BRIEF REVIEW
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Erectile dysfunction and cardiovascular disease

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Στυτική δυσλειτουργία και καρδιαγγειακά νοσήματα

Περίληψη στο τέλος του άρθρου

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Introduction

Although erectile dysfunction (ED) is not life threatening, this common problem can significantly affect the quality of life and psychological well being.[1] The Massachusetts Male Aging study, on 1,290 men aged 40–70 years, showed that 52% of men reported some degree of ED (17.1% mild, 25.2% moderate, 9.6% total).[2] ED becomes more common with advancing age and since the proportion of the older population is increasing, the prevalence of ED should also rise.[3] Data extrapolated from the USA in the 1940s estimates that currently around 7 to 10 million men in that country have ED.[4] Because ED is a sensitive issue it is likely that its prevalence is under-reported[4] but despite this, ED results in more than 400,000 outpatient visits and 30,000 hospital admissions in the USA per year.[5] Epidemiological studies carried out in Europe have demonstrated that 39% of men aged 18–70 years in France have some degree of ED and 11% have total ED[6] and in the UK, an estimated 17–19% of men are thought to suffer from ED.[7]

Nitric oxide and penile erectile physiology

Penile erection is a hemodynamic process, involving increased arterial inflow and restricted venous outflow, coordinated by corpus cavernosum smooth muscle relaxation.[8] Although this process is generally accepted to be under neuroregulatory control,[8–20] biochemical mediators released locally from the endothelium and/or smooth muscle also participate in initiating and maintaining erection.[21–23] Nitric oxide (NO), which is produced both in cavernosal nerves and endothelium, has recently been recognized to play a key role in the physiology of penile erection.[8–23]

In this brief review we consider the evidence showing that men with ischemic heart disease (IHD) have a high prevalence of ED. We also consider that this association may be related to the fact that the same risk factors (e.g. hypertension, dyslipidemia, smoking and diabetes) predict both erectile dysfunction and vascular disease.

The association between ED and IHD raises the important question of whether vasculogenic ED is yet an-

other manifestation of atherosclerosis. Impaired NO activity may provide a unifying explanation for such an association. There is convincing evidence that during erection the local release of NO and/or related factors produces relaxation of the corpus cavernosum.[8–23] Nonadrenergic, noncholinergic (NANC) nerve-mediated NO release appears to be the most important factor with respect to cavernosal smooth muscle relaxation.[9–20] However, the erectile process may, at least in part, be acetylcholine (Ach)-mediated in the human and rabbit corpus cavernosum.[21–23]

To date, most of studies support the concept that NO derived from the autonomic innervation of the penis operates locally as a post-ganglionic neurotransmitter of NANC-mediated penile erection.[8–20,24–32] Following its synthesis and release from nerve terminals, NO activates guanylate cyclase in vascular and trabecular smooth muscle.[22] The increased intracellular accumulation of cyclic guanosine monophosphate (cGMP) is then believed to cause corporeal smooth muscle relaxation via a chemical cascade.[26] Cyclic nucleotide phosphodiesterase enzymes (PDEs) present in the corpus cavernosum regulate the activity of cGMP.[27,28] Experimental studies have shown that PDE III and V isoenzymes both play an important role in cavernosal smooth muscle tone.[27,28] The inhibition of PDE V activity forms the basis of treating ED with sildenafil (Viagra™).[27,28]

Molecular mechanisms and the risk factors for ED

1. Diabetes mellitus (DM). DM represents one of the major organic causes of ED. As many as 50% of men with DM suffer from ED.[33] It is also well established that DM is associated with an increased incidence of vascular events.[32] A link between the pathogenesis of ED and decreased local NO activity was suggested because in isolated corpus cavernosum strips from diabetic patients with ED, both neurogenic and endothelium-dependent relaxations were impaired.[34] Similar findings were also apparent in rabbits with alloxan-induced DM.[35] Reduced relaxation to electrical field stimulation in cavernosal tissue taken from diabetic patients with ED has also been demonstrated.[36] This was associated with a lack of NO production (measured as the formation of nitrite) and not with the inability of the smooth muscle to relax.[36] Further insight into the mechanisms involved was provided by studies which showed a significant increase in NO synthase (NOS) binding sites (putative receptors) in rat cavernosum two months post-induction of DM.[37] This finding suggests that an impairment in NO bioavailability, either due to a lack of the substrate L-arginine, due to NO quenching [e.g. by advanced glycosylation end-products (AGEs)][38] or via inactivation by superoxide, plays a role in the pathogenesis of ED associated with DM.

Another link between ED and DM is the finding of raised circulating levels of endothelin-1 (ET-1),[39–41] a peptide belonging to a family of potent vasoconstrictors. To date, two major ET receptors have been identified and cloned: ET_A and ET_B.[42] ET-1 is considered a physiological antagonist of NO.[43,44] Several studies have indicated the potential importance of ET-1 in the modulation of corpus cavernosum smooth muscle tone.[39,45,46] Other studies have suggested that ET-1 may play a role in the development of MD.[47] Moreover, the plasma levels of ET-1 are higher in diabetics with ED than in diabetics without ED.[47]

Animal and human corpus cavernosum produces a range of eicosanoids including prostaglandins (PGs) $PGF_{2\alpha}$, PGE_2, PGI_2 and TXA_2.[48–51] Muscarinic (but not adrenergic) stimulation of both animal and human penile tissue results in the release of PGI_2.[49,50] Since PGI_2 is a vasodilator, it has been proposed that the release of this eicosanoid may be involved in the vasodilatory phenomenon associated with erection.[53] As a potent inhibitor of platelet adhesion and aggregation, the acute release of PGI_2 may also protect the penis from thrombosis during engorgement.[53] DM is associated with abnormal PG synthesis.[54–56] Streptozotocin-induced DM in the rat results in a marked inhibition of PGI_2 synthesis by both penile and vascular tissues.[57] Similarly, as we recently demonstrated in alloxan-induced diabetic rabbits there is impairment of cavernosal PGI_2 formation.[58] These effects relate to the duration rather than the severity of DM, thus mirroring the human situation.[59] The reduced PGI_2 synthesis reverts to normal following long-term administration of insulin.[57] A reduction in PGE_1 receptors has recently been reported in penile tissue obtained from diabetic men.[60]

2. Hypercholesterolemia. Hypercholesterolemia is a recognized risk factor for both vasculogenic ED[61,62] and IHD. Studies using a genetic rabbit model of hypercholesterolemia suggest that this lipid abnormality may account for ED because of changes in penile ET receptor distribution. These changes may, in turn, influence NOS-dependent mechanisms.[63] Experiments using cholesterol-fed rabbits have demonstrated that inhibition of NO synthesis promotes the development of atheroma-like lesions, whereas supplementation with L-arginine prevents these changes.[64]

It has been demonstrated that high-density lipoprotein (HDL) decreases the risk of both ED and IHD,[62] a fur-

ther similarity between the risk factors for ED and IHD. There is also evidence that decreased cholesterol increases arterial vasodilator activity[65] as well as cavernosal relaxation.[7]

3. Hypertension. Hypertension is also associated with both IHD and ED.[61] Decreased endothelium-dependent relaxation of isolated blood vessels has been described in experimental animal models of systemic and pulmonary hypertension.[66] These findings have been ascribed to either an attenuation of NO activity or augmented elaboration of an endothelium-derived contracting factor. More definitive date for a primary role of NO in the regulation of blood pressure has been shown in a mouse model with inactivation of the eNOS gene.[67] This impairment of endothelial NO bioavailability could be one explanation why hypertension is a risk factor for vasculogenic ED.[61]

Studies have suggested that ET-1 may have a role in the development of hypertension[68,69] as well as DM,[47] both of which are cardiovascular risk factors that are also associated with ED.[33–38,61,70] ET-1 potentiates the contractile response of vascular smooth muscle to other spasmogens.[71–73] Therefore, the physiological relevance of ET-1 may be related to its ability to augment the contractile responses of other vasomodulators present in the human corpus cavernosum.

The link between hypertension and ED is illustrated by abnormal penile vascular responses, as shown by dynamic testing (e.g. using papaverine and duplex sonography).[70] Hypertension acts synergistically with other vascular risk factors (e.g. DM and smoking) in terms of increasing the probability of ED.[70] Hypertension-related ED could also result from the use of certain antihypertensive agents (e.g. thiazides or ß-blockers). In contrast, doxazosin, a selective α_1-antagonist, used in the treatment of mild hypertension, has been shown to have the lowest incidence of ED in a trial assessing the treatment of mild hypertension,[74] where its effect did not differ significantly from that of placebo.

4. Smoking. Smoking is a risk factor for both atherogenesis and ED.[59,60] Smoking precipitates a number of acute changes which can affect normal erectile function, including impaired penile blood flow.[75,76] Cigarette smoking results in a transient increase in blood levels of the catecholamines, adrenaline and noradrenaline,[60] effects which appear to be mediated by nicotine.[77] As α-adrenoreceptor activation is associated with detumescence, this release of catecholamines may compromise normal erectile function. Smoking also produces profound acute morphological alterations in the vascular endothelium and enhances platelet and leukocytes adhesion to blood vessel walls.[78] Adherent platelets and leukocytes are activated to release a plethora of vasoconstrictors such as TXA_2, leukotrienes and serotonin[79] which could contribute further to ED.

Apart from the acute effects on the vascular system, the chronic consequence from smoking of vascular disruption leads to an increased risk of atherosclerosis.[60] This in turn leads to ED through atheroma formation in the pudendal arteries and possibly from altered function of the penile corporal smooth muscle itself.

5. Aging. Increasing age correlates with altered NO synthesis and erectile responses in the rat penis.[80] This could be one explanation for the increasing incidence of ED with aging in man.[80]

6. Radiation effects. Radiation has been shown to reduce the number of penile NOS containing nerves in the rat, possibly providing an explanation for the development of ED in men following pelvic irradiation.[81]

ED and IHD: Does defective NO activity contribute to the pathogenesis of both conditions?

As discussed above, numerous studies have shown that IHD and ED share common risk factors.[61,62] More recently, preliminary studies suggest that fibrinogen[82] and lipoprotein are risk factors for ED as well as for IHD. The long-term follow up of the Massachusetts Male Aging epidemiological study concluded that the risk of moderate or complete ED in patients with cardiovascular risk factors was 31%, higher than in an age-matched disease free control cohort in which the incidence was 19.6%.[39] It may also be relevant that the risk factors for IHD and ED behave synergistically in both conditions.[61]

Of equal interest are studies which show that the extent of IHD is related to the risk of concomitant ED. Two studies have shown a significant correlation between the presence of vasculogenic ED and clinically evident or subclinical IHD.[83,84] A significant correlation was reported between ED and the number of coronary vessels occluded on angiography[83] and patients with severe arteriogenic ED (assessed by duplex sonography) were shown to have a 16% risk of suffering from severe, although asymptomatic, IHD.[84]

Alterations in the endothelial L-arginine-NO pathway have been demonstrated in both atherosclerotic and hypercholesterolemic coronary arteries of humans and in animal models.[85–89] These studies support the concept that there is a reduction in NO bioavailability in these conditions. These findings are similar to those observed in the penile L-arginine-NO pathway and support the

concept that vasculogenic changes in the penile vascular bed in ED mirror those in the coronary arteries.

The role of NANC-mediated NO release in the coronary circulation is unclear, though NANC nerves have been implicated in coronary blood flow regulation.[90] It has been found that NANC-mediated NO production causes vasodilation of human cerebral arteries,[91] bovine basilar arteries[92] and canine superficial temporal arteries,[93] supporting a regulatory role in these vascular beds.

We have recently demonstrated that in the Watanabe rabbit model there is a significant decrease in ET_B-receptor binding sites in corpus cavernosum tissue compared with age-matched healthy controls.[63] This reduction, in part, involved endothelial ETB receptors[63] which have been shown in other vascular beds to mediate ET-1-induced vasorelaxation by stimulating NO formation.[94–96] However, the role of the ET_B receptor in the corpus cavernosum remains unclear and further studies are awaited.

Hence, it appears that normal erectile function involves a delicate balance between vasodilating and vasoconstricting factors. When this balance is disrupted, erectile dysfunction may result. ED and ischemic heart disease may not occur in the same patients by coincidence but may have common etiological factors. Consequently, medical practitioners who treat ED need to be aware of the possibility of underlying IHD and its clinical relevance in terms of "whole patient management".

Conclusions

NO plays a major role in the physiological regulation of penile erection, eliciting effects through the activation of guanylate cyclase and the subsequent production of cGMP. Impaired NO activity appears to play an important role in the pathogenesis of ED. This impaired NO activity may be similar to that which occurs in other forms of vascular disease or in the presence of cardiovascular risk factors (e.g. dyslipidemia, diabetes, smoking and hypertension).

The recent development of an effective, orally active, type V PDE inhibitor, sildenafil (Viagra) provides a novel method of therapy for patients with ED. It achieves this by inhibiting the hydrolysis of cGMP, produced via the L-arginine-NO pathway.

Further research in this area is needed to determine the precise pathophysiological role of NO, endothelin and possibly other mediators in this organ. This work may also provide further insights into the pathogenesis of cardiovascular diseases in general.

ΠΕΡΙΛΗΨΗ

Στυτική δυσλειτουργία και καρδιαγγειακά νοσήματα

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Στους ασθενείς με ισχαιμική καρδιοπάθεια (ΙΚ) παρατηρείται αυξημένη επίπτωση στυτικής δυσλειτουργίας (ΣΔ). Η συσχέτιση αυτή μπορεί να αποδοθεί στους παράγοντες κινδύνου, που είναι κοινοί και στις δύο καταστάσεις (π.χ. υπέρταση, δυσλιπιδαιμία, διαβήτης, κάπνισμα). Η δραστηριότητα του οξειδίου του αζώτου (ΝΟ) στους ιστούς του πέους και των αγγείων επηρεάζεται αρνητικά από αυτούς τους παράγοντες και, κατά συνέπεια, οι διαταραχές της είναι πιθανό να διαδραματίζουν παθογενετικό ρόλο, τόσο στη ΣΔ, όσο και στην ΙΚ. Οι διαταραχές της ΝΟ-δραστηριότητας, σε συνδυασμό με διαταραχές της σύνθεσης των εικοσανοειδών και την αύξηση της συγκέντρωσης της κυκλοφορούσας ενδοθηλίνης-1, ενδέχεται να αποτελούν εκδήλωση ενός ενιαίου βιοχημικού μηχανισμού, ο οποίος ευθύνεται για τη συσχέτιση της ΙΚ με τη ΣΔ. Η συνέχιση της έρευνας σ' αυτή την περιοχή είναι πιθανό να συμβάλει στην κατανόηση της παθογένειας των καρδιαγγειακών νοσημάτων, γενικώς.

Λέξεις ευρετηρίου: Ενδοθηλίνη, Καρδιαγγειακά νοσήματα, Οξείδιο του αζώτου, Σακχαρώδης διαβήτης, Στυτική δυσλειτουργία, Υπέρταση, Υπερχοληστερολαιμία

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