Neurotoxicity in Older Brains-

Does Anaesthesia trigger Delirium, Dementia or Alzheimer's Dementia?

Francois Stapelberg

Middlemore Hospital, University of Auckland, Auckland, New Zealand

Much emphasis of anaesthetic agents and their effects on the brain has been on neuroprotective mechanisms, including GABA potentiating effects of the volatile[1] and intravenous agents[2], α-2 blocking effects[3], antioxidant effects[4] apoptosis prevention[5] and preconditioning[6].

How then does one relate these theoretical advantages of anaesthetic agents to the common development of postoperative delirium (PD) in some patients[7]? The long-term effects of PD may include prolonged hospital stay, premature rest home placement, increased risk of death [8] and increased functional decline into dementia [9-12]. Whilst the likely role of central cholinergic deficiency remains a likely common pathway in delirium[13], it remain difficult to link the role of anaesthetic agents and intra-operative factors[14] to increased risk for delirium.

Persistent postoperative cognitive decline (POCD), experienced by patients as memory impairment, decreased executive function, early retirement and increased mortality risk[15] can occur in 10% of patients older than 60 undergoing non-cardiac surgery[16]; with a higher incidence in cardiac surgical patients[17]. No single mechanism explains this phenomenon. What is becoming clear is that anaesthetic agents may exert lasting effects on memory[18] and gene expression[19] that persist long after initial recovery from the anaesthetic.

A mechanism of neurotoxicity in older brains that has been suggested is that of anaesthetic agents inducing accumulation of hyperphosphorylated *tau* proteins [20], as well as enhancing oligomerisation of amyloid beta-precursor protein [21]. These cover two of the biochemical pathway hypotheses of Alzheimer's dementia[22]. These processes have been demonstrated in neural cell cultures, models of cell stress including Alzheimer's and Huntington's disease, as well as animal models[23]. Inhaled anaesthetic agents all appear to interact with neurodegeneration pathways that lead to cellular stress and neuronal apoptosis. [24]

This presentation will explore and review the current evidence for anaesthetic neurotoxicity in older patients, and whether these can be linked to cognitive decline, later neurological disease or indeed any post-operative outcome.

1. Bickler, P.E., et al., *gamma-Aminobutyric acid-A receptors contribute to isoflurane neuroprotection in organotypic hippocampal cultures.* Anesth Analg, 2003. **97**(2): p. 564-71, table of contents.

2. Jevtovic-Todorovic, V., et al., *Propofol and sodium thiopental protect against MK-801-induced neuronal necrosis in the posterior cingulate/retrosplenial cortex.* Brain Res, 2001. **913**(2): p. 185-9.
3. Rajakumaraswamy, N., et al., *Neuroprotective interaction produced by xenon and dexmedetomidine on in vitro and in vivo neuronal injury models.* Neurosci Lett, 2006. **409**(2): p. 128-33.
4. Yamaguchi, S., et al., *Propofol prevents lipid peroxidation following transient forebrain ischemia in gerbils.* Can J Anaesth, 2000. **47**(10): p. 1025-30.
5. Sanders, R.D., et al., *Dexmedetomidine provides cortical neuroprotection: impact on anaesthetic-induced neuroapoptosis in the rat developing brain.* Acta Anaesthesiol Scand, 2009.
6. Bantel, C., M. Maze, and S. Trapp, *Neuronal preconditioning by inhalational anesthetics: evidence for the role of plasmalemmal adenosine triphosphate-sensitive potassium channels.* Anesthesiology, 2009. **110**(5): p. 986-95.
7. Bruce, A.J., et al., *The incidence of delirium associated with orthopedic surgery: a meta-analytic review.* Int Psychogeriatr, 2007. **19**(2): p. 197-214.
8. Ely, E.W., et al., *Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit.* JAMA, 2004. **291**(14): p. 1753-62.
9. Deiner, S. and J.H. Silverstein, *Postoperative delirium and cognitive dysfunction.* Br J Anaesth, 2009. **103 Suppl 1**: p. i41-46.
10. Fong, T.G., et al., *Delirium accelerates cognitive decline in Alzheimer disease.* Neurology, 2009. **72**(18): p. 1570-5.
11. Koster, S., A.G. Hensens, and J. van der Palen, *The long-term cognitive and functional outcomes of postoperative delirium after cardiac surgery.* Ann Thorac Surg, 2009. **87**(5): p. 1469-74.
12. Bickel, H., et al., *High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study.* Dement Geriatr Cogn Disord, 2008. **26**(1): p. 26-31.
13. Trzepacz, P.T., *Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine.* Semin Clin Neuropsychiatry, 2000. **5**(2): p. 132-48.
14. Marcantonio, E.R., et al., *The association of intraoperative factors with the development of postoperative delirium.* Am J Med, 1998. **105**(5): p. 380-4.
15. Steinmetz, J., et al., *Long-term consequences of postoperative cognitive dysfunction.* Anesthesiology, 2009. **110**(3): p. 548-55.
16. Moller, J.T., et al., *Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction.* Lancet, 1998. **351**(9106): p. 857-61.
17. Newman, M.F., et al., *Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery.* N Engl J Med, 2001. **344**(6): p. 395-402.
18. Culley, D.J., et al., *The memory effects of general anesthesia persist for weeks in young and aged rats.* Anesthesia and analgesia, 2003. **96**(4): p. 1004-9, table of contents.
19. Futterer, C.D., et al., *Alterations in rat brain proteins after desflurane anesthesia.* Anesthesiology, 2004. **100**(2): p. 302-8.
20. Planel, E., et al., *Anesthesia leads to tau hyperphosphorylation through inhibition of phosphatase activity by hypothermia.* J Neurosci, 2007. **27**(12): p. 3090-7.
21. Eckenhoff, R.G., et al., *Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity.* Anesthesiology, 2004. **101**(3): p. 703-9.
22. Green, K.N., I.F. Smith, and F.M. Laferla, *Role of calcium in the pathogenesis of Alzheimer's disease and transgenic models.* Subcell Biochem, 2007. **45**: p. 507-21.
23. Wei, H. and Z. Xie, *Anesthesia, calcium homeostasis and Alzheimer's disease.* Curr Alzheimer Res, 2009. **6**(1): p. 30-5.
24. Yon, J.H., et al., *Anesthesia induces neuronal cell death in the developing rat brain via the intrinsic and extrinsic apoptotic pathways.* Neuroscience, 2005. **135**(3): p. 815-27.