Malignant Hyperthermia: The Genetic Disease is characterized by a runaway futile cycle operating at the acetylcholine (sodium channel) level

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Fall 1968

- Claude Taylor came to Enzyme Institute to discuss MH in Wisconsin.
- 2-weeks later UW Hospital had a 28 yr old patient who developed MH and died.
- Tim Galvez an anesthesia resident had given anesthetic for surgery ulcer project: pigs died.
- Tim and CHW went to UW Arlington swine farm and tested a 40# pig with hernia and it developed MH with rectal temp of 109F.
January 1969

- We returned to UW Arlington farm to check two litters of pigs that were closely related.

Saved 2 males and 3 females that were positive to halothane test for breeding stock.

The other pigs were used for experiments.

Isolated muscle, liver, and heart mitochondria for in vitro studies. Were not uncoupled!!!!!
Slide from UW Arlington Farms
Economic Importance-1972

- Human MH cases: (1.2 M Malpractice settlement)
- Porcine Stress Syndrome
- 1972-250-320 M
- PSE: 25% of carcasses in some packing plants
- Decreased feed efficiency
- Death losses at the farm
  - Baby pig mortality, transport deaths, heat stress.
<table>
<thead>
<tr>
<th>Amplitude</th>
<th>Frequency</th>
<th>Number of Muscles</th>
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<tbody>
<tr>
<td>220 ± 80</td>
<td>(140 - 300)</td>
<td>(490 - 590) (2.4 -</td>
</tr>
<tr>
<td>300 ± 120</td>
<td>(180 - 420)</td>
<td>(630 - 710) (2.5 -</td>
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<tr>
<td>300 ± 160</td>
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Expressed as mean ± sd (min-max limits).

The MUP Characteristics of Muscles of Four...
MUP times

MUP Characteristics in Muscle

![Graph showing MUP times for different groups with P<0.05]

P<0.05
MUP amplitude

MUP Characteristics in Muscle

Amplitude (v)

Control
MHS Youth
MHS Adult
Malignant Hyperthermia in KC 1965-1985

- 2,038,200 anesthetics performed
- 38 cases of MH
- 1: 53, 636
- Succinylcholine was used in 87% of MH cases
- Halothane, enflurane, isoflurane was used in 84% of MH cases
- 4 MH deaths pre-dantrolene
- 0 deaths post-dantrolene
Sevoflurane Development

- Sevoflurane synthesized at Baxter Labs-1971
- 1984-CHW contacted by Maruishi Pharm., Osaka, Japan
- Maruishi purchased Sevoflurane for $8,000,000
- ~1992 Abbott started selling Sevoflurane
- 2000- Court case in N. IL. Abbott selling $200 million per year of sevoflurane as Ultane
MH in KC 1996-2006

• 17/22 surgical-anesthesia units responded
• Total general inhalation anesthetics- 119,448 for 2006 x 10 = 1,194,480
• 2 MH cases = 1: 597,240
  – Diagnosed early
  – Treated with Dantrolene
  – Both cases survived
2D Graph 1

X Data
1965-1985
1996-2006

Y Data
0
10
20
30
40

Number MH cases
MH cases outside KC

• Medline search- 29 cases MH with sevoflurane
  – All cases used succinylcholine as muscle relaxant

  – Dantrolene used in all cases and 100% survival
MH cases with Death

• SPN of Lacrosse, WI
  – Shoulder injury from skiing
• SJK of West Palm Beach, FL
  – Inverted nipple surgery
Safe Muscle Relaxants

- Vecuronium
- Atracurium
- Organon 9426-Will actually prevent MH
Sodium channel structure
Sodium Potassium Pump
Organon 9426
Organon 9426

Dose Response - MH Pigs

Percent Block vs Log Dose (g/mL)

- Percent block 1 vs Dose 1
- Percent Block 2 vs Dose 2
- Percent Block 3 vs Dose 3
- Percent Block 4 vs Dose 4
- Percent Block 5 vs Dose 5
- Percent Block 6 vs Dose 6
- Percent Block 7 vs Dose 7
- Percent Block 8 vs Dose 8

Plot 1 Regr
Dose Response to 100% block

- Dose Response-ug/kg Org 9426
- Control pigs: 586.31
- MH pigs: 427.033
- 73% of the dose required by control pigs
Summary

• Fewer Na+ channels -30-35% decrease
• Total MH protection indicates an allosteric receptor site that regulates Na+ channel activity
• Succinylcholine holds open sodium channel
• Organon 9426 closes sodium channel to normal
• Genetic defect is a abnormal function at myonueral junction.