Commentary on: "Effect of sevoflurane anesthesia on the comprehensive mRNA expression profile of the mouse hippocampus"

Postoperative nausea and vomiting conundrum: RNA-seq to the rescue

The molecular bases for anesthesiology syndromes have attracted substantial research attention in recent years. There is growing evidence to suggest that complex changes in gene expression may predispose to the unpleasant postoperative nausea and vomiting (PONV) manifestations that includes nausea, vomiting, and retching, 24–48 hours after surgery (Sanger and Andrews, 2006). PONV can be difficult to manage, and may result in serious complications. Translational research has accumulated a large body of data that can be usefully extrapolated to humans. A current research focus has been to establish how volatile anesthetics such as sevoflurane are associated with a dose-dependent increase in the risk of PONV. Studies have shown that septohippocampal inactivation mediates the general anesthesia effect, with the suggestion that disruption to this system might be associated with the pro emetic action of anesthetics, as an undesirable side effect (Ma et al., 2002).

In their paper published in the current issue of *Medical Gas Research*, the authors hypothesized that the hippocampus, *via* dopaminergic neurons, may play a role in sevoflurane-induced PONV (Hayase, 2016). Using whole transcriptome sequencing technology, they collected mouse hippocampus gene expression profiles in response to sevoflurane, a known volatile anesthetic agent that induces PONV. Although a microarray-based approach would also capture expression data for thousands of genes, the RNA sequencing (RNA-seq) methodology, involving an intermediate cDNA library step, was used to generate more complete, discovery-oriented transcriptomes (Dong et al., 2015). After 1-hour anesthesia, it was shown that of 37,681 investigated genes, 5,459 were differentially expressed, including 345 that were markedly altered in response to sevoflurane. The most highly up-regulated gene was the Nogo receptor, which mediates axonal growth inhibition, and plays a role in regulating axonal regeneration and plasticity in the central nervous system. The dopamine receptor and tachykinin genes were also up-regulated. Of note, aprepitant is the first NK1 receptor (aka "tachykinin receptor 1") antagonist approved for use as an antiemetic (Hargreaves et al., 2011). While the role of area postrema and nucleus tractus solitarii (chemoreceptor trigger zone) in inducing nausea *via* dopamine is well known, the involvement of the hippocampus has been paid relatively little attention. In particular, the mRNA profile of the hippocampus at risk of PONV has not been studied. In addition, LIM-homeodomain-related genes, responsible for cell differentiation, were found to be highly down-regulated. Thus sevoflurane might act by inhibiting the differentiation of neural stem cells into neurons.

Interestingly, the alterations of expression for serotonin-related genes, which have been widely implicated in PONV, were found to be insignificant. Instead, muscarinic cholinergic receptors were highly up-regulated. This may indicate that although multiple brain structures appear to be involved in anaesthesia-induced emesis, the underlying gene changes are more region-specific. Moreover, exposure to anaesthetics, without surgery, as in this study, may not recruit the serotonin receptor system for emesis. Nevertheless, the risk of nausea and vomiting in response to sevoflurane alone might hinder new proposed applications, *e.g.*, as a preconditioning modality (Keep et al., 2010).

The gene analyses presented in this study are insightful and help to verify various theories on the molecular background for PONV, despite the differences between the emetic responses of mice and humans. Future work will have to establish whether the substantial fold changes exhibited by specific genes out weight the effects of small, but still significant changes to clusters of genes. Also, it remains to be seen whether the reported modifications in transcript abundance will be reflected at the functional, protein level. Importantly, this study corroborates the potential of neurokinin1 receptor antagonists and dopamine receptor antagonists as therapeutic antiemetics.

Further studies will allow us to determine whether the modulation of emesis by multiple factors, *e.g.*, the antiemetic impact of smoking on PONV are also linked to globally altered gene expression (Chimbira and Sweeney, 2000). Additional mechanistic insights for PONV could be provided by investigating gene expression profiles across genders, as it is known that females are three times more likely to suffer from PONV than male individuals (Oddby-Muhrbeck et al., 2002). Such an approach could help to pinpoint causation.

In addition the stability of the sevoflurane-induced gene expression profile necessitates further investigation. Hopefully RNA-seq studies will examine other structures involved with emesis, *e.g.*, located in the brain stem, possibly discovering hitherto unknown emetic pathways, while clarifying the roles of previously identified factors such as endogenous neurotransmitters, cytochromes, as well as the

cannabinoid and vanilloid receptors. However, it may also transpire that individual genetic makeup contributes to the risk of PONV; this possibility warrants further investigation.

The robust upregulation of Nogo receptor (reticulon 4 receptor-like 2) upon sevoflurane exposure carries implications for the inhibition of nerve fiber growth and, if substantiated, may be in line with concerns voiced over the use of anesthesia in the developing brain (Wang et al., 2014).

In conclusion, the results of this study may help to elucidate the pathogenesis of PONV, and should stimulate further research into the identification of promising new molecular targets for therapy.

Robert P. Ostrowski*, Katarzyna Stępień, Ewa Matyja

Department of Experimental and Clinical Neuropathology, M. Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland

***Correspondence to:** Robert P. Ostrowski, M.D., Ph.D., rostrowski@imdik.pan.pl.*
***orcid:** 0000-0003-1373-4452*
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