



Isoflurane and desflurane at clinically relevant concentrations induce amyloid β -peptide oligomerization: An NMR study [☆]

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ABSTRACT

Current understanding on Alzheimer's disease (AD) reveals that soluble amyloid β -peptide (A β) oligomeric formation plays an important role in AD pathophysiology. A potential role for several inhaled anesthetics in promoting A β oligomer formation has been suggested. Using a nuclear magnetic resonance (NMR) study, we previously demonstrated that at a high concentration (higher than clinically relevant concentrations), the inhaled anesthetics halothane and isoflurane, interact with specific amino acid residues (G29, A30, and I31) and induce A β oligomerization. The present study confirms this is true at a clinically relevant concentration. Isoflurane and desflurane induce A β oligomerization by inducing chemical shift changes of the critical amino acid residues (G29, A30, and I31), reinforcing the evidence that perturbation of these three crucial residues indeed plays an important role in oligomerization. These findings support the emerging hypothesis that several commonly used inhaled anesthetics could be involved in neurodegeneration, as well as risk factor for accelerating the onset of AD.

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Alzheimer's disease (AD) is the most common cause of progressive dementia. The molecular mechanism for the disease-promoting effect has been difficult to pinpoint, but emerging views point toward amyloid β -peptide (A β) oligomeric formation, which plays an important role in the pathogenesis of this disease [1].

Several anesthetics could promote A β oligomeric formation, suggesting a potential association between anesthesia and AD [2–6]. At clinically relevant concentrations, the inhaled anesthetics halothane and isoflurane-induced A β oligomerization, although molecular details were not well known [4,7]. Using NMR spectroscopic study, we have previously shown that these anesthetics, at a high concentration, interact with a specific region of the A β peptide and induce A β oligomerization [5]. In transgenic mice, in comparison with control group animals, more amyloid plaques were reported after administration of halothane and isoflurane [8]. It was also inferred that several commonly used inhaled anesthetics may cause brain damage which accelerates the onset of AD [3]. All these observations warrant further studies on A β peptide interaction with current inhaled anesthetics at clinically relevant concentrations which are used for anesthesia and sedation in intensive care units.

Recent research supports the use of volatile agents isoflurane and desflurane as the ideal sedative agents in intensive care units (ICU) because of their low blood solubility, metabolism less than 1%, and elimination independent of renal or hepatic function [9]. In addition, desflurane seems to be a promising new alternative to intravenous anesthetics for sedation of ventilated adult patients in ICU [10], and isoflurane is a safe and efficacious agent for inhalational sedation in ICU, with short wake-up times after termination of administration [11].

A consistent part of the population admitted to ICU present high levels of A β in the CNS (elderly and head-injured patients). The overall aim of our study was to investigate whether isoflurane and desflurane, at clinically relevant concentrations, interact with A β . The secondary objective was to show the time dependence for A β oligomerization, if any, due to these inhaled anesthetic agents.

Materials and methods

To address the two important above mentioned objectives, NMR experiments were designed to investigate time-dependent studies for A β peptide interaction with isoflurane and desflurane at a clinically relevant concentration.

Materials. In this study, desflurane (Baxter), isoflurane (Lancaster Synthesis Inc., USA), Deuterated SDS_{D25} (Cambridge Isotope Laboratories), and ¹⁵N-labeled A β 40 peptide (Recombinant Peptide Technologies, Atlanta, GA, USA) have been used. NMR data have been recorded using 5 and 3 mm NMR tubes purchased from Wilmad Lab Glass.

[☆] Part of the results will be presented at Biophysical Society meeting, Boston, Feb. 2009.

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