General Anesthesia and Alzheimers Disease Neuropathogenesis

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Principal Investigators

XIE, ZHONGCONG

Institution

MASSACHUSETTS GENERAL HOSPITAL

Contact information of lead PI
Country

USA

Title of project or programme

General Anesthesia and Alzheimers Disease Neuropathogenesis

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,212,186.24

Start date of award

01/02/2009

Total duration of award in years

4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

desflurane, General Anesthesia, Neuropathogenesis, Isoflurane, Anesthesia procedures

Research Abstract
DESCRIPTION (provided by applicant): Approximately 8.5 million Alzheimer's disease (AD) patients and a much greater number of senior patients who are vulnerable to AD will need surgical care under anesthesia every year around the world. Anesthesia and surgery have been

reported to induce cognitive dysfunction, which AD and senior patients are susceptible to developing. Therefore, it is necessary to identify anesthetics that will (""bad"") or will not (""good) promote AD pathogenesis and cognitive dysfunction, and to elucidate the underlying mechanisms. Our current R01 has established the system and shown the difference between the commonly used anesthetics isoflurane, desflurane, nitrous oxide and propofol on neurotoxicity. However, the underlying mechanisms remain unknown. Consistent with the findings that compounds with low chemical bond energy are unstable and thus can more easily form free radicals (FRs), which contribute to reactive oxygen species (ROS), our preliminary data have shown that isoflurane (with lower bond energy in ""Chloride-Carbon"") but not desflurane (with higher bond energy in ""Fluoride-Carbon""), increases levels of FRs and ROS. In the renewal R01, we will determine whether the difference in bond energy is the molecular basis by which isoflurane, but not desflurane, increases accumulation of FRs and ROS, and induces mitochondrial dysfunction, thereby causing activation of Tau kinase, leading to Tau phosphorylation and consequently learning and memory impairment. We will perform both mechanistic and translational studies by employing chemical and genetic tools through both in vitro (cultured cells, neurons and isolated mitochondria from mice) and in vivo (wild-type, AD transgenic, Tau and cyclophilin D knockout mice) approaches. We will test our hypothesis: isoflurane, but not desflurane, causes mitochondria-associated Tau phosphorylation, which interacts with AD gene mutation-induced Ab elevation, leading to more severe learning and memory impairment in three Specific Aims: 1) to systematically evaluate the effects of isoflurane, desflurane, nitrous oxide and propofol (alone or in combination) on mitochondrial function, Tau levels, and learning and memory in mice; 2) to investigate a chemical bond energy-based mechanism, which may elucidate why isoflurane and desflurane have different neurotoxic effects; 3) to determine the in vivo cause-effect relationship and targeted interventions using Tau and cyclophilin D knockout mice, FRs scavenge Vitamin C, antioxidant N-acetyl-L-cysteine, and mitochondrial permeability transition pore inhibitor cyclosporine A. This proposal aims at investigating an understudied yet important health topic. The anticipated results would: 1) identify so called ""good"" and ""bad"" anesthetic(s) affecting AD pathogenesis and cognitive function in mice; 2) elucidate new underlying mechanisms of anesthesia neurotoxicity; and 3) determine the strategy of prevention and treatment. These findings would conceptually advance anesthesia neurotoxicity research and promote more studies, including clinical investigation, and ultimately lead to safer anesthesia care and better postoperative outcomes for AD and senior patients.

Lay Summary

PUBLIC HEALTH RELEVANCE: Our current R01 studies have established the system and shown that the anesthetic isoflurane, but not desflurane, may promote Alzheimer's disease pathogenesis in vitro and in vivo. The proposed research in this renewal R01 will focus on mechanistic and translational studies. We will (1) identity various anesthetics and anesthesia regimens which will or will not promote Alzheimer's disease pathogenesis and induce impairment of learning and memory in wild-type and transgenic mice; (2) investigate the chemical bond energy-based and mitochondria-associated mechanisms of anesthesia neurotoxicity; and (3) determine the in vivo cause-effect relationship and explore the targeted interventions.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
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