PDE5 Inhibitors: Is There More to Come besides Erectile Dysfunction?

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To predict the future in research is impossible because already an adequate appreciation of today’s research is most difficult as I know from personal experience. My pre-predecessor, Prof. E. Schmiedt, invented extracorporeal shock wave lithotripsy (ESWL) with his group [1]. He told me that when they sent their first abstracts to the American Urological Association they were rejected for 2 consecutive years because their results were considered “unbelievable.” Regarding our topic for today, I had a similar experience with phosphodiesterases (PDEs) in erectile dysfunction (ED). When we applied for the poster prize of the International Society for Impotence Research in 1992 with an experimental study indicating that “PDE inhibitors are promising drugs for the treatment of ED” [2] (at least 12 mo before submission of the Viagra® patent application), we were not even attributed the third poster prize because “this work is in such a remote basic experimental field that it will never have any clinical application” (wording of the prize committee chairman).

So I will base my forecasts not on speculations but on solid results published during the last 2 yr. Here, PDE inhibitors seem to have great potential both for the treatment of benign prostatic hyperplasia (BPH) as well as for Peyronie’s disease.

1. BPH

Anatomic studies have shown that the enzymes required for the nitric oxide-PDE-protein kinase (NO-PDE-PK) pathway are abundantly expressed within the human prostatic zones [3,4]. The mere presence of these key enzymes of intracellular signal transduction in smooth muscle tone regulation within the prostatic tissue gained a much more pronounced boost in scientific attention when the presence of these enzymes was functionally supported by in vitro data of organ bath studies in fresh human prostates. Here it was depicted that inhibitors of PDE4 and PDE5 exerted a strong relaxing effect on precontracted strips of human prostatic tissue [5]. These experimental studies are clinically supported by anecdotal reports of a positive effect of an oral PDE5 inhibitor on symptomatic BPH. Furthermore, these reports were confirmed by two prospective randomized multicenter trials on the effect of a specific PDE5 inhibitor (vardenafil as well as tadalafil) on BPH-related symptoms (in publication). As far as we can tell from these studies, PDE5 inhibitors are the most promising drugs for the treatment of BPH and they seem to offer significant advantages over existing medical [6] and interventional [7] treatment options available today.

2. Peyronie’s disease

It becomes increasingly evident that specific inflammatory processes play a key role in the induction and maintenance of Peyronie’s disease [8]. This improved insight into the etiology of the disease renders conservative [9,10] and surgical [11] ther-
apeutic strategies used until now as non-targeted and at best “suboptimal,” at least for the beginning (and thus the prevention) of the disease. Here, the chronic use of a PDE5 inhibitor has shown profound beneficial effects on fibrotic changes of Peyronie-like disease both in vitro [12] and in vivo [13]. The experimental data are of such quality and their mode of action seems so well explained by pathophysiology that they changed my treatment pattern for the patient coming into my office with a rather early stage of Peyronie’s disease. I explain the experimental data and the theoretical background to him and if he then wishes, I prescribe a low dose of a PDE5 inhibitor to be taken at nighttime for at least 3 mo.

Thus, PDE5 inhibitors hold a most promising potential for two major indications with a significant portion of men in the general population affected and a hereto low standard of care compared to other major diseases such as hypertension where a plethora of efficacious classes of drugs allow for an individually adapted therapeutic regimen.

References