

# Neonatal Sevoflurane Exposure and Memory and Cognitive Impairments: The Role of Posttranslational Modifications

## Abstract

As technology has improved, an increasing number of newborns are receiving general anesthesia at a young age for surgical procedures, other interventions, or clinical evaluation. The anesthesia-induced neurotoxicity and apoptosis of nerve cells bring memory loss and cognitive decline. Sevoflurane is the anesthetic that is used most frequently on infants; However, it might be harmful to the brain. A solitary, short episode of sevoflurane openness little affects mental capability, yet drawn out or repetitive openness to general sedatives can hinder memory also, mental capability. However, the underlying mechanisms of this association remain a mystery. Posttranslational alterations (PTMs), which can be portrayed generally as the guideline of quality articulation, protein action, and protein capability, have started huge interest in neuroscience. A growing number of studies in recent years indicate that posttranslational modifications are a crucial mechanism that mediates anesthesia-induced long-term changes in gene transcription and protein functional deficits in memory and cognition in children. In light of these late discoveries, our paper surveys the impacts of sevoflurane on cognitive decline and mental disability examines how posttranslational alterations systems can add to sevoflurane-actuated neurotoxicity, and gives new experiences into the counteraction of sevoflurane-prompted memory and mental hindrances.

**Keywords:** Posttranslational modifications • Neonatal • Memory and cognitive impairment • Long term

## Introduction

The norm of care for a large number of techniques and medical procedures on infants is general sedation. General sedatives are regulated to a great many small kids every year to work with surgeries and assessments. Nearly 650,000 children under the age of three in the United States will be subjected to general anesthesia each year. The public has recently expressed concern that the high rates of synaptogenesis, neurogenesis, and neuronal maturation in the developing brain may increase the risk of adverse long-term effects of anesthetic exposure, despite the fact that general anesthesia is typically regarded as safe and reversible in adults. In particular, recent research has suggested that early administration of general anesthesia may cause abnormal brain development. For instance, approximately 12% of patients with normal cognitive function in the past. Sevoflurane, which was first utilized in clinical practice during the 1990s, has become one of the most frequently utilized inhalational sedatives in pediatric activities since it offers better hemodynamic solidness, speedier recuperation, and less respiratory bothering than other sedatives. However, there is conclusive evidence that, in both humans and animals, repeated exposure to sevoflurane based anesthetics can result in long-term cognitive impairment and neuropathological alterations in the brain. According to numerous preclinical studies, rodents may develop behavioural abnormalities as well as learning and memory impairments later in life from prolonged or repeated exposure to sevoflurane alone during the first few days after birth. This issue has been the subject of numerous attempts, and recent advances have resulted

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in a number of them. However, the processes that underlie the long-term effects of neonatal sevoflurane exposure on brain development remain a mystery [1].

### Post-Translational Modification of Histone

Posttranslational histone modifications are necessary for gene expression and the geometry of chromatin. The chromatin is in an unfavourable state for transcription because the positive charges of unmodified histone proteins encourage a close association with the negative charges of DNA. However, the charges and binding properties of histones are altered by acetylation, phosphorylation, and methylation. Acetylated histones are frequently linked to transcriptional activation because they serve as binding sites for the transcriptional machinery. Histone phosphorylation is linked to transcriptional activity, whereas histone methylation can facilitate both transcriptional activation and repression. These coupled PTMs of histone proteins control gene expression and act as a "histone code" by activating transcriptional machinery [2].

### Acetylation of Histone

Among the many forms of histone modifications, histone acetylation is one of the most studied mechanisms. Studies have shown that these alterations are important for brain development and function. An acetyl group is attached to lysine at the N-terminal tail of the nucleosome, which is the basic unit of DNA packing in eukaryotic cells. Enzymes that catalyze the acetylation of histones include Histone Acetyltransferases (HATs) and Histone Deacetylases (HDACs). HDACs inhibit transcription and reverse the activity of HATs by removing acetyl groups from histone tails. Since it is frequently linked to an increase in the expression of many genes that play a significant role in synaptic plasticity, learning, and memory in the brain, it is commonly believed that histone acetylation is beneficial for memory and cognition. Ongoing examinations have shown long-haul formative discernment deficiencies and changes in histone acetylation in rodents presented to sedatives during the pre-birth or neonatal stage. For instance, hippocampal levels of HDAC3 and HDAC8 were higher in adult sevoflurane-exposed neonatal mice than in HDAC1 or HDAC2 levels [3].

According to these studies, this process, which results in a decrease in histone acetylation, is a

major contributor to the memory and cognitive impairments brought on by neonatal anesthesia. Researchers were able to successfully reduce the neurocognitive impairment caused by general anesthesia as well as the dysregulation of histone acetylation in the hippocampus by utilizing the HDAC inhibitors Trichostatin A (TSA) and sodium butyrate [4].

### Phosphorylation of Histone

Protein phosphorylation is the posttranslational change that occurs the most frequently in eukaryotes. The formation of phosphodiester bonds can happen as an afterthought chain of serine; threonine and tyrosine (frequently alluded to as "deposits"). Neurons contain a large number of protein kinases, protein phosphatases, and phosphorylated proteins, many of which are necessary for controlling the morphology of neurons as well as a variety of cell processes, such as membrane excitability, secretory procedures, cytoskeletal organization, and cellular metabolism. Histone phosphorylation is another PTM that offers an unmistakable epigenetic mark to control chromatin elements. The "essayist" compounds liable for histone phosphorylation are kinases, which intercede the exchange of a phosphate moiety from the high-energy particle ATP. Protein Phosphatase 1 (PP1) and MAPK Phosphatase 1 (MKP1), on the other hand, are the "eraser" enzymes that get rid of these phosphate groups. Histone H3 phosphorylation has received a lot of attention because of its connection to chromosome condensation during mitosis. H3 phosphorylation is interestingly initiated by the activation of mutagenic signalling pathways. Several other kinases, such as Extracellular Signal-Regulated Kinase (ERK), aurora kinase family member increase in ploidy 1 (IPL1), and Mitogen and Stress Activated Protein Kinase 1 (MSK1) are downstream of ribosomal protein S6 kinase 2 (RSK2). RSK2 also mediates the phosphorylation of histone H3 on the serine 10 residue. Along with other histone modifications, H3 phosphorylation also regulates the transcriptional apparatus's binding to chromatin molecules, influencing important biological processes [5, 6].

### Methylation of Histone

Another mechanism that regulates the structure of the chromatin is histone methylation; methyl gatherings can be added by Histone Methyl Transferases (HMTs) or eliminated by Craze subordinate amine oxidase (KDM1 or LSD).

In expansion, histone methylation can cause transcriptional actuation, despite the fact that methylation is regularly considered a sign of transcriptional constraint. The methylation of Histone H3 at lysine 9 (H3K9) is associated with transcriptional repression [7].

Recent studies have examined the role of histone methylation in the storage of long-term memories. During the process of memory formation, researchers discovered that hippocampal H3K4 was trimethylated and hippocampal H3K9 was dimethylated, indicating that gene expression was altered. The expression of H3K9me3 and its binding to the BDNF exon IV promoter was significantly upregulated in mice after general anaesthesia surgery for 24 hours. These findings enhance our understanding of neonatal aesthetic neurotoxicity, particularly in light of the bidirectional regulation of this change and the paucity of in-depth research, despite the use of middle-aged mice as the study model [8].

### Phosphorylation of Tau protein

Phosphorylation regulates the stabilization and assembly of microtubules themselves, which in turn regulates the physiological functions of Tau, including its binding to microtubules. One of the earliest occurrences of AD, hyperphosphorylation of Tau contributes significantly to the impairment of neuronal function, memory, and cognition and may cause pathology in the brain. Phosphorylation gives another viewpoint on sevoflurane-prompted mental brokenness in neonatal mice. Tau phosphorylation alters the cognitive impairment that is caused by sevoflurane in neonatal mice. The microtubule-associated protein tau protein was first identified in 1975 that is restricted to the healthy brain's axonal compartment of neurons. The family of microtubule associated proteins known as tau proteins aid in the assembly of microtubules and maintain axonal integrity in mature neurons, and carry out tasks at the neuronal dendrites. Hyperphosphorylated and abnormally phosphorylated forms of Tau are the primary components of the intraneuronal Paired Helical Filaments (PHFs) that are seen in AD. Tauopathies, which are other neurodegenerative diseases with filaments of a similar type. Unnecessary Tau phosphorylation supports the production of unmanageable Tau clusters. According to Holmes and Diamond, the aggregate can alter the conformation of the template by leaving the initial cell, coming into contact with a connected cell, and then entering the cell to

produce additional aggregation. In addition, mice's cognitive performance can be affected by Tau phosphorylation. Tau phosphorylation via GSK-3 activation was induced in mice at postnatal day 6 by multiple exposures to 3% sevoflurane for two hours daily, but not by a single exposure. This phosphorylation expanded IL-6 levels and diminished PSD-95 levels in the hippocampus, prompting mental disability. Due to the fact that Tau knockout (Tau KO) mice did not exhibit these side effects, it is possible that Tau plays a significant role in the neuroinflammation and synaptic impairments that were caused by sevoflurane in mice. NUA family kinase 1 (NUAK1) is elevated in the brain in new-born mice due to decreased mitochondrial performance. NUA1 might cause Tau phosphorylation at serine 356 and forestall Tau corruption, resulting in a greater accumulation of Tau in neonatal mice's brain tissues than in adult mice's. Thus, neonatal mice are more defence less than grown-up mice to the beginning of Tau phosphorylation brought about by sevoflurane sedation. Intense 1.5% sevoflurane openness came about insignificant, portion ward, and reversible hyperphosphorylation of Tau in the hippocampus of 5-to-half-year-old mice. In addition, previous research demonstrated that, under normothermic conditions, repeated exposure to 2.5% sevoflurane causes persistent hyperphosphorylation of Tau at the Ser396/Ser404 and Thr181 phosphoepitopes. Following significant deficits in spatial learning and memory in mice, the Morris Water Maze (MWM) test was used. Because hyper phosphorylated Tau is a prominent component of neurofibrillary lesions, these earlier investigations highlight a potential mechanism through which anaesthetics may impair cognition and increase the risk of Alzheimer's disease. However, it is necessary to establish a direct link between cognitive impairment and the accumulation of phosphorylated Tau. Sevoflurane's ability to phosphorylate Tau and transport Tau from neurons to microglia via extracellular vesicle-associated trafficking was found to be the cause of IL-6 production and cognitive impairment [9, 10].

### Conclusion

Sevoflurane has emerged as the most widely used anesthetic due to its distinct pharmacological properties. However, there is increasing evidence to suggest that sevoflurane impairs cognitive function and long-term memory. There is currently no effective treatment for sevoflurane-

induced memory and cognitive impairments, despite extensive research. Given the effectiveness of therapeutic intervention utilizing HDAC inhibitors, however, PTMs intervention may be a promising potential targeted treatment to reduce the neurotoxic effects of anesthetics on developing brains. Additionally, we believe Tau phosphorylation requires additional research in the future.

## References

- Erndsen CE, Denu JM. Catalysis and substrate selection by histone/protein lysine acetyltransferases. *Curr Opin Struct Biol.* 18, 682-689 (2008).
- Binder LI, Frankfurter A, Rebhun LI. The distribution of tau in the mammalian central nervous system. *J Cell Biol.* 101, 1371-1378 (1985).
- Bradbury EM, Inglis RJ, Matthews HR *et al.* Phosphorylation of very-lysine-rich histone in *Physarum polycephalum*. Correlation with chromosome condensation. *Eur J Biochem.* 33, 131-139 (1973).
- Brioni JD, Varughese S, Ahmed R *et al.* A clinical review of inhalation anesthesia with sevoflurane: From early research to emerging topics. *J Anesth.* 31, 764-778 (2017).
- Buée L, Bussière T, Buée-Scherrer V *et al.* Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Res Brain Res Rev.* 33, 95-130.
- Buee L, Troquier L, Burnouf S *et al.* From tau phosphorylation to tau aggregation: What about neuronal death? *Biochem Soc Trans.* 38, 967-972 (2010).
- Chai G, Wu J, Fang R *et al.* Sevoflurane inhibits histone acetylation and contributes to cognitive dysfunction by enhancing the expression of ANP32A in aging mice. *Behav Brain Res.* 431, 113949 (2022).
- Chastain Potts SE, Tesic V, Tat QL *et al.* Sevoflurane exposure results in sex-specific transgenerational upregulation of target IEGs in the subiculum. *Mol Neurobiol.* 57, 11-22 (2020).
- Chun YS, Kwon OH, Chung S. O-GlcNAcylation of amyloid-beta precursor protein at threonine 576 residue regulates trafficking and processing. *Biochem Biophys Res Commun.* 490, 486-491 (2017).
- Chwang WB, Arthur JS, Schumacher A *et al.* The nuclear kinase mitogen- and stress-activated protein kinase 1 regulates hippocampal chromatin remodeling in memory formation. *J Neurosci.* 27, 12732-12742 (2007).