HOKKAIDO UNIVERSITY

Title	The Impact of Obesity on Postoperative Cognitive Dysfunction and the Neuroprotective Effects of Anesthetics Against Sepsis-Associated Encephalopathy
Author(s)	WANG, WEI
Description	配架番号：2947
Degree Grantor	北海道大学
Degree Name	博士(医学)
Dissertation Number	甲第16637号
Issue Date	2025-09-25
DOI	https://doi.org/10.14943/doctoral.k16637
Doc URL	https://hdl.handle.net/2115/98247
Type	doctoral thesis
File Information	WANG_Wei_abstract.pdf, 論文内容の要旨 https://creativecommons.org/licenses/by/4.0/

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

学位論文内容の要旨
（Summary of Dissertation）

博士の専攻分野の名称　博士（医　学）　氏 名　WANG WEI
（Degree conferred: Doctor of Philosophy）

学 位 論 文 題 名
（Dissertation Title）

The Impact of Obesity on Postoperative Cognitive Dysfunction and the Neuroprotective Effects of Anesthetics Against Sepsis-Associated Encephalopathy
（術後認知機能障害における肥満の影響および敗血症性関連脳症に対する麻酔薬の神経保護作用）

【Background】

With the aging population and increasing demand for surgical procedures, postoperative cognitive dysfunction (POCD) and inflammation-induced cognitive impairment have become significant medical concerns.
This study aims to investigate:

(1) POCD represents a significant challenge in modern medical care, especially affecting the elderly. With the increase in the number of surgeries, the incidence of POCD is increasing, affecting the quality of life of patients and placing a heavy burden on the global healthcare system. Although the occurrence of POCD is related to a variety of factors, increasing evidence suggests that neuroinflammation plays a crucial role in its occurrence and development. Advanced age, metabolic syndrome, obesity and other risk factors are associated with increased susceptibility to POCD. However, the exact mechanisms linking these factors to cognitive decline remain unclear. The relationship between obesity and POCD is of particular interest given the global obesity epidemic and its potential impact on surgical outcomes.

(2) Administration of lipopolysaccharide (LPS) is a common experimental model used to induce systemic inflammation, mimicking conditions like sepsis. This LPS-induced systemic inflammation can subsequently lead to Sepsis-Associated Encephalopathy (SAE) in the brain. SAE, in this context, frequently causes acute cognitive decline, which is associated with neuroinflammation, microglial activation, and disruption of the blood-brain barrier (BBB). Anesthetic agents like dexmedetomidine (DEX) possess known neuroprotective properties potentially linked to the vagus nerve-mediated Cholinergic Anti-inflammatory Pathway (CAP) via α7 nicotinic acetylcholine receptors (α7nAChRs). However, the neuroprotective potential and mechanisms of the newer ultra-short-acting benzodiazepine, remimazolam (REMI), particularly concerning the CAP, remain largely unexplored. There is a lack of studies simultaneously evaluating the neuroprotective effects of REMI and DEX and their dependence on vagal pathways in relevant models.

【Methods】

1. To investigate the effect of obesity on POCD, diet-induced obesity (DIO) mouse model was established. C57BL/6 mice were fed with normal diet (NOR) and high fat diet (HFD) for 8 weeks, respectively. POCD was induced by tibial fracture surgery or intraperitoneal injection of high mobility group box-1 (HMGB-1). Cognitive function was

assessed using the Trace-fear Conditioning (TFC) test, a well-established method for assessing hippocampal-dependent memory in rodents. A test was performed 72 h after the intervention to evaluate the short-term cognitive effect. Blood and hippocampus tissues were collected for determination of inflammatory markers (IL-1β, TNF-α, IL-6) and leptin levels by enzyme-linked immunosorbent assay (ELISA).

2. C57BL/6 mice received IP LPS (1 mg/kg). Treatment groups included Control (saline), LPS, REMI (16 mg/kg IP + 8 mg/kg SC), DEX (30 μg/kg IP), REMI+LPS, and DEX+LPS. Additional groups received the selective α7nAChR antagonist methyllycaconitine (MLA; 4 mg/kg IP) 30 minutes prior to REMI/DEX/LPS. Cognitive function (TFC) was assessed 24 hours post-LPS. Hippocampal CA3 neuropathology was assessed via NeuN immunohistochemistry. Serum/hippocampal cytokines (TNF-α, IL-1β, IL-6) were measured by ELISA. BBB integrity was assessed via hippocampal albumin Western Blot. Vagal pathway involvement was probed by measuring lung Netrin-1 expression via Western Blot.

【Results】

(1) HFD mice exhibited significant weight gain and impaired baseline cognitive function (reduced TFC freezing time) compared to NOR mice. However, neither tibial fracture surgery nor HMGB-1 injection resulted in a significantly greater cognitive deficit in HFD mice compared to NOR mice under these experimental conditions. HMGB-1 injection significantly increased hippocampal IL-1β and IL-6 levels, with HFD+HMGB-1 mice showing significantly higher levels than NOR+HMGB-1 mice. Serum leptin was elevated in HFD mice, but hippocampal leptin levels were similar to NOR mice, suggesting central leptin resistance.

(2) LPS administration significantly impaired TFC freezing time, induced significant CA3 neuronal damage, increased serum/hippocampal TNF-α, IL-1β, and IL-6, increased hippocampal albumin (indicating BBB disruption), and decreased lung Netrin-1 expression. Pretreatment with either REMI or DEX significantly attenuated LPS-induced cognitive impairment, reduced CA3 neuronal damage, decreased cytokine levels, limited hippocampal albumin extravasation, and reversed the downregulation of lung Netrin-1. Crucially, the neuroprotective effects of both REMI and DEX were significantly blocked by pretreatment with the α7nAChR antagonist MLA.

【Discussion】

1. These findings suggest the interaction between obesity and acute postsurgical/inflammatory cognitive decline may be complex and model-dependent, potentially influenced by factors like obesity duration or central leptin resistance. The lack of exacerbated decline post-insult in HFD mice, despite heightened hippocampal inflammation after HMGB-1, warrants further investigation into underlying mechanisms and model limitations.

2. Both REMI and DEX demonstrate significant and comparable neuroprotective effects against LPS-induced acute cognitive impairment, neuroinflammation, hippocampal neuronal injury, and BBB disruption. The profound blockade of cognitive protection by MLA strongly indicates that α7nAChR activation is a critical component mediating the beneficial effects of both anesthetic agents. The restoration of lung Netrin-1, a marker modulated by vagal activity, further supports the involvement of the CAP. This suggests REMI, like DEX, engages α7nAChR-dependent cholinergic anti-inflammatory signaling.

【Conclusion】

1. Diet-induced obesity impairs baseline cognition in mice, but its role in exacerbating acute post-insult cognitive decline appears complex under the specific conditions tested, emphasizing the need for further research.

2. REMI and DEX exert robust neuroprotective effects against LPS-induced cognitive dysfunction and neuropathology. These effects involve mitigating neuroinflammation and BBB damage and are critically dependent, at least partially, on the activation of α7nAChRs, strongly implicating the vagus nerve-mediated cholinergic anti-inflammatory pathway. These findings establish REMI as a potent neuroprotective agent comparable to DEX in this model and reveal a shared reliance on α7nAChR signaling, suggesting potential therapeutic applications for both drugs in mitigating acute neurological complications associated with systemic inflammation, such as SAE.