Opiorphins role in the development of priapism associated with sickle cell disease.

Shibo Fu MD, PhD, Moses Tar MD, Kelvin Davies Ph.D.

Kelvin P. Davies PhD
Professor of Urology
Professor of Physiology and Biophysics
Albert Einstein College of Medicine.
Priapism is Associated with Sickle Cell Disease.

Priapism is a prolonged erection in the absence of sexual stimulation.

Priapism lasting more than 24 hours is associated with a 44-90% rate of erectile dysfunction.

The probability of a man with sickle cell disease developing priapism is 29-42%.

Sickle cell disease affects 70,000–100,000 people, mainly African Americans, in the USA and 20-25 million Worldwide.
Priapism: the flip side of the erectile function coin. (Unlike ED there are no preventative pharmacologic treatments)

Heightened tone (contracted) = less blood flow = flaccidity
Reduced tone (relaxed) = more blood flow = erection
Our interest in the role of opiorphins in erectile function began in 2007.

We approached the study of priapism associated with sickle cell as a disease of hypoxia.

Rat corporal smooth muscle cells in vitro.

Normoxic (control) or hypoxic conditions. Looked at 3 genes:

Hypoxia increases expression:

Rat opioid (sialorphin).

HIF-1a (the accepted mediator of the hypoxic response, usually through post-translational mechanisms).

A2BR- Adenosine-2 Binding Receptor (known to be up-regulated in sickle cell corpora, involved in the adenosine pathways relaxing smooth muscle).

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Sialorphin (rat opiorphin) up-regulates HIF-1a and A2BR

Rat Corporal Smooth Muscle Cells incubated with sialorphin increased expression of HIF-1A and A2BR (both transcription and protein levels).
Using a HIF-1A Inhibitor we demonstrated that activation of A2BR by sialorphin is dependent on HIF-1A.
Hypoxic up-regulation of HIF-1a in corporal smooth muscle cells is dependent on Vcsa1, the rat opiorphin gene.

Efficient knock-down of Vcsa1 by siRNA
Vcsa1-siRNA treated cells no longer have hypoxic upregulated HIF-1A gene

Vcsa1-siRNA treated cells no longer have hypoxic upregulated HIF-1A protein
Gene expression in the Corpora of Sickle Cell Mice at 5-weeks (pre-priapic) and 12 weeks (priapic)
Conclusion: Opiorphin is a key-factor in the Cause of Priapism Associated with Sickle Cell Disease.

- Hypoxia induces expression of opiorphin, *hif-1a* and *a2br* “genes involved in smooth muscle regulation”.
- Hypoxic up-regulation of *hif-1a* and *a2br* is dependent on opiorphin.
- Opiorphin regulates *hif-1a* and *a2br* expression, and opiorphin regulation of *a2br* is mediated through *hif-1a*.
Identifies opiorphin, and the downstream pathways which opiorphins regulate, as potential targets for treating priapism.

Opiorphin level in the blood is potentially a useful biomarker for predicting a sickle cell related priapic crisis.

Excessive activation of “relaxant” pathways can contribute to the development of priapism whereas aberrant activation of smooth muscle “constrictor” pathways leads to ED. So may identify targets for treatments of ED.
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