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Research progress on mitochondrial mechanisms of sensitivity to inhalational anesthetics

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Abstract: Experimental animals and people have different sensitivity to inhalational anesthetics, which is related to the depth of anesthesia during general anesthesia and the perioperative safety of patients. Studying the mechanism of inhalational anesthetics sensitivity is related to the improvement of postoperative outcomes in patients. Mitochondria are important organelles for energy metabolism in the body, and changes in mitochondrial structure and function are involved in the mechanism of inhalational anesthetics sensitivity. Current research indicates that mitochondrial related gene mutations, metabolic pathways, ion channels, and other factors are involved in the mechanism of inhalational anesthetics sensitivity. In view of this, this article reviews the research progress in several aspects such as inhalational anesthetics sensitivity overview, mitochondrial related gene mutations, metabolic pathways, ion channels, etc.

Keywords: Inhalation anesthetics; Mitochondria; Sensitivity; Energy metabolism

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The mechanism of action of general anesthetics is one of the major scientific problems urgently needing resolution in the field of natural sciences [1]. Research into this scientific issue is crucial for the safety of general anesthesia and the development of new types of general anesthetics drugs. According to a 2019 report in *Lancet*, every year there are 313 million surgeries performed globally, and the vast majority of them require completion under general anesthesia [2]. However, within 30 days post-anesthesia, 4.2 million people die, ranking anesthesia-related deaths as the third leading cause globally, following ischemic heart disease and stroke [2]. Inhalation anesthetics are widely used in clinical anesthesia for their sedative, analgesic, and muscle relaxant effects. Whether in basic research or clinical practice, researchers have found differences in the minimum alveolar concentration required for inhalation anesthetics between experimental animals and humans maintaining the same depth of anesthesia, indicating sensitivity differences between them. Differences in inhalation anesthetic sensitivity are related to the depth of anesthesia during general anesthesia. Excessive anesthesia depth can cause delayed awakening or even increase postoperative mortality rates in patients, while shallow anesthesia can lead to hemodynamic fluctuations, cardiovascular events, and intraoperative awareness [3]. Moreover, increased sensitivity to inhalation anesthetics often predicts poor postoperative outcomes; for example, patients highly sensitive to sevoflurane tend to have prolonged extubation time [4].

Mitochondria are semi-autonomous double-membrane organelles that provide the majority of cellular energy through the citric acid cycle and oxidative phosphorylation. For a long time, inhibition of mitochondrial function has been considered a toxic side effect of general anesthetics [5]. From nematodes to mammals, including humans, defects in mitochondrial function increase sensitivity to inhalational anesthetics [6-7], suggesting a possible link between energy metabolism and sensitivity to inhalational anesthetics. Research has found that metabolites related to mitochondrial energy metabolism, mitochondrial ion channels, and other factors are associated with sensitivity to inhalational anesthetics. Therefore, this article provides a brief overview of mitochondrial sensitivity, mitochondrial-related genes, metabolites, ion channels, and mechanisms related to sensitivity to inhalational anesthetics.

1 Overview of Sensitivity to Inhalation Anesthetics

Inhalation anesthetics encompass a group of general anesthetics with diverse chemical structures and pharmacological effects, including volatile liquids (such as ether, isoflurane, sevoflurane, desflurane) and inorganic gases (such as nitrous oxide, xenon). Volatile liquids are also commonly used in clinical settings. Inhalation anesthetics exhibit sedative, analgesic, and muscle relaxant properties simultaneously. Therefore,

they are preferred for minimally stimulating, short-duration surgical or diagnostic procedures. They are also prioritized for patient obese, elderly, and patients with hepatic or renal dysfunction. Third-generation inhalation anesthetics like sevoflurane and desflurane offer advantages such as rapid onset, quick recovery, organ protection, and minimal impact on circulatory function. Precise control of drug dosage during maintenance through end-tidal concentration monitoring has led to the widespread clinical application of inhalation anesthetics.

1.1 Mechanism of Action of Inhalation Anesthetics

Since the first use of ether in surgery, the use of inhalation anesthetics has evolved over 170 years. Despite their widespread clinical use, their specific mechanisms of action remain unclear, hindering efforts to reduce their toxic side effects, adverse reactions, and optimize their anesthetic effects [8]. The main theories regarding the mechanism of action of inhalation anesthetics include lipid theory and protein theory. Current consensus suggests that inhalation anesthetics exert pharmacological effects by acting on different molecular targets within the central nervous system, leading to specific pharmacological actions. For instance, regions like the hippocampus and amygdala are primarily involved in the amnesic effects of inhalation anesthetics [9], while the cerebral cortex and hypothalamus participate in loss of consciousness [10]. Research indicates that inhalation anesthetics can affect ion channels or receptors in the central nervous system, inhibit phagocytosis, and disrupt synaptic transmission [11-12].

1.2 Mechanisms of Sensitivity to Inhalation Anesthetics

Sensitivity to inhalation anesthetics refers to significant differences in the required end-tidal concentration of inhalation anesthetics to maintain the same depth of anesthesia among experimental animals or patients. Studies indicate that genetic variations and subsequent changes in downstream metabolites are related to sensitivity to inhalation anesthetics. Additionally, abnormalities in mitochondrial structure and function are also associated with sensitivity to inhalation anesthetics. Mitochondrial-related genes, ion channels, metabolite changes, and alterations in mitochondrial energy metabolism affect sensitivity to inhalation anesthetics in experimental animals or humans. Inhibiting mitochondrial respiratory function enhances the anesthetic efficacy of inhalation anesthetics [12]. Therefore, further research on mitochondria holds promise for elucidating the mechanisms of sensitivity to inhalation anesthetics and the mechanisms of general anesthesia overall.

2 Inhalational Anesthetic Sensitivity and Mitochondrial Mechanisms

2.1 Mitochondrial-related Genes and Inhalational Anesthetic Sensitivity

Mitochondrial complex I, a rate-limiting enzyme in the mitochondrial respiratory electron transport chain, has been implicated as the primary molecular mechanism affecting sensitivity to inhalational anesthetics. Studies have suggested that inhibiting the function of mitochondrial complex I contributes significantly to altered sensitivity to inhalational anesthetics in both experimental animals and patients [6-7]. Genetic variations affecting mitochondrial-related genes have been linked to sensitivity to inhalational anesthetics in experimental animals such as fruit flies, nematodes, and mice [13]. For instance, mutations in the *gas-1* and *ND23* genes, which encode subunits of mitochondrial complex I, impact mitochondrial respiratory function. Research using nematodes with *gas-1* mutations has shown significantly increased sensitivity to isoflurane [14], and fruit flies with *ND23* mutations also exhibit increased sensitivity to inhalational anesthetics [13].

Changes in sensitivity to inhalational anesthetics in these experimental animals are associated with reduced ATP synthesis due to mitochondrial complex I gene mutations, leading to disruptions in neurotransmitter transmission and cellular transport processes in the nervous system. Ultimately, these alterations affect the efficacy of inhalational anesthetics on the central nervous system [15-16]. In short, this is because countless biological processes within the central nervous system are highly dependent on energy, and changes in mitochondrial function are bound to affect ATP production and affect neurological function, ultimately leading to changes in anesthesia sensitivity [17]. Therefore, mitochondrial gene mutations can lead to changes in the sensitivity of inhaled anesthetics, and gene mutations that affect the sensitivity of inhaled anesthetics may help identify genes and related gene products involved in regulating arousal [18].

2.2 Other Energy Metabolism-related Genes and Inhalational Anesthetic Sensitivity

In addition to mutations in mitochondrial complex I affecting inhalational anesthetic sensitivity, mutations in other genes related to mitochondrial energy metabolism are also associated with sensitivity to inhalational anesthetics. A clinical study using whole-exome sequencing of patients with differential sensitivity to sevoflurane identified 8 single nucleotide polymorphisms (SNPs) across 4 genes—*FAT2* (SNPs

rs174272, rs174271, and rs174261), *ADI1* (SNP rs117278), *NEDD4* (SNPs rs70048, rs70049, and rs70056) and *FOXRED2* (SNP rs144281) [19]. Mutations in *FAT2*, *ADI1*, and *NEDD4* genes are associated with altered sensitivity, all of which affect mitochondrial energy metabolism. Whether F*OXRED2* mutations affect anesthetic sensitivity through oxidative stress response requires further validation. Thus, differences in the frequencies of these SNP mutations are likely to impact gene function, affecting the roles of these genes' encoded proteins in mitochondrial energy metabolism and possibly influencing differential sensitivity to sevoflurane among patients. In conclusion, mitochondrial energy metabolism has been extensively studied in relation to sensitivity to inhalational anesthetics in experimental animals, and genes related to energy metabolism may become a new focus for general anesthesia.

2.3 Mitochondrial-related Metabolites and Metabolic Pathways and Inhalational Anesthetic Sensitivity

Inhalational anesthetics can rapidly and significantly influence organism metabolism [20], and the metabolic status of the organism may, in turn, affect the efficacy of general anesthetics. Changes in whole-body or local tissue metabolites may affect mitochondrial-related metabolism, thereby influencing mechanisms of sensitivity to inhalational anesthetics.

A metabolomic study of patients with differential sensitivity to sevoflurane revealed that ethyl 5-aminopentanoate levels were higher in the low-sensitivity group compared to the high-sensitivity group. This difference is attributed to variations in ethyl 5-aminopentanoate causing differences in lysine degradation, which affects mitochondrial respiratory function and energy metabolism to varying degrees, potentially contributing to differential sensitivity to sevoflurane among patients [21]. Additionally, the study indicated that levels of L-glutamine, glutamic acid, L-selenocysteine, and sphingosine may be associated with sensitivity to sevoflurane, as these metabolites are involved in the tricarboxylic acid cycle and glutamate metabolism, which can affect sensitivity to inhalational anesthetics [22]. In another basic research study, it was found that chronic hypoxic conditioning increases O-glycosylation in the brain, particularly in the thalamus, accelerates de novo synthesis of glutamine by astrocytes, and activates glutamine synthetase, thereby accelerating the glutamine-glutamate cycle and reducing sensitivity to sevoflurane anesthesia in mice [23]. It has been demonstrated that glutamate-related metabolism can mediate differences in sensitivity to inhalational anesthetics [22]. Thus, changes in metabolites causing alterations in mitochondrial energy metabolism may lead to changes in sensitivity to sevoflurane anesthesia. These studies, focusing on metabolites and metabolic pathways, provide new insights into anesthesia management for patients with differential sensitivity to inhalational anesthetics.

2.4 Mitochondrial Ion Channels and Sensitivity to Inhalational Anesthetics

2.4.1 Two-pore-domain potassium channels and Sensitivity to Inhalational Anesthetics

General anesthetics promote the opening of potassium channels, enhancing inward potassium currents, thereby reducing neuronal excitability and facilitating unconsciousness [24]. TWIK-related potassium (TREK) channels are part of the two-pore-domain potassium (K_{2P}) channel family, abundant in the central nervous system where they help regulate intrinsic neuronal excitability. TREK-1, a type of potassium ion channel within this family, is sensitive to anesthesia and activated by phospholipase D2 (PLD2) [25]. Genetic deletion of *TREK-1* reduces sensitivity to inhalational anesthetics in mice. Clinically used concentrations of inhalational anesthetics activate *TREK-1*, making this channel a relevant target for these drugs [26]. Moreover, the sustained opening of TREK potassium channels activated by isoflurane is the reason why isoflurane has a lower Minimum Alveolar Concentration (MAC). Norfluoxetine, as a TREK channel blocker, can block TREK channels and restore MAC to normal [27], indicating that MAC changes in inhaled anesthetics are related to TREK potassium channels.

Given that *TREK-1* activation depends on PLD2, inhalational anesthetics can directly affect PLD2 in the plasma membrane to activate this ion channel. These findings suggest that membrane-mediated sensitivity mechanisms of inhalational anesthetics may involve related proteins [28]. Further research indicates that AMP kinase-dependent phosphorylation of TREK channels is influenced by mitochondrial energy output [29], suggesting mitochondrial function changes may affect the channel's function [30]. Thus, the two-pore-domain potassium channel TREK is associated with sensitivity to inhaled anesthetics, and its mechanism may still involve changes in mitochondrial function, affecting the function of this ion channel.

2.4.2 Sodium Ion Channels and Sensitivity to Inhalational Anesthetics

Nav1.6 is a primary voltage-gated sodium channel in the central and peripheral nervous systems, crucial for generating and sustaining neuronal currents. Decreased activity of Nav1.6 sodium channels in mice increases sensitivity to inhalational anesthetics, possibly due to reduced neuronal excitability associated with Na^+ [31]. Thus, Nav1.6 involvement in mouse sensitivity to inhalational anesthetics suggests it may serve as a target for these drugs [31]. It is well-known that ion channel mechanisms are closely linked to ATP, with

mitochondria being the primary site of ATP production. Research suggests a novel potassium ion channel in rat brain mitochondria inhibited by Na^+; during neuronal excitation and increased intracellular sodium concentration, Na^+ inhibit brain mitochondrial sodium-sensitive potassium ion channels and complex I activity [32]. Therefore, reduced Nav1.6 channel activity enhances sensitivity to inhalational anesthetics, potentially involving inhibition of mitochondrial complex I. However, the precise relationship between these mechanisms remains unclear. Thus, Nav1.6 channels may be considered a target for future research on inhalational anesthetic sensitivity.

3 Prospects

In summary, mitochondrial complex I and energy metabolism-related gene mutations, mitochondrial-related metabolites and pathways, and mitochondrial ion channels participate in the mitochondrial mechanisms of inhalational anesthetic sensitivity. Additionally, direct mitochondrial damage can alter sensitivity [33]. Interestingly, only mitochondrial complex I subunits are associated with inhalational anesthetic sensitivity, whereas mutations in complexes II-V do not affect sensitivity [34], requiring further investigation into the specific mechanisms involved. Inhibiting mitochondrial respiratory function can increase anesthetic efficacy in experimental animals [12]. Therefore, patients with mitochondrial-related functional impairments or structural defects should be cautious of heightened sensitivity to inhalational anesthetics during general anesthesia, aiming to prevent deep anesthesia during the perioperative period as much as possible. In conclusion, future research should focus on mitochondrial mechanisms of inhalational anesthetic sensitivity, crucial for patient postoperative outcomes and providing new directions for understanding the mechanisms of inhalational anesthetics.

Conflict of Interest None

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· 研究进展 ·

吸入麻醉药敏感性的线粒体机制研究进展

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摘要：实验动物和人均对吸入麻醉药存在敏感性差异，这关系到全身麻醉期间的麻醉深度及患者的围术期安全。研究吸入麻醉药敏感性的机制，有助於改善患者术后结局。线粒体是机体能量代谢的重要细胞器，线粒体结构与功能的变化参与了吸入麻醉药敏感性的机制。目前的研究表明，线粒体相关基因突变、代谢通路、离子通道等参与了吸入麻醉药敏感性的机制。鉴于此，本文从吸入麻醉药敏感性概述、线粒体相关基因突变、代谢通路、离子通道等几个方面的研究进展进行综述。

关键词：吸入麻醉药；线粒体；敏感性；能量代谢

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Research progress on mitochondrial mechanisms of sensitivity to inhalational anesthetics

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Abstract: Experimental animals and people have different sensitivity to inhalational anesthetics, which is related to the depth of anesthesia during general anesthesia and the perioperative safety of patients. Studying the mechanism of inhalational anesthetics sensitivity is helpful to improve the postoperative outcomes of patients. Mitochondria are important organelles for energy metabolism in the body, and changes in mitochondrial structure and function are involved in the mechanism of inhalational anesthetics sensitivity. Current research indicates that mitochondrial related gene mutations, metabolic pathways, ion channels, and other factors are involved in the mechanism of inhalational anesthetics sensitivity. In view of this, this article reviews the research progress in several aspects such as inhalational anesthetics sensitivity overview, mitochondrial related gene mutations, metabolic pathways, ion channels, etc.

Keywords: Inhalational anesthetics; Mitochondria; Sensitivity; Energy metabolism

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全身麻醉药物的作用机制被列为自然科学领域亟待解决的重大科学问题之一[1]，研究这一科学问题关系到全身麻醉的安全和新型全身麻醉药物的开发。2019 年 *Lancet* 杂志报道，全球每年有 3.13 亿人实施手术治疗，其中绝大多数手术需要在全身麻醉下完成[2]。然而，麻醉手术后 30 d 内死亡 420 万人，占整体死亡原因的第 3 位，仅次于缺血性心脏病和脑卒中[2]。吸入麻醉药物具有镇静、镇痛和肌肉松弛作用，被广泛用于临床麻醉。无论是在基础研究中还是临床实践中，研究者均发现在维持相同麻醉深度的情况下，实验动物或人所需的呼气末吸入麻醉药浓度有差异，提示实验动物和人对吸入麻醉药存在敏感性差异。吸入麻醉药敏感性差异与全身麻醉期间的麻醉深度相关，麻醉过深会引起苏醒延迟、甚至增加患者的术后死亡率，麻醉过浅容易引起血流动力学波动、引发心脑血管不良事件、导致发生术中知晓等[3]。此外，吸入麻醉药敏感性增加往往预示着患者的不良术后结局，对七氟烷敏感性高的患者拔除气管导管的时间往往会延长[4]。

线粒体主要通过柠檬酸循环和氧化磷酸化为细胞提供大部分能量。长期以来，线粒体功能的抑制一直被认为是全身

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麻醉药的毒副作用[5]。从线虫到哺乳动物甚至人类，线粒体功能缺陷会增加吸入麻醉药的敏感性[6-7]，提示能量代谢可能与吸入麻醉药的敏感性有关。研究发现，与线粒体能量代谢相关的代谢物，线粒体相关离子通道等与吸入麻醉药的敏感性相关。故本文将从线粒体敏感性概述，线粒体相关基因、代谢物，离子通道等与吸入麻醉药敏感性机制做一综述。

1　吸入麻醉药敏感性概述

吸入麻醉药是一类化学结构和药理作用各异的全身麻醉药，包括挥发性液体（如乙醚、异氟烷、七氟烷、地氟烷）和无机气体（如氧化亚氮、疝气），挥发性液体在临床的应用较多。吸入麻醉药同时具备镇静、镇痛和肌肉松弛作用。因此，在刺激小、持续时间短的手术或诊疗操作中，可仅选用吸入麻醉药。同时，对肥胖、老年、肝肾功能障碍患者，也可以优先选择吸入麻醉药。并且，七氟烷和地氟烷等第三代新型吸入麻醉药，具有起效快、苏醒快、保护器官、对循环功能影响小等优势。在基于呼气末浓度监测的吸入麻醉维持过程中，可以精准调控药物用量，这使得吸入麻醉药的临床运用越来越广泛。

1.1　吸入麻醉药的作用机制　自乙醚第一次被用于外科手术以来，吸入麻醉药的使用已经超过了 170 年。虽然，吸入麻醉药被广泛用于临床麻醉，但其具体作用机制不清楚，这不利于降低其毒副作用和不良反应，以及优化吸入麻醉效果。吸入麻醉药的作用机制主要的学说有脂质学说和蛋白质学说[8]。目前学者们普遍认为，吸入麻醉药通过作用于中枢神经系统不同部位的不同分子靶点产生相应的药理学作用成分。例如海马、外侧杏仁核等大脑区域主要参与吸入麻醉药的遗忘作用[9]，大脑皮层及下丘脑等部位主要参与意识消失作用[10]。研究表明，吸入麻醉药可通过影响中枢神经系统的离子通道或受体、抑制胞吞以及突触传递等机制发挥效应[11-12]。

1.2　吸入麻醉药敏感性的机制　吸入麻醉药的敏感性是指在维持相同麻醉深度的情况下，实验动物或患者所需的呼气末吸入麻醉药浓度有差异。研究表明，遗传变异和其导致的下游物质代谢改变等与吸入麻醉药的敏感性有关。另外，线粒体结构与功能异常，同样与吸入麻醉药敏感性有关。线粒体相关基因、离体通道等会影响线粒体的功能，一些基因突变、离子通道、代谢物变化、线粒体能量代谢改变等会影响对吸入麻醉药的敏感性。研究表明，抑制线粒体的呼吸功能，加强了吸入麻醉药的麻醉效能[12]。因此针对线粒体的研究，有望进一步解释吸入麻醉药敏感性的机制和全麻机制。

2　吸入麻醉药敏感性的线粒体机制

2.1　线粒体相关基因与吸入麻醉药敏感性　线粒体复合体Ⅰ为线粒体呼吸电子传递链中的限速酶，抑制线粒体复合体Ⅰ的功能被认为是影响吸入麻醉药敏感性的最可能的分子作用机制。无论是实验动物还是患者，复合体Ⅰ缺陷都导致该生物对吸入麻醉药存在高敏感性[6-7]。遗传变异会影响吸入麻醉药的敏感性，某些线粒体相关基因突变与果蝇、线虫和小鼠等实验动物对吸入麻醉药的敏感性有关[13]。例如，*gas*-1 基因和 *ND*23 基因是编码线粒体复合体Ⅰ的一个亚基，*gas*-1 基因和 *ND*23 基因突变会影响线粒体的呼吸功能。有研究通过异氟烷麻醉 *gas*-1 基因突变的线虫发现，该类线虫对异氟烷的敏感性显著增加[14]，果蝇因存在 *ND*23 基因突变也对吸入麻醉药的敏感性增加[13]。

这些实验动物对吸入麻醉药敏感性的改变，与线粒体复合体Ⅰ基因突变导致 ATP 的合成减少有关，缺乏 ATP 而导致神经系统中，兴奋性或抑制性神经递质传递和细胞胞吞胞吐障碍，导致吸入麻醉药作用于中枢神经系统的效力发生改变，最终导致吸入麻醉药敏感性发生变化[15-16]。简而言之，这是由于中枢神经系统内的无数生物过程高度依赖能量，线粒体功能改变势必会影响 ATP 的产生而影响神经系统功能，并最终导致麻醉敏感性改变[17]。因此，线粒体基因突变可导致吸入麻醉药的敏感性改变，而影响吸入麻醉药敏感性的基因突变可能有助于识别参与调控唤醒的基因和相关基因产物[18]。

2.2　其他与能量代谢相关基因与吸入麻醉药敏感性　除了复合体Ⅰ突变导致吸入麻醉药敏感性改变外，其他与线粒体能量代谢相关的基因突变也与吸入麻醉药的敏感性相关。在一项七氟烷敏感性差异患者的全外显子测序的临床研究中发现，4 个基因共 8 个单核苷酸多态性（SNP）与患者对七氟烷的敏感性有关，分别为 FAT2（SNP rs174272、rs174271 和 rs174261）、ADI1（SNP rs117278）、NEDD4（SNP rs70048、rs70049 和 rs70056）和 FOXRED2（SNP rs144281）[19]。其中 *FAT*2 基因突变、*ADI*1 基因突变和 *NEDD*4 基因突变致敏感性改变，都与影响了线粒体能量代谢有关。而 *FOXRED*2 基因突变是否通过氧化应激反应影响麻醉敏感性尚需进一步验证。这些 SNP 突变频率的差异，会影响其基因的功能，导致这些基因编码的蛋白质在线粒体能量代谢中的作用有差异，可能与患者对七氟烷的敏感性差异有关。总之，线粒体能量代谢已被研究证明与实验动物对吸入麻醉药的敏感性有关，与能量代谢相关的基因可能成为全身麻醉的新关注点。

2.3　线粒体相关代谢物和代谢通路与吸入麻醉药的敏感性　吸入麻醉药可以快速而显著地影响机体的代谢[20]，而机体的代谢状态也可能反过来影响全身麻醉药的效力。机体全身或者局部组织代谢物的变化可能会影响线粒体相关代谢，从而涉及到吸入麻醉药的敏感性机制。

相关七氟烷敏感性差异患者的血浆代谢组学研究结果表明，5-氨基戊酸乙酯在低敏感组高于高敏感组，这是由于 5-氨基戊酸乙酯引起赖氨酸降解程度的差异，在不同程度上影响了线粒体的呼吸功能和能量代谢，这可能与患者对七氟烷存在敏感性差异有关[21]。此外，该研究还表明 *L*-谷氨酰胺、焦谷氨酸、*L*-硒代半胱氨酸和鞘氨醇的含量可能与患者对七氟烷的敏感性有关，这是由于这几种代谢物与能量代谢的三羧酸循环和谷氨酸代谢有关，谷氨酸代谢也能影响吸入麻醉药的敏感性[22]。在另一基础研究中发现，低氧吸入可增加大脑，尤其是丘脑区域的 O-糖基化修饰，加速星形胶质细胞从头合成谷氨酰胺，同时激活谷氨酰胺合成酶，加速谷氨酸-谷氨酰胺循环，从而降低小鼠对七氟烷的麻醉敏感性[23]。且有研究已经证明了谷氨酸能相关代谢可介导吸入麻醉药的敏感

性差异[22]。可见,代谢物改变引起线粒体能量代谢改变,从而使七氟烷的麻醉敏感性发生变化。

2.4　线粒体相关离子通道与吸入麻醉药的敏感性

2.4.1　双孔钾离子通道与吸入麻醉药敏感性　全身麻醉药可促进钾离子通道的打开,增强钾离子内流电流,从而降低神经元兴奋性,有助于机体向无意识方向转换[24]。TREK 钾离子通道是双孔钾离子通道家族的一部分,这些通道在中枢神经系统中很丰富,有助于调节内在神经元兴奋性。TREK-1 作为钾离子通道中的一种,是一种具有麻醉敏感性的双孔钾离子(K2P)通道,由磷脂酶 D2(PLD2)激活[25],TREK-1 的基因缺失可降低小鼠的吸入麻醉药敏感性。临床上使用的吸入麻醉药浓度可激活 TREK-1,使该通道成为体内吸入麻醉药的相关靶点[26]。并且,异氟烷激活的 TREK 钾通道的持续开放是驱动异氟烷拥有较低的最低肺泡有效浓度(minimum alveolar concentration, MAC)的原因,去甲氟西汀作为 TREK 通道的阻断剂,可阻断 TREK 通道而使 MAC 恢复到正常情况[27],这说明吸入麻醉药的 MAC 改变与 TREK 钾通道有关。

由于 TREK-1 激活取决于 PLD2,吸入麻醉药可直接作用于质膜脂质的 PLD2 以激活该离子通道。这些发现表明,膜介导的吸入麻醉药的敏感性机制可考虑相关蛋白质也可能与吸入麻醉药的敏感性相关[28]。进一步研究发现,由于 TREK 通道的磷酸化依赖于 AMP 激酶[29],线粒体的能量输出可直接影响 AMP 激酶和 TREK 通道的功能[30]。可见,双孔钾离子通道 TREK 与吸入麻醉药敏感性相关,其机制可能还是涉及到线粒体功能改变,影响该离子通道的功能。

2.4.2　钠离子通道与吸入麻醉药敏感性　Nav1.6 是中枢和周围神经系统中主要的电压门控钠离子通道,Nav1.6 通道在神经元电流的产生和维持中发挥重要作用,小鼠 Nav1.6 钠通道活性的降低可增加小鼠对吸入麻醉药的敏感性,这种敏感性改变可能是由于与钠离子相关的神经元兴奋性降低引起的[31]。可见,Nav1.6 参与了小鼠对吸入麻醉药的敏感性机制,且该通道可能是吸入麻醉药的作用靶点[31]。众所周知,离子通道的作用机制与 ATP 密切相关,线粒体是产生 ATP 的主要场所。有研究提出,在大鼠脑线粒体中存在一种可以被钠离子抑制的新型钾离子通道,在神经元兴奋性和细胞内钠离子浓度升高的过程中,钠离子可抑制脑线粒体钠敏感钾离子通道,以及复合物Ⅰ的活性[32]。由此,Nav1.6 通道活性的降低,增加了吸入麻醉药的敏感性,其机制也可能是抑制线粒体复合体Ⅰ,但两者的具体关系目前还尚未明确。因此 Nav1.6 通道可作为未来吸入麻醉药敏感性研究的靶点。

3　展　望

综上所述,线粒体复合体Ⅰ和能量代谢相关基因突变,线粒体相关代谢物和相关代谢通路,线粒体相关离子通道等参与了吸入麻醉药敏感性的线粒体作用机制。此外,线粒体功能直接损伤也会导致敏感性改变[33]。但有趣的是,与吸入麻醉药敏感性相关的线粒体亚基只有线粒体复合体Ⅰ,复合体Ⅱ~Ⅴ中的突变不会导致敏感性改变[34],这其中涉及的具体机制还需进一步探讨。但可以明确的是,抑制线粒体的呼吸功能,可增加吸入麻醉药的麻醉效能,即实验动物对吸入麻醉药的敏感性增加[12]。因此,存在线粒体相关功能抑制和结构缺陷的患者在接受全身麻醉时,应警惕其可能出现对吸入麻醉药高敏的现象,从而尽可能避免围术期深麻醉情况的发生。总之,未来应着重于吸入麻醉药敏感性的线粒体机制研究,这不仅关系到患者的术后结局,还可为揭示吸入麻醉药物的作用机制提供新的研究方向。

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