Mitochondria and Anesthesia: Teleconference Dec 2, 2011

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Points to make:

1. Disclaimer

2. Mitochondria – normal functions and stress response

3. Impact of Anesthesia (and surgery) on Mitochondrial function

4. Impact of Anesthesia (and surgery) on Mitochondrial function

5. Recommendations

1. Disclaimer

I am a metabolic physician and a laboratory physician. I have an interest in the effect of anesthesia on mitochondrial function as it affects the patients with mitochondrial disease whom I care for. However, I am not an anesthetist and, as such, defer to physicians who are anesthetists when making recommendations re: a particular plan of anesthetic management in an individual case.

2. Mitochondria – normal functions and stress response

Mitochondria have multiple roles:

- ATP (energy) production via the combustion of high energy nutrients (electron transport chain)
- heat generation via (uncoupling of the electron transport chain)
- metabolism of many molecules in conjunction with other compartments in the cell
- response to the cellular stress response (apoptosis)
- Calcium signalling

3. Anesthesia: an introduction

Anesthesia for the purpose of surgery

- induction/provision of a decreased level of consciousness associated with amnesia
- provision of a relatively pain free state for all or a part of the body
- induction of partial or total inhibition of muscle contractions for all or a part of the body

Table I: Types of anesthetic agents and Glossary of terms

Type	Description
Induction Agent	Medication utilized to rapidly cause sedation at the outset of an anesthetic procedure. Short acting.
Maintenance Agent	Medication: (inhalational or intravenous anesthetic) which cause prolonged sedation and is used during the course of a surgical procedure
Muscle relaxant	Medication used to prevent muscles from contracting during surgery
Depolarizing muscle relaxant	Muscle relaxant which prevents muscle contraction in 2 steps: step 1) medication binds to a muscle receptor (acetylcholine receptor) and, initially, causes many muscle fibres to contract in an uncoordinated fashion. Step 2) medication does not dissociate from the receptor but also no longer stimulates the muscle cell. The continued presence of the medication on the receptors prevents the body's own stimulator (acetylcholine) from activating the receptor, leading to relaxed muscles.
Non-depolarizing muscle relaxant	Muscle relaxant which works by preventing the binding of acetylcholine to the acetylcholine receptor on muscle cells. This blocking activity prevents the muscles from contracting. Unlike depolarizing agents, the non-depolarizing agents do not cause initial large scale muscle fibre contractions.
Analgesic	Medication which reduces the sensation of pain by a means other than sedation.
Inhalational (volatile) anesthetic	A medication that is inhaled. Many traditional sedating anesthetics are inhaled.
Intravenous anesthetic	A medication which is infused through a vein. Some sedative anesthetics are infused and may achieve similar effectiveness as compared to inhalational anesthetics
Light anesthesia	Anesthesia which has a minimal sedating effect allowing the patient to maintain some consciousness during a surgery

Type	Description
Deep anesthesia	Anesthesia which sedates the patient to a degree that they are unable to awaken until the medication is cleared from the body. Under deep anesthesia, the patient is unable to care for or protect themselves. The anesthetist must monitor the patient through a period of deep anesthesia to provide assistance with mainenance of normal physiologic functions (eg maintaining heart rate, blood pressure, blood flow, breathing).
Minimal Conscious Sedation	Anesthesia in which the patient is given light sedation and analgesics but retains consciousness during the procedure.
General anesthetic	Anesthesia in which the body / mind as a whole is anesthetized (sedated, paralyzed, analgesics to take effect after the patient awakens from sedation) via inhalational or intravenous anesthesia.
Local anesthetic	Anesthesia in which pain control is administered to only a small part of the body. The remainder of the body is not anesthetized by the local anesthetic. May be used in combination with a general anesthetic.
Regional Anesthesia	Anesthesia in which a region of the body is anesthetized but not the entire body.
Spinal anesthesia	A form of regional anesthesia in which local anesthetic is introduced into the spinal fluid leading to loss of sensation and function of muscles in the lower half of the body.

Table 2: Commonly used anesthetic agents

Name	Class	Side Effects
Propofol	Intravenous anesthetic that can be used as an induction Agent, Maintenance Agent	Propofol related infusion syndrome: metabolic acidosis, cardiac failure with conduction abnormalities, kidney failure and rhabdomyolysis (see below).
Etomidate	Induction agent which minimizes hypotension	Transient impact on adrenal function; Possible concern given finding of abnormal electrolytes (low Na, high K) in 3 of 20 MELAS surgeries
Midazolam	Sedative / induction	
Halothane, Sevoflurane Desevoflurane, Isoflurane,	Inhalational (volatile) anesthetics	Pharmacological preconditioning with volatile anesthetics, or anesthetic-induced preconditioning (APC), is a phenomenon whereby a brief exposure to volatile anesthetic agents protects the heart from the potentially fatal consequences of a subsequent prolonged period of myocardial ischemia and reperfusion. Halothane is associated with a greater predisposition to malignant hyperthermia as compared to other volatile anesthetics
Nitrous (N2O)	Weak Inhalational anesthetic	
Succinylcholine	Depolarizing muscle relaxant	May trigger hyperkalemia in patients with myopathy; May trigger malignant hyperthermia in patients with myopathy.
Vecuronium	Relatively short acting non depolarizing muscle relaxant	
Rocuronium	Short acting non depolarizing muscle relaxant	
Atracurium, Pancuronium, cisatracurium	Other non depolarizing muscle relaxants	Prolonged weakness post operative if the dose exceeds

Name	Class	Side Effects
		requirements (eg patient with fewer acetylcholine receptors)
Sodium Thiopental	Intravenous Induction agent (a barbiturate)	Decreases blood flow to brain while maintaining normal brain oxygen utilization (NADH generation). A useful characteristic in a patient with brain injury
Ketamine	Short acting dissociative (amnesia, analgesia, lack of awareness of pain) anesthetic	
Fentanyl	Analgesic	Depress respiration
Bupivacaine; lidocaine	Local anesthetic	Bupivacaine (or local anesthetic) induced myopathy is characterized by abnormal mitochondrial function.

4. Impact of Anesthesia (and surgery) on Mitochondrial function

Anesthetic agents/medications:

- may impair mitochondrial ETC function directly
- may exacerbate cellular dysfunction that results from ETC dysfunction
  - energy deficits
  - reactive oxygen species generation (ROS)

Surgery:

- generates an inflammatory response in a local environment
  - the inflammatory response generates inflammatory cytokines which act systemically although are concentrated in the area of injury
  - inflammatory cytokines:
    - impair the mitochondrial ETC
    - exacerbate cellular dysfunction that results from ETC dysfunction
    - generation of ROS
  - inflammatory cytokine production is maximized when there is concurrent infection, a relatively common complication of surgery

Malignant Hyperthermia:

- Caused by a loss of regulation of normal muscle contraction leading to
  - abnormal sustained muscle contractions leading to
    - high body temperature and muscle damage with characteristic chemical abnormalities in the blood (high potassium, high Creatine kinase)
- occurs in response to depolarizing muscle relaxants and volatile anesthetics (eg halothane) if the patient is susceptible to this severe side effect
  - eg energy deficit in the muscle that is exacerbated by an anesthetic agent like halothane or succinyl choline
  - mitochondrial patients are not thought to be at high risk for malignant hyperthermia although previously they were based on isolated case reports
  - succinylcholine and halothane are avoided in mitochondrial patients out of prudence

Propofol Related Infusion Syndrome (PRIS):

- Caused by prolonged administration of propofol to patients susceptible to the PRIS syndrome
  - Heart, muscle and kidney disease along with lactic acidosis are characteristic abnormalities. Many patients with this syndrome die (18 to 50%)
  - Risk factors for PRIS:
    - Children
    - high dose of propofol
      - long time period and higher rate of infusion
    - Infection at the same time as surgery
    - High catecholamine / cortisol states (stress response hormones)
    - low carbohydrate / high fat loading
    - Underlying metabolic disorder (eg mitochondrial disease?)

- Three reported series of anesthetics in mitochondrial disease found no complications from propofol induction (ie short use only at the very beginning of surgery)

Given that surgery and anesthesia have potential negative effects on mitochondrial function, how should physicians of patients with mitochondrial disease approach the question of surgery?

i) Is there a definite need for surgery? Sometimes the answer is clear – yes or no. Sometimes, the answer is less clear and a discussion of risks and benefits of surgery are required. The risks of surgery are (theoretically) greater in mitochondrial disease patients as compared to healthy controls.

ii) If the risks of avoiding surgery are too great, proceed with caution keeping in mind which anesthetic agents might be associated with greater risk in patients with mitochondrial disease. Also keep in mind, that a good anesthetic response is necessary to permit the surgery.

Table 3: Impact of Anesthetic Agents on Mitochondrial Function and Mitochondrial Disease.

Anesthetic Agent	Cell Study	Animal Study	Human Study
Propofol	Therapeutic concentrations of propofol specifically reduce the mitochondrial membrane potential, and impair ATP production rates.	Propofol related infusion syndrome in rabbits with prolonged administration of profopol and lipid. No PRIS in rabbits given volatile anesthetic and lipids.	Multiple case reports of propofol related infusion syndrome (PRIS) associated with prolonged use of propofol above a certain dose. Some case reports of PRIS with shorter doses. Prospective study of non mitochondrial disease patients (1017): 1% developed PRIS after 24 hours of use. 18% mortality rate.
Halothane	At higher than clinical doses, volatile anaesthetic agents reduce oxidative phosphorylation in		Case report of induction of arrhythmias in KSS patient with pre-operative conduction abnormality.

Anesthetic Agent	Cell Study	Animal Study	Human Study
	cell-free studies in isolated mitochondria		
Etomidate			Cases of unusual sensitivity
Sevoflurane, Isoflurane	Complex I has been found to be the most sensitive step in oxidative phosphorylation to inhibition by volatile anaesthetics, requiring very low doses of sevoflurane to reach a bispectral index value of 60		Used without incident in several reviews of mitochondrial disease patients
Nitrous (N2O)	no indication that aerobic respiration is impaired		Used without incident previous review
Succinylcholine			One case of mitochondrial disease and SC induced hyperkalemia; one case report of MH
Rocuronium and other non depolarizing muscle relaxants			Used without incident in previous reviews, in some cases higher doses required presumably due to interactions with anti-seizure medications that were also used at the same time
Sodium thiopental			Cases of unusual sensitivity
Ketamine			
Fentanyl / Remifentanyl	Clinical concentration: no effect Higher doses: inhibition of the ETC (III, IV, V)		
Bupivacaine, lidocaine	Bupivacaine induces ultrastructural changes in mitochondria, loss of mitochondrial membrane potential and impaired ATP synthesis		

Anesthetic Agent	Cell Study	Animal Study	Human Study
	observed in cells, animal and humans		

5. Recommendations

i) As with any patient, consider the risks and benefits of surgery keeping in mind the increased risk of complications that is present in patients with mitochondrial disease.

ii) Obtain a pre-surgical anesthetic consultation wherever possible. Inform the anesthetist of your medical condition. The anesthetist can then plan to use a strategy that is optimal for the planned surgery in a patient with mitochondrial disease.

Things to review prior to surgery:

- Opt for a **planned surgery** if possible (eg planned cesaerean section vs spontaneous birth with possible complications)
- **Swallowing problems** – increased risk for aspiration. Employ fasting prior to surgery to minimize gastric acidity and gastric volume
- **Respiratory function** is frequently compromised before surgery and patients are at a higher risk of postoperative respiratory complications. Minimize use of respiratory depressants
- **Cardiac signal conduction abnormalities** – more common in mito patients and will be exacerbated by the surgical / ansesthetic procedure. A cardiovascularly stable anesthetic is required.
- **Glucose control:** patients may be susceptible to hypoglycaemia or hyperglycemia. Minimize glucose fluctuations with:
    - Minimal fasting ie first operation of the day
    - Starting intravenous glucose administration pre-operatively
    - Monitor glucose during the operation. Provide insulin if the glucose level is too high.
- **Oxidative phosporylation:** minimize requirements by keeping temperature stable and by minimizing stress (ie sufficient anesthesia, analgesia)
- **Intravenous fluids:** no clear benefit to any particular type. Ringer's lactate is avoided but, where this solution has been used, there have not been problems.
- **Electrolyte balance:** monitor sodium and potassium frequently before during and after surgery / anesthesia given frequent abnormalities observed in a series of MELAS patients. Etomidate would theoretically worsen this predisposition.
- **Anesthetics:**
    - Avoid total intravenous anesthesia utilizing propofol to avoid propofol related infusion syndrome.
    - Use volatile anesthetics with lower predisposition to malignant hyperthermia (eg sevoflurane)
    - Ketamine / N_2O may be a preferred option for procedural sedation
    - Local anesthetics: Avoid using for regional anesthesia, if feasible.
- **Muscle relaxants:** No clear benefit.
    - Succinylcholine is generally avoided but, where it has been used, there is no obvious predisposition to hyperkalemia or malignant hyperthermia complications outside of a single case report.
    - Non-depolarizing muscle relaxants. Minimize dose if there is myopathy. Pay attention to interaction between anti-epileptic medications and the actions of Non depolarizing muscle relaxants.