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Título	Nitric Oxide Resistance in Priapism Associated with Sickle Cell Disease: Mechanisms, Therapeutic Challenges, and Future Directions
Autores	Dalila Andrade Pereira, Fabiano Beraldi Calmasini, Fernando Ferreira Costa, Arthur L Burnett, Fábio Henrique Silva
Autor (es) USF	Dalila Andrade Pereira, Fábio Henrique Silva
Autores Internacionais	Arthur L Burnett
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Resumo	Patients with sickle cell disease (SCD) display priapism, a prolonged penile erection in the absence of sexual arousal. The current pharmacological treatments for SCD-associated priapism are limited and focused on acute interventions rather than prevention. Thus, there is an urgent need for new drug targets and preventive pharmacological therapies for this condition. This review focuses on the molecular mechanisms linked to the dysfunction of the NO-cyclic guanosine monophosphate (cGMP)-phosphodiesterase type 5 (PDE5) pathway implicated in SCD-associated priapism. In murine models of SCD, reduced NO-cGMP bioavailability in the corpus cavernosum is associated with elevated plasma hemoglobin levels, increased ROS levels that inactive NO, and testosterone deficiency that leads to eNOS downregulation. We discuss the consequences of the reduced cGMP-dependent PDE5 activity in response to these molecular changes, highlighting it as the primary pathophysiological mechanism leading to excessive corpus cavernosum relaxation, culminating in priapism. We also further discuss the impact of intravascular hemolysis on therapeutic approaches, present current pharmacological strategies targeting the NO-cGMP-PDE5 pathway in the penis, and identify potential pharmacological targets for future priapism therapies. In men with SCD and priapism, PDE5 inhibitor therapy and testosterone replacement have shown promising results. Recent preclinical research reported the beneficial effect of treatment with haptoglobin and NO donors. Significant strides have been made in understanding the pathophysiology of SCD-associated priapism. Significance Statement This review discusses the molecular changes that reduce NO-cGMP bioavailability in the penis in SCD and highlights pharmacological targets and therapeutic strategies for the treatment of priapism, including PDE5 inhibitors, hormonal modulators, NO donors, soluble guanylate cyclase stimulators, haptoglobin, hemopexin, and antioxidants.
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