Strategies in the oral pharmacotherapy of male erectile dysfunction viewed from bench and bedside (Part II)

Christian G. Stief, Stefan Ückert and Udo Jonas

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Abstract

The development of selective inhibitors of phosphodiesterase (PDE) 5 and introduction of these compounds as effective, safe and well-tolerated orally active drugs for the treatment of erectile dysfunction (ED) has become a world-wide clinical and pharmaceutical success and also brought further attention to the physiological mechanisms involved in the control of normal male sexual function. This includes both peripheral intracellular signal transduction in the penis as well as central brain and spinal cord pathways controlling penile erection. Increasing knowledge of intracellular signal propagation in cavernous smooth muscle tone regulation has provided the basis for identifying new and more selective pharmacological approaches to manage ED. As a consequence, beyond the PDE5 inhibitors sildenafil, vardenafil and tadalafil, the potential use of several new drugs acting via different pathways in the treatment of ED is now being discussed. A brief overview is given on the status of specific compounds that could become important in the future oral pharmacotherapy of male ED. © 2005 WPMH GmbH. Published by Elsevier Ireland Ltd.

Christian G. Stief, PhD, MD
Ludwig-Maximilian-University, Academic Hospital Grosshadern, Department of Urology, Munich, Germany

Stefan Ückert, PhD
Hannover Medical School, Department of Urology, Hannover, Germany

Udo Jonas, PhD, MD
Hannover Medical School, Department of Urology, Hannover, Germany

Correspondence Author:
E-mail:
sue_de_99@yahoo.de

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Abbreviations

ED, erectile dysfunction
sGC, guanylyl cyclase
cGMP, cyclic guanosine monophosphate
NO, nitric oxide
EFS, electrical field stimulation
PDE, phosphodiesterase
α-MSH, melanocyte-stimulating hormone
ACTH, adrenocorticotropin (adrenocorticotropic hormone)
MC-R, melanocortin receptors
GH, growth hormone
LH, luteinizing hormone
FSH, follicle-stimulating hormone
IGF-1, insulin-like growth factor
NOS, nitric oxide synthase
rGH, recombinant GH

Future strategies in the oral treatment of erectile dysfunction (ED)

Anti-serotoninergic agents

For more than a decade the serotoninergic pathways have been speculated to have a role in controlling male sexual function, especially the maintenance of penile flaccidity and initiation of detumescence. Findings, mainly from animal studies, have been contradictory with regard to the pro-erectile or anti-erectile properties of serotonin (5-Hydroxytryptamine, 5-HT) [1,2,3]. Although several publications have addressed the use of serotoninergic drugs such as clomipramine, sertraline, fluoxetine and paroxetine for treating patients who prematurely ejaculate, only a few studies suggested

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that the serotoninergic system has an inhibitory effect on sexual behaviour and that, thus, agents with anti-serotoninergic properties might be beneficial to increase sexual activity and facilitate penile erection [4,5,6].

The hypothesis of the inhibition of spinal sexual reflexes - including the ability to achieve penile erection - especially by the activation of 5-HT_{1A}-, 5-HT_{1B}- and 5-HT_{2A}-receptors is strongly supported by recent findings indicating that 5-HT might be released from respective receptor sites in the human corpus cavernosum in response to sexual arousal when the penis becomes tumescent and rigid [7].

Only a few compounds with anti-serotoninergic properties (trazodone, ketanserin and mianserin) have been evaluated in what have been small preliminary studies for their efficacy in the treatment of male ED. Mianserin and trazodone belong to the group of non-tricyclic antidepressant agents. The use of trazodone in the treatment of erectile dysfunction has seldom been reported in the literature [8,9]. The anti-serotoninergic activity of the drug is exerted through its major metabolite m-chloro-phenylpiperazine. Mianserin and ketanserin mainly act via $5HT_{1A}$-and $5HT_{2}$-receptor antagonism. Intravenous infusion of ketanserin, which was used to observe the improvement in flow rates in patients with benign prostatic hyperplasia, resulted in penile tumescence [10]. In a preliminary, double-blind, placebo-controlled trial, all three compounds were superior to placebo in improving erectile function in patients with ED. Doses three times a day for 30 days of trazodone (50 mg), ketanserin (20 mg) or mianserin (10 mg) resulted in improved erections and an increase in the frequency of successful intercourse in 65%, 20% and 32%, respectively, of the patients (placebo 13%). All drugs were well tolerated with moderate sedation, fatigue, vertigo and slightly blurred vision being the most frequent side effects. Due to the primary antidepressive and anxiolytic action of the drugs, the authors concluded that anti-serotoninergic agents might be beneficial in patients with psychogenic rather than organogenic impotence [11]. Nevertheless, the overall safety and efficacy of anti-serotoninergics in the treatment of ED remains to be assessed further in a larger groups of patients with different causes of ED.

Agents stimulating the activity of soluble guanylyl cyclase

The main intracellular receptor for nitric oxide (NO) is the soluble form of the enzyme guanylyl cyclase (sGC). This is a heterodimeric protein consisting of an α and ß subunit. Both subunits present a homologous domain which constitute the catalytic centre known to generate cyclic guanosine monophosphate (cGMP). The enzyme also contains a prosthetic heme attached to a histidine residue of the ß subunit which is essentially required for the activation of the enzyme by NO. Although the binding of NO occurs in the ß subunit, both subunits are required for the stimulation of enzyme activity [12,13]. Since the pharmacological activation of sGC has been recognized to have great potential for the treatment of a wide variety of diseases, several agents have been identified which have the ability to stimulate the enzyme. Classic NO donors (i.e. organic nitrates) may exert serious drawbacks, but compounds that can activate sGC in a manner independent from the release of NO offer an advance [14]. Such compounds have been developed recently by several pharmaceutical companies and are characterized as non-NO-based sGC activators due to a mechanism of action that involves the binding of the entire drug molecule to the heme moiety.

The prototype of non-NO-based sGC activators is YC-1, originally identified as a potent inhibitor of platelet aggregation [15]. The stimulating effect of YC-1 cannot be blocked by NO scavengers, indicating that the action of the drug is independent of NO. YC-1 has been shown to reverse the tension induced by norepinephrine of isolated rabbit corpus cavernosum and enhance the phasic relaxations induced by means of transmural electrical field stimulation (EFS) in rat corpus cavernosum. These effects were paralleled by an increase in tissue levels of cGMP. Injected intracavernously, YC-1 induced erections in the rat [16,17]. A group of non-NO-based sGC activators (BAY 41-2272, BAY 41-8543 and BAY 58-2667) developed by Bayer Pharmaceuticals, Germany, are considerably more potent than YC-1. Although the effects of BAY 41-2272 and BAY 41-8543 are dependent on the interaction with the heme moiety of sGC, BAY 58-2667 is independent of heme. Heme-dependent sGC activators stimulate sGC in a synergistic manner with NO and require the

presence of the heme group. Therefore, they are sensitive to blockade by sGC inhibitors such as the quinoxaline derivative ODQ. Only BAY 41-2272 has been investigated in erectile tissues. It brought about relaxation of rabbit and human cavernosal strips that had been contracted with phenylephrine and was found to be 32 times more potent than YC-1 and twice as potent as the NO donor spermine-NONate. Treating conscious rabbits with the compound intravenously and orally induced only weak penile erections, however, the efficacy of BAY 41-2272 was potentiated by simultaneously giving a NO donor [18–21].

Two other NO-independent sGC activators, A-344905 and A-350619, that have been developed by Abbott Laboratories, USA, have been shown to reverse the phenylephrine-induced contraction of isolated rabbit cavernosal strips with an EC_{50} of 17 μM and 14 μM, respectively. In the rat, both compounds induced penile rigidity when injected into the cavernous compartment and enhanced apomorphine-induced erections when given systemically [22,23].

Recently, another new class of compounds has gained interest among clinical researchers. These agents are exemplified by NO-releasing derivatives of phosphodiesterase (PDE) 5 inhibitors. The French company NicOx developed NCX 911, a NO-releasing derivative of sildenafil citrate. This product releases NO spontaneously in aqueous solutions and increases intracellular cGMP concentrations by activating sGC in the absence of endogenous NO and by inhibiting PDE5. NCX 911 was more potent than sildenafil in reversing the norepinephrine-induced tension of isolated human corpus cavernosum strips and enhancing the EFS-induced relaxation of the tissue. Sildenafil had only little effects on tissue cGMP in the absence of endogenous NO, but NCX 911 increased cGMP in a concentration-dependent manner [24]. In the anaesthetized male rat, the increase in intracavernous pressure induced by electrical stimulation of the cavernous nerve was enhanced after the intravenous injection of both sildenafil and NCX 911, whereas NCX 911 was found to be more potent [25].

Alpha adrenergic blockers (Phentolamine)

Penile flaccidity and detumescence in men is known to be mediated by postganglionic sympathetic nerve fibres and the binding of adrenergic transmitters to the numerous receptor subtypes of the α-adrenoceptor family, mainly the $alpha_1$ subtype, on the surface of arterial and cavernous smooth muscle cells. This keeps the penis in the flaccid state or, alternatively, makes the relaxed cavernous smooth muscle contract.

Erectile impotence is often reported to be associated with dysfunctions of the autonomic sympathetic control, and there is strong evidence that this may also include abnormalities in the central or peripheral release or degradation of adrenergic neurotransmitters [26,27]. Thus, partial blockade or withdrawal of the adrenergic influence on the corpus cavernosum may compensate for this imbalance in order to facilitate erection and to prolong erectile episodes. Systemic application of α-adrenergic antagonists can produce penile erection or priapism.

Phentolamine is an adrenergic antagonist that blocks α-adrenergic receptors with no specificity for either the α_1 or α_2 subtype. For more than 40 years, phentolamine has been approved in the main pharmaceutical markets for treating pheochromocytoma-related hypertension and dermal necrosis. Since 1984, phentolamine mesylate has been used for intracavernous injection or as a buccal formulation in the therapy of male erectile dysfunction [28,29]. A new oral formulation of the drug (Vasomax™), originally developed by Zonagen and licensed to Schering-Plough, was recently investigated in double-blind, placebo-controlled studies for safety and efficacy in the treatment of mild to moderate ED. In receptor binding studies using membrane preparations isolated from rabbit corpus cavernosum, phentolamine competitively displaced the specific α_1-receptor ligand prazosin and α_2-receptor ligand rauwolscine (α-yohimbine) [30]. The high affinity of phentolamine mesylate towards α_1-adrenergic and α_2-adrenergic receptors suggests that 30 min after the oral ingestion of 40 mg of the drug, the mean phentolamine plasma concentration (approx. 40–50 nM) ensures sufficient blockade of α-receptors in the corpus cavernosum penis, thereby resulting in the inhibition of sympathetic physiologic activity. More then 3800 subjects were evaluated in these studies using 40 mg and 80 mg phentolamine, which was effective in enhancing erectile function in the patients. Three to four times more patients who

received the drug than those who received placebo reported satisfaction with the medication. At a dose of 40 mg 55% and at one of 80 mg 60% of men were able to achieve vaginal penetration. An improvement in the erectile function score was reported by 40% of men who received the 40-mg dose and 53% of those who received the 80-mg dose. All trends of response were the same, regardless of any concomitant medication. Phentolamine was well tolerated with no serious adverse events observed. Even in patients with known cardiovascular diseases, the incidence of adverse events was not significantly different from the entire study group. The incidence of side effects at doses of 40 mg was <2% in the total patient population, with headache and rhinitis being most frequent (5.5% and 18.4%, respectively) [31,32]. Nevertheless, at the time of writing this, phase III trials on phentolamine mesylate in the US are still on hold because of reports that superphysiological doses of the drug may stimulate the proliferation of brown fat cells in rodents.

Melanocortin receptor agonists

Whether the hypothalamic-adrenal axis contributes to the maintenance of mammalian normal sexual function, especially in the control of sexual arousal, penile erection and seminal emission, has been discussed for more than two decades. The major effectors, melanocortins and glucocorticoids, have been suggested to elicit facilitatory effects on male sexual interest and activity [33,34]. The melanocortins alpha-melanocyte-stimulating hormone (α-MSH) and adrenocorticotropin (adrenocorticotropic hormone, ACTH) are known to regulate important homeostatic behaviours mediated by the hypothalamus and also to influence sexual function including penile erection and sexual motivation [35,36,37]. Melanocortins are believed to act on dopaminergic neurons located in hypothalamic pro-erectile centres, thus stimulating the central and spinal release of oxytocin.

The effects of melanocortins are mediated via binding to melanocortin receptors (MC-R, designated as MC1-R to MC5-R). These receptors have been identified in the skin and gastrointestinal tract as well as in the central nervous system and the reproductive tract of male and female mammals [38]. In particular the expression of MC5-R in peripheral tissues provides a relation to the central and peripheral control of sexual behaviour [39].

The influence of melanocortins on male sexual function is supported by the finding that treatment with ACTH 1-17, which is known to stimulate the adrenal production of cortisol by binding to specific receptor sites located in the zona fasciculata of the adrenal gland cortex, notably increased sexual performance in male patients affected by psychogenic ED [40]. Melanotan II, a synthetic cyclic heptapetide, known to act as a non-selective MC-R agonist, has been reported to induce erections in rodents, dogs, and humans [41]. A double-blind, placebo-controlled study showed that melanotan II given subcutaneously to men with organic and pyschogenic ED induced penile erections in the absence of visual or tactile sexual stimulation. The latency time to first erection ranged from 15–270 min, with a mean time of 115 min. The majority of erections, as assessed by means of real-time RigiScan, were considered to be sufficient for vaginal penetration. Moreover, an increase in sexual desire was reported by the patients. Statistically significant differences in erectile activity and sexual desire were found between patients who received either melanotan II or placebo. Moderate to severe nausea and yawning were the most common side effects. The incidence and severity of nausea was reduced with the second dose of the drug, indicating a first dose effect. No cardiovascular events were reported [42]. Although the addition of erotic stimuli may reduce the prolonged latency time for melanotan II and lead to more rapid erectile responses, the incidence of severe nausea (up to 15%) and mode of drug application raised questions about the potential clinical use of the drug. Modification of drug delivery may enhance its acceptability for clinical use.

More recently, the erectogenic potential of PT 141, a cyclic heptapeptide melanocortin analogue, was shown following intranasal application of the drug to healthy men and patients with ED responding to Viagra. The erectile response to 7 mg PT 141 was significant compared with placebo, with the onset of the erection occurring within approximately 30 min. The drug was well tolerated, with flushing being the most frequent side effect [43]. In conclusion, the mechanism of action of

melanocortins may be clinically advantageous in men with ED. As a number of melanocortin agonists have been synthesized [44], their investigation in clinical trials would be of particular interest and they may in future be seen as an effective treatment for ED.

Growth factors and somatomedins: human growth hormone (GH)

Although not considered a classic sex hormone, GH has been suggested to be involved in sexual maturation and to play a regulatory role in male reproductive function. This hormone not only mediates secretion of the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) but also has a physiological significance in early testosterone stimulation. Growth hormone is also produced extrapituitary in gonadal and mammary tissues, indicating that it has a local autocrine or paracrine action in the reproductive tract. Deficiency of GH can cause fatigue, loss of sexual desire and erections, oligospermie or azoospermie [45,46,47]. The biological effects of GH have been hypothesised to include stimulation of endothelial NO formation mediated by the peptide insulin-like growth factor (IGF-1). Some evidence from a rat model supports this hypothesis; treating the rats with GH enhanced the regeneration of nitric oxide synthase (NOS)-containing nerve fibres in the intracavernosal and dorsal penile nerves after unilateral cavernous nerve neurotomy [48]. The investigators supposed that GH affected this regeneration either by a direct anabolic action or by stimulating IGF-1 synthesis.

Another study reported that treating GH-deficient patients with recombinant GH (rGH) resulted in an increase in systemic NO metabolites, enhanced urinary cGMP excretion and had beneficial effects on the cardiovascular system [49]. Physiological doses of recombinant rGH have been shown to elicit dose-dependent relaxation of isolated human corpus cavernosum strips. This relaxing potency was paralleled by a several-fold increase in tissue levels of cGMP [50]. Recent results from our laboratory showed that the potency of GH to stimulate cGMP was more sensitive to the sGC-inhibitor ODQ than to the NOS-inhibitor L-NOARG, indicating an effect of the hormone on the activity of sGC. Concentrations of GH from 1–100 nM increased the phasic relaxation of isolated human corpus cavernosum elicited by means of EFS. These effects were similar to those exerted by the PDE5 inhibitor sildenafil citrate (Viagra™). Moreover, GH in concentrations of 0.1, 0.5 and 1 μM was able to reverse in part the inhibition by L-NOARG (10 μM) of the EFS-induced phasic relaxation of isolated human erectile tissue [51]. Serum levels of GH significantly increased in the systemic and cavernous blood of healthy men with the onset of sexual arousal, when the flaccid became tumescent. In contrast, this increase in GH was found to be negligible in patients with an organogenic cause of ED [52]. Screening of 161 consecutive patients presenting with ED revealed that most had serum levels of IGF-1 significantly below the normal age-adapted values [53]. These data were considered evidence that GH might be of major importance in the maintenance of male erectile capability. As mentioned above, a vast body of literature indicates that the hormone may exert its effect either through the stimulation of cGMP production, the IGF-1-mediated preservation of endothelial and neuronal NOS protein expression or the augmentation of androgenic action in target tissues, including the male reproductive and genital tract.

Controversy surrounds whether treating older men with GH reverses or prevents transient impairments in body functions commonly associated with ageing. Some studies indicate that GH given long term to healthy older men with IGF-1 concentrations below those found in young men has a beneficial effect on general well-being, bone density, body composition and body function, but other investigators were unable to determine any changes in muscle strength, exercise endurance or overall quality of life [54,55]. Unfortunately, the studies did not assess libido, sexual desire and sexual function of the male volunteers before and after the weekly treatment with GH. An important consideration is whether long-term treatment with GH is potentially harmful especially in increasing the risk of diabetes mellitus and cancer in elderly men as older age is associated with an increased incidence of such diseases. Although no causal relation of GH and IGF-1 for diabetes and prostate cancer has been proved, a degree of concern remains about giving older men GH [56,57,58].

Several over-the-counter suppliers offer various oral formulations of GH. As GH is a peptide and, therefore, subject to degradation by

gastric acid, to date, none of the formulations have been shown to be efficacious. Some pharmaceutical companies are making serious efforts to characterize new GH secretagogues and develop galenic compositions feasible for oral or nasal application. Among these compounds are NN 703, NNC 26-0194 and NNC 26-0235, all of which are derivatives of the peptidergic GH secretagogue ipamoreline, as well as the GH-releasing peptide (GHRP) mimetic MK-677. NN 703 and MK-677 have been shown to possess sufficient bioavailability and elevate plasma concentrations of GH or IGF-1 after oral physiological doses [59,60]. Other compounds supposed to stimulate the release of GH are branched-chain amino acids. The physiological NO-precursor L-arginine is known to increase serum concentrations of GH transiently but only for less than one hour. Interestingly, giving L-arginine orally has been reported to have some beneficial effects on erectile function in patients with ED [61]. As to whether the amino acid exerts this effect through the stimulation of NO-formation by neuronal and endothelial NOS and, finally, the NO-mediated cGMP-production by sGC or by triggering the release of GH remains to be clarified.

In conclusion, the studies which have so far addressed the putative relation between GH, corpus cavernosum physiology and male sexual function should be viewed as an exciting and important beginning. It remains to be evaluated whether GH or GH secretagogues can consistently increase the endogenous production of cGMP and are efficacious and safe in men with an organogenic cause of ED.

Conclusion

Based on the more extensive knowledge and the understanding of the physiological mechanisms regulating male erectile function, orally delivered drugs have been established as a logical and straightforward pharmacological approach for treating male ED. Increased public awareness in this field will undoubtedly promote the identification of new compounds that might be effective in the treatment of this sexual disorder [62,63,64]. Due to the unending charge to conceive a first-line treatment more advanced than the previous options and with superior efficacy and safety, research efforts will continue to offer a promising future for the therapy of ED. Although the ideal drug for the treatment of ED should somehow involve the NO/cGMP cascade, upcoming strategies will also take into account compounds modulating signal transduction mediated by cyclic adenosine monophosphate, as well as combining agents to affect multiple peripheral intracellular targets (e.g. a drug that combines PDE5 inhibitory and NO-releasing properties). Future orally delivered selective drugs will be efficacious in terms of maximizing erectile function and exert limited systemic adverse events.

Conflict of interest

None of the authors has declared a financial interest in a company which manufactures, distributes or is developing drugs of the type discussed in the article.

This article is the third in a series of articles on erectile dysfunction and the second of a two-part overview of the current status of specific compounds that are or will be important in oral pharmacotherapy of male ED. Further articles in the series will continue to take up specific areas of erectile dysfunction and will be published in future issues of the journal.

References

[1] Rehman J, Kaynan A, Christ G, Valcic M, Maayani S, Melman A. Modification of sexual behaviour of Long-Evans male rats by drugs acting on the 5-HT_{1A} receptor. Brain Res 1999;821:414–25.

[2] Tang Y, Rampin O, Calas A, Facchinetti P, Guiliano F. Oxytocinergic and serotonergic innervation of identified lumbosacral nuclei controlling penile erection in the male rat. Neuroscience 1998;82:241–54.

[3] Witt MA, Grantmyre JE. Ejaculatory failure. World J Urol 1993;11:89–95.

[4] Svensson L, Hansen S. Spinal monoaminergic modulation of masculine copulatory behaviour in the rat. Brain Res 1984;302:315–21.

[5] Gorzalka BB, Mendelson SD, Watson NV. Serotonin receptor subtypes and sexual behaviour. Ann NY Acad Sci 1990;600:445–6.

[6] Aizenberg D, Gur S, Zemishlany Z, Granek M, Jeczmien P, Weizman A. Mianserin, a 5-$HT_{2A/2C}$ and alpha$_2$ antagonist, in the treatment of sexual dysfunction induced by serotonin reuptake inhibitors. Clin Neuropharmacol 1997;20:210–4.

[7] Ückert S, Fuhlenriede MH, Becker AJ, Stief CG, Scheller F, Knapp WH, et al. Is there an inhibitory role of cortisol in the mechanism of male sexual arousal and penile erection? Urol Res 2003;31:402–6.
[8] Lal S, Rios O, Thavundayil JX. Treatment of impotence with trazodone: a case report. J Urol 1990;143:819–20.
[9] Adaikan PG, Ng SC, Chan C, Ratnam SS. Oral trazodone in the treatment of total secondary impotence in a diabetic patient. Br J Urol 1991;63:771–2.
[10] Horby-Petersen J, Nielsen FC, Schmidt PF. Penile tumescence after injection of a serotonin antagonist (ketanserin). Br J Urol 1988;62:277–8.
[11] Kurt Ü, Özkardes H, Altug U, Germiyanoglu C, Gürdal M, Erol D. The efficacy of antiserotoninergic agents in the treatment of erectile dysfunction. J Urol 1994;152:407–9.
[12] Denninger JW, Marletta MA. Guanylate cyclase and the NO/cGMP signaling pathway. Biochim Biophys Acta 1999;1411:334–50.
[13] Lee YC, Martin E, Murad F. Human recombinant soluble guanylyl cyclase: expression, purification, and regulation. Proc Natl Acad Sci USA 2000;97:10763–8.
[14] Hobbs AJ. Soluble guanylate cyclase: an old therapeutic target re-visited. Br J Pharmacol 2002;136:637–40.
[15] Friebe A, Müllershausen F, Smolenski A, Walter U, Schultz G, Koesling D. YC-1 potentiates nitric oxide- and carbon monoxide-induced cyclic GMP effects in human platelets. Mol Pharmacol 1998;54:962–7.
[16] Mizusawa H, Hedlund P, Brioni JD, Sullivan JP, Andersson K-E. Nitric oxide independent activation of guanylate cyclase by YC-1 causes erectile responses in the rat. J Urol 2002;167:2276–81.
[17] Nakane M, Hsieh G, Miller LN, Chang R, Terranova MA, Moreland RB, et al. Activation of soluble guanylate cyclase causes relaxation of corpus cavernosum tissue: synergism of nitric oxide and YC-1. Int J Impot Res 2002;14:121–7.
[18] Bischoff E, Schramm M, Straub A, Feurer A, Stasch JP. BAY 41-2272: a stimulator of soluble guanylyl cyclase induces nitric oxide dependent penile erection. Urology 2003;61:464–7.
[19] Straub A, Stasch JP, Alonso-Alija C, Benet-Buchholz I, Ducke B, Feurer A, et al. NO-independent stimulators of soluble guanylate cyclase. Bioorg Med Chem Lett 2001;11:781–4.
[20] Stasch JP, Dembowsky K, Perzborn E, Stahl E, Schramm M. Cardiovascular actions of a novel NO-independent guanylyl cyclase stimulator, BAY 41-8543: in vivo studies. Br J Pharmacol 2002;135:344–55.
[21] Stasch JP, Alonso-Alija C, Apeler H, Dembowsky K, Feurer A, Minuth T, et al. Pharmacological actions of a novel NO-independent guanylyl cyclase stimulator, BAY 41-8543: in vitro studies. Br J Pharmacol 2002;135:333–43.
[22] Moreland RB, Hsieh GC, Nakane M, Miller LN, Chang R, Kolasa T, et al. Novel soluble guanylate cyclase activators A-344905 and A-305619 activate sGC in vitro and facilitate penile erection in rats. J Urol 2002;167(No. 4, Suppl):S938.
[23] Miller LN, Nakane M, Hsieh GC, Chang R, Kolasa T, Moreland RB, et al. A-350619: a novel activator of soluble guanylyl cyclase. Life Sci 2003;72:1015–25.
[24] Seidler M, Ückert S, Waldkirch E, Stief CG, Oelke M, Tsikas D, et al. In vitro effects of a novel class of nitric oxide (NO)-donating compounds on isolated human erectile tissue. Eur Urol 2002;42:523–8.
[25] Riffaud JP, Bernarbe J, Giuliano F, Jones R, Jeremy J. Pharmacological profile of sildenafil nitrate (NCX 911) in various models of penile erection. Inflammation Res 2001; 50(Suppl 3):S84.
[26] Kuensch E, Reiners K, Müller-Mattheis V, Strohmeyer T, Ackermann R, Freund H-J. Neurological risk profile in organic erectile dysfunction. J Neurol Neurosurg Psych 1992;55:275–81.
[27] Becker AJ, Ückert S, Stief CG, Scheller F, Knapp WH, Hartmann U, et al. Cavernous and systemic plasma levels of norepinephrine and epinephrine during different penile conditions in healthy males and patients with erectile dysfunction. Urology 2002;59:281–6.
[28] Krane RJ, Goldstein I, Saenz de Tejada I. Medical progress: Impotence. N Engl J Med 1989;321:1648–59.
[29] Wagner G, Lacy S, Lewis R, Zorgniotti A, Buccal phentolamine – a pilot trial for male erectile dysfunction at three separate clinics. Int J Impot Res 1994;6(Suppl 1):D78.
[30] Traish A, Gupta S, Gallant C, Huang YH, Goldstein I. Phentolamine mesylate relaxes penile corpus cavernosum tissue by adrenergic and non-adrenergic mechanisms. Int J Impot Res 1998;10:215–23.
[31] Goldstein I, the VASOMAX Study Group. Efficacy and safety of oral phentolamine (VASOMAX) for the treatment of minimal erectile dysfunction. J Urol 1998;159(Suppl): 240.
[32] Goldstein I. First-line therapy: alpha-adrenergic receptor antagonists – clinical. Podium presentation, Masters Course in Erectile Dysfunction, Boston MA, USA, 29.06. – 30.06.1999, Coordinated by the Ithaka Center for Postgraduate Medical Education 1999.
[33] Borg KE, Esbenshade KL, Johnson BH. Cortisol, Growth hormone, and testosterone concentrations during mating behaviour in bulls and boars. J Anim Sci 1991;69:230–40.
[34] Penson DF, Ng C, Rajfer J, Gonzales-Cavidad NF. Adrenal control of erectile function and nitric oxide synthase in the rat penis. Endocrinology 1997;138:3925–32.
[35] Argiolas A, Melis MR, Gessa GL. Yawning and penile erection: central dopamine – oxytocin – adrenocorticotropin connection. Ann NY Acad Sci 1988;525:330–7.
[36] Vergoni AV, Bertolini P, Mutulis F, Wikberg JE, Schioth HB. Differential influence of a selective melanocortin MC4 receptor antagonist (HS014) on melanocortin-induced behavioural effects in rats. Eur J Pharmacol 1998;362:95–101.
[37] Bretto LA, Gorzalka BB. Melatonin enhances sexual behaviour in the male rat. Physiol Behav 2000;68:483–6.
[38] Mountjoy KG, Robbins LS, Mortrud MT, Cone RD. The cloning of a familiy of genes that encode the melanocortin receptors. Science 1992;257:1248–51.
[39] van der Kraan M, Adan RA, Entwistle ML, Gispen WH, Burbach JP, Tatro JB. Expression of melanocortin-5 receptor in secretory epithelia supports a functional role in exocrine and endocrine glands. Endocrinology 1998;139:2348–55.
[40] Isidori A, Di Luigi L, Conte D. ACTH 1 –17 and sexual behaviour. Ric Clin Lab 1984;14:247–51.
[41] Wessells H, Fuciurelli K, Hansen J, Hadley ME, Hruby VJ, Dorr RT, et al. Synthetic melanotropic peptide initiates erections in men with psychogenic erectile dysfunction: a double-blind, placebo-controlled cross-over study. J Urol 1998;160:389–93.
[42] Wessells H, Levine N, Hadley ME, Dorr R, Hruby VJ. Melanocortin receptor agonists, penile erection, and sexual motivation: human studies with Melanotan II. Int J Impot Res 2000;12(Suppl 4):S74–9.
[43] Diamond LE, Earle DC, Rosen RC, Willett MS, Molinoff PB. Double-blind, placebo-controlled evaluation of the safety, pharmacokinetic properties and pharmacodynamic effects of intranasal PT 141, a melanocortin receptor agonist, in healthy males and patients with mild to moderate erectile dysfunction. Int J Impot Res 2004;16:51–9.
[44] Levine N, Sheftel SN, Eytan T, Dorr RT, Hadley ME, Weinrach JC, et al. Induction of skin tanning by subcutaneous adminstration of a potent synthetic melanotropin. JAMA 1991;266:2730–6.
[45] Hull KL, Harvey S. Growth hormone: a reproductive endocrine-paracrine regulator. Rev Reprod 2000;5:175–82.
[46] Chandrashekar V, Bartke A. The role of growth hormone in the control of gonadotropin secretion in adult male rats. Endocrinology 1998;139:1067–74.
[47] Juul A, Andersson AM, Pedersen SA, Jorgensen JO, Christiansen JS, Groome NP, et al. Effects of growth hormone replacement therapy on IGF-related parameters and on pituitary-gonadal axis in GH-defi-

cient males. A double-blind, placebo-controlled crossover study. Horm Res 1998;49: 269–78.
[48] Jung GW, Spencer EM, Lue TF. Growth hormone enhances regeneration of nitric oxide synthase-containing penile nerves after cavernous nerve neurotomy in rats. J Urol 1998;160:1899–904.
[49] Böger RH, Skamira C, Bode-Böger SM, Brabant EG, von zur Mühlen A, Frölich JC. Nitric oxide may mediate the hemodynamic effects of recombinant growth hormone in patients with acquired growth hormone deficiency. J Clin Invest 1996;98:2706–13.
[50] Becker AJ, Ückert S, Stief CG, Truss MC, Machtens S, Scheller F, et al. Possible role of human growth hormone in penile erection. J Urol 2000;164:2138–42.
[51] Ness BO, Ückert S, Becker AJ, Stief CG, Scheller F, Knapp WH, et al. unpublished data 2004.
[52] Becker AJ, Ückert S, Stief CG, Scheller F, Knapp WH, Hartmann U, et al. Serum levels of human growth hormone during different penile conditions in the cavernous and systemic blood of healthy men and patients with erectile dysfunction. Urology 2002;59:609–14.
[53] Becker AJ, Ückert S, Stief CG, Jonas U. Growth hormone, somatomedins and men's health. The Aging Male 2002;5:258–62.
[54] Rudman D, Feller AG, Nagraj HS, Gregans GA, Lalitha PY, Goldberg AF, et al. Effects of growth hormone in men over 60 years old. N Engl J Med 1990;323:1–6.
[55] Papadakis MA, Grady D, Black D, Tierney MJ, Gooding GA, Schambelan M, et al. Growth hormone replacement in older men improves body composition but not functional ability. Ann Intern Med 1996; 124:708–16.
[56] Jeffcoate W. Can growth hormone therapy cause diabetes? Lancet 2000;355:589–90.
[57] Monson JP, Bengtsson BA, Abs R, Feldt-Rasmussen U, Wüster C. Can growth hormone therapy cause diabetes? Letter to the Editor Lancet 2000;355:1728.
[58] Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, et al. Plasma insulin-like growth factor 1 and prostate cancer risk: a prospective study. Science 1998;279:563–6.
[59] Hansen BS, Raun K, Nielsen KK, Johansen PB, Hansen TK, Peschke B, et al. Pharmacological characterizaion of a new oral GH secretagogue, NN 703. Eur J Endocrinol 1999;141:180–9.
[60] Chapman IM, Pescovitz OH, Murphy G, Treep T, Cericho KA, Krupa D, et al. Oral administration of growth hormone (GH) releasing peptide mimetic MK-677 stimulates the GH/insulin-like growth factor I axis in selected GH-deficient adults. J Clin Endocrinol Metab 1997;82:3455–63.
[61] Zorgniotti AW, Lizza EF. Effect of large doses of the nitric oxide precursor L-arginine on erectile dysfunction. Int J Impot Res 1994; 6:33–5.
[62] Ho GD, Silverman L, Bercovici A, Puchalski C, Tulshian D, Xia Y, et al. Synthesis and evaluation of potent and selective cGMP-phosphodiesterase inhibitors. Bioorg Med Chem Lett 1999;9:7–12.
[63] Rotella DP, Sun Z, Zhu J, Krupinski J, Pongrac R, Selinger L, et al. Optimization of substituted N-3-benzylimidazoquinazolinone sulfonamides as potent and selective PDE5 inhibitors. J Med Chem 2000;43: 5037–43.
[64] Guay D, Hamel P, Blouin M, Brideau C, Chan CC, Chauret N, et al. Discovery of L-791.943: a potent, selective, non-emetic and orally active phosphodiesterase 4 inhibitor. Bioorg Med Chem Lett 2002;12:1457–61.