentration at 2-3 a.m. and then starts to decrease [17]. The disruption of the normal sleep schedule may affect the circadian rhythm of TSH and thyroid hormone secretion. Studies exhibited

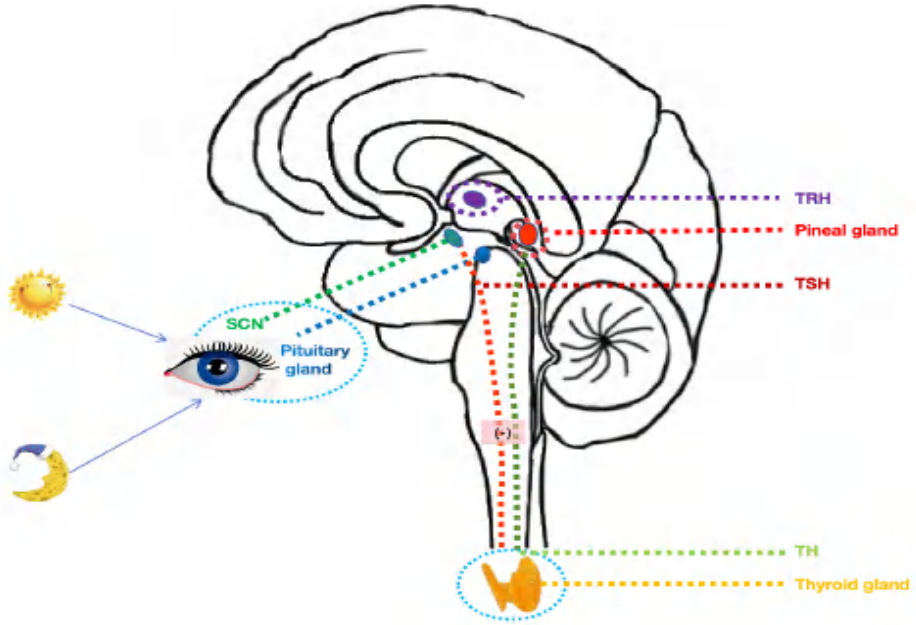

Figure 1. Schematic diagram of circadian rhythm regulation of HPT axis. HPT, hypothalamic-pituitary-thyroid; SCN, suprachiasmatic nucleus; TRH, thyrotropin-releasing hormone; TSH, thyrotropin; TH, thyroid hormone.

that blood levels of TSH hormone showed significant circadian fluctuations, and the peak of TSH hormone secretion tended to occur at night [17, 19].

In addition, there was a strong correlation between the circadian profile of blood FT3 and TSH. There is also a significant correlation between circadian fluctuations in blood FT3 and TSH fluctuations. Ninety minutes after the peak TSH fluctuation, there was also a peak secretion of FT3, and the amplitude of circadian fluctuations of FT4 was lower [17-20].

Sleep inhibits TSH release and can reduce diurnal TSH fluctuations, which in turn affects HPT axis hormone secretion [21-23]. Additional sleep after sleep deprivation can significantly inhibit TSH secretion. The existence of a regulatory effect of sleep on the HPT axis has been further demonstrated [24-26].

TSH release is inhibited during sleep, which is related to the sleep-wake cycle and sleep architecture, and the amplitude of TSH oscillations is not affected by gender, body mass index (BMI), or age. However, the onset of the nocturnal TSH surge is significantly delayed with increasing BMI but advanced with increasing age [23].
In patients with normal thyroid function or subclinical hypothyroidism associated with somnolence, levothyroxine tablets may improve somnolence. In replacement therapy for hypothyroid patients, excessive levothyroxine tablets or incorrect administration may cause insomnia along with symptoms of euphoria such as sweating, headache, restlessness, agitation, palpitations, and diarrhea [27, 28].

T4 and T3 enter the cell membrane via a carrier-mediated adenosine triphosphate-dependent transport process [29, 30]. Much of the T4 is deiodinated to the T3 form, which interacts with the thyroid hormone receptor and binds to the X-like receptor of vitamin A and the thyroid hormone responsive element of the gene. This action either upregulates or downregulates the transcription of genes that lead to the formation of proteins contributing to the cellular response to thyroid hormone [31].

Sleep restriction or sleep deprivation can significantly increase blood thyroid hormone levels, adenosine triphosphate (ATP) concentrations, and neuronal excitability. ATP can act as an excitatory neurotransmitter alone or can enhance HPT axis-sleep interactions [27, 32, 33].

Dopamine (DA) is a neurotransmitter associated with a variety of functions in the body and can regulate a number of different physiological activities. DA has a regulatory effect on sleep: too little DA secretion can lead to too much sleep, while too much DA secretion can lead to too little sleep due to hyperexcitability. Also, DA can inhibit the body's secretion of TSH and thyroid hormones and plays a role in preventing thyroid nodules [34, 35].

Sleep alterations and their effect on thyroid hormone secretion

Sleep restriction has previously been shown to differentially alter HPT axis activity. In sleep-restricted subjects, the nocturnal blood TSH is decreased while blood FT4 is increasing, and this persists during the sleep restriction period and is reversed when sleep is restored [36, 37].

Another study confirmed that TSH changes in sleep-restricted subjects were not affected by light stimulation, suggesting that the effect of sleep restriction on HPT axis is independent of mechanisms affecting the circadian rhythm of sleep. Scientists speculate that the mechanism may be through altered sympathetic tone activity, which in turn leads to altered TSH activity [38, 39].

Reduced sleep has been shown to increase sympathetic activity and interfere with HPT axis activity, resulting in decreased TSH and increased T4 [24, 36]. The study by Kessler et al. suggests that the duration of sleep deprivation affects the secretion pattern of thyroid hormones in HPT axis [38]. Compared to unrestricted sleep, sleep deprivation leads to lower blood TSH and FT4 in adult women [38]. The above changes were less pronounced in male subjects, suggesting gender differences in the above effects.

In order to maintain the metabolic needs of the brain, the reduced thyroid hormone increases the body's catabolism, which is used to maintain alertness and stress resistance.

Interaction between sleep and HPT axis

The endocrine homeostasis maintained by HPT axis under physiological conditions is closely linked to sleep. Sleep and HPT axis interact to regulate energy and metabolic homeostasis, and alterations in one can lead to dysregulation in the other [5]. Therefore, it is of great value to characterize the mechanisms and clinical manifestations of the interdependence between sleep and the HPT axis.

TSH influences the quality and architecture of sleep

Sleep quality has been shown to influence the circadian rhythm of TSH and thyroid hormone secretion. Short-term sleep restriction significantly reduces the amplitude of nocturnal TSH secretion and may regulate active thyroid hormone secretion by increasing sympathetic tone [24-26]. Conversely, TSH and active thyroid hormones influence sleep quality and sleep architecture. For example, low TSH levels allow for slow-wave sleep and maintenance of normal sleep architecture, whereas insufficient or excessive secretion of active thyroid hormones adversely affects sleep quality and quantity [25, 26, 39].

The role of thyroid hormones in sleep deprivation (SD)

SD is a distressing as it induces a sense of malaise and impairs overall functioning in the affected individual. However, in some cases, SD may be critical to an individual's survival, because it can lead to a dramatic increase in thyroid hormone activity, which is a central mechanism of SD. This condition prompts the pituitary gland to release more thyrotropic hormone, leading to an initial dramatic surge in the HPT axis [40, 41].

Due to the close interconnection between the autonomic nervous system and the HPT axis, prolonged SD leads to sympathetic activation, elevated TSH, and the duration of abnormal wake exceeds the duration of sleep [36, 38]. As a compensatory response to SD, the increase in thyroid hormone activity further enhances purinergic neurotransmission, which increases synaptic transmission by activating a mitochondria-dependent increase in ATP [36, 40, 41].

Hypothyroidism and sleep disorders

Non-rapid Eye Movement

In hypothyroid patients, T4 insufficiency is now considered to be the main cause of fatigue and sleepiness. Total sleep time is not significantly altered in hypothyroid patients but is mainly characterized by decreased non-rapid eye movement 1 (N1) and non-rapid eye movement 2 (N2) as well as non-rapid eye movement 3 (N3) and REM, suggesting poor sleep quality [42, 43]. Another study suggested that hypothyroidism may lead to a reduction in the number of awakenings and slow-wave sleep (SWS) through a mechanism related to disturbances in thyroid hormone, TSH, and TRH secretion [44-47].

Because hypothyroidism is often associated with obstructive sleep apnea (OSA) syndrome, it may trigger or exacerbate pre-existing airway obstruction and respiratory sleep apnea. Compared to OSA patients with normal thyroid function, patients complicated with hypothyroidism have increased adverse markers of OSA (Epworth scale, sleep oxygen saturation <90%, hypoventilation index, etc.) [48]. Mechanisms include blunted response to hypercapnia and hypoxia, deposition of airway mucin exacerbat-

ing upper airway narrowing, retrosternal goitre inducing positional dyspnea, increased BMI, and altered respiratory muscle activity [49-51].

In patients with subclinical hypothyroidism, low thyroid hormone can lead to increased sleep latency, decreased sleep duration, and decreased sleep satisfaction, along with anxiety, impatience, and muscle and joint pain [47, 52].

Hypothyroidism, OSA and sleep disorders

In a population-based clinical study of OSA, the prevalence of OSA was 24% in adult men and 9% in women [53]. After adjusting for demographic characteristics (BMI, alcohol consumption, smoking, etc.), Thavaraputta et al. confirmed a significant association between hypothyroidism and OSA. Another study confirmed that obese patients without sleep disorders often have hypothyroidism [54, 55].

The above studies suggest that hypothyroidism may lead to OSA, and the specific mechanism may be similar to the pathogenesis of OSA [56]. In addition, T4 replacement therapy has previously been shown to improve sleepiness and fatigue in OSA patients [57]. Thyroid hormone therapy may partially ameliorate apneic episodes and hypoxemia, thus improving sleep structure and duration [58]. However, there is no conclusive evidence regarding hypothyroidism and the pathogenesis of OSA. Thyroid hormones do not predict the degree of airway obstruction in OSA [59-61].

In a clinical study of 271 patients, researchers evaluated the correlation between OSA and thyroid hormone levels. Among patients diagnosed with OSA, 0.4% had combined hypothyroidism; in patients previously diagnosed without OSA, 1.4% had combined hypothyroidism; in patients newly diagnosed with OSA, 11.1% had combined hypothyroidism; in newly diagnosed patients without OSA, 4% had combined hypothyroidism [51]. The above results suggest that patients with OSA are more likely to have hypothyroidism. However, the degree of hypothyroidism does not appear to predict the degree of airway obstruction.

Hypothyroidism treatment and sleep disorders

Thyroid function replacement therapy and sleep disorders

Sleep-disordered breathing is common in patients with primary hypothyroidism. In patients with idiopathic narcolepsy, patients with combined subclinical hypothyroidism have shortened sleep latency and prolonged total sleep time, but normal NREM/REM scores.

T4 therapy reversed the SD in 10/12 patients, and the mechanism may be related to improved upper airway stenosis [62]. In addition, levothyroxine relieves excessive daytime sleepiness, anxiety, and insomnia due to hypothyroidism [63-65].

Effect of continuous positive airway pressure (CPAP) treatment on serum thyroid hormone levels

Changes in serum thyroid hormone levels before and after CPAP treatment have been studied previously. Patients with OSA were found to have altered baseline thyroid hormone levels. In these patients, CPAP attenuated the changes in FT3 and TSH seen in patients with non-thyroid disease syndromes. The mechanism may be related to CPAP's capacity to reduce hypoxemia and inflammatory responses. In contrast, CPAP treatment did not have these effects in patients with normal baseline hormone levels [66-68]. In the future, it is necessary to select patients with consistent baseline hormone levels for further in-depth study.

Effect of thyroidectomy on the airway of patients with OSA

High BMI with narrow upper airway stenosis is an important predisposing factor for OSA. As the disease progresses, mucopolysaccharides are deposited along the oropharyngeal structures, causing thickening of the pharyngeal wall and pharyngeal dilator muscles, further exacerbating airway narrowing.

Untreated hypothyroidism is thought to exacerbate upper airway narrowing by depositing mucopolysaccharides along the oropharyngeal structures, which can lead to thickening of the pharyngeal wall and hypovolemic myopathy of the pharyngeal dilator muscles. In addition, retrosternal goiters may directly compress the trachea and worsen dyspnea [61, 69, 70]. A meta-analysis found that the symptoms of airway obstruction was alleviated in patients with OSA who underwent thyroidectomy, especially positional dyspnea [71, 72].

Hyperthyroidism and sleep disorders

Elevated circulating T4 is commonly associated with thyroid hyperstimulation, thyroid nodules with abnormal function, increased or excessively decreased T4 uptake, and pituitary tumors with excessive TSH secretion. It is well known

that hyperthyroidism and thyrotoxicosis can lead to sleep disturbances, usually thought to be related to thyroid-induced hyperarousal [73-75].

In hyperthyroidism, immunoglobulins are overactivated by T4, followed by clinical symptoms such as sleep disturbance, prolonged sleep latency, difficulty in maintaining sleep, compensatory daytime somnolence, changes in appetite, abnormal bowel movements, increased anxiety, and increased tremor. Sleep disturbance is an important hallmark of hyperthyroidism, and the degree of TSH, T3, and T4 abnormalities is closely related to the severity of sleep disturbance [76, 77]. In several clinical studies, patients with hyperthyroidism developed hypodynamic sleep, mainly characterized by decreased sleep duration and SWS [78-81]. Kraemer et al. found that excess T4 can increase REM density and body motor function in thyrotoxicosis patients, and Sridhar et al. found that thyrotoxicosis can lead to decreased sleep efficiency and duration, as well as a significant increased sleep latency [76, 82]. These are consistent with other studies which reported that endogenous hyperthyroidism led to sleep disturbances [82-84].

Hyperthyroidism treatment and sleep disorders

Excessive use of iodine-containing tablets can cause symptoms similar to hyperthyroidism, such as insomnia and heart palpitations, and insomnia may improve when drug suspension [85, 86]. Studies have confirmed that growth hormone and SWS are closely related. Hyperthyroidism can inhibit the release of growth hormone and reduce the duration of SWS, which can be reversed by propylthiouracil [87]. Patients undergoing radioiodine ablation therapy often complain of sleep disturbance, especially older patients [88].

In a study of Graves Disease (GD) recurrence after discontinuation of antithyroid medication, investigators found that the recurrence rate in patients with comorbid insomnia was three times higher than in patients without insomnia. In similar studies in children, children with GD recurrences were more likely to have reduced sleep duration than control children. Prolonged sleep duration may improve the prognosis of children with GD [89, 90]. However, the above studies only examined sleep duration and did not investigate the effect of sleep quality on GD relapse.

Thyroid nodules, thyroid cancer, and sleep disorders

Gene expression in the thyroid gland is now thought to be associated with altered circadian patterns. Thyroid diseases such as hypothyroidism, hyperthyroidism, and thyroid cancer can affect the peripheral biological clock. In addition, genes affecting circadian rhythms have been identified in other tumors such as leukemia, breast cancer, endometrial cancer, and colorectal cancer [91-98].

Most thyroid nodules are benign, and only about 5% develop into thyroid cancer. Patients with benign nodules have less psychological distress and sleep disturbance than those with thyroid nodules suspected to be cancerous [5]. It has been reported that elevated serum TSH level is associated with the incidence of thyroid cancer in humans, but the relationship between circadian disruption and thyroid cancer requires further investigation [4]. Changes in the expression of biological clock genes have been reported during the malignant transformation of thyroid nodules [92]. Pharmacological modulation of biological clock mechanisms may provide new strategies for the treatment of thyroid malignancies. Symptoms such as nausea and vomiting, insomnia, and anorexia were improved in patients with differentiated thyroid cancer after one month of radioactive iodine treatment [97].

Alterations in circadian genomics are an area of great scientific interest from the standpoint of carcinogenesis and possible therapeutic approaches. An in-depth understanding of circadian rhythm dynamics in patients with thyroid malignancies may aid in their early diagnosis and provide insights into the effects of thyroid cancer on sleep [86, 98]. Mannic et al. found that the expression level of Bmal1 was upregulated in tissue samples of follicular thyroid cancer (FTC) and papillary thyroid cancer (PTC) compared to normal thyroid and benign nodules, whereas the expression level of Cry2 was downregulated in FTC and PTC [92]. Human thyroid cells derived from normal thyroid tissue showed expression of the brain and muscle arnt-like 1 (BMAL1) gene. BMAL1 protein can form a heterodimer with clock circadian regulator (CLCOK) protein and participate in the regulation of cellular rhythmic changes.

Thyroid cells derived from FTC and PTC exhibited clock transcript oscillations similar to those from normal thyroid tissue and benign nodules (except Per2 alterations in PTC), whereas cells derived from poorly differentiated thyroid carcinoma exhibited markedly altered circadian

oscillations. The characterization of altered thyroid clock mechanisms during malignant transformation of thyroid nodules contributes to the understanding of the link between the biological clock and oncogenic transformation. In addition, it helps to improve the preoperative diagnosis of thyroid nodules [92].

Hypothyroidism and restless legs syndrome (RLS)

RLS and thyroid function

The prevalence of RLS is approximately 0.1-15% in the normal population. At night or at rest, patients with RLS experience discomfort in the lower extremities, accompanied by irresistible leg movements [99-101]. Patients with RLS are often comorbid with sleep disorders and anxiety and depression [102, 103]. RLS is classified into idiopathic and secondary types. Secondary RLS is common in pregnancy women and patients with multiple sclerosis, Parkinson's disease, anemia, iron deficiency, and chronic renal failure [104, 105]. MEIS1 is currently considered a susceptibility gene for RLS [106-108]. Although the pathogenesis of RLS is still unclear, RLS has been shown to be closely related to DA and iron deficiency in the nervous system [101, 108].

A growing number of studies have confirmed that the dopaminergic system is related to the HPT axis [34, 109-112]. DA decreases thyroid hormone and thyroid-stimulating hormone (TSH) and increases TRH release over time [35]. In animal studies of RLS, nigrostriatal 18F-dopa uptake was found to be reduced and presynaptic DA was decreased [112, 113]. These findings facilitate a detailed study of the mechanisms by which DA dysfunction promotes the pathogenesis of RLS. In idiopathic RLS cadavers, DA 2 receptors were found to be reduced compared to controls, and the degree of reduction was correlated with the severity of RLS [114]. It has been shown that exogenous supplementation with DA or DA agonists can reduce the symptoms of RLS, further confirming that DA dysfunction exists in RLS patients [115].

Thyroid hormone axis and hypothyroidism with iron and DA systems

Previous studies have confirmed that either iron deficiency or anemia is highly associated with the development of RLS and hypothyroidism [116]. In contrast, after iron supplementation, patients had increased T4 and decreased TSH. It has also been suggested that there is an interaction between thyroid function and the iron metabolism system [116-118]. A clinical study in pregnant women found that pregnant women with comorbid RLS were more likely to develop hypothyroidism [119-123]. The mechanisms underlying the relationship between iron metabolism and thyroid hormones are unclear, and it is currently believed that TRH upregulates total iron-binding protein in the pituitary gland [124, 125]. Neuropathological studies have found iron and ferritin deficiencies in the striatum and ventral midbrain nucleus in patients with RLS, along with DA overload [126-128]. Neuroimaging and cerebrospinal fluid biochemical analyses suggest that iron deficiency is prevalent in the brain of RLS patients [129, 130].

TRH, black cortisol system, and RLS

Pro-opiomelanocortin (POMC) neurons originating in the arcuate nucleus of the hypothalamus can send excitatory neuronal projections to TRH neurons in the paraventricular nucleus [131]. Hypothalamic POMC neurons can produce melanocortin (MC), and there is a marked circadian regularity in blood MC levels, which may have a regulatory effect on sleep architecture [132-139]. When MC was injected into rodents, the animals exhibited RLS-like clinical features and nociceptive sensitization [140, 141].

DA can inhibit α-melanocyte activity in MC, which is a possible mechanism by which dopaminergic drugs lead to stereotyped responses [137-141]. In mice with high expression of alpha-melanocyte-stimulating hormone, impaired negative feedback can increase hypothalamic TRH mRNA and blood thyroid hormone [131, 139, 141]. Similar changes are present in patients with hypothyroidism combined with RLS. POMC is seen in the anterior pituitary, pituitary mesenchymal cells, and the hypothalamus [142-144].

Thyroid disease, tinnitus, and sleep disorders

Tinnitus is a phantom sound, such as buzzing and hissing, in the ear or inside the skull that patients experience in the absence of an external sound source, which may last for a period of time. Patients may experience tinnitus symptoms after a long period of insomnia, and some patients may experience tinnitus symptoms first before it leading to insomnia. A study found that in the tinnitus group, the incidence of insomnia is 28.1% in men and 36.1% in women [145].

Hyperthyroidism with tinnitus and insomnia

A cohort study found that the risk of combined

tinnitus in patients with hyperthyroidism was 1.38 times higher than that in patients without hyperthyroid (95% CI=1.27-1.50) [145, 146]. In addition, dizziness, insomnia, anxiety and/or hearing loss may be risk factors for combined tinnitus in hyperthyroidism [145, 146]. The above studies suggest an association between thyroid function and tinnitus, but the mechanism by which thyrotoxicosis causing tinnitus is unknown. In addition to T4 affecting cochlear maturation, other mechanisms include potassium channels, Na+/K+ ion gradient across the vessel wall, and thyroid hormone-sympathetic adrenal system interaction [146]. The next step should be to observe whether tinnitus appears to improve after treatment of hyperthyroidism.

Hypothyroidism with tinnitus and insomnia

Tinnitus was also found to be associated with hypothyroidism. After correcting confounding factors such as age, sex, and economic status, the overall incidence of tinnitus was significantly higher in hypothyroid patients than in non-hypothyroid patients (9.49/1,000 vs. 6.03/1,000 annually) [147].

The mechanisms by which hypothyroidism causing tinnitus include altered sympathoadrenal activity due to thyroid status, altered cochlear blood flow, and thyroid hormones affecting neuronal maturation [147-150]. In animal models of congenital hypothyroidism, the auditory system develops abnormally [151, 152]. Childhood hypothyroidism also causes hearing loss in children [153].

Sleep disorder and hypothyroidism in pregnancy

Hypothyroidism in pregnancy is one of the most common endocrine disorders in pregnancy. The causes of hypothyroidism in pregnancy may be related to the high basal metabolism of pregnant women, relative thyroid insufficiency, increased consumption of thyroid-stimulating hormones, specific iodine leakage, dilution of thyroid hormones in the blood, increased iodine consumption, and decreased T4 stores [154-157].

A study reported that 64.0% of pregnant women with normal thyroid function had one or more symptoms resembling hypothyroidism, with the most common comorbid symptoms being insomnia and drowsiness (30.3%), followed by fatigue (20.3%) [158]. In addition, sleep disturbances in some hypothyroid pregnant women may be associated with psychoneurological abnormalities due to hypothyroidism [159].

Thyroid function changes induced by immunotherapy

Abnormal thyroid function is more common in patients undergoing tumor immunotherapy. Thyrotoxicity or hyperthyroidism usually occurs first, with 80% eventually progressing to hypothyroidism [160, 161]. Increased doses and drug combinations may lead to a higher incidence and earlier onset of immune-related adverse events. Therefore, it is particularly important to study immunotherapy-associated hypothyroidism.

Immunotherapy-associated hypothyroidism usually has insidious symptoms, and adverse effects are usually grade 2 or milder, with very few serious adverse effects [162]. In these patients, fatigue, tiredness, hoarseness, drowsiness, and dry skin are the most common clinical manifestations. Therefore, if these patients present with fatigue and drowsiness that cannot be explained by other causes, it is important to consider whether they have immunotherapy-associated hypothyroidism and to treat it as soon as possible. It is currently believed that the mechanisms may include: 1) over-activation or destruction of the autoimmune system, leading to some destruction of normal thyroid cells [160-167]; 2) elevation of inflammatory factors such as IL-17; 3) elevation of autoantibody levels (TSH, anti-thyroglobulin antibodies (TGAb), etc.), reduction of immune tolerance, or reduction of immune tolerance [59-61, 168]; and 4) genetic factors, e.g., the single nucleotide polymorphisms of CTLA-4 in Asians may confer a greater susceptibility to thyroiditis, which in turn may lead to hypothyroidism [62].

Other drugs affecting T4 concentration

Following non-pharmacological (SD, 12-hour fasting, 14-day calorie-restricted diet) and pharmacological (ethanol, haloperidol, clozapine, etc.) treatments, more pronounced changes in 5'D-II activity and thyroid hormone concentrations were observed in up to 10 regions of the rat brain, suggesting that iodothyronine metabolism in the central nervous system may be mediated by other pathways of iodothyronine metabolism in the CNS [168]. The above suggests that 5'D-II activity and thyroid hormone concentrations in the CNS are highly sensitive to a variety of events that may cause changes in neuronal activity. In an animal study of thyroid hormone stimulation of central cholinergic neuronal function, the latency to betaine-induced REM showed a moderately significant negative correlation with free T4 index [169].

Recognition and research progress of Chinese medicine on thyroid-related insomnia

According to Chinese medicine theory, the locus of insomnia mainly lies in heart and closely related to liver (gall bladder), spleen (stomach) and kidneys. The etiology and pathogenesis of insomnia mainly include the imbalance of yin and yang, disturbance of qi and blood, the disharmony between ying and wei, and the disturbance of the heart by evil-qi [170, 171].

"Ying" disease

Although there is no concept of thyroid nodules in Chinese medicine, from the point of clinical symptoms and etiology of thyroid nodules, it is very similar to the internal disease "Ying" in Chinese medicine which believes that the formation of "Ying" disease is due to the factors such as internal injuries to emotions and feelings, improper diet, as well as physical factors.

According to Traditional Chinese Medicine (TCM), qi stagnation, phlegm condensation, and blood stasis are the basic pathological changes of "Ying" disease [172]. The appearance of thyroid nodules is related to the malfunction of the liver, spleen, and kidney, and the core mechanism is stagnation of liver qi and spleen dysfunction. When joy and anger are out of order, the seven emotions are disrupted, causing stagnation in the human body's emotions and feelings, leading to qi imbalance. This marks the onset of generalized qi stagnation, progressing subsequently to phlegm stagnation and blood stasis, ultimately contributing to the development of thyroid nodules. In the later stages of "Ying" disease, the weakening of the liver, spleen and kidney, and the imbalance of qi, blood, yin and yang are the main pathogenic mechanisms [173-175].

Relevance of "Ying" disease, depression and insomnia

The heart is the organ similar to the monarch and is responsible for spirit and mental activity. Patients with "Ying" disease are often disturbed by blood stasis and phlegm opacity. In the early stage, they are often accompanied by fire-heat, which affects the physiological function of the heart, thus disturbing the heart and mind, manifesting symptoms such as palpitations, tachycardia, dizziness, and insomnia.

The Liver meridian of Foot Jueyin starts from the big toe, goes up into the calf, through the diaphragm and then enters the lower forehead, i.e., the neck and throat, after traveling along the trachea. Patients with "Ying" disease have blood and phlegm stagnation in the Liver meridian, which affects the operation of qi and blood in the Liver meridian, resulting in hyperactivity of "Liver" yang and "Liver" qi stagnation. Since the liver stores blood and the blood shelters the soul, when the liver meridian is disturbed, it is difficult for the soul to be at peace, so patients with "Ying" disease often manifest depression, chest distention and tightness, irritability and insomnia [176-178]. Therefore, it is of great significance to actively utilize TCM to improve the mental status of such patients [179, 180].

Knowledge and research progress of Chinese medicine on insomnia and wasting due to thyroid disease

Hyperthyroidism is a type of disease mainly characterized by the enlargement of nodules on both sides of the laryngeal nodes in the front of the neck, caused by the interaction of qi stagnation, blood stasis, and phlegm coagulation as demonstrated in TCM theroy [181, 182].

The initial onset of insomnia and wasting due to thyroid disease is accompanied by excessive internal heat, and the long duration of the internal heat will inevitabley harm Yin and body fluids. The location of the lesions mainly includes heart, liver and kidneys. Ancient medical practitioners keenly recognized the close relationship between emotions and thyroid disease, and believed that emotional disorders resulted imbalance of qi and blood is its pathological basis, and the treatment focuses on nourishing the heart and liver, revitalizing blood, or psychotherapy. Due to the leading knowledge about the pathogenicity of emotional disease, TCM has accumulated a wealth of experience in the use of medicines in the course of development, and has unique advantages and efficacy in the treatment of psychiatric symptoms associated with hyperthyroidism, such as insomnia and anxiety [183, 184].

Progress in the study of Chinese medicine syndromes of autoimmune thyroiditis

Autoimmune thyroiditis is a common clinical organ-specific immune disease, of which Hashimoto's thyroiditis (HT) is the most common [185, 186].

Yang et al. data-mined 77 research papers on HT evidence in Chinese medicine and obtained a total of 17 typical symptoms. The top 8 signs with the highest frequency were spleen-kidney yang deficiency, qi stagnation and phlegm con-

gestion, qi and yin deficiency, phlegm and stasis entanglement, liver depression and qi stagnation, phlegm congestion and blood stasis, qi stagnation and blood stasis, and yin deficiency and fire exuberance [187, 188]. The decomposition of these signs yielded eight pathognomonic elements, namely qi stagnation, phlegm congestion, excessive internal heat, blood stasis, dampness obstruction, yin deficiency, qi deficiency, and yang deficiency.

In addition, the information of the four described TCM diagnoses of HT were clustered, analyzed and summarized to correspond to four types of evidence: spleen and kidney yang deficiency, yin deficiency and fire exuberance, qi stagnation and phlegm condensation, and phlegm and stasis association. It is believed that emotional disturbances are the main causative factors for the development of HT. Long-term worry, depression or irritation can lead to liver stagnation and spleen deficiency, impaired qi and blood circulation, as well as abnormal fluid transport, resulting in the development of thyroid diseases.

III. Diagnosis and treatment of TSD

Definition and classification of TSD

Definition

TSD is characterized by fatigue and weakness, frequent and persistent difficulty in falling asleep and/or maintaining sleep, resulting in a feeling of dissatisfaction with sleep. TSD may be accompanied by sleepiness, weakness upon awakening or impairment of other systemic functions. Sleep disturbances may be resolved after treatment of thyroid diseases.

Proposed classification

According to the International Classification of Sleep Disorders (ICSD-3), we first categorized TSD into chronic TSD, short-term TSD, and other types of TSD [189, 190]. Other types of TSD should be considered if the patient does not meet the criteria for chronic and/or short-term TSD, and the diagnosis must be made with caution. Unlike chronic TSD, the diagnosis of transient TSD does not require a duration of ≥3 months and a frequency of ≥3 episodes/week.

Diagnosis and differential diagnosis

Diagnosis of TSD

a. Sleep disorder characterized by frequent and persistent sleepiness, difficulty in falling asleep and/or difficulty in staying asleep, resulting in an unsatisfactory sleep experience.
b. Sleep disorders are closely related with the development of thyroid disease.
c. Sleep disorders can be cured or alleviated after treatment of thyroid disease.
d. Polysomnography shows abnormal sleep architecture along with (or without) structural or functional abnormalities of the thyroid gland; sleep architecture improves after treatment of thyroid disease.

Differential diagnosis

The following differential diagnoses must be considered in TSD:

a. Primary sleep-disordered breathing.
b. Sleep disorders caused by somatic diseases, including neurological, cardiovascular, respiratory, digestive, genitourinary, musculoskeletal, and other sleep disorders.
c. Sleep disorders related to psychiatric disorders.
d. Sleep disorders associated with thyroid medications, including psychoactive substances/drugs such as antidepressants, central nervous system stimulants, cardiovascular drugs, narcotic analgesics, and asthma medications.
e. Sleep disorders caused by formaldehyde, alcohol and tobacco. These drugs, alone or in combination, can cause sleep disturbances.

Principles of TSD treatment

Our proposed treatment principles include:

a. Treating thyroid precursors;
b. Increasing effective sleep time and/or improve sleep quality;
c. Improving daytime functional impairments associated with sleep disturbances;
d. Reducing or eliminating the risk of conversion of short-term sleep disturbances to chronic sleep disorder;
e. Reducing the risk of sleep disorder-related somatic disorders or comorbid psychiatric disorders;
f. Providing individualized, comprehensive, and evidence-based treatments such as herbal medicine, acupuncture, massage, and aerobic exercise;
g. Adopting comfort anesthesia diagnostic and treatment techniques according to the type of primary thyroid disorder and the type of sleep disorder;
h. Improving psycho-behavioral problems associated with insomnia;
i. Avoiding the adverse effects of medications or therapeutic interventions.

IV. Summary and Prospects

With the increasingly fierce social competition and the accelerated pace of life and work, sleep disorders have become common and frequent clinical diseases, among which insomnia is the most common sleep disorder. However, the nomenclature, diagnostic criteria, classification criteria and efficacy evaluation criteria of TSD are still unclear, which greatly affects the determination of efficacy and further in-depth research. Therefore, it is urgent to clarify their definition and pathogenesis, and establish unified diagnostic, classification, and efficacy evaluation criteria.

The holistic view is one of the fundamental features of anesthesia therapeutics in the new century [191]. The HPT axis and sleep disorders are closely related and mutually interact with each other. Improvement in the function of the HPT axis is accompanied by the improvement of sleep quality. In addition, anesthetic approach for the treatment of sleep disorders has a palliative effect on HPT axis disorders. In the treatment of TSD, it is recommended to rely on the theories that integrate western and Chinese medicine, emphasizing holistic diagnosis and treatment, as well as precise medicine.

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Effects of general anesthetics on the cognitive function of pediatric patients: A review

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Highlights

- General anesthetics may cause neurotoxicity.
- Single general anesthesia before 3 years of age does not affect cognitive function in pediatric patients.
- The effect of general anesthetics on the cognitive function of pediatric patients is related to the number of anesthesia sessions, duration and the depth of anesthetic exposure.

Abstract

The consequences induced by the use of general anesthetics and better options of the drugs in children and infants have been topics of controversy due to the concerns about their potential impact on cognitive function. To address these concerns and ensure the safety of pediatric general anesthesia, this paper reviews existing basic and clinical studies that have investigated the mechanisms of general anesthetics on pediatric cognitive function. In this paper, the basic research on neurotoxicity of general anesthetics and the clinical research on the effects of general anesthesia drugs on cognitive function in children in recent years were analyzed and summarized. Although some of the clinical studies have suggested that general anesthesia in children or infants may cause neurocognitive damage and a series of behavioral complications, the results of the retrospective studies need to be viewed with caution as they may lack effective control for relevant factors that could have impacts in the perioperative period. It remains uncertain whether general anesthetics affect the cognitive function of pediatric patients. Further research is needed to establish clear evidence-based recommendations for clinical prevention and treatment measures to minimize the potential risks associated with the use of general anesthetics.

Keywords: General anesthesia, pediatric patients, anesthetics, cognitive dysfunction

Introduction

Pediatric patients are more active, easily agitated and less cooperative during surgical procedures in a conscious state. As the development of anesthesia technology and the continuous updating of anesthetics, general anesthesia has become increasingly important in pediatric surgery. However, concerns have been raised regarding the safety of general anesthetics in children due to their immature brain and nerve development. Certainly, the factors causing pediatric cognitive impairment include not only the side effects of general anesthetics, but also the influence of other drugs used in the surgery. Moreover, the adverse physiological state of the pediatric patients during the operation may also cause damage to their nerves, such as intraoperative ischemia, hypoxia, hypotension, acidosis, and stress reaction. This paper is devoted to summarizing the effects of general anesthesia drugs on the cognitive function of pediatrics. Studies have indicated that the effects of general anesthetics on the cognition of children may involve N-methyl-D-aspartate (NMDA) compensatory mechanisms, synaptic modification, β-amyloid (Aβ) deposition, and neurotrophic apoptosis [1]. Although several

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clinical studies have explored this issue, most of them are still in the early stages. Therefore, further research is needed to establish clear evidence-based recommendations for the prevention and treatment of the potential risks associated with the use of general anesthetics in children.

The primary references for this paper and the findings of each study are derived from authoritative textbooks, China National Knowledge Infrastructure and PubMed. To ascertain the definition of pediatrics, the growth and development of neuron and the physiological characteristics of children, we consulted textbooks such as Zhufutang Practical Pediatrics and Clinical Pediatrics. Additionally, to investigate the potential impact of general anesthetics on nervous system, we searched publications in China National Knowledge Infrastructure and PubMed, using keywords “neuro”, “anesthesia” and “pediatric”, and retrieved relevant articles published within the last five years. These articles were then sorted and analyzed according to their abstract and main text. Furthermore, to examine the relationship between general anesthesia and cognitive dysfunction of children, we also conducted a search using the keywords “pediatric”, “general anesthesia” and “cognitive dysfunction”, and then screened out the articles and sorted to obtain relevant clinical studies.

Definition of Pediatric

Generally, the neonatal period is the first 28 days after birth; infancy lasts from 28 days to one year after birth; early childhood is defined as the second and third years after birth; preschool lasts from 3 to 6 years of age; and school-age is from 6 or 7 to 11 or 12 years of age [2]. Most of the current studies on the effects of general anesthetics on pediatric cognitive function have focused on the early childhood period, and the reason is that the growth and development of the children before the toddler period is rapid, with a high incidence of anesthesia-related risk events, particularly in the neonatal and infantile periods [3]. So, the physiological characteristics of different periods should be taken into consideration for the safety management of anesthetics.

Neurophysiological characteristics of pediatrics

Pediatrics is a field of medicine that requires special attention due to the unique physiological characteristics of children. One of the most notable features of pediatrics before early childhood is the rapid development of the central nervous system. During late pregnancy and the first few years postnatally, the brain develops rapidly, which is known as the period of explosive brain growth [4]. During this stage, nerve cells are differentiating, and synapses are being formed between neurons. Conditioned reflexes are also gradually being produced. However, the cortex is not yet mature enough to withstand hyperthermia, toxins, or other adverse stimuli. So, this period is particularly vulnerable to drugs that interfere with physiological functions. Numerous clinical studies have shown that many general anesthetics can cause morphological and functional changes in developing brain, including accelerating neuronal apoptosis. Large doses and prolonged exposures of anesthetics can significantly affect the nervous system, but it is hard to establish a definitive limit on the duration of general anesthesia which has no unequivocal effect on neurodevelopment [5]. Furthermore, the insufficient research and evidence on the long-term effects of general anesthetics also pose a significant safety challenge for general anesthesia in pediatric patients undergoing surgery.

Assessment of pediatric cognitive function

Cognition, the process of acquiring or applying knowledge and processing information, is considered to be the most fundamental aspect of human mental functioning. It encompasses a wide range of mental processes, including perception, sensation, memory, thinking, imagination, and language [6]. The main assessment methods commonly used clinically to test pediatric cognitive function include the Processing Speed Task, Wechsler Preschool and Primary School Intelligence Scale, 4th Edition, Working Memory Task, Mallen Fine Motor Scale, and the Purdue Nail Board [7]. The Processing Speed Task is a measure of basic cognitive functions that are essential for effectively processing information. The WPPSI-IV and Working Memory Task assess higher cognitive functions to predict children’s cognitive abilities. The Mallen Fine Motor Scale and the Purdue Nail Board are tools used to assess learning abilities and behavioral problems [8].

Cognitive dysfunction is a disorder characterized by the impairment in one or more cognitive functions and would affect individual’s daily life or social abilities [9]. When cognitive dysfunction is observed in children, it often manifests as specific disorders, including thinking disorders such as disorders of associative processes and logical thinking, memory disorders such as memory deficits and errors, and

perceptual disorders such as hypersensitivity or dulled sensations, as well as hallucinations [10]. These children may experience frequent mumbling, aphasia, and various psychiatric disorders. The impacts of cognitive dysfunction on children's lives are significant and can even be life-altering. Therefore, before conducting general anesthesia surgery on children, it is crucial to comprehensively assess the potential impact of anesthetics, surgery and other factors on their cognitive function. Safe and reasonable preparation for the operation should be carried out, with a focus on minimizing possible safety issues.

Common drugs used in pediatric general anesthesia

Intravenous anesthetics

Propofol

Propofol is one of the most widely used intravenous anesthetics in the world and is also the most commonly used anesthetics in pediatric general anesthesia [11]. Propofol has various pharmacological effects and properties, including anesthetic induction, sedation, analgesia, anti-inflammatory, antioxidant, immunomodulation, neuroprotection, antiplatelet, antiemetic, etc. [12]. Propofol mainly acts by activating the inhibitory amino acid receptor γ-aminobutyric acid (GABA) and inhibit the release of excitatory neurotransmitter to enhance GABA-mediated transmission. Its pharmacological mechanism is also associated with the regulation of GluN2B-containing N-methyl-D-aspartate (NMDA) and extracellular signal-regulated kinase 1 and 2 pathways in spinal dorsal horn neurons to exert analgesic effects.

Wang et al. reported that propofol could reduce the stress response during surgery, decrease the release of inflammatory factors, thereby alleviating neuroinflammation and protecting nervous system [13, 14]. Although most studies have concluded that propofol has neuroprotective effects, Yao et al. concluded that propofol might still cause postoperative cognitive dysfunction in pediatric patients, and this effect could be substantially eliminated in combination with sevoflurane [15, 16].

Etomidate

Etomidate is a commonly used short-acting intravenous anesthetic, which is commonly used clinically for the induction and maintenance of anesthesia for short surgical procedures, as well as pediatric general anesthesia [17, 18]. Etomidate has sedative, analgesic and intraocular pressure-lowering effects, and functions by regulating gamma-aminobutyric acid (GABAA) receptors, the main inhibitory neurotransmitter receptors in the mammalian brain, leading to a sedative-hypnotic effect.

However, Xu et al. reported that etomidate was neurotoxic, which may be related to its inhibition of excitation in developing neurons and the elevation of intracellular calcium ion concentration, leading to neuron damage and apoptosis [19]. At the same time, they also highlighted that etomidate had a strong inhibitory effect on developing neurons, which brought to light its potential impact on neurodevelopment in children. Yang et al. also noted through a comparative study that etomidate could lead to postoperative cognitive impairment in children [20].

Ketamine

Ketamine is the only intravenous anesthetic with a definite analgesic effect, widely used in clinical practice and general anesthesia in pediatric patients, with properties of anesthesia, analgesia, anti-inflammation and antidepressant [21]. It primarily targets on NMDA receptors, non-competitively blocking them and consequently producing analgesic effects [22]. It has been suggested that ketamine is an analgesic; meanwhile, it also agonizes opioid receptors and exerts analgesic effects.

However, it was suggested that ketamine may cause neurotoxicity and induce neuron apoptosis, and possibly lead to the abnormality of the phosphorylation of hippocampus-specific proteins, as well as the expression of neuronal cell receptors and the immunity of the nervous system [23, 24]. Su et al. suggested in their study that ketamine could cause cognitive deficits in pediatric patients, which may be closely related to its neurotoxic effects [25].

Inhalational anesthetics

Sevoflurane

Sevoflurane, as a widely used inhalational anesthetic, has different effects on the nervous system, circulatory system, respiratory system, liver and kidney functions [26]. Due to its high efficacy of anesthesia, it is used in the surgeries in all ages. Sevoflurane is particularly suitable for pediatric general anesthesia due to its characteristics of non-irritation, rapid induction and fast awakening [27]. It acts on the GABAA receptor [28].

Table 1. Receptors of commonly used anesthetics and possible effects on nerves

	GABAA	NMDA	AMPA	neurotoxicity
Propofol	++	-	-	yes
Etomidate	++	/	/	yes
Ketamine	+	--	/	yes
Sevoflurane	+	- [40]	- [41]	yes
Isoflurane	+	-	-	yes
Enflurane	/	--	--	maybe

Note: GABAA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; ++, significant excitation; +, excitation; --, significant inhibition; -, inhibition; /, no significant effect.

However, Liu et al. reported that sevoflurane increased neuron apoptosis and neuronal cell damage, impairing the plasticity of neural circuit [29]. In addition, sevoflurane has been shown to cause developmental neurotoxicity due to its τ phosphorylation and neuroendocrine effects [30]. Zhang et al. found that long-term anesthesia with sevoflurane in pediatric patients could cause damage to the hippocampus, which is likely to be one of the causes of pediatric cognitive dysfunction induced by sevoflurane [31].

Isoflurane

Isoflurane has similar pharmacological effects to sevoflurane, but has a pronounced effect of muscular relaxation. It is more effective in general anesthesia, so it is also widely used in surgeries [32]. Isoflurane primarily targets on multiple membrane proteins, including glycine and GABAA receptor, as well as the two-pore structure of the K^+ channel [33].

Many researchers suggest that isoflurane may be neurotoxic to developing brain [34]. This may be related to the fact that isoflurane is an NMDA receptor antagonist that can lead to neuron apoptosis [35]. Zhang et al. reported that isoflurane might cause damage to the cognitive function in pediatric patients, and this effect may be more serious than the adverse effects caused by sevoflurane [36]. Deng et al. found that exposed to isoflurane over 3 hours may cause higher positive rate in Denver Developmental Screening Test (DDST), suggesting a potential risk in the development of children [37].

Enflurane

Enflurane has moderate intensity, faster efficacy of induction and awakening, with a wide range of safety. It acts on NMDA receptors and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors, which affects synaptic transmission.

Zhang et al. reported the neurotoxicity of enflurane and suggested that it may cause postoperative cognitive dysfunction [38]. Liu et al. revealed that this may be related to the significantly elevated levels of β-amyloid and phosphorylated tau in the hippocampus at an early stage [39]. The targets of various anesthetics and the possible toxicity are shown in **Table 1**.

Compound anesthesia

Most of the pediatric general anesthesia procedures are now performed using compound anesthesia, combining inhalational anesthesia with intravenous anesthesia, to achieve better effects. The most used inhalational anesthetic is sevoflurane, while the most used intravenous anesthetic is propofol, both of which have the advantages of fast onset of action, short awakening time, less effect on circulation and better anesthesia effect [42].

Compound anesthesia has many advantages and is widely used, but it also has to face the common adverse effects of intravenous and inhalational anesthetics. Its effects on the pediatric nervous system can no longer be inferred from one single drug, but the interactions between different drugs, which is more complex and unpredictable. So, it is more important to study the effects of compound anesthesia on the cognitive function of pediatric patients.

Basic research on the neurotoxicity of general anesthetics

Numerous basic studies have illustrated that the effects of general anesthetics on the cognition in children may involve different factors, including NMDA compensatory mechanisms, synaptic modification, Aβ deposition, neurotrophic apoptosis and so on. Possible mechanisms of cognitive dysfunction caused by general anesthetics in children are summarized in **Figure 1**.

Effects of general anesthetics on synaptic function

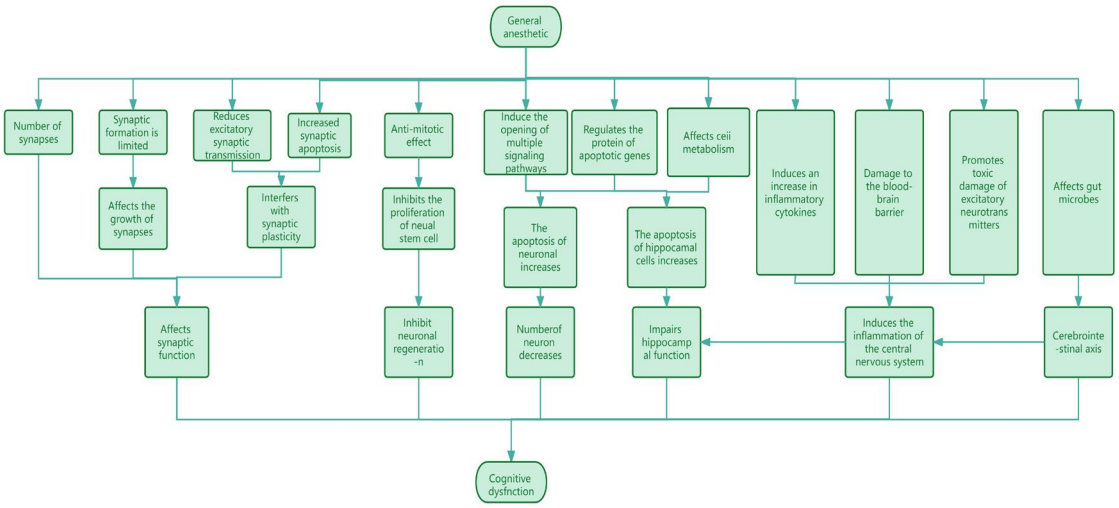

Figure 1. The possible mechanism of cognitive dysfunction caused by general anesthetics in children.

Synapses play a crucial role in learning and memory, serving as the foundation of long-term memory formation. The formation of synapses directly affects cognitive function which plays a major role in the development of pediatric neurological functions [43, 44]. Study has shown that sevoflurane induces spatial learning memory deficits in APP/PS1 mice, as well as elevates the production of intracellular Aβ, leading to the autophagy and impairment of synapses [45]. Moreover, study has indicated that general anesthesia can affect synaptogenesis in an age-dependent manner. Anesthetics may cause a decline in the number of dendritic spines and limited synapse formation during peak synaptic development [46]. In addition, anesthetics interfere with the normal physiological process of nerve regeneration and may regulate the growth of microglia, leading to postoperative cognitive dysfunction by mediating the decline in the expression of brain-derived neurotrophic factor (BDNF) [47, 48].

It was found that isoflurane could interfere with synaptic plasticity and lead to an increased apoptosis of synaptic spines [49]. Study also demonstrated that isoflurane reduced excitatory synaptic transmission in the hippocampus, affecting synaptic plasticity [50]. Shi et al. showed that isoflurane could cause changes in the presynaptic and postsynaptic membranes, as well as the destruction of synaptic vesicles [51]. These may be closely related to cognitive impairment.

It has been noted that ketamine abuse may decrease the expression of hippocampal postsynaptic density protein and affect the growth, plasticity, and transmission of excitatory synapses [23, 52]. These provide a possible direction for further investigation into how ketamine induces cognitive dysfunction.

Inhibition of neuron regeneration by general anesthetics

In the developing brain, neural progenitor cells have a greater capacity to divide and multiply, which also affects the development and maturation of the entire nervous system, especially the regeneration of neurons in the subventricular zone and the dentate gyrus of the brain, which play an important role in learning and memory [53]. Studies have found that general anesthetics, such as isoflurane, have inhibitory effects on the regeneration of neurons, which in turn affects the cognitive function in pediatric patients [54, 55]. The dose-dependent inhibitory effect of isoflurane on neural regeneration may be closely related to its anti-mitotic effect [56].

Yang et al. pointed out that isoflurane possibly inhibited the proliferation of the nervous system and made them prematurely differentiate into neurons, resulting in impaired cognitive function [57]. Gao et al. also showed that high concentrations of isoflurane inhibited the proliferation of neural stem cells in the dentate gyrus of the hippocampus of aged rats [21].

Similarly, Zhang et al. found that sevoflurane also affected the proliferation of neural stem cells by modulating RTN4, thereby leading to cognitive dysfunction [58]. Santos et al. noted that ketamine affected the proliferative regeneration of the central nervous system in zebrafish, but the effects on humans are unclear [59].

Effects of general anesthetics on the nervous system

Neuron apoptosis and the impairment of hippocampus function

Hippocampus, as a part of the limbic system, is mainly inseparable from the storage and conversion of short-term memory, as well as orientation and other functions. Therefore, hippocampus directly affect the learning and memory ability, as well as general cognitive function. Since general anesthetics can affect the normal physiological function of the hippocampus by impacting the apoptosis of neurons, they may also affect the cognitive function of pediatric patients. These anesthetics mainly activate GABAA receptors, inhibit NMDA receptors, and lead to sedative effect.

In 1999, Ikonomidou et al. found for the first time that after the administration of ketamine, a large number of apoptotic brain neurons were found in the brain of threats [60]. Subsequently, a large number of basic experimental studies on the cerebral neurotoxicity of general anesthetics emerged.

Liao et al. observed the hippocampal cells after exposing the rats in isoflurane and found that isoflurane triggered cell apoptosis by activating p38-MAPK signaling pathway [61]. Other studies have also shown that exposing to 3% sevoflurane for 4h caused increasing apoptosis of granule cells in hippocampus DG region, which was mediated by involving IκB/NF-κB /P65 signaling pathway, affecting the differentiation of late precursor cells in the dentate gyrus of the hippocampus to immature and mature neurons, and resulting in the recent spatial memory dysfunction in rats [62]. By establishing animal and cellular experiment models of isoflurane neurotoxicity, Yang et al. found that isoflurane could reduce mitochondrial membrane potential and promote the compensatory increase of respiratory chain function by opening mitochondrial ATP sensitivity potassium channels, and this process simultaneously contributed to the increasing production of reactive oxygen species (ROS), the excessive accumulation of which would disrupt energy production and activate the mitochondrial endogenous apoptotic pathway, resulting in cellular damage and neurotoxicity. These can lead to the impairment of cognitive function, specifically, learning and memory deficits [63].

Besides isoflurane, other anesthetics also have similar effects. Zhang et al. found that sevoflurane may cause excessive autophagy of hippocampal neural stem cells, in turn leading to cognitive impairment [64]. Su et al. revealed that propofol could induce apoptosis and autophagy of hippocampal cells in mice [65]. High doses of propofol were also found to induce apoptosis in neurons, affecting the cognitive function of mice [66]. Ketamine was reported to increase the expression of cellular caspase-3, causing neuron apoptosis and affecting the cognitive function of young SD rats [67].

Generally, most of the animal research aimed to investigate how the anesthetics function on different signaling pathways, the production of proteins encoded by apoptotic genes and the cellular metabolism. These studies indicate that anesthetics could induce neuron apoptosis and the damage of hippocampal region, affecting the cognitive function of the animals. However, the precise mechanisms of hippocampus damage are still unclear [68].

Inflammatory responses in the central nervous system induced by anesthetics

The effects of general anesthetics on pediatric cognitive function are primarily attributed to their impact on the developing nerve cells, including affecting the number of neurons, promoting apoptosis, as well as affecting the inflammatory responses of nervous system, which induces the increase of inflammatory factors [46, 69]. Numerous studies have indicated that cognitive dysfunction is resulted from the reduction of the number of neural stem cells and formation of neurons, as well as developmental neuroinflammation [70].

Hu et al. found that isoflurane induced an increased expression of inflammatory factors such as IL-1, IL-6 and TNF-α in the brain of mice [71]. The accumulation of a large number of inflammatory factors damages hippocampal neurons are “important players” in the transmission of information in the central nervous system. The accumulation of a large number of inflammatory factors creates long-duration potentials that inhibit the function of hippocampal neurons, leading to the alterations of their function. This promotes the development of excitatory neurotransmitters, such as glutamine, thereby inducing the inflammatory responses in central nervous system [72]. These may cause reversible or irreversible damage to the cognitive function of children.

Huang et al. stated that possible mechanisms of sevoflurane-induced inflammatory responses in the nervous system include the modulation of microglia function, the disruption of the blood-brain barrier (BBB), the alteration of intestinal flora, and the alleviation of cholinergic

neurotransmission [73]. Hou et al. also pointed out that sevoflurane could induce IL-6 secretion and trigger the inflammatory response in the nervous system. Sevoflurane may also activate microglia, and the inflammatory responses triggered by sevoflurane can result in postoperative cognitive dysfunction [74-76].

Hou et al. found that propofol could target the activation of transglutaminase 2 (TGM2)-mediated or NF-κB-mediated signaling pathways [77]. Guan et al. reported that propofol could down-regulate ROS/PI3K/Akt/mTOR/HIF-1α signaling pathway activity, while Liu proposed propofol might mediate immunomodulatory mechanisms [78, 79]. These possible mechanisms could result in the suppression of microglia and attenuated inflammatory responses of the nervous system, which is also considered one of the reasons for the neuroprotective effects of propofol [80].

Effects of general anesthetics on gut microbiology

Gut microbiology has been a hot topic of research in recent years, and studies have found that anesthetics may influence gut microbiology, and the changes of intestinal flora caused by anesthetics may contribute to postoperative cognitive impairment [81, 82]. Lu et al. suggested that gut microbes may influence neurological function through the brain-gut axis, leading to cognitive deficits, but the role played by the brain-gut axis is not clear yet [83]. Similarly, others also found that anesthetics might cause changes in the composition of gut microbes and lead to inflammation [84]. Moreover, anesthetics can cause the impairment of the BBB, which can further induce neuroinflammation, leading to neurological damage and impaired cognitive function.

Clinical research on the effects of general anesthetics on the cognitive function in pediatrics

The study of neurotoxicity of anesthetics aims to investigate whether general anesthesia has an impact on neurological function and its potential mechanisms. However, the question of whether this effect causes cognitive dysfunction in pediatric patients still requires further assessment by clinical studies and evidence-based medicine. In recent years, numerous retrospective clinical studies have been conducted to explore the effects of general anesthesia on pediatric cognitive function.

Hu et al. conducted a retrospective study on over 1,000 children, divided them into two groups based on whether exposed to general anesthesia before the age of 3, and assessed their cognitive functions via medical testing and school follow-up [71]. Their results revealed that changes in cognitive function induced by general anesthesia in children may be associated with the number of times they received general anesthesia before the age of 3, and a single exposure to general anesthesia medication was not associated with any abnormalities in cognitive function. Shi et al. conducted a retrospective study on 61 children and also showed that general anesthetics did not cause cognitive dysfunction in pediatric patients within 3 months after surgery [85].

Nevertheless, there are studies that suggest general anesthetics may have long-term effects on cognitive function in pediatric patients [86]. Partanen et al. proposed that prolonged exposure to general anesthetics was a risk factor for clinically significant neurocognitive decline [87]. Additionally, in preterm infants who underwent surgery for conditions such as congenital heart disease and necrotizing small intestinal colitis, researchers found that general anesthetics could also lead to cognitive dysfunction [88].

The majority of such retrospective clinical studies have concluded that a single general anesthetic procedure before the age of 3 will not result in long-term cognitive dysfunction [89]. However, multiple general anesthetic procedures before the age of 3 may cause cognitive dysfunction and even long-term effects on cognitive function in children [90]. This may be linked to the rapid development of the nervous system and brain in the neonatal and early childhood period [91].

Currently, larger-scale clinical prospective studies worldwide are the Pediatric Anesthesia Neurodevelopmental Assessment (PANDA) study, the Mayo Children's Anesthesia Safety (MASK) study, and the General Anesthesia or General Anesthesia in the Waking Region (GAS) study. Compared to retrospective studies, these prospective studies are well-planned and have clearer research objectives. In contrast, retrospective studies have practicality and induction, and different conclusions can be drawn from these two types of studies with different reference values.

According to the summary data, the latest PANDA study conducted neuropsychological test between children aged 8-15 who had undergone hernia surgery and their siblings and obtained inconsistent neurodevelopmental assessment

Table 2. Summary of clinical studies in recent years

Title	Author	Year	Research subjects	Research	Possible mechanism	Findings
Association between Exposure of Young Children to Procedures Requiring General Anesthesia and Learning and Behavioural Outcomes in a Population- based Birth Cohort.	Hu D [71]	2017	Children under 3 years of age	A comparative study of cognitive function in children exposed and unexposed to general anesthesia before the age of 3 years to investigate whether there is an effect of general anesthesia on pediatric cognitive functioning.	Exposure to general anesthetic drugs leaves immaturely developed nerves vulnerable. Adverse effects due to surgical operations, such as surgical stress reactions.	General anesthesia causes cognitive changes in children that may be related to the number of general anesthetics received before the age of 3 years, and single exposure to general anesthesia drugs did not reveal abnormalities in their cognitive functioning.
Neuropsychological and Behavioural Outcomes after Exposure of Young Children to Procedures Requiring General Anesthesia: The Mayo Anesthesia Safety The Mayo Anesthesia Safety in Kids (MASK) Study	David O [7]	2018	Children under 3 years of age	Unexposed, individually exposed and multiply exposed children born in Olmsted County, Minnesota, from 1994 to 2007 were sampled using a propensity-guided approach and underwent neuropsychological testing at ages 8 to 12 or 15 to 20.	Multiple, but not single, exposures to anesthesia are associated with an increased risk of ADHD, learning disabilities and reduced performance on the group-managed competence and achievement assessments, which was possible associated with child and family factors.	Anesthesia exposure before age 3 years old was not associated with deficits in the primary outcome of general intelligence.
Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre, randomised, controlled equivalence trial A randomised, controlled equivalence trial	McCann ME [94]	2019	Infants with a gestational age of less than 60 weeks	Infants with a gestational age of less than 60 weeks, randomly receiving awake regional anesthesia or sevoflurane-based general anesthesia and undergoing inguinal hernia, who had no previous risk factors for general anesthesia or neurological injury.	Both hippocampal and non-hippocampal memories are deficient. Potential for cumulative effects on subtle individual or multiple deficits in skills development.	Slightly less than 1 hour of general anesthesia in early infancy does not alter neurodevelopmental outcomes at 5 years of age compared with awake regional anesthesia.
Longitudinal associations between exposure to anesthesia and neurocognitive functioning in pediatric medulloblastoma.	Partanen M [87]	2021	Children before and after the age of 3 years	Pediatric medulloblastoma patients receive risk-adapted craniospinal photon irradiation followed by four cycles of high-dose chemotherapy and stem cell salvage. Neurocognitive testing was completed at study baseline (post-surgery and <2 weeks after initiation of radiation therapy) and annually for 5 years.	Anesthesia may induce apoptosis and cell death, thereby affecting neurological and cognitive development. General anesthetic drugs may selectively target damage to the hippocampus and learning performance.	Increased anesthetic exposure is a risk factor for clinically significant neurocognitive decline, in addition to age at diagnosis and treatment risk group factors.
Prospectively assessed neurodevelopmental outcomes in studies of anaesthetic neurotoxicity in children: a systematic review and meta-analysis.	Caleb Ing [92]	2021	Children under 18 years of age	Studies evaluating neurodevelopmental outcomes and prospectively enrolling children exposed to a single GA procedure compared with unexposed, and outcomes were evaluated using random-effects meta-analyses.	Influence of subjective parental factors.	A single GA exposure was associated with statistically significant increases in parent reports of behavioral problems with no difference in general intelligence.
Longitudinal assessment of cognitive function in young children undergoing general anesthesia.	Shi Y [85]	2022	Children aged 2.5-6 years	A retrospective study of 61 children undergoing general anesthetic surgery	Neurodevelopment impairment caused by perioperative event take years to become apparent, and may be improved by surgery.	General anesthesia for elective surgery in young children is not associated with a decline in working memory, processing speed and fine motor skills in the first 3 months postoperatively.

Title	Author	Year	Research subjects	Research	Possible mechanism	Findings
Multiple General Anesthesia in Children: A Systematic Review of Its Effect on Neurodevelopment	Colletti G [95]	2023	Children under 4 years of age	Pooled analysis by summarizing the main literature and clinical studies of recent years.	Cognitive deficits induced by multiple exposures to general anesthesia may identify an increased risk of anesthesia-related neurotoxicity. Association between multiple general anesthetic procedures and deficits in certain neuropsychological skills.	Controlled studies on mGA administered before 4 years of age agree that there is a higher risk of neurodevelopmental delay in children receiving them.
Association Between Receipt of General Anesthesia During Childhood and Attention Deficit Hyperactive Disorder and Neurodevelopment	Song JY [97]	2023	Children with a median age of 3.75 years	Follow-up and research analysis of children under 3 years of age undergoing general anesthesia to find associations between general anesthesia and adverse neurodevelopmental and behavioral disorders in children.	Repeated and prolonged exposure to general anesthesia in children under 3 years of age may cause neuronal damage. General anesthesia during periods similar to infancy and early childhood alters prefrontal cortex and reduces axonal connectivity. Exposure to anesthetics may induce developmental neurotoxicity and accelerate neurodegeneration in young children.	Exposure to general anesthesia with ETI in children is associated with an increased risk of ADHD and adverse results of neurodevelopmental screening test.

Note: ADHD, attention deficit and hyperactivity disorder; ETI, endotracheal intubation.

results [92, 93]. The MASK study was a comparative study of 308 single-exposure general anesthesia children under 3, with 206 multiple-exposure children and 411 unexposed children selected from the same community [7]. Children under 6 months of age were divided into two groups, a general anesthesia group and a local anesthesia group for comparison [94]. These three studies arrived at very similar conclusions, indicating that there were no significant differences in cognitive function between single anesthesia-exposed and unexposed children [95]. Moreover, a clinical trial also found that single anesthesia may not cause neurodevelopmental effects [96]. However, a secondary analysis of the MASK study suggested that the number of anesthesia sessions was associated with the effects of anesthetics on cognitive function, and multiple sessions of general anesthesia in pediatric patients may result in the alterations of processing speed [97]. These may have neurodevelopmental effects. Although the differences were not significant, they were associated with a potentially increased incidence of impairments in internalizing behaviors and executive functioning.

This suggests that the three prospective studies align with the conclusions drawn from the retrospective studies. In summary, a single general anesthetic procedure administered before the age of 3 does not result in long-term cognitive impairment; however, multiple general anesthetic procedures administered before the age of 3 may lead to cognitive impairment or even cause long-term effects on cognitive functioning in pediatric patients.

Meanwhile, Wang et al. conducted research on 76 children who underwent thyroglossal adenostomy and found that when the anesthetic depth index (Narcotrend anesthesia value, NT value) was between 80 and 94 under the monitoring of NT value, the removal of tracheal tubes could effectively reduce the risk of cognitive dysfunction in children [98]. This finding may offer new insights into clinical research, and it is consistent with previous studies that have demonstrated the influence of anesthesia duration on cognitive function [99].

However, the limitation of these studies might be that it is not possible to control all the potential influence factors such as the social, family, educational background of the children, as well as the psychological factors, which have great impact on their cognitive function. Additionally, due to the limitation of sample size, it is difficult to generalize the findings in most of the studies. Furthermore, it could be a great challenge to conduct psychological testing on large population, and subtle changes may not be detected in studies that involve the entire population. These limitations highlight the need to explore more appropriate solutions. The effects of general anesthetics on neurodevelopment and cognitive function in pediatric patients and the development of new anesthetics still require

a large number of rigorous clinical studies. A summary of relevant clinical studies in recent years is shown in **Table 2**.

Conclusion

Regarding the effects induced by general anesthesia on pediatric patients, most of the current research focus on whether general anesthetics influence the cognitive function and the possible mechanisms [100]. Scholars have also conducted studies and analyses on this issue, and a relatively unified conclusion was reached. Namely, general anesthetics may cause neuro toxicity by inducing neuronal apoptosis, inhibiting neuron regeneration, and impairing synaptic and autophagic functions [101]. Clinical studies generally agree that a single exposure to general anesthesia before the age of 3 years does not affect cognitive function, and that the effects of general anesthetics on cognitive function in children are related to the number of anesthesia sessions and the duration and depth of anesthetic exposure [102]. However, the specific mechanisms and effects on pediatrics cannot be fully determined at present, and further studies are needed.

In conclusion, most current basic and clinical studies have only been able to demonstrate that general anesthetics may have neurotoxicity, but the exact mechanism remains unclear. The effects of general anesthesia on cognitive function in children may be related to the number of exposures and the duration of anesthesia, but other factors such as surgical procedures and interferences cannot be excluded. Therefore, further research is needed to upgrade the experimental apparatus and improve the accuracy of assessment methods for the neurotoxicity of general anesthetics. It is necessary to conduct more prospective studies, coupled with retrospective studies, in the clinical aspect. There is currently no reliable basis to prove that general anesthesia has an effect on pediatric cognitive dysfunction, which requires future research to urgently refine the experimental protocol and clarify the precise impacts and mechanisms. These may be helpful to provide prevention measures and suggestions for anesthesia in children.

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Research progress on the pharmacological activity and mechanism of chlorogenic acid in alleviating acute kidney injury in sepsis patients

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Highlights

- The pharmacological action of chlorogenic acid was summarized.
- The mechanism of acute kidney injury (AKI) was investigated.
- The signaling pathways through which chlorogenic acid plays its role in AKI were summarized for the first time.
- A possible new drug for treating a common perioperative complication, namely sepsis-induced AKI, is revealed.

Abstract

Sepsis-induced acute kidney injury (SAKI) is a serious perioperative complication and a common clinical syndrome characterized by a rapid deterioration in renal function with a high incidence of 70%. The causes of SAKI include impaired mitochondrial function of renal tubular epithelial cells, oxidative stress, inflammatory reaction and renal microcirculation disorder. Chlorogenic acid, as a natural product of plant origin, has various biological activities, such as antibacterial, antiviral, and anti-tumor, and plays a significant role in the treatment of SAKI. This article reviews the pharmacological activities of chlorogenic acid and the signaling pathways involved in relieving SAKI, in order to provide a theoretical basis for in-depth study of the mechanisms underlying the alleviation of SAKI and the confirmation of potential therapeutic targets.

Keywords: Chlorogenic acid, sepsis-induced acute kidney injury, pharmacological activity, mechanism, signaling pathway

Introduction

As one of the most common perioperative complications, sepsis is a condition characterized by multi-organ dysfunction caused by the host's response to infection, often involving acute kidney injury (AKI). Patients with sepsis usually have a poor prognosis, leading to longer stays in the intensive care unit, higher mortality rates, increased rates of long-term disability, and decreased quality of life [1]. Chlorogenic acid (CGA) is a natural product of 1-bit carboxyl group of caffeic acid and 3-bit hydroxy-condensedated ester of quinic acid. It causes few adverse reactions and can be highly tolerated, offering unique advantages in the treatment of sepsis-induced acute kidney injury (SAKI). At present, CGA is commercially obtained from plants, such as Duzhong leaves, dandelion, honeysuckle, and tobacco leaves [2]. To date, it has been established that CGA has a good therapeutic effect on SAKI, possibly because of its biological activities, such as cardiovascular protection, antioxidant effect, lipid -lowering effect, and anti-inflammatory effect [3-6].

In recent years, CGA has been valued by many scholars. Studies of Zhang and Chen have

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shown that CGA can reduce the small intestine damage of stress-type chickens by inhibiting inflammatory reactions and oxidizing, and can also improve antioxidant capacity [7, 8]. This paper summarizes the pharmacological activities of CGA in alleviating SAKI, aiming to provide reference for in-depth study of mechanisms and related signal pathway of CGA in SAKI.

Pharmacological activities of CGA

Cardiovascular protective effect

CGA has shown good efficacy in the treatment of cardiovascular and thromboembolic diseases. Myocardial hypertrophy can cause an increase in the incidence and mortality of cardiovascular diseases [9]. Studies have shown that the CGA pretreatment can reduce the apoptosis rate of H9c2 myocardial cells and reduce the reactive oxygen species (ROS) through nuclear factor κappa B (NF-κB) signaling pathway [10]. ROS plays a role in inhibiting myocardial hypertrophy and thus protecting the cardiovascular system. Study has pointed out that CGA reduces the damage of vascular endothelial cells by removing oxygen free radicals and anti-lipid peroxidation, which has a protective effect on the cardiovascular system [11].

Antioxidant effect

When the body is exposed to harmful stimuli, the balance of the oxidation system and the antioxidant system can be disrupted [12]. This imbalance leads to the enhancement of the oxidation system, resulting in oxidative stress within the body and the excessive production of ROS and reactive nitrogen species. Study of Ferrare found that CGA has a very strong antioxidant effect, which can accelerate wound repair in diabetic rats by playing an antioxidant role without affecting the levels of superoxide dismutase (SOD) and catalase in wound [13]. It has been shown that CGA can reduce lung tissue damage and reduce the content of malondialdehyde (MDA), ROS and inflammatory factors [14]. Song reported that CGA eliminated and inhibited the production of ROS by enhancing antioxidant stress defense [15]. Other studies have also proven that CGA extracted from honeysuckle leaves and flavonoids can play a good antioxidant role [16, 17]. CGA intervention can inhibit the reduction of the anti-apoptotic protein B-cell lymphoma-2 (Bcl-2) and the increase of the apoptotic protein BCL-2-associated X protein (Bax) [18]. Feng et al. detected the antioxidant effect of CGA in vivo and in vitro, and found that CGA has an anti-inflammatory activity and exerts protective effect against chronic kidney injury [19].

Lipid-lowering effect

CGA is marketed under the trade name Svetol and is incorporated into products such as coffee and chewing gum as additives for weight loss. In the treatment of obesity, research shows that CGA can regulate sugar and lipid metabolism [20]. Shirkhani et al. observed the changes in weight, plasma lipid content and related gene expression in mice fed with a high-fat diet (HFD) for 7 weeks that treated by CGA [21]. The results showed that CGA reduced the increase in weight and fat caused by HFD, improved blood lipid status, reduced plasma toxicity, and regulated the expression of ribonucleic acid related to fat and fat decomposition. It is indicated that CGA can regulate intestinal microbiota and help improve HFD-induced obesity. Study of Ma et al. exhibited that CGA promoted the oxidative degradation of lipids, and inhibiting mouse fat synthesis reduced fat and weight by regulating the expression of liver fat metabolism-related genes and proteins [22].

Anti-inflammatory effect

Inflammatory reaction is a physiological reaction of tissue damage caused by exogenous or endogenous factors [23]. A large number of studies have shown that lipopolysaccharides (LPS) can induce changes in the surface adhesion molecules of neutrophils [24]. After activation, a large number of super-oxides and a series of inflammatory factors are produced to form a cascade of inflammatory response, which mainly causes local tissue and cell damage through free radicals and inflammatory factors. In the study of Gao, CGA administration significantly reduced intestinal inflammation in mice, reduced the levels of pro-inflammatory cytokines interleukin (IL)-1β and IL-6, and increased the expression levels of anti-inflammatory factor IL-10 and antioxidant-related genes catalase, Glutathione Peroxidase 1, Glutathione Peroxidase 2 and SOD 1 [25]. Shimizu showed that CGA enhanced the antioxidant and anti-inflammatory ability of broiler intestines by inhibiting DNA methylation, and its effects on inflammation and DNA methylation lasted until the later stage of growth [26].

The pathogenesis of SAKI

Sepsis is a life-threatening multi-organ dysfunction caused by the dysfunction of body response to infection [27]. During the progression of sepsis, patients can have multiple organ dysfunction syndrome and even multi-organ

failure, and the kidney is one of the organs that often involved. Studies have shown that the pathogenesis of SAKI is related to oxidative stress injury, inflammation, and microcirculation disorders [28].

Inflammation

During sepsis, inflammatory mediators derived from pathogen-associated molecular patterns (PAMPs) and synthesized by activated immune cells release damage-associated molecular patterns (DAMPs), leading to host cell damage. DAMPs and PAMPs can be recognized by renal tubular epithelial cells (RTECs) through transmembrane or intracellular pattern recognition receptors (PRRs) [29].

After PRRs combined with PAMPs and DAMPs (**Figure 1**), immune cells are activated to kill microorganisms. They secrete pro-inflammatory factors, such as tumor necrosis factor-α (TNF-α), IL-1α, IL-6 and chemokines, enhance the expression of co-stimulation factors, activate high-efficiency T cells, produce metabolites of arachidonic acid, initiate exogenous coagulation pathways through tissue factors and facilitate the formation of activated thrombin. Subsequently, these processes amplify thrombosis through a cascade reaction of the internal coagulation pathway. Through the LPS-induced SAKI model, Li's research team found that the levels of TNF-α and IL-1β in the model group were higher than those in the pseudo-surgery group [30]. Also, the HE stained pathological sections revealed degeneration and necrosis in the renal tubular epithelial cells in the model group. The renal tubules exhibited a proteinaceous cast formation and significant dilation. Additionally, there was renal interstitial congestion edema, accompanied by infiltration of a large number of inflammatory cells.

The molecular weight of DAMS/PAMPs is small enough to be filtered in the glomerulus. The filtered DAMS/PAMPs entering the renal tubular lumen can be recognized by toll like receptors (TLRs) on the surface of RTECS, and can also affect RTECS through the leakage of adjacent peritubular capillaries. After PAMPs bind to DAMPs, PAMPs/DAMPs can activate signal transduction pathways, and then recognize the TLRs on the surface of RTECS that can increase downstream inflammatory signal cascades, pro-inflammatory cytokines and ROS synthesis [31].

Oxidative stress injury

Oxidative stress occurs in the human body when there is an imbalance between oxidation and antioxidant systems. During sepsis, inflammatory mediators and PRRs combine to trigger inflammatory cascade reaction, increase pro-inflammatory factors, cooperate with oxidative stress, and trigger the aggregation of multinucleated neutrophils. Neutrophils can produce superoxide through the complex process of "oxidative burst". The oxidation system mainly includes active free radicals, such as ROS and reactive nitrogen species. The research team of Daenen reported that in the process of sepsis, the outbreak leads to an increase in ROS [32]. This increase results in dysfunction, shedding, or apoptosis of glomerular or renal tubular epithelial cells, and in severe cases, widespread cell death occurs. Neutrophil-induced oxidative enhancement further attracts pro-inflammatory chemokines, promotes the recruitment of leukocytes to tissue injury sites, and initiates a cytokine storm, leading to the further generation of ROS.

Microcirculation disorder

The traditional view holds that pre-renal injury is caused by insufficient renal perfusion, that is, the reduction of renal blood flow is one of the main causes of SAKI [33]. However, novel evidence shows that SAKI can occur without low renal perfusion, but along with stable hemodynamics, or even normal or increased renal blood flow [34]. It is suggested that microcirculation dysfunction may play an important role in the development of renal injury.

In sepsis, tissue damage leads to an increase in inducible nitric oxide synthase (iNOS) expression and the uneven distribution of iNOS in the kidney [35]. Simultaneously, the activity of endothelial NO synthase decreases, leading to uneven regional concentration of NO. The dysfunction of NO synthase leads to the reduced NO-mediated endothelium-dependent vasodilation, disrupting the balance of renal microcirculation.

Mechanisms of CGA in the treatment of SAKI: anti-inflammatory and antioxidant effects

CGA is one of the active ingredients of many Chinese herbal medicines. It has biological activities such as anti-tumor, antioxidant, and anti-inflammatory, along with advantages of few adverse reactions and good body tolerance in the treatment of a variety of diseases. It is reported that LPS-induced inflammatory cytokines play an important role in the pathogenesis of SAKI. LPS-induced SAKI can lead to severe renal pathological damage, including

destroying glomerular structure, degenerating renal tubular epithelial cells, and decreasing renal function biochemical indicators (such as urea nitrogen, creatinine, kidney injury molecule 1, neutrophil gelatinase-associated lipocalin) and pro-inflammatory cytokines (such as TNF- α and IL-1 β in serum and renal tissue). The renal oxidative stress indexes include ROS, MDA and SOD. A large number of studies have shown that reducing the levels of pro-inflammatory cytokines and oxidative stress indicators can alleviate SAKI. Peng's study confirmed that CGA could regulate inflammation and oxidative stress response, where excessive inflammatory response is an important cause of SAKI [36]. TNF-α, as an important promoter of SAKI, can cause damage to renal tubular epithelial cells, thereby leading to SAKI. IL-1 β and IL-6, alongside TNF-α, are pivotal inflammatory mediators in the cytokine cascade, inducing a cascade reaction that triggers an excessive systemic inflammatory response.

The production of macrophages in sepsis can induce the synthesis of a large number of free radicals, leading to oxidative stress. However, renal antioxidant system lacks the capacity to adequately remove these excessive free radicals, resulting in an imbalance in oxidation/antioxidation of the kidney, which attacks the cellular lipid substances. MDA is the end product of lipid peroxidation process, and its level can reflect the extent of lipid peroxidation damage in the body. ROS-induced oxidative damage can promote the development and progression of SAKI.

Study of Zhou showed that CGA could effectively improve the inflammatory response induced by AKI in a dose dependent manner through TNF-α and IL-1β in rat serum [37]. Han's team found that CGA pretreatment could reduce the expression of inflammatory factors and the levels of ROS and MDA and increase the activity of SOD [38]. CGA may be achieved by regulating nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase 1 (HO-1) signaling pathway.

Signaling pathways

Nrf2/NLRP3 signaling pathway

Nrf2 is a basic leucine zipper redox-sensitive transcription factor with anti-inflammatory effect, serving as the primary regulatory factor for genetic protection in various cells. Under static conditions, Nrf2 remains inactive as it interacts with Kelch-like ECH-associated protein 1 (Keap1). In response to oxidative and inflammatory stress, Nrf2 is released from Keap1 and transported to the nucleus to trans-activate the expression of cell protection genes such as HO-1 and quinoneoxidoreductase (NQO1) so as to eliminate oxidative stress and inflammation. Study showed that CGA significantly increased the expression of Nrf2, promoted its entry into the nucleus, and increased the expression of HO-1 and NQO1 proteins [39]. According to the research results of Zheng et al., CGA can inhibit oxidative stress and inflammation by activating the Nrf2/HO-1 signaling pathway [40]. As one of the most studied and important members of the Nod-like receptor family of PRRs, Nod-like receptor family 3 (NLRP3) inflammasome consists of NLRP3, apoptosis-associated speck-like protein containing a CARD and cysteinyl aspartate specific proteinase(caspase)-1 preforms, and its central role is to activate the aspartic proteolytic enzyme containing cysteine [41]. Active cleaved caspase-1 is produced, which cleaves the pro-inflammatory cytokines IL-1β and IL-18 to be biologically active. Nrf2 inhibits the production of ROS, which has a positive regulatory relationship with the activity of the NLRP3 inflammasome, and ROS is required for the activation of the NLRP3 inflammasome [42, 43]. ROS, serving as an intermediate in the activation of Nrf2 and NLRP3 inflammasome, can counter the NLRP3 inflammasome by reducing ROS production. Nrf2 has a protective effect against oxidative and inflammatory damage by inhibiting the activity of NLRP3 inflammasome. Some studies have reported that CGA can inhibit the activation of NLRP3 inflammasome [44]. In summary, CGA plays an important role in Nrf2/NLRP3 signaling pathway. Specifically, CGA activates HO-1/Nrf2 signaling pathway through Nrf2, promotes protein expression of Nrf2, HO-1 and NQO1, inhibits production of ROS and activation of NLRP3 inflammasome, and reduces the level of inflammatory factors, thereby improving renal function (**Figure 1**).

TLR4/NF-κB signaling pathway

As an important cell membrane receptor, TLR4 plays a key role in the process of inflammation reaction. As a downstream effector of TLR4 signaling pathway, recombinant NF-κB is bound to the inhibitor of NF-κB (IκB) in normal physiological state by heterodimer composed of inactive NF-κB p65 and p50. In a pathological state, IκB kinase can specifically phosphorylate IκB and promote the transfer of NF-κB p65 into the nucleus, causing the body to release inflammatory factors that trigger inflammatory response. Studies have shown that CGA can effectively down-regulate the expression of TLR4 protein in renal tissue and inhibit the phosphorylation of-

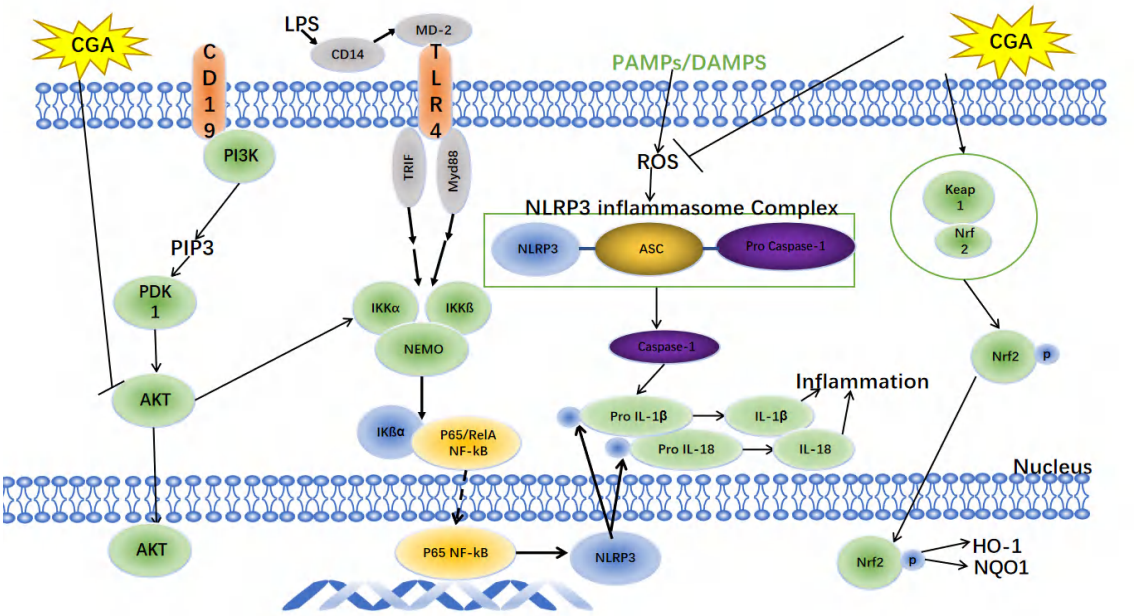

Figure1. Signaling pathway involved in CGA-mediated treatment of SAKI. SAKI, sepsis-induced acute kidney injury; CGA, chlorogenic acid; LPS, lipopolysaccharides; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; TLR4, toll like receptor 4; ROS, reactive oxygen species; NF-κB, nuclear factor κappa B; Nrf2, nuclear factor erythroid 2-related factor 2; NLRP3, Nod-like receptor family 3; IL, interleukin; HO-1, heme oxygenase 1; NQO1, quinoneoxidoreductase; IκBα, inhibitor kappa B α; IKKβ, inhibitor of kappa B kinase; IKKα, IκB kinase α; TRIF, Toll/IL-1 receptor domain containing adaptor inducing IFN-β; Myd88, myeloid differentiation primary response gene 88; Keap1, Kelch-like ECH-associated protein 1; caspase-1, cysteinyl aspartate specific proteinase 1; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; PDK1, pyruvate dehydrogenase kinase isozyme 1; CD19, B-lymphocyte antigen CD19 precursor; CD14, cluster of differentiation 14; PIP3, 3-phosphate phosphatidylinositol; ASC, apoptosis-associated speck-like protein containing a caspase-recruitment domain; MD-2, myeloid differentiation protein-2; NEMO, nuclear factor-κappa B essential modulator.

Table1. Mechanism and signaling pathway of CGA in treating SAKI

Medicine	Types of signaling pathway	Molecular substances	Pharmacology
CGA	Nrf2/NLRP3 signaling pathway	Nrf2, Keap1, HO-1, NQO1, ROS, NLRP3, cleaved caspase-1, IL-18, IL-1β	Oxidative stress and inflammation
	TLR4/NF-κB signaling pathway	TLR4, Myd88, P65 NF-κB, IκBα	inflammation
	PI3K/AKT signaling pathway	PI3K, AKT, p-AKT, Bcl-2, ROS	Oxidative stress

Note: CGA, chlorogenic acid; SAKI, sepsis-induced acute kidney injury; Nrf2, Nuclear Factor erythroid 2-Related Factor 2; NLRP3, Nod-like receptor family 3; TLR4, toll like receptor 4; NF-κB, recombinant nuclear factor kappa B; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; Keap1, Kelch-like ECH-associated protein 1; HO-1, heme oxygenase 1; NQO1, quinoneoxidoreductase; ROS, reactive oxygen species; caspase-1, cysteinyl aspartate specific proteinase 1; IL, interleukin; Myd88, myeloid differentiation primary response gene 88; IκBα, ecombinant inhibitory subunit of NF kappa Bα; Bcl-2, B-cell lymphoma-2.

NF-κB p65 and IκBα [45]. Studies have reported that TLR4/NF-κB signaling pathway plays a role in diseases such as acute kidney injury [46]. Zhou et al. suggested that CGA could inhibit TLR4/NF-κB pathway to alleviate acute kidney injury in sepsis patients (**Figure 1**) [37].

Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway

The PI3K/AKT signal pathway is involved in the onset of various diseases, including cancer, cardiovascular disease, nerve disease, endocrine disorders, etc. As a proto-oncogene, AKT protein kinase is an important downstream component of PI3K, which is activated upstream to produce the second messenger phosphatidylinositol 3,4,5-triphosphate (PI-3,4,5-P3). PI3K binds to

the N-terminal pleckstrin homology domain of AKT, facilitating the translocation of AKT from the cytoplasm to cell membrane. Moreover, AKT is activated through pyruvate dehydrogenase kinase isozyme 1-mediated phosphorylation site. The activation of the PI3K/AKT signaling pathway can lead to the onset of diseases. Studies have demonstrated that CGA can significantly inhibit the expression of p-PI3K, p-Akt and Bcl-2 proteins, while inducing an increase in Bax protein expression [47]. The higher the concentration of CGA, the more obvious the changes in protein expression. In addition, CGA can reduce the activation of PI3K/Akt signaling pathway and interfere with the PI3K/AKT pathway, leading to a decrease in p65 entering into the nucleus, as well as a reduction in the production of inflammatory factors and ROS [48]. Zhou proposed the potential of CGA to prevent hyperuricemic nephropathy (CKD) by regulating PI3K/Akt pathway (**Figure 1**) [37].

Conclusion

CGA is a low-cost and easily obtained natural product with various biological activities. However, in China, the biosynthesis of CGA, its pharmacological activities, as well as research and development are relatively undeveloped. Despite having abundant CGA plant sources, China has not fully utilized this rich resource, resulting in significantly lower utilization efficiency compared to developed countries. As CGA research continues to advance, our understanding of its potential benefits grows more comprehensive. It is hoped that CGA can be utilized not only as a therapeutic drug for diseases such as SAKI in clinical practice, but also be processed into medicinal diets to promote the overall well-being of people.

In **Table 1**, we summarize the pharmacological effects and signaling pathways of CGA in alleviating SAKI, as well as the molecular substances involved in the mechanism of action: CGA exerts anti-inflammatory and antioxidant effects on SAKI via the Nrf2/NLRP3 signaling pathway, CGA plays an anti-inflammatory role in the treatment of SAKI via TLR4/NF-κB signaling pathway, and CGA fulfills an antioxidant role in SAKI through the PI3K/AKT signaling pathway.

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Perioperative care in hypoadrenalism: A narrative review

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Highlights

- Amongst the many causes of adrenal insufficiency, primary adrenal failure or Addison's disease is an important cause of hypoadrenalism.
- Adreanl insufficiency is a common medical problem in surgical patients and can cause preventable major ad verse events.
- It is important to identify patients at high-risk of adrenal insufficiency and to give appropriate replacements perioperatively.
- Current guidelines clearly outline the required amount of steroid dose during the intraoperative and postopera tive period in patients with insufficient adrenal function.

Abstract

Impaired production of adrenal hormones or hypoadrenalism is not uncommon and has various aetiologies. Untreated hypoadrenalism during operative period can lead to preventable major adverse events. Identification and risk stratification in those who have hypoadrenalism is an important part of preoperative assessment. There are multiple guidelines on intraoperative care and anaesthesia for patients with adrenal insufficiency. The aim of this review is to discuss the available evidence and optimal management approaches for surgical patients with hypoadrenalism during intra- and post-operative periods.

Keywords: Hypoadrenalism, adrenal insufficiency, perioperative care, surgery

Introduction

Adrenal insufficiency or hypoadrenalism is not uncommon in surgical patients. Hypoadrenalism can be primary, secondary or tertiary. Diseases in adrenal gland such as infarction, infection or tumour can cause primary hypoadrenalism. Addison's disease is a rare primary endocrine disease of the adrenal gland that affects 10 in 100,000 people across the world [1]. Its incidence in Australia is about 100 new diagnosis per year with 2,500 affected across the country [2]. Other situations with adrenal insufficiency are secondary hypoadrenalism from hypopituitarism or adrenocorticotropic hormone (ACTH) axis suppression. Patients with adrenal insufficiency require lifelong glucocorticoid therapy to maintain vital body functions including balanced immune system, cardiovascular system and glycaemic metabolism [3]. The maintenance dose of glucocorticoid therapy is not sufficient in stress situations [4]. Perioperative period is associated with significant stress to the human endocrine system, and extra glucocorticoid supplementation is essential throughout this period. However, a limited number of universally accepted guidelines are available on glucocorticoid supplementation during perioperative period for patients on longer term replacements. The aim of this review is to summarize current consensus on perioperative management of adrenal insufficiency.

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Table 1. Adrenal hormones / catecholamines and their function

Adrenal gland	Zone	Hormone category	Compound	Function
Cortex	Glomerularis	Mineralocorticoids	Aldosterone	Salt and water regulation
	Fascicularis	Glucocorticoids	Cortisol Cortisone Corticosterone	Glucose metabolism Immune modulation Vascular effect
	Reticularis	Androgens	Dehydroepiandrosterone	Masculinization
Medulla		Catecholamines	Epinephrine Norepinephrine	Stress response

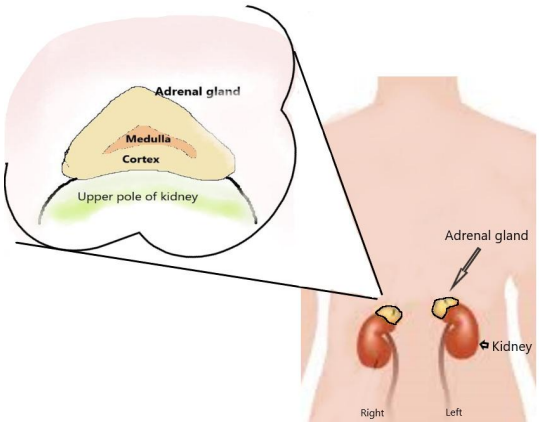

Figure 1. Anatomy of the adrenal gland.

Pathophysiology of adrenal insufficiency

There are two adrenal glands in human body. They are located over the superior pole of both kidneys and are also known as suprarenal glands [1]. Each gland consists of an outer cortex and an inner medulla (See **Figure 1**). The cortex is developed from mesothelial cells, and the medulla is derived from the neural crest which belongs to the ectoderm embryologically [3]. These two small glands produce several hormones that are responsible for regulating multiple physiological functions including blood pressure, metabolism, and immunity. The embryological development of the gland is related to its function.

Adrenal cortex produces corticosteroid hormones which are released in response to hypothalamic and pituitary hormones. The main corticosteroid hormones are glucocorticoids, mineralocorticoids, and androgens. On the other hand, the adrenal medulla produces catecholamines in response to sympathetic stimulation. These are epinephrine and norepinephrine, also known as adrenaline and noradrenaline [4]. **Table 1** further describes the function of the adrenal hormones and catecholamines.

Inability of adrenal gland to produce appropriate amounts of these hormones (**Table 1**) leads to adrenal diseases. This could either be hormone deficiency or excess. Primary adrenal insufficiency is low levels or absence of glucocorticoids production. This is also known as Addison's disease because it was first described by Thomas Addison [5]. The commonest cause for Addison's disease was tuberculosis at that time. However multiple causes are responsible for adrenal insufficiency and the commonest one is autoimmune adrenalitis (See **Table 2**) [6]. Autoimmune adrenalitis affects primarily the adrenal cortex. The pathogenesis involves both humoral and cell mediated immune mechanisms. Furthermore, other autoimmune disorders, such as polyglandular autoimmune syndrome type 1 and 2, are identified in about half of the patients with autoimmune adrenalitis [7, 8].

The diagnosis of adrenal insufficiency is based on ACTH stimulation test or "synacthen test" in suspected patients with clinical symptoms and positive basic laboratory tests [9]. Imaging studies and adrenal antibodies are used to identify the cause for adrenal insufficiency. Glucocorticoid replacement is the treatment of choice [9].

Preoperative assessment

The perioperative period exerts significant stress on the human body secondary to a number of factors, such as hypoxia, tissue inflammation, altered body fluids, and anaesthetic drugs. This perioperative stress activates the hypothalamic pituitary adrenal axis, which can be seen during various surgical procedures [10, 11]. As a result, glucocorticoid (cortisol) levels are increased perioperatively. However, the hypothalamic pituitary adrenal response is not consistent throughout the perioperative period with maximal ACTH and cortisol levels being recorded at the time of extubating or recovering from anaesthesia [10-12]. Furthermore, the cortisol levels slowly decline to normal in about 48 to 72 hours, while ACTH declines faster, within 24 hours [11, 12]. Cortisol has many vital functions during stress periods, including modulation of carbohydrate-protein-lipid me-

Table 2. Causes of adrenal insufficiency

Mechanism	Pathology
Autoimmune	Autoimmune adrenalitis
Infective	Bacterial -Tuberculosis
	Fungal infection- Histoplasmosis
	Spirochaete- Syphilis
	Viral- HIV
	Parasitic- Trypanosomiasis
Drugs	Rifampicin, Ketoconazole, Fluconazole, Phenytoin, Barbiturate
Malignancy	Lymphoma, Primary Breast/Lung/gastrointestinal cancer
Vascular	Bleeding or infarction of adrenal
Other	Congenital adrenal hypoplasia, Adrenoleukodystrophy, Amyloidosis

tabolism, maintenance of vascular tone and endothelial integrity, immune modulation, and potentiation of catecholamine action [13]. Patients with adrenal insufficiency (with or without cortisol replacement) lack this response and require extra doses to meet the demand during the perioperative period. Hypoadrenalism increases perioperative mortality and morbidity, particularly in those who develop adrenal crisis [14]. Perioperative management strategies for patients with adrenal insufficiency is crucial to minimize complications. The initial step of the management is preoperative evaluation of the adrenal disease.

Those patients diagnosed with Addison's disease, but are not on glucocorticoid replacements, necessitate assessment of their adrenal function and commencement of replacements as early as possible. Other patients with high degree of clinical suspicion for hypoadrenalism, require full workup to assess adrenal function as well as investigations to assess the causes (**Table 2**) [15]. Early initiation of cortisol treatment is advisable to achieve stable adrenal function by the time of surgery. However, clear guidelines regarding the recommended interval between treatment initiation and the surgical intervention are limited. In such cases, seeking endocrinology opinions from a specialist are warranted. Patients with a diagnosis of Addison's disease and on cortisol replacement, require close assessment in a preoperative or booking clinic. History of cortisol management, previous adrenal crisis details, medication adjustment strategies used in the past, and operative history should be taken in detail as a part of preoperative consultation. Collaboration with the patient's endocrinologist is the best practice [15-18]. There are no absolute contraindications for elective surgical procedures in individuals with adrenal insufficiency. However, clinical stability of the adrenal pathology is important with endocrinologist involvement in high-risk surgeries. Extra monitoring is recommended for day procedures.

Patients on glucocorticoid replacement could develop side effects from excess steroid levels. A detailed examination should be performed to look for Cushingoid signs. One of the commonest adverse effects of steroid therapy is immune suppression. This is through genomic mechanisms which suppress synthesis of proinflammatory cytokines, including interleukins, prostaglandins, and interferons, predominantly in chronic supratherapeutic use of steroids [18]. Steroid-induced myopathy and osteoporosis are well known adverse effects of excess steroid therapy. Dose-dependent increases in fasting and postprandial glucose levels and development of diabetes are rare in Addison's disease. However, type 1 diabetes is reported in 12% of individuals with Addison's disease secondary to autoimmune adrenalitis [7]. Other associated endocrine disorders, such as hypothyroidism (autoimmune polyglandular syndrome type 2) and hypoparathyroidism (autoimmune polyglandular syndrome type 2) should be excluded, if not investigated previously [6, 7]. Routine cardio-respiratory risk stratification is recommended for patients with diagnosis of Addison's disease who have other comorbidities.

Intraoperative care and anaesthesia

Patients with Addison's disease require close monitoring during the operative period. The normal stress glucocorticoid response is absent or blunted in patients with Addison's disease, which can lead to multiple complications. Continuous secretion of ACTH from the pituitary with high serum cortisol and epinephrine was reported during anaesthesia and recovery [11]. Inadequate cortisol and adrenaline response leads to poor vascular tone and hypotension. Prolonged stress leads to shock, also called "adrenal crisis" [19]. This necessitates extra

Table 3. Current guidelines on perioperative care of Addison's disease

Guideline	Authors	Major recommendations
Endocrine Society Clinical Practice Guideline 2016	Bornstein SR et al., 2016 [2]	Stress dosing in adrenal insufficiency
Emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients	Arlt W et al., 2016. The Society for Endocrinology Clinical Committee [22]	Steroid emergency card
Surgical guidelines for Addison's Disease and other forms of adrenal insufficiency 2017	Wass et al., 2017. Addison's Disease Self-Help Group [23]	List the ten main types of surgical procedures with different level of steroid cover for each
Potentially Life Threatening Steroid Dependency, Steroids and Saline Requirements for Surgery and Dentistry 2017	The Canadian Addison Society 2017 [24]	Based on the UK Addison's Disease Self Help Group
Supplemental perioperative steroids for surgical patients with adrenal insufficiency 2012	Yong et al., 2012. [25] Cochrane Systematic Review	Supplemental perioperative steroids were not required during surgery for patients with adrenal insufficiency (small number of patients)
Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency 2014	Husebye ES et al., 2014 [26]	Recommendations on diagnosis therapy and follow up
Guidelines for the management of glucocorticoids during the perioperative period for patients with adrenal insufficiency	Woodcock et al., 2020. Guidelines from the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology UK [17]	Describe guidelines for primary and secondary adrenal insufficiency during various operative procedures

doses of glucocorticoids for patients undergoing anaesthesia.

However, this intraoperative cortisol response is affected by many surgical and anaesthetic factors [20]. Adrenocortical secretion can be supressed in anaesthesia. Regional anaesthesia can suppress neural input to hypothalamus. Some anaesthetic medications, such as Etomidate, can directly suppress adrenal cortex [21].

Various guidelines and recommendations describe appropriate use of steroid therapy during operative procedures (See **Table 3**). Amongst these, the guidelines from the "Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology United Kingdom" is used in most perioperative services across Australia [17]. This guideline recommends a loading dose followed by infusion of hydrocortisone at the time of induction in patients with primary or secondary adrenal insufficiency. The Hydrocortisone infusion is advised to continue until commencement of oral feed. Double of the regular dose of steroid should be commenced afterwards for up to 48 hours (See **Table 4**). Management of perioperative adrenal insufficiency in children is described in the guideline separately [17]. It is important to be aware that Dexamethasone is not appropriate glucocorticoid replacement in Addison's disease as it has no mineralocorticoid activity [17]. Therefore, this guideline clearly separates patients with adrenal insufficiency (primary or secondary) and patients receiving steroid therapy for other conditions, to avoid complications.

Despite glucocorticoid replacement therapy, acute adrenal insufficiency or adrenal crisis could develop in patients with Addison's disease during the perioperative period. Undiagnosed patients who are not on replacement are at high risk of experiencing adrenal crisis. Although the complete pathophysiology of adrenal crisis is not fully understood, it is possibly due to the lack of adrenal hormones to support the stress during surgery and anaesthesia. This can be a life-threatening condition if untreated [14]. Early identification is important to improve perioperative outcome in such patients.

Table 4. Adult perioperative steroid therapy for adrenal insufficiency

Severity of surgical stress	Primary and secondary adrenal insufficiency		Receiving adrenosuppresive doses of steroids (prednisolone equivalent ≥ 5 mg for ≥ 4 weeks)	
	Intra-operative	Post-operative	Intra-operative	Post-operative
Major surgery - Under anaesthesia (GA/LA) Include CS	HC 100 mg IV on induction followed by IV infusion of HC 200 mg/24 h	HC 200 mg/24h by IV infusion while NBM **Or** HC 50 mg 6 hly IM Resume oral – double HC doses for 48 h or for up to a week (with rapid recovery 24 h)	HC 100 mg IV on induction followed by IV infusion of HC 200 mg/24 h **Or** Dexamethasone 6–8 mg IV, if used, will suffice for 24 h	HC 100 mg/24 h IV infusion while NBM **Or** HC 50 mg every 6 hly IM Resume oral GC normal dose if recovery is uncomplicated. Otherwise, continue double oral dose for up to a week
Body surface and intermediate surgery	Same as above	Same as above	HC 100 mg, IV at induction, followed by IV infusion of HC 200 mg/24 h **Or** Dexamethasone 6–8 mg IV, if used, will suffice for 24 h	Double regular GC for 48 h, then continue usual dose if uncomplicated
Bowel procedures requiring laxatives/enema	Consider IV fluids and IV GC during preparation, HC 100 mg IV **Or** IM at the start of procedure	Resume enteral – double hydrocortisone doses for 24 h	Continue normal GC dose. Equivalent IV dose if prolonged NBM Treat as per primary adrenal insufficiency if concerned about hypothalamo-pituitary-adrenal axis function, and risk of adrenal insufficiency	
Labour and vaginal delivery	HC 100 mg IV at onset of labour, followed by IV infusion of HC 200 mg/24 h **Or** HC 100 mg IM followed by 50 mg 6 hly IM	Resume enteral – double hydrocortisone doses for 48 h	HC 100 mg IV at onset of labour, followed IV infusion of HC 200 mg/24 h **Or** HC 100 mg IM followed by 50 mg 6 hly IM	

Note: HC, Hydrocortisone; IV, intravenous; IM, intramuscular; GC, glucocorticoid; FC, fludrocortisone; NBM, nil by mouth; GA, general anaesthesia; LA, local anaesthesia; CS, caesarian section; hly, hourly.

Table 5. Management of adrenal crisis in adults

Immediate	Maintenance
1. **Hydrocortisone** immediate bolus injection of 100 mg hydrocortisone IV/IM followed by continuous IV infusion of 200 mg Hydrocortisone per 24 h **Or Hydrocortisone** IV/IM 50 mg 6 hourly 2. Rehydration with rapid IV 1000 mL of **isotonic saline** infusion within the first hour, followed by further IV rehydration as required (usually 4–6 L in 24 h; monitor for fluid overload in case of renal impairment and in elderly patients) • **Contact an endocrinologist**	• Tapering of hydrocortisone can be started after clinical recovery. • In patients with primary adrenal insufficiency, mineralocorticoid replacement (starting dose 100 micrograms fludrocortisone once daily) as soon as the daily glucocorticoid dose is below 50 mg hydrocortisone/24 h • Investigation of the underlying cause of disease

Clinical symptoms of adrenal crisis include low blood pressure, sudden abdominal or leg pain, vomiting, confusion, seizure, and lethargy. However, clinical assessment is limited during intraoperative and immediate post-operative period. Laboratory findings are more important perioperatively in suspected patients including hyponatremia, hyperkalaemia, hypoglycaemia, and hypercalcaemia. It's crucial to note that diagnostic tests should not delay the treatments of the condition [22]. The primary treatment of adrenal crisis is administration of glucocorti-

coids, specifically hydrocortisone (See **Table 5**) [23-27].

Postoperative management

Careful monitoring of patients with Addison's disease after surgical procedures is equally important as intraoperative care. Maintenance glucocorticoid therapy from intra-operative period needs to be continued based on type of surgery and recovery status (See **Table 4** and **5**). Prolonged hypotension and cardiovascular instability are reported in patients with adrenal insufficiency after surgical procedures [28]. Special attention is required in post-operative patients who are not taking oral diet, and glucocorticoid replacement should continue intravenously or intramuscularly as per recommendations [17].

Furthermore, patients with Addison's disease have issues with wound healing and immunity. Their wounds should be monitored closely, and a low threshold is recommended for septic screen if there is any evidence of postoperative infections [29]. Glycaemic monitoring is also important as the risk of hyperglycaemia is associated with excess steroid replacement, and hypoglycaemia is common with adrenal insufficiency [2].

Conclusion

Perioperative care with adequate glucocorticoid replacement is very important in patients with hypoadrenalism during operative procedures. These patients require additional glucocorticoid doses during surgery and anaesthesia. Current guidelines clearly outline the required amount of steroid dose during the intraoperative and postoperative period. Acute adrenal insufficiency or adrenal crisis is a life-threatening condition which could occur in patients with Addison's disease during surgery, and early identification and treatment to minimize complications and mortality are critical.

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