REVIEW ARTICLE

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A link between PKR, inflammasome and synaptic plasticity:Is it an emerging therapeutic option for cognitive dysfunction?

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Abstract

A cognitive decline biomarker candidate, RNA-dependent protein kinase R (PKR), is proposed to play a crucial role on inflammation, and psychiatric disorders through prolonged metabolic stress, cellular and molecular imbalance by regulating central cellular processes including mRNA translation, transcriptional control, apoptosis, and cell proliferation. PKR is an interferon-induced serine/threonine protein kinase and a well-known master regulator of protein synthesis via phosphorylating the translation initiation factor α (eIF2α). Inflammasome assembly consists of large multiprotein complexes that are activated by the pathogen or damage-associated signals resulting in the formation of pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-18, and high-mobility group box 1 (HMGB1) protein. Release of pro-inflammatory cytokines and chemokines triggered by the host's innate immune response against harmful pathogens coordinated by inflammasomes. PKR and inflammasomes have share similar function including innate immunity and defense against viruses. The upstream molecular mechanisms underlying the regulation of inflammasome activation poorly identified. Here, we focused on the role of PKR on the regulation of inflammasome assembly formation by summarizing current investigations that are linked to inflammation/neuroinflammation-driven synaptic plasticity. Virus, inflammatory, and toxic cellular signals activate this protein kinase and then it initiates translation blockade via its downstream target. PKR activation also contributes to inflammation and immune dysfunction through the regulation of inflammatory cell signaling pathways. Cytokines regulated by inflammasomes are critical mediators of psychiatric diseases and neurodegenerative disorders. Previous works have suggested that systemic inflammation could contribute to neuroinflammation and related neurodegeneration via activation of inflammasome assembly. Previous researches found that PKR physically interacted with different inflammasomes. Recent investigations highlighted a key role for PKR in the regulation of inflammasome-mediated diseases and cognitive function. PKR might be a valid target to modulate neuroinflammation and neurodegeneration by modulating inflammasomes. Hence, it is conceivable to hypothesize that PKR could be a pharmacologically alluring objective for treating neuroinflammatory diseases by modulating inflammasome activation in parallel with learning and memory deficits. In the future, the assessment of this kinase levels in blood of patients would enable us to find novel biomarkers to struggle neuroinflammatory process in neurodegenerative and psychiatric diseases.

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INTRODUCTION

Transient systemic inflammation has been shown to cause an alternation in behavior through activation of microglia and level of cytokines detected in the brain and in the body. These changes have been associated with the sudden clinical deterioration upon systemic inflammation. Thus, systemic inflammation and subsequent activation of microglia trigger cytokine storm with reactive oxygen species (ROS) production or even drive neuronal dysfunction associated with dementia. Double-stranded RNA (dsRNA)-dependent protein kinase (PKR) could play a role in these molecular events that resulted in neuronal cell apoptosis and neuronal injury [1,2].

Protein kinases are ubiquitous and have a crucial role in the intracellular signal transduction pathways associated with gene transcription and/or DNA synthesis [3]. To date, serine/threonine or tyrosine kinases are characterized one of the most important protein kinase

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families in humans. The serine/threonine kinases have been identified as a cytoplasmic protein. PKR is a member of serine/threonine kinase family integrating protein translation and transcription in response to stress signals [4–6]. PKR was discovered to be transcripted in response to interferon (IFN)-inducible protein and initially identified to mediate anti-viral defense mechanism. Recently, it was clarified that PKR served as a central player in proliferation, mRNA translation, and transcription besides regulation of apoptosis. It is a serine-threonine kinase expressed constitutively in mammalian cells and dysregulation of this kinase activation has been implicated in neurodegeneration, inflammation, and psychiatric disorders [7–9].

The Structural Characteristic of PKR

PKR is comprised of an N-terminal regulatory dsRNA binding domain (dsRBD) involving two dsRNA binding motifs (dsRBMs) with C-terminal catalytic kinase domain consisting of phosphorylation sites (Figure 1). These motifs (dsRBM1 and dsRBM2) are separated by a flexible amino acid linker and interacted to the kinase domain. A secondary structure for each dsRBM peptides has an identical characteristic consisting of an α-β-β-β-α architecture. The catalytic domain of PKR is formed by N-terminal lobe and C-terminal lobe. Additionally, the kinase domain is located on the surface of the C-terminal lobe whereas the N-lobe is responsible for the dimerization of PKR [10,11].

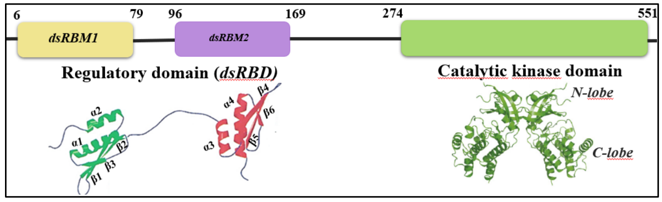

Figure 1. PKR structure consisting of two functionally distinct domains [10,11]. N and C indicates N-terminal and C-terminal lobes of kinase domain. dsRBM, double-stranded RNA (dsRNA) binding motif.

PKR Activity

Autophosphorylation and activation of kinase activity following dimerization require for PKR activity (Figure 2). It was shown that active sites of this kinase are repressed by the second motif. This masking effect is reversible when one of the PKR activating ligands trigger a functional dimerization and subsequent conformational shift and ATP binding. It was thought that a fully active enzyme is coordinated by autophosphorylation and the conformational rearrangement. Thus, PKR enzyme phosphorylates the main protein substrate eukaryotic initiation factor alpha (eIF2α) and phospho-eIF2α inhibits translation initiation [10,12].

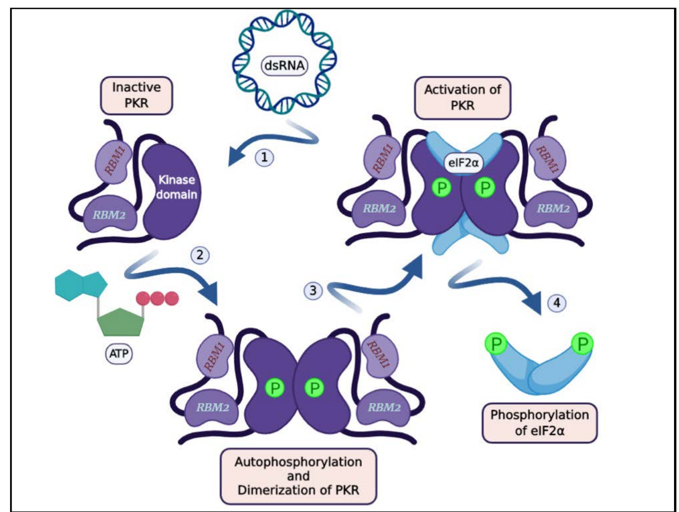

Figure 2. Schematic representation of PKR activity [10,12]. While PKR monomer is an inactive and unphosphorylated form, dsRNA or other activators are capable of stimulating dimerization. Autoinhibitory conformation of this kinase is disrupted by activating ligands leading to dimerization and ATP binding followed by phosphorylation of PKR's protein substrates like eIF2α. P shows phosphorylation. ATP, adenosine triphosphate; RBM, double-stranded RNA (dsRNA) binding motif; eIF2α, eukaryotic initiation factor-2 alpha; PKR, dsRNA-dependent protein kinase.

Upstream Modulators

PKR is activated in response to dsRNA, pro-inflammatory stimuli, growth factor, cytokines, and oxidative stress [7] (Figure 3). RAX and its human homolog PACT is a physiologic activator of PKR. Additionally, heparin is a well-known inducer of PKR autophosphorylation [8].

Downstream Targets

Despite the fact that eIF2α is the most well-characterized downstream target, viral proteins have also been shown to be substrates of PKR (Figure 3). In addition, several signal transduction pathways such as interferon regulatory factor 1 (IRF-1), signal transducer and activator of transcription (STAT), p53, c-Jun N-terminal protein kinase (JNK), and p38, as well as nuclear factor κB (NF-κB) pathway are mediated by PKR activation [6,8,13].

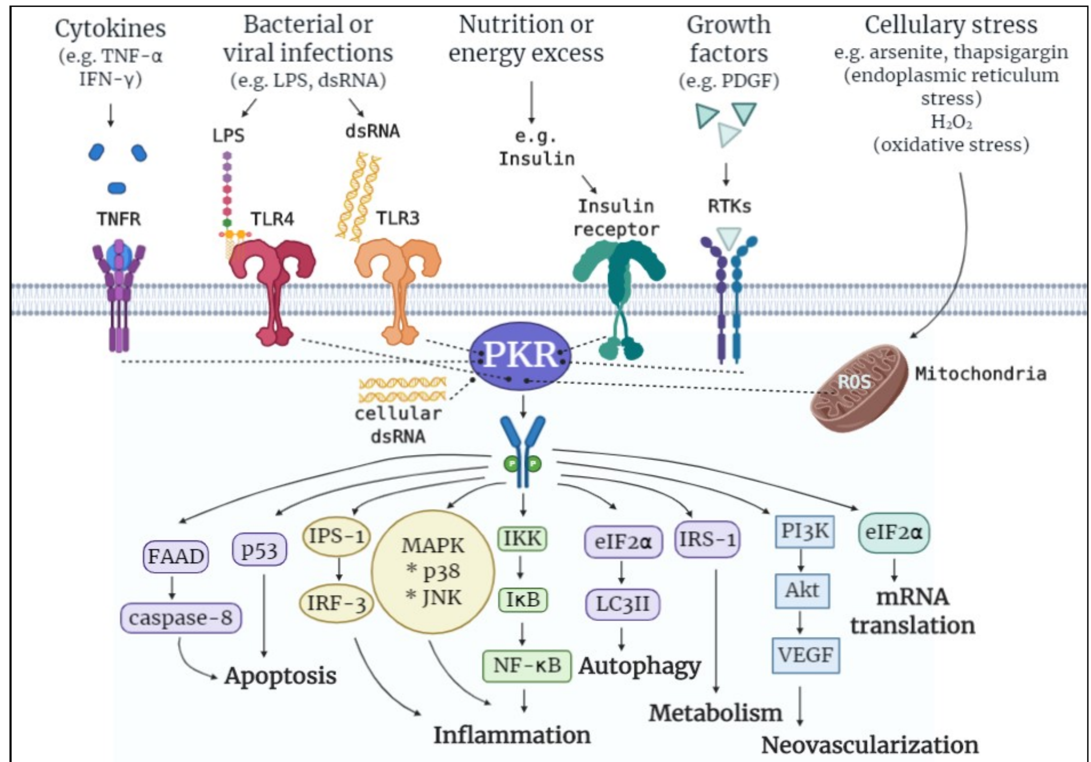

Figure 3. Upstream activators and downstream targets of PKR [15,16]. dsRNA, double-stranded RNA; eIF2α, eukaryotic initiation factor 2α; FADD, Fas-associated protein with death domain; IFN, interferon; IKK, inhibitor of κB (IκB) kinase; IPS-1, interferon-ß-promoter simulator 1; IRF, interferon regulatory factor; IRS, insulin receptor substrate; JNK, jun N-terminal protein kinase; LC3, light chain 3; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κB; PDGF, platelet-derived growth factor; PKR, dsRNA-dependent protein kinase; PI3K, phosphoinositide 3-kinase; RTKs, receptor tyrosine kinases; ROS, reactive oxygen species; STAT, signal transducer and activation of transcription factor; TLR, Toll-like receptor; TNF, tumour necrosis factor; VEGF, vascular endotelial growth factor.

PKR Inhibitors

To better understand the mechanism of PKR activity on the signaling pathways linked to inflammation, novel inhibitors of PKR have been investigated previously [14]. From a pharmacological point of view, an extremely limited number of PKR inhibitors have been described. So far 26 different ATP-binding site inhibitors screened to target the catalytic activity of PKR which are basically the oxindole/imidazole derivatives. Activity of PKR is inhibited by using a cell penetrating peptide which contains the 21-amino acid peptide corresponding to the first dsRBD of PKR [14]. The most widely used pharmacological PKR inhibitor is the highly potent small molecule named as a C16 or imoxim which targets the ATP binding site of PKR. Intraperitoneally administration of C16 can cross the blood brain barrier and has been successfully used in mice and rats to reveal memory enhancement. Monoclonal antibodies and genetic tools such as siRNA or viral vectors can also used to inhibit PKR [9]. Another approach was identifying molecules which can protect macrophages from anthrax lethal toxin-induced cell death through inflammasome activation and therefore led to the identification of a new compound. But in this case the compound (7-desacetoxy-6,7-dehydrogedunin (7DG) did not interfere with the PKR kinase activity [14].

Impact of PKR in inflammatory diseases

As mentioned earlier, tumour necrosis factor (TNF)-α, IL-1, and interferon (IFN)-γ induced PKR activity and subsequent regulation of inflammation-related signaling pathways including JNK, mitogen-activated protein kinases (MAPKs), IRFs, and NF-κB pathway have resulted in the formation of several pro-inflammatory genes [9,15–17]. Carret-Rebillat et al. (2015) demonstrated that systemic LPS-induced neuroinflammation and consequent microglial activation and cytokine production were PKR-dependent [2]. In an encephalitis model induced in mice, knock-out of PKR was shown to prevent increased levels of pro-inflammatory genes in the brain compared to wild-type mice [9]. Interestingly, previous studies suggested that PKR had a detrimental role in Alzheimer's disease related neurotoxicity by activating pro-apoptotic caspase-3 and caspase-8 which could be consistent with increased cytokine release linked with amyloid beta (Aβ) toxicity [18–20]. On the other side, up-regulation of anti-inflammatory genes like IL-10 correlated with the impaired pro-inflammatory response in PKR knock-out (KO) mice compared to wild type (WT) mice [9]. Previously, it was found that inflammatory signals-induced increased levels of pro-inflammatory IL-1β and cleaved caspase 3 besides

reduced levels of anti-inflammatory IL-10 were abolished by pharmacological inhibition of PKR [20,21]. Consistent with these findings, Ma et al. (2018) reported the upregulated expression of PKR by TNF-α stimulation led to an increase in COX-2 and IL-8 in human chondrocytes [22]. It was clearly demonstrated that PKR contributed to myocardial inflammation caused by systolic overload-induced chronic heart failure, thus knockdown of PKR attenuated TNF-α expression and leukocyte infiltration [23]. In another investigation, significant activation of PKR was observed in the lungs of lipopolysaccharide (LPS)-induced acute lung injury (ALI) mice and LPS-challenged macrophages. This study concluded that the protective effects of PKR inhibition on ALI progression were accomplished through the regulation of inflammatory response [24].

The Relationship Between PKR and Inflammasome

The innate immune response is the first line defense system activated by pattern-recognition receptors (PRRs) in response to several pathogens or dead cells. The inflammasomes are described as a multiprotein complex mediating host defenses against invading pathogens through the programmed cell death called “pyroptosis”. A canonical inflammasome assembly is a group of large proteins and typically defined by a sensor known as PRRs, an adaptor named apoptosis-associated speck-like protein containing a caspase-activation and recruitment domain (ASC) with the effector protein pro-caspase-1 [25,26]. In regards to the activation of inflammasomes, PRRs recognize pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) released from microbial components, damaged or dying cells thereby stimulate enhanced inflammation [25]. Recently, Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR)-containing proteins (NLRs), Rig-I-like receptors (RLRs), C-type lectin receptors (CLRs) and absent in melanoma 2 (AIM2)-like receptors (ALRs) have been described as PRRs [27]. So far, five members of PRRs were identified such as NLR family members NLRP1, NLRP2, NLRP3, NLRP6, NLRC4, NLRP9b, and IFI16 as well as absent-in-melanoma 2 (AIM2) and pyrin which were responsible to form inflammasomes in response to a variety of activators, including extracellular ATP, bacterial toxins and metabolites [27,28]. The proteolytic function of inflammasomes primarily rely on protein-protein interactions regulated by a pyrin domain (PYD) and/or a caspase recruitment domain (CARD) [27,29]. The inflammasomes are called NLRP or NLRC receptors according to the PYD or CARD content [29] (Figure 4). These inflammasome-forming receptors have either containing PYD or CARD domain in addition to common NACHT domains and leucine-rich repeats. On the other hand, AIM2-like receptors (AIM2 and IFI16) are composed of an N-terminal PYD and a C-terminal hematopoietic interferon inducible nuclear protein with a 200-amino-acid repeat domain (HIN200). In humans, MEFV gene encoded pyrin that can form inflammasomes in response to enterotoxins [29].

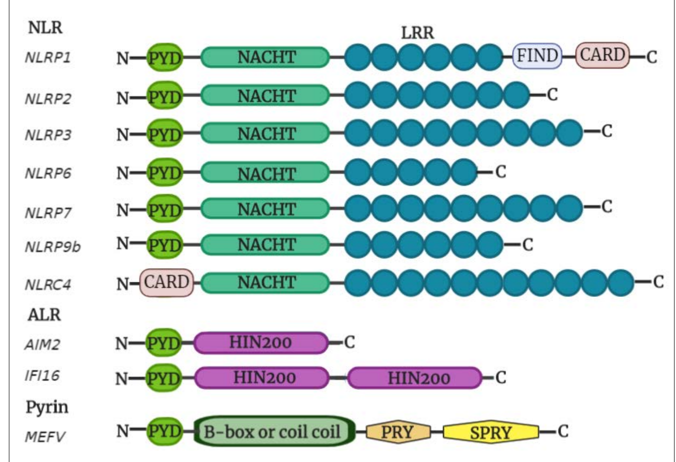

Figure 4. The structure of inflammasomes [27]. ALR, AIM2-like receptor; dsDNA, double-stranded DNA; dsRNA, double – stranded RNA; NLR, the nucleotide – binding oligomerization domain (NOD)-like receptors; LRRs, leucine-rich repeats; PYD, pyrin domain; CARD, caspase recruitment domain; AIM2, absent in melanoma 2; HIN200, haematopoietic interferon-inducible nuclear protein with 200 amino acids.

One of the main roles of the NLR family is to regulate the production of pro-inflammatory cytokines and chemokines triggered by the host’s innate immune response against harmful pathogens or environmental factors [30]. Typically, inflammasome activation occurred by a stimulus which in turn orchestrates caspase-1-dependent cleavage of pro-IL-1β and pro-IL-18 into the biologically active cytokines and the release of high mobility group box 1 (HMGB1) [24,31,32]. Gasdermin D (GSDMD) is also cleaved into active form through the maturation and activation of caspase-1, thereby stimulating inflammatory cell death (pyroptosis) [29]. It is noteworthy that major glial cells namely microglia and astrocyte responsible for innate immunity in the brain are found to express PRRs like TLR4 that can participate in the assembly and activation of the inflammasome by driving the caspase-1-mediated cleavage of IL-1β [33]. NLRP3 inflammasome has also been indicated in case of neuroinflammation-related disease such as Alzheimer’s which is similar to the role of PKR [18-20,33]. PKR has been shown to control inflammasome complex that could lead to increased production of inflammatory signals [2]. It has been observed that PKR physically interacted with different inflammasomes like NLRP1, NLRP3, NLRC4, and AIM2 and then regulated inflammasome assembling by autophosphorylation [17]. Lu and colleagues reported for the first time that a significant decrease in HMGB1 secretion correlated with the inhibition of caspase-1 activation and IL-1β cleavage in peritoneal macrophages derived from PKR-knockout (PKR−/−) mice stimulated with various immune stimulants compared to WT mice [17]. Similar results were obtained with the pharmacological inhibition of PKR in parallel with the severe impairments of inflammasome activation [17]. In LPS-primed cells, both NLRP1 and NLRP3 activators triggered apoptosis was found PKR-dependent [34]. Hett and groups also implied that apoptotic pathway

may not be essential for inflammasome activation due to the lack of ASC speck formation in LPS-primed cells [34]. Consistent with previous findings, another research group clearly demonstrated that PKR inhibitor protected against increased expression of caspase-1, NLRP3, HMGB1 and IL-1β and cell activity after challenged with LPS [24]. Contrary to these results, genetic deletion of PKR did not prevent inflammasome activation in mice fed with high-fat diet [35]. The repressive function of PKR on cryopyrin inflammasome activation is claimed to be mediated by inflammasome components inhibition [31]. It was also implied that no role for PKR in controlling NLRP3, NLRC4 and AIM2 activation in bone marrow macrophages isolated from two different mouse strains deficient in PKR following treated with known activators [36]. These contradictory findings may be due to the deletion of different gene domain PKR or in-vitro studies that may not reflect the in-vivo physiological situation. All these previous findings indicate that PKR activation might participate in inflammasome activation. Apart from this contradiction, it has been suggested that autophagy suppresses inflammasome activation and HMGB1 release [37,38]. Surprisingly, PKR has previously been linked with autophagy regulation via eIF2α [39] but never been identified entirely how PKR is involved in the inflammasome activation regarding the autophagy process.

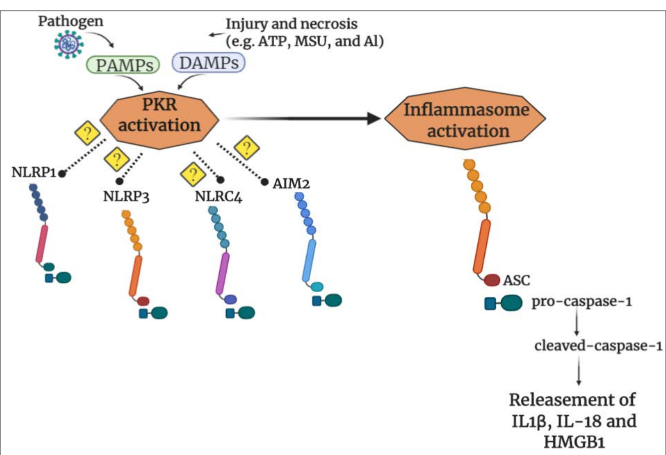

Figure 5. Potential role of PKR in inflammasome signaling [15]. Al, aluminium; AIM2, absent in melanoma 2; ATP, adenosine triphosphate; DAMPs, damage-associated molecular patterns; HMGB1, high-mobility group box-1; IL, interleukin; Msu, monosodium urate; NLRC4, NLR family CARD domain-containing; NLRP, NOD-like receptor (NLR) family pyrin domain-containing; PAMPs, pathogen-associated molecular patterns; PKR, dsRNA-dependent protein kinase.

The Importance of PKR and Inflammasome Assembly in Synaptic Plasticity

Recent studies suggested that inflammasome-dependent inflammatory responses may contribute to the pathophysiology of neuroinflammation in psychiatric as well as neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS) [40–42]. Deficits in brain-derived neurotrophic factor (BDNF) signaling, the most important regulator of synaptic plasticity, has been implicated to play a crucial role in the pathogenesis of a variety of neurological and psychiatric disorders [43]. Thus, BDNF signaling is linked with long-term potentiation (LTP) which refers to a prolonged increase in the magnitude of postsynaptic response to the presynaptic stimulus at a certain strength thought to underlie cognitive dysfunction seen in above-mentioned diseases [3,43]. Latest advances suggested that pro-inflammatory cytokines, especially IL-1β and IL-18, negatively impacted on LTP depending on the synaptic concentration of these immune mediators [44]. Heneka et al. (2013) demonstrated that NLRP3 or caspase-1 deficiency completely reversed LTP suppression and improved spatial memory in AD transgenic mice [45]. It is a well-known that glial cells actively contribute to neurotransmission, neuronal excitability, and several forms of synaptic plasticity by modulating cytokines [46]. Previously, microglial NLRP3 inflammasome activation by Aβ was found to result with the maturation and releasement of IL-1β. A recent study also implied that Aβ-mediated inhibition of synaptic plasticity might relate with inflammasome triggered IL-1 release and they reported prevention of the synaptic plasticity deficit in an animal model of AD by using MCC950, an NLRP3 inflammasome inhibitor [47]. Murphy et al. (2012) pointed out ATP-induced P2X7 inflammasome assembly in parallel with the incapability of aged rats to sustain LTP in LPS-primed microglia were inhibited by a specific P2X7 receptor antagonist, GSK1370319A [48]. It was also reported that improvement of cognitive performance was associated with NLRP3/caspase-1/IL-1β axis activation with a positive correlation of increased expression levels of synapse associated protein and the number of dendritic spines in a widely used AD-like model showing memory deficits [49]. In line with previous data, the authors obtained a better cognitive function by alleviating synaptic dysfunction and neuronal apoptosis and suppressing microglia and astrocyte activation and pro-inflammatory cytokine production via regulation of the NLRP3 inflammasome pathway and related nuclear factor erythroid 2-related factor (NRF2) signaling (a negative regulator of NLRP3 inflammasome expression and activity) following kainic acid-induced seizure [50].

It is noteworthy that protein synthesis is a prerequisite for the consolidation of flexible short-term memory into more stable, long-term memory. Apart from cytokines belonging IL-1 family, overexpressed type I and type II interferons have also a potential inhibitory role in the modulation of synaptic plasticity during a neuroinflammatory process [44]. Since PKR is inducible by type I interferon and called as a master regulator of protein synthesis, this kinase directly implicated in learning and memory [9]. Moreover, protein synthesis is increased through mRNA translation during memory consolidation concerning a decrease in phosphorylation levels of eIF2α. It is plausible that decreasing eIF2α phosphorylation directly or indirectly by its regulatory kinases such as PKR associated with long term memory enhancement. Previous studies already

demonstrated that higher PKR and its downstream effector (eIF2α) phosphorylation, partially colocalized with tau hyperphosphorylation [51-53] and increased PKR levels in cerebrospinal fluid from patients with AD in correlation with mild cognitive impairment [54]. In a mice AD model, treatment with C16 (PKR inhibitor) almost completely rescued fear memory deficits and restored LTP impairment whereas it did not affect $A\beta_{1-42}$ level [55]. Similar to this study, it was also observed cognitive rescue effects of C16 on the novel object recognition task and LTP impairment in $A\beta_{1-42}$-injected mice [56]. Paccalin and colleagues were the first reporting a significant alteration of PKR and eIF2 phosphorylation in lymphocytes of patients with AD and these modifications were correlated with cognitive and memory test scores compared with age-matched control patients [57]. Phosphorylated PKR was also detected in nuclear fractions prepeared from the brains of sporadic AD patients [58]. These results associated with another study suggest that higher PKR levels were also detectable over the course of the AD disease. To determine PKR as a candidate biomarker, changes in the levels of this kinase remain to be explored during the silent and preclinical periods of AD [59]. On the other hand, recent studies identified AD as a form of “type-3 diabetes”. Insulin resistance and disruption of glucose metabolism are the most common pathophysiological features shared by type-2 diabetes mellitus (T2DM) and AD. An increasing body of evidence suggests that metabolic disorders like obesity and T2DM are also known to be major contributors to chronic inflammation favoring AD progression [60,61]. These studies strengthened the notion that metabolic inflammasome (metaflammasome) has an important role in mediating chronic low-grade inflammation associated with the stimulation of PKR [62]. Vlourenco et al. (2013) revealed that activation of pro-inflammatory signaling mediated β-amyloid oligomers-induced brain insulin receptor substrate (IRS-1) inhibition related to PKR-dependent eIF2α phosphorylation [62]. In parallel to these results, high-fat diet-induced significant increased in the levels of activated brain metaflammasome proteins (PKR, JNK, IRS1, and IKKbeta) and weight gain in addition to increased blood insulin level was observed in WT and also in PKR-KO mice [60]. Therefore, PKR is a well-known central component of the metaflammasome and modulation of this kinase could be a novel target for synaptic loss and memory impairment that is a pathogenic mechanism shared between AD and diabetes.

Concluding Remarks

PKR and inflammasome complexes have a critical role in cognitive deficits especially inflammation-driven synaptic function. To the best of our knowledge, there are no previous attempts that have been investigated the PKR and inflammasome interaction in terms of synaptic plasticity in preclinical or clinical studies. Therefore, further studies are necessary to show their relation in learning and memory deficits thought to impaired synaptic plasticity caused by neuroinflammation which is the most important pathophysiologic event in neurodegenerative and also psychiatric diseases worldwide.

In spite of the accumulating evidence regarding upstream mechanisms for inflammasome activation, all the features of the pathway remain poorly understood. The above-mentioned findings strongly indicate that PKR might serve a therapeutic potential for the treatment of inflammasome-mediated diseases. To end contradictory findings, there is a great interest in new studies investigating how the entire deletion of the PKR has interacted with inflammasome activation. Nevertheless, the precise role of PKR-regulated inflammasome activation still needs to be clarified regarding the modulation of the autophagy process in the translational studies. Finally, investigations about the upstream mechanism of inflammasome assembly will drive our understanding of the inflammation pathophysiology linked with psychiatric diseases. Furthermore, examining the specific inhibition of PKR by targeting directly the inflammasome might represent a new area of research that led to the prevention of not only neurodegenerative disorders associated with neuroinflammation but most probably also psychiatric disorders. In terms of future clinical trials, these assumptions could be assessed simultaneously in blood of patients as a possible biomarker for the discovery and design of novel drug targets in clinical applications of neuropsychiatry.

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