CHEMISTRY 4000

Problem Set #7: Sildenafil (aka Viagra®)

Fall 2017

Dr. Susan Findlay

Sildenafil (aka Viagra®)

- Sildenafil was initially developed to treat hypertension. It functions by inhibiting cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). The theory was that inhibition of cGMP metabolism would increase available cGMP and promote relaxation of smooth muscle cells in the kidney and blood vessels.

- Since it turns out that there is no PDE5 in the kidneys, this approach failed and interest turned to whether or not sildenafil could be used to increase blood flow to the heart muscles – potentially allowing for treatment of angina.

- While initial clinical trials showed that sildenafil did indeed increase blood flow in some areas, it was not a successful angina treatment. Thus began its third and most successful incarnation – as medication for erectile disfunction (compensating for low nitric oxide (NO) production – where NO stimulates cGMP production).

Sildenafil (aka Viagra®)

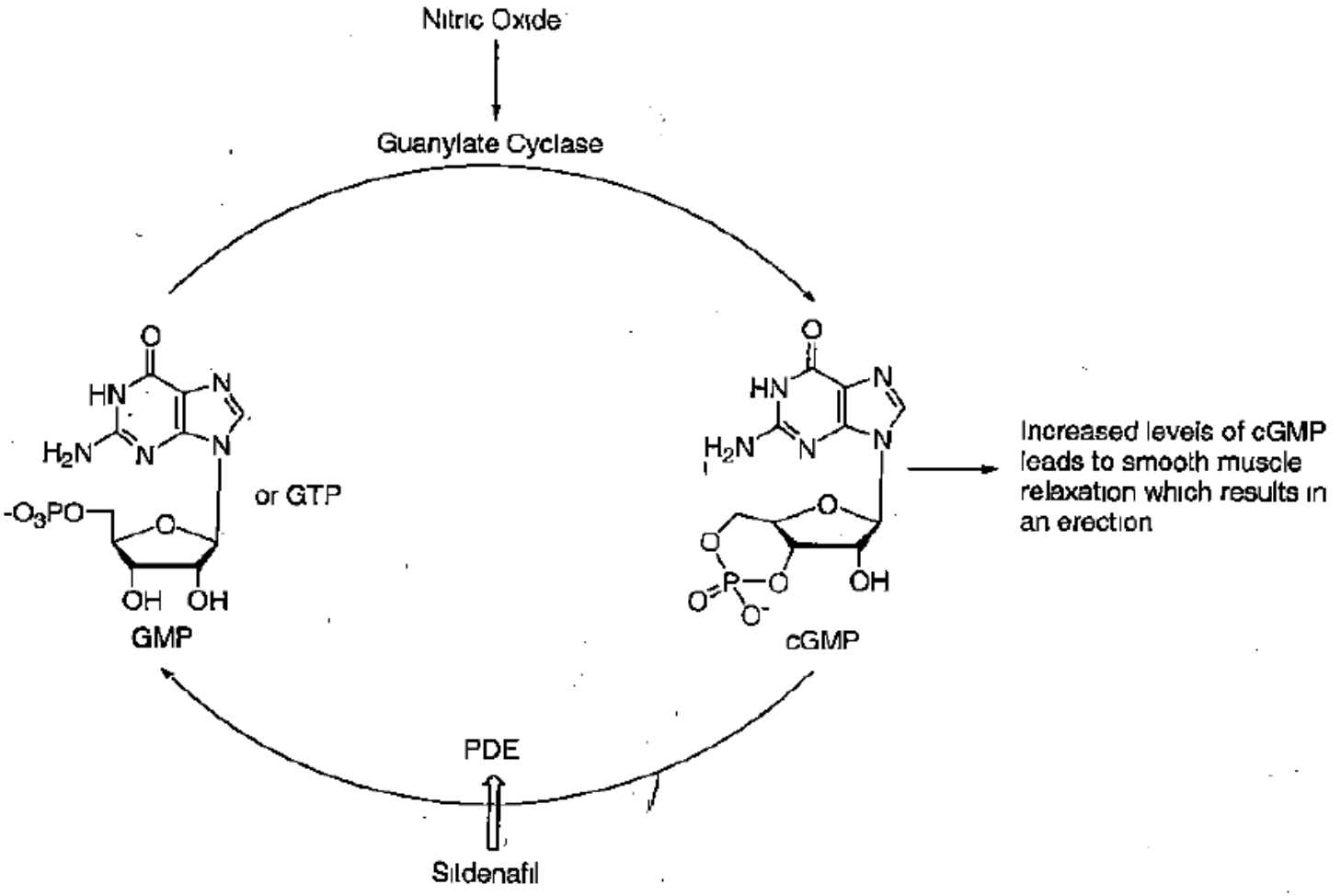

Figure 1. Role of nitric oxide, cGMP, phosphodiesterase and sildenafil in erectile function.

Sildenafil (aka Viagra®)

- Sildenafil (aka Viagra®) was patented by Pfizer in 1996, and the Canadian patent was due to expire in 2014. In November 2012, the Canadian Supreme Court upheld an appeal by Teva Pharmaceutical Industries which claimed that the patent was invalid because it was incomplete.

- Section 27(3)(b) of *The Patent Act* requires that disclosure must include sufficient information "to enable any person skilled in the art or science to which it pertains" to produce it – but the Pfizer patent referred to 270,000,000,000,000,000,000 compounds – of which only one is the active ingredient in Viagra. In fairness to Pfizer, patenting a number of related compounds for one potential use is common – though the number is usually substantially lower.

- Teva challenged the patent in several countries, but Canada is the first in which their challenge was upheld.

Sildenafil (aka Viagra®)

- The structure of sildenafil is: