

# Arachidonate Cascade in the Intensive Insulin Therapy for Critically Ill Patients with Sepsis: Roles of Prostaglandins on Hyperglycemia-Impaired Immunity

Tatsurou Yagami\*, Yasuhiro Yamamoto, Hiromi Kohma and Kenkichi Takase

*Division of Physiology, Department of Pharmaceutical Health Care, Faculty of Pharmaceutical Sciences, Himeji Dokkyo University, 2-1, kami-ohno 7-Chome, Himeji, Hyogo, 670-8524, Japan*

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**Abstract:** Intensive insulin therapy to control blood glucose level increases survival among critically ill patients in intensive care unit and hospital. Hyperglycemia is potentially harmful because it acts as a procoagulant, induces insulin resistance, causes apoptosis, impairs neutrophil function, increases the infection rate and is associated with the risk of morbidity and mortality. Hyperglycemia and insulin resistance are virtually universally in sepsis, which is the leading cause of death in critically ill patients. Initially, sepsis is characterized by a hyper-inflammatory response; but as sepsis persists, there is a shift toward an anti-inflammatory immunosuppressive state. The intensive insulin therapy also reduces the infection rate and the mortality in septic patients. Arachidonate cascade is one of the factors associated with hyperglycemia, sepsis and infection. The cascade is involved in the upregulation of proinflammatory cytokines and the dysfunction of immune cells. Especially, we focused on prostaglandin D<sub>2</sub> (PGD<sub>2</sub>), which is produced from innate and adaptive immune cells. PGD<sub>2</sub> is non-enzymatically metabolized to 15-deoxy-Δ<sup>12,14</sup>-PGJ<sub>2</sub>, (15d-PGJ<sub>2</sub>). 15d-PGJ<sub>2</sub> is an endogenous ligand for the nuclear receptor, peroxysome proliferators-activated receptor γ (PPARγ) and induces apoptosis in the both immune cells. This review presents plausible roles of arachidonate cascade in hyperglycemia-impaired immunity. Furthermore, we shed light on therapeutic potentials of PPARγ ligands for critically ill patients under the insulin resistant state.

**Keywords:** Arachidonate cascade, 15-deoxy-Δ<sup>12,14</sup>-prostaglandin J<sub>2</sub>, intensive insulin therapy, peroxysome proliferators-activated receptor γ, insulin resistance, thiazolidine.

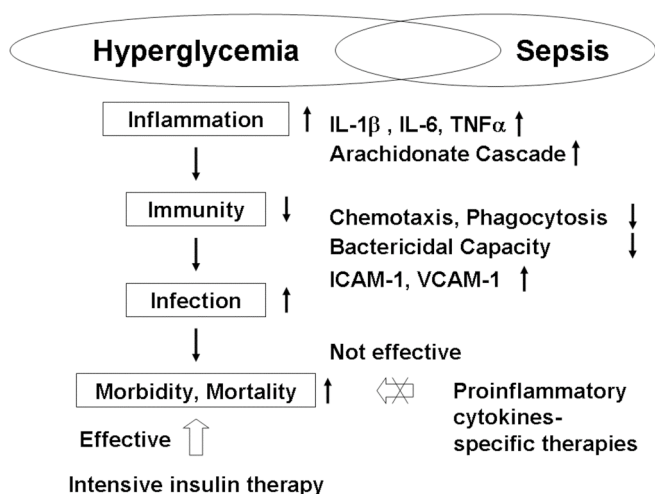
## INTRODUCTION

In 2001, a landmark paper was published. Van den Berghe *et al.* reported that intensive insulin therapy to control blood glucose level increases survival among critically ill patients in intensive care unit (ICU) and hospital [1]. Intensive insulin therapy does not only ameliorate the mortality by the prevention of hyperglycemia, but also does by the non-glycemic metabolic effects. The therapy partially corrects this lipid profile, which in multivariate logistic regression analysis explains a significant part of the reduced mortality and organ failure [2]. Intensive insulin therapy mitigates the cortisol response to critical illness, without altering cortisol-binding activity, which is also statistically related to improved outcome [3]. The administration of insulin resulted in lower pro-inflammatory cytokines and proteins and enhanced anti-inflammatory mediators in children with burn injury, but not a cohort of critically ill surgical patients [4]. Insulin has also shown to improve myocardial function and to protect the myocardium during endotoxemic shock, acute myocardial infarction, open heart surgery and other critical conditions [5]. Endothelial dysfunction with excessive leukocyte adhesion and aggregation, in combination with accelerated intravascular coagulation and thrombosis, limits perfusion in the microcirculatory blood vessels. This results in cellular

hypoxia, which can culminate in organ failure and death [6]. Therefore, prevention of endothelial dysfunction may contribute to the protective effects of insulin therapy on organ failure and death in critical illness in general and in sepsis in particular [7]. Intensive insulin therapy reduced endothelial activation, as reflected in lower levels of adhesion molecules. Conversely, intensive insulin therapy reduced the levels of asymmetric dimethylarginine [8], an endogenous inhibitor of NOS activity, which competes with cellular transport of its substrate arginine and thus interferes with NO production. The modulation of this arginine derivative by insulin is associated with a better outcome, probably mediated by reducing the inhibition of the constitutively expressed endothelial NOS [9], contributing to preservation of organ blood flow.

Hyperglycemia is common in critically ill patients, even if they have not previously had diabetes. Hyperglycemia exerts different effects on the early events of the innate immune response with interactions between leukocytes and vascular endothelium (Fig. 1). The adhesion of monocytes and neutrophils to the endothelium is mediated by integrin receptors. Hyperglycemia is correlated with increased plasma concentrations of E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) [10]. Chemotaxis [11] and phagocytosis [12] of neutrophil are impaired during hyperglycemia. Plasma levels of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) [13] and interleukin-1β (IL-1β) [14] are increased during acute hyperglycemia.

\*Address correspondence to this author at the Himeji Dokkyo University, 2-1, kami-ohno 7-Chome, Himeji, Hyogo, 670-8524, Japan; Tel: +81-792236813; Fax: +81-792850352; E-mail: yagami@himeji-du.ac.jp



**Fig. (1).** Hyperglycemia and sepsis. Hyperglycemia and sepsis present common symptoms, hyperinflammation and immunosuppression. In hyperinflammation, proinflammatory cytokines *e.g.* interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin 6 (IL-6) and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), are up-regulated. Arachidonate cascade are enhanced. In immunosuppressive state, adhesion ligands *e.g.* intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are upregulated. Chemotactic and phagocytotic activities are suppressed in neutrophils, leading to the impairment in bactericidal capacity. Increased risk of infection, morbidity and mortality are declined by intensive insulin therapy, but not by proinflammatory cytokines-specific therapies.

In ICU, multiple-organ failure with proven-septic focus is the first cause of death [1]. Sepsis represents an over-exuberant inflammatory response in which unbridled cytokine-mediated host defense mechanisms induce significant cell and organ injury. However, numerous clinical trials of cytokine or anti-inflammatory-specific agents, for example, TNF- $\alpha$ - and IL-1 $\beta$ -specific therapies, either failed to improve survival in patients with sepsis or, in some cases, exacerbated the condition (Fig. 1). These failures led to a reassessment of the concept that death in sepsis is due to a hyper-inflammatory response [15]. Indeed, clinically relevant animal models of sepsis, as well as studies of patients with sepsis, showed that the initial hyper-inflammatory response in sepsis is quickly followed by the development of a sustained anti-inflammatory or immunosuppressive state [16]. Most patients with sepsis will survive in the initial few days and develop a protracted hypo-inflammatory, immunosuppressive state that is manifested by an inability to eradicate the primary infection and/or the development of new secondary infections. The fact that many of the pathogens responsible for the secondary, hospital-acquired infections are not particularly virulent in patients with normal, competent immune systems which highlights the immunosuppressed state of patients with sepsis (Fig. 1).

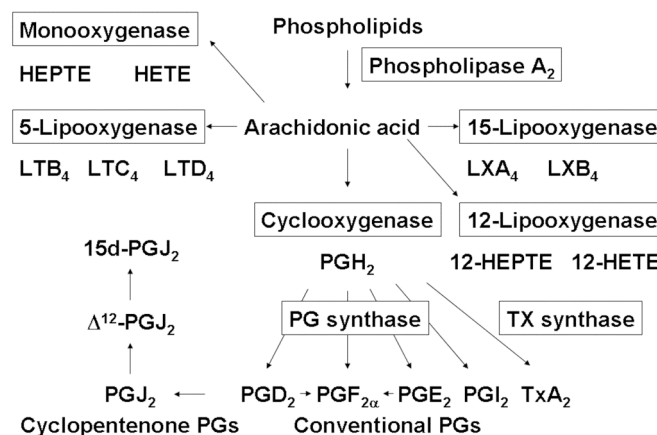
Intensive insulin therapy reduces the largest number of death in the multiple-organ failure with detectable septic focus. The therapy does also reduce mortalities in multiple-organ failure without detectable septic focus and severe brain damage, but not in acute cardiovascular collapse. Furthermore, the incidence of septic patients with infection

is reduced by intensive insulin treatment [1]. Arachidonate cascade is one of factors associated with hyperglycemia, sepsis and infection. Furthermore, the cascade is involved in the up-regulation of proinflammatory cytokines and adhesion ligands and the dysfunction of immune cells. In this review, we presented pathological roles of arachidonate cascade in critically ill patients with sepsis, and focused on the plausible involvement of prostaglandins in hyperglycemia-impaired immunity.

## ARACHIDONATE CASCADE

In the arachidonate cascade, several enzymes including phospholipase A<sub>2</sub> (PLA<sub>2</sub>), cyclooxygenase (COX) and lipoxygenase (LOX) are involved (Fig. 2). PLA<sub>2</sub> belongs to a family of enzymes (EC3.1.1.4.) that catalyze the cleavage of fatty acids from the *sn*-2 position of glycerophospholipids to produce free fatty acids and lysophospholipids [17]. PLA<sub>2</sub>s participate in a wide variety of physiological processes, including phospholipid digestion, remodeling of cell membranes and host defense. They also take part in other processes by producing precursors of various types of biologically active lipid mediators, such as prostaglandins (PGs), leukotrienes (LTs), thromboxanes (TXs) and platelet-activating factor. In the mammalian system, more than 20 different isoforms of PLA<sub>2</sub> have been identified, and different PLA<sub>2</sub>s have been shown to participate in pathophysiological events related to cell injury, inflammation, and apoptosis [17,18]. According to their

## Arachidonate cascade



**Fig. (2).** Arachidonate cascade. Phospholipase A<sub>2</sub> liberates free fatty acids such as arachidonic acid from the *sn*-2 position of glycerophospholipids. Arachidonic acid is metabolized by cyclooxygenase to prostaglandin H<sub>2</sub> (PGH<sub>2</sub>). PGH<sub>2</sub> is metabolized to PGD<sub>2</sub>, PGF<sub>2 $\alpha$</sub> , PGE<sub>2</sub>, PGI<sub>2</sub> and thromboxanes (TXA<sub>2</sub>) by corresponding PG synthases and TXA<sub>2</sub> synthase, respectively. Conventional PG, PGD<sub>2</sub>, is non-enzymatically metabolized to cyclopentenone PGs such as PGJ<sub>2</sub>,  $\Delta^{12}$ -PGJ<sub>2</sub> and 15d-PGJ<sub>2</sub>. Arachidonic acid is also metabolized by monooxygenase to hydroperoxyeicosatetraenoic acids (HEPTes) and hydroxyeicosatetraenoic acids (HETEs), by 5-lipoxygenase to leukotrienes (LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>), by 12-lipoxygenase to 12-HEPTes and 12-HETEs and by 5-lipoxygenase to lipoxins (LXA<sub>4</sub>, LXB<sub>4</sub>), respectively. Proteins enclosed in square are enzymes.

Tables 1. Characterization of PLA<sub>2</sub>

	sPLA <sub>2</sub>	cPLA <sub>2</sub>	iPLA <sub>2</sub>	PAF-AH
Type	IB, IIA, IIC, IID, IIE, IIF, V, X, XII	IVA, IVB, IVC, IVD, IVE, IVF	VIA, VIB	VIIA, VIIIB VIII, VIIIB
Molecular Weight	14kDa	85kDa	80kDa	50kDa
Localization	Extracellular	Cytosol	Cytosol	Extracellular Cytosol Membrane
Calcium	Stimulated	Translocation	None	None
Substrate	PtdCho	PtdCho	PtdCho	PAF Oxidized lipids
Fatty acid	None	AA	Linoleic acid	DHA, AA

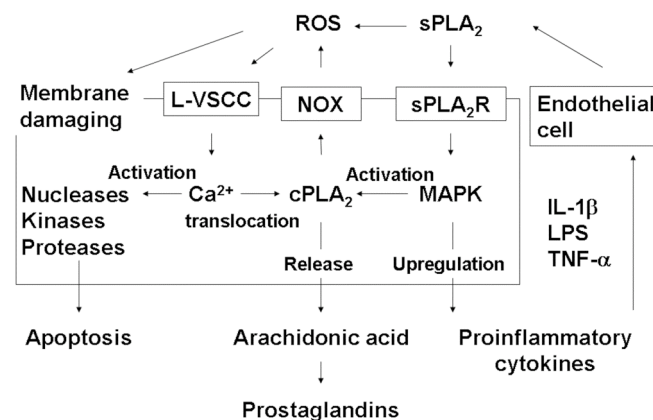
AA: arachidonic acid, DHA: docosahexanoic acid, PAF-AH: platelet-activating factor-acetylhydrolase, PtdCho: phosphatidyl choline.

biochemical features such as cellular localization, requirement of Ca<sup>2+</sup>, substrate specificity and the primary structure, these PLA<sub>2</sub>s are classified into several families, including low molecular weight secretory PLA<sub>2</sub> (sPLA<sub>2</sub>), Ca<sup>2+</sup>-sensitive arachidonoyl-specific 85-kDa cytosolic PLA<sub>2</sub> (cPLA<sub>2</sub>), Ca<sup>2+</sup>-independent PLA<sub>2</sub> (iPLA<sub>2</sub>), and platelet-activating factor -acetylhydrolase. In the mammalian, sPLA<sub>2</sub> (IB, IIA, IIC, IID, IIE, IIF, V, X and XII), cPLA<sub>2</sub> (IVA, IVB, IVC, IVD and IVE), iPLA<sub>2</sub> (VIA and VIB) and platelet-activating factor -acetylhydrolase (VIIA, VIIIB, VIIIA and VIIIB) have been detected [19] (Table 1).

### Secreted PLA<sub>2</sub>s

Secretory PLA<sub>2</sub>-IIA is found in many cells and tissues and its expression is modulated by various inflammatory cytokines (Fig. 3), such as IL-1 $\beta$  and TNF- $\alpha$  [20]. Serum sPLA<sub>2</sub> levels are elevated in critically ill patients, particularly in those with sepsis [21]. Higher levels of sPLA<sub>2</sub> have been reported in septic patients who died compared with those who survived [22]. PLA<sub>2</sub> may mediate some of the clinical features of septic shock, as parenteral administration of purified exogenous sPLA<sub>2</sub> produces hypotension in experimental models, and sPLA<sub>2</sub> levels have been found to correlate directly with the magnitude and duration of circulatory collapse [23]. Secretory PLA<sub>2</sub> can interact with external cell membrane through direct binding to phospholipid or specific cell surface sPLA<sub>2</sub> receptors (Fig. 3). The M-type sPLA<sub>2</sub> receptors present on mast cell [24], skeletal muscle cell [25] and human neutrophils [26] belong to the superfamily of C-type lectins and bind with high affinity to the snake venom sPLA<sub>2</sub> OS<sub>1</sub> and OS<sub>2</sub>, sPLA<sub>2</sub>-IB and rabbit and mouse sPLA<sub>2</sub>-IIA, but not with bee venom sPLA<sub>2</sub>-III and very weakly to human sPLA<sub>2</sub>-IIA. The N-type sPLA<sub>2</sub> receptors identified in rat brain have high affinity for OS<sub>2</sub>, sPLA<sub>2</sub>-IB and bee venom sPLA<sub>2</sub>-III. sPLA<sub>2</sub>-IIA potentiates Ca<sup>2+</sup> influx through L-type voltage-sensitive calcium channel [27] and induces apoptosis [28]. High-affinity binding sites of sPLA<sub>2</sub>-IB exist on the plasma membrane [29]. Secretory PLA<sub>2</sub>-IB also induces the excess

influx of Ca<sup>2+</sup> into cells *via* L-type voltage-sensitive calcium channel [30], and subsequently apoptosis [31].



Mast cell, Neutrophil, Monocyte, Macrophage, Apoptotic T cell, B cell

**Fig. (3).** Secretory PLA<sub>2</sub> binds to sPLA<sub>2</sub> receptor (sPLA<sub>2</sub>R) in peripheral tissues and central nervous system, respectively. sPLA<sub>2</sub>R-stimulated mitogen activated protein kinase (MAPK) activates cPLA<sub>2</sub> and upregulates proinflammatory cytokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ), lipopolysaccharide (LPS) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Cytosolic PLA<sub>2</sub> liberates arachidonic acid from phospholipids, generates eicosanoids *via* cyclooxygenase (COX) and produces reactive oxygen species (ROS) *via* NADPH oxidase (NOX), respectively. ROS does not only damage membranes but also flow Ca<sup>2+</sup> into cytosol *via* L-type voltage-sensitive calcium channel (L-VSCC). Elevated concentration of intracellular Ca<sup>2+</sup> ([Ca<sup>2+</sup>]<sub>i</sub>) translocates cPLA<sub>2</sub> to membranes and releases arachidonic acid. Moreover, Ca<sup>2+</sup>-dependent nucleases, kinases and proteases induce apoptosis.

### Cytosolic PLA<sub>2</sub>s

cPLA<sub>2</sub> belongs to the group IV PLA<sub>2</sub>s (Table 1). Although four isoforms, *i.e.*, cPLA<sub>2</sub> $\alpha$ , - $\beta$ , - $\gamma$  and - $\delta$ , have been identified. The 85 kDa cPLA<sub>2</sub> $\alpha$  has been studied most extensively. cPLA<sub>2</sub> requires micromolar Ca<sup>2+</sup> for activity;

however unlike sPLA<sub>2</sub>, Ca<sup>2+</sup> is necessary for binding cPLA<sub>2</sub> to membrane or phospholipids vesicles rather than for catalysis. An increase in intracellular Ca<sup>2+</sup> concentration promotes binding of Ca<sup>2+</sup> ions to the C2 domain and then allows cPLA<sub>2</sub> to translocate from the cytosol to the perinuclear region including the Golgi apparatus, endoplasmic reticulum and nuclear envelope [32,33]. Activation of cPLA<sub>2</sub> proceeds primarily through phosphorylation [14]. This protein is comprised of a C2 domain and multiple phosphorylation sites, including two consensus sites (Ser<sup>505</sup> and Ser<sup>727</sup>) for phosphorylation by mitogen-activated protein kinases (MAPKs) [14] and a Ser<sup>515</sup> site for Ca<sup>2+</sup>/calmodulin-dependent protein kinase [34]. cPLA<sub>2</sub> is activated by calcium-dependent translocation of the enzyme from a cytosolic location to perinuclear membranes, and releases arachidonic acids (Fig. 3) [24-26]. cPLA<sub>2</sub> can also target other subcellular membranes, including mitochondrial and plasma membranes. Studies with neutrophils indicated a transient recruitment of cPLA<sub>2</sub> to the NADPH oxidase (NOX) complex in plasma membrane [35]. NOX is composed of the membrane-bound subunits gp91 phox (Nox2)/Nox1/Nox4 and p22 phox, and the catalytic site of the oxidase and cytosolic components p47 phox and p67 phox. Cytosolic PLA<sub>2</sub> specifically binds to p47 phox and that p47 phox is sufficient to anchor cPLA<sub>2</sub> to the assembled oxidase on the plasma membranes upon stimulation [36].

### Ca<sup>2+</sup>-Independent PLA<sub>2</sub>s

The iPLA<sub>2</sub> family is comprised of group VIA and VIB (Table 1). Group VIA enzyme has at least five splice variants, all with ankyrin repeats, whereas group VIB iPLA<sub>2</sub> lacks ankyrin repeats but consists of a signal motif for peroxisome localization. In normal rat brain, >70% of PLA<sub>2</sub> activity can be attributed to iPLA<sub>2</sub>s. iPLA<sub>2</sub> is the dominant PLA<sub>2</sub> in the cytosolic fraction, and generally regarded as house keeping enzymes for the maintenance of membrane phospholipids [37]. iPLA<sub>2</sub> displays a substrate preference toward the fatty acid chain in the *sn*-2 position of phosphatidylcholine of linoleyl > palmitoyl > oleoyl > arachidonyl, and a head group preference for choline > ethanolamine >> inositol.

### Cyclooxygenase and Eicosanoids

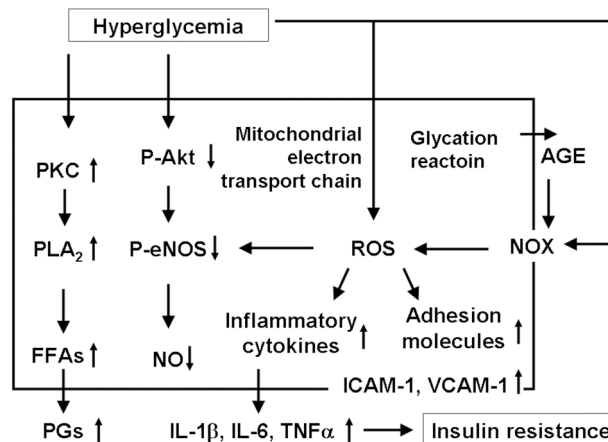
COX is classified into three forms, a constitutive form, COX-1, a mitogen-inducible form, COX-2 and a variant of COX-1, COX-3 [38]. Once the arachidonic acid has been supplied, both isoforms of COX form PGH<sub>2</sub> via identical enzymatic processes (Fig. 2). Following these steps, PGH<sub>2</sub> can be metabolized by different enzyme pathways to a range of products with potent biological effects. The profile of products made by cells expressing COX-1/COX-3 or COX-2 is therefore determined by the presence of different downstream enzymes. Eicosanoids such as PGs and LTs are well characterized both in metabolic pathways and in signaling pathways through their respective cell surface G protein-coupled receptors [39-42]. Eicosanoids modulate cellular function during a variety of physiological and pathological processes [43]. Eicosanoids are divided into two groups according to their mechanism of action: the conventional eicosanoids, e.g., PGD<sub>2</sub> and PGE<sub>2</sub>, the

cyclopentenone-type PGs, e.g., PGJ<sub>2</sub> and PGA<sub>2</sub>. PGD<sub>2</sub> is non-enzymatically dehydrated to produce PGJ<sub>2</sub>, Δ<sup>12</sup>-PGJ<sub>2</sub>, and 15-deoxy-Δ<sup>12,14</sup>-PGJ<sub>2</sub> (15d-PGJ<sub>2</sub>) (Fig. 2) [44,45].

## GLUCOSE TOXICITY

### Oxidative Stress

Glucose toxicity, in its narrow sense, can indicate a clinical condition where control of diabetes in particular is poor since hyperglycemia itself reduces the insulin secretion capacity of pancreatic cells, and resultant increase in insulin resistance leads to further hyperglycemia. As shown in Fig. (4), oxidative stress is associated with the molecular mechanism of the decreased insulin biosynthesis and secretion, which is the main etiology of glucose toxicity [46]. High glucose produces reactive oxygen species (ROS), such as superoxides (O<sub>2</sub><sup>•</sup>), hydroxyl radicals (OH<sup>•</sup>), peroxy radicals (ROO<sup>•</sup>) or nitric oxide, through the activation of NADPH oxidase (NOX) [47]. On the other hand, it also decreases eNOS and Akt phosphorylation and bioavailable NO (Graphical Abstract) [48]. Hyperglycemia increases free fatty acids and various inflammatory cytokines e.g., IL-1β, IL-6 and TNF-α [49,50]. Free fatty acids and TNF-α are likely to be involved in the development of insulin resistance [51].



**Fig. (4).** The increased oxidative stress in a hyperglycemic state. Hyperglycemia induces ROS through activation of the glycation reaction and electron transport chain in mitochondria. Also, advanced glycosylation end products (AGEs), insulin, and angiotensin II induce ROS through activation of NADPH oxidase (NOX). Increased ROS are involved in the development of atherosclerosis in various aspects. First, ROS decrease nitric oxide levels, which leads to endothelial cell dysfunction. Second, ROS increase expression of various adhesion molecules such as ICAM-1 and VCAM-1, which leads to inflammatory cell recruitment. Finally, ROS increase expression of inflammatory cytokines (IL-1β, IL-6 and TNF-α) and activate various stress signaling such as JNK and Pim-1, which leads to the cell proliferation. Moreover, hyperglycemia activates Ca<sup>2+</sup>-dependent protein kinase (PKC) and PLA<sub>2</sub>, liberates free fatty acids (FFAs) and generates PGs.

### Infection

Infection is one of glucose toxicities. The high infection rate is ascribed to pathogenetic mechanisms including

Tables 2. DP1, DP2 (CRTH2) and PPAR $\gamma$ 

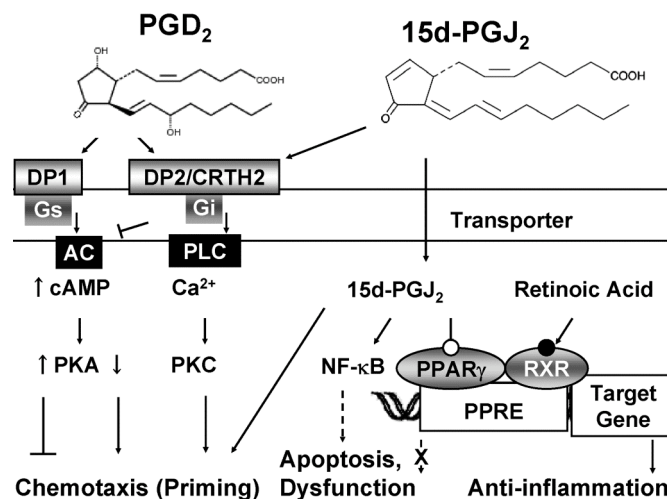
	PGs	DP1	CRTH2	PPAR $\gamma$	15d-PGJ <sub>2</sub> (nM)	15d-PGJ <sub>2</sub> ( $\mu$ M)
Innate immune cells						
Mast cell	PGD <sub>2</sub>					Apoptosis
Dendritic cell	PGD <sub>2</sub> PGE <sub>2</sub> TXA <sub>2</sub>	Detected	Not detected	Detected		Apoptosis
Macrophage	PGD <sub>2</sub>	Not detected	Detected	Detected		
Neutrophil	PGD <sub>2</sub>			Detected Chemotaxis↓		Apoptosis
Eosinophil	PGD <sub>2</sub>	Detected	Detected Chemotaxis↑		Priming	Apoptosis
Basophil			Detected Chemotaxis↑			
Addaptive immune cells						
Th2 cell	PGD <sub>2</sub>		Detected Chemotaxis↑	Detected		
B cell				Proliferation		Apoptosis
				Antibody production		

defects in immunity. Immunity can be divided into two systems, innate immunity and adaptive immunity. In the innate immunity, mast cells, dendritic cells, macrophage, natural killer cells, complement protein, and granulocytes including basophils and eosinophils, which contribute to this system (Table 2).

Innate immune recognition of pathogens is mediated mainly through the Toll-like receptors (TLRs) (Fig. 5), which are stimulated by different microbial stimuli [52]. Stimulation of TLRs increase eicosanoids [53], which are a class of lipid mediators involved in inflammatory as well as other physiological processes. LTC<sub>4</sub> and PGD<sub>2</sub> were generated in response to TLR2 agonists [54]. TLRs signal through a cytoplasmic TIR domain that associates with the adaptor protein MyD88, leading to stimulation of downstream kinases such as extracellular signal-regulated kinase and activation of cPLA<sub>2</sub> [53]. Engagement of bacterial structures to cellular TLRs leads to the activation of the nuclear factor (NF)- $\kappa$ B signaling pathway [55]. NF- $\kappa$ B regulates the secretion of proinflammatory mediators (Fig. 5).

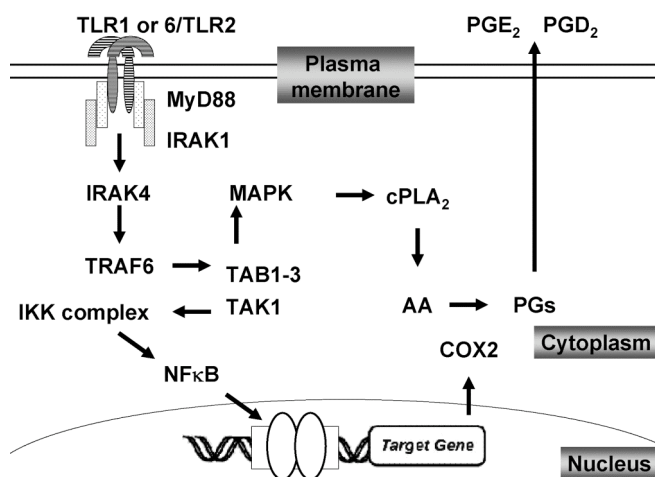
Specific cell populations of the innate immune system such as antigen presenting dendritic cells are critical in promoting primary T and B cells response and probably bridge the gap between innate and adaptive immunity. During the acute phase response, the release of cytokines including TNF- $\alpha$ , IL-1 and IL-6 from inflammatory and other cells leads to the expression of sPLA<sub>2</sub>-IIA and release of the enzyme into circulation [56]. An abnormally high value of serum PLA<sub>2</sub> was observed in 18 of 30 patients (60%) at ICU [57]. Secretory PLA<sub>2</sub>-IIA is found in high

concentrations in the circulation of patients with acute pancreatitis and certain cancers and in the synovial fluid



**Fig. (5).** Receptors for PGD<sub>2</sub> and 15d-PGJ<sub>2</sub>. PGD<sub>2</sub> activates adenylate cyclase (AC) via DP1-the stimulatory GTP-binding protein (Gs) and inactivates it via DP2/CRTH2-inhibitory GTP-binding protein (Gi), respectively. Elevated level of intracellular cAMP stimulates cAMP-dependent protein kinase (PKA) and suppresses chemotaxis. 15d-PGJ<sub>2</sub> also activates phospholipase C (PLC) via DP2/CRTH2-Gi. PLC produces inositol triphosphate (IP<sub>3</sub>) and releases calcium from endoplasmic reticulum to cytosol. Elevated level of intracellular Ca<sup>2+</sup> activates Ca<sup>2+</sup>-dependent protein kinase (PKC) and stimulates chemotaxis. 15d-PGJ<sub>2</sub> also stimulates chemotaxis via CRTH2-Gi and suppresses it via PPAR $\gamma$ .

from patients with rheumatoid arthritis [58]. Several mammalian sPLA<sub>2</sub> such as sPLA<sub>2</sub>-IIA also bind to heparan sulfate proteoglycans like glypican-1 [58]. The binding of sPLA<sub>2</sub>-IIA to heparan sulfate proteoglycans is required for exogenous sPLA<sub>2</sub>-IIA-catalyzed AA release from apoptotic human T cells [59].



**Fig. (6).** Arachidonate cascade in the innate immunity. Toll-like receptors (TLRs) recognize distinct microbial- or host-derived molecules and trigger innate immune responses. Shown are signal pathways for TLR2. TLR1, 2, 4, 5, and 6 are located primarily on the plasma membrane and TLR3, 7, 8, and 9 are localized to endosomal compartments. With the exception of TLR3 and TLR4, all other TLRs solely utilize MyD88, IRAK1, IRAK4 and TAK1 as central signal transducing machinery. TAK1 activates MAPK pathway and release AA. TAK1 also activates TNF- $\alpha$ -induced  $\kappa$ B inhibitor (I $\kappa$ B) kinase (IKK) complex composed of IKK $\alpha$ , IKK $\beta$  and IKK $\alpha$ /NEMO, which induces phosphorylation of I $\kappa$ B which releases NF- $\kappa$ B to translocate to the nucleus, and induces COX2. COX2 metabolizes AA to PGs, e.g. PGE<sub>2</sub> and PGD<sub>2</sub>.

## Inflammation

The inflammatory response that initiates the maturation and migration of innate immune cells involves soluble mediators such as cytokine, nitric oxide and prostanoids [60]. Dendritic cells predominantly produce PGE<sub>2</sub> and TXA<sub>2</sub>, while mast cells produce PGD<sub>2</sub> (Table 2). PGD<sub>2</sub> is also produced in significant amounts by dendritic cells [61], macrophages [62], neutrophils [63], eosinophils [64], Th2 cells [65] and endothelial cells [66]. Two G-protein-coupled receptors for PGD<sub>2</sub> have been described to date: type 1 receptor for PGD<sub>2</sub> (DP1) and type 2 receptor for PGD<sub>2</sub> (DP2)/chemoattractant receptor homologous molecule expressed on Th2 cells (CRTH2). DP1 is coupled with the stimulatory GTP-binding protein, stimulate adenylate cyclase and elevation in cyclic AMP levels, which are usually associated with the inactivation of eosinophils (Fig. 4) [67]. On the other hand, DP2/CRTH2 is also a seven transmembrane-spanning protein, activate phospholipase C *via* the inhibitory GTP-binding protein, elevates intracellular Ca<sup>2+</sup> concentration and expressed by Th2 cells, eosinophils, and basophils [68] (Fig. 4). DP2/CRTH2 has been shown to have a broader spectrum of ligands, as it is also activated by several PGD<sub>2</sub> metabolites, including 13,14-dihydro-15-keto-

PGD<sub>2</sub>, PGJ<sub>2</sub>,  $\Delta^{12}$ -PGJ<sub>2</sub> and 15d-PGJ<sub>2</sub> [69] as well as 9 $\alpha$ ,11 $\beta$ -PGF<sub>2</sub> and its stereoisomer PGF<sub>2</sub> $\alpha$  [70] and a TX metabolite, 11-dehydro-TXB<sub>2</sub> [71]. DP2/CRTH2 activation can lead to a plethora of biological effects that includes the induction of the chemotaxis of eosinophils, basophils, and Th2 cells [68,72]. DP2/CRTH2 agonists are prime eosinophils for chemotaxis toward other chemoattractants and are capable of mediating the rapid mobilization of eosinophils from the isolated hind limb of guinea pigs [73].

## Hyperglycemia-Induced Immunodeficiency

Hyperglycemia in the acute phase causes the functional decline of neutrophils, and is a risk factor that causes infection in the perioperative period [74]. Recent basic researches have found that the functional decline of neutrophil is caused by a hyperglycemic state [75], and that the mechanism of this decline includes increased adhesive capacity and diminished chemotaxis, phagocytic activity [76] and bactericidal capacity [77]. A depression in primary and secondary immune responses was due to altered T-cell function and phagocytic activity in macrophages [78]. Intracellular oxidative stress initiates apoptotic processes and is toxic to primary T cells [79]. Enhanced oxidative stress plays an important role in the development of immunodeficiency [80]. The presence of high glucose in lymph node and spleen lymphocyte cultures decreased cell viability [81]. The apoptosis of macrophages might occur with high glucose concentrations, leading to the spreading of lipids from macrophages into intracellular spaces in the vessel wall [82].

## SEPSIS

Sepsis is defined as a systemic inflammatory response syndrome secondary to infection. It represents a leading cause of death in critically ill patients, mainly due to the development of organ dysfunction and tissue hypoperfusion [83]. The pathogenesis of sepsis is thought to include an initial hyperinflammatory reaction evoked by infectious pathogens, followed by a hypo- or dysregulated inflammatory state [84]. Neutrophils represent the predominant cellular component at sites of acute inflammation. These cells serve a critical role in host defense with transendothelial migration of neutrophils being a crucial component of the immune/inflammatory response [85]. Emerging evidence indicates that sepsis, most commonly caused by bacteria, results in impaired host defenses, including a reduced ability of neutrophils to migrate appropriately [86]. Moreover, higher mortality rates have been observed in patients with sepsis-induced immune deactivation [87].

## Sepsis-Induced Immunodeficiency

The type of immune cells lost during sepsis has been characterized by subsequent immunohistochemical analysis of the spleen of patients following autopsy [88]. These phenotypic studies reveal a striking decrease in the number of B cells and CD<sup>4+</sup> T cells in spleens from patients with sepsis compared with spleens from critically ill control patients without sepsis [88]. Similarly, there is a remarkable

decrease in the number of follicular and interdigitating dendritic cells in spleens from patients with sepsis versus control patients without sepsis [89], but not decrease in the number of neutrophils. Chemotaxis is significantly lower in patients than in healthy controls and associated with spontaneous adherence and increased expression of adhesion molecules.

15d-PGJ<sub>2</sub> is a ligand for the nuclear receptor, peroxysome proliferators-activated receptor (PPAR $\gamma$ ) [90,91]. Neutrophils constitutively express PPAR $\gamma$ , which is up-regulated by the sepsis-induced cytokines TNF- $\alpha$  and IL-4. Chemotactic responses of neutrophils to formylmethionyl-leucyl-phenylalanine and IL-8 are inhibited by treatment with the PPAR $\gamma$  ligands, troglitazone and 15d-PGJ<sub>2</sub>, and by transfection of neutrophils-like HL-60 cells with a constitutively active PPAR $\gamma$  construct. Inhibition of chemotaxis by PPAR $\gamma$  ligands correlates with decreases in extracellular signal-regulated kinase-1 and -2 activation, actin polymerization, and adherence to a fibrinogen substrate. Furthermore, neutrophilic expression of PPAR $\gamma$  is increased in sepsis patients and mice with either of two models of sepsis. Treatment with the PPAR $\gamma$  antagonist, GW9662, significantly reverses the inhibition of neutrophilic chemotaxis and increased peritoneal neutrophilic recruitment in murine sepsis. PPAR $\gamma$  activation is involved in chemotactic responses of neutrophils *in vitro* and may play a role in the migration of these cells *in vivo* [92].

### Sepsis-Induced Apoptosis

The key role of apoptosis in patients with sepsis is shown in a unique study in which patients in ICU who died of sepsis were compared with patients in intensive-care units who died of non-septic aetiologies [93]. Autopsies of patients with sepsis reveal extensive apoptosis of lymphocytes and gastrointestinal epithelial cells. The type of immune cells lost during sepsis is characterized by subsequent immunohistochemical analysis of the spleen of patients following autopsy [89,94]. These phenotypic studies reveal a striking decrease in the number of B cells and CD4<sup>+</sup> T cells in spleens from patients with sepsis compared with spleens from critically ill control patients without sepsis [93].

Many inflammatory mediators retard granulocyte apoptosis. PGD<sub>2</sub> and its metabolite PGJ<sub>2</sub> selectively induce eosinophil, but not neutrophil apoptosis. The sequential metabolites  $\Delta^{12}$ -PGJ<sub>2</sub> and 15d-PGJ<sub>2</sub> induce caspase-dependent apoptosis in both granulocytes, an effect that does not involve de novo protein synthesis. Despite the fact that  $\Delta^{12}$ -PGJ<sub>2</sub> and 15d-PGJ<sub>2</sub> are PPAR $\gamma$  activators, apoptosis was not mimicked by synthetic PPAR $\gamma$  and PPAR $\alpha$  ligands or blocked by an irreversible PPAR $\gamma$  antagonist. Furthermore,  $\Delta^{12}$ -PGJ<sub>2</sub> and 15d-PGJ<sub>2</sub> inhibited lipopolysaccharide-induced I $\kappa$ B $\alpha$  degradation and subsequent inhibition of neutrophil apoptosis, suggesting that apoptosis is mediated *via* PPAR $\gamma$ -independent inhibition of NF- $\kappa$ B activation. TNF- $\alpha$ -mediated loss of cytoplasmic I $\kappa$ B $\alpha$  in eosinophils is inhibited by 15d-PGJ<sub>2</sub> in a concentration-dependent manner [95].

PPAR $\gamma$  ligands, including the endogenous ligand 15d-PGJ<sub>2</sub> and synthetic ligands like ciglitazone and troglitazone,

all induce apoptosis in normal and malignant human B lymphocytes. Dominant-negative PPAR $\gamma$  and a PPAR $\gamma$  antagonist prevent PPAR $\gamma$  activation but do not prevent B cell apoptosis induced by 15d-PGJ<sub>2</sub> or ciglitazone. In addition, a PPAR $\gamma$  agonist that is a structural analog of 15d-PGJ<sub>2</sub>, and lacks the electrophilic carbon of the 15d-PGJ<sub>2</sub> cyclopentenone ring, activates PPAR $\gamma$  but does not kill B lymphocytes, further supporting a non-PPAR $\gamma$ -mediated mechanism. 15d-PGJ<sub>2</sub>, but not ciglitazone, potently induces reactive oxygen species in B lymphocytes, implicating the reactive nature of the 15d-PGJ<sub>2</sub> structure in the apoptosis mechanism. In addition, 15d-PGJ<sub>2</sub> causes an almost complete depletion of intracellular glutathione. Moreover, incubation with glutathione reduced ethyl ester, an antioxidant, prevents apoptosis induced by 15d-PGJ<sub>2</sub>, but not by ciglitazone [96].

### ARACHIDONATE CASCADE-RELATED DRUGS

Specific PLA<sub>2</sub> inhibitors have been developed recently. They are not yet commercially available or approved by regulatory agencies, but clinical studies have been launched to assess their utility in the treatment of patients with cardiovascular diseases.

COX inhibitors are commercially available as non-steroidal anti-inflammatory drugs. Inflammation participates in the pathogenesis of type 2 diabetes (T2D) [97] which increases the production of proinflammatory cytokines and chemokines (e.g., IL-1 $\beta$ , TNF- $\alpha$  and IL-6). Inflammatory mediators induce insulin resistance locally in fat and liver, and systemically in skeletal muscle. Salicylates lower glucose in patients with diabetes [98], while nonacetylated (e.g., sodium salicylate, salsalate, and trilisate) and acetylated forms (aspirin) of salicylate are widely available. Even at low doses, aspirin effectively inhibits cyclooxygenase enzymes, COX-1 and COX-2, through covalent transacetylation of active site serine residues; this irreversibly inactivates the enzymes and prevents catalysis of the committed step in prostaglandin synthesis [99]. Lacking an acetyl group, nonacetylated salicylates do not modify cyclooxygenase enzymes. At significantly higher concentrations than those required for COX inhibition, both nonacetylated salicylates and aspirin inhibit the IKK $\beta$ /NF- $\kappa$ B axis [100], a pharmacologically distinct drug target. While a 2-week course of high-dose (approximately 7 g/d) aspirin reduces glucose and lipid levels and improves insulin sensitivity in patients with diabetes [101], prolonged exposure to such high doses of aspirin would have unacceptable side effects, especially potentially serious gastrointestinal bleeding. Salsalate, a prodrug form of salicylate, improves *in vivo* glucose and lipid homeostasis, and support targeting of inflammation and NF- $\kappa$ B as a therapeutic approach in T2D [97].

PPAR $\gamma$  agonists, thiazolidinediones (TZDs), have been used for the treatment of hyperglycemia in T2D. Troglitazone was the first TZD to be introduced into clinical practice, but was withdrawn due to hepatitis. Currently, pioglitazone can be used as monotherapy or in combination with other glucose-lowering agents. The recent PROspective pioglitazone Clinical Trial in macroVascular Events (PROactive) study provided tentative evidence that

pioglitazone may have a beneficial effect on cardiovascular risk in T2D, an effect independent of its glucose-lowering properties [102]. TZDs decrease insulin levels, suggesting that they act as insulin sensitizers and enhance glucose uptake by insulin-sensitive tissues *via* PPAR $\gamma$  [103]. The activated receptors alter the expression of genes involved in lipid metabolism and promote fatty acid uptake and storage in adipose tissue. Elevated FFA levels are associated with insulin resistance. PPAR $\gamma$  activation by TZDs reduces the amount of circulating FFA in the body *via* adipocyte differentiation and apoptosis. As lipolysis and levels of circulating FFA are reduced by PPAR $\gamma$  activation, adipose tissue mass is increased, so other insulin-sensitive tissues such as liver, skeletal muscle and possibly pancreatic  $\beta$ -cells are spared the harmful metabolic effects of high concentrations of FFA that induce insulin resistance [104]. Glucose metabolism by liver and muscle is therefore improved. The 'lipotoxicity' in pancreatic  $\beta$ -cells from elevated fat content is also reduced which leads to decreased  $\beta$ -cell apoptosis, improved  $\beta$ -cell mass and therefore insulin secretion in T2D subjects [104]. TZDs also reduce macrophage numbers *via* PPAR $\gamma$  in adipose tissue. The expression of proinflammatory genes is inhibited, and production of the cytokines IL-6 and TNF- $\alpha$  is reduced [105]. Expression of insulin receptor substrate-2, a protein with a facilitatory role in the insulin signaling pathway, is increased in adipose tissue cultured with PPAR $\gamma$  agonists with subsequent enhancement of insulin sensitivity [106]. Treatment with PPAR $\gamma$  agonists results in significantly improved glycemia in diabetic mice and is associated with an increase in circulating adiponectin levels [107]. Nanomolar levels of natural (15d-PGJ<sub>2</sub>) or synthetic PPAR $\gamma$  ligands enhanced B cell proliferation and significantly stimulated plasma cell differentiation and antibody production [108].

## CONCLUSIONS

Hyperglycemia induces insulin resistance and increases the risk of morbidity and mortality substantially among critically ill patients. Arachidonate metabolites are increased, and proinflammatory cytokines are produced under the condition of high glucose. Hyperglycemia is potentially harmful because it acts as a procoagulant [109], induces apoptosis [110], impairs neutrophil function, increases the risk of infection and is associated with an increased risk of death. Sepsis is the leading cause of death in critically ill patients. Hyperglycemia and insulin resistance are virtually universal in sepsis. Initially, sepsis is characterized by increases in inflammatory mediators; but as sepsis persists, there is a shift toward an anti-inflammatory immunosuppressive state [111,112]. If hyperglycemia is observed, all patients are recommended to receive glucose testing on admission to the hospital and glucose-lowering therapy. While conventional glucose-lowering interventions that aim to maintain blood glucose levels between 140–180 mg/dL are recommended for critically ill patients [113], intensive glucose-lowering protocols having target glucose levels set at <110 mg/dL remain controversial [114]. Thus, insulin is recommended in the treatment of acute hyperglycemia in critically ill patients. Since hyperglycemia induces insulin resistance, we shed light on therapeutic

potentials of PPAR $\gamma$  ligands for critically ill patients under the insulin resistant state. Further investigation of aggressive glucose-lowering therapy in specific patient populations is required.

## CONFLICT OF INTEREST

Declared none.

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