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Protein kinase R and the metabolic syndrome

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Abstract. Metabolic syndrome greatly increases the risk for developing metabolic and cardiovascular disorders and has reached epidemic proportions globally. Despite recent advances in medical science, scientific understandings on the root mechanisms of metabolic syndrome are still not fully understood, and such insufficient knowledge contributes to the relative lack of effective treatments for such diseases. Protein Kinase R (PKR) is a serine threonine kinase activated during various stress conditions. Activation of PKR can increase reactive oxygen product generation, cause oxidative stress and inflammation. In this review we discuss the potential role of PKR in metabolic syndrome, pathways activated by it and the interrelationship between pathways activated, modes of propagation if one of the pathways is inhibited or activated. Specific and effective inhibitors of PKR are being developed and can become potential treatment for metabolic syndrome and prevent many diseases.

Keywords: PKR, metabolic syndrome, inflammation, insulin resistance

1. Introduction

Metabolic syndrome is a group of multiple disorders such as high blood pressure, high fasting plasma glucose (hyperglycemia), low HDL cholesterol, high tri-glyceride levels and obesity which ultimately increases the risk of developing cardiovascular disease and Type 2 diabetes. It is an energy utilization disorder and involves the simultaneous presence of 3 of the aforementioned 5 disorders [1]. These conditions invoke stress related response in the body, one of which is Protein Kinase R (PKR). RNA activated/dependent protein kinase (PKR) is a serine threonine kinase that can directly couple to the metabolic pathway due to its catalytic activity and has a role in pathogen recognition [2]. PKR is activated by a number of signals, such as high cholesterol diet [3], pathogens, irradiation, heme limitation [4–10] endoplasmic reticulum (ER) stress and mechanical stress [11]. PKR contains two dsRNA binding domains, one at its N-terminal and the other at its C-terminal [4–5, 12]. It is essential that both the terminals remain active in order to ensure protein Kinase activity. Mutating the lysine-64 end of the domain reduces the binding capacity of RNA domain [13, 14]. In the presence of a pathogen, the double stranded RNA binds to the N-terminal of the PKR enzyme and leads to the phosphorylation of eukaryotic initiation factor

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(eIF2A). It activates eIF2AK2 (eukaryotic translation initiation factor 2-alpha kinase 2) which is coded by the eIF2AK2 gene [2, 15]. This increases phosphorylation of eIF2 and provide the kinase enzyme better access to its substrate [13, 16]. Increase in eIF2α leads to the inhibition of translation thereby impeding further replication of the virus. In normal state, eIF2 combines with methionyl t-RNA and GTP, which is followed by its combination with the 40 S ribosomal subunit. This complex recognizes the start codon during translation. When the larger subunit is additionally combining with this complex, the GTP-eIF2 complex is hydrolyzed to a GDP complex. During an infection, once eIF2 is phosphorylated to its eIF2α form, the conversion of GTP-eIF2 complex to GDP is inhibited. This results in blocking translation due to low GDP levels and thus prevents viral replication in cells [17, 18]. Erythrocyte aggregation has also been reported to be associated with insulin resistance, obesity as well as hypertension. Oxidative stress and chronic inflammation are key features of metabolic syndrome. It has been reported earlier that prooxidants and adipocytokines generated in metabolic syndrome alter erythrocyte morphology, increase whole blood viscosity and decrease erythrocyte deformability. The combination of oxidative stress, inflammation and hematological factors have a detrimental effect in metabolic syndrome due to the disturbance in microcirculation [19, 20, 21].

Since the metabolic syndrome is made up of a group of different pathologies, there is no single treatment available as of now. However, therapies that address several of the risk factors concurrently are being researched and provide hope for the future. The starting event or pathology of the metabolic syndrome is not fully understood. In the following sections, we will discuss the involvement of PKR in pathogenesis of obesity, diabetes, insulin resistance and cardiovascular disorders. Since research on PKR and the metabolic syndrome is still in its nascent stage, it is not possible at this stage to tie the various reports into a cohesive mechanism of how PKR is involved in the pathogenesis of metabolic syndrome.

1.1. PKR and obesity

A number of stress and inflammatory responses are observed in metabolic tissues during obesity. As the disease progresses a number of inflammatory and stress responses are evoked in metabolic tissues

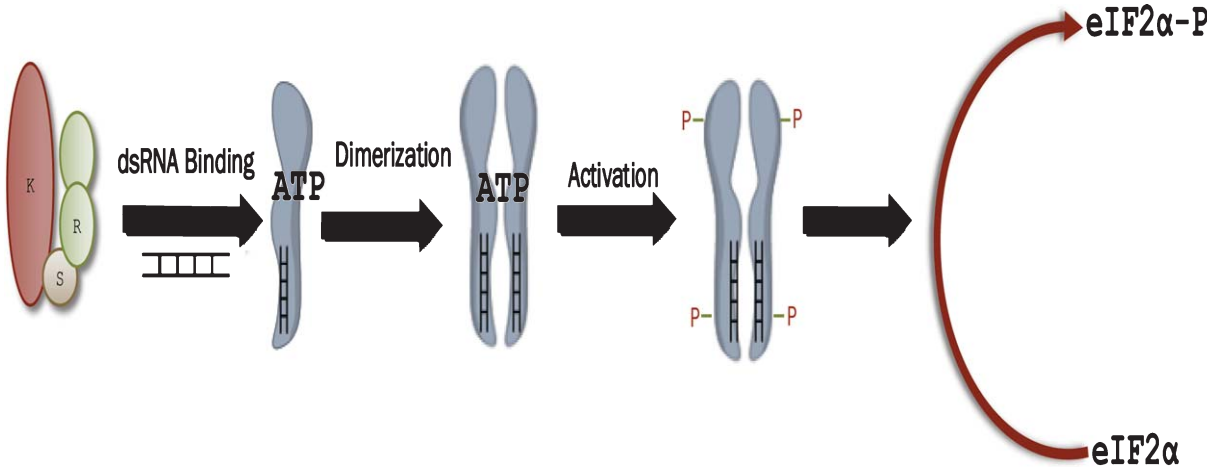

Fig. 1. Mechanism of PKR activation. The dsRNA binding domain (R), the spacer (S), and the protein kinase domain (K) are shown [22].

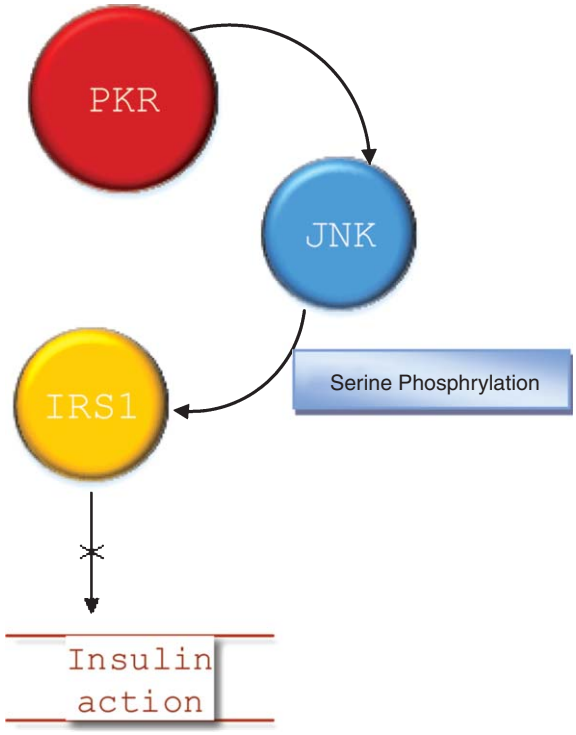

Fig. 2. PKR induced modification of insulin action [22].

leading to chronic inflammation which ultimately leads to the inhibition of insulin receptor signaling and disruption of systemic metabolic homeostasis. Nakamura et al. observed activation of many local low-grade inflammatory and chronic responses which are eventually responsible for the development of insulin resistance in obesity [3]. Both immune and non-immune responses are evoked during this process, referred to as metaflammation [23]. There are only a few receptors that are available which are capable of acting in response to not only metabolic disorders, but also pathogen infections. PKR is one such receptor, which was originally identified as a pathogen sensor but now has also been found to be capable of acting in combination with major inflammatory pathways [2]. PKR is activated by fatty acids, endoplasmic reticulum stress and controls major inflammatory signaling pathways. PKR can act in conjunction with major inflammatory signaling pathways that are involved in metabolic homeostasis, like c-Jun N-teminal kinase (JNK) and IκB kinase (IKK) [24–26]. A marked increase in dietary and genetic obesity is simultaneously accompanied by PKR activation, while its absence helps reduce metabolic deterioration, since excessive nutrients or energy that is available in the body gets utilized. Thus PKR is a critical component of inflammatory complex and it responds to both nutrient and organelle dysfunction [3]. Increased leptin receptor expression, increased PKR activity and increased PKR protein expression was observed in liver and white adipose tissue (WAT) of obese mice as compared to lean control mice [3]. Mice fed high fat diet (HFD) showed higher leptin and PKR activity than lean control mice. However in skeletal muscle of genetic obese (ob/ob) mice, PKR activity showed negligible regulation [3].

PKR is also implicated in regulating molecular integration of nutrient and pathogen sensing pathways in obese mice. Carvalho et al. reported increased PKR activation in liver, muscle, and adipose tissue

of obese humans and after bariatric surgery, reduction in PKR activation accompanied by a decrease in protein kinases like endoplasmic reticulum kinase, c-Jun N-terminal kinase, inhibitor of kappa β kinase, and insulin receptor substrate-1 serine 312 phosphorylation in subcutaneous adipose tissue from these patients [27]. In PKR knockout (N-$Pkr^{-/-)}$ mice, there is an improvement in insulin sensitivity as well as in glucose tolerance and a reduction in fasting blood glucose related to decrease in PP2A phosphatase activity and a parallel increase in insulin-induced Akt phosphorylation, and decrease in glucagon secretion as compared to wild type ($Pkr^{+/+}$) control mice. In diet induced obese mice, the absence of PKR protects the mice from obesity and insulin resistance by preventing the activation of JNK and IKKβ, thus indicating that PKR is an important modulator of insulin signaling under normal physiological conditions and in obesity [28]. Dietary and genetic obesity causes marked activation of PKR in adipose and liver tissues and absence of PKR alleviates metabolic deterioration due to nutrient or energy excess in mice [3]. Nakamura et al. treated PKR knockout ($Pkr^{-/-}$) and wild type mice ($Pkr^{+/+)}$ with *in vivo* lipid infusion and found that upon exposure, only the $Pkr^{+/+}$ mice showed increased PKR activity, due to PKR activation by metabolic stress and excessive nutrients [3]. Mouse Embryonic Fibroblasts (MEF) on exposure to free fatty acids (FFA) demonstrated the similar results (increased PKR activity) [3]. Besides PKR another enzyme, Toll like receptor 4 (TLR4) (29) is known to show activity in the presence of excess nutrients. In order to determine if TLR4 is involved in PKR activation, TLR4 knockout ($TLR4^{-/-}$) mice were exposed to high fat diet, however no significant difference in PKR activity was observed between ($TLR4^{-/-}$) and control ($TLR4+^{/+}$) mice thus indicating TLR4 is not involved in PKR activation [3].

In obese men and women adipose tissue and liver showed an increased activation of c-jun N-terminal kinase (JNK), the inhibitor of k kinase (IKK), and PKR in comparison to lean control non obese group. The inflammasome and the Toll-like receptors (TLRs) of the innate immune system are also activated. Inflammatory signals and excess nutrients may activate the TLRs pathways and ultimately JNK, IKK, and PKR. These kinases will further regulate downstream transcriptional programs through the transcription factors activator protein-1 (AP-1), NF-κB, and interferon regulatory factor (IRF), inducing upregulation of inflammatory mediator gene expression. The increase in cytokines aggravates receptor activation by establishing a positive feedback loop of inflammation and the inhibitory signaling of metabolic pathways [29].

1.2. PKR and diabetes

Metabolic syndrome is associated with elevated blood glucose levels, which in turn will affect plasma insulin levels. It has been reported earlier that in PKR knockout ($Pkr^{-/-}$) mice, fasting plasma glucose is reduced while insulin action and insulin-induced Akt phosphorylation is improved as compared to wild type control ($Pkr^{+/+}$) mice. PKR is known to phosphorylate the regulatory subunit of PP2A, which then activates the catalytic subunit of PP2A inducing its phosphatase activity [25]. Mice islet β-cells and insulinoma cell lines exposed to high glucose and proinflammatory cytokines showed significantly increased PKR activity associated with significantly inhibited cell proliferation by arresting cell cycle at G1 phase. PKR activation abolished the pro-proliferative effects of IGF-I by activating JNK and disrupting IRS1/PI3K/Akt signaling pathway [30].

Inhibition of PKR reduces stress-induced JNK activation and IRS1 serine phosphorylation *in vitro* and *in vivo* [31]. PKR is known to directly target and modify the insulin receptor and thus inhibiting insulin action. It has been reported earlier that PKR induces the inhibitory phosphorylation of IRS at site Ser312 and activates the transcription factor, Foxo1, which in turn up-regulates the protein expression level of

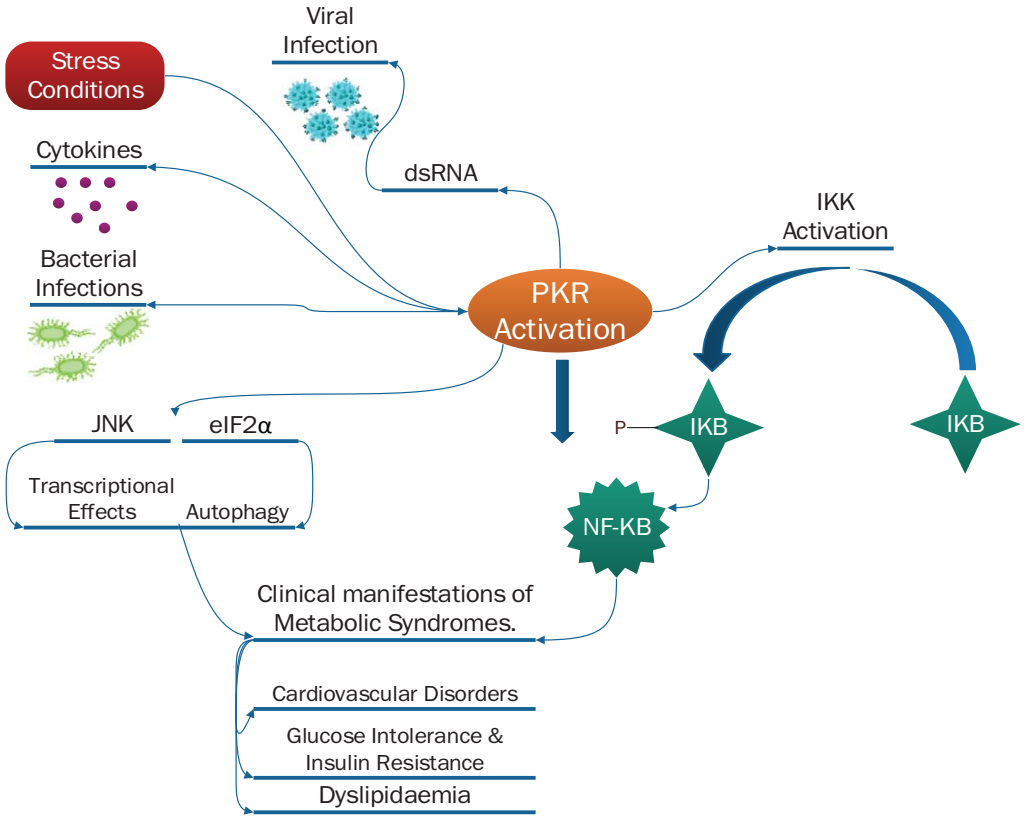

Fig. 3. Different pathways of PKR activation [3].

IRS2 [31]. Knockout of PKR ($Pkr^{-/-}$) in mice showed protection against insulin resistance and diabetes [3]. Thus pharmacologically targeting PKR may be an effective therapeutic strategy for the treatment of type 2 diabetes. Under stress condition, JNK negatively controls insulin signaling through serine phosphorylation of IRS1instead of the normal tyrosine phosphorylation [32]. JNK activation by PKR may also lead to serine phosphorylation of IRS1. Nakamura et al. tested this theory by taking Pkr knockout ($Pkr^{-/-}$) and wild type ($Pkr^{+/+}$) MEFs and exposing them to palmitic acid and thapsigargin. In Wild type ($Pkr^{+/+}$) MEFs phosphorylation of IRS1 was observed whereas in PKR knockout ($Pkr^{-/-}$) MEF's, no IRS1 phosphorylation was observed. This proves that PKR is involved in the eventual phosphorylation of IRS1 [3]. Garcia et al. reported that treating wild type ($Pkr^{+/+}$) and PKR knockout ($Pkr^{-/-}$) MEFs with polyinosinic-polycytidylic (PolyI.C), a direct activator of PKR, IRS1 phosphorylation was only observed in in wild type ($Pkr^{+/+}$) MEFs [33].

Einarson et al. confirmed the interaction between PKR and IRS1 by Pull down assays, when a direct interaction was observed between IRS1 and PKR [34]. Nakamura et al. reported that PKR causes the direct phosphorylation of the serine 307 residue of IRS1, using TNF-α (known to activate PKR) and TG on both wild type ($Pkr^{+/+}$) and PKR knockout ($Pkr^{-/-}$) MEFs and demonstrated the extent of IRS1 phosphorylation using a phospho specific antibody. It was found that the WT MEFs were able to show the excessive phosphorylation, unlike their counterparts [3].

PKR plays an important role in insulin resistance as well. Nakamura et al. exposed wild type ($Pkr^{+/+}$) and PKR knockout ($Pkr^{-/-}$) mice to high fat diet and observe an increase in insulin induced Akt phos-

Table 1
Effect of PKR knockout on different metabolic parameters [3]

Factor	$Pkr^{+/+}$ (HFD)	$Pkr^{-/-}$ (HFD)
Insulin resistance	Present	Absent
Obesity	Present	Absent
Leptin levels	High	Low
Adinopectin levels	No significant change	No significant change
Glucose levels	High	Low
Adipose tissue content	High	Low

phorylation (Serine 473) in liver and adipose tissue of PKR knockout ($Pkr^{-/-}$) mice as compared to wild type ($Pkr^{+/+}$) control mice (3).

1.3. PKR and cardiovascular disorders

Young et al. reported the significance of endoplasmic reticulum (ER) stress as signaling event for angiotensin II-induced hypertension in cells of central nervous system [35]. PKR is a 2α kinase initiation factor and is known to inhibit translation of mRNA under stress condition [19]. It also initiates signalling of apoptosis and inflammation, independent of translational regulation. Congestive heart failure (CHF) is associated with inflammation, cardiomyocyte hypertrophy, and apoptosis [36]. Various factors have been reported to contribute to development of CHF like oxidative stress [36], chronic inflammation, and Toll receptor activation [37]. The chronic inflammations also play role in defence against viral myocarditis [38]. From reported literature, it is evident that PKR is not only an anti-viral factor activated by interferons but also induced or activated in various forms of stress [39–43] and PKR activation due to viral infection may be beneficial in inhibiting viral replication and infections by repression of inflammatory signalling and translation. However, activated PKR induces cellular stress in the heart leading to significant increase in inflammation and apoptosis ultimately leading to chronic pathological conditions such as congestive heart failure (CHF) [33].

Wang et al. and group reported PKR expression in human suffering from CHF. There was significant increase in myocardial expression and translocation of PKR in human patients and mice suffering from CHF [33]. They utilized left ventricular (LV) samples from a human CHF patient, and PKR knockout mice to investigate role of PKR. PKR has significant role in development of CHF by intensifying apoptosis and inflammation of cardiomyocytes by inducing chronic transverse aortic constriction (TAC). On the basis of their research it is evident that PKR inhibition can be utilized as a therapeutic target to treat CHF, as deletion or blocking PKR protects heart from systolic-overload-induced congestive heart failure [33]. B. Tian et al. studied myotonic dystrophy CTG repeat in 3' untranslated region of protein kinase (DMPK). They hypothesized the mechanism for myotonic dystrophy to be due to increased affinity of CUG repeats towards PKR, which was proved by activation of PKR *in vitro*. It was concluded that dsRNA binding is responsible for nuclear retention or toxicity due expanded CUG repeats. This repeats occur much more extended almost 30 times in heart and brain [44]. Early myotonic dystrophy leads to heart block, muscle wasting, and neuropsychiatric impairment [45]. It is evident blocking of this interaction CUG repeats and PKR in heart muscle or skeletal muscle can prevent myotonic dystrophy.

Bleiblo et al. has shown that natural RNA derived from bacteria binds to and activates PKR and this bacterial RNA induces human cardiac myocyte apoptosis in a PKR-dependent manner [46].

1.4. Therapeutic potential of PKR inhibitors in components of the metabolic syndrome

The main limitation we have in this area is that the role of PKR in various aspects of the metabolic syndrome is still in the initial stages of investigation and more and more reports are coming out. Even then, these reports deal with the conditions of hypertension, obesity and diabetes as single entities and describe limited findings on the effects of PKR change in cultured cells and animal models. Apparently, it will take some time before an integrated picture of the role of PKR in the metabolic syndrome starts emerging. As such, the initiating events in the pathogenesis of the metabolic syndrome are also still far from clear.

2. Conclusion and future prospects

The present review indicates that PKR plays a crucial role in the many complications of metabolic disorders. Many important questions still remain to be addressed. Current understanding on the inflammatory mechanisms of metabolic syndrome and related disorders are still in its primitive stage. We anticipate in near future eventually these findings will be translated into novel and effective treatments/preventions against metabolic and related diseases.

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