Cysteine 42 of Protein Kinase G 1α is Critical for Erection Generation
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PKG Activation

• Classical activation via NO pathway
  – NO $\rightarrow$ sGC $\rightarrow$ cGMP $\rightarrow$ PKG

• Redox activation by dimerization
  – NO and cGMP independent activation
  – Cysteine 42 regulates dimerization
  – Changes in affinity for PKG substrates and PKG cellular localization

(Burgoyne et al, Science 2007)
PKG1α^{C42S} Mouse (Cys → Ser Mutation)

Cysteine → Serine
Objective 1

• To determine the importance of redox activation of PKG1α on erectile function
Objective 2

• To determine if redox activation of PKG1α mediates the effects of the pro-erectile drugs sildenafil and BAY 60-2770 (an sGC activator)
Effect of Sildenafil

Detumescence

Erectile Function

N = 6-9 / group

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Effect of BAY-2770

Erectile Function

\[ \text{AUC/MAP} = \frac{\text{[mmHg]*s/mmHg]}}{\text{[mmHg]*s/mmHg]} \]

- WT + Veh
- WT + BAY
- PKG\(^{C42S}\) + Veh
- PKG\(^{C42S}\) + BAY

\[ N = 5-9 / \text{group} \]
Conclusions

• Cys 42 of PKG1α appears to be an important point of action for nerve stimulated erection generation

• Cys 42 may regulate the erectogenic effects of sildenafil and BAY 60-2770