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Exploring the Neurological Impacts of Sevoflurane: A Comprehensive Review

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Abstract: ***Inhalational anesthetic, sevoflurane, is commonly used as a part of general anesthesia but the neurotoxic effects of this potent gas have raised questions, especially in vulnerable groups including pediatric and elderly patients. This review centers on the processes via which exposure to sevoflurane during development may result in adverse long-term effects on the brain. This review addresses the current understanding of sevoflurane-induced neurotoxicity by discussing potential causes such as oxidative stress, neuroinflammation, death of neural cells, mitochondrial malfunction, and apoptosis.***

Keywords: Sevoflurane, Neurotoxicity, Neurodegeneration, Neuroinflammation

1. Introduction

Sevoflurane is a halogenated ether ($C_4H_3F_7O$) known for its non-flammable nature, low blood-gas partition coefficient, and minimal pungency, making it ideal for inhalational anesthesia induction [1]. Because of its quick emergence and quick induction profile upon inhalation, sevoflurane has been utilized widely in both adult and pediatric anesthesia [2,3]. Due to this remarkable rapid induction and recovery ability of sevoflurane, it is highly suitable for both ambulatory surgery and outpatient operations. In contrast to the usage of most other anesthetics, the anesthetic has a low blood solubility [4], which causes very rapid onsets and offsets in both metabolism and effect separation [5].

Neurotoxicity is the term used to describe the impairment that can be induced to nerve tissues, leading to malfunctions in peripheral nerves and neurons in the central nervous system (CNS). These can be anything from medications, chemicals, or toxins found in the environment to natural substances. Headaches, vertigo, or seizures are symptoms of acute neurotoxicity; long-term memory loss, mood swings, and even degenerative illnesses of the central nervous system have been linked to chronic exposure [6].

Even though sevoflurane has an amazing pharmacology and is employed in modern general anesthesia administration, it has the ability to cause neurotoxicity and have negative effects on the brain. There are various mechanisms that can lead to neurotoxicity when using sevoflurane. The mechanisms underlying neurotoxicity include neuronal cell death, neuronal cell damage, neuroinflammation, oxidative stress, and mitochondrial malfunction [7].

Strong evidence that sevoflurane may have neurotoxic effects, especially during critical stages of brain development, comes from investigations done on mice and rats. Sevoflurane exposure has been shown in several trials to cause behavioral abnormalities, cognitive impairments, and death of brain cells, raising serious questions regarding the drug's safety. The application of these discoveries to people, however, has proven less certain. Sevoflurane's effects on human neurodevelopment and cognition have only partially been explored by clinical trials [8].

2. Neurotoxicity Mechanisms

2.1 Effect on cellular and molecular pathways

Sevoflurane activates neuronal apoptosis by regulating HIPK2/AKT/mTOR and miR-211-5p signaling pathways mainly, in the hippocampus.

2.1.1 The HIPK2 (Homeodomain-interacting protein kinase-2) signaling is normally turned on during lethal DNA damage leading to activation of independent apoptotic and autophagy pathways. Sevoflurane exposure can modulate the activity of HIPK2 upregulating p53 activity leading to apoptosis in the neuronal cells.

mTOR (mammalian Target of Rapamycin) is a serine-threonine kinase which regulates autophagy and helps in clearing out damaged organelles and proteins within neurons, maintaining neuronal health. Impairment of mTOR pathway by sevoflurane exposure can disrupt neuronal activity due to accumulation of misfolded proteins and autophagic dysregulation. This phenomenon triggers neurodegeneration making way for diseases like Alzheimer's and Parkinson's.

AKT (AK strain transforming) also called Protein Kinase B is a serine-threonine kinase which activates the mTOR pathway by regulating cellular proliferation and inhibiting apoptosis.

While sevoflurane upregulates phosphorylation of HIPK2 enhancing apoptosis, it inhibits the phosphorylation of AKT and mTOR pathways impairing their ability to promote cell survival hence leading to neuronal cell death. Study has shown that ubiquitous protein, A64, antagonist of HIPK2 can significantly reduce activation of AKT/mTOR pathway further reducing the apoptosis induced by sevoflurane [9].

2.1.2 miR-211-5p is a micro RNA functioning in post transcriptional regulation of gene expression. It binds to target mRNAs and inhibit their translation. One such target is Efemp2 (EGF containing Fibulin Extracellular Matrix Protein-2) which maintains tissue integrity and inhibits apoptosis. Sevoflurane exposure upregulates expression of miR-211-5p which in turn negates the function of Efemp2, triggering neuronal apoptosis [10,11].

2.2 Neuroinflammation

2.2.1 GAS-5 (Growth Arrest Specific 5) is a long non-coding RNA (lncRNA) with significant regulatory role in a number of biological processes and immunological responses. Study on neonatal mice has shown that sevoflurane treatment causes over-expression of GAS-5 inducing neuroinflammation in the microglia, immune cells of the central nervous system, by the release of pro-inflammatory cytokines. Microglia has two distinct phenotypes; pro-inflammatory M1 and anti-inflammatory M2 phenotype. On exposure to sevoflurane, microglia undergo polarization, adopting the M1 phenotype resulting in persistent inflammation [12].

2.2.2 ELAVL1 (Embryonic Lethal Abnormal Vision Like-1) or Human Antigen R is another gene involved in neuroinflammation [13]. ELAVL1 has significant role in post transcriptional gene expression and is important for mRNA stability. It targets and binds to 3'-UTR of mRNAs encoding for pro-inflammatory cytokines like IL-6 and IL-1β, increasing their stability and resulting in translation as well.

2.3 Oxidative stress and ferroptosis

Mitochondrial damage by ROS is one of the severe effects of sevoflurane. As electron transport chain is present in the mitochondrial membrane, mitochondria serve as a major source of production of hydroxyl free radicals and superoxide anions. Sevoflurane is known to trigger over-production of ROS [14,15] leading to imbalance in the levels of free radicals and antioxidants; this is called oxidative stress. This phenomenon can oxidize membranes including mitochondrial membrane thus activating caspases that drive apoptosis.

Ferroptosis is a type of programmed cell death caused by iron dependent lipid peroxidation [16,17]. It is characterized by the accumulation of reactive oxygen species. Sevoflurane disturbs intracellular iron homeostasis by altering the iron transport and storage proteins like transferrin and ferritin respectively, causing accumulation of iron. Iron catalyzes the conversion of the free radical hydrogen peroxide to highly reactive oxygen species, hydroxyl ion which further propels ferroptosis and lipid peroxidation.

3. Developmental neurotoxicity

3.1 Multiple exposures

Study has shown that multiple exposures to local anesthesia before the age of 3 years are linked with distinct patterns of limitations in neuropsychological skills in children [18]. Sevoflurane is known to induce motor skill deficits as well as neurodevelopmental disorders. Moreover, repeated exposures to sevoflurane in neonatal mice resulted in over-activation of excitatory neurons in the prefrontal cortex leading to impulsive behaviors like ADHD [19].

3.2 Prenatal exposure

Findings have revealed that frequent exposures of sevoflurane during mid trimester can stimulate premature differentiation of NSC (neural stem cells) in developing brain of rat offspring through miR-410-3p/ATN1 pathway [20]. miR-410-3p is a non-coding RNA that targets mRNA of Atrophin 1 (ATN1) gene and regulates developmental and neurological pathways. Sevoflurane downregulates the expression of ATN1 leading to permanent neuron loss in the offspring.

3.3 Hormonal changes

Study has evidenced that sevoflurane can affect hormonal levels in developing animals. Numerous exposures of the sevoflurane have shown to affect reproductive hormones. In male neonatal rats, increase of serum testosterone level was observed while increase in serum estradiol was observed in both males and females [21]. Such changes tend to cause adverse health effects like seizures that can be detected by electroencephalography.

4. Cognitive and Behavioral effects

4.1 Cognitive Impairment

Repeated and long-term exposure to sevoflurane causes cognitive impairment and behavioral changes especially in vulnerable populations such as infants, pediatric, and the elderly. Sevoflurane causes neurotoxicity through mechanisms such as glutamate transporter dysfunction, oxidative stress, neuroinflammation, and alterations in MAPK (mitogen-activated protein kinase) signaling pathways, in the cortex and hippocampus region responsible for learning and memory [22].

Glutamate transporters that regulate the levels of glutamate, are a primary excitatory neurotransmitter in the brain. These have significant function in removing excess glutamate from the synaptic cleft. Sevoflurane downregulates expression of glutamate transporters impairing the ability to clear glutamate from the synaptic cleft, increasing the risk of excitotoxicity [23].

The mitogen-activated protein kinase (MAPK) pathways are signaling cascades which regulate cell growth, differentiation, survival and apoptosis. ERK (Extracellular signal-regulated kinase), JNK (c-Jun N-terminal kinase) and p38 MAPK are the major pathways of MAPK. Sevoflurane exposure activates MAPK pathways and leads to increased p38 and JNK phosphorylation, promoting apoptosis, particularly in vulnerable regions like the hippocampus and cortex.

Findings from studies conducted on 3 x Tg mice, carrying mutations associated with Alzheimer's disease, show that sevoflurane exposure has affected critical pathways involved in maintaining neurotransmitter balance, stress response and survival signaling, leading to apoptosis in brain regions responsible for cognitive functions [24]. Similar study conducted on wild type mice, without any genetic mutations,

did not exhibit significant cognitive deterioration when exposed to sevoflurane. The study indicates that sevoflurane affects people more severely if they are predisposed to neurodegeneration.

Study has found that repeated exposure to sevoflurane harms the learning and memory abilities of young rats by disrupting the key pathways in brain by causing imbalance in the tPA/PAI-1 system [25]. The tPA/PAI-1 system is responsible for conversion of proBDNF (precursor to brain-derived neurotrophic factor) to BDNF (brain-derived neurotrophic factor), influencing memory and learning.

Tissue Plasminogen Activator (tPA) is an enzyme whose primary function is to convert plasminogen to plasmin, an important clotting factor, in circulatory system but is also active in the brain, plays a crucial role in neuronal plasticity, memory formation, and learning [26]. BDNF is essential for synaptic plasticity and cognitive function. BDNF binds to TRkB (Tropomyosin receptor kinase B) activating signaling pathways that lead to growth of new neurons and synapses, and increased plasticity. On the other hand, PAI-1 is Plasminogen Activator Inhibitor-1 which inhibits the formation of BDNF leading to impaired synaptic plasticity and memory.

4.2 Brain State Changes

A study depicted resting state functional MRI (rs-fMRI) data of patients under awake and under general anesthesia (GA) condition with sevoflurane. During GA condition, brain showed low functional connectivity state indicating a stable but suppressed state. Contrastingly, the awake brain showed dynamic switching between multiple states including high connectivity state indicating active cognitive processing and consciousness [27].

5. Protective Strategies and Therapeutic Approaches - Pharmacological Interventions

Lipid Metabolism in microglia is identified as an important factor for neuroprotection. TREM2 (Triggering receptor expressed on myeloid cells 2) is essential for regulating lipid metabolism in microglia. It is a receptor commonly found in the CNS (Central Nervous System), and gets activated when it binds to different type of ligands. The effects of TREM2 activation causes enhanced phagocytosis and also lipid metabolism regulation by promoting the clearance and recycling of lipids, which is important in conditions such as neuro-degeneration where excess lipids are released. It also causes microglia shift to a M2-like anti-inflammatory stage from M1-like pro-inflammatory stage, hence causing tissue repair and neuroprotection [28,29]. This is attained by reducing inflammation and promoting healing through processes such as remyelination (repairing of myelin sheath) and neurogenesis (formation of new neurons).
Quercetin a natural flavonoid is known for its antioxidant, anti-inflammatory properties, is combined with Cu2-xSe (Copper selenide) nanoparticles, that improves its bioavailability. The developed nanoparticle, called CSPQ (Quercetin- Modified Nanoparticles), has shown to reduce the neurotoxic effects of sevoflurane by modulating lipid metabolism, activation of TREM2 signaling pathway and promotion of M2-like microglial polarization. Study confirmed the importance of TREM2 in effectiveness of CSPQ by silencing TREM2 gene in microglial cells which resulted in loss of neuroprotective function of CSPQ [30].

Recent studies have found neuroprotective effects in Midazolam, a Benzodiazapine commonly used for providing sedation, and as a pre-anesthetic medication. In vitro experiments conducted on hippocampal neurons showed that midazolam reduces neuronal death and promotes maturation [31]. Confirmation of these results was made by administering midazolam in mice with behavioral deficits, caused by neurotoxic effects on sevoflurane exposure. Midazolam's neuroprotective effect is mediated through the ERK (Extracellular signal- Regulated Kinase) signaling pathway. ERK is a part of MAPK signaling pathway, which is important for cell survival, preventing apoptosis, and promoting neuronal growth [32].

Solasonine found in Solanum nigrum L, a plant with medicinal properties, has shown to have anti-tumor, anti-oxidant, and anti-inflammatory effects. Research studies has shown the neuroprotective effects of solasonine, both in vitro and in vivo, by activation of AMPK/FoxO3a signaling pathway [33]. AMPK (AMP-activated protein kinase) helps in reducing oxidative damage during neurodegeneration. AMPK phosphorylates FoxO3a (Forkhead box O3a) which is an important transcription factor for expression of anti-apoptotic proteins and anti-oxidants. Thus, the activation of AMPK/FoxO3a pathway counteracts the neurotoxic effects of sevoflurane.

Echinatin, a natural compound with antioxidant, anti-inflammatory properties, has shown neuroprotective effects. Echinatin has shown to suppress ferroptosis by restoring the iron balance, improving the antioxidant defense, and anti-inflammatory effects, in both neuronal cell cultures and mice models [34].

6. Conclusion

As important as sevoflurane is, as an anesthetic agent, there is a need for further research for its careful use especially in vulnerable population like infants and elderly people. Further investigation into other mechanisms of action of sevoflurane, in context of neurotoxicity, is required. Pre-clinical studies have to be translated to clinical trials and follow-up studies on human.

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