

SNACC QUIZ 40
ANESTHETIC NEUROTOXICITY

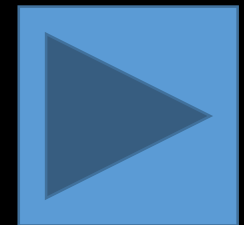
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COMMITTEE OF THE SNACC



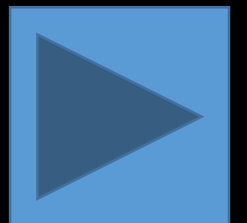
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Objectives

- Review the pathologic processes which cause Anesthetic induced developmental neurotoxicity(AIDN)
- List current studies investigating the effects of Neurotoxicity
- Recognize factors important to AIDN
- Describe mechanisms of neurotoxicity in the Elderly
- Comprehend practical guidelines associated with AIDN

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1. The following are true statements regarding anesthetic neurotoxicity except

- A. Inhalational agents can cause neuro-apoptosis in pediatric population
- B. Intravenous agents are relatively safe in neonates
- C. It is recommended to reduce the duration of exposure to < 2hours
- D. Neuro-apoptosis is the mechanism of neurotoxicity

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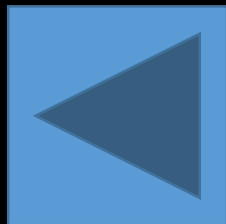


A. Inhalationals can cause neuro-apoptosis in pediatric population.

- This is true. Developmental neurotoxicity is a common feature of all three drugs, isoflurane, sevoflurane and desflurane.

Anesthesiology.2011 Mar;114(3):578-87. Istaphanous GK, Howard J et al;Comparison of the neuroapoptotic properties of equipotent anesthetic concentrations of desflurane, isoflurane, or sevoflurane in neonatal mice.

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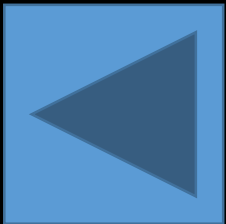
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B. Intravenous agents are relatively safe in neonates



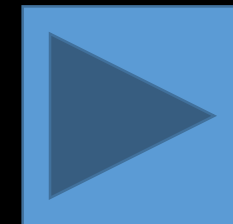
- This is not true. Many intravenous anesthetics, among them barbiturates, benzodiazepines, propofol, and etomidate promote inhibitory neurotransmission by enhancing GABA-A-induced currents in neuronal tissue. A small number of intravenous anesthetics (for example ketamine) inhibit excitatory neurotransmission by blocking N-methyl-D-aspartate (NMDA) receptors, a subtype of glutamate receptors.
- The modulation of these receptors causes significant imbalance in their functioning, only recently has it been recognized that this could be potentially damaging to neuronal cells in immature brains.

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Anesthesiol Clin. 2016 Sep;34(3):439-51.
General Anesthetics and Neurotoxicity: How Much Do We Know?
Jevtovic-Todorovic V.

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C. It is recommended to reduce the duration of exposure to < 2 hours.

This is True.

In several clinical studies, no behavioral, academic, or cognitive abnormalities have been observed following anesthetic exposures of less than 2h (Davidson et al., 2016; Fan et al., 2013). Furthermore deficits have been observed following exposure times of 2 h or longer (Andropoulos et al., 2014; Wilder et al., 2009).

Taken together, three factors appear to induce AIDN in animal models

1. Susceptibility during developmental phase
2. Higher dosage of anesthetic
3. Longer duration of exposure.

Davidson, A.J., et al; Lancet 387 (10015), 239–250, 2016

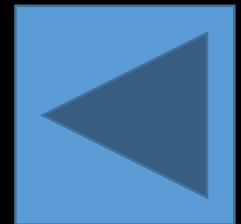
Fan, Q., et al J. Anesth. 27 (4), 493–499, 2013

Andropoulos, D.B., et al, Paediatr. Anaesth. 24 (3), 266–274, 2014

Wilder, R.T., et al; Anesthesiology 110 (4), 796–804, 2009

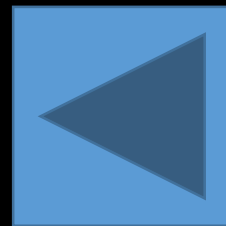
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D. Neuro-apoptosis is the mechanism of neurotoxicity

- This is true.
- Anesthetic agents initiate apoptosis through several mechanisms like mitochondrial disruption and endoplasmic reticulum release of calcium. Caspase activation is the final stage after intrinsic and extrinsic apoptotic cascade initiation.



2. You are the anesthesiologist caring for a 6 month old child presenting for inguinal hernia repair. The parents would like to know the risk of general anesthesia. What conclusions can be reached about neurodevelopmental outcomes in children less than 2 years old? (Which is true)

- A. There is no evidence that less than 1 h of sevoflurane anesthesia in infancy increases the risk of adverse neurodevelopmental outcome compared with awake-regional anesthesia
- B. Local anesthetics are toxic to children less than 2 years old
- C. Regional anesthesia with sedation is not an acceptable alternative to general anesthesia in children
- D. General anesthesia does not affect learning and memory in children who receive multiple anesthetics before 2 years old.

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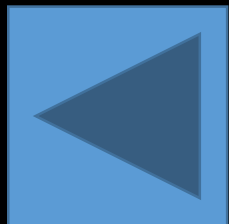
A. There is no evidence that -less than 1 h of sevoflurane anesthesia in infancy increases the risk of adverse neurodevelopmental outcome compared with awake-regional anesthesia



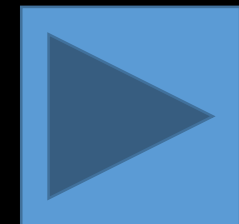
- This is a true statement. A brief anesthetic duration less than 1 hour would not increase risk of neurodevelopmental outcome according to the GAS study; see below.
- In an international assessor-masked randomised controlled equivalence trial, the investigators recruited infants born at greater than weeks' gestation and younger than 2 months, and who had inguinal herniorrhaphy, Infants were randomly assigned to receive either awake-regional anaesthesia or sevoflurane-based general anesthesia. The primary outcome was Intelligence Quotient measured at 5 years and secondary outcome was neurodevelopment score at 2 years. The results of the primary outcome are not yet available. For the secondary outcome, they found no evidence that just less than 1 h of sevoflurane anaesthesia in infancy increases the risk of adverse neurodevelopmental outcome at 2 years of age compared with awake-regional anaesthesia.

Davidson, A.J., etal; **Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial.** *Lancet* 387 (10015), 239–250, 2016

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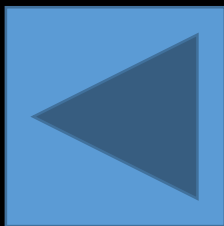
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B. Local anesthetics are toxic to children less than 2 years old

- This is not True.
- Currently, there is no evidence to suggest that local anesthetics are toxic to young children

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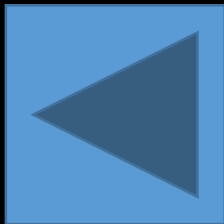


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C. Regional anesthesia with sedation is not an acceptable alternative to general anesthesia in children

- Regional anesthesia with sedation is a perfectly acceptable alternative to general anesthesia depending on the type of surgery (i.e. herniorrhaphy).

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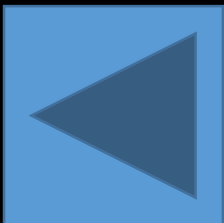


D. General anesthesia does not affect learning and memory in children who receive multiple anesthetics before 2 years old.

- This is not correct. Multiple exposures to General anesthesia may affect learning and memory.
- There is still ongoing debate as to whether children who receive multiple anesthetics before 2 years of age are more likely to have learning disabilities and alterations in memory later in life.
- A retrospective cohort study looked at over 5000 children born from 1976 through 1982. They found more reading, written, language, and math learning disabilities in the 593 patients who had more than one exposure to anesthesia (example- two, three or multiple times) before the age of 4 years compared to those not receiving anesthesia or one exposure to anesthesia. Risk factors for learning disabilities included more than one anesthetic exposure and general anesthesia lasting longer than 2 hours.

Wilder RT, Flick RP, Sprung J, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *Anesthesiology*. 2009;110:796–804.

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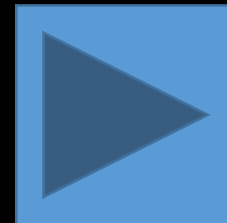


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3. The following are mechanisms of anesthetic induced developmental neurotoxicity except

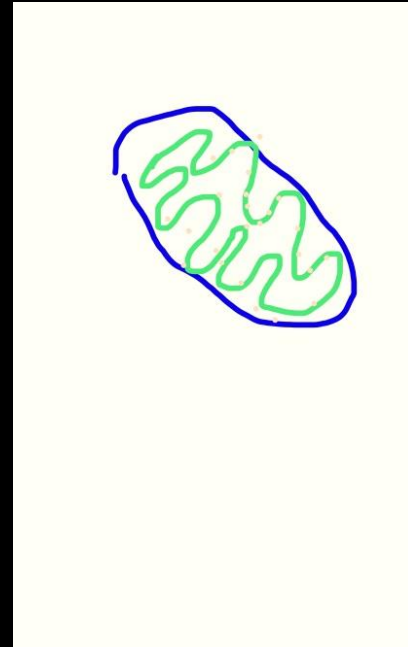
- A. Mitochondrial disruption.
- B. Release of calcium from the endoplasmic reticulum.
- C. Autophagy.
- D. Tauopathy and destabilization of micro tubules.

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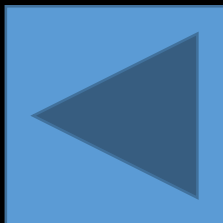
Mitochondrial disruption

- This is True.
- General anesthetics could jeopardize the integrity of the mitochondrial membrane and activate the intrinsic apoptotic cascade. Early exposure to general anesthesia causes mitochondrial enlargement and disruption of the cristae and inner mitochondrial membrane. General anesthetics may disturb mitochondrial fission and fusion leading to anesthetic-induced developmental neurodegeneration.



Sanchez V., Feinstein S.D., Lunardi N., et al: General anesthesia causes long-term impairment of mitochondrial morphogenesis and synaptic transmission in developing rat brain. *Anesthesiology* 2011; 115: pp. 992-1002

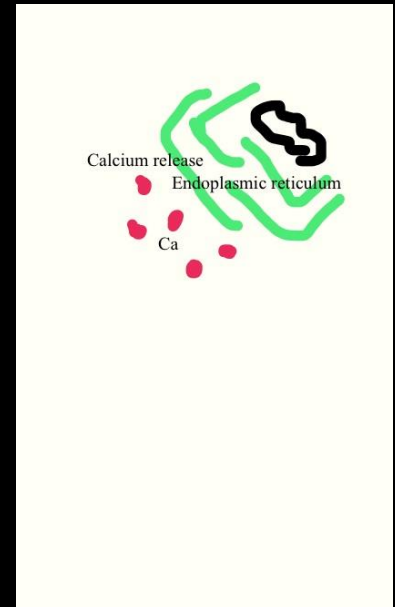
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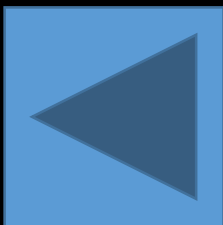
B. Release of calcium from endoplasmic reticulum

- This is True.
- The endoplasmic reticulum could be an important target of anesthesia-induced developmental neurotoxicity. Isoflurane, Sevoflurane and desflurane activates inositol 1,4,5-trisphosphate receptors ($\text{InsP}_3 \text{ R}$), producing an exaggerated and prolonged calcium release, and increases cytosolic calcium.



Zhao Y., Liang G., Chen Q., et al: Anesthetic-induced neurodegeneration mediated via inositol 1,4,5-trisphosphate receptors. J Pharmacol Exp Ther 2010; 333: pp. 14-22

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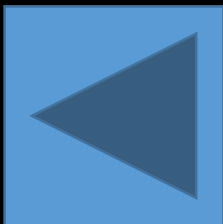
C. Autophagy

This is True.

General anesthetics increase the formation of autophagic bodies, hence it is likely that anesthesia kills developing neurons in part by inducing autophagic stress.

Millers Anesthesia, Perioperative and anesthesia neurotoxicity

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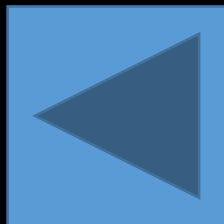
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D. Tauopathy and destabilization of micro tubules

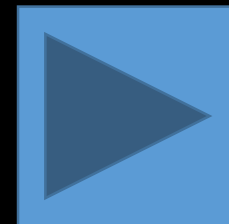


- This is the correct answer. Tauopathy and destabilization of microtubules do not contribute to pediatric neurotoxicity.
- The accumulation of the Tau(t) protein otherwise called neurofibrillary tangles can occur in Alzheimer's dementia. The potential for accumulation of this protein in multiple exposures to isoflurane and sevoflurane are thought to contribute to neurotoxicity in the elderly.

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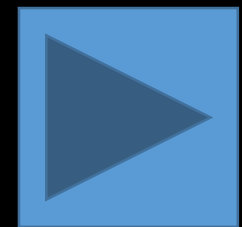
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4. There is evidence for the following anesthetics to cause neurodegeneration in developing neurons except

- A. Volatile anesthetics
- B. Propofol
- C. Dexmedetomidine
- D. Ketamine

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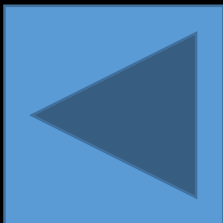
A. Volatile Anesthetics

- This has been implicated in neurotoxicity .
- We now have considerable *in vitro* and animal data implicating volatile anesthetics in inducing neurotoxicity. These changes are dependent on dose and long duration of anesthetic exposure. Also, infant rats received a combination of drugs commonly used in pediatric anesthesia (midazolam, nitrous oxide, and isoflurane) in doses sufficient to maintain a surgical plane of anesthesia for 6 hrs and it was observed that this caused widespread apoptotic neurodegeneration in the developing brain.

Chiao S, Zuo Z. A Double-Edged Sword: Volatile Anesthetic Effects on the Neonatal Brain. *Brain Sciences*. 2014;4(2):273-294.
Jevtovic-Todorovic V et al; Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci*. 2003;23:876–882



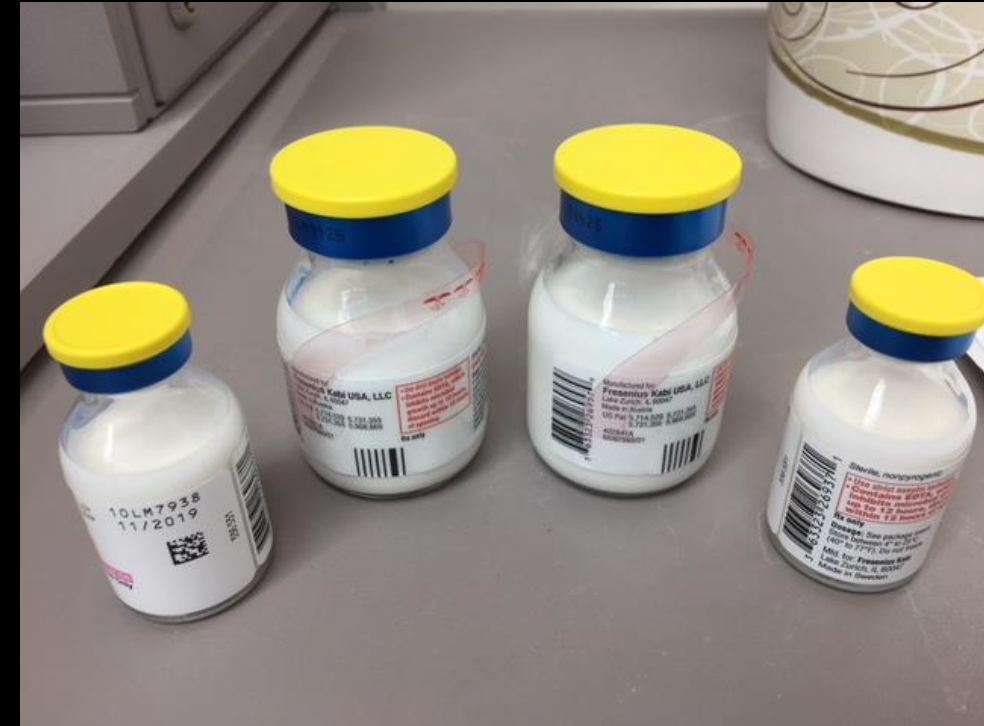
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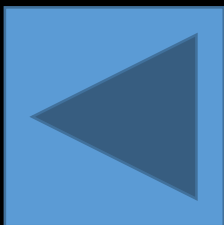
B. Propofol

- Growing evidence shows that propofol could induce developmental neurotoxicity in multiple models (e.g., animal model and cell culture system), raising serious concerns regarding the safety of using it in propofol anesthesia. Propofol causes developmental neurotoxicity by cell death in neurons and oligodendrocytes, dysregulation of neurogenesis, abnormal dendritic development, and decreases in neurotrophic factor expression.



Bosnjak ZJ, Logan S, Liu Y, Bai X. Recent Insights into Molecular Mechanisms of Propofol-Induced Developmental Neurotoxicity: Implications for the Protective Strategies. *Anesthesia and analgesia*. 2016;123(5):1286-1296.

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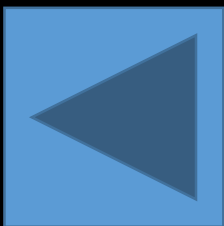
C. Dexmedetomidine



- Recent evidence has demonstrated the anti-apoptotic effect of dexmedetomidine in different brain injury models. It was found to prevent cortical apoptosis in vitro and in vivo and attenuate isoflurane-induced injury in the developing brain, providing neurocognitive protection.

Robert D. Sanders, et al; Dexmedetomidine Attenuates Isoflurane-induced Neurocognitive Impairment in Neonatal Rats. *Anesthesiology* 2009;110(5):1077-1085

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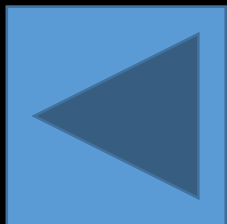


D. Ketamine

- Ketamine is an NMDA antagonist. Blockade of N-methyl-D-aspartate (NMDA) glutamate receptors for only a few hours during late fetal or early neonatal life triggered widespread apoptotic neurodegeneration in the developing rat brain, suggesting that the excitatory neurotransmitter glutamate, acting at NMDA receptors, controls neuronal survival. These findings may have relevance to human neurodevelopmental disorders involving prenatal (drug-abusing mothers) or postnatal (pediatric anesthesia) exposure to drugs that block NMDA receptors.

Ikonomidou C., Bosch F., Miksa M., Bittigau P., Vockler J., Dikranian K., et al. . (1999). Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. *Science* 283, 70–74.

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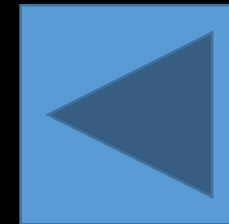


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5. You have 79 year old patient coming in for a pituitary surgery. The family is worried about cognitive dysfunction in the postoperative period. All the following are potential mechanisms by which anesthetics can cause neurotoxic effects in elderly patients except?

- A. Excessive accumulation of amyloid- Beta and neurofibrillary tangles.
- B. Altered calcium homeostasis
- C. Neuroinflammation triggered by surgically-induced systemic inflammation
- D. Developmental Apoptosis

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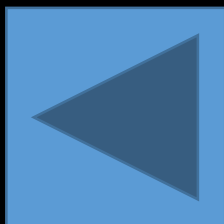


A. Excessive accumulation of amyloid- Beta and neurofibrillary tangles

- This is True.
- Amyloid- β is the protein that is strongly implicated in the pathogenesis of Alzheimers dementia. Excessive amyloid- β accumulates extracellularly and forms plaques. These plaques cause direct neuronal toxicity and an inflammatory response by interacting with the brain's primary immune surveillance cell, the microglia. It is thought that the inhaled anesthetics promote amyloid- β production and aggregation and lead to cognitive decline.

Eckenhoff R.G., Johansson J.S., Wei H., et al: Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. *Anesthesiology* 2004; 101: pp. 703-709

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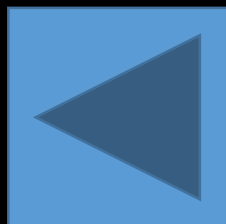
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B. Altered calcium homeostasis

- This is True.
- Another major mechanism thought to underlie Alzheimer's dementia is calcium dysregulation. This is one mechanism that might be shared with neurotoxicity of the young . It is now thought that mutations in calcium channels, or exposure to drugs that interact with them, may lead to an exaggerated release of calcium triggering apoptosis. Propofol appears to be much less provocative in this regard.

Wei H., and Xie Z.: Anesthesia, calcium homeostasis and Alzheimer's disease. Curr Alzheimer Res 2009; 6: pp. 30-35

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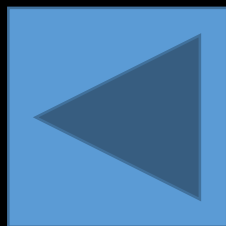


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C. Neuroinflammation triggered by surgically-induced systemic inflammation

- This is True.
- Inflammation can contribute to cognitive decline. This may be through the release of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α).

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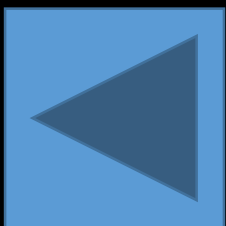
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D. Developmental Apoptosis



- This is False.
- This is a phenomenon in the developing brain and not in older population.
- During the phase of synaptogenesis in the developing brain, there is a fine balance between γ -aminobutyric acid (GABA)-mediated versus glutamate-mediated neurotransmission. A disturbance in the glutamatergic and GABAergic balance during this crucial stage of brain development may excessively signal developing neurons to undergo apoptosis. General anesthetics could potentially disrupt the glutamate and GABA signaling balance promoting excessive activation of neuroapoptosis.

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