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# The role of protein kinase R in dystonia

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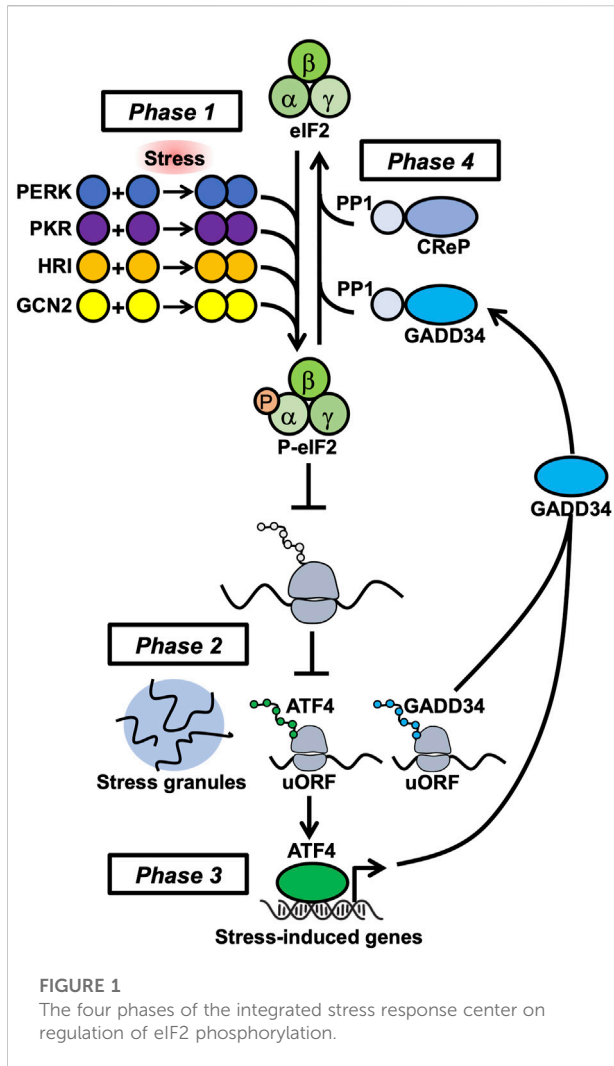
Dystonia is a progressive neurological motor disease with few treatment options and no cure. This review synthesizes the results of recent studies that implicate protein kinase R in mediating the molecular mechanisms of dystonia pathogenesis. Mutations in the PKR gene *EIF2AK2* and the PKR activator protein PACT are associated with early-onset generalized dystonia. Protein kinase R (PKR) is important for neuronal function. Genetic depletion or inhibition of PKR is associated with increased long-term potentiation and memory, while also causing neuronal hyper-excitability and seizures in mouse models. PKR also senses double stranded RNA within cells and activates the integrated stress response (ISR). The ISR is a conserved signaling pathway that hinges on controlled translational suppression to remodel gene expression during stress. When PKR is activated through binding double stranded RNA or the PKR activator protein PACT, PKR dimerizes, autophosphorylates, and phosphorylates the translation initiation factor eIF2. Translation suppression by p-eIF2 causes stress granule formation and the upregulation of stress-induced genes. The ISR is thought to drive cellular resilience during acute stress. However, chronic ISR activation is associated with neurological diseases, traumatic brain injury, and aging. Neurodevelopmental and neurodegenerative diseases are associated with mutations in other integrated stress response genes, suggesting a critical role for ISR regulation in neuronal health. A growing body of work suggests the ISR is also dysfunctional in dystonia. Future research investigating the molecular mechanisms of the ISR in dystonia will likely reveal therapeutic targets and treatment strategies for this currently incurable disease.

## KEYWORDS

protein kinase R, integrated stress response, *EIF2AK2*, dystonia, translation regulation

## Introduction

Dystonia is a progressive neurological movement disorder that results in painful, uncontrolled muscle spasms with loss of motor function. The etiology of dystonia is complex and can be associated with genetic mutations or traumas such as traumatic brain injury. Human genetics data, studies on traumatic brain injury, and motor neurodegenerative conditions implicate the integrated stress response (ISR) as a critical pathway for neuronal dysfunction in dystonia pathogenesis. This article will



focus on the evidence in the literature that suggests that dysregulation of the ISR signaling pathway contributes to the onset and progression of dystonia.

Alleles of the protein kinase R (PKR) gene *EIF2AK2* and the PKR activator protein *PACT* [1] are associated with early-onset generalized dystonia. Missense variants in PKR are likely pathogenic because they were absent in gnomAD suggesting they are not found in the general population, they were observed in six unrelated families on three continents and are *de novo*, dominantly or recessively inherited, and they occur in the functional domain of PKR required for double stranded RNA binding [2, 3]. Early-onset generalized dystonia patients exhibited progressive muscle spasms and postural changes starting in the upper or lower extremities beginning in infancy or childhood [1]. Developmental delay and neurological symptoms including mild cognitive deficits, abnormal brain MRI, spasticity, and seizures were also observed in a subset of patients. Importantly, patients with this early-onset generalized dystonia experience seizures and

neurological regression following a viral illness and/or fever [2, 3], suggesting that defects in the cellular stress response may underlie neuropathogenesis. In support of this idea, early-onset generalized dystonia patient-derived fibroblasts exhibit increased ISR signaling in long-term stress conditions [2]. Traumatic brain injury, a known trigger of dystonia, causes long-term, chronic activation of the ISR [4]. These and other observations implicate dysregulation of the ISR in the pathogenesis of dystonia.

## The role of PKR in the integrated stress response

At the molecular level, PKR plays a critical role in activating the ISR by sensing stresses and globally suppressing protein biosynthesis in the cell. The ISR is a signaling pathway that modifies transcription and translation in response to intracellular signatures of stress. Acute activation of the ISR is thought to promote cell survival, while chronic ISR activation is proposed to drive cell death [5]. The ISR pathway progresses through four phases (Figure 1). First, stress-sensing protein kinases PKR, PERK (PKR-like endoplasmic reticulum kinase), GCN2 (general control non-derepressible 2), or HRI (heme-regulated inhibitor) are activated by molecular signatures that are proxies for underlying stresses including immune factors, proteostasis and endoplasmic reticulum defects, toxic metalloids, and pathogens. Protein kinase R binds double-stranded RNA (dsRNA) [6–9] and can be activated by protein-protein interactions (e.g., with PACT) during other stress conditions (such as endoplasmic reticulum stress) to initiate the ISR. Double-stranded RNA can accumulate within cells during viral infection and upon expression of endogenous genes that form complementary transcripts (e.g., repetitive nuclear sequences and endogenous retroviruses). These kinases dimerize, autophosphorylate, and phosphorylate the major translation initiation factor eIF2 $\alpha$  to inhibit translation initiation. Stress granules form from non-translating mRNAs and the first wave of stress-induced genes (such as ATF4) are selectively translated through upstream open reading frame (uORF) and/or non-canonical initiation mechanisms. Next, newly translated stress-induced transcription factors (e.g., ATF4) stimulate stress-induced gene transcription of uORF-mediated genes such as GADD34. Paradoxically, transcriptional targets of ATF4 include both adaptive genes that restore homeostasis and apoptotic genes that drive cell death [10]. Finally, the stress-induced gene GADD34 interacts with the serine/threonine protein phosphatase 1 PP1 to dephosphorylate p-eIF2 $\alpha$  and de-repress translation. Translation re-initiation corresponds with stress granule disassembly or clearance and amplifies stress-induced gene expression. Thus, PKR plays a critical role in activating the ISR pathway, which mediates cellular resilience to stress through reprogramming translation.

## The role of PKR in neurological function and disease

A growing body of work suggests that PKR plays important roles in neuronal function in the brain [2, 11–13]. Neuronal synapses harbor a unique proteome that drives neuronal excitability and synaptic plasticity to enable learning and memory [14, 15]. PKR is an important regulator of neuronal excitability. Additionally, PKR emerged evolutionarily in vertebrates as nervous systems gained complexity [16]. Deletion of the PKR gene or pharmacological inhibition of PKR enhances late long-term potentiation associated with increased learning and memory behaviors in murine models [12]. However, inhibition or depletion of PKR also results in neuronal network hyper-excitability *in vitro* and *in vivo* and seizures in a mouse model [12]. Forcing PKR dimerization in mouse hippocampal CA1 neurons inhibits late-long-term potentiation and is associated with impaired context-dependent memory [17]. Further, the target of PKR, eIF2 $\alpha$ , plays a role in memory consolidation that may occur through the regulation of local translation [18]. Phosphorylation of eIF2 $\alpha$  regulates late-long term potentiation and long-term memory through a mechanism that likely involves translation of specific mRNAs at the synapse. In line with these results, the small molecule inhibitor of the ISR that targets eIF2 $\alpha$  called ISRIB (integrated stress response inhibitor) similarly increases learning and memory in mice [19, 20]. Neurons have long distal axons and dendrites that can extend up to a meter from the cell body and rely heavily on local translation of RNAs that are trafficked to synapses for their function. Therefore, one possibility is that defects in neuronal function that contribute to dystonia pathogenesis could result in part from aberrant gene expression due to PKR dysfunction.

In addition to its role in neuronal function, activated PKR is observed in numerous neurodegenerative disease contexts. Brain tissue from patients with Creutzfeldt-Jakob's, Parkinson's, Huntington's, Amyotrophic lateral sclerosis, and Alzheimer's diseases exhibit markers of increased PKR activation [21–24]. Individuals with Down Syndrome have a dramatically increased risk of developing Alzheimer's disease, and tissues from individuals with Down Syndrome have increased PKR activation [13]. Importantly, chemical or genetic suppression of PKR activity or the ISR rescued memory and synaptic plasticity phenotypes in a mouse model of Down Syndrome [13]. In addition to early-onset generalized dystonia, heterozygous missense mutations in the PKR gene are also associated with LEUDEN Syndrome, which is characterized by leukoencephalopathy, developmental delay, and neurologic decompensation [11]. Similarly to *EIF2AK2* early-onset generalized dystonia, neurological regression was also observed in LEUDEN Syndrome patients following physiological stressors including viral infections and febrile illness that could cause PKR activation [11]. Beyond PKR

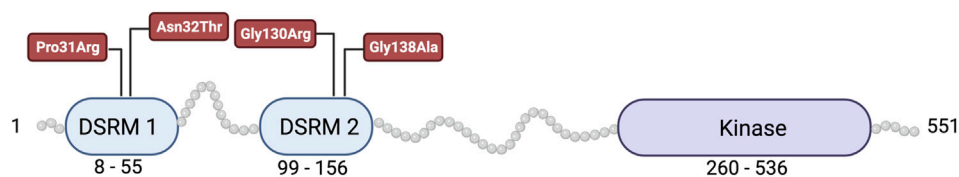
signaling, chronic and/or severe ISR activation is associated with neurodegeneration [18], and mutations in ISR genes are associated with rare genetic developmental disorders [25]. Together, these studies suggest that precise regulation of PKR is important for neurological health.

## Protein kinase R in dystonia

Protein kinase R dysfunction may cause early-onset dystonia pathogenesis. Human genetics data suggest four *EIF2AK2* variants, Pro31Arg, Asn32Thr, Gly130Arg, and Gly138Ala are causative of early-onset generalized dystonia (Figure 2) [2, 3]. These *EIF2AK2* variants were heterozygous or homozygous. Pedigree analysis of affected patients demonstrated *de novo*, dominant, or recessive inheritance of *EIF2AK2* mutations associated with early-onset generalized dystonia. The Gly130Arg (c.388G>A) mutation was observed in nine patients from three unrelated families and was heterozygous or occurred *de novo*. The Gly138Ala (c. 413G>C) mutation was also heterozygous in a fourth affected family, suggesting these mutations are autosomal dominant. The Asn32Thr (c.95A>C) mutation was observed in a fifth affected family but was homozygous in the affected patient. The Pro31Arg (c.92C>G) mutation was observed in one heterozygous patient [3]. All four missense variants occur in the double-stranded RNA binding motifs of the PKR protein, which is critical for PKR function. Further, mutations in the PKR activator protein PACT have also been associated with a heritable dystonia [26–29].

Intriguingly, patients with *EIF2AK2* early-onset generalized dystonia experience seizures and neurologic regression following viral and/or febrile illness that could drive the onset or progression of dystonia [2, 3]. Because PKR is a stress-sensing kinase that initiates the ISR, these results suggest physiological stresses in the context of PKR dysfunction might trigger dystonia. Beyond PKR in dystonia, mutations in the other stress-sensing kinases of the ISR pathway, GCN2, HRI, and PERK, are associated with neurological diseases (reviewed in [25]). Additionally, mutations in other ISR pathway genes including *EIF2B* genes are associated with progressive white matter loss that occurs with physiological stresses including febrile illness [18]. Rare mutations in *ATF4*, a key transcription factor induced by the integrated stress response pathway, are associated with sporadic cervical dystonia [30]. Together, the results of these studies suggest that dysregulation of PKR contributes to dystonia pathogenesis through altered ISR pathway activation.

Limited data in the literature suggest that *EIF2AK2* mutations associated with early-onset generalized dystonia can hyperactivate PKR and upregulate the ISR [2]. Phosphorylation of PKR was four- to six-fold upregulated upon poly(I:C) stress (a double-stranded RNA mimic) in fibroblasts from early-onset generalized dystonia patients with either Asn32Thr or Gly130Arg mutations compared to unaffected controls. In line



**FIGURE 2**

Protein kinase R contains two double-stranded RNA binding motifs (DSRM) and a kinase domain. The four mutations in PKR associated with early-onset generalized dystonia are indicated in red.

with this observation, these patient-derived fibroblasts exhibited an approximately three-fold increase in p-eIF2 $\alpha$  compared to unaffected controls upon poly(I:C) stress [2]. The implications of this study are that dystonia patient cells are hyper-sensitive to stress, which could lead to a persistent or irreversible ISR.

In addition to human genetics findings, several lines of evidence suggest that perturbation of the ISR pathway plays a key role in dystonia pathogenesis. Dysregulation of the stress response has been observed in models of other heritable dystonias including those caused by *PACT*, *TOR1A*, *THAP1*, and *SGCE* mutations [27, 30–32]. The results of *in vitro* assays using purified PKR suggest dystonia-associated *PACT* mutations cause PKR hyperphosphorylation [27]. Further, analysis of lymphoblasts from one *DYT16* patient suggests persistent eIF2 $\alpha$  phosphorylation after endoplasmic reticulum stress could contribute to dystonia pathogenesis [27]. Intriguingly, a genome-wide siRNA screen to rescue subcellular localization defects of a mutant *TOR1A* associated with *DYT1* in tissue culture cells revealed eIF2 $\alpha$  signaling was the top enriched pathway among hits [30]. Depletion of PKR or other eIF2 $\alpha$  kinases worsened the mutant *TOR1A* localization defect, while blocking p-eIF2 $\alpha$  dephosphorylation pharmacologically with Salubrinal rescued *TOR1A* subcellular localization [30]. Strikingly, Salubrinal treatment improved neonatal survival of a mouse model of *DYT1* and rescued long-term synaptic depression in corticostriatal neurons in brain slices [30]. The eIF2 $\alpha$  signaling pathway was significantly dysregulated in brain tissues of *Thap1* $\pm$  mice in a model of *DYT6* and a derivative of Salubrinal rescued long-term synaptic depression in brain slices [31]. Additionally, the PKR gene *Eif2ak2* and the stress-induced gene *Fos* were significantly upregulated in cerebellar tissue from a mouse model of *SGCE* myoclonus dystonia [32]. Together, these data suggest that dysregulation of the ISR could contribute to progressive neurological disorders including dystonia.

## Discussion

An emerging area of research suggests a critical role for protein kinase R and the integrated stress response in dystonia

pathogenesis. Human genetics data suggest mutations in the genes encoding PKR or the PKR activator protein PACT associated with early-onset generalized dystonia increase PKR function by hyperactivation of the ISR. Two molecular mechanisms could underlie this observation. First, PKR mutations could increase PKR activity, sensitizing the cell to stress and hyper-activating the ISR. Such a mechanism could occur if the mutations increase the binding affinity of PKR to RNA, increase the affinity of PKR homodimerization, increase PKR kinase activity, or reduce the inactivation or degradation of the activated PKR dimer. Such a mechanism is likely considering the observations that PKR and eIF2 $\alpha$  are hyper-phosphorylated in poly(I:C)-stressed cells derived from early-onset dystonia patients. Yet, a second possibility is that mutations in PKR associated with dystonia decrease PKR function and cause an irreversible ISR. Such a mechanism may be less likely to occur because early-onset dystonia patient fibroblasts exhibited increased phospho-PKR levels upon poly(I:C) stress [2]. Because PKR plays additional roles in neuronal excitability, an important area of future research will be in elucidating the mechanisms by which neuronal function are impaired by PKR hyperactivation. These possible mechanisms must be interrogated experimentally to understand the mechanisms of generalized dystonia, elucidate diverse neurological phenotypes associated with PKR dysfunction, and pinpoint therapeutic intervention strategies for rational drug design. Not only will such research shed light on the molecular mechanisms of dystonia, but this area of work holds promise for revealing common aspects of neurodegenerative and neurodevelopmental disorders.

## Author contributions

BD and SM wrote and edited the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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