Dexmedetomidine attenuates up-regulation of the *Rtn4rl2* gene and restores down-regulation of the *Syt1* gene induced by sevoflurane/surgery stress in the hippocampus of elderly mice

Shunsuke Tachibana, Michiaki Yamakage

Department of Anaesthesiology, Sapporo Medical University, Sapporo, Japan

Background and Goal of Study:

Postoperative cognitive dysfunction (POCD) is an important complication after sevoflurane/surgery stress. In human studies, it has been shown that surgery causes systemic inflammation, neuronal inflammation and cognitive dysfunction in elderly patients. We reported that the comprehensive mRNA profile of neurons in the mouse hippocampus was dramatically changed by exposure to sevoflurane¹. *Rtn4rl2* (*Reticulon 4 receptor like 2*) was shown to be the most up-regulated gene in that transcriptome analysis. We hypothesized that sevoflurane/surgery stress regulates the target genes associated with neuronal inflammation and that dexmedetomidine (Dex) has the neuroprotective effect. The goal of this study was to determine the influence of sevoflurane/surgery stress on mRNA expression in the hippocampus of elderly mice.

Materials and Methods:

All of the experimental protocols were approved by the Animal Care and Use Committee of Sapporo Medical University School of Medicine, Japan.

Twenty-four male mice (53 weeks of age) were divided into four groups: naïve, sevoflurane exposure (Sevo), operation (Ope), and operation with Dex i.p. (Dex) groups. Mice in the Sevo group were exposed to 2.5% of sevoflurane for 1 h. Mice in the Ope group were anaesthetized with 2.5% of sevoflurane and a 10-mm longitudinal incision was made in the lower abdomen. Mice in the Dex group were injected with 10 µg/kg of dexmedetomidine 30 minutes before the surgical procedure. After 1 h, the hippocampus of each mouse was punched out, and total RNAs were isolated from the hippocampus. cDNAs were generated by reverse transcription. Taqman probes specific for *Rtn4rl2* and *Syt1* (*Synaptotagmin 1*) were used for quantitative real-time polymerase chain reaction (qRT-PCR). Target gene expression was analysed using the comparative CT ($\Delta\Delta CT$) method compared with *Gapdh* as a control. In qRT-PCR analysis, data were analysed using one-way ANOVA with post-hoc Bonferroni correction.

Figure 1. Group classification and experimental protocols.

Results:

Rtn4rl2 expression was increased in the Ope group and was reduced in the Dex group. *Syt1* expression was not changed significantly in the Ope group but was increased in the Dex group (Figure 2).

Figure 2. Data are expressed as means $\pm$ S.D. (standard deviation). *P* values are as follows: * ; $p<0.05$, † ; $p<0.01$.

Discussion:

Under the condition of sevoflurane and surgery stress, *Rtn4rl2* (i.e., Nogo), which is highly expressed in the cerebral cortex, shows axon outgrowth inhibitory activity after CNS myelin injury². Dexmedetomidine might promote myelin regeneration by attenuating *Rtn4rl2* up-regulation. *Syt1*, which is highly expressed in synaptic vesicles and growth cones, is involved in neurotransmitter release and synaptic exocytosis³. Dexmedetomidine also might protect synapse by restoring and increasing *Syt1* expression.

Conclusions:

The target genes associated with neuroinflammation were influenced by sevoflurane/surgery stress and dexmedetomidine intervention. These findings may be the key for elucidating the mechanism of POCD.

References

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