Tadalafil Supresses Glycogenolysis Stimulation Caused by AMPc in the Rat Liver

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Tadalafil is used for treating erectile dysfunction and it acts mainly by inhibiting the enzyme phosphodiesterase 5. This action reduces the rate of cyclic nucleotide hydrolysis, namely cGMP and cAMP. The latter is especially important in the liver as a regulator of several metabolic fluxes. With this principle in mind the purpose of the present work was to verify if the compound affects hepatic glycogenolysis, which is one of the primary targets of cAMP. Livers from fed male Wistar rats (200-250 g) were perfused using hemoglobin-free perfusion fluid (pH 7.4) saturated with a mixture of O₂ and CO₂ (95:5%). Glucose release from endogenous glycogen (glycogenolysis) was measured as well as glycolysis and O₂ consumption. The working hypothesis was that tadalafil should increase glycogenolysis if it retards cAMP hydrolysis. However, no effects at all were found under basal conditions for tadalafil concentrations in the range between 0.25 and 10 μM. However, when glycogenolysis was stimulated by exogenous 5 μM cAMP, tadalafil had a clear and time-dependent inhibitory effect on the cAMP-stimulated glucose release. Constant infusion of tadalafil eventually abolished 100% of the stimulatory action of cAMP (I₅₀ = 0.52±0.11 μM). The mechanism of this unexpected action is now being investigated. The possible mechanisms include: a) inhibition of cAMP transport; b) direct interference with the intracellular mechanism of action of cAMP. Irrespective of the mechanism the results show that the overall physiological actions of tadalafil are far from being well understood as fact that justifies continuation of the experimental efforts.

Key words: tadalafil, phosphodiesterase, cAMP, glycogenolysis, liver.
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