

Smaller molecular-sized anaesthetics oligomerize A β peptide simulating Alzheimer's disease: a relevant issue

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Alzheimer's disease is a growing global public health concern. Advanced research protocols to understand the pathogenesis of the molecular mechanisms of Alzheimer's disease run parallel to dedicated research to determine the risk factors in this global scientific crusade. Detailed understanding of the underlying molecular mechanisms of this disease suggests that the amyloid beta peptide (A β), hallmark of the disease, is subject to A β oligomerization, a process that increases synaptotoxicity. Increased aggregation of A β through the stabilization of intermediate toxic oligomers is thought to contribute to neurocognitive dysfunction [1]. However, the mechanistic relationship remains unclear.

It has been hypothesized that several commonly used inhaled anaesthetics could be involved in neurodegeneration, promoting the 'toxic' aggregation (oligomerization) of A β and contributing to an accelerated onset of Alzheimer's disease [2–4].

After surgery, elderly patients often experience a transient reversible state, characterized by cognitive alteration associated with memory loss and lack of concentration, resembling the cognitive dysfunction evidenced in Alzheimer's disease [5]. With increased life expectancy, more and more aged individuals will undergo surgery under anaesthesia for various reasons, which compounds the chances of cognitive dysfunction in such individuals. Age, prolonged surgery and complex surgical procedures are among the listed factors contributing to postoperative cognitive dysfunction (POCD) in the International Study of Post-Operative Cognitive Dysfunction (ISPOCD1) [6]. ISPOCD2 (1997–2001) recommendations strongly emphasized strict anaesthesia protocol, covering specific areas from choice of drug to anaesthetic technique. However, the bane of POCD continues to mar surgical

outcome in some elderly patients, in spite of adherence to these measures.

Current literature supports the potential involvement of the mechanism of Alzheimer's disease neuropathogenesis in the genesis of POCD. This suggests an investigation of the biophysical characteristics of these anaesthetics (inhaled and intravenous) at a molecular level.

Molecular sizes of inhaled and intravenous anaesthetics are quite different, as are their biochemical and biophysical characteristics. These differences seem to play a basic role in the anaesthetics–A β interaction. Inhaled anaesthetics (halothane, isoflurane, sevoflurane and desflurane) consist of various halogenated, small-sized molecules [7], and calculated cerebral concentrations are in the range of 0.26–0.57 mmol l⁻¹, based on clinically relevant concentrations in the blood [3,7]. On the other hand, intravenous anaesthetics (propofol and thiopental) consist of large-sized molecules, and concentrations are lower in the brain, with calculated cerebral values of approximately 0.15 mmol l⁻¹ and approximately 0.075 mmol l⁻¹, respectively. The molecular sizes of inhaled anaesthetics are in the range of 90–140 Å³, whereas those of intravenous anaesthetics start from 190 Å³.

The molecular size of an anaesthetic has a profound influence on the oligomerization process of A β . In-depth molecular details have recently been revealed using the state-of-the-art nuclear magnetic resonance (NMR) technique [3], and implications for central cholinergic neurons have been explored [8]. The critical amino acid residues G29, A30 and I31 of A β , located in the loop region connecting the two helices of A β , are mainly involved in the interaction of isoflurane and halothane with A β , leading to A β oligomerization. In further NMR studies, isoflurane and desflurane molecules interacted at concentrations comparable to those obtained during sedation in the ICU setting, with A β peptides producing A β oligomerization after 9 days and 25 days, respectively [2].

As opposed to inhaled anaesthetic studies, NMR studies involving intravenous anaesthetics led to different observations. Thiopental, an intravenous anaesthetic, did not oligomerize A β at all, even at higher concentrations [3]. In another NMR study, diazepam did not oligomerize A β (unpublished data). The bulkier thiopental or diazepam could not fit into the pocket containing the three crucial

amino acid residues mentioned above and hence A β peptide oligomerization was not found, even at a much higher concentration [3]. Earlier NMR studies conducted at very high concentrations (i.e. well beyond the clinical range) proved that propofol leads to A β oligomerization [3], but, pending further study at clinically relevant concentrations, conclusions regarding propofol cannot be drawn.

Our results are in accordance with some animal model studies, which showed that isoflurane and halothane increase the plaque load in a mouse model with Alzheimer's disease pathology [1,9]. Very recently, it was reported that isoflurane induced acceleration of neurofibrillary disorder in a mouse model of tauopathy [10].

Is oligomerization of A β a potentially relevant issue? High levels of A β are naturally present in the central nervous system (CNS) of an aged population and in the brains of the majority of patients admitted to ICUs for management of head injuries and trauma. If higher amounts of A β are available in the brain to interact with anaesthetics (i.e. during general anaesthesia in the elderly or prolonged sedation in ICU patients), then the administration of general anaesthetics affecting the rate at which A β bind together could increase a patient's risk manifold.

For decades, inhaled anaesthetics have been the drugs of choice for general anaesthesia. Today we know that these general anaesthetics simulate the mechanism of Alzheimer's disease pathology in experimental models. Future research in this area is mandatory to formulate a safer anaesthetic protocol, especially for the elderly and patients at risk. It is important to evaluate the molecular interactions of A β with all drugs administered during general anaesthesia and in the perioperative period to find out whether these drugs promote toxic A β aggregation at clinical concentrations.

In conclusion, pending further confirmation from clinical studies, it would be prudent to avoid the use of high concentrations and/or prolonged administration of inhaled anaesthetics in patients with increased natural (aged population), acquired (patients with trauma or head injury) or pathological (patients with neurodegenerative disorders) levels of A β peptide. Molecular details [2,3] obtained from NMR techniques show that molecular size of the anaesthetics indeed plays a central role in A β oligomerization. Clinical correlation must be sought through carefully designed human studies, which will provide answers in this emerging area of clinical significance.

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