



**Karolinska  
Institutet**

**Institutionen för fysiologi och farmakologi  
Sektionen för anestesi- och intensivvård**

# **Effects of sevoflurane anesthesia on cognitive function and cholinergic signaling**

**AKADEMISK AVHANDLING**

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i föreläsningssal Rolf Luft, Karolinska Universitetssjukhuset, Solna.

**Fredagen den 14 oktober 2011 kl 09.00**

av

**Andreas Wiklund**

Leg. läkare

*Huvudhandledare:*

Professor Lars I Eriksson  
Karolinska Institutet  
Institutionen för fysiologi och farmakologi

*Bihandledare:*

Med. Dr. Eva Sundman  
Karolinska Institutet  
Institutionen för fysiologi och farmakologi

Docent Gunnar Schulte

Karolinska Institutet  
Institutionen för fysiologi och farmakologi  
Enheden för receptorbiologi och signalering

*Fakultetsopponent:*

Professor Mikael Bodelsson  
Lunds Universitet  
Institutionen för kliniska vetenskaper

*Betygsnämnd:*

Professor Torsten Gordh  
Uppsala Universitet  
Institutionen för kirurgiska vetenskaper  
Enheten för anestesiologi och intensivvård

Professor Sven-Ove Ögren

Karolinska Institutet  
Institutionen för neurovetenskap

Professor Göran Engberg

Karolinska Institutet  
Institutionen för fysiologi och farmakologi

**Stockholm 2011**

## **ABSTRACT**

In recent years, concerns have been raised regarding the potential negative impact of anesthetic drugs in postoperative cognitive dysfunction. This thesis is an attempt to contribute to the understanding of the underlying mechanisms. Previous animal studies have suggested that volatile anesthetics can cause long-lasting cognitive alterations in various settings. Based on the strong association between cholinergic function and cognitive performance, we have focused our studies on the long-term effects of volatile anesthetics on cholinergic neurotransmission.

By using a combination of laboratory animal experiments and molecular biology techniques in cultured cells, we have described effects of sevoflurane anesthesia on cognitive function and cholinergic signaling. Our studies on spontaneous exploratory behavior, anxiety, object memory and analyses of behavioral organization in mice show that for some aspects of cognitive performance sevoflurane can cause long-lasting effects, while other aspects are unaltered by anesthesia. We have shown that age and preexisting cholinergic dysfunction are factors that influence the results. A normal cholinergic system, as represented by young wild type mice, seems to protect from behavioral alterations after anesthesia.

Our results suggest that sevoflurane causes a sustained attenuation in acetylcholine-induced phosphorylation of important intracellular kinases. We have linked our findings to signaling via muscarinic acetylcholine receptors, and we have also demonstrated that the effect of sevoflurane is not likely exerted by reducing the receptor population on the cell surface, nor by altering the total amount of receptor protein available for ligand binding.

The overall conclusion from the results of this thesis is that under certain experimental conditions, sevoflurane induces long-lasting alterations both in animal behavior and in cellular signaling.

**Key words:** Postoperative cognitive dysfunction, sevoflurane, acetylcholine, nicotinic acetylcholine receptors, muscarinic acetylcholine receptors, anesthesia, episodic-like memory, spatial memory

ISBN 978-91-7457-449-4