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Título	Haptoglobin treatment contributes to regulating nitric oxide signal and reduces oxidative stress in the penis: A preventive treatment for priapism in sickle cell disease
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Resumo	Background: In sickle cell disease (SCD), reduced bioavailability of endothelial NO and cGMP results in reduced expression of phosphodiesterase type 5 (PDE5), thus impairing the penile erection control mechanism and resulting in prolonged penile erection (priapism). In SCD, reduced NO bioavailability is associated with excess plasma hemoglobin due to intravascular hemolysis and increased oxidative stress. Haptoglobin is the plasma protein responsible for reducing plasma hemoglobin levels, but in SCD, haptoglobin levels are reduced, which favors the accumulation of hemoglobin in plasma. Therefore, we aimed to evaluate the effects of haptoglobin treatment on functional and molecular alterations of erectile function, focusing on the contractile and relaxant mechanisms of corpus cavernosum (CC), as well as oxidative stress. Methods: SCD mice were treated with haptoglobin (400 mg/kg, subcutaneous) or vehicle of Monday, Wednesday and Friday for a period of 1 month. Corpus cavernosum strips were dissected free and placed in organ baths. Cumulative concentration-response curves to the acetylcholine, sodium nitroprusside, phenylephrine and KCL, as well as to electrical field stimulation (EFS), were obtained in CC. Protein expressions of eNOS, phosphorylation of eNOS at Ser-1177, nNOS, PDE5, ROCK1, ROCK2, gp91phox, 3-nitrotyrosine, and 4-HNE were measured by western blot in CC. Results: Increased CC relaxant responses to acetylcholine, sodium nitroprusside and electrical-field stimulation were reduced by haptoglobin in SCD mice. Reduced CC contractile responses to phenylephrine and KCl were increased by haptoglobin in SCD mice. Haptoglobin prevented downregulated eNOS, p-eNOS (Ser-1177), PDE5, and

	ROCK2 protein expressions and reduced protein expressions of reactive oxygen species markers, NADPH oxidase subunit gp91phox, 3-nitrotyrosine and 4-HNE in penises from SCD mice. Haptoglobin treatment did not affect ROCK1 and nNOS protein expressions in penises from SCD mice. Basal cGMP production was lower in the SCD group, which was normalized by haptoglobin treatment. Conclusion: Treatment with haptoglobin improved erectile function due to up-regulation of eNOS-PDE5 expression and down-regulation of the gp91phox subunit of NADPH oxidase and oxidative/nitrosative stress in the penises of SCD mice. Treatment with haptoglobin also increased contractile activity due to up-regulation of ROCK2. Therefore, haptoglobin treatment may be an additional strategy to prevent priapism in SCD.
Fomento	Fapesp