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Endothelial dysfunction in neuroprogressive disorders—causes and suggested treatments

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Abstract

Background: Potential routes whereby systemic inflammation, oxidative stress and mitochondrial dysfunction may drive the development of endothelial dysfunction and atherosclerosis, even in an environment of low cholesterol, are examined.

Main text: Key molecular players involved in the regulation of endothelial cell function are described, including PECAM-1, VE-cadherin, VEGFRs, SFK, Rho GEF TRIO, RAC-1, ITAM, SHP-2, MAPK/ERK, STAT-3, NF-κB, PI3K/AKT, eNOS, nitric oxide, miRNAs, KLF-4 and KLF-2. The key roles of platelet activation, xanthene oxidase and myeloperoxidase in the genesis of endothelial cell dysfunction and activation are detailed. The following roles of circulating reactive oxygen species (ROS), reactive nitrogen species and pro-inflammatory cytokines in the development of endothelial cell dysfunction are then described: paracrine signalling by circulating hydrogen peroxide, inhibition of eNOS and increased levels of mitochondrial ROS, including compromised mitochondrial dynamics, loss of calcium ion homeostasis and inactivation of SIRT-1-mediated signalling pathways. Next, loss of cellular redox homeostasis is considered, including further aspects of the roles of hydrogen peroxide signalling, the pathological consequences of elevated NF-κB, compromised S-nitrosylation and the development of hypernitrosylation and increased transcription of atherogenic miRNAs. These molecular aspects are then applied to neuroprogressive disorders by considering the following potential generators of endothelial dysfunction and activation in major depressive disorder, bipolar disorder and schizophrenia: NF-κB; platelet activation; atherogenic miRs; myeloperoxidase; xanthene oxidase and uric acid; and inflammation, oxidative stress, nitrosative stress and mitochondrial dysfunction.
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Conclusions: Finally, on the basis of the above molecular mechanisms, details are given of potential treatment options for mitigating endothelial cell dysfunction and activation in neuroprogressive disorders.

Background

Recent large meta-analyses of prospective studies have shown that individuals diagnosed with major depressive disorder (MDD) have a significantly increased risk for the development of cardiovascular diseases (CVDs) even when the data are adjusted for confounding variables [1–3]. The evidence suggests that MDD patients experience a 30% increase in CVDs and an approximately 36% increase in mortality due to CVDs compared to age- and sex-matched population norms [2, 3]. The situation in bipolar disorder (BPD) is similar with meta-analyses of prospective studies revealing that the incidence of death due to cardiovascular disease (CVD) is approximately double when compared to the general population [3–5]. The risk of developing CHD may be even greater [5–7]. The importance of CVD as a source of morbidity and mortality in BPD is thrown into stark relief by the presence of data suggesting that this condition may be responsible for up to 40% of deaths in this group of patients [4]. Perhaps unsurprisingly, the weight of evidence also suggests a significantly increased risk of developing CVD in patients afforded a diagnosis of schizophrenia (SZ) [3, 8, 9].

However, authors investigating lipid profiles in patients with neuroprogressive disorders have reported somewhat counterintuitive results with low total and low-density lipoprotein (LDL) cholesterol being the predominant observations. For example, low total cholesterol (TC) and LDL cholesterol (LDLC) have been reported by several prospective studies and meta-analyses investigating lipid profiles in patients afforded a diagnosis of MDD [10–14]. Interestingly, TC and LDL levels may be normalised in responders to electroconvulsive therapy (ECT) [10, 14], reviewed in [15]. Low high-density lipoprotein (HDL) is another common finding in these individuals, which is somewhat more in line with a lipid profile expected in patients at increased risk of developing CVD [13, 14, 16, 17]. Total and LDL cholesterol also appear to be lower in treatment-naïve patients with BPD compared with age- and sex-matched controls [18]. There is also an accumulating body of evidence to suggest that TC levels are lower in patients enduring acute mania compared with levels seen in patients in the depressive phase of their illness [19–21]. In addition, two large meta-analyses have shown decreased levels of TC and LDL in patients with first-episode SZ [22, 23].

This pattern of reduced levels of total and LDL cholesterol is often seen in other illnesses characterised by increased cardiovascular risk and is often described as the lipid paradox [24, 25]. The weight of evidence suggests that the cause of this phenomenon is, at least in part, elevated levels of systemic inflammation [26–30].

This may well be the case in patients with neuroprogressive disorders, as chronic peripheral inflammation, as evidenced by elevated tumour necrosis factor-alpha (TNF-α) and other pro-inflammatory cytokines (PICs), plays a major role in the pathophysiology of SZ [31–33], BPD [34–37] and MDD [38–41].

Importantly, peripheral inflammation also plays a major role in the development of atherosclerosis and CVD [42–44] independently of cholesterol or LDL levels [45–47]. This point is further emphasised by data suggesting that the reduction of systemic inflammation leads to a reduction of cardiovascular events while controlling for levels of total and LDL cholesterol [45–47].

Hence, the presence of systemic inflammation in patients with neuroprogressive disorders may explain increased cardiovascular risk in these individuals even in the context of low TC and HDL. It is also noteworthy that systemic oxidative stress [48–50] and mitochondrial dysfunction [51–53] are also acknowledged players in the pathogenesis of atherosclerosis. This is of interest as oxidative stress [54–58] and mitochondrial dysfunction are involved in the pathophysiology of all the aforementioned neuroprogressive illnesses [58–61].

Mitochondrial dysfunction [62–64], oxidative stress [65, 66] and inflammation [67, 68] are also causatively associated with the development of endothelial dysfunction, activation and senescence. These are relevant observations as endothelial dysfunction [69, 70] and endothelial senescence [71–73] are among the earliest observed abnormalities in the development of atherosclerosis and play an indispensable role in the development of fibrous lesions, consisting of a lipid-rich necrotic core and a cap composed of migratory smooth muscle cells, in large arteries characteristic of the disease. Unsurprisingly, endothelial dysfunction plays an important role in the development of CVD associated with increased risk in apparently disease-free patients with normal Framingham scorers [74–77]. Furthermore, several prospective studies and meta-analyses have demonstrated the presence of endothelial dysfunction in all phases of BPD [78], reviewed in [79]. Similar findings have been reported by researchers investigating the presence of endothelial dysfunction in SZ [80, 81] and MDD [6, 82].

Given the above, it seems reasonable to suggest that the endothelial dysfunction secondary to inflammation, oxidative stress and mitochondrial dysfunction seen in neuroprogressive disorders may be a major factor explaining increased cardiovascular risk in these patients. We have recently proposed that high levels of inflammation, oxidative stress and mitochondrial dysfunction involved in the pathophysiology of MDD, BPD and SZ could potentially explain high levels of obesity, insulin resistance, metabolic syndrome, type 2 diabetes mellitus (T2D) and hypertension seen in patients with these illnesses [56].

This paper examines potential routes whereby systemic inflammation, oxidative stress and mitochondrial dysfunction may drive the development of endothelial dysfunction and atherosclerosis, even in an environment of low cholesterol. In order to do so, we will examine the processes involved in the development of endothelial dysfunction and atherosclerosis in the absence of systemically elevated levels of inflammation, oxidative stress and mitochondrial dysfunction. We will then examine how this triad of abnormalities may mimic such processes. In particular, we will examine how circulating levels of PICs and reactive oxygen species (ROS) may induce inflammation, oxidative stress and mitochondrial dysfunction within endothelial cells (ECs) either directly or indirectly via inducing high levels of platelets, myeloperoxidase and xanthene oxidase activity, which are all independently associated with increased cardiovascular risk [45, 83–85]. We begin with the mechanisms which maintain an anti-inflammatory environment in ECs in physiological conditions and also drive the induction of a pro-inflammatory environment as a prelude to the development of EC dysfunction.

The development of atherosclerosis

The endothelium plays many vital physiological roles in addition to the delivery of blood which are broadly connected with the maintenance of homeostasis. Metabolically active ECs regulate vasomotor tone, leucocyte trafficking and egress, platelet activity, angiogenesis and multiple aspects of innate and humoral immunity—reviewed in [86]. In physiological conditions of normal blood flow, high shear stress maintains an anti-inflammatory signalling cascade mediated by elevated levels of Krüppel-like factor 2 (KLF2) and via a 5′ AMP-activated protein kinase (AMPK)-dependent mechanism [87–89]. This constitutive activation of KLF2 also plays a major role in maintaining endothelial barrier integrity and EC anti-oxidant systems via the upregulation of nuclear factor erythroid 2-related factor 2 (Nrf2) and endothelial nitric oxide synthase (eNOS) activity, coupled with an increase in occludin synthesis [89–91]. High shear stress also exerts other important and beneficial effects on EC function and metabolism via increased production of nitric oxide, suppression of mitochondrial ROS production and regulation of glycolysis [92].

However, in atheroprone areas of arterial branches and bends, denuded levels of glycolax [93], decreased activity of manganese superoxide dismutase (MnSOD) [94] and low or oscillatory blood flow induce a chronic inflammatory state in resident ECs via the initial upregulation of JNK, p38 MAPK, RelA, IKK, p65 and ultimately the persistent activation of NF-κB [95–99], reviewed in [100].

Disturbed or oscillatory flow patterns can also result in the development of inflammatory status within ECs by inducing the development of endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR) via the activation of the PI3k Akt signalling pathway [101, 102]. Activation of the UPR can exacerbate the inflammatory environment within ECs by stimulating further increases in levels of NF-κB activation [103, 104]. Disturbed blood flow can also induce EC senescence via the activation of the p53/p21 pathways leading to a senescence-induced secretory phenotype characterised by low levels of NO, increased activity of the transcription factors pCREB and Elk and elevated levels of p38 MAPK, PICs and ROS [105, 106]. Senescence and UPR activation may increase EC activation and dysfunction as a result of increased activity of NF-κB, p38 MAPK, pCREB and Elk, which lead to increased levels of PICs and ROS production coupled with reduced levels of NO due to inhibition of eNOS [105, 106]. It is important to stress that EC senescence and upregulation of the UPR are considered to be major independent risk factors for the development of atherosclerosis because of their role in exacerbating EC activation and dysfunction, as discussed above [71, 107, 108].

EC activation results in increased permeability to circulating lipoproteins coupled with a significant accumulation of extracellular matrix proteins, which facilitates the sequestration of the highly atherogenic oxidised apolipoprotein B (apoB), the main constituent of LDL in the intima region of the arterial wall [70, 109], reviewed in [69]. The activation of the endothelium also promotes the recruitment of circulating monocytes and their ultimate recruitment into the arterial intima via the upregulation of EC chemokines, most notably CCL5, CXCL1, the cytokines MCP-1 and IL-8 and the surface adherence proteins VCAM-1, ICAM-1 and P-selectin EC and several glycosaminoglycans [110–112]. The internalisation of oxidised LDL (oxLDL) by macrophage scavenger receptors and subsequent foam cell formation is a vital step in the development of atherosclerosis, and this process has been the subject of intense research and discussed in depth in several excellent reviews [113–115]. The argument examined here is that abnormally high

levels of EC dysfunction, senescence and activation enable excessive levels of LDL and macrophage recruitment into the intima, thereby fostering the development of atherosclerosis in a low cholesterol environment. In the case of neuroprogressive illnesses, the proposed sources of such endothelial dysfunction and activation are excessive levels of PICs, ROS, reactive nitrogen species (RNS) and mitochondrial dysfunction, which is discussed and detailed below. However, while the inflammatory consequences of low or oscillatory blood flow patterns have been discussed above, no information has been provided which explains the mechanisms involved and how they might be compromised in an environment of chronic inflammation and oxidative stress. Hence, this area will be addressed in the next section of the paper with a focus on three main players, namely the mechanosensitive proteins platelet endothelial cell adhesion molecule-1 (PECAM-1) and VE-cadherin and a family of flow-sensitive microRNAs (miRNAs).

Molecular players involved in regulating EC function

Unsurprisingly, there has been extensive research aimed at delineating the mechanisms which enable changes in blood flow dynamics to produce beneficial or pathological consequences within ECs, and several mechanosensory sensors and transducers have been proposed, reviewed in [116]. The weight of evidence thus far suggests that the process is initiated and regulated by a "mechanosensory" complex of proteins located at EC junctions composed of PECAM-1 indirectly connected to the cytoskeleton via vimentin, VE-cadherin and the functionally pleiotropic vascular endothelial growth factor receptors VEGFRs 1 and 2 [117, 118]. Fluid stress modulates tension between PECAM-1 and VE-cadherin, which in physiological conditions results in increased tension across PECAM-1 and reduced tension across VE-cadherin [117, 119, 120]. A diagrammatic representation of this mechanosensory complex and its mode of action is provided in Fig. 1.

Briefly, PECAM-1 transduced forces activate as yet unidentified src family kinases (SFKs) leading to the transactivation of VEGFRs; VE-cadherin, on the other hand, serves as an adaptor interacting with VEGFRs, inducing their activation in flow [121]. The flow sensing capacity of VE-cadherin is dependent on the SFK-mediated phosphorylation status of Tyr 658, which is at maximum during shear stress [121, 122]. This is important as phosphorylation-dependent VE-cadherin signalling via the scaffolding protein Rho GEF TRIO and upregulation

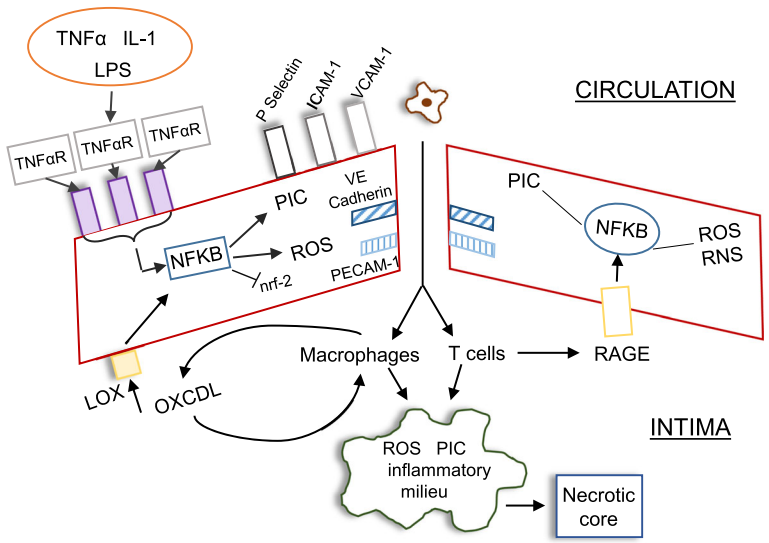

Fig. 1 The antagonistic relationship between NF-κB and KLF in endothelial dysfunction. In physiological conditions, the vascular endothelial is largely maintained in quiescent and impermeable state by the constitutive activity of KLFs and the mechanosensory proteins VE-cadherin and PECAM-1. The upregulation of the former results in the upregulation of nrf-2 and eNOS together with concomitant inhibition of mtROS production while inhibiting the transcriptional activity of NF-κB, while the activity of VE-cadherin and PECAM-1 physically increases the contact between two adjacent ECs. In an environment of chronic inflammation, however, the activation of NF-κB, induced by inflammatory mediators such as TNF-α or LPS, directly or indirectly inhibits the activity of KLF, PECAM-1 and VE-cadherin leading to a loss of tight junction integrity and the development of EC activation. The latter is associated with upregulation of surface chemokine receptors and adhesion factors resulting in the recruitment of LDL, activated monocytes and T cells into the vascular intima. The resultant oxidation of LDL and internalisation by monocyte-derived macrophages leads to foam cell formation and the development of a plaque with a highly necrotic core. Oxidised LDL can provoke increased activation and dysfunction of ECs via engagement with LOX-1 receptors allowing for the development of self-amplifying vascular and systemic inflammation

of RAC-1 enable and regulate the actin cytoskeleton reorganisation which determines the EC responses to different flows [123, 124]. The level of VE-cadherin phosphorylation also plays a large role in maintaining tight junction integrity [125] and forms part of the EC defences against inflammatory agents and leucocyte binding [124].

Levels of phosphorylation also determine the activity of PECAM-1. In this instance, phosphorylation levels of the so-called tyrosine-based inhibition sequence (ITAM) largely determine its signalling capabilities, which regulate actin cytoskeleton rearrangement, tight junction integrity and intracellular signalling pathways, reviewed in [126]. Briefly, in physiological conditions, phosphorylation of ITAM leads to the recruitment of SHP-2 and subsequent phosphorylation and activation of MAPK/ERK pathways and STAT-3, ultimately leading to the inhibition of NF-κB activity [127–129]. Conversely, in conditions of low shear stress, reduced levels of ITAM phosphorylation relieve the inhibition of NF-κB nuclear translocation, leading to a cascade of inflammatory signalling thought to be mediated via the activation of the PI3K/AKT pathway [130–132].

It should also be noted that PECAM-1 is associated with eNOS at the plasma membrane and this association allows the regulation of this protein's activity and that of VE-cadherin by changes in levels of NO [130, 132, 133]. Unsurprisingly, dysfunction of PECAM-1 and/or VE-cadherin is associated with the development of atherosclerosis and CVDs [130, 132, 133]. Importantly, such dysfunction may be induced by a range of atherogenic pro-inflammatory miRNAs, reviewed in [134]. The role of miRNAs in the regulation of EC function and their potential role in the development of EC pathology are discussed below.

Flow-sensitive miRNAs, often described as "mechano-miRs", modulate the expression of EC genes and hence play indispensable roles in the regulation of EC homeostasis and the development of atherosclerosis, and can regulate endothelial dysfunction and atherosclerosis [135, 136]. miRNAs such as miR-200, 92a, 143/145, 134 and 155 have been identified as major players in the development of EC dysfunction [135, 136], and their transcription and translation are increased as a result of disturbed flow [137–139]. Readers interested in a detailed consideration of this topic are referred to excellent treatments of the subject by [139, 140].

Upregulation of miR-92 activity would appear to play an indispensable role in the development of EC dysfunction as evidence from animal studies suggests that the development of atherosclerosis may be arrested or even reversed by inhibition of this molecule [141, 142]. Mechanistically, this miR exerts pathology mainly by inducing decreases in the activity of KLF-4 and KLF-2 leading to the upregulation of NF-κB [143–146]. The antagonistic relationship between these KLFs and NF-κB is due to the fact that they compete for access to p300/CBP which acts as an essential coactivator for both transcription factors; hence, a decrease in KLF-2 and KLF-4 leads to upregulated NF-κB activity and vice versa [147, 148]. Elevated miR-92a activity also results in increased phosphorylation of the NF-κB subunit p65 via a mechanism which remains to be delineated [146]. The net effect of upregulated miR-92a activity is increased expression of inflammatory and endothelial adhesion markers such as PICs, E-selectin, CCL2 and VCAM-1, and decreased activity of eNOS, which in their entirety increase atherosusceptibility [143, 149]. The weight of evidence also suggests that other miRNAs involved in inducing EC dysfunction, such as miRs 155, 200, 34 and 146, also inhibit KLF-4 and KLF-2, leading to the upregulation of NF-κB [137, 150–154]. The actions of KLFs in regulating the development of EC activation are diagrammatically represented in Fig. 2.

The paper now moves on to discuss how the various elements driving the pathophysiology of neuroprogressive illnesses might conspire to produce very high levels of endothelial dysfunction and increased levels of atherosclerosis. The discussion commences with a consideration of the

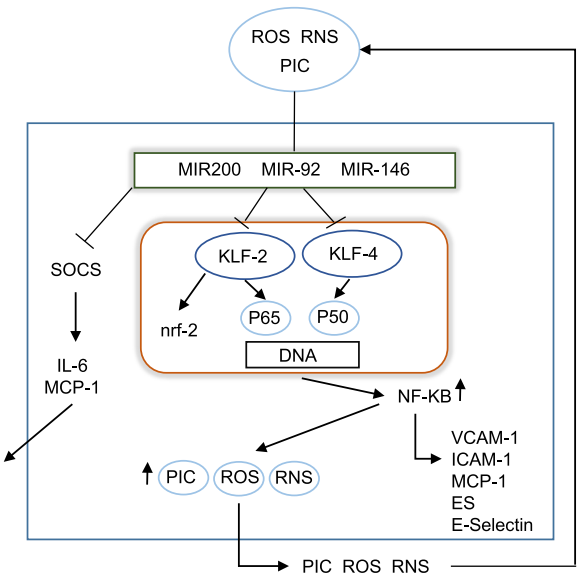

Fig. 2 The pathogenic effects of upregulated atherogenic mechanosensory miRNAs. In conditions of high sheer stress, mechanosensitive miRNAs play a major role in maintaining the function and integrity of the vascular epithelium. However, in an environment of chronic inflammation and oxidative stress, the consequent upregulation of atherogenic miRNAs such as miRNA-92 induces EC dysfunction and activation by inhibiting the activity of KLFs and, to a lesser extent, SOCS-1. The resultant upregulation of NF-κB and SOCS-1 increases the internal production of PICs, MCP-1 and IL-6 and stimulates the increased expression of adhesion factors and chemokines on the EC surface. The resultant release of cytokines into the environment increases the inflammatory milieu and may establish a self-amplifying environment of inflammation and oxidative stress with the ECs and beyond

effects of platelet activation (PA), increased xanthene oxidase (XO) activity and elevated levels of myeloperoxidase (MPO), which are all characteristic abnormalities found in an environment of chronic inflammation and oxidative stress.

The roles of platelet activation, xanthene oxidase and myeloperoxidase in the genesis of EC dysfunction and activation

Role of activated platelets

Platelets may be activated by high levels of circulating PICs and ROS [155–157], reviewed in [158]. This is of importance from a pathophysiological perspective as PA is a major source of systemic inflammation and oxidative stress [159, 160]. Activated platelets secrete high levels of PICs and ROS and a plethora of chemokines, TNF superfamily members and adhesion factors which make an independent and collective contribution to initiating or exacerbating levels of EC activation and dysfunction [161–163], reviewed in [164]. For example, the TNF superfamily member LIGHT enhances platelet EC adhesion, EC dysfunction and EC activation by stimulating elevated activity of NF-κB via a pathway dependent on MAPK [165–167]. It should also be noted that platelet-mediated release of LIGHT may also be a source of increased systemic inflammation [165]. The weight of evidence suggests that platelet-secreted CD40L, another TNF superfamily member, also plays a major role in initiating or exacerbating EC dysfunction and activation via several routes [168]. Such routes include increased activity and transcytosis of metalloproteins, reduction of NO production and elevated transcription of NF-κB [168–170]. Platelet-derived CD40L also appears to make an independent contribution to the initiation and/or exacerbation of systemic inflammation and oxidative stress [169].

There are some 50 members of the chemokine family, and many are secreted by activated platelets; clearly, a detailed consideration of this area is beyond the scope of this paper. Hence, readers interested in the area are encouraged to consult the work of [171]. However, two platelet-derived chemokines, CCL5, also known as RANTES, and CCL4, also known as platelet factor 4 (PF4), have been the subject of intense research, reviewed in [172, 173], and as their activities are germane to the central theme of this paper, their modes of action will be briefly discussed below.

RANTES promotes leucocyte recruitment to the endothelium in much the same manner as other platelet-derived cytokines. However, this chemokine also promotes leucocyte survival and polarised activation towards a PIC- and ROS-secreting phenotype coupled with increasing adhesion of such leucocytes to ECs [174, 175]. PF4 possesses several unusual properties, in addition to leucocyte recruitment, which encourage the development of endothelial dysfunction and increased systemic inflammation. Such properties include the promotion of monocyte differentiation into macrophages, suppression of macrophage apoptosis, anchoring macrophages to ECs and binding to LDL [176, 177]. The weight of evidence suggests that engagement of PF4 and LDL increases the binding affinity of the latter to LDL receptors on platelets, macrophages and ECs while inhibiting endocytotic "machinery" retaining the lipoprotein at the surface, allowing enhanced exposure to ROS and inflammatory molecules resulting in its increased oxidation [177–179]. Moreover, there is evidence to suggest that the internalisation of PF4-oxLDL complexes by macrophage scavenger receptors increases the efficiency of foam cell formation over tenfold [180]. These data are of interest as they offer another route by which levels of oxLDL and the efficiency of the lipoprotein in inducing foam cell formation may be increased and thereby potentially compensate for relatively low levels of LDL in the circulation. Finally, there are data to suggest that initial activated platelet-mediated oxidation of LDL further enhances PA via a MAPK- and NADPH oxidase 2 (NOX2)-dependent signalling pathway, further increasing systemic levels of ROS, RNS and PICs [177].

Role of xanthene oxidase

High levels and activity of XO constitute a characteristic feature of many illnesses and conditions, such as T2D and metabolic syndrome, whose pathophysiology is driven at least in part by chronic systemic oxidative stress and inflammation [181, 182]. The weight of evidence also suggests that high levels of circulating XO act as a major driver of endothelial dysfunction and atherosclerosis [183], reviewed in [184]. The pathogenic role of XO is further emphasised by data produced by several meta-analyses and prospective studies demonstrating a significant and large improvement in endothelial function following XO inhibition in patients with CVD [84, 185–187]. A recent meta-analysis of large prospective randomised controlled trials (RCTs) has also reported large reductions in cardiovascular morbidity and mortality achieved by the inhibition of XO by allopurinol [188].

One mechanism which appears to be associated with the positive effects of XO is a decrease in systemic and vascular oxidative stress [84, 185–187]. This is unsurprising given the fact that circulating activated XO is a major, if not the predominant, source of hydrogen peroxide and superoxide in patients displaying high levels of systemic inflammation and oxidative stress [183, 189, 190]. The source of increased circulating XO in such conditions is not fully delineated but appears to be associated with increased transcription stimulated by the presence of high levels of TNF-α and other PICs [191, 192]. In contrast, the mechanism explaining ROS production by XO is well documented and occurs as a result of their role in catalysing

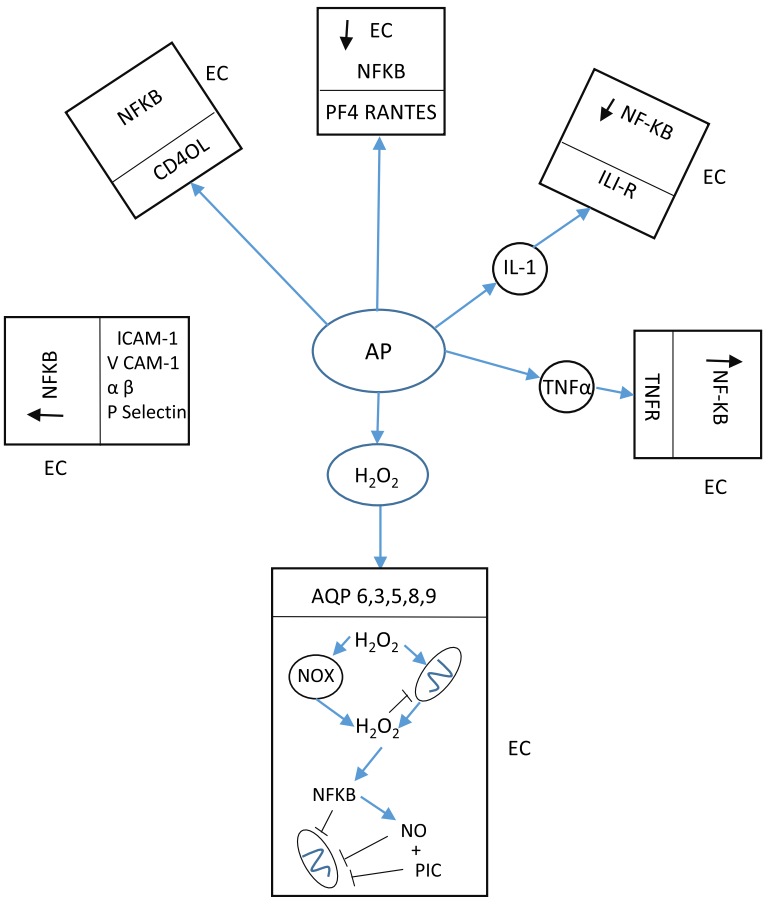

Fig. 3 The damaging effects of activated platelets on endothelial cell function and activation. Activated platelets release large quantities of PICs, ROS and chemokines such as CD40, RANTES and PF4. PICS and CD40 can engage their cognate receptors on the surface of ECs activating downstream signalling pathways culminating in the activation of NF-κB. PF4 and RANTES may also engage with the surface of ECs, thereby summoning leucocytes and stimulating their differentiation and activation via a range of mechanisms ultimately also resulting in EC NF-κB activation. In addition, high levels of circulating hydrogen peroxide, produced by the activity of platelets, neutrophils and allopurinol, may directly enter ECs via aquaporin receptors. Such influx results in the activation of hydrogen peroxide production by NOX enzymes and mitochondria ultimately acting as another vehicle driving NF-κB upregulation. The subsequent upregulation of NO, PICs and ROS also compromises mitochondrial ATP production while the NF-κB-mediated downregulation of SIRT-1, PGC-1α and PPAR-γ inhibit mitochondrial biogenesis and disrupt many mechanisms regulating mitochondrial dynamics. The result is self-amplifying inflammation oxidative stress and mitochondrial dysfunction within the EC and potentially an increase in systemic inflammation

the oxidation of hypoxanthine [193, 194]. The pathways involved in purine catabolism are illustrated in Fig. 3. The direct effect of XO in inducing EC dysfunction appears to be induced by binding to the EC membranes before being internalised via endocytosis [195–197]. Once internalised, XO acts as a source of increased superoxide and hydrogen peroxide levels contributing to increasing levels of oxidative stress and inflammation [198]. Increased levels of XO activity can also make an indirect contribution to increasing levels of inflammation and oxidative stress by catalysing the production of uric acid (UA).

Increased levels of uric acid

Impaired EC function is also associated with increased UA levels in the plasma [195, 199]. Moreover, several authors have reported an inverse association between UA levels and EC function [200, 201]. There is also evidence to suggest that increased levels of circulating UA are associated with an increased risk of cardiovascular morbidity and mortality [202–204]. There remains the question as to whether such an association is a consequence of increased XO activity, but nevertheless, the current weight of evidence strongly suggests that elevated UA levels are an independent predictor of CVD [203, 205].

The internalisation of UA into ECs appears to be facilitated by a range of different surface membrane urate transporters such as Glut-9 and URAT-1 [206–208]. Readers interested in the classification and mechanisms enabling the performance of these receptors are invited to consult an elegant and comprehensive review on the

subject by [209]. The consequences of UA internalisation include increased levels of PICs, chemokines, EC adhesion molecules and ROS, coupled with elevated activity of NF-κB and reduced production of NO which all contribute to the development of EC dysfunction [208, 210–212].

The mechanisms underpinning this pattern of pathology and the subsequent development of endothelial dysfunction appear to be numerous. For example, UA internalisation may induce ROS-, PIC- and NF-κB-mediated EC dysfunction by the stimulation of HGMB1/Rage signalling [211, 213]. Readers interested in a detailed consideration of the mechanism involved are referred to the work of [214]. There may also be other mechanisms involved as UA may act as an alarmin, and in some circumstances, high levels of this purine lead to activation of the NLRP3 inflammasome [215, 216]. Internalised UA may also increase activity of NF-κB levels, and inflammatory and oxidative and nitrosative stress (I&ONS) within ECs, by inhibiting eNOS via disruption of the association of the enzyme with its primary activator calmodulin [217] and inducing the activation of NOX [218–220]. There is also evidence to suggest that circulating UA can activate PPRs on ECs, which would be another route resulting in the activation of NF-κB [221]. Other mechanisms whereby high levels of circulating UA may induce elevated levels of I&ONS in ECs involve the activation of the (pro)rennin receptor found on the surface of ECs [212, 222] and activation of the vascular renin angiotensin system and/or ERK signalling [223–225].

Myeloperoxidase

Elevated levels and activity of MPO in the circulation are an accepted marker of systemic oxidative stress and inflammation [226, 227]. This is unsurprising given that elevated MPO levels in the circulation are the result of ROS- and PIC-mediated degranulation of neutrophils, which act as the main reservoir of this enzyme in humans [226–228]. From a pathological perspective, it is important to note that active MPO is a major source of ROS, RNS and reactive radicals responsible for causing severe cellular damage, most pertinently to the protective endothelial glycocalyx layer, tight junction integrity and individual ECs [227, 229].

There is also evidence to suggest that MPO binding to APOB-100 is one of the molecular players responsible for the oxidation of LDL [230]. Furthermore, the MPO-oxLDL complex (MOX-LDL) also has a potent effect on EC and macrophage activation, with the resultant secreting of PICs and ROS which appears to be greater than that achieved by oxLDL alone, thereby making a significant contribution to increasing levels of intracellular and extracellular inflammation and oxidative stress [230–232]. In addition, it would appear that the internalisation of MOX-LDL by macrophage scavenger receptors greatly increases the efficiency of foam cell formation [230, 233]. This is of interest given the relatively low levels of LDL generally present in patients with neuroprogressive disorders as it offers a plausible mechanism which might increase the atherogenicity of the LDL present.

Several research teams have reported an association between, on the one hand, chronically elevated MPO activity and increased EC dysfunction and, on the other hand, increased cardiovascular morbidity and mortality [234, 235]. There is some suggestion that increased levels and activity of MPO may also be a consequence of elevated XO activity [236, 237]. This would be consistent with increased levels of oxidative stress driven by the superoxide, hydrogen peroxide and UA produced by circulating XO, which can induce neutrophil degranulation and MPO release into the circulation [227, 238]. The reduction in MPO levels achieved by XO inhibition in prospective RCTs also hints at the dependence of elevated levels of MPO on increased XO activity [236, 237]. However, it would appear that the adverse effects of MPO are independent of those exerted by XO and UA.

The internalisation of MPO by ECs is achieved via a different mechanism from that of the internalisation of XO and UA. In this instance, the transfer of MPO into ECs is achieved either by the contact of neutrophils and ECs via beta integrins [235] or via the engagement of free MPO with EC surface cytokeratin-1 receptors [238]. This internalisation is thought to contribute to the development and/or exacerbation of EC dysfunction by increasing the catabolism of NO and via the chlorination of arginine thereby inhibiting the activity of eNOS [239–241].

Having reviewed the roles of PA, XO, UA and MPO in the development of EC dysfunction and activation, the next section considers the role of circulating ROS, RNS and PICs in the development of such pathology.

Roles of circulating ROS, RNS and PICs in the development of EC dysfunction

Paracrine signalling by circulating hydrogen peroxide

In a state of systemic ONS, circulating ROS directly interact with ECs resulting in increased ROS production within these cells. Mechanistically, this is achieved via the diffusion of hydrogen peroxide into ECs, which is facilitated by the presence of plasma membrane water channels or aquaporins (AQPs), most notably AQP1 and 3, leading to the activation of several NOXs [242–244]. Evidence suggests that in this scenario, activated NOX2 and NOX4 are the most important players being, in the main, generators of superoxide radicals and hydrogen peroxide, respectively [245, 246]. Readers interested in the role of NOXs in the regulation of cellular redox homeostasis and their responses to various stimuli are referred to elegant reviews by [247, 248], and these

matters will not be considered further here. From a pathological perspective, however, the activation of NOX 2 and NOX 4 increases ROS production by mitochondria and XO, which act to increase ROS production further by NOXs, forming a self-amplifying positive feedback loop [249, 250]. This level of ROS production could of course be further amplified by internalised MPO, XO or UA originating in the cytoplasm via the mechanisms discussed above. In any event, spirally increasing levels of ROS can induce several dimensions of pathology including inhibited eNOS activity, loss of cellular redox homeostasis and increasing mitochondrial damage contributing to the development of endothelial dysfunction, activation and senescence via several routes which are discussed below.

Inhibition of eNOS

Increasing levels of hydrogen peroxide may stimulate increased activation of eNOS via a pathway involving the phosphorylation of Akt and AMPK [251, 252]. This is important from a pathological perspective as the increased level of NO produced by the stimulation of this enzyme within the EC may react with superoxide produced by NOXs and XO to form peroxynitrite with devastating consequences as far as the production of NO by eNOS is concerned for reasons explained below [253–255].

In physiological conditions, eNOS exists as a dimer with a reductase domain composed of flavins, a calmodulin binding site and NADPH, together with an oxidase domain composed of a haem active site bound to arginine, oxygen and tetrahydrobiopterin (BH_4) [256, 257]. This structure allows the transfer of electrons from NADPH to the haem site where the bound oxygen is reduced before being incorporated into arginine to form NO and citrulline [256, 257]. Crucially, BH_4 is an indispensable cofactor in this reaction [258], reviewed in [259].

Increased levels of peroxynitrite readily disrupt the dimeric eNOS complex, via oxidation and glutathionylation of the zinc-sulphur complex, of cysteine residues in the reductase domain, which leads to utilisation of oxygen as the terminal electron donor rather than arginine. In addition, peroxynitrite induces the oxidation of BH_4, leading to its dissociation from the enzyme's active site [260, 261]. The net effect is the formation of BH_4-depleted eNOS monomers which produce high levels of superoxide rather than NO, which is described as uncoupling [254, 262]. The structure of eNOS is depicted in Fig. 2. For the sake of completeness, it should be noted that increased ROS can also adversely affect the activity of eNOS via the MAPK-induced phosphorylation of Thr495/Tyr657 and by stimulating increased production of asymmetric dimethylarginine (ADMA) which acts as an endogenous inhibitor of the enzyme, reviewed in [263]. Unsurprisingly, eNOS uncoupling and the generation of superoxide play a major role in the development of atherosclerotic plaques and the onset of CVD [255, 264]. Mechanistically, this is partly due to increased levels of hydrogen peroxide and superoxide production by NOX, XO, eNOS uncoupling and mitochondria, which may induce damage to DNA, lipids and proteins within the organelle leading to a cycle of ever-increasing levels of superoxide production by electron transport chain (ETC) enzymes coupled with ever-increasing bioenergetic decline and increasing hydrogen peroxide levels in the cytosol [249, 250, 255, 263].

We now move to discuss the pathological consequences of excessive mitochondrial ROS (mtROS) production in ECs and elsewhere.

Increasing levels of mtROS

Overview

Excessive levels of mtROS production are causatively associated with the pathogenesis of EC senescence [72, 265, 266], the development of EC dysfunction [267, 268] and in the development of atherosclerosis [269, 270]. The importance of mitochondrial dysfunction in the genesis of atherosclerosis is emphasised by data suggesting that the severity of atherosclerosis in humans correlates with the level of mtROS production in ECs [271]. Clearly, induced EC cell senescence is one factor explaining the relationship between excessive mtROS and increased development of EC dysfunction and accelerated atherosclerosis [72, 272], reviewed in [107]. However, other factors are also involved which we discuss below.

Compromised mitochondrial dynamics

mtROS is a major cause of compromised mitochondrial dynamics, typified by an imbalance between mitogenesis and mitophagy, accompanied by increased levels of fission and decreased levels of fusion, leading to a disruption of networks and fragmentation of individual mitochondria [273–276]. This is of major pathophysiological importance as mitochondria perform essential roles in EC signalling affected by changes in mitochondrial dynamics in response to environmental cues [277, 278]. Unsurprisingly, defects in mitochondrial dynamics are causatively associated with increased EC activation and dysfunction [279, 280].

Loss of calcium homeostasis

Excessive levels of mtROS production may be a source of dysregulated calcium homeostasis resulting in a distinctive pattern of increased intramitochondrial Ca^{2+} in mitochondria and a loss of Ca^{2+} from the ER [266, 281, 282]. This is of importance as this pattern of Ca^{2+} distribution within EC mitochondria also plays a major role

in the development of EC senescence [266, 281, 282]. The increase in intramitochondrial calcium ions may also exert detrimental effects on ATP production and lead to further increases in mtROS production, creating a spiral of ever-increasing mitochondrial dysfunction, reviewed in [58]. Given the importance of disturbed mitochondrial dynamics in the genesis of EC dysfunction, it should be noted that elevated mitochondrial calcium ion levels regulate many aspects of mitochondrial dynamics, such as organelle biogenesis and motility, via several mechanisms which include elevating the expression of PGC-1α and increasing mitochondrial fission [283–285].

Inactivation of SIRT-1-mediated signalling pathways

Excessive levels of mtROS production and elevated cytosolic ROS also decrease the activity of sirtuins (SIRTs), most notably SIRT-1 [286, 287]. This is pertinent as these deacetylases normally play an important role in inhibiting the development of senescence in vascular ECs, reviewed in [288]. The inactivation of SIRTs may also be another factor in the development of compromised mitochondrial dynamics, mitophagy and mitogenesis via reduced activity of PGC-1α and PPAR-γ [289, 290]. Impaired activity of this coactivator and transcription factor can also promote disturbances in mitochondrial dynamics by preventing the upregulation of UCP-2 [291, 292]. The activity of this protein is important in maintaining mitochondrial networks and preventing mitochondrial dysfunction via the activation of p53 [293]. Unsurprisingly, UCP-2 also plays an important role in maintaining EC function and the prevention of senescence in an environment of oxidative stress [294, 295]. Readers interested in a more comprehensive explanation of the factors involved in preventing and inducing the development of EC senescence are invited to consult the following reviews [107, 265].

Clearly, excessive levels of mtROS production exert several pathological consequences as outlined above. We now consider the pathological consequences of increased mtROS and NOX in the cytosol, which may result in dysfunctional cellular signalling normally regulated by physiological levels of hydrogen peroxide and NO, leading to a loss of redox homeostasis.

Loss of cellular redox homeostasis

Physiological and pathological roles of hydrogen peroxide signalling

In the absence of ONS, cytosolic hydrogen peroxide, ultimately derived from the activity of the ETC and NOX enzymes, plays an indispensable role in the regulation of cellular signalling pathways and redox homeostasis [296], reviewed in [244]. Crucially, this radical species also plays an essential role in the maintenance of EC quiescence function [297–299]. Hydrogen peroxide signalling also plays a vital role in fostering cell survival in an environment of increasing ONS via the activation of several kinases including PI3/Akt [300].

These roles are mainly affected by the two-electron oxidation of cysteine thiolate anions to sulfenic acid which may then form intramolecular or extramolecular disulphide bonds or undergo further oxidation to sulfenic acid. Readers interested in a detailed consideration of the biochemistry and thermodynamic parameters involved are invited to consult the work of [244, 301]. However, there are two key points to make from the perspective of this paper. First, these oxidative modifications act as redox switches changing the activity, function and location of proteins and enzymes in a hydrogen peroxide concentration-dependent manner, which in turn affect the performance of signalling systems as the cellular redox environment changes [244]. Second, within physiological limits, these modifications are reversible and are recovered by anti-oxidant enzymes and systems such as the thioredoxin glutathione systems, with peroxiredoxins and glutaredoxins playing prominent roles [297, 302].

However, in an environment of chronic ONS, increasing hydrogen peroxide levels have pathogenic consequences, not least by inducing over-oxidation of crucial functional cysteine groups in the thioredoxin [58, 303] and glutathione systems, potentially rendering both systems inactive [304]. It should be noted that such inactivation may be reversible if caused by oxidation of thiolate anions to sulfenic acid but the weight of evidence suggests that the oxidation of the latter to sulfonic acid is not [305]. This essentially permanent disruption of redox-based cellular signalling may be one factor explaining the relatively disappointing responses achieved by anti-oxidant therapy in neurodegenerative and neuroprogressive illnesses. The loss of redox homeostasis and increasing levels of hydrogen peroxide may also be accompanied by increased activity of NF-κB.

Pathological consequences of elevated NF-κB

Over time, excessive levels of hydrogen peroxide induce the activation of NF-κB in ECs and other tissues [246, 306]. This is a major driver of EC senescence and activation [307, 308], reviewed in [309]. As previously discussed, one major cause of endothelial activation is inhibition of KLF-2 and KLF-4 and readers interested in a detailed consideration of the various streams of pathology flowing from this scenario and the complicated interplay between these transcription factors are invited to consult the work of [310, 311]. However, it should be noted that NF-κB can induce EC dysfunction via a number of other routes including the disruption of EC fatty acid metabolism and by stimulating the switch in energy

production from oxidative phosphorylation to energy production via glycolysis [312–314], reviewed in [315].

There is also a wealth of evidence from in vivo and in vitro studies reporting a causative association between elevated levels of NF-κB activity and increased transcription of inducible nitric oxide synthase (iNOS) leading to excessive production of NO in the intracellular and extracellular environments [316, 317]. This association is unsurprising given that the promoter region of the iNOS gene possesses several NF-κB binding sites and given the promiscuous nature of NF-κB as a transcription factor [318]. The pathological consequences of increased levels of NO are well documented, not least by acting as a source of increased peroxynitrite production, as highlighted above. Increased levels of this radical also lead to compromised cellular redox signalling by dysregulating the S-nitrosylation of proteins, which is an abnormality playing a causative role in the development of CVDs and also appears to play a role in the pathogenesis of neurodegenerative and neuroprogressive illnesses [319–321].

In addition, NF-κB plays a major role in the activation of atherogenic and inflammatory miRNAs which are known to play an important role in the development of EC dysfunction and atherosclerosis in an environment of ONS [322], reviewed in [323]. This is achieved by stimulating the transcription of these miRNAs and via a more general role in initiating, maintaining and amplifying the production of PICs, RNS and ROS [290, 324]. Hence, the activation of NF-κB would appear to be a pivotal event leading to the disruption of NO-mediated redox signalling and a significant increase in the EC population of atherogenic miRNAs which have a range of pathological consequences relevant to the central theme of this paper. Therefore, we will consider each in turn, beginning with the effects of disrupted S-nitrosylation.

Compromised S-nitrosylation and the development of hypernitrosylation

In physiological conditions, reversible S-nitrosylation is the other major player regulating the activity of redox-sensitive proteins, enzymes and signalling pathways. The basic mechanisms involved are reviewed in [325, 326]. Increased protein nitrosylation is initially a defensive response to increased levels of oxidative stress and plays a vital role in maintaining conformation and function in such an environment [319].

However, in the face of pathological increases in RNS and ROS levels, the mechanisms responsible for maintaining the reversibility of S-nitrosylation break down leading to a state described as protein hypernitrosylation [327]. This is important from a pathological perspective as levels of protein S-nitrosylation regulate many specific EC functions including tight junction permeability, inflammatory status and survival, reviewed in [328]. More specifically, excessive and irreversible S-nitrosylation in ECs is associated with disturbed fatty acid metabolism and compromised ETC function as evidenced by reduced activity of complexes I, III and IV [329, 330]. Evidence suggests that a state of hypernitrosylation is also a major cause of EC dysfunction and activation [319, 331]. One cause of such EC activation, driven by high levels of protein S-nitrosylation, appears to be loss of the normal level of association between VE-cadherin and beta-catenin and compromised small GTPase activity [332, 333]. Excessive and irreversible S-nitrosylation also disrupts mRNA splicing and translation in ECs, resulting in a dysfunctional proteome [331].

Increased transcription of atherogenic miRNAs

The transcription and activity of miRNAs are influenced by changes in the methylation and histone acetylation status of DNA within the promoter regions of genes encoding their production. Thus, data confirming that many atherogenic mechanosensitive miRs are upregulated in a cellular environment dominated by excessive levels of ROS, RNS and PICs is unsurprising. Crucially, this scenario applies to miR-92a, which is activated by elevated levels of hydrogen peroxide [334, 335] and is widely regarded as an indispensable player in the development of atherosclerosis mediated either by disturbed flow or by increased oxidative stress. There is also accumulating evidence to suggest that other members of the miR-92 cluster, such as miR-92b, are upregulated in an environment of upregulated ROS production [336–338]. This is of interest as several transcripts of the miR-17-92 cluster appear to reduce the activity of KLFs and may well play an under-discussed role in the development of endothelial dysfunction in inflammatory conditions [152]. miR-34 is another KLF inhibitor upregulated by high levels of hydrogen peroxide [154, 339, 340]. This is also true of miR-200 [151, 341, 342], and it also plays a role in inhibiting KLFs [151]. Additionally, this miR may also encourage the development of atherosclerosis via a mechanism involving the disruption of the SIRT-1-FOXO3a signalling pathway which normally operates to limit ROS production in ECs likely by inhibiting the assembly and activation of NOX [342–344]. It should be emphasised that disrupted SIRT-1 signalling is an important element in the development of CVD [345]. miR-155 is another KLF inhibitor playing an important role in EC cell dysfunction induced in an environment of chronic inflammation, although its activation in these conditions appears to be secondary to elevated NF-κB rather than upregulated ROS [152, 346, 347].

miR-146 is yet another miRNA which plays a role in inhibiting KLFs and is also upregulated as a result of increased NF-κB activity [347, 348]. There is also evidence to suggest that this miR may be directly upregulated by ROS-mediated demethylation of DNA within the

promoter region of the encoding gene [349]. miR-146 also belongs to a class of miRs described as "mitomiRs" whose upregulation can disturb the expression of mitochondrial genes governing the performance of the ETC leading to upregulated ROS production, compromised energy production and damage to functional and/or structural proteins within the organelle [350, 351]. This is of particular importance from the perspective of this paper as the activation of this group of miRs is considered to be a major element in the genesis and maintenance of EC senescence, reviewed in [351].

Thus far, we have suggested several abnormalities which could account for high rates of endothelial dysfunction and atherosclerosis in patients with neuroprogressive disorders in an environment of relatively reduced cholesterol. However, we have not considered evidence which demonstrates whether these abnormalities have actually been reported in patients with these illnesses. Hence, this omission will be addressed in the next section before considering treatment approaches.

Potential generators of EC dysfunction and activation in MDD, BPD and SZ

NF-κB

Elevated activity of NF-κB has been reported in the plasma and peripheral blood mononuclear cells (PBMCs) of patients with first-episode SZ before the onset of any treatment [352, 353]. Increased levels of NF-κB expression and activity have also been repeatedly reported in these compartments in patients subject to a diagnosis of MDD and BPD whether in the symptomatic phases of their illness or during remission [354, 355].

Platelet activation

Increased inflammation-mediated PA, as measured by increased platelet volume, has also been repeatedly reported in patients with MDD [356–358]. There is also extensive evidence of PA in patients with BPD compared with healthy controls [359–361]. There are also data to suggest that the level of PA may be greater in patients with acute mania compared with patients in the depressive or euthymic phases of the illness [362]. The picture appears to be less clear in patients with SZ, however, likely due to the effects of anti-psychotic medication which may suppress at least some signalling pathways involved in stimulating PA [363]. That being said, there is accumulating evidence to suggest that PA may be increased in at least some treatment-naïve first-episode patients [360, 364, 365].

Atherogenic miRs

Many of the miRs known to play a causative role in the development of EC dysfunction and atherosclerosis are also upregulated in many patients with neuroprogressive illnesses. For example, upregulation of miR-34 has been reported in drug-free MDD, BPD and SZ patients [366]. There is also evidence of upregulated miR-146 and miR-200 activity in patients with MDD and BPD, reviewed in [367]. There would appear to be no evidence that this is the case in SZ, however, although a recent review suggested that the expression of miR-92 was upregulated, or at least dysregulated, in some first-episode patients [368].

Myeloperoxidase

Increased plasma MPO activity is another common finding in patients with MDD [369, 370], BPD [227, 371] and SZ [372]. In addition, there is some evidence to suggest that increased levels of this enzyme may be involved in the pathophysiology of neuroprogressive illnesses and may be a state marker in MDD [370] and BPD [371]. However, this apparent association may be because an elevated level of MPO is an accepted marker of systemic inflammation and oxidative stress, as noted above.

Xanthine oxidase and uric acid

Many studies have produced copious evidence of increased XO activity and high levels of UA in the circulation in all phases of BPD [373–375], although serum UA levels appear to be at their highest in mania [58]. This may be a consequence of increased levels of inflammation in this phase of the illness compared with euthymia and depression, reviewed in [58]. Several prospective studies and meta-analyses have also confirmed an improvement in the symptoms of mania following XO inhibition via allopurinol [375, 376]. There have also been reports of increased XO activity in the brain of at least some SZ patients [377, 378], and there have been several reports of increased XO activity in patients in the periphery [379–381]. However, levels of XO activity and UA in the serum appear to be low in first-episode drug-naïve SZ patients [382, 383]. The situation in MDD is also mixed in that there is some evidence of increased XO activity in the brain and periphery of some MDD patients [384, 385] and there has been a report that high UA levels in MDD patients are predictive of a transition to bipolarity [386]. However, once again, the weight of evidence suggests that serum UA is low in the majority of MDD patients [387, 388].

The findings in patients presenting with first-episode SZ cited above are somewhat surprising as evidence suggests that the high levels of inflammation and oxidative stress reported in such individuals should promote the conversion of xanthine dehydrogenase to XO and increase levels of the latter [192, 389]. However, this apparent paradox might be explained by the high levels of allantoin reported in first-episode treatment-naïve SZ patients, which suggests increased UA oxidation [390].

Briefly, unlike other mammals, humans do not possess urate oxidase, and hence, allantoin production can only result from the action of oxidants. In this case, it should be noted that UA is very vulnerable to oxidation by peroxynitrite with the resultant production of a range of highly cytotoxic radicals whose role in pathology appears to be under-discussed [391, 392]. Hence, low UA levels may be detected in first-episode patients even with reasonable levels of XO activity. This proposal seems acceptable given evidence of high peroxynitrite activity in the plasma of such individuals [393]. There is also evidence to suggest that disturbed purine catabolism evident in first-episode treatment-naïve patient's results in reduced levels of xanthene, which would also explain low UA levels even with relatively high levels of active XO [382, 383]. It should also be noted that UA is responsible for some 60% of radical scavenging capacity in blood, and thus, it is not difficult to conceive of a scenario in which high levels of ROS seen in many patients with MDD would lead to depleted UA levels in an environment of activated XO [382, 394]. A literature search fails to reveal any evidence of published research investigating circulating allantoin levels in MDD patients which could add support or otherwise for this proposition.

Inflammation, oxidative stress, nitrosative stress and mitochondrial dysfunction

There is extensive evidence of increased inflammatory markers such as TNF-α and C-reactive protein (CRP) in the tissues of patients with SZ [31–33], BPD [34–37] and MDD [38–41]. The existence of elevated ROS and RNS, and a compromised anti-oxidant response network in the blood and tissues of these patients, has also been demonstrated beyond reasonable doubt [54–58]. The presence of gross mitochondrial dysfunction in the peripheral tissues, platelets and PBMCs of patients with MDD, BPD and SZ has also been repeatedly demonstrated [58–61].

Interdependency of endothelial dysfunction and inflammation

There is extensive evidence of impaired vascular dysfunction, inflammation and senescence in MDD patients. This includes high levels of sICAM-1 and VCAM-1 [395, 396] von Willebrand factor (vWF) [397–399] and elevated levels of TNF-α, IL-6 and C-reactive protein, reviewed in [400]. In addition, vWF may be considered as a trait marker for MDD as this molecule is consistently higher in patients with depression irrespective of anti-depressant (AD) status [397, 399]. Furthermore, a strong positive correlation between sICAM and sVCAM-1 levels and the extent of white matter hyperintensities in MDD patients has been reported suggesting a causative role of endothelial dysfunction in the development of the illness [395]. This proposition is supported by a study reporting a positive and robust correlation between the extent of vascular inflammation and arterial stiffness and the severity of depressive symptoms and dysfunction [401], reviewed in [402]. Understandably, there has been a great deal of research into the causes of endothelial dysfunction in MDD and most evidence suggests that it may be due at least in part to increased NADPH oxidase-mediated superoxide levels in ECs and a subsequent reduction in NO-mediated vasodilation [403, 404], reviewed in [405].

Numerous research teams have provided evidence of endothelial activation inflammation and dysfunction in BPD irrespective of the phase of the illness. Levels of dysfunction may however vary between patients in the depressive euthymic and depressive states of this psychiatric illness and during the course of the illness [78, 396, 406]. For example, BPD patients in a later, progressive stage of disease display significantly higher levels of sICAM-1 levels compared to individuals in an earlier stage of their illness [407]. High sICAM levels are found in the manic and depressive phases of BPD suggesting that sICAM-1 may be a trait marker [396]. However, there is evidence to suggest that sICAM levels are higher in mania than the depressive phase of the illness, indicating that sICAM could also be a useful state marker in the illness [408]. Furthermore, levels of endocan and urotensin-II, which are markers of EC senescence and activation, respectively [409, 410], are higher in patients with acute mania than those in the euthymic state which in turn were higher than healthy controls [78]. Increased endothelial cell activation in mania is suggestive of elevated levels of NF-κB which is consistent with data demonstrating higher levels of inflammation and oxidative stress in mania compared to other phases of the illness—reviewed in [58]. Hence, the level of endothelial dysfunction seen in BPD may be related to high levels of systemic PICs, ROS and RNS.

There is extensive evidence of endothelial dysfunction and inflammation in many patients with SZ which includes high levels of sICAM-1, sVCAM1 and vWF in the periphery and high levels of VCAM-1, VE-cadherin and a range of tight junction proteins in the brain [411–415]. However, there is increasing evidence that endothelial activation and dysfunction may be confined to or at least be greatly enhanced in an inflammatory subtype of schizophrenia [411, 415]. However, in these latter patients, levels of vWF display a robust and positive correlation with disease severity [412, 416] and increase during psychotic episodes [413]. Finally, it is noteworthy that there is an inverse linear relationship between vWF levels and basal ganglia volume that strongly suggests the involvement of inflammation-mediated endothelial damage in the pathophysiology of the syndrome in at least some patients [79, 412].

Effects of anti-depressants and anti-psychotic therapy on endothelial function

Several authors of large prospective studies have reported significantly reduced cardiovascular events in MDD patients who responded to antidepressant therapy (AD) compared to those who did not [417, 418]. Decreased platelet activity is another replicated finding in MDD patients in remission following prolonged AD consumption [419, 420]. Responders to AD display significant improvements in markers of endothelial dysfunction and inflammation as measured by increased flow-dependent endothelial-mediated dilation and decreased levels of IL-6 [397, 419, 421, 422]. For example Lopez-Vilchez and fellow workers' reported endothelial inflammation and significant endothelial damage and inflammation in their trial participants at diagnosis which normalised following treatment with escitalopram for 24 weeks which suggests that endothelial dysfunction in MDD patients is reversible [397]. It is also noteworthy that the weight of evidence suggests that vascular and hemodynamic parameters improve in responders to AD therapy irrespective of cardiovascular risk or the consumption of medicines aimed at treating blood pressure known to impact vascular function [423]. ADs may not be equally effective in improving endothelial dysfunction however, and there is some evidence to suggest that improved endothelial function may be greater in males than females [424].

There is also some evidence to suggest that the benefits of low-dose lithium in BPD and stroke may arise in part from improved endothelial function and decreased levels of EC inflammation and death [425–427]. There is also some suggestion that this may be true of valproate and lamotrigine [428]. However, the data regarding valproate is mixed and there is evidence that this drug compromises endothelial function in many patients—reviewed in [429]. The data regarding the use of atypical psychotics in SZ looks equally bleak with accumulating evidence suggesting that atypical anti-psychotics have a detrimental effect on endothelial function [430, 431], reviewed in [432]. However, some authors have reported decreased levels of iCAM-1 in SZ patients following administration of atypical anti-psychotics suggesting that the effects of these drugs on the vascular endothelium are more complex than is generally appreciated [433], reviewed in [396].

Socioeconomic behavioural and psychosocial factors in the development of CVD

Several behavioural psychosocial and socioeconomic factors are associated with increased risk of CVD [434–436]. Socioeconomic disadvantage (SED) is associated in longitudinal studies with significantly increased levels of T2D, obesity, MDD, anxiety, BPD, SZ and hypertension in adolescence and later adulthood [437–441]. These illnesses are all associated with high levels of vascular senescence [107, 442–444] and high levels of systemic inflammation reviewed in [56]. This is of relevance as endothelial cell senescence [73] and low-grade systemic inflammation [445, 446] play important causative roles in the development and acceleration of CVD. Hence, increased systemic low-grade inflammation and endothelial senescence in childhood and adolescence go some way to explaining the association between SED in children and increased risk of CVD in adulthood.

Several studies have reported a significant causative association between increased low-grade systemic inflammation and high-fat, high-carbohydrate diets [447, 448], sedentary behaviour or suboptimal physical activity [449, 450], lack of sleep [451, 452], smoking [453, 454] and alcohol consumption [455]. This contributes to an understanding of the various lifestyle risk factors operative during childhood and adolescence and the development of CVD.

Bipolar mania or depression and MDD are independently associated with increased endothelial dysfunction as assessed by the reactive hyperaemia index and flow-mediated dilation (FMD) [456, 457]. In addition, behaviours such as smoking, diet, physical activity and social interactions all influence the risk of developing MDD, BPD and SZ [458, 459]. Furthermore, these behaviours appear to be more common in socioeconomically disadvantaged children and adolescents [436]. These findings illustrate the complexity and interdependence of the factors underpinning experiences during childhood and behaviours during childhood and adolescence and future CVD risk and the need for holistic remedial measures. In addition, there is evidence to suggest that the behaviours and psychological distress associated with socioeconomic deprivation may result from limited life choices and are in many cases not related to personality or any underlying psychological abnormalities [460]. It is however interesting to note that the association between socioeconomic deprivation and CVD may stem from perceived rather than objective socioeconomic status [461]. In fact, there is data suggesting that lower subjective social status is associated with impaired EC function and vasodilation rather than objective measures of income and education [462, 463].

Finally, several authors have reported significant associations between type D personality (negative affectivity and social inhibition) [464, 465] and depressive or irritable temperament [466, 467]. The causes of these associations are not fully understood, but in the case of type D personality, adverse lifestyle choices predictive of CVD development appear to be an important factor while irritable temperament is predictive of increased vascular stiffness and hypertension [465, 468, 469]. There is also an argument that a type D personality and/or an irritable

temperament make an individual more susceptible to the effects of environmental stressors and experience the physiological effects of chronic stress such as increased glucocorticoid receptor resistance [470]. This is relevant from the perspective of increased CVD risk as this state is an acknowledged cause of endothelial dysfunction and activation [471, 472]. Prolonged elevation of glucocorticosteroids also compromises endothelial function via several other routes such as increasing production of EC, hydrogen peroxide and superoxide levels and reducing the production of endothelial nitric oxide synthase [473, 474].

The origin of endothelial dysfunction in mental illnesses—a working hypothesis

High levels of IL-6, IL-1 and TNF-α are commonly reported in patients with MDD and BPD both in the periphery and in the brain [475–478]. This is also true of many patients with SZ [60, 411]. In addition, there is a consensus that oxidative and nitrosative stress is involved in the pathophysiology of all three illnesses as previously discussed [58, 60]. This is relevant as numerous research teams have described that increased endothelial cell activation is stimulated by increased levels of ROS and RNS [479, 480]. Increased levels of TNF-α, IL-6 and IL-1 are also well-documented causes of increased activation, senescence and dysfunction of the vascular endothelium [481, 482]. In addition, ADs reduce levels of TNF-α, IL-6 and other PICs [483, 484]. They also reduce levels of ROS while stimulating enzymatic and non-enzymatic anti-oxidant systems [485, 486]. Hence, the improvements in vascular function following AD therapy may be related to reduced levels of inflammation and oxidative stress. In addition, lithium reduces oxidative stress and inflammation [487], suggesting that the proposed benefits of the drug on endothelial function may also be due to reduced levels of PICs, ROS and RNS. Thus, it seems reasonable to propose that the endothelial dysfunction seen in MDD, BPD and SZ is a consequence of the oxidative stress and inflammation attribute of the illnesses.

We tentatively suggest that the initial stages of endothelial dysfunction and activation are instigated by TNF-α and ROS which are secreted by activated macrophages. These appear to be involved in the pathophysiology of mental illnesses at a very early stage in their development [488, 489]. High levels of TNF-α and the ROS superoxide and hydroxyl radicals are vital elements in the development of ECs as they play a dominant role in degrading the protective glycolax layer lining the luminal side of the vascular endothelial layer which otherwise protects these cells against the effects of inflammatory mediators [490–492].

Once exposed, ECs are vulnerable to activation and/or damage resulting from engagement of TNF-α, IL-1β and IL-6 with their cognate receptors [490, 493]—reviewed in [494]. The resultant activation of NF-κB produces the same range of pathological consequences as seen in the process of atherosclerosis instigated by adverse changes in arterial blood flow described above. There is much evidence to support this process as an initial cause of endothelial dysfunction in mental illnesses and cytokine- and ROS-mediated atherosclerosis is now recognised as a separate endophenotype distinct from atherosclerotic processes exacerbated by dyslipidaemia [495].

However, despite our current working hypothesis, we would caution against the view of endothelial dysfunction as an epiphenomenon in MDD, BPD and SZ. In fact, there is extensive evidence that endothelial activation and dysfunction may play a major role in the development and exacerbation of systemic inflammation and increased activation of the coagulation cascade in a process described as immunothrombosis, and hence, an activated endothelium is likely to play a pathophysiological role in each of these illnesses [490, 496].

Treatment suggestions

Statins

There is extensive evidence of improved eNOS function following statin administration [497, 498]. However, the bulk of such evidence originates from in vitro studies involving levels far exceeding doses used in clinical studies [499]. In addition, there appears to be little or no benefit on eNOS function when a statin is administered in vivo [500]. Reports of decreased eNOS activity and NO levels, either during therapy or following discontinuation, are also a concern [501, 502]. However, there is extensive evidence of improved endothelial function in individuals prescribed statins for hyperlipidaemia and peripheral vascular disease and in patients at high risk due to cigarette consumption [500–504]. Unfortunately, this effect does not appear to extend to individuals with normal levels of cholesterol [500, 502, 503]. Similarly, evidence provided by research teams investigating the in vivo effect of statin administration on platelet function suggests that any measurable benefit is limited to ADP-stimulated PA in patients with hyperlipidaemia [505, 506]. Despite such ambiguity, evidence that in vivo administration of statins produces a significant reduction in MPO levels in conditions such as T2D and acute coronary syndrome is encouraging, although there does not seem to be any published evidence regarding statin-mediated effects on MPO levels in patients with normal levels of cholesterol [507, 508]. In addition, there are data, albeit from animal and in vitro studies, to suggest that statin therapy might upregulate levels of KLF-4 and/or KLF-2, which is clearly a desirable therapeutic attribute [509–511]. However, there are also reports of decreased KLF-2 and KLF-4 following statin administration [509–511].

There is also some suggestion that statin-induced muscle damage may be mediated, at least in part, by increasing the activity of XO [512].

More positively, several research teams have reported significant decreases in CRP levels following prolonged statin therapy, which is significant as CRP levels are a powerful predictor of myocardial infarction [513–515]. There is also some evidence to suggest that statin usage reduces circulating levels of TNF-α in patients with hyperlipidaemia and may also reduce activity of NF-κB in established CVD [516–518]. The situation as far as the management of oxidative stress is concerned appears to be more uncertain, however, with a suggestion that lipid peroxidation may be alleviated in the circulation following statin therapy, but levels of ROS may well be increased. For example, a recent meta-analysis concluded that malondialdehyde (MDA) levels in the bloodstream were reduced in patients with hyperlipidaemia compared with pre-treatment levels [519]. However, this does not appear to be the case in people with normal cholesterol levels [520]. Furthermore, there is accumulating evidence to suggest that statin usage increases mtROS production leading to elevated levels of circulating and intracellular hydrogen peroxide [521, 522], reviewed in [523].

There is also accumulating evidence suggesting that statin usage inhibits the enzymes of the ETC in muscle cells and elsewhere leading to significant levels of mitochondrial dysfunction and increasing levels of hydrogen peroxide [521, 524]. There is also increasing concern about statin toxicity [525] and increased risk of developing T2D [526, 527]. The data associating statin usage with increased oxidative stress and mitochondrial dysfunction clearly give pause for thought as oxidative stress and mitochondrial dysfunction are thought to play a pivotal role in the pathophysiology of neuroprogressive illnesses, as discussed above.

The mechanisms explaining statin-induced mitochondrial dysfunction are not fully understood but would appear to involve other factors in addition to inhibition of the ETC, such as compromised AMPK- and mTOR-regulated signalling pathways [521, 524]. Perhaps most importantly, this phenomenon also appears to be due to impaired synthesis of coenzyme Q_{10} (CoQ) [528, 529]. The potentially paramount importance of this latter mechanism is emphasised by evidence that statin-induced myopathy, resulting from induced mitochondrial dysfunction, may be greatly ameliorated or even extinguished following supplementation with CoQ [530, 531]. Hence, combining the use of statins and CoQ would appear to be advisable if the former is administered to the patients described in this paper. There is also the potential for therapeutic synergy between the two preparations as far as relieving endothelial dysfunction and inhibiting the development or progression of atherosclerosis is concerned, reviewed in [532]. Hence, we consider this proposal below.

Coenzyme Q_{10}

There is a substantial and accumulating body of evidence suggesting significant and relatively large improvements in endothelial function following CoQ administration in individuals with established CVD and those who are CVD-free [533], reviewed in [534]. Moreover, these positive effects appear to be mediated by improved mitochondrial function and the reduction in mtROS-mediated EC dysfunction and reduced EC senescence [535–538]. There are also reports of improvement in endothelial function in T2D and CVD following CoQ supplementation in patients optimally treated with statins [539, 540]. These data would appear to strengthen further the argument for combining these two preparations in an attempt to mitigate CVD risk in patients with neuroprogressive illnesses [539, 540]. Given the above information, it probably comes as no surprise to learn that there are several studies suggesting that CoQ arrests the development of atherosclerosis (reviewed in [541]), CVD morbidity and CVD mortality [542], although it should be noted that the results reported by such studies are somewhat inconsistent [543].

Several research teams have also reported reduced PA following CoQ supplementation, which is consistent with a potential role in mitigating the risk of developing CVD [544–546]. However, there do not appear to be any published studies investigating the effect of CoQ on XO in humans and the evidence regarding any effect on UA is mixed, with decreases and increases in circulating levels being reported [547, 548]. In addition, data supporting the use of CoQ supplementation as a means of reducing MPO levels in the circulation are currently limited to the results of a solitary study confirming a significant benefit when co-administered with n-3 polyunsaturated fatty acids (PUFAs) [549]. Furthermore, a literature search has failed to locate any published study examining the effects of CoQ on KLFs, whether in vivo or in vitro.

The anti-inflammatory effect of CoQ supplementation is well established as several recent meta-analyses and prospective studies have reported a significant decrease in PICs and surrogate markers of elevated ROS and RNS in the peripheral circulation following CoQ administration in several illnesses, most notably metabolic syndrome and multiple sclerosis [550–553]. There is also some evidence to suggest that these effects are mediated by reduced activity of NF-κB [535, 554]. Several authors have also reported significantly improved mitochondrial function following the administration of standard formulations of CoQ and a formulation modified specifically

to target mitochondria and often described as mitoQ [535, 537, 538].

In addition, there is evidence to suggest that CoQ supplementation may reduce the severity of symptoms experienced by patients with BPD in the depressive phase of their illness [555, 556]. There is also a solitary study reporting a significant reduction in the negative symptoms suffered by many patients with SZ following prolonged supplementation with this quinone [557]. Furthermore, CoQ supplementation has the potential to alleviate the shortfall in the production of this molecule seen in many patients with MDD [558]. The cause of this observed phenomenon is not fully understood, but it should be noted that chronic oxidative stress is a major cause of CoQ depletion [559–561]. It should also be noted that depleted CoQ levels are an independent cause of mitochondrial dysfunction [562, 563]. This coenzyme also has an excellent record of tolerability and safety established in a plethora of long-term studies, even at levels up to 2400 mg per day [564, 565].

CoQ depletion in a cellular environment of chronic oxidative stress may also be potentially addressed with the addition of n-3 PUFAs which improves the synthesis of the former molecule [566]. There is also evidence to suggest that a combination of CoQ and n-3 PUFAs, most notably docosahexaenoic acid (DHA), or eicosapentaenoic acid (EPA), may result in synergistic benefits in the treatment of atherosclerosis [567]. This would also seem to be true of a combination of n-3 PUFAs and statins [568], reviewed in [569]. Moreover, recent data suggest that the benefits may be even greater with "triple therapy" without any significant decrease in tolerability or overall increase in side effects [570]. Hence, the examination of potential benefits of n-3 PUFA supplementation and its ability to target identified contributors to the development of endothelial dysfunction and atherosclerosis will form the final section of this paper.

n-3 PUFAs

Several reviews and meta-analyses have highlighted significant and relatively large improvements in endothelial function following supplementation with EPA or DHA as measured by flow-mediated dilation [571–573]. The fact that this benefit would appear to apply to individuals with a high risk of developing CVD and individuals whose risk of developing such a disease appears to be normal or low is encouraging [571–573]. Data suggesting that dietary supplementation with EPA and/or DHA improves platelet function and decreases PA in low- and high-risk individuals also suggests that PUFA supplementation may be of value in addressing high CVD risk in patients with neuroprogressive illnesses [574, 575], reviewed in [576]. A solitary report of improved KLF-4 activity following DHA or EPA is also noteworthy [577]. However, there would appear to be no effect on MPO levels following supplementation with DHA, at least in healthy volunteers, although the doses of PUFAs involved were low and MPO levels were normal in the participants involved [578].

RCTs and meta-analyses involving human participants without and with evidence of underlying pathology have reported significant reductions in levels of PICs in the circulation following prolonged dietary supplementation with n-3 PUFAs [579–581]. There is extensive evidence of a significant and large reduction in levels of circulating oxidative stress markers such as MDA and isoprostanes following n-3 PUFA supplementation [582–584]. There is also evidence to suggest that EPA or DHA improves mitochondrial function and may protect mitochondrial membranes from radical-mediated damage [585, 586].

A recent large study reported a negative correlation between plasma EPA concentration and levels of IL-6 and TNF-α in patients with BPD [587]. Reduced circulating PUFA levels would also appear to be associated with increased circulating markers of inflammation and oxidative stress in patients with SZ, at least in the acute phase of their illness [588]. These results are echoed by meta-analyses reporting low circulating PUFA levels in the blood of patients with MDD, which also appears to be associated with increased production of PICs and ROS [589]. Finally, there is also accumulating evidence suggesting that DHA and/or EPA supplementation may make a significant contribution to alleviating symptoms in patients with neuroprogressive illnesses, reviewed in [590, 591].

Conclusions

In this paper, it has been shown how systemic inflammation, oxidative stress and mitochondrial dysfunction may drive the development of endothelial dysfunction and atherosclerosis. In particular, circulating PICs and ROS may induce inflammation, oxidative stress and mitochondrial dysfunction within ECs, either directly or indirectly via inducing high levels of platelets and PA, and increased MPO and XO activity, which are independently associated with increased cardiovascular risk. The applications of these and related molecular mechanisms to MDD, BPD and SZ have been described in detail, including evidence for the role of potential generators of EC dysfunction and activation in such neuroprogressive disorders. It is recommended that the treatment suggestions based on these molecular mechanisms which are mentioned in this paper should be the subject of further, well-powered RCTs.

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