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COMMENTARY

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

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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.
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Abbreviations: cGMP, guanosine 3′S′-cyclic monophosphate; K_{ATP}, ATP-sensitive potassium channels; L-NAME, *N*(G)-nitro-L-arginine methyl ester; NO, nitric oxide; ODQ, 1*H*-[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 (1*H*-[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_{ATP}) blocker glibenclamide was also capable of reversing sildenafil's gastroprotective

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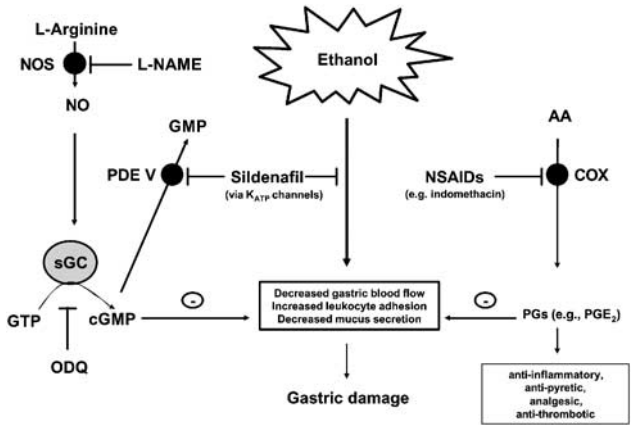

Figure 1 Ethanol induces gastric mucosal injury through the release of inflammatory mediators which in turn induce vasoconstriction/ischaemia and cell death. Non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin inhibit cyclooxygenase (COX) enzymes to prevent the formation of prostaglandins (PGs) from the membrane lipid arachidonic acid (AA). Products of COX activity, such as PGE_2, 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 1*H*-[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_{ATP}) blocker glibenclamide is capable of reversing sildenafil's gastroprotective effect against ethanol-induced gastric damage suggesting that ATP K_{ATP} 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_{ATP} pathway (Figure adapted from Sawatzky *et al.*, 2005).

effect, which is in keeping with a number of recent models demonstrating that these K_{ATP} 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_{ATP} 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).

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