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Review

Modulation of preeclampsia by the cholinergic anti-inflammatory pathway: Therapeutic perspectives

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ABSTRACT

The cholinergic anti-inflammatory pathway (CAP) is vital for the orchestration of the immune and inflammatory responses under normal and challenged conditions. Over the past two decades, peripheral and central circuits of CAP have been shown to be critically involved in dampening the inflammatory reaction in a wide array of inflammatory disorders. Additionally, emerging evidence supports a key role for CAP in the regulation of the female reproductive system during gestation as well as in the advent of serious pregnancy-related inflammatory insults such as preeclampsia (PE). Within this framework, the modulatory action of CAP encompasses the perinatal maternal and fetal adverse consequences that surface due to antenatal PE programming. Albeit, a considerable gap still exists in our knowledge of the precise cellular and molecular underpinnings of PE/CAP interaction, which hampered global efforts in safeguarding effective preventive or therapeutic measures against PE complications. Here, we summarize reports in the literature regarding the roles of peripheral and reflex cholinergic neuroinflammatory pathways of nicotinic acetylcholine receptors (nAChRs) in reprogramming PE complications in mothers and their progenies. The possible contributions of α7-nAChRs, cholinesterases, immune cells, adhesion molecules, angiogenesis, and endothelial dysfunction to the interaction have also been reviewed.

1. Introduction

Preeclampsia (PE) is a serious medical condition that appears in about 2–8% of pregnancies worldwide [1]. Despite the extensive research that has been conducted over the last few decades, PE remains a considerable cause of maternal as well as neonatal mortality and morbidity. Pathologically, PE is characterized chiefly by hypertension and proteinuria, and often culminates in serious disturbances in vital organs such as heart, kidney, liver and central nervous system (CNS) [2,3]. The mechanisms that underlie maternal and fetal perturbations during PE and potential therapeutic interventions remain largely defective or unidentified [4]. Nevertheless, one prevailing hypothesis suggests that the disorder is triggered by limited spiral artery invasion resulting in an inadequate utero-placental blood flow and diminished placental perfusion [5]. As a consequence of this emerging ischemia, a number of cellular derangements ensue including angiogenic dysregulation, systemic inflammatory response and imbalance of innate and adaptive immunity [4]. Eclampsia is one of the most serious complications of PE [6]. Several mechanisms have been proposed to explain the transition of pregnant females from PE into eclampsia. One hypothesis suggests that cerebral myogenic vasoconstriction and impaired cerebral blood flow autoregulation precipitate vasogenic edema [7]. The disruption and increased permeability of the blood brain barrier promote vasogenic edema. The subsequent extracellular space expansion in the enclosed area of the skull leads to progressive cerebral compression and the development of conventional neurological symptoms such as headache, nausea, vomiting and convulsions [8]. The dysfunctional blood brain barrier permits the passage of deleterious proteins and serum components into the brain and facilitates the eruption of seizures [9]. Moreover, the leakage of systemic cytokines into cerebral space promotes microglial neuroinflammation, neuronal excitability, and seizure susceptibility [10].

The cholinergic anti-inflammatory pathway (CAP) is a key regulator of inflammation during physiological and pathological conditions [11].

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In essence, a multitude of experimental studies have shown that upregulation of CAP constructively curtails inflammatory disorders including ischemia–reperfusion [12], sepsis [13], multiple sclerosis [14] and arthritis [15]. In a series of recent studies, we convincingly demonstrated the importance of CAP in protecting against the deleterious cardiovascular, renal, inflammatory, and survivability consequences of endotoxemia [16–20]. Borovikova and colleagues [21] were the first to reveal the presence of a neuronal anti-inflammatory machinery in which the brain stimulates the release of acetylcholine (ACh) from vagal efferent in response to inflammatory stimuli. The released ACh activates specific units of nicotinic acetylcholine receptors (nAChRs), principally the α7-nAChR, in immune cells to shut down the generation and release of pro-inflammatory cytokines [22]. Activation of CAP by α7-nAChR agonists, e.g., nicotine, inhibits release of multiple inflammatory cytokines including interleukin-1 (IL–1), tumor necrosis factor-alpha (TNF-α), and high mobility group box 1 (HMGB1), with the consequent suppression of local and systemic inflammatory response [23]. The downregulating effects of α7-nAChRs on inflammatory cascades that predispose to several critical illnesses have been repeatedly validated [24].

A careful review of the literature in the field of obstetrics and gynecology yields some insight into the understanding of the role of CAP in the female reproductive system. Almost all of the components of the inflammatory machinery, starting from macrophages and Toll-like receptors to the production of cytokines have been characterized in the reproductive system during the early and late phases of pregnancy [25–27]. The synthesis and release of cytokines are implicated in one way or another in all stages of the female reproduction including ovulation, placentation, regulation of placental blood flow, fetal development, cervical ripening, and parturition [25,28–32]. Importantly, the endogenous neurotransmitter, ACh, and nicotine are believed to stimulate α7-nAChRs on macrophages and interfere with the inflammatory cascade and cytokine surge triggered by Toll-like receptors and other inflammatory stimuli. Consequently, the CAP pathway appears to have substantial contribution to physiological and pathological regulation of female reproduction and pregnancy.

The synthesis, release and metabolism of ACh are dysregulated in placental tissues of PE females [33–35]. Moreover, the expression of α7-nAChRs is altered in placentas of PE females compared with those of normal pregnancies [33,36]. Considering the significant contribution of cytokines and inflammation to the pathogenesis of PE [37], it is reasonable to posit that the CAP might be a key player in the development of PE and its manipulation could represent a promising therapeutic strategy in PE. As outlined below, several lines of evidence exist that demonstrate a favorable role for CAP in offsetting the harmful complications of PE. To our knowledge, this is the first review to compile and summarize the evidence characterizing the therapeutic potential of central and peripheral pathways of CAP in PE. Furthermore, this review will shed the light on the most important mechanisms implicated in the PE-CAP interplay.

2. Placental basis of PE

Although the exact mechanism remains undisclosed, the pathogenesis of PE is mostly believed to be initiated by abnormal or dysfunctional placentation. The latter is provoked by irregularities in cellular pathways related to placental hypoxia, deficient heme oxygenase expression, genetic factors, oxidative stress, inflammation, and altered natural killer cell signaling [38]. Notably, systemic and placental inflammatory machineries have also been implicated in pathogenesis of PE [39]. Regardless of the etiology, abnormal placentation results in placental ischemia and consequently placental production of antiangiogenic factors and their release into the circulation. In normal pregnancy, the process of pseudo-vasculogenesis takes place in which cytotrophoblasts are transformed from an epithelial to endothelial subtype following the invasion of uterine arteries [40]. For this process to be completed successfully, cytotrophoblasts need to upregulate the expression of molecules that are required for uterine invasion, namely vascular endothelial growth factor (VEGF) and placental growth factor (PLGF). Conversely, the phenomenon of pseudo-vasculogenesis is incomplete in PE resulting in placental ischemia and release of hypoxia inducible factors. These latter downregulate expression of VEGF family members while upregulating the production of their inhibitors [41].

The roles of several placental antiangiogenic factors in PE pathophysiology have been identified in the last few years. For instance, the soluble fms-like tyrosine kinase 1 (sFlt-1) is a circulating receptor that captures and binds to VEGF and PLGF disallowing their binding to endothelial cell surface receptors and resulting in endothelial dysfunction. Previous studies revealed that sFlt1 levels increase in serum of preeclamptic patients and that their elevations correlate with reduced levels of circulating free VEGF and PLGF [42]. The soluble endoglins (sEngs) is another placenta related protein that is elevated during PE and binds to circulating transforming growth factor beta (TGF-β), thereby averting its binding to its interaction with TGF-β receptors [43]. Taken together, the interruption of VEGF and TGF-β signaling would result in enhancement of surface adhesion molecules and leukocyte adhesion, and consequently impairment of endothelium vasodilation and vascular autoregulation. This might explain the molecular mechanism of endothelial dysfunction and hypertension seen in PE. This view is strongly supported by experimental studies, which showed that the administration of sFlt-1 and sEng to pregnant rats evokes hallmark features of PE [44].

3. Maternal and fetal complications of PE

3.1. Maternal complications

PE is characterized by a systemic hypertension newly identified after 20 weeks of pregnancy and accompanied by considerable proteinuria and uteroplacental disturbances. If PE is associated with severe multiple complications posing very high risk of maternal and fetal morbidity and mortality, then it can be considered as severe PE. Persistent arterial hypertension (systolic blood pressure, SBP $\geq$ 160 mmHg or DBP $\geq$ 110 mmHg) or severe maternal organic perturbations (renal, hepatic, hematologic or cardiorespiratory dysfunction) characterize the presence of severe PE [45]. Besides, eclampsia takes place when pregnant preeclamptic women develop generalized motor seizures which might not be attributed to a coexisting neurological disorder [46]. Multiple serious complications can be generated in preeclamptic women demanding careful assessment and management by healthcare professionals. These complications may affect multiple systems including renal (acute renal failure), cardiovascular (pulmonary edema), hematological (coagulopathy and hemolysis) and hepatic (liver ischemia and dysfunction) systems [45].

PE evokes damage in the glomerular membrane causing reduction of glomerular filtration and renal blood flow and consequently renal dysfunction. The hypoxic conditions in PE promote placenta to release large amounts of sFlt-1, which interferes with the binding of VEGF to its receptors on podocytes and endothelial cells and disturbs the filtration barrier [47]. Glomerular endotheliosis together with thrombotic microangiopathy are the two main characteristics of kidney dysfunction in PE. There might be hyperuricemia in PE, but this is transient with plasma uric acid levels returning to normal values following delivery [48]. PE related oliguria, on the other hand, usually has a pre-renal cause, and thus saline administration is recommended in this case until normalization of urinary output [49]. Although the PE related kidney damage is ameliorated after the childbirth, permanent renal impairment may continue as a long-term complication [50].

Pulmonary edema is another maternal complication of PE with a seemingly multifactorial etiology. The elevation in capillary permeability, decrease in colloidal osmotic pressure and increase in vascular hydrostatic pressure associated with PE promote fluid extravasation in

the alveolar space and interstitium [51]. The identification and management of PE pulmonary edema is analogous to those of non-pregnant population. Therefore, IV furosemide, oxygen therapy, water restriction and vasodilators (hydralazine or nifedipine to reduce afterload) are recommended [51].

Hemolysis, elevated liver enzymes and low platelets syndrome (HELLP syndrome) are also serious complications of severe preeclampsia [52]. This syndrome is often characterized by hepatic dysfunction, microangiopathic hemolytic anemia and thrombocytopenia. In addition, severe proteinuria or hypertension might be present. HELLP syndrome usually develops with an acute onset and rapid deterioration of the maternal health condition. A significant portion of the cases presents prior to 28 weeks of gestation [53].

3.2. Fetal complications

PE is also a culprit in causing serious fetal complications including neonatal death, stillbirth, growth restriction, and prematurity connected consequences from early delivery [54]. Since an appropriate angiogenesis is a must for appropriate pulmonary vascular and airway development, the presence of an antiangiogenic condition like PE may predispose the neonates to broncho-pulmonary dysplasia. Indeed, offspring born to preeclamptic mothers with intrauterine growth restriction have a considerably higher odds ratio of developing bronchopulmonary dysplasia [55]. Additionally, PE predisposes infants to cardiovascular diseases. Previous reports indicate that children of preeclamptic mothers have higher pulmonary arterial pressure compared with those born to normal pregnancies. Thus, PE seems to have a lasting effect on the offspring‘s systemic and pulmonary circulation [44].

Besides, thrombocytopenia is a documented complication in neonates from preeclamptic mothers. The neonatal decrease in platelet count is usually identified within first 1–3 days after delivery, and is generally resolved by second week in most cases [56]. The etiology of this thrombocytopenia is unknown, however one potential explanation is that the PE related fetal hypoxia interferes with the fetal megakaryocyte proliferation [57]. Similarly, the PE induced uteroplacental insufficiency has a depressant impact on fetal bone marrow and production of myeloid cells which would provoke a reduction in neutrophil count, known as neutropenia [58]. Indeed, neonates born to preeclamptic pregnancies have increased risk of developing neutropenia compared to control newborns [59]. In this context, neutropenia is often self-limited, but it might demand treatment with granulocyte-colony stimulating factor in some severe cases [60].

Given the fact that fetuses are highly sensitive to disturbances in the uteroplacental blood flow, it is reasonable to predict that preeclamptic insults occurring during susceptible periods of fetal development would have lasting impact on the neonates and can increase the risk of diseases later in life beyond the immediate post-delivery period. As expected, accumulating evidence indicate that in utero PE programming increases the risk of various adulthood diseases including hypertension, obesity and coronary artery diseases [61]. For instance, a large population cohort study, which followed more than 1.5 million offspring from PE and control mothers over 27 years, demonstrated that exposure to PE during gestation increases risk of metabolic, endocrine, and nutritional disorders during early-adulthood [62]. Other observational studies also indicate that history of maternal PE correlates with elevated risk of diabetes and cardiovascular derangements in adulthood [63].

4. Pathogenic role of CAP in PE

Experimental and clinical studies have shown that several key components of CAP, e.g., acetylcholine, nAChRs, and cholinesterases, are altered in placentas and other tissues of PE females. This has led to the assumption that such modifications in CAP signaling might be causally related to PE pathogenesis.

4.1. Pharmacology of nAChRs

nAChRs are a large family of ligand-gated ion channel receptors that comprise approximately 17 subunits (α 1–10, β 1–4, γ, δ, and ε) and exhibit a variety of physiological and pathophysiological roles [64,65]. The prevailing assembly conformation of these subunits is heteromeric, despite the occasional presence of homomeric confirmations, particularly in α7 subunits [66]. Beside their classical locations in the nervous system and the motor end plate on skeletal muscles, several nAChR isoforms have been characterized in multiple non-neuronal (e.g., endothelial and epithelial) and immune cells (e.g., lymphocytes and macrophages) [67]. The α7 homomeric and α4β2 heteromeric subunits are among the most abundant types of nAChRs. The α7 unit usually binds to α-bungarotoxin and has fast kinetics and relatively low affinity for nicotine. Contrarily, the α4β2 receptor virtually has relatively slow kinetics, high affinity for nicotine, and does not bind α-bungarotoxin [65]. All neuronal nAChR subtypes in mammals are permeable to small monovalent and divalent cations including Na^+, K^+, and Ca^{2+}. Stimulation of nAChRs via endogenous (ACh) or exogenous (nicotine) agonists generally stabilize the ion channel at its open conformation for several milliseconds allowing the transient passage of small cations prior to the reversion of the channel to resting state or its transformation to a desensitized conformation that is unresponsive to further stimuli [68]. Temporary receptor exposure to high concentrations of synaptic acetylcholine induces synchronous opening of the nAChRs' channel pores [67].

Compared with other nAChRs, the α7-nAChR has a relatively higher permeability and selectivity for Ca^{2+}. The Ca^{2+} influx via α7-nAChR can also induce Ca^{2+} release from intracellular stores, which further amplifies the levels of cytosolic Ca^{2+}. Therefore, Ca^{2+} seems to transduce the α7-nAChR actions and modulate interrelated signaling pathways and gene expression networks [69]. The aforementioned ionotropic actions of α7-nAChR are reinforced by metabotropic interaction of α7-nAChRs with Gq heterotrimeric G proteins and consequent stimulation of phospholipase C, generation of IP3, and mobilization of intracellular Ca^{2+} [70].

4.2. α7-nAChR modulators

The α7 receptor is the most studied subtype of nAChRs in inflammatory, cardiovascular, and metabolic research [22,69]. The investigation of physiological and pathophysiological roles of α7-nAChR was facilitated by the availability of selective and non-selective pharmacologic ligands. Mice deficient in the cholinergic receptor nicotinic α7 subunit gene (CHRNA7), a gene that codes for α7-nAChRs, have also been exploited [71]. In pharmacologic studies, conventional non-selective agonists (ACh, nicotine and choline), as well as selective full or partial agonists (GTS-21, PHA 568487, PNU 282987, CAP-55 and ICH3, for α7-nAChR) have been utilized [69]. Undoubtedly, the use of selective α7-nAChR agonists is preferred and expected to produce fewer undesirable effects compared to non-selective molecules. For example, α7-nAChRs are not present in high quantities in autonomic ganglia [72], and therefore selective α7 agonists would have a lower potential to exhibit unwanted autonomic adverse effects such as sympathetic overactivity, hypertension, tachycardia, and cardiac autonomic dysfunction [73]. Some α7 receptor agonists such as NS 6740 and m-bromo PEP are termed silent agonists as they evoke receptor desensitization and modulate inflammation with little or no channel opening [74].

Other maneuvers to target the α7-nAChR have been identified including the utilization of positive allosteric modulators, which enhance other agonists' action at α7-nAChR. Such modulators include PNU 120596, 5-hydroxyindole, A 867744, and B 973B and can be divided into two categories. The first category increases the agonist induced current amplitude, while the second enhances current amplitude together with reactivating desensitized receptors [75]. On the other hand, selective antagonists for α7-nAChR have been employed in

reported studies including α-bungarotoxin [65] and methyllcaconitine [20]. Furthermore, the gene product of CHRFAM7A, which is a partial duplication of CHRNA7, has been shown to act as a dominant negative modulator of human α7-nAChRs [76].

For the past two decades, pharmacologists and medicinal chemists have been conducting experimental and clinical studies to identify and evaluate the utility of α7-nAChR modulators in various medical disorders. Given the widespread distribution of α7-nAChR in the nervous system and its pivotal role in the regulation of neuroinflammation, it is not surprising that the majority of clinical trials on α7-nAChR modulators have been carried out in the context of CNS diseases such as Alzheimer's disease, Parkinson's disease, schizophrenia, attention deficit hyperactivity disorder, and nicotine addiction [77]. Despite promising preclinical reports, clinical studies on the therapeutic potential of α7-nAChR modulators in inflammatory disorders are limited. Interestingly, the activation of α7-nAChR by GTS-21 in healthy human subjects reduces TNF-α and elevates IL-10 plasma levels during endotoxemia indicating a shift to an upregulated anti-inflammatory state [78]. Besides, a recent clinical trial has been conducted to evaluate the efficiency of vagal nerve stimulation, an activator of CAP and α7-nAChR, in alleviating inflammatory and immune insults in osteoarthritis [79]. Other ongoing trials are being performed to test effects of vagal stimulation on inflammatory and immune complications in septic shock (ClinicalTrials.gov Identifier: NCT03992378), ulcerative colitis (NCT03908073), Crohn disease (NCT03863704), osteoarthritis (NCT04381624) and kidney transplant patients (NCT04256837). To this date, most of the developed agonists for α7-nAChR are partial agonists or orthosteric ligands that are capable only of evoking a small maximal current even if all receptors are occupied by the drug [80]. Table 1 summarizes the α7-nAChR modulators that have been tested in clinical trials.

Currently, none of the α7-nAChR drugs has been approved by internationally recognized health authorities for therapeutic purposes. In fact, a large number of clinical trials on α7-nAChR agonists were either suspended or terminated altogether. Due to the limited availability of data and inadequate reporting by pharmaceutical companies, we cannot accurately identify the causes of this clinical failure. However, two main reasons can be cited for the halting of these trials. (i) Some drugs failed to produce the anticipated therapeutic action in human subjects. For example, ABT-126 did not result in statistically significant improvement in cognitive functions of Alzheimer patients when applied as a monotherapy [81] or as a co-therapy with cholinesterase inhibitors [82]. Two phase-3 trials of EVP-6124 (NCT01716975, NCT01714661) showed that the drug failed to achieve the primary endpoint of improving cognitive function in schizophrenia, and the study was consequently terminated. Similarly, AZD0328 was suspended during phase II clinical trial (NCT00669903) by AstraZeneca for being unlikely to meet the required therapeutic targets. Another example is the failure of AQW051 to ameliorate Parkinson's disease signs and symptoms [83]. The inability of these α7 agonists to elicit positive therapeutic responses despite the promising pre-clinical reports may be related to differences in pharmacodynamic profiles between human subjects and experimental animals. Another possible reason may relate to the improper design of these trials. For example, in the abovementioned EVP-6124 trial, the medication failed to attain the primary clinical endpoint, despite the fact that the drug produced strong beneficial procognitive effects, due to unexpected strong effects of the placebo group which eliminated the statistical significance between the two groups [77]. Importantly, the clinical failure experienced in these trials should not discourage the clinical testing of these α7 agonists in other indications such as inflammatory disorders. (ii) Some trials were terminated due to the manifestation of severe side effects. For instance, four phase-3 trials for EVP-6124 in Alzheimer were terminated in 2016 due to incidence of rare but severe gastrointestinal side effects [84]. Additionally, the phase-2 trial for SSR180711 in Alzheimer (NCT00602680) was terminated in 2008 by Sanofi for insufficient expected benefit and risk [77]. The drug APN1125 was developed by CoMentis for schizophrenia and was suspended in 2016 in a phase I/phase II clinical trial (NCT02724917) for business-related matters.

Table 1
α7-nAChR agonists and allosteric modulators in clinical trials for therapeutic purposes.

Disease	α7-nAChR modulator	ClinicalTrials.gov Identifier
Schizophrenia	GTS-21/DMXB-A (Partial agonist)	NCT01400477
	ABT-126/Nelonicline (Agonist)	NCT01655680
	AZD0328 (Partial agonist)	NCT00669903
	EVP-6124/Encenicline (Partial agonist)	NCT01716975
	MEM3454/RG3487 (Partial agonist)	NCT00725855
	AQW051 (Partial agonist)	NCT01730768
	TC-5619 (Fll agonist)	NCT01003379
	APN1125 (Partial agonist)	NCT02724917
	BMS-933043 (Partial agonist)	NCT01605994
	Tropisetron (Partial agonist)	NCT00435370
	AVL-3288 (Type-1 positive allosteric modulator)	NCT02978599
Alzheimer disease	GTS-21/DMXB-A (Partial agonist)	NCT00414622
	ABT-126 (Agonist)	NCT01527916
	AZD0328 (Partial agonist)	NCT00687141
	EVP-6124/Encenicline (Partial agonist)	NCT01073228
	MEM3454/RG3487 (Partial agonist)	NCT00454870
	AQW051 (Partial agonist)	NCT00582855
	TC-5619 (Full agonist)	NCT01254448
	SSR-180711 (Partial agonist)	NCT00602680
Attention deficit hyperactivity disorder	GTS-21/DMXB-A (Partial agonist)	NCT00419445
	TC-5619 (Full agonist)	NCT01472991
Nicotinic addition	GTS-21/DMXB-A (Partial agonist)	NCT02432066
	EVP-6124/Encenicline (Partial agonist)	NCT01480232
Parkinson disease	AQW051 (Partial agonist)	NCT01474421
	AZD0328 (Partial agonist)	NCT04810104
Postoperative Pain	Tropisetron (Partial agonist)	NCT01304953
Human endotoxemia	GTS-21 (Partial agonist)	NCT00783068
Septic shock	Transcutaneous vagus nerve stimulation (The vagus nerve activates the splenic nerve, splenic T cells, and α7-nAChRs on macrophages)	NCT03992378
Osteoarthritis	Transcutaneous Vagal Stimulation	NCT04381624 and NCT04520516
inflammatory bowel disease (Ulcerative Colitis and Crohn Disease)	Transcutaneous vagal nerve stimulation	NCT03908073 and NCT03863704
Irritable Bowel Syndrome	Transcutaneous vagal nerve stimulation	NCT02420158
Kidney transplant	Transcutaneous electrical auricular stimulation of the vagus nerve	NCT04256837
Type 2 Diabetes	TC-6987 (open channel stabilizer)	NCT01293669
Obesity	GTS-21/DMXB-A (Partial agonist)	NCT02458313

Despite safety concerns associated with some α7 agonists, other clinical trials described α7 drugs as being well tolerated with mild to moderate side effects [81–85]. Generally, the reported adverse effects associated with α7 agents were either neuropsychiatric (such as dizziness, depression, apathy, anxiety, agitation, dyskinesia, fatigue, visual hallucination, confusion, delirium and disorientation), gastrointestinal (such as constipation, nausea, vomiting, diarrhea, and stomachaches) or miscellaneous (such as headache, falls, urinary tract infections, hip fracture, muscle spasms, pharyngolaryngeal pain and somnolence) [81–85]. The incidence of these adverse effects may be attributed at

least partly to the interaction of α7-nAChR agonists with other receptor sites [77]. For example, GTS-21, MEM3454 and tropisetron, display some antagonistic activity at 5-HT3 receptors particularly when used in high concentrations [86–88]. Furthermore, EVP-6124 and GTS-21 cross react with glutamatergic and dopaminergic receptors [89 90]. That said, the current credible clinical evidence with regards to the vital physiological and pathophysiological roles of α7-nAChRs still encourages the exploitation of selective α7-nAChR agonists in management of inflammatory and CNS disorders.

4.3. PE modulation of nAChRs

The expression of α7-nAChRs on both mRNA and protein levels has been documented in placental cells [91]. In this subsection of the review, we will bring in studies that have reported on the expression of α7-nAChRs under preeclamptic conditions and their potential involvement in the pathogenesis of PE. Molecular studies carried out in human and animal placentas produced important observations that can be categorized into 4 settings.

First, most of these studies demonstrated an increase in the protein expression of α7-nAChRs in placental as well as cord vascular tissues under preeclamptic conditions [33,36,92–94]. The most plausible hypothesis that could explain this phenomenon is that α7-nAChRs are upregulated in PE as an adaptive mechanism to help mitigate the detrimental consequences of the disease. Through their anti-inflammatory and proangiogenic properties, α7-nAChRs would function to counteract or at least minimize preeclamptic complications. A similar counter-regulatory role for α7-nAChRs has been demonstrated in other inflammatory disorders such as sepsis and ischemic injuries [18,95].

Second, despite the consistent reporting of elevated production of α7 receptors, their mRNA levels in PE seem to be unchanged when compared with placentas of non-PE subjects [36,92,94,96]. The discordance between mRNA and protein levels of α7-nAChRs in preeclamptic placentas is not unusual phenomenon and has been found in previous studies assessing the expression of other molecular entities [97]. These findings may indicate that mRNA levels of the receptor are short-lived and transitory, whereas the protein levels persist until the samples were collected in these studies. Indeed, the stability of mRNA and proteins varies due possibly to their functional properties [98]. Another likely mechanism could involve disparity in post-transcriptional regulation or rates of transcription and translation [99]. Whatever the reason for this observed discrepancy between transcription and translation levels, the translation rate and protein quantity are still the most important factor that is correlated with actual protein expression levels [100].

Third, the activation of CAP, via nicotine or choline supplementation, was found to eliminate the PE-related elevation of α7-nAChR expression and restore normal expression levels of the protein in placental tissues [93,94]. Obviously, the amelioration of the inflammatory response by exogenous CAP facilitators would create an environment that favors the restoration of the stress-linked α7-nAChR upregulation to physiologic levels. This resembles the cascade of events reported in a previous study from our laboratory [18] and by others [101]. These latter studies showed that α7-nAChR expressions are elevated after inflammatory challenges by lipopolysaccharide (LPS) or ischemic injuries and that pharmacologic CAP activation diminishes the inflammatory insult and simultaneously normalizes the expression profiles of α7-receptors. Collectively, the possibility of a feedback loop between α7-nAChRs and placental inflammation and a therapeutic benefit for α7-nAChR agonism in inflammatory states cannot be overlooked [102].

Fourth, the impact of PE on α7-nAChR expression in maternal circulation appears to be different from the placental effect. Xu et al. [103] reported a decline in α7-nAChR expression in peripheral monocytes isolated from preeclamptic women. More importantly, this study found an association between the decrease in peripheral α7-nAChR levels and the systemic elevation of pro-inflammatory cytokines (TNF-α and IL-1β) as well as the reduction of anti-inflammatory cytokine (IL-10). Upon further investigations, the authors attributed this association to the ability of α7-nAChRs to promote the polarization of macrophages from pro-inflammatory M1 to anti-inflammatory subtype M2. Additionally, the drop in α7-nAChR levels was shown to correlate with heightened NF-κB activity which leads to expression of many inflammatory mediators. Therefore, the results of this study point out to two important conclusions. First, the PE effect on α7-nAChR expression seems to be tissue specific since it was elevated in the placenta but decreased in peripheral monocytes. Second, the downregulation of peripheral α7-nAChR expression might be implicated in the development of preeclampsia via creating an environment that favors the upregulation of NF-κB pathway and pro-inflammatory cytokine production along with suppression of anti-inflammatory cytokine release. Despite these findings, it is still obscure whether the decrease in peripheral α7-nAChR expression is the cause or the effect of PE development. Interestingly, studies in α7-nAChR knockout mice showed these animals develop aggravated hypertension following kidney clip surgery compared with wild type rodents which indicates that the disablement of CAP predisposes to hypertension development [104]. More studies are necessary to investigate the probable causative link between α7-nAChRs and PE.

Apart from α7-nAChRs, PE has been shown to modify the expression patterns of other nicotinic receptor subtypes. PE augments the expression of α9 and δ while reducing that of β2 subunit [36,105]. The changes in β2 subunits are interesting particularly in view of reports including our own describing an anti-inflammatory role for α4β2-nAChRs, of which the β2 is an essential subunit [18,106]. In addition, the anti-inflammatory actions of nicotine were found to be dependent also on α4β2 receptors along with the α7 unit. For instance, studies have shown that some of the anti-inflammatory nicotinic effects are blocked in the presence of selective α4β2 blockers [18]. Besides, nicotine suppresses cytokine release in macrophages that have α4β2 but lack α7 receptors [107]. It is, therefore, reasonable to assume that the downregulation of β2 expression could result in the dysfunction of placental α4β2-nAChRs, loss of their favorable anti-inflammatory impact and subsequently exacerbation of the placental inflammatory process characteristic to PE. The reason for the divergence between placental expressions of β2 (decrease) and α7 (increase) subunits during PE is not clear. However, evidence of a disparity in the expression of these proteins under hypoxic conditions exits. Unlike α7 subunit whose expression increases [95], the mRNA and protein expression of β2 were suppressed by hypoxia [108]. This may be related to PE, given the contribution of placental ischemia to PE development. Admittedly, there is a scarce of data regarding role and expression of α4β2-nAChRs in preeclamptic placentas compared with α7-nAChRs. This makes it harder to deduce the exact role of α4β2 receptor in PE pathophysiology and its modulation in preeclamptic tissues.

4.4. PE modulation of acetylcholinesterases

Acetylcholinesterase (AChE) is the enzyme responsible for the degradation of neuronal ACh and interruption of cholinergic neurotransmission at ganglionic and postsynaptic sites of the parasympathetic nervous system. Butyrylcholinesterase (pseudocholinesterase, BChE) is a nonspecific cholinesterase that is found in plasma and help regulate levels of choline-based esters including ACh [109]. Contradictory results are available regarding the way by which the expression and activity of cholinestrases would be altered in preeclamptic tissues. Although there are reports of increased or unchanged levels of AChE and BChE in preeclamptic subjects [110,111], the majority of studies points to a marked reduction in the preeclamptic levels of these enzymes. For example, Zheng et al. [33] showed that mRNA transcription and protein translation of AChE are reduced in placentas of preeclamptic patients. Additionally, the magnitude of the reduction of AChE expression is

proportionally related to PE severity [33]. Alternatively, levels and activity of BChE in maternal circulation as well as in fetal umbilical cord blood have been repeatedly shown to be diminished in PE compared with healthy pregnancy [112–116]. Similar decreases in cholinesterase activity have been documented in severe trauma and sepsis [117,118].

Although liver injury that sometimes develops as a complication of PE could contribute to the decreased production of AChE and BChE [119], no signs for liver injury were evident in the abovementioned studies [33,112–116]. The diminished cholinesterase activity is most likely a compensatory mechanism to increase the availability of ACh and maintain the upregulated state of CAP signaling. As detailed above, the heightened CAP activity is essential to restrain the progression of PE. This viewpoint is bolstered by the findings that the increases in ACh levels in preeclamptic placentas [35] negatively correlate with placental production and release of sFlt1 [120]. While the compensatory role of CAP in the pathogenesis of PE has been recognized, the specific roles and integration between biosynthetic and degrading machineries of ACh in this context remain mostly unknown.

Proton pump inhibitors (PPIs) are often used during pregnancy to reduce gastric acid secretion and reflux. Recent evidence suggests that gestational use of PPIs facilitates the development and progression of PE via inhibiting the ACh synthesizing enzyme choline acetyltransferase and reducing ACh bioavailability [121]. The latter could possibly account for the notorious increase in PE risk associated with PPI use during pregnancy [122,123]. This view sharply contrasts with other studies in which PPIs were found to decrease serum cholinesterase activity [124] and dampen down pathophysiological events associated with PE including the rises in antiangiogenic factors (sFlt-1 and sEng), endothelial dysfunction, oxidative stress, inflammation, and hypertension [125]. It is possible that the interplay between PPIs and PE could vary depending on the gestational phase during which PPI is taken and the type PPI [124 125]. More studies are apparently necessary to assess the roles of ACh biosynthesis and degradation in the PPTs/PE interaction and possible involvement of the cholinergic anti-inflammatory pathway in this framework.

4.5. Central and peripheral pathways of CAP

The early years of the 21st century witnessed multiple experimental findings that formed the basis for what is now known as the inflammatory reflex and CAP. The novel studies by Borovikova and colleagues [21] and Bernik et al. [126] were the first to show that direct electrical stimulation of the vagus efferent magnificently protected against the development of endotoxic shock and simultaneously suppressed plasma TNF-α, indicating that the anti-inflammatory signals is generated and descend from the CNS via the vagus nerve to ameliorate peripheral inflammation. Further, the same studies demonstrated that central administration of the anti-inflammatory drug CNI-1493 significantly abrogated LPS-related elevation of plasma TNF-α.

As shown in Fig. 1, the inflammatory reflex is initiated in conditions when the afferent branch of the vagus nerve senses inflammation related products including cytokines, pathogen associated molecular patterns, and damage associated molecular patterns usually via receptors of cytokine and pattern recognition subtypes [127]. This vagal nerve activity is then transmitted centrally through the CNS to the efferent branch of the vagus nerve and subsequently to the splenic nerve. The stimulation of splenic nerves triggers the release of norepinephrine which activates β2-adrenergic receptors on T cells in the spleen leading to the release of ACh from these cells. Afterwards, ACh activates α7-nAChRs which are expressed on macrophages causing the reduction of pro-inflammatory cytokine production (e.g., TNFα) and alleviation of inflammation [128]. Activated α7-nAChRs trigger several intracellular downstream mechanisms that interfere with the NF-κB pathway [16], the Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) pathway [129] and the NLR family, pyrin domain-containing 3 (NLRP3) inflammasome [130]. This efferent branch of the inflammatory reflex was later given the terminology of the cholinergic anti-inflammatory pathway.

The inflammatory signals from peripheral pathway (afferent vagus) enter the CNS through the nucleus tractus solitarious (NTS), which has polysynaptic connections to other important brain locations including the rostral ventrolateral medulla (RVLM) and paraventricular nucleus (PVN) [131]. The PVN is linked to the production and release of corticotropin releasing hormone which contributes to the hypothalamo-pituitary-adrenal axis. This connection between the NTS and PVN reveals a potential pathway which can regulate the neurohormonal anti-inflammatory responses. Synaptic linking is also available between the NTS and C1 neurons in the RVLM, a region of the ventral brainstem that

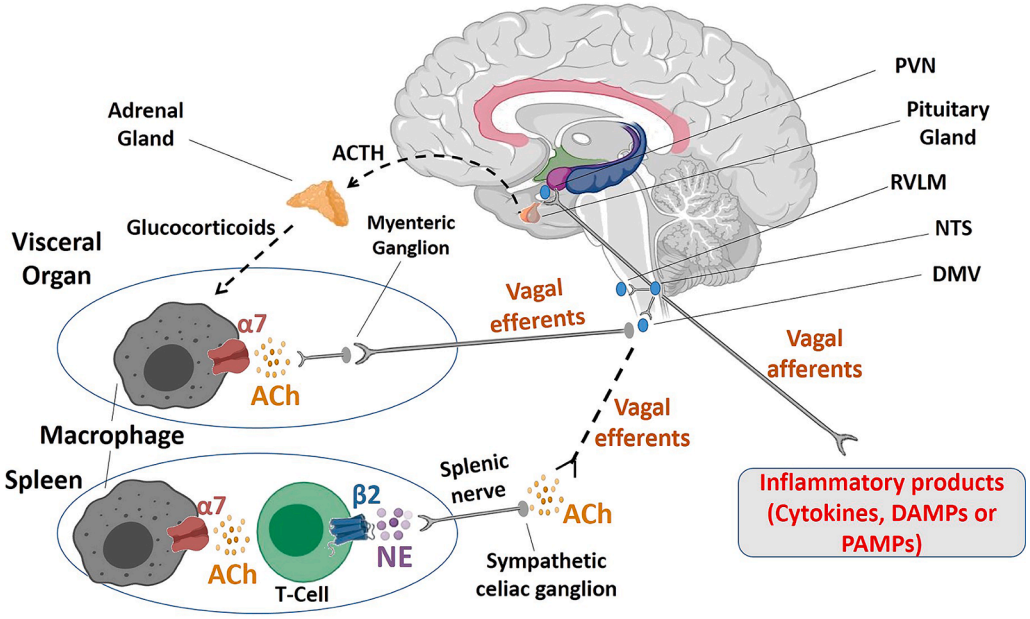

Fig. 1. A summary of the interplay between peripheral and central pathways in the immune response. Abbreviations: ACh, acetylcholine; ACTH, adrenocorticotrophic hormone; DAMPs, damage associated molecular patterns; DMV, dorsal motor nucleus; NE, norepinephrine; NF-κB, nuclear factor kappa B; NTS, nucleus tractus solitaries; PAMPs, pathogen associated molecular patterns; PVN, paraventricular nucleus; RVLM, rostral ventrolateral medulla.

is responsible for cardiovascular homeostasis and regulation of both resting levels and reflex regulation of sympathetic outflow [132]. Finally, the signals go into the dorsal motor nucleus of the vagus (DMN) from which the efferent vagus signaling emerges [128]. This indicate that these central sites have key roles in the inflammatory response. Indeed, NTS and RVLM have been shown to modulate the inflammatory and cardiovascular consequences of systemic inflammatory conditions [19]. A summary of the interplay between peripheral and central cholinergic pathways and immune response is illustrated in Fig. 1.

4.6. CAP upregulation guards against PE

Since the discovery of CAP, accumulating evidence has shown the significance and safeguard conferred by this pathway against a wide array of inflammatory and cardiovascular disorders [24]. Given the critical role of placental inflammation in the pathogenesis of PE [37], the issue whether CAP activation would provide any therapeutic benefit during PE was investigated. This viewpoint was supported by observations that smoking and its major constituent nicotine diminish the risk and incidence of PE [133]. Table 2 provides a summary of published articles that document the protective and beneficial effects of CAP against PE. The majority of these studies utilized nicotine as the main pharmacologic tool to stimulate α7-nAChRs and in turn activate the CAP. However, few studies have tested the effects of other cholinergic drugs (e.g., choline) and specific α7-nAChR agonists (e.g., GTS-21, CAP55, PHA-543613, and PNU-282987). A summary of PE complications that are relieved by nicotinic drugs are outlined in Fig. 2. Clinically, nicotine has been utilized as a therapeutic modality for inflammatory disorders like ulcerative colitis [134]. The nicotine replacement therapy has been demonstrated to be a safe and efficient approach for smoking cessation during pregnancy [135]. Evidence ranging from controlled trials to cohort studies suggest that the use of nicotine replacement therapy in pregnant women is associated with reduced risk of stillbirths, low birth weights and premature delivery [136,137]. Nicotine was found to protect against some of the complications of pregnancy including PE. For instance, nicotine pretreatment prevents most of the harmful consequences associated with PE in experimental studies. Nicotine protects pregnant rats from increases in SBP and urinary protein excretion in LPS [96,138] and placental ischemia [139] models of PE. Furthermore, nicotine lowers the elevations in serum and placental levels of pro-inflammatory mediators, including TNFα, IL-1b, IL-6 and IFN-γ, in inflammatory models of PE [94,96,140]. Nicotine also suppresses the enhanced leucocytes infiltration in the placental chorionic plate [94] and NF-kB p65 upregulation in these models [96].

Unlike the reported reconciliatory action of nicotine against maternal PE complications, there is a divergence on whether nicotine has a similar positive impact on fetuses. While nicotine alleviates PE related decreases in live fetal numbers and pup weights [96,138,140], it does not favorably affect the PE induced decrease in fetal weight and increase in fraction fetal resorbed [139]. The difference in nicotine dosing can be excluded as the cause for this nonconformity as all of these studies employed a dose of 1 mg nicotine/kg/day. Contrarily, the difference in PE rat model might offer a plausible explanation. All of the studies in which nicotine showed promising protective effects for the fetuses have been undertaken in the LPS model of PE [96,138,140], in which the maternal immunologic response and placental inflammation play a central role in pathogenesis of PE. This contrast with the effects of nicotine in PE models induced by placental ischemia that follows surgical reduction of placental blood flow [139]. Overall, a more robust and advantageous effects for nicotine are likely to manifest in PE models in which inflammation is the main pathogenic factor.

The beneficial effects of nicotine are not limited to PE but extends also to eclampsia, a more serious condition with unexplained mal seizures that develop as a complication in females with preeclampsia [46]. Nicotine delays the onset of seizures in pregnant preeclamptic rats and reduces the behavioral seizure scores [138]. Notably, in the same LPS-based PE model complicated by pentylenetetrazol-induced seizures, nicotine considerably mitigates the eclampsia associated decline in fetal weight, live fetal number, and placental weight, along with dampening down the elevation in the percentage of fetal malformation and resorption [138].

Apart from the advantageous effects of nicotine during PE, maternal

Table 2
Beneficial effects of CAP in in-vivo or in-vitro models of PE.

PE Model	Nicotinic drug effects	Reference
LPS in rats	Nicotine reduces LPS-induced rises in serum and placental pro-inflammatory cytokines	[96]
	Nicotine inhibits the LPS-induced increments in TNF-α and IL-6 and reverses LPS-related decreases in fetal number and weight	[140]
	Nicotine decreases leucocytes infiltration in placental chorionic plate	[94]
	Choline reverses LPS negative effects on pregnancy and concomitant increases in serum and placental inflammatory cytokines (e.g., NF-κB), and AKT phosphorylation)	[93]
Uterine perfusion restriction in rats	Nicotine opposes the increase in blood pressure	[139]
Human placental LPS stimulation	Nicotine, GTS-21 and CAP55 reduce cytokine production by placenta cells via inhibiting NF-kB	[91]
	Nicotine suppresses production of LPS-stimulated placental pro-inflammatory cytokines	[94]
Human trophoblast cells under hypoxic conditions	Nicotine promotes secretion of vascular endothelial growth factor from human trophoblast cells under hypoxic conditions and improves the proliferation and tube formation capacity of human umbilical endothelial cells	[198]
Human umbilical vein endothelial cells (HUVECs) as a model of the maternal vascular endothelium.	Nicotine preserves endothelial cell survivability and suppresses IL-6 and NF-kB production	[168]
	Nicotine facilitates production of placental growth factor and restores soluble fms-like tyrosine kinase 1 and/or soluble endoglin-reduced endothelial migration and tube formation	[197]
	Nicotine dose dependently inhibits intercellular adhesion molecule expression and suppresses integrin expressions of CD62L, CD11a, and CD11b in neutrophils	[206]
	Nicotine reduces sFlt-1, sENG and PlGF release by trophoblast cells and modulates TGF-beta release and VEGF mRNA expression by HUVECs	[195]
LPS plus PTZ induced eclampsia-like rats model	Nicotine improves fetal outcomes increases eclampsia-like seizure threshold, and decreases systolic pressure, maternal serum inflammatory cytokines, neuronal loss, and expression of hippocampal microglial activation markers	[138]
Randomized controlled trial of healthy pregnant women	Choline lowers placental and circulating levels of antiangiogenic factor fms-like tyrosine kinase-1	[120]
Monocytes isolated from peripheral venous blood of preeclamptic human females	PNU-282987 increases IL-10 and counterbalances decreases in NF-κB, TNF-α, IL-1β, and IL-6	[103]

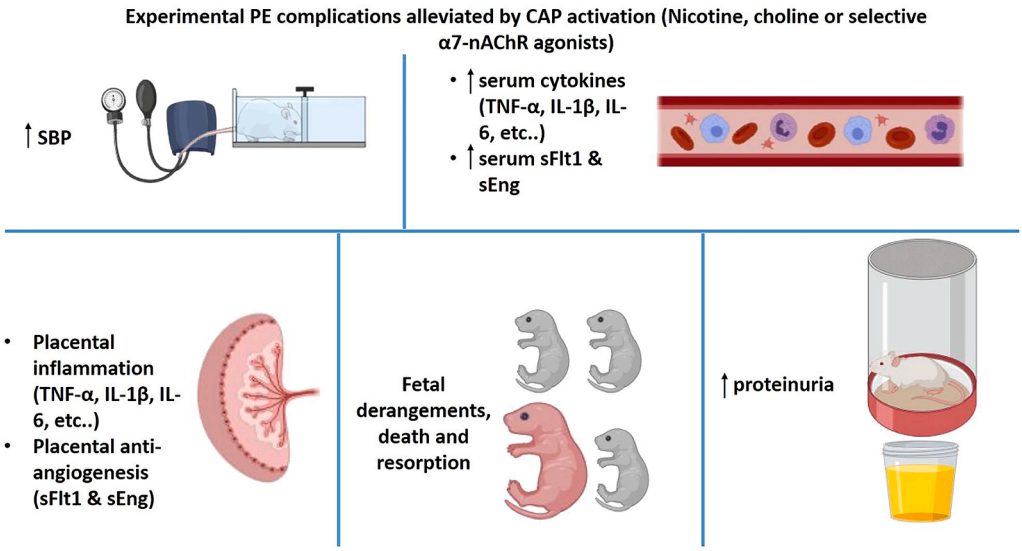

Fig. 2. An outline of various PE complications identified in experimental rats that could be alleviated by CAP upregulation. Such complications include hypertension, proteinuria, fetal death and resorption, elevated levels of serum and placental antiangiogenic as well as pro-inflammatory factors. Abbreviations: alpha; α7-nAChR, alpha-7 nicotinic acetylcholine receptors; CAP, cholinergic anti-inflammatory pathway; IL-1β, interleukin 1 beta; IL-6, interleukin 6; PE, preeclampsia; SBP, systolic blood pressure; sEng, soluble endoglins; sFlt1, soluble fms-like tyrosine kinase-1; TNF-α, tumor necrosis factor.

and fetal damages that are inflicted by smoking/nicotine cannot be overlooked. For instance, nicotine administration has been implicated in elevating the blood pressure in humans [141] as well as rats [142]. Nicotine induced hypertension can be accredited to its ability to stimulate nAChRs on postganglionic sympathetic neurons and adrenal medulla resulting in the release of catecholamines and hence vasoconstriction [143]. Additionally, nicotine may cause hypertension via enhancing kidney macrophage infiltration [144]. Taken together, it seems that nicotine may have competing actions as vasoconstriction and hypertension, which may function to restrain it advantageous anti-inflammatory sequel. The likelihood that these contradictory actions may overshadow a clear impact of nicotine in eliminating PE related hypertension warrants further investigation. In addition to these maternal side effects, it is important to consider the possible adverse nicotinic actions on fetuses. Intrauterine nicotine exposure causes fetal brain damage [145] and neurodevelopmental dysregulations [146]. Other studies have indicated the potential interference by nicotine with fetal growth. Such interference might be related to nicotine's influence on placental cholinergic receptors and consequently suppression of Ach-mediated facilitation of transplacental amino acid transport [147]. Nicotine is also responsible for the notorious association between smoking and preterm delivery through promoting prostaglandin E2 synthesis [148].

It is worth mentioning that dose adjustment of nicotine is necessary when used in PE in order to avoid its undesirable maternal and fetal sequels. A dose of 1 mg/kg/day of nicotine was used in previous studies for testing the protective effects of nicotine in rat models of PE [94,96,138–140]. This particular dose is believed to produce blood levels of nicotine that are not high enough to cause maternal and fetal complications [149,150]. In some of these studies, the effect of the of 1 mg/kg/day dose of nicotine in rats with normal pregnancies was determined and found to evoke no changes in blood pressure, inflammatory cytokines, fetal numbers, or fetal weights. Nevertheless, minor transient behavioral alterations were evident in pregnant rats shortly after administration of nicotine [96,139]. In a recent publication, we found that α7-nAChR activation by doses of nicotine or PHA-543613 in the microgram scale promotes neovascularization and offers a promising therapeutic strategy for myocardial infarction [151]. Therefore, adjusting the dose of nicotine can be of paramount importance in these circumstances to achieve protective actions of nicotine without the potential adverse ones.

Remarkably, the potential applicability of CAP upregulation as a therapeutic intervention against human PE may demand more specific targeting of α7-nAChRs, the nAChR unit that is mostly responsible for the anti-inflammatory properties. This strategy deems necessary to limit the non-specificity in the nicotine interaction with the cardiovascular system. Accordingly, targeting of CAP with specific α7-nAChRs agonists would elicit lower collateral cardiovascular and neural toxicity [152] and offers a promising approach for the alleviation of preeclamptic complications that might erupt prior to or after the onset of placental disturbances. It is noteworthy that selective α7-nAChRs agonists, such as GTS-21 and CAP55, have been validated as an effective intervention in reducing placental inflammatory responses following LPS challenge [91]. Obviously, further basic and clinical studies are necessary in order to ascertain the safety, efficacy, and clinical validity of this viewpoint.

Choline is another cholinergic drug that demonstrated some encouraging effects against PE in both experimental and clinical studies. In the LPS model of rat PE, choline treatment mitigated maternal (hypertension, proteinuria, elevated serum and placental pro-inflammatory cytokines) and fetal complications (fetal loss and growth restriction) of PE [93]. In addition, a clinical study has shown that maternal choline intake downregulates the PE related biomarker and antiangiogenic factor sFlt1 in serum and placental tissues. It is concluded that supplementing the maternal diet with choline may ameliorate placental angiogenesis and alleviate some of PE complications [120]. However, it should be noted that choline appears to be weaker in preventing PE related outcomes compared with nicotine [96]. This may be ascribed to lower affinity for α7-nAChRs and lower concentration achieved at receptor site [93]. While choline can stimulate α7-nAChRs [153,154] and activate CAP, caution should be taken when interpreting choline results since it has other α7-nAChR-independent placental effects. For instance, choline administration alters epigenetics of placentas and the expression of multiple important mediators of PE pathogenesis [155]. Additionally, choline facilitates placental production of ACh, and consequently modulates cellular proliferation, amino acid transport, vasodilation, and placental expression of sFlt1 [120].

5. Mechanisms of CAP protection

The understanding of the mechanisms that underscore CAP protection in PE will help identify specific therapeutic targets for future drug development. An overview of these mechanisms is detailed below and summarized in Fig. 3.

5.1. *Activation of α7-nAChRs*

Over the last two decades, compelling evidence has accumulated that the activation of α7-nAChRs represents a principal step in the processing

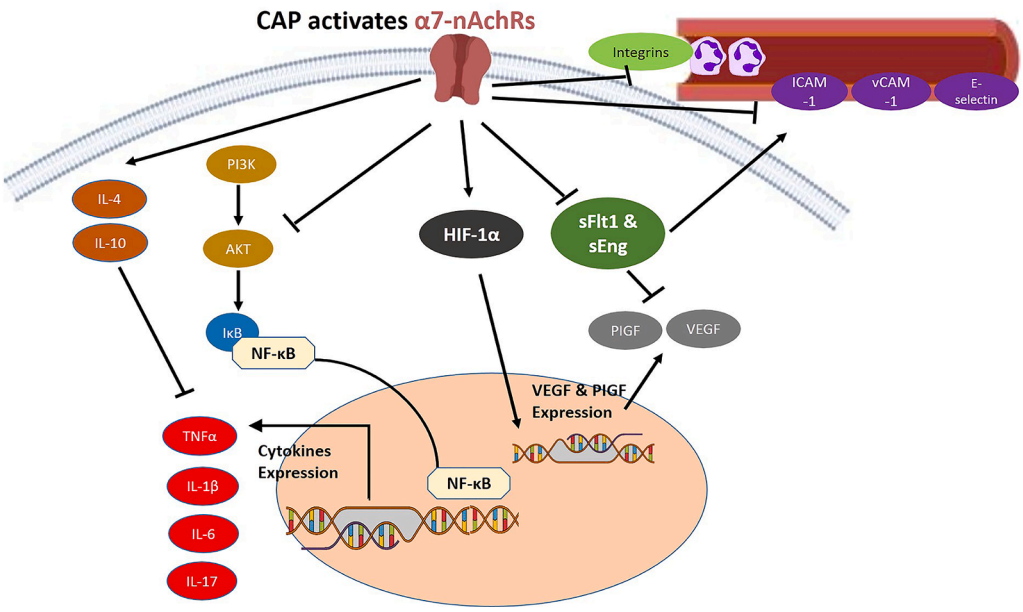

Fig. 3. An illustration of potential mechanisms involved in CAP protection against PE related inflammation, anti-angiogenesis and endothelial dysfunction. CAP (i) inhibits cytokine production in placental macrophages (placental inflammation), blood monocytes (systemic inflammation) and central microglia (neuroinflammation), (ii) decreases anti-angiogenic factors and increases pro-angiogenic factors in placental trophoblasts and umbilical vein endothelial cells, and (iii) alleviates endothelial dysfunction and leukocyte adhesion. Abbreviations: α7-nAChR, alpha-7 nicotinic acetylcholine receptors; AKT, Ak strain transforming or protein kinase B; CAP, cholinergic anti-inflammatory pathway; HIF-1α, hypoxia-inducible factor 1-alpha; ICAM-1, intercellular adhesion molecule-1; IkB, inhibitor of kB; IL-17, interleukin 17; IL-1β, interleukin 1 beta; IL-4, interleukin 4; IL-6, interleukin 6; IL-10, interleukin 10; NF-κB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; PIGF, placenta growth factor; sEng, soluble endoglins; sFlt1, soluble fms-like tyrosine kinase-1; TNF-α, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

of CAP [24]. The α7-nAChR is a ligand-gated receptor and is one of the most widespread subtypes of nicotinic receptors, with specific distribution into immune, nervous, cardiovascular and renal systems [11,156,157]. The macrophageal α7-nAChRs are believed to regulate the production and release of pro-inflammatory mediators following exposure to inflammatory stimuli [158]. The activation of α7-nAChRs brings about the protective actions of CAP in lung [159], CNS [157], heart [160], and kidney inflammation [16].

Intriguingly, the α7-nAChR has been characterized in human and rat placentas [161]. The involvement of α7-nAChR in the CAP-PE interaction is confirmed by studies that evaluated the capability of pharmacologic elimination of α7-nAChR to block CAP actions and augment PE features. For instance, Liu et al. [96] showed that the counteraction by nicotine of PE associated hypertension, proteinuria and elevated levels of inflammatory markers in serum and placenta were diminished following injection of the α7-nAChR antagonist α-bungarotoxin (α-BGT). Similarly, α-BGT abolished the favorable actions of nicotine on blood pressure, placental weight, and fetal outcome (live fetal number, weight, resorption and malformation) in PE rodents [138]. Nonselective blockade of nicotinic receptor by mecamylamine also reversed the downregulating actions of nicotine and other nicotinic agonists on TNF-α production by placental cells [91]. Kobayashi et al. [162] reported that scopolamine butylbromide, an anticholinergic medication, precipitates eclamptic seizures in patients with severe PE. Because the anticholinergic therapy is expected to result in sympathetic hyperactivity, vasoconstriction, and subsequently eclamptic seizures, it is plausible to propose that cholinergic receptors act tonically to restrain PE-related symptoms.

The protective effects of CAP and nicotine have been reproduced using selective agonists for α7-nAChRs. For example, Dowling et al. [91] showed that both GTS-21 and CAP55 acted in a dose-dependent fashion to diminish the elevated TNF-α, NF-κB, IL-1β, IL-6, and IL-8 levels in LPS stimulated placental cells. The effect of CAP55 was comparable to nicotine while that of GTS-21 was even greater with no cytotoxic effects. Another in-vitro study reported that targeted stimulation of α7-nAChRs with PNU-282987 interfered with the NF-κB pathway and ameliorated the alterations in inflammatory cytokine expression within peripheral monocytes isolated from preeclamptic women [103].

Molecular studies were also performed to determine the gene and protein expressions of α7-nAChR in placental tissues of PE models. These studies showed that resolution of PE symptoms or complications was paralleled with normalization of α7-nAChR expression upon treatment with CAP activators, like nicotine or choline [93,94,96]. Collectively, the aforesaid pharmacological and molecular studies point toward a key role for α7-nAChRs in protecting against placental inflammation and associated maternal and fetal anomalies during PE.

5.2. CAP inhibits PE-evoked immune cell recruitment and inflammation

Healthy pregnancy is often accompanied by a mild systemic inflammatory response and upregulation of several components of the inflammatory machinery. This systemic inflammation intensifies with the advancement of pregnancy specially during the second half as a part of an acute phase reaction [163]. PE tends to heighten this inflammatory process and considerably upregulate inflammatory cytokines and chemokines [164]. This strong systemic inflammatory response has been blamed for the later development of PE complications [39]. The exact mechanism for the PE linked increase in systemic inflammation is still undetermined. Nonetheless, peripheral monocytes are thought to play a significant role in this process [103]. Considering the higher activity of blood monocytes in preeclamptic women [165] and the positive correlation between monocyte activity and severity of PE [166], it has been postulated that peripheral monocyte activation culminates in enhanced placental inflammation and macrophage filtration and thus worsening of PE [167]. In a recent study by Xu et al. [103], the release of TNF-α, IL-1β, and IL-6 was higher from monocytes isolated from preeclamptic women compared with those from non-pregnant and normotensive pregnant women. When stimulated with LPS, preeclamptic monocytes showed greater increase in production of these cytokines compared with control ones. Importantly, the same study showed that α7-nAChR-dependent CAP activation attenuates the activation of preeclamptic peripheral monocytes and release of inflammatory cytokines.

Another player that contributes to the PE systemic inflammation is the maternal endothelial cells [168], which have been shown to express nAChRs [169]. For instance, vascular endothelial cells are a major source of IL-6 in preeclamptic females [170]. In addition, serum isolated

from preeclamptic individuals is characterized by facilitated IL-6 production from human umbilical vein endothelial cells (HUVECs), which clearly implicates endothelial cells in the inflammatory response triggered by PE [168]. Remarkably, nicotine treatment blunted cytokine production from HUVECs stimulated with preeclamptic serum, which highlights the ability of CAP to protect from systemic inflammation in maternal endothelial cells during PE [168].

The placenta represents a maternal-fetal interface on which the fetus growth and viability are completely reliant [171]. The maternal systemic inflammation during PE does not develop in isolation from placental inflammation. In fact, placental cytokines are indispensable for physiological and pathological regulation of inflammation during PE [37,172] and are modulated by CAP. The placental and serum inflammatory response induced by gestational LPS in rats is attenuated by choline supplementation via a α7-nAChR-dependent mechanism [93]. Also, PE promotes leukocytes infiltration into the chorionic plate of the placenta, a process that is significantly impaired after nicotine administration [94]. Alternatively, in-vitro studies were conducted on LPS-stimulated cultured human placenta cells to simulate the PE induced placental inflammation. In these studies, nicotine addition to the medium notably decreases mRNA and protein expression of TNF-α, IL-1β, IL-2, IL-6, IL-8, IL-17 and IFN-γ following LPS insult [91,94]. Consequently, it is reasonable to postulate that CAP serves to rescue fetuses in preeclamptic animals via repression of cytokine upregulation and leukocyte infiltration in placental tissues.

The depressant action of CAP on systemic and placental inflammation during PE could be attributed to its interaction with NF-κB. The latter is a family of inflammation connected transcription factors whose activation is triggered by foreign molecules (e.g., LPS) or endogenous damage indicators (TNF-α and IL-1β) [173–178]. In normal cells, NF-κB is sequestered in the cytoplasm in the form of an inactive NF-κB-IκBa complex. Upon stimulation, I-κB is phosphorylated and NF-κB is translocated into the nucleus where it upregulates the transcription of multiple inflammatory gene products [179]. There is evidence that support the central role of NF-κB pathway in the inflammatory response of circulating immune cells [180], vascular endothelial cells [181] and placental tissues [93] during PE. Immunohistochemical analysis showed a higher immunostaining of NF-κB in the placenta isolated from PE women compared with normal pregnancy. Besides, NF-κB staining in placentas of severe PE individuals is stronger than those with mild PE, signifying the pathological role of NF-κB in PE [33]. The diminution of NF-κB activity has been implicated in the defensive role of CAP against PE. For instance, in-vitro experiments on peripheral monocytes from preeclamptic patients reported that α7-nAChR agonists inhibit NF-κB activity and correct the overall cytokine profile in these immune cells [103]. Sharentuya et al. [168] demonstrated that nicotine significantly attenuates NF-κB activation in umbilical vein endothelial cells of preeclamptic humans. Nicotine and more selective α7-nAChR agonists interfere with NF-κB activity in isolated human placental cells [91]. Likewise, choline supplementation abrogated PE induced I-κB phosphorylation and NF-κB nuclear translocation in rat placentas [93].

NF-κB is believed to be regulated by PI3K/AKT pathway [182]. The maternal LPS challenge leads to placental AKT (protein kinase B) phosphorylation [183]. The α7-nAChR agonist, GTS-21, prevents NF-κB activation through suppression of PI3K/AKT pathway in LPS stimulated cells [184]. Further, the ability of choline to reduce PE placental NF-kB activation is coupled with its repression of PE placental AKT phosphorylation [93]. Collectively, CAP activators act mainly on α7-nAChRs to inhibit the PI3K/AKT pathway which in turn prevent the nuclear translocation and activation of NF-κB resulting in widespread suppression of systemic and placental production of inflammatory cytokines.

Both IL-4 and IL-10 are anti-inflammatory cytokines with important roles in regulating the human immune response and via counterbalancing inflammatory insults sparked by pro-inflammatory mediators [185,186]. During PE, unlike the rises in serum levels of pro-inflammatory cytokines, IL-4 and IL-10 levels are actually decreased [187] which is an expected outcome given the polarization of peripheral monocytes to M1 pro-inflammatory subtype in the blood of preeclamptic patients [188]. The activation of α7-nAChRs, selectively by PNU-282987 or non-selectively by nicotine or choline, reverses the inhibitory effects of PE on serum IL-4 and IL-10 [93,103,138]. This effect could contribute to the successful systemic anti-inflammatory actions of CAP observed during PE. The results of placental IL-4 and IL-10 are less consistent. While placental IL-4 appears to be decreased by PE and enhanced by CAP [93], placental IL-10 may not be affected or slightly increased in PE representing a potential counterbalance to pro-inflammatory cytokines. In this setting, nicotine does not downregulate the elevated placental IL-10 levels as with other cytokines, which can be helpful in controlling local inflammation in this tissue [94,140].

The excessive activation of the innate immune complement system, a series of cell surface proteins that complements the ability of phagocytic cells and antibodies to recognize and clear pathogens and altered host cells [189], is another factor that is believed to contribute significantly to pathogenesis of PE. The antagonism of receptors for the complement activation products C3a or C5a attenuates hypertension provoked by placental ischemia and endothelial dysfunction [190]. However, when the effect of nicotine was tested on PE complement activation, one study reported that nicotine did not influence complement activity which indicates that the anti-inflammatory effects of CAP might be complement independent [139].

5.3. CAP improves PE associated angiogenesis perturbations

One of the prevailing hypotheses predisposing to PE is the reduction in uteroplacental perfusion triggered by altered invasion of spiral arteries [5]. In this circumstance, the placenta releases large amounts of soluble antiangiogenic factors into the maternal circulation which sequester proangiogenic factors and evoke systemic endothelial dysfunction [191]. Among these factors, only two give the strongest correlation with PE severity and outcomes, namely sFlt1 (also known as soluble vascular endothelial growth factor receptor 1 or sVEGFR1) and sEng [192]. Whereas sFlt1 binds to circulating VEGF and PLGF, blocking their association with their endothelial receptors [193], sEng impedes intracellular signaling of TGF-β1 in endothelial cells [43]. This enhanced antiangiogenic machinery at the expense of inhibited proangiogenic activity is considered a hallmark for PE and results in suppression of the angiogenesis, induction of maternal vascular endothelial dysfunction and consequently hypertension [194]. Thus, restoring the angiogenic balance in the placental tissues is paramount to PE management.

In addition to its anti-inflammatory properties, CAP has recently attracted ample attention by its proangiogenic effects. Romani et al. [195] reported that nicotine and its metabolite cotinine effectively suppress sFlt-1 and sEng release from placentas and enhance PLGF as well as VEGF secretion from umbilical vein endothelial cells isolated from healthy pregnant women. Further studies illustrated that the cholinergic pathway and nicotine have α7-nAChR dependent proangiogenic impact on isolated HUVECs [196]. In essence, nicotine was shown to stimulate angiogenic functions of HUVECs, including endothelial migration and tube formation, in a dose dependent manner [197].

The ability of CAP and nicotine to negate the angiogenic disturbances in PE-like conditions has also been examined. An interesting study by Zhao et al. [198] investigated the effect of nicotine on the hypoxia induced alterations of angiogenic factors secretion from human trophoblast cells. These cells have high invasion capacity and contribute to remodeling uterine and spiral arteries in the early phases of pregnancy through their interaction with endothelial cells. For example, proangiogenic factors released from trophoblast cells induce proliferation and tube formation in endothelial cells [199]. Contrarily, PE-associated ischemia renders trophoblasts hypoxic and thus increasing their secretion of antiangiogenic factors which is a direct cause for maternal endothelial dysfunction [200]. Therefore, it is important to

closely observe nicotinic effects on angiogenic imbalance that arise in hypoxic human trophoblasts. In the study by Zhao et al. [198], nicotine enhances VEGF production by hypoxic trophoblast cells which could be attributed to the significant nicotinic augmentation of VEGF transcription via hypoxia-inducible factor-1α dependent mechanism. In the same study. Nicotine also considerably inhibits trophoblast sFlt1 release which could be a second contributing factor to the nicotine induced elevation of VEGF levels. Further, the increased VEGF secretion in nicotine-treated hypoxic trophoblasts improves the proliferation and tube formation capacity of HUVECs, suggesting an improvement in the endothelial function [198].

Elevated levels of sFlt1 and sEng in maternal circulation have been demonstrated in PE patients and have been proposed as a direct cause for endothelial dysfunction [191]. In this context, the elegant study by Mimura et al. [197] investigated the ability of nicotine to counteract the detrimental endothelial effects of sFlt1 and sEng and restore normal angiogenic functions of HUVECs. The data from this study indicated that sFlt1 and sEng impaired essential endothelial angiogenic functions, including endothelial migration and tube formation, effects that were normalized upon co-exposure to nicotine. These actions were paralleled with nicotinic enhancement of proangiogenic protein (PLGF) production, suggesting that nicotine recovers damaged endothelial cell angiogenesis probably via upregulation of PLGF secretion [197].

Consistent with these reports that establish proangiogenic properties for nicotine and CAP, nicotine treatment increases proliferation and cell number of HUVECs highlighting the potential of nicotine serving as a survival factor for the endothelium [168]. Moreover, clinical studies showed that maternal choline intake downregulates the PE-related biomarker and antiangiogenic factor sFlt1 in the serum and placental tissues, suggesting that supplementing maternal diets with choline may ameliorate placental angiogenesis and alleviate PE complications [120]. Collectively, these findings implicate the proangiogenic outcome of CAP activators in PE management. Further basic and clinical investigations are required to validate the therapeutic relevance of this assumption.

5.4. CAP guards against leukocyte adhesion and endothelial dysfunction

Neutrophil activation and consequent endothelial dysfunction are chief contributors to pathogenesis of PE [201]. High blood levels of soluble cell surface molecules, including soluble intercellular adhesion molecule 1, soluble vascular cell adhesion molecule 1 and soluble E-selectin are found in preeclamptic patients [202]. Other clinical studies revealed that PE is associated with elevated endothelial adhesion molecules, neutrophil activation, and CD11b expression, highlighting the possibility of leukocyte adhesion to endothelial cells during PE [203]. Indeed, endothelial cells isolated from preeclamptic individuals showed evidence of enhanced neutrophil endothelial interaction and adhesion [204]. Speer et al. [205] studied the impact of nicotine treatment on in-vivo leukocyte interaction and adhesion to uterine vascular endothelial cells under ischemic condition in pregnant rabbits. The treatment of female rabbits with nicotine suppresses leukocyte adhesion to uterine vascular endothelial cells as evaluated by intravital microscopy [205].

The same research group undertook another study [206] to discern how nicotine could decrease leukocyte-endothelial adhesion in an in-vitro model of HUVECs and neutrophils isolated from normal pregnant women. The expression of neutrophil integrins (CD62L, CD11a, and CD11b) as well as endothelial intercellular adhesion molecule (ICAM) were investigated in the absence and presence of nicotine. The analyses showed that nicotine exerts dose-dependent inhibitory effects on endothelial ICAM expression and neutrophil expression of CD62L, CD11a, and CD11b. Because these molecules have crucial role in the process of leukocyte adhesion with endothelial cells [203], these results could explain the mechanism by which nicotine inhibits neutrophil endothelial interaction in pregnancy and consequently protects from endothelial dysfunction.

Indeed, the down-regulatory effects of the cholinergic pathway on the leukocyte-endothelial activation and adhesion during inflammation have been shown in other studies both in-vivo and in-vitro. Nicotine, for example, reduces the endothelial cell activation via suppression of intercellular adhesion molecule 1, vascular adhesion molecule 1 and E-selectin expression as well as chemokines production by the endothelium in response to inflammatory stimuli [169]. Nicotine, also, decreases the levels of CD11b which is a beta 2 integrin implicated in neutrophil activation, adhesion and chemotaxis [207]. Interestingly, the mRNA and protein expression of α7-nAChR have been observed in the endothelium together with reports that reveal the key role of α7-nAChR in mediating the actions of nicotine on the endothelial cells [208]. As expected, the cholinergic inhibitory actions on leucocyte-endothelial activation and adhesion have been reproduced using CAP55, an α7-nAChR agonist [169], and blocked following addition of methyllycaconitine, a selective α7-nAChR antagonist [209]. Given these findings, it may be reasonable to posit that α7-nAChR is an important mediator of the cholinergic inhibition of neutrophil-endothelial interaction and its protection from endothelial dysfunction in preeclampsia.

5.5. CAP mitigates central neuroinflammation

Neuroinflammation is an important component in the pathogenesis of eclampsia, a complication of PE that is characterized by mal seizures [46]. Prior to eclampsia, patients usually develop an intensified peripheral inflammatory response along with dysfunctional blood brain barrier. The latter event facilitates the entrance of inflammatory mediators and cells leading to enhanced activity of microglia, which are macrophage like cells in the brain and neuroinflammation [10,210]. The exaggerated neuroinflammatory response leads to neural loss, hippocampal lesions and amplification of neuronal excitability, and consequent seizure outbreak.

In their eclampsia rat model, Li et al. [138] reported that nicotine administration mitigated the disturbances in serum inflammatory profile and suppressed concomitant neuroinflammation, microglial activity and neural loss. These effects may explain the ability of nicotine to delay the onset of seizures in pregnant preeclamptic rats and reduce the behavioral seizure scores as well as the incidence of stage-5 seizures. Considering that microglial cells express the α7-nAChRs, [211], it is conceivable that brain CAP would shield against the heightened neuroinflammation that develops in eclamptic seizures.

Recent reports from our laboratory [3,19] examined the role of central neuroinflammation in the interplay between CAP, PE fetal programming and endotoxemia. In one study, neuroanatomical pools of toll-like receptor-4 in brainstem areas of the NTS and RVLM have been implicated in the PE associated fetal programming that amplified endotoxic cardiovascular complications in adult male offspring. Consequently, PE appears to worsen endotoxic symptoms of hypotension, tachycardia, and cardiac autonomic dysfunction in preeclamptic offspring through exacerbation of neuroinflammatory signal [3]. In addition, we showed that the central anti-inflammatory pathways of brainstem α7 and α4β2 nicotinic acetylcholine receptors underlie the CAP counteraction of endotoxic neuroinflammatory and cardiovascular complications [19].

6. Effect of smoking on CAP/PE interaction

Since nicotine is a major constituent of the cigarette smoke, it is important to review how smoking would impact the risk and influences of PE. At least two systematic reviews published over the last two decades have come to the conclusion that smoking by pregnant women is associated with reduction in the incidence and risk of PE [133,212]. Besides, lower sFlt1 serum concentrations have been reported in pregnant smokers [213]. This apparently privileged effect of smoking on PE risk is not seen in females who quit smoking prior to onset of pregnancy [214]. Although nicotine is responsible for the protective action of smoking against PE, the credit might also be attributed to some other

components of the cigarette smoke. This conclusion gains support from the following observations: (i) the use of smokeless tobacco product which contained nicotine did not reproduce the reduction of PE risk seen with cigarette smoking [215], (ii) in-vitro cellular expression of PLGF, and VEGF were enhanced by cigarette smoke extract but not nicotine [216], and (iii) cigarette smoke reduced sFlt secretion by cultured placental cells [217], while nicotine alone failed to do so [91]. Therefore, it seems that other chemicals within cigarette smoke may be responsible for regulation of angiogenic factors. With the availability of more than 4000 different chemicals in regular cigarette smoke, it is clearly difficult to identify the effects of each individual substance on PE.

Among these chemicals, carbon monoxide (CO) has been proposed as a possible arbitrator of the protective effects of smoking. In addition to being a component of cigarette smoke, smoking itself induces heme oxygenase-1 expression in placental tissues and subsequently increases production of endogenous CO [218]. Preeclamptic patients have lower CO levels in their exhaled breath suggesting an inverse association between CO levels and incidence of PE [219]. CO is known for its potent vasodilator and anti-inflammatory properties [16,220], which could protect against placental disturbances during PE. Further, in-vivo experiments showed that administration of CO donor molecule mitigates PE induced hypertension but without improving fetal outcomes [221]. Moreover, CO and its releasing molecules were reported to decrease sFlt1 and sEng levels in placental and endothelial cell cultures, which may account for smoking-related reduction in PE risk [222]. Notably, nicotine has been shown to induce the expression of heme oxygenase-1 enzyme which produces CO [16]. However, whether CO contributes to the protective effects of nicotine and CAP during PE has not been investigated.

While it is true that nicotine alone cannot explain all of the beneficial effects of smoking against PE, nicotine is still a major product in cigarette smoking and there is a strong possibility that smoking protects from PE at least in part due to nicotine and CAP upregulation in pregnant females. Furthermore, a strong association was found between cotinine (metabolite of nicotine) levels in smokers and reduced risk of PE [223,224]. To summarize, the specific chemicals responsible for the positive impact of smoking against PE are not fully determined at this moment. However, it is likely that the actions of smoking are multifactorial and multiple pathways are implicated in this smoking-PE interaction. CAP activation by nicotine is probably the most important trail in this interaction.

Despite the multitude of research articles that linked smoking to preeclamptic risk reduction, several studies cautioned against the use of smoking as a therapeutic modality during pregnancy as it could generally worsen the outcomes of PE [225,226]. Additionally, the negative correlation between smoking and PE is not always a consistent finding since smoking increases risk of PE in individuals with chronic hypertension [227]. The advantageous effect of smoking in reducing PE incidence may simply be the result of the restricted growth of fetus and placenta as well as the increased tendency to preterm labor, as the smoking related reduction of PE risk has been observed more strongly in babies affected by growth restriction compared with larger babies [228]. Therefore, smoking induced placental damage and growth restriction could reduce release of antiangiogenic and pro-inflammatory factors from placenta explaining the protective impact on maternal cardiovascular parameters. Taking into consideration other pregnancy-associated hazardous actions of smoking [229], it becomes clear that smoking is not a reasonable option to combat PE. Actually, nicotine replacement therapy has been suggested as a safe alternative that can aid smoking cessation during pregnancy [135].

7. Other cardiovascular effects of nicotine

As mentioned previously, the beneficial anti-inflammatory actions of nicotine in PE might be obscured by other possible adverse effects of the drug on the cardiovascular system. Nicotine has been shown to raise blood pressure in humans [141] as well as rats [142], which can be attributed to its ability to stimulate nAChRs on postganglionic sympathetic neurons and adrenal medulla resulting in the release of catecholamines and hence vasoconstriction and increased vascular resistance [143]. The enhanced renal macrophage infiltration can also be blamed for the hypertensive response elicited by nicotine [144]. Moreover, nicotine has long been believed to suppress the arterial baroreceptor activity, which could account for the increased vulnerability of smokers to cardiovascular risk [230]. Nicotine attenuates baroreflex gain partly through reducing arterial compliance and stretch receptor responsiveness [231]. The interference with central pathways integrating the baroreceptor input into autonomic discharges is another possible mechanism for the nicotine suppression of baroreflexes [232].

More recent studies from our laboratory indicate that the interaction of nicotine with baroreflex chronotropic responses depends largely on factors such as subject sex, hormonal milieu, nature of the baroreflex heart rate response (bradycardia vs. tachycardia), and duration of exposure to nicotine [233–236]. Acutely administered nicotine impairs baroreceptor-mediated tachycardia in female rat preparations with depleted (ovariectomized or diestrus) and not physiologic estrogen contents, inferring a protective action for estrogen against reflex autonomic disturbances caused by nicotine [234]. Pharmacologic antagonist studies demonstrate that the presence of functional circuits of estrogenic receptors in the central nervous system is necessary for the down-regulating action of estrogen on the baroreflex inhibitory action of nicotine in ovariectomized rats [234]. Unlike its acute effects, the baroreflex attenuation by long-term nicotine exposure is exacerbated by estrogen because (i) chronic nicotine dose-dependently attenuates reflex heart rate responses in control, sham-operated rats via inhibition of the estrogen-mediated facilitation of vagal activity and nitric oxide synthase/heme oxygenase-coupled cGMP/$MAPK_{ERK}$ signaling, and (ii) this effect of nicotine vanishes in ovariecomized rats and reappears upon treatment with estrogen or the estrogen receptor modulator raloxifene [235–238]. Taken together, the blood pressure and baroreflex actions of nicotine may act in one way or another to oppose or at least restrain the beneficial anti-inflammatory influences of nicotine.

Another point of conflict relates to the widespread and distinct effects of nicotine on vascular tone and reactivity. Nicotine may cause vasodilation, vasoconstriction, or no effect at all on vascular tone. Discrepancies in animal species, tissues, dose and duration of nicotine regimens are likely contributing factors to the divergent vascular effects of nicotine [239,240]. The vasoconstrictor action of nicotine has been accounted for by sympathetic neural stimulation [241], endothelial dysfunction [242], or vasopressin [16] or endothelin [243]. Contradictory reports are available as regards cellular sites that mediate the vasodilator effect of nicotine. Nicotine causes nicotinic cutaneous and renal vasodilation via activation of NOS, prostanoids and potassium channels [244–247]. The Hormonal state of female rats variably affects the interaction of nicotine with adenosinergically-mediated vasodilations in the renal vasculature, with the latter enhanced and depressed by nicotine in estrogen- and progesterone-replaced ovariectomized rats, respectively [248]. In the rat tail artery, nicotine produces opposite effects (increase or decrease) on K^+ currents depending on the concentration of the drug [249]. Alternatively, β-adrenoceptor-mediated renal vasodilations are attenuated by nicotine through the impairment of estrogen-NOS signaling [250,251]. The question whether cardiovascular and renovascular regulation in preeclampsia could be similarly affected by nicotine remains to be explored.

8. Conclusions and future directions

Peripheral and central cholinergic pathways are fundamentally important for the initiation and progression of PE. Intriguingly, the upregulation of CAP constitutes a promising approach for managing PE and guarding against its maternal and fetal complications. Based on the data reviewed here, we postulate that nAChR agonists, particularly of

the α7 type, and α7 positive allosteric modulators represent a new pharmacological approach to improve inflammatory and angiogenic anomalies provoked by PE. The issue whether these therapies could be applied safely and effectively in humans warrants further clinical examination. Despite the great advancement in our knowledge of the counterbalancing role of CAP against inflammation over the last 20 years, the exact key molecular mechanisms involved in this interaction remain largely undisclosed. The activation of α7nAChR produces a variety of cellular effects that alleviate inflammation and improves angiogenic and endothelial dysfunctions. Accordingly, the identification of missing signaling molecules that are recruited following α7nAChR activation would help us to develop more targeted therapeutic strategies for PE.

As PE modulation of α7nAChRs is tissue specific (placental, peripheral circulation, central nervous system), further studies using genetically (knockout) or pharmacologically eliminated α7nAChR animals are recommended to characterize more accurately the role of α7 units in PE pathogenesis. This would also help in designing novel experimental PE models that better reflect the clinical course of PE. Additionally, given that the majority of existing α7 agonists display cross reactivity with other receptors such as 5-HT3, glutamate and dopamine [77,86,89,90], the development of drugs that selectively target α7 units can further restrain the potential of adverse effects. It is also fundamentally important to investigate in-depth the link between PE and other nicotinic receptor subtypes, especially α4β2 subunit, given the preliminary reports that demonstrate pathophysiological changes in the expression profile of these receptors during PE. Besides, more basic and clinical studies are required to elucidate the precise role of intracellular defensive machineries such as heme oxygenase-1 and heat shock protein 70 pathways in the PE-CAP interaction. As the transcutaneous stimulation of the vagus nerve has recently shown favorable outcomes in inflammatory conditions [79], the implementation of non-pharmacologic approaches for CAP activation, e.g., electrical vagal stimulation, is another possible avenue.

CRediT authorship contribution statement

Abdalla M. Wedn: Conceptualization, Methodology, Validation, Writing – original draft. **Hany M. El-Bassossy:** Conceptualization, Methodology, Writing - review & editing. **Ali H. Eid:** Conceptualization, Methodology, Writing - review & editing. **Mahmoud M. El-Mas:** Conceptualization, Supervision, Funding acquisition, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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