

## COMMENTARY

# Sildenafil reduces alcohol-induced gastric damage: just say 'NO'

R Duffin<sup>1</sup>, CA Shaw<sup>2</sup> and AG Rossi<sup>1</sup>

<sup>1</sup>MRC Centre for Inflammation Research, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK and

<sup>2</sup>Centre for Cardiovascular Science, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

Although sildenafil (Viagra) and other phosphodiesterase V (PDE V) inhibitors are increasingly recognized for their use in the treatment of male erectile dysfunction and perhaps more recently pulmonary artery hypertension, less is known of their potential beneficial effects in other situations. Medeiros *et al.*, in the current issue of the *British Journal of Pharmacology*, report that sildenafil dramatically reduces alcohol-induced gastric damage in rats. The authors provide convincing evidence that such protection not only occurs via the nitric oxide (NO)/cGMP pathway, but also involves regulation of ATP-sensitive potassium channels. Therefore, in addition to exerting anti-impotence efficacy, PDE V inhibitors may provide significant beneficial effects from mucosal injury induced by alcohol.

*British Journal of Pharmacology* (2008) 153, 623–624; doi:10.1038/sj.bjp.0707642; published online 17 December 2007

**Keywords:** nitric oxide; alcohol; Viagra; gastric damage

**Abbreviations:** cGMP, guanosine 3'S'-cyclic monophosphate; K<sub>ATP</sub>, ATP-sensitive potassium channels; L-NAME, N(G)-nitro-L-arginine methyl ester; NO, nitric oxide; ODQ, 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one; PDE V, phosphodiesterase V; PGs, prostaglandins; sGC, soluble guanylate cyclase

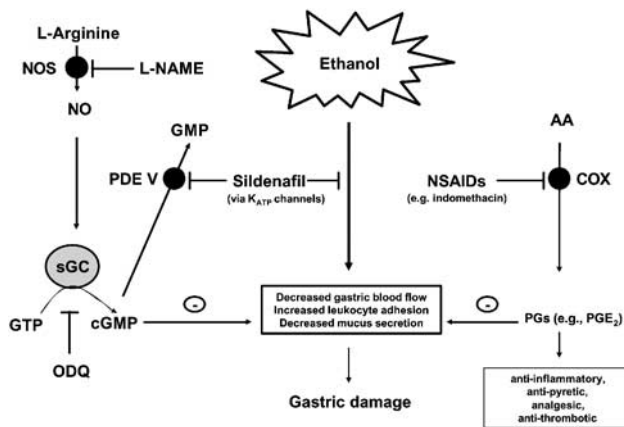
Sildenafil (Viagra) is a commonly prescribed drug for the treatment of male erectile dysfunction (impotence) and is occasionally used to reduce pulmonary arterial hypertension and to alleviate the symptoms associated with Raynaud's phenomenon (Ghofrani *et al.*, 2006). Its main mechanism of action during the treatment of male impotence is essentially to enhance the effect of nitric oxide (NO) released from parasympathetic nerves in the corpus cavernosum of the penis. Released NO interacts with sGC (soluble guanylate cyclase), resulting in increased levels of cGMP. Sildenafil is a selective and potent inhibitor of the enzyme responsible for the breakdown of cGMP, PDE V (phosphodiesterase V), and therefore effectively raises the intracellular concentration of cGMP. Elevated levels of cGMP then mediate vasodilation and consequently augment erectile function (Francis and Corbin, 2005; Ghofrani *et al.*, 2006). Increasingly, sildenafil and other drugs that similarly act via the NO/cGMP pathway (for example, tadalafil (Cialis) and vardenafil (Levitra)) have found widespread recreational use to boost sexual performance and enjoyment (Aldridge and Measham, 1999; Smith and Romanelli, 2005). Consequently, they are often used in

conjunction with the consumption of alcohol. Although taking sildenafil in combination with alcohol is not recommended, no major side effects with low, 'social', amounts of alcohol have been reported (Leslie *et al.*, 2004; Grinshpoon *et al.*, 2007). However, one of the many side effects associated with alcohol consumption alone is damage to the gut mucosa (Szabo *et al.*, 1985; Rajendram and Preedy, 2005).

A previous article in this journal clearly demonstrated that sildenafil, by amplifying the effects of endogenous NO, prevents indomethacin-induced gastropathy, possibly by reducing leukocyte adherence and maintaining gastric blood flow (Santos *et al.*, 2005; Sawatzky *et al.*, 2005). An interesting article in the current issue of this journal (Medeiros *et al.*, 2008) reports that sildenafil also dramatically reduces alcohol-induced gastric damage in rats. Using histological assessment of macroscopic gastric lesions in the gut mucosa, Medeiros *et al.* demonstrate that sildenafil ameliorates ethanol-induced gastric haemorrhagic damage, oedema and epithelial cell loss. The NOS inhibitor L-NAME (N(G)-nitro-L-arginine methyl ester) dose dependently reversed the protective effects of sildenafil, and the effect of L-NAME was prevented when the NO precursor L-arginine was co-administered. Furthermore, the sGC inhibitor ODQ (1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one) reversed the protective effects of sildenafil, demonstrating that the protective mechanism is cGMP dependent. Interestingly, the ATP-sensitive potassium channel (K<sub>ATP</sub>) blocker glibenclamide was also capable of reversing sildenafil's gastroprotective

Correspondence: Professor AG Rossi, MRC Centre for Inflammation Research (Room W2.04), Queen's Medical Research Institute, University of Edinburgh Medical School, 47 Little France Crescent, Edinburgh EH16 4TJ, UK.  
E-mail: a.g.rossi@ed.ac.uk

Received 11 October 2007; accepted 22 November 2007; published online 17 December 2007



**Figure 1** Ethanol induces gastric mucosal injury through the release of inflammatory mediators which in turn induce vasoconstriction/ischaemia and cell death. Non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin inhibit cyclooxygenase (COX) enzymes to prevent the formation of prostaglandins (PGs) from the membrane lipid arachidonic acid (AA). Products of COX activity, such as PGE<sub>2</sub>, also act to limit gastric damage by increasing blood flow and reducing leukocyte adhesion. Inhibition of PG formation by NSAIDs therefore results in increased gastropathy. Sildenafil, by inhibiting phosphodiesterase V (PDE V), prevents the breakdown of cGMP to GMP. In addition, it also reduces gastric damage by augmenting gastric blood flow and limiting leukocyte adhesion. Nitric oxide (NO), formed by the action of NOS enzymes on L-arginine, acts upon soluble guanylate cyclase (sGC) to convert GTP to cGMP. Inhibition of sGC by 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ) reverses any protective effect of sildenafil against ethanol-induced gastric damage. Furthermore, the ATP-sensitive potassium channel (K<sub>ATP</sub>) blocker glibenclamide is capable of reversing sildenafil's gastroprotective effect against ethanol-induced gastric damage suggesting that ATP K<sub>ATP</sub> channels are also involved in regulating gastric protection. Importantly then, sildenafil offers protection against ethanol-induced gastric damage via activation of the NO/cGMP/K<sub>ATP</sub> pathway (Figure adapted from Sawatzky *et al.*, 2005).

effect, which is in keeping with a number of recent models demonstrating that these K<sub>ATP</sub> channels regulate gastric protection (Ockaili *et al.*, 2002; Vale *et al.*, 2007). Thus, it appears that inhibition of PDE V by sildenafil increases the survival of cGMP generated in response to endogenous NO and affords protection against alcohol-induced gastric damage, possibly via activation of K<sub>ATP</sub> channels.

In conclusion, PDE V inhibitors such as sildenafil might help prevent the unwanted gastric side effects of alcohol. It

therefore appears that, in addition to the powerful anti-impotence therapy for which they are now famous, drugs such as sildenafil have the potential to provide significant gastroprotection not only from gastric damage induced by non-steroidal anti-inflammatory drugs, but also from alcohol-mediated mucosal injury (Figure 1).

## References

- Aldridge J, Measham F (1999). Sildenafil (Viagra) is used as a recreational drug in England. *BMJ* **318**: 669.
- Francis SH, Corbin JD (2005). Sildenafil: efficacy, safety, tolerability and mechanism of action in treating erectile dysfunction. *Expert Opin Drug Metab Toxicol* **1**: 283–293.
- Ghofrani HA, Osterloh IH, Grimminger F (2006). Sildenafil: from angina to erectile dysfunction to pulmonary hypertension and beyond. *Nat Rev Drug Discov* **5**: 689–702.
- Grinshpoon A, Margolis A, Weizman A, Ponizovsky AM (2007). Sildenafil citrate in the treatment of sexual dysfunction and its effect on quality of life in alcohol dependent men: preliminary findings. *Alcohol Alcohol* **42**: 340–346.
- Leslie SJ, Atkins G, Oliver JJ, Webb DJ (2004). No adverse hemodynamic interaction between sildenafil and red wine. *Clin Pharmacol Ther* **76**: 365–370.
- Medeiros JVR, Gadelha GG, Lima SJ, Garcia JA, Soares PMG, Santos AA *et al.* (2008). Role of NO/cGMP/K<sub>ATP</sub> pathway in protective effect of sildenafil against ethanol-induced gastric damage in rats. *Br J Pharmacol* **153**: 722–728 (this issue).
- Ockaili R, Salloum F, Hawkins J, Kukreja RC (2002). Sildenafil (Viagra) induces powerful cardioprotective effect via opening of mitochondrial K(ATP) channels in rabbits. *Am J Physiol Heart Circ Physiol* **283**: H1263–H1269.
- Rajendram R, Preedy VR (2005). Effect of alcohol consumption on the gut. *Dig Dis* **23**: 214–221.
- Santos CL, Souza MH, Gomes AS, Lemos HP, Santos AA, Cunha FQ *et al.* (2005). Sildenafil prevents indomethacin-induced gastropathy in rats: role of leukocyte adherence and gastric blood flow. *Br J Pharmacol* **146**: 481–486.
- Sawatzky DA, Megson IL, Rossi AG (2005). Sildenafil offers protection against NSAID-induced gastric injury. *Br J Pharmacol* **146**: 477–478.
- Smith KM, Romanelli F (2005). Recreational use and misuse of phosphodiesterase 5 inhibitors. *J Am Pharm Assoc* **45**: 63–72.
- Szabo S, Trier JS, Brown A, Schnoor J (1985). Early vascular injury and increased vascular permeability in gastric mucosal injury caused by ethanol in the rat. *Gastroenterology* **88**: 228–236.
- Vale ML, Rolim DE, Cavalcante IF, Ribeiro RA, Souza MH (2007). Role of NO/cGMP/K(ATP) pathway in antinociceptive effect of sildenafil in zymosan writhing response in mice. *Inflamm Res* **56**: 83–88.