Review

Platelets, oxidant stress and erectile dysfunction: an hypothesis

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1. Introduction

The successful use of sildenafil (Viagra\textsuperscript{w}) to treat vasculogenic erectile dysfunction (VED) has heightened awareness of the widespread prevalence of this disorder [1–3]. Sildenafil acts through the augmentation of nitric oxide (NO) actions on vascular/corpus cavernosal smooth muscle cell relaxation [1–4] (Fig. 1). Thus, the therapeutic use of sildenafil has also highlighted the central role played by NO in mediating normal erection and in the pathogenesis of VED. Nevertheless, we still know little about the basic pathophysiology of VED. Since prevention is preferable to cure, it is imperative to improve our understanding of the pathophysiology of VED. In this brief review, we suggest that another major consequence of diminished NO formation is the increased adhesion of platelets and leukocytes, in particular neutrophils, which may counter erection through release of vasoconstrictors, superoxide and other oxygen free radicals. We also suggest that erection itself may trigger events that contribute to exacerbation of the disorder in the long-term, again through the adhesion of platelets and leukocytes.

2. Erectile dysfunction, vascular disease and oxidant stress

Patients with vascular disease are at a greater risk of developing VED [5–9]. Similarly, the risk factors for atherosclerosis (diabetes mellitus, hyperlipidaemia, age and smoking) are also risk factors for VED [5–9]. These risk factors act synergistically to augment VED as they do for atherosclerosis. Common to both the pathophysiology of VED and atherosclerotic disease is endothelial dysfunction, in particular the release and actions of NO [7,10–15]. In both patients with VED and in laboratory animal models of VED, impaired NO release by non-adrenergic, non-cholinergic (NANC) fibres and the endothelium of the corpus cavernosum has been demonstrated [7,10–15]. Similarly, diminished NO release from non-pudendal vasculature is associated with atherosclerosis and the risk factors thereof [16]. The release of NO from the endothelium as well as NANC nerve endings is now considered central to the initiation and maintenance of erection [4,7,11] (Fig. 1). NO stimulates the formation of cyclic GMP in the smooth muscle component of arteries, arterioles and the corpus cavernosum which then elicits relaxation through resequstration of calcium [3,7,17].

Although the mechanisms underlying impairment of NO in the penile circulation in atherosclerotic patients have not been determined, they have been investigated in other blood vessels [6,18]. In arteries from animals with atherosclerosis, there is increased superoxide formation (O$_2^-$) due to a reduction in the activity of antioxidant enzymes, in particular, superoxide dismutase (SOD) [16,18–20]. In turn, O$_2^-$ reacts with NO to form the potent oxidant, peroxynitrite (ONOO$^-$) [21,22] thereby reducing the availa-
Fig. 1. Key events in normal penile erection — the central role of NO. Upon sexual arousal, sympathetic drive initiates erection through both sympathetic and non-adrenergic, non-cholinergic (NANC) innervation of the corpus cavernosum and pudendal arteries. NANC fibres release NO and acetylcholine stimulates the release of NO from local endothelium by activation of NO synthase (NOS). NO promotes relaxation of arterial and cavernosal smooth muscle through activation of guanylate cyclase and suppression of activator Ca$^{2+}$ which in turn results in erection. It is now well established that impairment of the above systems is central to the aetiology of vasculopathic erectile dysfunction. Sildenafil promotes erection through inhibition of type V phosphodiesterase which blocks the metabolism of cGMP to inactive GMP. Thus, cGMP accumulates thereby promoting relaxation of the relevant VSMCs.

Fig. 2. Hypothetical interaction of platelets, neutrophils and the endothelium in vasculopathic erectile dysfunction. (A) In a sexually non-excited state, patients with vascular disease have depressed endothelial NO output due to increased superoxide formation by diseased smooth muscle cells. Depressed basal NO output and the superimposition of risk factors also elicits over-expression of adhesion molecules, predisposing adhesion of platelets and neutrophils to the vasculature. (B) On erection there is an increase in shear and flow which in turn promotes: (a) adhesion of platelets due to depressed NO availability and the already present increased adhesion molecule expression; (b) concomitant release of a battery of vasoconstrictors, including TXA$_2$, and 5HT, which promotes acute vasoconstriction and therefore fluidity as well as the further adhesion of platelets; (c) co-adhesion of neutrophils to platelets as well as the endothelium through the expression of adhesion molecules, releasing large amounts of superoxide (O$_2^-$) which reduces available NO by the formation of peroxynitrite (ONOO$^-$), countering erectile drive as well as promoting further the adhesion of platelets and neutrophils. A vicious circle ensues. ONOO also breaks down to generate the proatherogenic free radicals OH and NO$^-$; (d) release from adherent platelets and neutrophils of other growth factors, cytokines and chemokines that promote deleterious phenotypic changes in VSMCs as well as damaging corpus cavernosum through the generation of O$_2^-$ [23]. Although ONOO relaxes smooth muscle tissue via cGMP formation, it is 1000 times less potent than NO [24]. However, ONOO also degrades to form nitrite and hydroxyl radicals, both highly toxic to endothelial cells [22,23,25]. Superoxide inhibits the formation of prostacyclin (PGI$_2$) [26] which is also produced by both the endothelium and smooth muscle component of penile tissue and associated vasculature [27–31]. PGI$_2$ release in both the laboratory animal penis and human corpus cavernosum, is stimulated by parasympathomimetics and is impaired by risk factors for VED [27–31]. O$_2^-$ also exerts a
directing contraction of vascular smooth muscle cells (VSMCs) [32–34]. O₂ can give rise to other free radicals including hydrogen peroxide (H₂O₂), and hydroxyl radicals [34] which apart from interfering with NO and PGI₂ formation are directly injurious to the endothelium [34–36].

3. Platelet–neutrophil interactions

Another major consequence of a reduced availability of NO (and PGI₂) is the adhesion of platelets and neutrophils to vascular tissue walls [26,37]. NO and PGI₂ are potent inhibitors of platelet and leukocyte adhesion [26,37], which through the elevation of cGMP suppresses the expression of adhesion molecules, including P-selectin and GPIIbIIIa [26,37–39]. On adhesion and aggregation, platelets release the vasoconstrictors, thromboxane A₂ (TXA₂) and serotonin (5-hydroxytryptamine, 5-HT) [39]. It follows that the local release of these substances in the penile circulation would be ‘anti-erectile’ since vasoconstrictors promote flaccidity [4]. An appropriate illustration of the impact of platelet adhesion on vascular tone is unstable angina in which there is increased platelet adhesion [40,41]. It was suggested that the release of 5-HT and TXA₂ by adherent platelets interact synergistically to elicit acute constriction of the coronary arteries in angina [40,41]. Furthermore, it was demonstrated that neutrophils co-adhere with platelets in this scenario [40,41] which would impair NO-mediated relaxation since neutrophils release large amounts of O₂ which reacts with NO to form ONOO. Neutrophils and other leukocytes release (or contain) a number of other agents with vasoconstrictor activity, including leukotrienes, lipoxins and leukotoxins, platelet activating factor, angiotensins and endothelins [26,39,42]. Others workers have reported that leukocytes release factors, as yet unidentified, which have direct vascular contractile factors and factors that inhibit endothelium dependent relaxation [43–45]. The release of these various vasoconstrictors may well come into play locally in the penis, particularly where a dysfunctional or compromised endothelium is present (Fig. 2).

Another important consideration is that in patients with vascular disease or where the risk factors thereof are present, platelets are hyper-responsive (i.e. they aggregate in response to lower concentrations of agonists) [30]. More importantly, the expression of adhesion molecules is increased in these platelets, in particular GPIIbIIIa and P-selectin [46–48], which promote adhesion of platelets to both the endothelium and neutrophils [46–48]. Similarly, the expression of adhesion molecules [including, platelet endothelial cell adhesion molecule-1 (PECAM), intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM) and E-selectin] is increased in the endothelium in atherosclerosis and in patients with risk factors for atherosclerosis [48–51].

The haemodynamics of erection itself elicit local relevant changes in the penile circulation. Erection occurs when there is an increase in arterial inflow relative to venous outflow into the penis which results in an increase in intracorporeal pressure [52,53]. Although not demonstrated in the penis during erection, increased blood flow results in increased shear stress, a potent stimulator of NO release in most vascular beds [54]. This latter system may constitute an autoregulatory system that controls blood flow independently of the autonomic nervous system. Thus, where a healthy endothelium is present, the abrupt increase in blood flow initiated by sympathetic/NANC drive results in a haemodynamic generation of NO which would result in further promotion of erection and hence prevention of platelet and neutrophil adhesion. An intrinsic autoregulatory protection mechanism is also provided by NO release in response to erection.

Where vasculopathy is present, however, the consequences of erection may be quite different. Under high shear, platelets adhere more readily to vascular walls [55]. Since NO is impaired and adhesion molecules are likely to be already expressed in patients with VED, increased flow and shear stress would lead to increased adhesion of platelets (Fig. 2). In turn, platelet released substances, in particular vasoconstrictors, would compromise erection (Fig. 2).

Apart from the acute consequences on erection, platelet and neutrophil adhesion, albeit transient, may have longer-term exacerbating effects on the penile vasculature. Along with vasoconstrictors, platelets and neutrophils release a battery of growth factors and cytokines including platelet derived growth factor (PDGF), basic fibroblast growth factor, transforming growth factor-β, interleukins and tumour necrosing factor-α [31,39]. These released substances cause fundamental alterations to VSMC biology including the change of VSMCs from a contractile to a proliferative and secretory phenotype [56]. However, we know remarkably little about the vascular biology of penile tissue in disease states. Furthermore, these released substances promote the expression of adhesion molecules in both endothelial cells and VSMCs [57], further enhancing the adhesion of platelets and neutrophils. A ‘vicious circle’ is set up by each erection which results in accelerated pathology (Fig. 2).

4. Therapeutic strategies for reducing erectile dysfunction in the long-term

Although sildenafil has proved to be something of a magic bullet in the acute treatment of VED, little consideration has been paid to preventative approaches in the long-term. Further deterioration in endothelial function, as was outlined above, must be prevented otherwise sildenafil...
will ultimately fail to work. The hypothesis presented in this article predicts that any treatment aimed at retarding atherogenesis and its complications may be beneficial in limiting the progression and severity of VED. Since NO is central to erection of the penis, perhaps more so than in any other vascular bed, it follows that other strategies for normalising NO formation may be useful in treating VED in the long-term. Given the potential role for platelets in VED, it would also seem obvious to suggest that the chronic administration of aspirin may prove beneficial in patients with VED. However, aspirin has one major drawback: it does not prevent the expression of surface adhesion molecules and therefore not the adhesion of platelets to the endothelium/subendothelium or neutrophils [39]. Aspirin also inhibits the formation of PGL₂, an inhibitor of platelet and leukocyte adhesion [39]. Since NO is a potent inhibitor of platelet and neutrophil adhesion we have suggested that the co-administration of an NO donor may circumvent this limitation of aspirin [39]. One potentially useful class of drugs are the NO–aspirin adducts, which possess the ability to release NO, thus intrinsically compensating for the limitations of aspirin, but retaining the capacity to inhibit TXA₂ release. Finally, as we have proposed, oxidant stress may be central to both the acute and long-term pathophysiology of erectile dysfunction. Thus, antioxidant therapy (e.g. vitamins C and E) may have favourable effects.

It would be valuable in clinical trials involving the assessment of drugs used to treat atherosclerotic disease (e.g. anti-platelet agents, NO donors, anti-hypertensives, NO–NSAID adducts, statins, fibrates) to ask in patient questionnaires whether any improvement in erectile function has been experienced. Subsequent drug therapy should also be designed in accordance with the risk factor that determines erectile dysfunction i.e. the presence of risk factors such as hypercholesterolaemia, tobacco addiction, hypertension or diabetes mellitus.

5. Concluding remarks

Since VED is associated with endothelial dysfunction it is reasonable to suggest that platelets and leukocytes may adhere to cavernosal walls during erection due to increased shear stress. In turn, the local release of vasoconstrictors and oxygen free radicals by these adherent cells would promote contraction of the cavernosal tissue and therefore acutely impair erection. In the long-term, these events would exacerbate dysfunction in the penile and cavernosal vasculature, as has been well documented for other vascular beds. Whether this is the case is difficult to prove but experiments in which the measurement of vasoconstrictors, adhesion molecules and inflammogens in blood samples are collected from arteries entering and veins leaving the penis during erection in animal models (diabetic or lipidaemic) would go some way to answering the hypothesis. Such models could also be used to investigate the effect of pharmacological interventions both acutely and in the long-term. It is further suggested that drugs that are beneficial in the treatment of atherogenesis may prove beneficial in reducing VED, since patients with vascular disease (and the risk factors thereof) are at a higher risk of developing VED. The corollary is that drug regimes that reduce long-term VED may also be beneficial in reducing atherogenesis and related disorders.

References


