Questions to be Addressed

• What is the Clinical Condition of Postoperative Cognitive Dysfunction (POCD)?
• What is the pathogenesis for POCD?
• Why does POCD not occur in all patients if trauma-induced inflammation is the cause?
• Why are Metabolic Syndrome patients at higher risk for POCD?
Post Operative Cognitive Dysfunction

Risk Factor: Infection


- 1218 patients aged at least 60 years undergoing major non-cardiac surgery with general anaesthesia
- 25.8% of patients had POCD one week after surgery; 9.9% persisted 3 months postop
- Risk Factor: Infection

Regional vs General: No Influence on Prevalence of POCD


Age as a Predictor of cognitive dysfunction after major noncardiac surgery


- 1064 patients undergoing major non-cardiac surgery with general anaesthesia
- 36.6% (18-39 yr), 30.4% (40-59 yr), 41.4% (>60 yr) patients had POCD at hospital discharge and 5.7%, 5.6% and 12.7% at 3 months postop respectively

Projection of the U.S. Population by Age
Postoperative Cognitive Dysfunction
• Impairment established by
  – Variety of cognitive tests
  – No consensus on diagnostic criteria
    • Use arbitrary statistical thresholds
• Risk Factors that increase Prevalence
  – Age
  – Infection
  – Metabolic Syndrome
• Long-term consequences
  – Loss of Job and/or independence
  – Higher Mortality Rate

Is POCD a Validated Clinical Construct?
• Avidan et al: Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness. Anesthesiology 2009
• Avidan MS, Evers AS: Review of clinical evidence for persistent cognitive decline or incident dementia attributable to surgery or general anesthesia. J Alzheimers Dis 2011
• Selnes et al: Cognitive and Neurologic outcomes after coronary-artery bypass graft surgery. NEJM 2012

CAD patients with or without surgery, have similar cognitive decline

Is POCD a Validated Disease?

Anesthesia

Age in Years

Cognition

- Normal population
- At-risk population
- At-risk population with surgery?
Animal model of Postoperative Cognitive Decline

- Why
  - Overcome problem of “controls”
  - Establish the independent contributions
    - Anesthesia
    - Surgery
- Validated by enhanced vulnerability
  - Age
  - Infection
  - Metabolic Syndrome

Projected Growth of Arthroplasty Surgery in the USA

“Orthopedic” Surgical model
Trace Fear Conditioning

Surgery induces memory deficit in mice

Contextual trace fear conditioning, POD 3

Cibelli M et al, Ann Neurol 2010

Peripheral Surgery Disrupts the Blood Brain Barrier

Anesthesia + Surgery
Circulating macrophages penetrate into the hippocampus shortly after surgery


Surgery-induced neuroinflammation

- Increase of IL's and PGE2 in the CSF
  - Buvanendran A et al. Upregulation of prostaglandin E2 and interleukins in the central nervous system and peripheral tissue during and after surgery in humans. Anesthesiology. 2006;104(3):403-10

- Increase of IL-6 in CSF after OP Coronary Artery Bypass Grafts
  - Kalman J et al. Elevated levels of inflammatory biomarkers in the cerebrospinal fluid after coronary artery bypass surgery are predictors of cognitive decline. Neurochem Intern 2006; 48: 177-80

Aseptic Trauma-induces Hippocampal Neuroinflammation that results in *Transient* Postoperative cognitive decline (PCD)

Does generation of trauma-induced brain inflammation produce a “survival” benefit to the injured organism?

- Pro-inflammatory cytokines in the Brain
  - Fever
  - Anorexia
  - Lethargy
  - Cognitive Decline
  - Disinclination to indulge in procreative behavior

- Stay in “cave”
  - Protected from predators
  - Further injury

- LTP disruption
- Cytokine release
- Glial activation
What causes the neuroinflammation to stop?

What causes persistent neuroinflammation?

- Continuing Provocation
  - Perioperative infection
- Underlying Neurologic Disease
  - Stroke
  - Neurodegenerative Disorders
- Failure of Inflammation Resolving Mechanisms

Prevention of Resolving Mechanism Enhances Postoperative Neuroinflammation

Surgery Alone
Surgery + α7nAChR antagonist
Surgery-induced cognitive decline is exaggerated by disrupting, and ameliorated by facilitating, resolution.

Human Risk Factors can be reproduced in animal model

- Infection exacerbates surgery-induced cognitive decline (Fidalgo et al. Neurosci Letts 2011)
- Surgery-induced cognitive decline is enhanced with advanced age (Roszyk et al. Exp Gerontol 2008)
- Metabolic Syndrome

Metabolic Syndrome Patients are Particularly Vulnerable to POCD

Low Capacity (LCR) vs High Capacity Runner (HCR) Rats
Acute Postoperative Cognitive Decline is exacerbated in Metabolic Syndrome

Morris Water Maze (MWM) test
Path to locate submerged platform

Swimming Speed is similar

Department of Anesthesia and Perioperative Care
Postoperative learning dysfunction persists at 5 months – Time to locate platform in MWM

Postoperative memory dysfunction persists at 5 months - MWM probe trial
The exaggerated & persistent postoperative cognitive decline in Metabolic Syndrome is associated with dysfunction of the innate immune response.

LPS-stimulation of circulating immunocytes release more pro-inflammatory Cytokines in Rats with MetaS both pre and postoperation.

The exaggerated innate immune response in Metabolic Syndrome is associated with dysregulation of inflammation-resolution.

Cholinergic inhibition of LPS-stimulated TNF-α release is attenuated in the Metabolic Syndrome.
Postoperatively, LCR rats produce less inflammation-resolving Lipoxin A4 but more inflammation-enhancing leukotriene B4

Summary of Results with LCR vs HCR rats

- LCR rats have enhanced neuroinflammation and more severe and persistent cognitive decline
- LCR rats have disrupted $\alpha_7$ nAChR-mediated inflammation-resolution mechanism
  - cellular components are reduced
  - cellular responses are reduced
  - cellular ratios are inverted
- LCR rats have qualitatively different humoral inflammation-resolving response to surgery

Are these results extrapolatable to Clinical Condition of POCD?

- Evidence for systemic and neuroinflammatory response to elective orthopedic surgery
- Immune system homeostatic mechanisms are less effective with advancing age
- Infection represents a “second” inflammatory hit that overwhelms resolving mechanism
- Metabolic Syndrome is characterized by disorder of resolution of inflammation and of abnormality in cholinergic function

Clinical Questions

- Can we prospectively identify surgical patients that will not resolve postoperative neuroinflammation and cognitive decline?
- Can we promote resolution of postoperative inflammation in patients that are at risk?
- Does failure to resolve inflammation produce other postoperative complications?
  - Conversion from acute to chronic postoperative pain
  - Thrombo-embolism
  - Infection