Hemolysis Contributes to PDE5 Dysregulation and Priapism in Sickle Cell Bone Marrow Transplanted Mice

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Disclosure

I have no actual or potential conflict of interest to this presentation.
• Priapism is a penile erection that persists without sexual purpose.

  Broderick et al. JSM, 2010.

• Types of priapism
  1. Ischemic priapism (95%)
  2. Nonischemic priapism

    Recurrent ischemic priapism is called stuttering priapism

  Burnett & Sharlip. JSM, 2013.
Stuttering Priapism

• Clinical manifestations
  – Typically painful
  – Sleep related
  – Less than 4 hours in duration
  – Generally self-limiting

• Therapeutic dilemma
  – Young patients
  – Risk of erectile dysfunction: 25%
  – Current guidelines remain less than ideal

Sickle Cell Disease and Priapism

• The most common cause of priapism is sickle cell disease (SCD).
  – 63% of the pediatric cases
  – 23% of the adult cases


• 72% of the men with SCD have a history of stuttering priapism.

Adeyoyi et al. BJU Int, 2002.
Preventive Treatment of Stuttering Priapism

• Hormonal therapy
  – Gonadotropin-releasing hormone agonists, antiandrogens, 5α-reductase inhibitors

• $\alpha / \beta$ -agonist: etilefrine, turbutaline etc.

• Phosphodiesterase 5 (PDE5) inhibitors
Pathophysiology of Priapism

- Nitric oxide (NO) imbalance and PDE 5 dysregulation
  

- RhoA / Rho-kinase expression changes
  

- Opiorphin-associated priapism
  

- Adenosine overproduction
  
Nitric Oxide Imbalance → PDE5 Dysregulation
• PDE5 dysregulation resulting from altered NO/cGMP/PKG signaling cause priapism. 

• As a result of PDE5 dysregulation, cGMP generated in the erectile tissue cannot be degraded. 
  Burnett et al. Urology, 2006

• Altered erectile homeostasis can be restored by PDE5 inhibitors (PDE5i).

What causes NO imbalance in SCD?
Hemolysis Decreases NO Bioactivity in SCD

A. Free hemoglobin (Hb) reacts with NO to produce metHb and nitrate.

B. Arginase from erythrocytes converts L-Arginine into Ornithine.

C. Reactive oxygen species (ROS) reduces NO bioavailability.

Hemolysis and Priapism

• Chronic hemolysis in transgenic SCD mice induced:
  – NO/cGMP/PDE5 dysregulation
  – Overproduction of ROS
  – Priapism

  PDE5i treatment alleviated all of the above.

Acute Hemolysis Model

- Bone marrow transplantation (BMT) from sickle mice (BM-SS) is known to:
  - Induce acute hemolysis of blood
  - Make mice have a sickle phenotype


- Using BM-SS, this study examines:
  1. Effect of acute hemolysis on the molecular changes in the penis
  2. Role of PDE5i treatment in acute setting
BMT Protocol

Erythropoietin X 4 days

Myeloablative irradiation (950 cGy)

Recipient C57BL/6

Recipient C57BL/6

C57BL/6

Control

BM-SS

± Sildenafil (100mg/kg; 3 weeks)

Sickle Cell Mouse
Methods

• Erectile function assessment:
  • Intracavernous pressure (ICP) measurement by cavernous nerve stimulation (CNS)
  • Frequency of spontaneous erectile response
    – Pre and post CNS

• Biochemical assessment of the penes:
  • Nitric oxide synthase (NOS) activities
  • Protein kinase G (PKG) activities
  • PDE5 activities
  • ROS generation
Enhanced ICP in BM-SS, Lowered by Sildenafil

* p<0.05 vs control, ** p<0.05 vs BM-SS
Sildenafil Decreased Priapic Activity in BM-SS Mice

* p<0.05 vs control
** p<0.05 vs BM-SS

![Graph showing frequency of erections per hour (erections/hr) for different groups: Control, BM-SS, BM-SS + Sildenafil. The graph includes error bars, and the pre-CNS and post-CNS periods are indicated.](image)
Sildenafil Corrected Downregulated NOS/PKG Activities in BM-SS

**Calcium-dependent NOS Activity**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>BM-SS</th>
<th>BM-SS + Sildenafil</th>
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<tbody>
<tr>
<td>Citrulline Formation (pmol * mg protein⁻¹ * hr⁻¹)</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
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* p<0.05 vs control, ** p<0.05 vs BM-SS

**PKG Activity**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>BM-SS</th>
<th>BM-SS + Sildenafil</th>
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<tbody>
<tr>
<td>% Control Activity</td>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
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* p<0.05 vs control, ** p<0.05 vs BM-SS
Sildenafil Increased PDE5 Activity in BM-SS

* p<0.05 vs control, ** p<0.05 vs BM-SS
Higher ROS Generation in BM-SS Mice Reduced with Sildenafil

* p<0.05 vs control, ** p<0.05 vs BM-SS
Conclusion

• Priapic activity in BMT sickle mice can be attributed to NO/PDE5 dysregulation.

• Sildenafil treatment ameliorates priapism due to:
  – Restored NO balance
  – Decreased ROS generation
  – Increased PDE5 activity
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