Vericiguat Rescues Cyclic Guanosine Monophosphate Production In Human Aortic Vascular Smooth Muscle Cells And Augments Vasorelaxation In Aortic Rings Exposed To High Glucose

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Background

- Endothelial cell dependent vascular smooth muscle cell (VSMC) function is mediated by bioavailable nitric oxide (NO)
- NO stimulates soluble guanylyl cyclase (sGC) production of the second messenger, cyclic guanosine monophosphate (cGMP) and results in VSMC relaxation.
- NO bioavailability is impaired in inflammatory states such as hyperglycemia.
- We examined whether the sGC stimulator vericiguat, augments cGMP production in VSMC exposed to hyperglycemia and explored its effect on vasorelaxation in isolated aortic rings.

Methods

- Aortic Human VSMCs were exposed to hyperglycemia (30 mM D-glucose) or normal glucose (control, 4.5 mM D-glucose + 25.5 mM L-glucose) for 24h
- Cells were treated with 1uM vericiguat or control. All groups were treated with PDE5 inhibitor sildenafil (1uM) and NO donor, DETA NONOate (0.1uM)
- Thoracic aortas were obtained from male c57BL/6 mice and exposed to high glucose or normal glucose control for 24h. Aortic rings were pre-contracted with phenylephrine (1uM) and dose response curves to Acetylcholine (Ach), vericiguat, or sodium nitroprusside (SNP) were constructed

Results

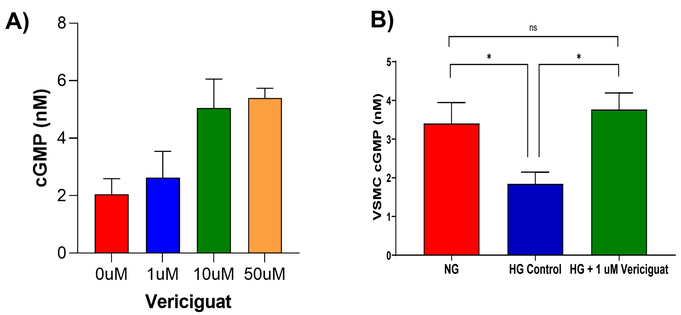

Figure 1: (A) cGMP levels in VSMCs treated with varying concentrations of Vericiguat. (B) cGMP production of VSMCs subjected to normal glucose, high glucose, and high glucose +1μM Vericiguat. *p<0.05 by one-way ANOVA

Results

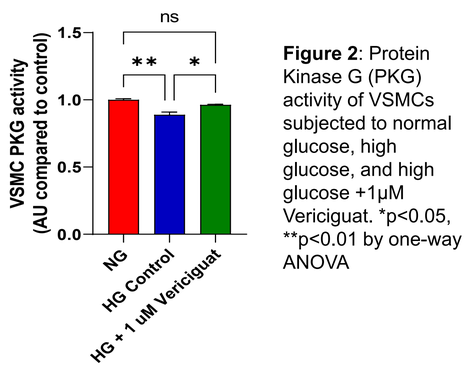

Figure 2: Protein Kinase G (PKG) activity of VSMCs subjected to normal glucose, high glucose, and high glucose +1μM Vericiguat. *p<0.05, **p<0.01 by one-way ANOVA

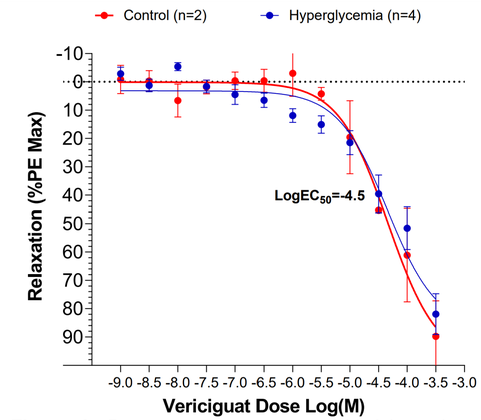

Figure 3: Dose response curves of Vericiguat in aorta pre-treated with high glucose or normal glucose

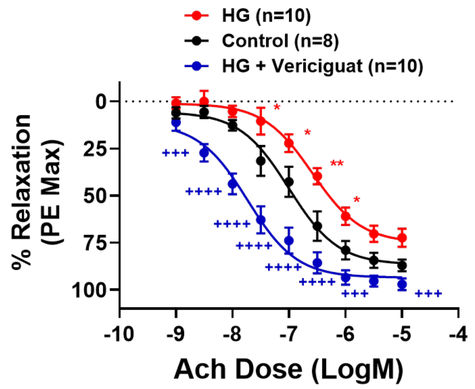

Figure 4: (A) Acetylcholine (Ach) dose response of vessels subjected to control, high glucose, and high glucose +Vericiguat*p<0.05 vs Control by one-way ANOVA. **p<0.01 by Control by one-way ANOVA. +++ p<0.001 vs HG by one-way ANOVA. ++++ p<0.0001 vs HG by one-way ANOVA.

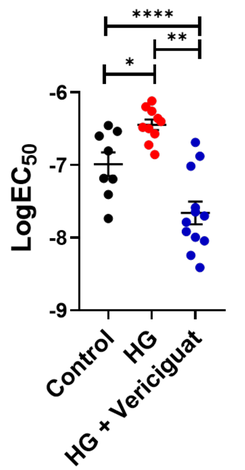

Figure 5: $Log_{EC}50$ of Ach dose response curves in Figure 4. *p<0.05, **p<0.01, ****p<0.001 by one-way ANOVA.

Results

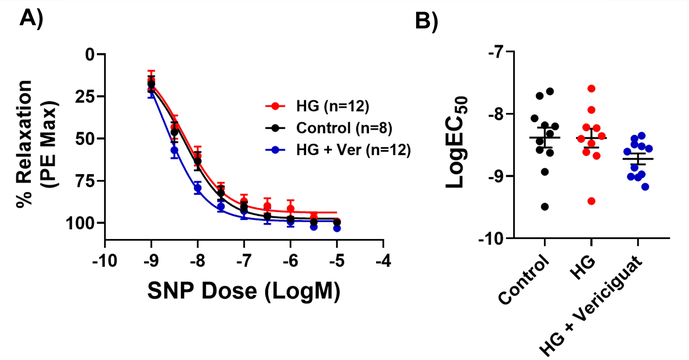

Figure 6: (A) Sodium Nitroprusside (SNP) dose response curves of aorta subjected to control, high glucose, and high glucose +Vericiguat. (B) $Log_{EC}50$ of SNP dose response curves.

Conclusions

- cGMP levels are decreased in human aortic vascular smooth muscle cells exposed to pro-inflammatory stimuli high glucose. The sGC stimulator vericiguat rescues cGMP production and signaling in the setting of high glucose.
- High glucose impairs acetylcholine mediated vasorelaxation in isolated mouse aorta. Vericiguat enhances endothelial dependent acetylcholine-mediated vasorelaxation
- Clinical studies are warranted to investigate vericiguat as a therapeutic agent to improve vascular endothelial-dependent function, which is impaired in hyperglycemia and other pro-inflammatory states

Acknowledgments

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