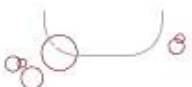




A case study of

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The Mitochondrial Encephalopathy, Lactic Acidosis with Stroke-like Episodes (MELAS) Syndrome



Presented by Carol Lam,
Pharmacy Intern, TKOH
27th March 2007

Outline

Introduction

Clinical presentations

Pathogenesis

Management

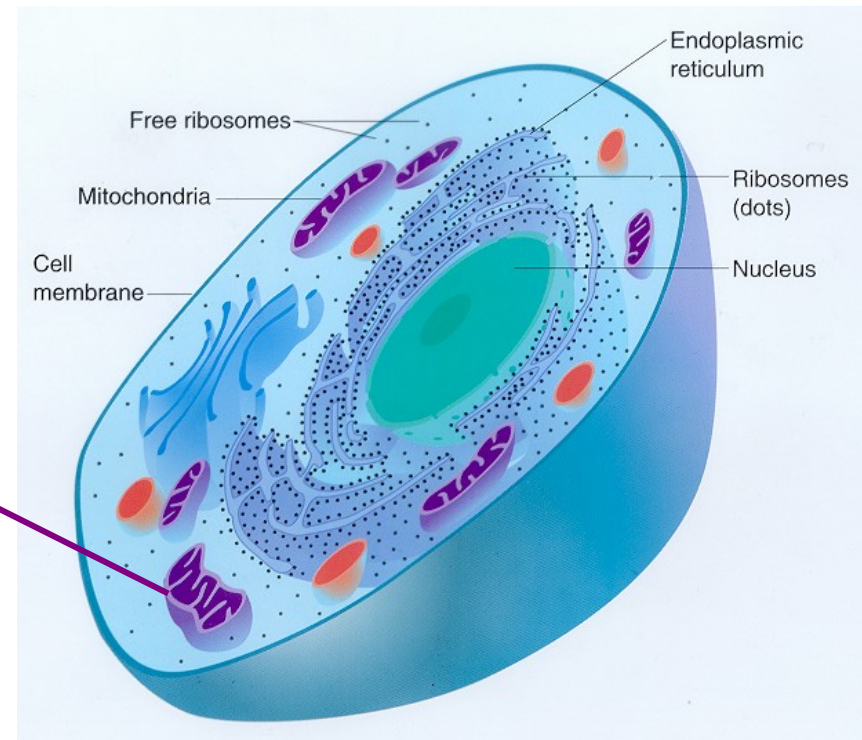
Role of pharmacists

Conclusions

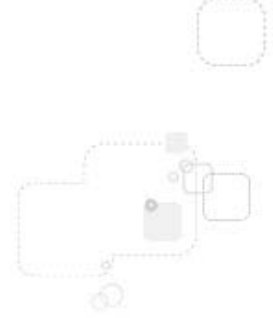
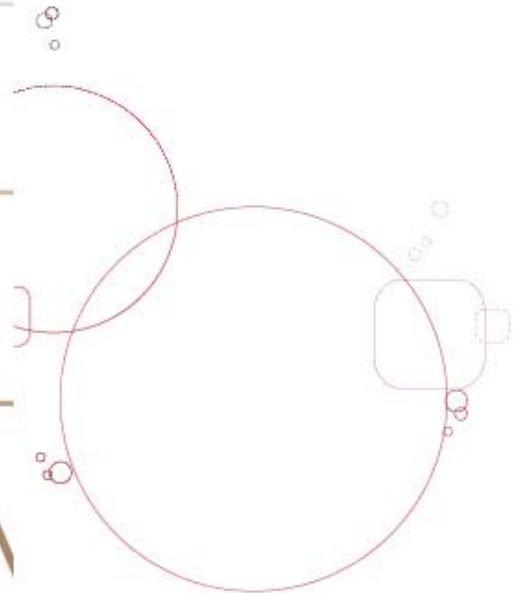
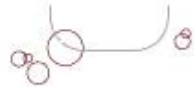
Introduction

A multisystem disorder of mitochondrial dysfunction due to *mitochondrial DNA (mtDNA)* mutations

- Maternally inherited
- Northern England:
1 in 6
- Northern England:
1 in 13 000



Case study



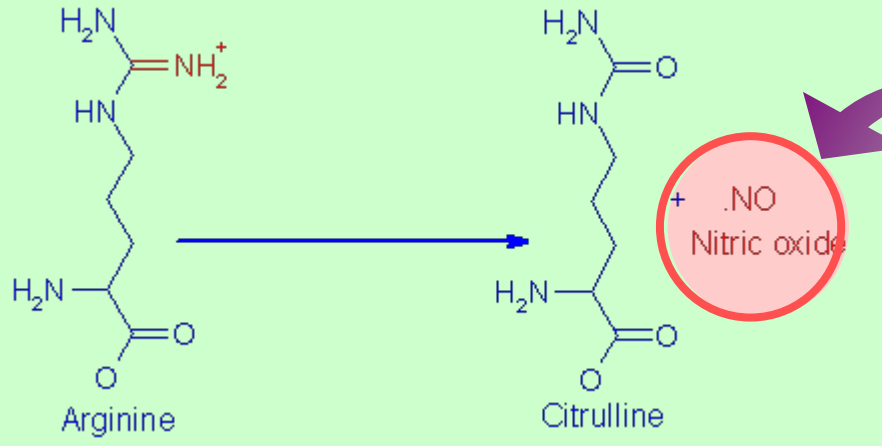
Clinical presentations

- – Mitochondrial encephalopathy w/ seizures and/or dementia
 - – Mitochondrial myopathy, evidenced by lactic acidosis and/ or ragged red fibers on muscle biopsy
 - – stroke-like episodes, typically before age 40 yo
- MELAS Syndrome**
- Normal early psychomotor development
 - Recurrent headache, vomiting
 - Muscle weakness, fatigue, exercise intolerance
 - Short stature
 - Sensorineural hearing loss
 - Hemiparesis
 - Cortical blindness

Pathogenesis

Vasoconstriction

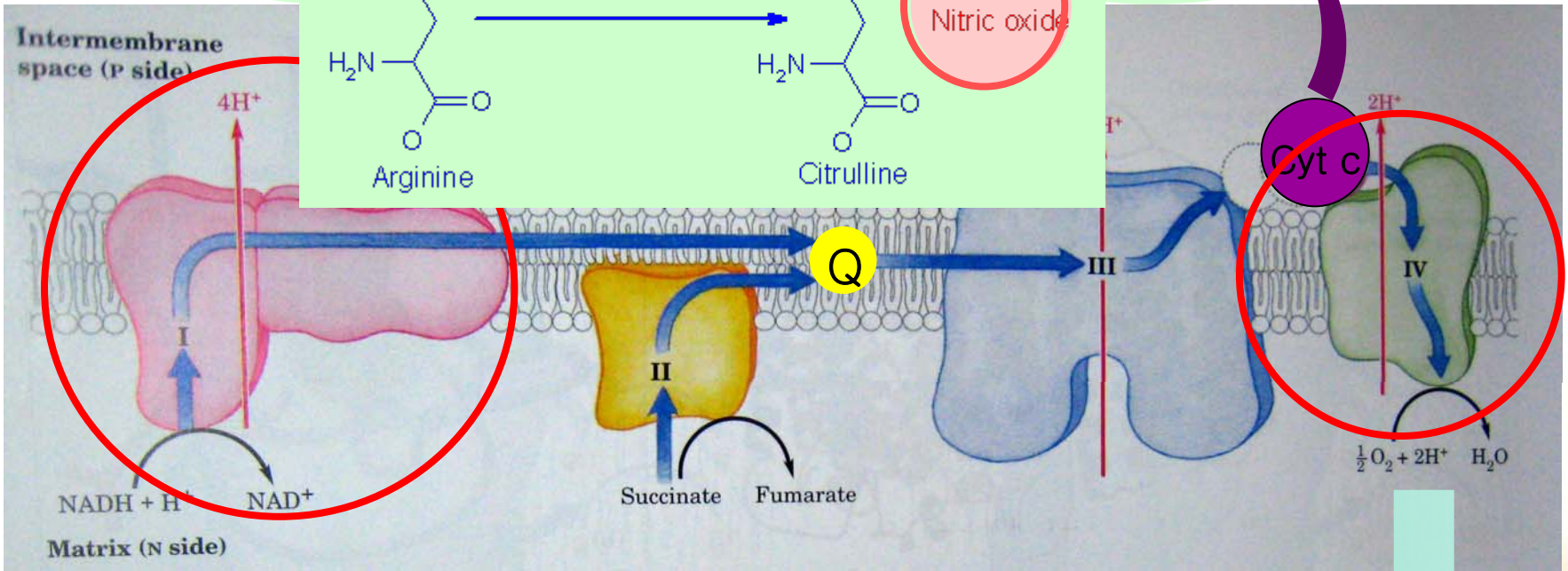
Glut



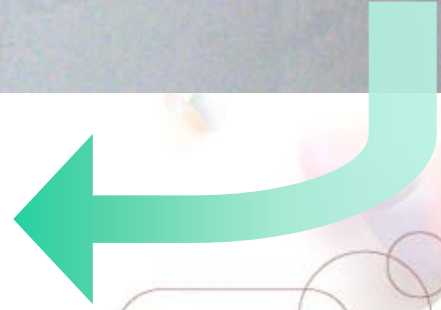
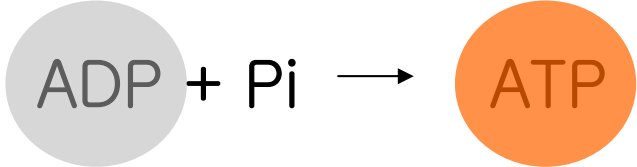
+ .NO
Nitric oxide

no acids

Cyt c



↑ Reactive oxygen species

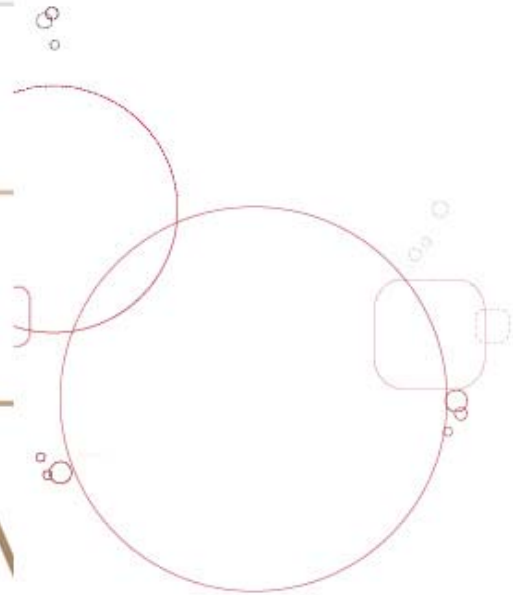
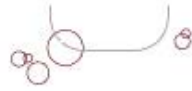


Management



- Pharmacological treatments
 - Antiepileptic drugs
 - Cocktail of vitamins & supplement
 - Others

Case study



Antiepileptic drugs

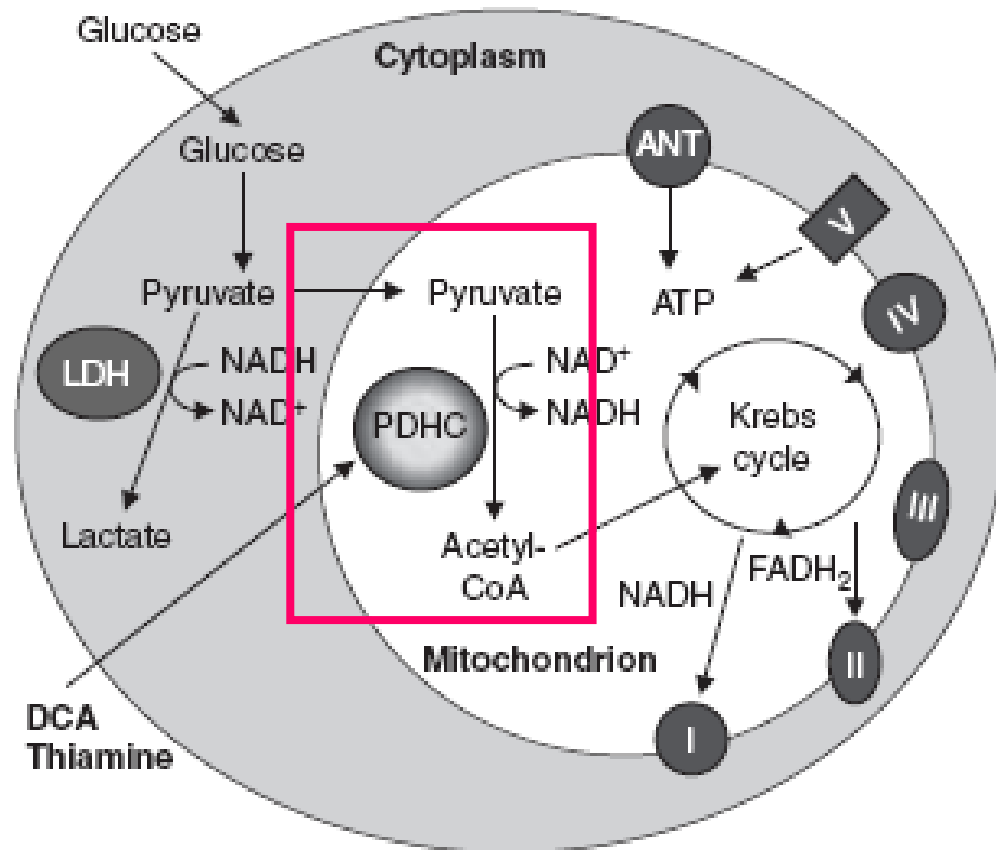
- Newer antiepileptics – gabapentin, lamotrigine
 - neuroprotective
- Carbamazepine/ oxcarbazepine
 - S/e: blood dyscrasia, hyponatremia, liver toxicity
- Phenobarbital and benzodiazepines
 - Interfere w/ mitochondrial function in vitro
- Valproate
 - Causes mitochondrial ultrastructural changes
 - Decrease rates of oxidative phosphorylation
 - Avoid

Cocktail of vitamins & supplements

- Thiamine (Vitamin B1)
- Riboflavin (Vitamin B2)
- Nicotinamide (Vitamin B3)
- Ubidecarenone (Coenzyme Q10)
- Idebenone
- Succinate
- Cytochrome C
- Menadione (Vitamin K3)
- Ascorbic acid (Vitamin C)
- Thiocctic acid (α -lipoic Acid)
- Levocarnitine
- Creatine
- Vitamin E
- Folic acid

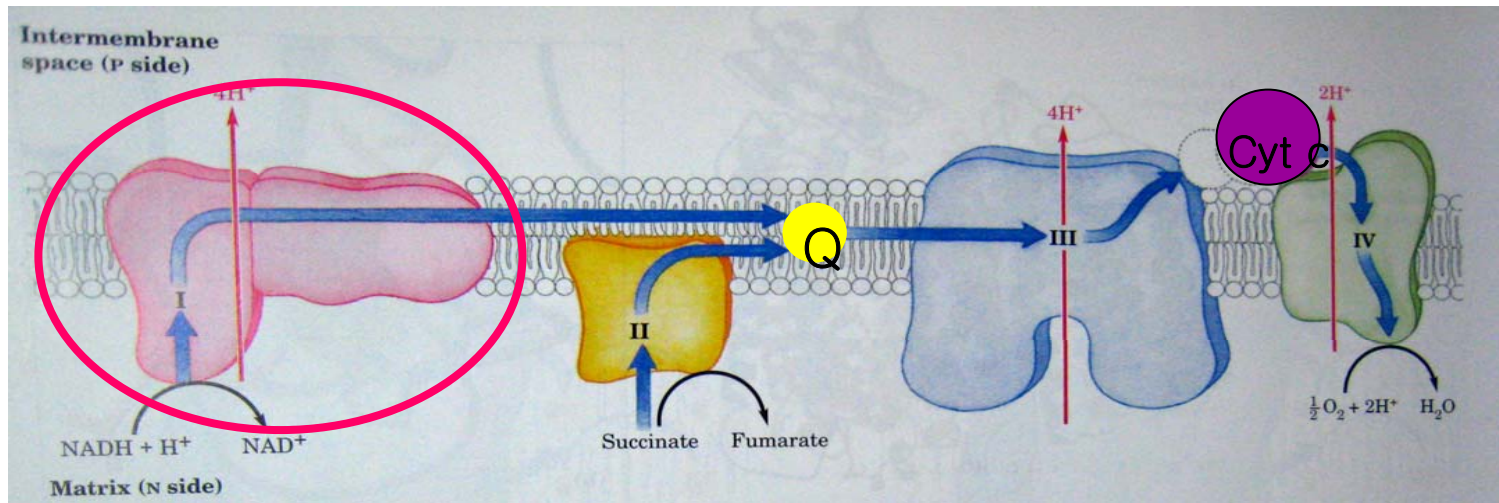
Thiamine (Vitamin B1)

- Coenzyme of pyruvate to Acetyl-CoA
- Thiamine deficiency
 - Improve neurolog
- Confirmed lactic
- No reported s/e



Riboflavin (Vitamin B2)

- Cofactor in complex 1 and complex II
 - Flavin mononucleotide FMN



- No reported s/e

Ubidecarenone (Coenzyme Q10)

- e⁻ transfer from complex I and II to III

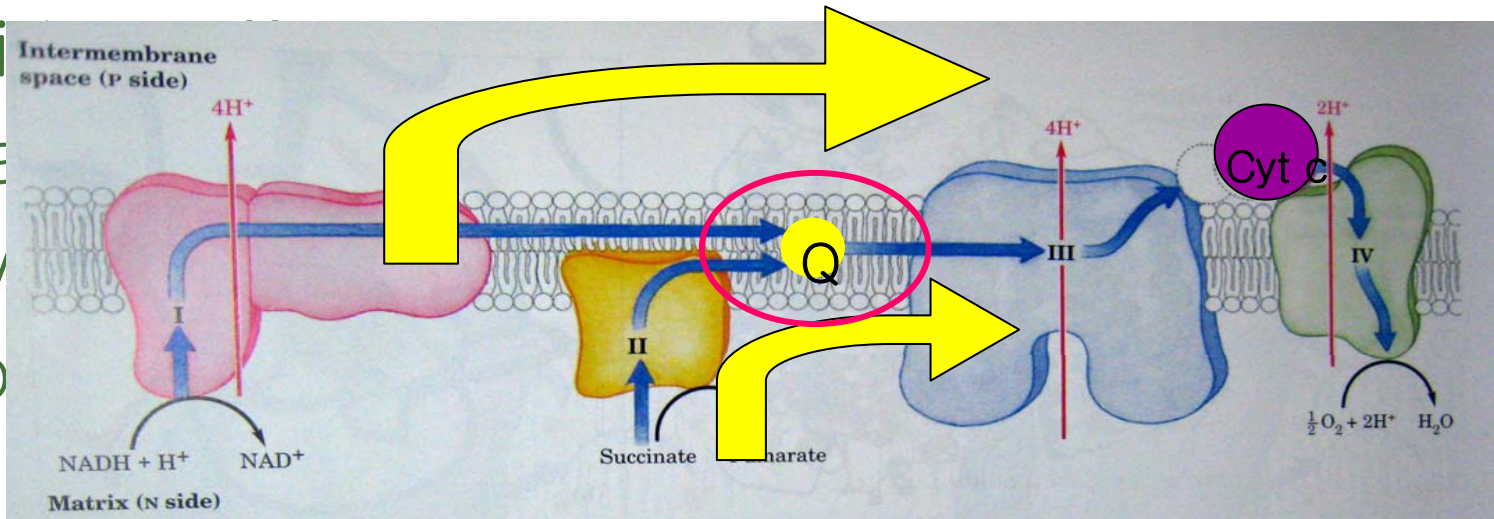
- Antioxi

- Decrease

- Improve

- No rep

- 1 drug



- Harmful in *severe* mitochondrial disease?

- Alternative ~ Idebenone

Ascorbic acid (Vitamin C), Vitamin E, Folic acid

- Improve electron transfer
- Antioxidant effect
- Unclear efficacy
- Generally safe
- Vitamin C: Calcium oxalate nephrolithiasis in high dose

Other therapeutic approaches

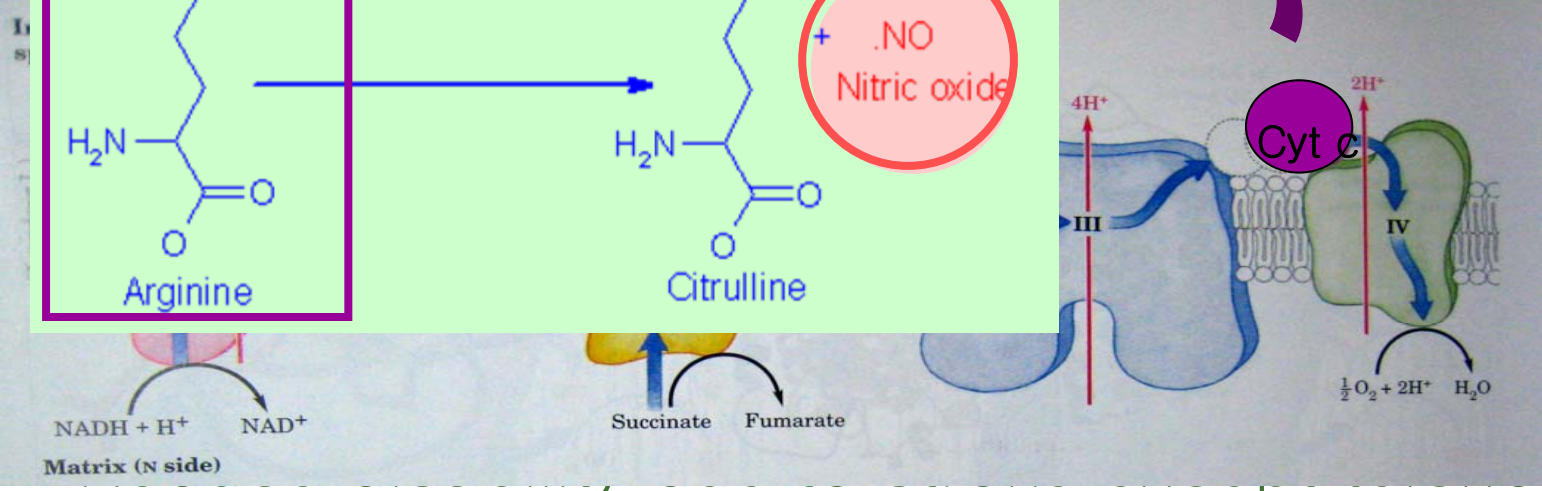
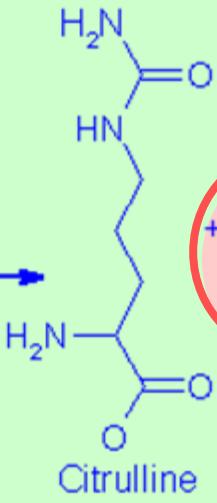
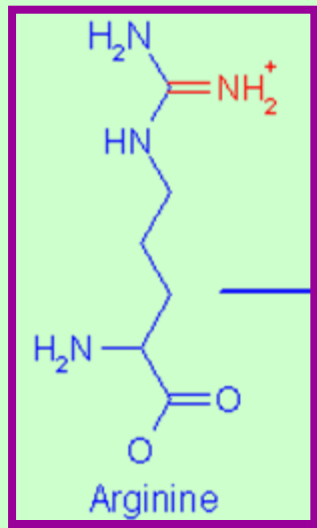
- Arginine
- Sodium Dichloroacetate
- Corticosteroids

Arginine

stroke-like episodes

Vasodilation

+ .NO
Nitric oxide

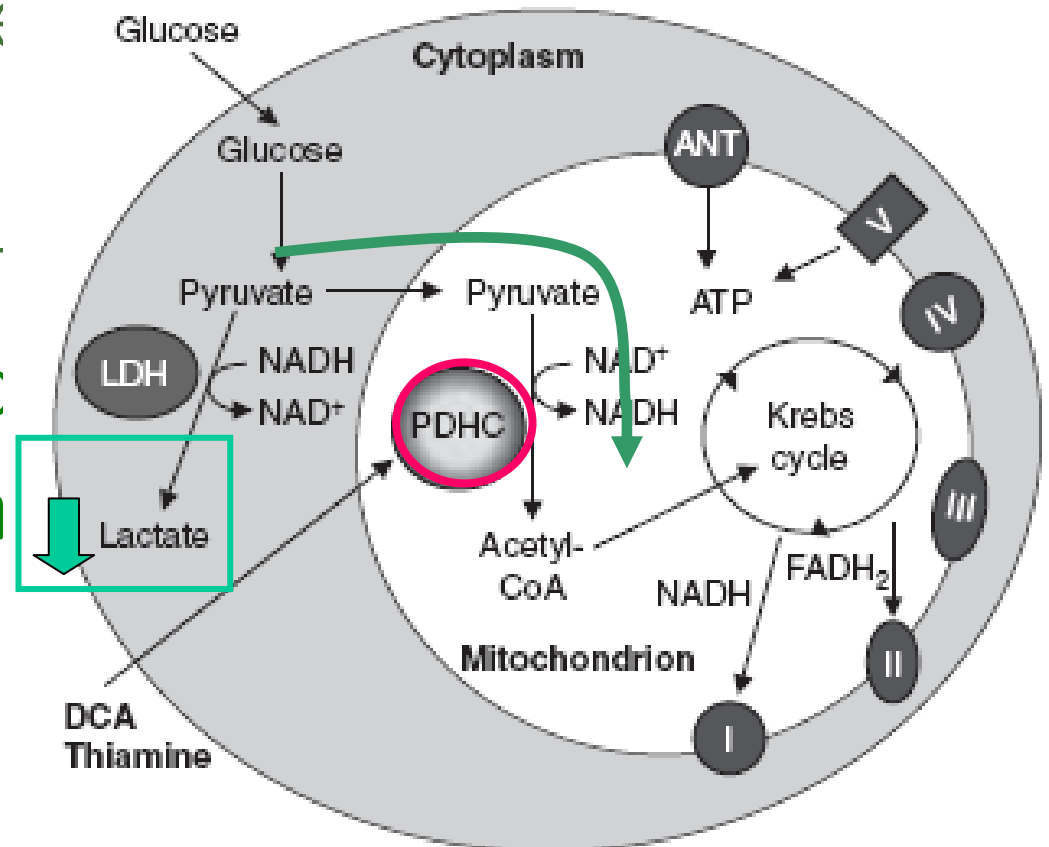


- Headaches associated w/ rapid arginine infusion
- Hypotension
- Metabolic acidosis (Arginine HCl)

Arginine level

Sodium Dichloroacetate (DCA)

- Inhibit phosphorylation of PDHC
- Reduce Pyruvate
- Has been used
- Controversial ef
- Peripheral neurc
- Mild liver dysfun
- Hypocalcaemia



Role of pharmacists

- Ensure supply of drugs
- Provide drug information
- Ensure patient safety
 - Drugs to avoid
 - Dose and adverse effects of drugs
- Non-pharmacological counselling

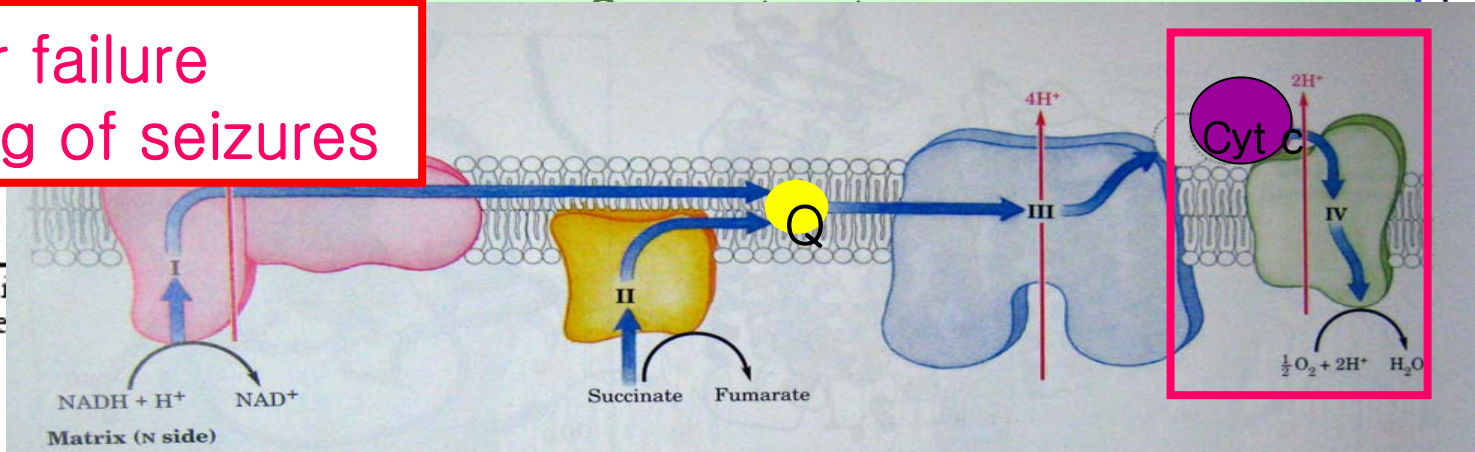
Drugs to avoid?

- Drugs interfering respiratory chain/ causing mitochondrial toxicity

Complex	Inhibitors
I (NADH dehydrogenase)	1-methyl-4-phenylpyridinium (MPP ⁺)*, piericin A, Ranaolazine, rotenone, triton
II (Succinate dehydrogenase)	2, 9-demethyl harmanium, 3-nitropropionic acid, pentamidine, (TTFA).
III (Cytochrome b ₅ 582 c oxidoreductase)	Amilorin, 2-substituted acridines, myxothiazol, various β -methoxyacrylates, hydroxyquinone analogs, and chromone inhibitors.

- Causes mitochondrial ultrastructural changes
- Decrease rates of oxidative phosphorylation
 - Inhibit Cytochrome C oxidase activity
 - Impair complex IV activity

Fatal liver failure
Worsening of seizures



* MPP⁺ is the neurotoxicant
** Indirect and non-specific

Drugs to avoid?

- Drugs posing oxidative stress
 - Paracetamol
- Drugs causing acidosis
 - Lactated Ringer's solution, Metformin
- Drugs triggering malignant hyperthermia
 - Inhalational anesthetics e.g. halothane, enflurane
 - Depolarising muscle relaxants e.g. succinylcholine
 - Avoid if h/o adverse effects in the patient or family
- Drugs exacerbating the conditions
 - **Sodium dichloroacetate**
 - Carbamazepine/ oxcarbamazepine

Table I. Therapeutic compounds used in the treatment of mitochondrial myopathy, encephalopathy, lactic acidosis with stroke-like episodes (MELAS) syndrome

Treatment	Dosage	Mechanism of effect	Adverse effects
Thiamine (vitamin B ₁)	50–100 mg/day PO	Thiamine pyrophosphate is a coenzyme for PDHC	No adverse effects with dosages up to 200 mg/day
Riboflavin (vitamin B ₂)	50–200 mg/day PO	Cofactor for electron transport by complex I, complex II and ETF; consider if documented complex I deficiency is present	No adverse effects with the given dosage range
Nicotinamide (vitamin B ₃)	50 mg/day PO (children) 500 mg/day PO (adults)	Increased supply of NAD ⁺ may counterbalance complex I deficiency	Elevated LFTs, nausea, vomiting, diarrhoea, flushing, headaches
Ubidecarenone (coenzyme Q ₁₀)	3.4–10 mg/kg/day PO (children) 200–400 mg/day PO (adults)	Facilitates transfer of electrons from complex I and II to complex III; may not cross the blood-brain barrier	No adverse effects
Idebenone	90 mg/day Limited data regarding use in paediatric population	Electron carrier in the mitochondrial respiratory chain; antioxidant against lipid peroxidation; crosses the blood-brain barrier	No adverse effects
Succinate	6 g/day (adult dose)	Bypasses complex I to activate complex II	No adverse effects
Cytochrome C	6.5 mg/day IV	Transfers electrons between complexes I and III; released from mitochondria into the cytosol	No adverse effects
Menadione (vitamin K ₃)	40–80 mg/day PO	Stimulates oxygen utilisation in the mitochondria; increases NADPH production	Haemolytic anaemia, hyperbilirubinaemia and kernicterus, thus contraindicated for use in neonates, pregnant women and children
Ascorbic acid (vitamin C)	25 mg/kg/day, with upper limit 1g PO	Improves mitochondrial electron transfer; antioxidant	Nephrotoxicity
Thioctic acid (α-lipoic acid)	300–600 mg/day PO	Co-factor of α-ketoglutarate dehydrogenase	No adverse effects
Levocarnitine (L-carnitine)	1g PO tid (adults) 100 mg/kg/day (3 g/day maximum dosage) [children]	Facilitates transport of long-chain fatty acids into mitochondria; may have urinary carnitine losses	Fishy odour due to intestinal metabolism, frank diarrhoea
Corticosteroids	Dexamethasone 16 mg/day, prednisone 2 mg/kg/day, methylprednisolone 1 g/day	Stabilises membranes; reduces inflammation; modulates the peroxidation of phospholipids	May increase catabolism
Creatine	20 g/day for 2wks then 2–5 g/day (adults) 100 mg/kg/day (range 80–350 mg/kg/day) [children]	Essential for energy production; TP synthase cofactor	Adverse effects on renal function (patients with pre-existing condition)
Arginine	0.5 g/kg/day IV (acute episodes) 0.5 g/kg/day PO (during interictal periods for children) or 10 g/m ² /day (for adults)	Increases NO synthesis; vasodilation	Headaches, hypotension
Sodium dichloroacetate	50 mg/kg q12h then 25 mg/kg bid PO	Inhibits phosphorylation of PDHC, thereby reducing conversion of pyruvate to lactate	Peripheral neuropathy, hypocalcaemia, liver dysfunction

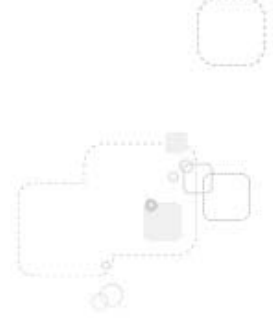
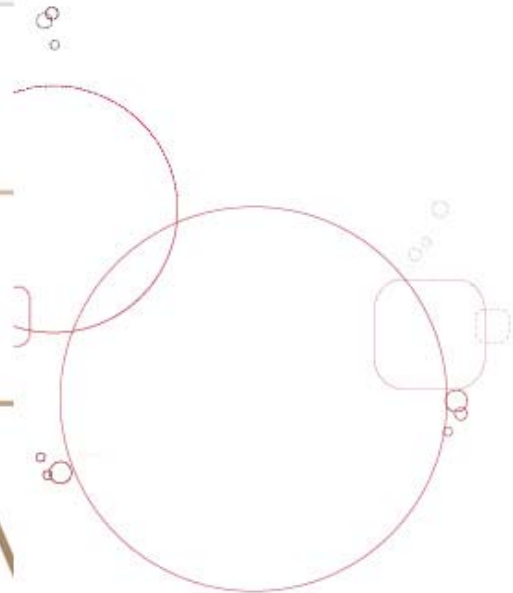
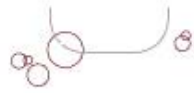
- S/e: N/V, diarrhoea, flushing, headache, dizziness
- High doses – Increase LFT, parenchymal liver injury
- Contraindicated w/ underlying liver disease
- Adults: Max 500mg/day
- Children: 50mg/day
- May be harmful in severe mitochondrial dysfunction (1 drug unrelated death)

ATP = adenosine triphosphate; bid = twice daily; CoA = coenzyme A; ETF = electron transfer flavoprotein; IV = intravenously; LFTs = liver function tests; NAD⁺ = nicotinamide adenine dinucleotide, oxidised form; NADH = nicotinamide adenine dinucleotide, reduced form; NO = nitric oxide; PDHC = pyruvate dehydrogenase complex; PO = orally; q12h = every 12 hours; tid = three times daily.

Non-pharmacological counselling

- Avoid temperature extremes
- Avoid high glucose load
 - Small, frequent meals? Pre-bedtime snack?
- Avoid harmful drugs or self medications
- Assure monitored aerobic exercise

Conclusions



Conclusions

- – Antiepileptics, Thiamine, Riboflavin
- – Ubidecarenone, thiamine, DCA
- – Arginine, DCA

MELAS Syndrome

Be alert to.....

Valproic acid, anesthetics, lactated Ringer's solution, metformin, sodium dichloroacetate.....

Thank You



Q & A



References

- Scaglia F. Northrop JL. The mitochondrial myopathy encephalopathy, lactic acidosis with stroke-like episodes (MELAS) syndrome: a review of treatment options. *CNS Drugs*. 20(6):443–64, 2006.
- DiMauro S. Hirano M. Schon EA. Approaches to the treatment of mitochondrial diseases. *Muscle & Nerve*. 34(3):265–83, 2006 Sep
- Stroh EM. Winterkorn JM. Jalkh AE. Lessell S. MELAS syndrome: a mitochondrially inherited disorder. *International Ophthalmology Clinics*. 33(2):169–78, 1993.
- Gold DR. Cohen BH. Treatment of mitochondrial cytopathies. *Seminars in Neurology*. 21(3):309–25, 2001 Sep.
- Finsterer J. Central nervous system manifestations of mitochondrial disorders. *Acta Neurologica Scandinavica*. 114(4):217–38, 2006 Oct.
- Amacher DE. Drug-associated mitochondrial toxicity and its detection. *Current Medicinal Chemistry*. 12(16):1829–39, 2005.
- MELAS geneReview. Available from <http://www.geneclinics.org> [assessed on 12/3/2007]
- Remes AM, Liimatta EV, Winqvist S, et al. Ubiquinone and nicotinamide treatment of patients with the 3243A-->G mtDNA mutation. *Neurology* 2002; 59 (8): 1275–7