Treat Preeclampsia by Targeting NFκB by Drugs

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Preeclampsia (PE) is characterised by high levels and activity of the transcription factor Nuclear Factor kappa B (NFκB) in the maternal blood and placental cells. This factor is responsible for the regulation of over 400 genes known to influence processes related to inflammation, apoptosis and angiogenesis, and cellular responses to oxidative stress and hypoxia. Although high NFκB activity induces hypoxia and inflammation, which are beneficial for the process of implantation, NFκB level should be reduced in the later stages of physiological pregnancy to favour maternal immunosuppression and maintain gestation. It is believed that the downregulation of NFκB activity by pharmacotherapy might be a promising way to treat preeclampsia.

Treatment Preeclampsia Nuclear Factor Kappa B NFκB

1. Introduction

Preeclampsia (PE) is responsible for 5–10% of pregnancy complications and is recognized as one of the most common reasons for maternal and foetal death. While it generally appears after week 20 of pregnancy, cases with very early (i.e., before week 20) and very late symptoms (i.e., in the first 6 weeks after birth) have been reported [1][2]. The guidelines presented by international obstetrics and gynaecology societies characterise preeclampsia as the sudden occurrence of hypertension (i.e., >140 mmHg systolic or >90 mmHg diastolic) in previously normotensive women, accompanied by proteinuria (i.e., >300 mg for 24 h or at least 2+ on a dipstick). Preeclampsia can also be recognised by the presence of hypertension complicated by at least one of the following symptoms: serum creatinine level >1 mg/dL, elevated transaminase levels, thrombocytopenia, haemolysis, neurological disorders, or uteroplacental dysfunction (i.e., foetal growth restriction) [3][4].

A considerable body of evidence indicates that blood from patients with preeclampsia demonstrates a high level of inflammatory factors (such as: TNF-α, IFN-γ, IL6 or IL1) and reactive oxygen species (ROS), and that preeclamptic placentas display features indicative of chronic hypoxia throughout the gestation period [5][6][7]. Inflammation, oxidative stress, ineffective angiogenesis, and hypoxia are regulated at the cellular level by numerous pathways, most of which are under the control of nuclear factor kappa B (NFκB) [8]. NFκB level and activity are both upregulated in maternal and placental cells, and as this upregulation is strongly linked with the pathomechanism of preeclampsia, it is possible that preeclampsia could be treated by drugs targeting the mechanism of NFκB activation. Interestingly a number of agents already adopted for the prophylaxis and treatment of preeclampsia are believed to modulate NFκB activity.

2. NFκB and Its Relationship with Preeclampsia Development

To prepare for pregnancy, the endometrium demonstrates an extensive increase in NFκB expression to prepare maternal tissues for the opening of the implantation window in the case of fertilization [9][10][11], and this NFκB activation continues in the uterus during the implantation period [8][9][10]. NFκB activation affects the regulation of inflammatory factors, such as TNFα, IL6, IL8, and IFN-γ, secreted by the endometrial cells, as well as by the natural killer cells (NK), macrophages, dendritic cells, or lymphocytes of the maternal immune system that are recruited to the site of implantation [7].

It is possible that the intensity of inflammatory reaction, related to the strength of NFκB activation, might play a significant role in the success of implantation. The rise in the levels of proinflammatory cytokines may disturb the delicate inflammatory reactions at the feto–maternal interface during implantation, leading to its failure or pregnancy loss [12]. Moreover, such abnormal maternal inflammation has been also found to impair the remodeling of uterine spiral arteries and alter uteroplacental perfusion, leading to the development of features of preeclampsia in a rat model [13]. Abnormal, shallow placentation forces trophoblastic cells to live under hypoxic conditions, which generates oxidative stress and intensifies the inflammatory reaction. These processes are strongly influenced by the presence of NFκB, whose level and activity is downregulated over the course of a non-complicated gestation. In preeclampsia, NFκB level and activity are significantly elevated in the maternal blood and have been found to be up to 10-fold higher in placentas than controls [14][15].

Interestingly, although preeclampsia is characterised by elevated NFκB activity, its mechanism of activation remains poorly explored. It is postulated that oxidative stress favours the degradation of NFκB inhibitors in lymphocytes and aortic endothelial cells by proteosomes [16][17]; however, no such findings have been noted in human umbilical vein endothelial cells or preeclamptic placental samples [18][19].

Unstimulated cells demonstrate only basal levels of NFκB in the cytoplasm. This level is maintained by various inhibitors, of which IκBα (NF-Kappa B Inhibitor Alpha) and IκBβ (NF-Kappa B Inhibitor Beta) are the most common. These bind to NFκB and prevent its activation i.e., its phosphorylation and translocation into nucleus. However, in environments rich in reactive oxygen species or cytokines, NFκB activation takes place, driven by various NFκB activators. Among these, IKKα (Inhibitor of Nuclear Factor Kappa B Kinase Subunit Alpha), IKKβ (Inhibitor of Nuclear Factor Kappa B Kinase Subunit Beta), IKKγ (Inhibitor of Nuclear Factor Kappa B Kinase Subunit Gamma), and CK2 (Casein kinase 2) are implicated in the three most widely-studied pathways: canonical, non-canonical, and atypical [20].

Interestingly, in preeclamptic placentas, the canonical, non-canonical, and atypical activation pathways do not seem to play a significant role in the process of NFκB activation. In the canonical pathway, various NFκB activators (i.e., IKKα, IKKβ and IKKγ) are downregulated, whereas the inhibitors (i.e., IκBα, IκBβ) are upregulated [18][21]. Similarly, NFκB activators participating in the non-canonical (i.e., IKKα) and atypical pathways (i.e., CK2) are also downregulated. This suggests that preeclamptic placentas employ specific NFκB activation mechanics: their activity is independent of IKKα, IKKβ, IKKγ, and CK2, and avoids the cytoplasmic and proteosomal degradation by

NFκB inhibitors such as IκBα or IκBβ. Some studies suggest that this mechanism may be dependent on the activity of a p53/RSK1 (Tumour Protein p53/Ribosomal Protein S6 Kinase A1) complex [18][20].

Independently of the molecular mechanism of NFκB activation, this factor is strongly linked with oxidative stress and inflammation. Under such conditions, placental cells secrete a range of proteins controlling vascular function, such as arginase II, endothelin-1 or soluble fms-like tyrosine kinase 1 (sFlt-1), and undergo apoptosis, shedding apoptotic debris into the maternal circulation. All of these factors contribute to maternal endothelial dysfunction, which the main cause of clinical symptoms in patients with preeclampsia [22][23][24][25][26][27].

3. Targeting NFκB by Aspirin

Early supplementation with low doses of aspirin, i.e., acetylsalicylic acid (ASA), is effective in preventing preeclampsia. However, although aspirin treatment improves the outcome of pregnancy, reducing the risk of preterm preeclampsia by approximately 30–62%, conflicting data exists regarding the optimal dose and time of initiation of ASA intake [28][29][30]. In numerous countries, the guidelines prepared by cardiology, gynaecology and obstetrics societies recommend the initiation of aspirin treatment before week 20 (optimum before week 16) of gestation among high- and moderate-risk women (**Table 1**).

Table 1. Recommendations given by selected organisations regarding ASA supplementation as preeclampsia prophylaxis among moderate and high-risk groups *.

Selected Word Organisation (Year)	ASA Dose	Initiation ASA Supplement	Bibliograph
World Health Organisation (WHO) (2011)	75 mg/day	<week 20	[31]
German Society of Gynaecology and Obstetrics (DGGG) (2015)	100 mg/day	no data	[32]
French Society of Cardiology (FESC)/French Society of Hypertension (2016)	75–160 mg/day	<week 20	[33]
The American College of Obstetricians and Gynaecologists (ACOG) (2018)	81 mg/day	week 12–28 Optimum <16	[34]
European Society of cardiology (ESC)/European Society of Hypertension (ESH) (2018)	100–150 mg/day	week 12	[35]
New Zealand Committee of the Royal Australian & New Zealand College of Obstetricians & Gynaecologists (RANZCOG) New Zealand College of Midwives (NZCOM) (2018)	≥75 mg/day optimum 100 mg/day	week 12	[36]

Selected Word Organisation (Year)	ASA Dose	Initiation ASA Supplement	Bibliograph
The International Society for the Study of Hypertension in Pregnancy (ISSHP) (2018)	75–162 mg/day	<week 20 Optimum <16	[37]
International Federation of Gynaecology and Obstetrics (FIGO) (2019)	150 mg/day (at night)	week 11–14	[38]
National Institute for Health and Care Excellence (NICE) (2019)	75–150 mg/day **	week 12	[39]
Polish Society of Hypertension (PTNT), Polish Cardiac Society (PTK) and Polish Society of Gynaecologists and Obstetricians (PTGiP) (2019)	100–150 mg/day	<week 16	[40]
International Society of Hypertension (ISH) (2020)	75–162 mg/day	week 12	[41]
Society for Maternal-Fetal Medicine (SMFM) (2020)	81 mg/day	week 12–28 Optimum <16	[42]

* The mentioned risk factors may vary slightly between organisations. Generally, high risk is associated with a history of preeclampsia, an adverse outcome in a previous pregnancy, expecting more than one child, chronic hypertension or with type 1 or 2 diabetes mellitus; renal disease; or autoimmunological disorders. Moderate risk is associated with more than one of the following factors: nulliparity (first pregnancy), age over 35–40 years, obesity, first-degree family history of preeclampsia, low socioeconomic status, personal history of low birthweight, previous adverse pregnancy outcome, or pregnancy interval of more than 10 years between pregnancies. ** Although this use is common in UK clinical practice, aspirin did not have marketing authorisation in the UK for this indication.

After oral consumption, aspirin is quickly absorbed in the stomach and hydrolysed into salicylic acid in the intestinal circulation. The distribution of the drug peaks 30 min from oral administration. The half-life of aspirin varies between species with the 13–31 min in human subjects. Aspirin is most widely known for inhibiting arachidonic acid, which is converted into prostaglandins and thromboxane A2 (TXA2) by cyclooxygenase 1 (COX-1) or cyclooxygenase 2 (COX-2). The former is a constitutive enzyme, while the latter an inducible by inflammatory reaction, hypoxia or oxidative stress enzyme [43].

In preeclampsia, the presence of free radicals, cytokines, and sFlt-1 influences endothelial dysfunction and COX activation, shifting the PGI2/TXA2 ratio in favour of TXA2 production [43]. It is believed that aspirin treatment lowers thromboxane production by inhibiting COX activity. However, its action is much broader: it may well modify the cellular response, influencing NFκB regulation pathways. Experiments conducted on lipopolysaccharide (LPS)-stimulated human and mouse lymphocyte cell lines, such as Jurkat T and PD 31, indicate that salicylate supplementation of the cell medium inhibited the expression of genes regulated by NFκB in these cells.

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Aspirin is an efficient agent in the inhibition of inflammatory reaction. ASA administration results in the downregulation of the transcription of the pro-inflammatory cytokines TNFα, IFN-γ, IL6, and IL8, whose genes are regulated by NFκB [44]; all of these cytokines are strongly linked with the pathomechanism of preeclampsia. It is possible that oral administration of ASA before 16 weeks of gestation effectively inhibits the secretion of these factors by maternal immunological cells, enabling a switch from a pro-inflammatory cytokine profile, associated with Th1 and Th17 cells, to an anti-inflammatory one, associated with Th2 lymphocytes. This switch is desirable for maintaining the correct course of pregnancy [45]. This anti-inflammatory activity of salicylates is linked with the regulation of NFκB activity; indeed, aspirin prevents NFκB nuclear translocation and its consequent binding to the motif element on DNA [46][47]. Alternatively, it was also found that aspirin serves as a competitive inhibitor of ATP, binding to the IKKβ protein, one of the activators of NFκB in the canonical pathway [48]. Following its inactivation, IKKβ cannot activate NFκB, thus inhibiting its nuclear translocation [48][49].

In human umbilical vein endothelial cells (HUVECs), aspirin treatment has been found to counter the mechanism of NFκB-binding with DNA in response to TNFα. This dose-dependent inhibition was related to a reduction in the expression of VCAM-1 and E-selectin; indeed, the NFκB binding motif is present in the genes coding for these molecules [50].

As inflammatory processes taking place during placentation are linked to cancer development [51], it is possible that cancer cells and placental cells might demonstrate a similar response to aspirin treatment. HeLa cells were found to be sensitized to TNFα by aspirin, resulting in apoptosis, and this action was directly related to the repression of NFκB [52]. Moreover, supplementation of cell culture medium by aspirin in an environment rich in TNFα and IL6 or reactive oxygen species (ROS) reduced the phosphorylation and/or degradation of NFκB inhibitors i.e., IκBα and IκBβ [52][53].

4. Antihypertensive Therapy Modulates the NFκB Pathway

4.1. Agonist of Alpha-2 Adrenergic Receptors and NFκB

Methyldopa is an agonist of alpha-2 adrenergic receptors, which inhibit vasoconstriction and down-regulate catecholamine levels in the blood. As this drug regulates blood pressure without affecting the maternal uterine artery, it does not appear to have any negative impact on uteroplacental circulation or foetal growth [54]. Alpha-2 adrenergic receptor agonists were found to influence the transcriptional activity of NFκB in PC12 cell line. Although its precise mechanism has never been studied, it has been suggested that alpha-2 adrenergic receptor activation induces the transcriptional nature of NFκB via phosphoinositide-3-kinase (PI3K) [55], a known upstream regulator of NFκB [7][56].

4.2. Beta-Blockers Modulate NFκB Activation Pathways

Labetalol representing beta-blockers is widely used as a first-line antihypertensive drug during pregnancy. It non-selectively antagonizes both beta-1 and beta-2 adrenergic receptors and also works as a selective inhibitor of

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alpha-adrenergic receptors. Interestingly, the activation of beta2 adrenergic receptors downregulates NFκB activation in HUVEC cells by lowering the level of the active (phosphorylated at Serine 536) form of NFκB in the nucleus. This nuclear depletion was related to the inhibition of phosphorylation and proteosomal degradation of kappa B inhibitor i.e., IκBα. This effect was totally reversed by beta-blockers [57], which might suggest that beta-blockers act as strong inductors of NFκB transcriptional activity in HUVEC cells.

4.3. Calcium Channel Blockers Inhibit the NFκB Activation Pathways

Calcium antagonists, i.e., calcium channel blockers including nifedipine, are recommended by numerous cardiologic, genecology, and obstetrician societies for the treatment of hypertension in pregnancy [35][40][58][59]. The ACOG Committee recommends the immediate release of nifedipine as a first-line drug for severe intrapartum or postpartum hypertension treatment [59]; however, the Society of Obstetric Medicine of Australian and New Zealand (SOMANZ) proposes that nifedipine should be considered as a second-line agent for lowering blood pressure in preeclampsia and for treating gestational or chronic hypertension [60].

Calcium channel blockers work by inhibiting calcium influx into vascular smooth muscle cells, resulting in arterial vasodilation and reduction of systemic vascular resistance [54][54]. Numerous in vitro studies indicate that calcium channel blockers participate in the suppression of immune reaction via the inhibition of activity of lymphocytes, macrophages or mast cells [61]. Interestingly, this function is probably realized via regulation of NFκB activation pathways. In a human epithelium-like lung carcinoma cell line, nifedipine was found to significantly inhibit the NFκB/DNA binding reaction, which may partly explain its immunosuppressive effect.

4.4. Hydralazine and Its Association with NFκB

The most controversial drug adopted for treating hypertension in pregnancy is hydralazine, as its use is associated with various adverse effects during pregnancy. Therefore, it is included as a second-line agent, when the other drugs have failed to achieve adequate blood pressure [35][58][60]. This drug is admitted as a first-line medication in the management of severe intrapartum or postpartum hypertension according to ACOG Committee recommendations [59]. Although its mode of action and association with the NFκB is still unclear, it was found to negatively regulate NFκB expression in a human fibroblast cell line [62]. However, in contrast, hydrazine treatment does not appear to influence the concentration or activity of NFκB in kidney and heart tissue from rats harbouring both human renin and angiotensin genes [63], nor modify NFκB activation pathways in human endothelial cells after stimulation with toxic concentrations of oxyLDL [64].

5. Targeting NFκB by Magnesium Sulphate Adopted for Prevention of Neurological Complication of Preeclampsia

Some of the most dangerous symptoms accompanying hypertension in preeclamptic women are associated with neurological disorders. Magnesium sulphate appears to demonstrate efficacy in the prevention of seizures in severe preeclamptic or eclamptic women. However, although moderately elevated serum magnesium is linked to a

Canonical, non-canonical and atypical pathways of nuclear factor κB activation in preeclampsia. *Int. J. Mol. Sci.* **2020**, *21*, 5574, https://doi.org/10.3390/ijms21155574.

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reduction of blood pressure [65], this drug is not recommended for hypertension treatment [3]. The seizure prophylaxis involving magnesium sulphate should be initiated in women with gestational hypertension with severe features or preeclampsia with severe features or eclampsia [3]. Magnesium sulphate is known to have an inhibitory effect on neural synapses; however, in addition to being a competitive antagonist to calcium, magnesium also controls over 300 enzymatic reactions, including those associated with glucose utilisation, protein, or nucleic acid synthesis [65]. In addition, this drug is frequently linked with NFκB activity and immunosuppression. The administration of magnesium sulphate to pregnant rats exposed to LPS was associated with a reduction of NFκB level and its activity in the brain of the foetus. This anti-NFκB property of magnesium was linked with the attenuation of foetal brain inflammation [66]. Similar results were also observed by others. In primary microglia cells from Sprague–Dawley rats, the secretion of prostaglandin (PGE2), IL1β, and TNF-α was suppressed after incubation with LPS in the presence of magnesium sulphate; this was also associated with lowered NFκB activity. Magnesium sulphate inhibits NFκB nuclear translocation, and thus its binding capacity to DNA, in a dose dependent manner after exposure to LPS [67].

Magnesium sulphate was also found to downregulate the inflammatory reaction in intrapartum women, term, and preterm neonates [68]. Monocytes isolated from umbilical cord blood and peripheral blood demonstrated lowered cytokine production (i.e., TNFα and IL6) after stimulation by LPS in the presence of magnesium sulphate. Magnesium inhibited the degradation of IκBα and thus increased its level in the cells; hence, monocytes exposed to magnesium salt presented low nuclear concentrations of phosphorylated NFκB after incubation with LPS [68].

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