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PYRUVATE KINASE MODULATION IN THE BRAIN UNDER STRESS FACTORS: STRUCTURAL, DEVELOPMENTAL AND MOLECULAR PERSPECTIVES

Leyla Huseynova

Department of Physiology, Azerbaijan State Pedagogical University, Baku, Azerbaijan

Abstract. Distinct environmental stressors such as hypoxia, ischemia and non-ionizing electromagnetic fields (EMF) can substantially alter the metabolism of neural cells. In this context, pyruvate kinase (PK) signaling pathway which serves as a key enzymatic modulator of glycolysis and other metabolic cascades is highly sensitive to these stress factors. According to in vivo studies, while the cortex and hippocampus reveal a noticeable drop in PK activity, the brainstem regions display a relative resilience or compensatory adaptation in response to stressors. The vulnerability also is affected by developmental stages, as the brain of neonates show a persistent suppression of PK activity in contrast to adult brains that reveal compensatory mechanisms. Mechanistically, hypoxia/ischemia and EMF can induce oxidative stress, stabilize HIF-1α and stimulate a shift in PK isoenzyme expression. As a result, neural cells might survive or undergo processes such as apoptosis or pyroptosis. The current review attempts to shed light on regulation of PK pathway under environmental stress, underlying the structural heterogeneity, developmental sensitivity and molecular adaptations. This information underscores the role of PK as a biomarker of neural damages, while it might also be a potential target of intervention in the future.

Keywords: *Pyruvate kinase, neural metabolism, environmental stressors, glycolysis modulation, brain development.*

Corresponding Author: *Leyla Huseynova, Department of Physiology, Azerbaijan State Pedagogical University, Baku, Azerbaijan, e-mail: leyla.huseynova@adpu.edu.az*

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1. Introduction

The brain, as the body's most energy-intensive organ, depends on glucose metabolism to preserves its activity (Biro, 2022; Ghasemi *et al*., 2025). Glycolysis is a key metabolic pathway which provides ATP and other intermediate metabolite required for neural cell survival, plasticity and neurotransmitter release (Barros *et al*., 2021; Goyal *et al*., 2023). Accordingly, pyruvate kinase (PK) is the central glycolytic enzyme that catalyzes the production ATP and phosphoenolpyruvate (Lu *et al*., 2021). Thus, the regulation of PK activity is pivotal in neural energy homeostasis and its impediment could be associated to different pathologic conditions. There are four isoforms of PK (PKM1, PKM2, PKR and PKL) (Han *et al*., 2021). The selective splicing of PKM pre-mRNA results in the production of PKM1 and PKM2 (Luo & Semenza, 2012). While PKM1 is mostly expressed in neuron, PKM2 is highly detected in astrocytes (Wei *et al*., 2020). Meanwhile, recent studies have focused on the role of PKM2 which not only regulates metabolism but also interferes with cell signaling pathways in relation with proliferation, apoptosis and survival (Christofk *et al*., 2008). In particular, the interaction of PKM2 with hypoxia-induced factor 1 α (HIF-1 α) mediated the transactivation of HIF-1 α target genes

such as lactate dehydrogenase A in an upward trend (Luo *et al*., 2011). This indicates more lactate production in astrocytes in relation to PKM1 (Lee *et al*., 2022).This is important, since lactate is the potential substitute of glucose under pathophysiological conditions (Gladden, 2004; Schurr, 2006). Numerous studies have demonstrated that lactate can protects neural cells in different pathologies via preserving the metabolic capability of neurons (Ros *et al*., 2001; Holloway *et al*., 2007; Annoni *et al*., 2021).

Hypoxia as one of the most frequent environmental stressors can substantially influence brain metabolism (Feng *et al*., 2024; Hou *et al*., 2024). Both acute and chronic hypoxic insults can profoundly alter metabolism via affecting different signaling pathways, PK enzyme being one of them. In addition to hypoxia, non-ionizing electromagnetic fields (EMF) have also raised concerns by affecting brain metabolism and functionality (Lai & Levitt, 2024). The current review aims to clarify the potential role of PK and its isoforms in neurons exposed to environmental stressors underlying the structural heterogeneity, developmental sensitivity and molecular adaptations.

2. Pyruvate Kinase in the Brain: Structure and Role

The phosphorylation of ADP and further production of ATP and pyruvate is catalyzed by the function of pyruvate kinase (PK) enzyme (Al-Samkari *et al*., 2022). This reaction is the final step of glycolysis and can restrict its rate. Therefore, PK acts as a key regulator of cellular energy metabolism. The high ATP demand of neural cells which is critical for the release of neurotransmitters, firing of action potential and ion homeostasis turns PK into a pivotal molecular modulator in the brain (Yao *et al*., 2023).

There are different isofroms of PK enzyme, which are encoded by distinct genes and/or generated by alternate splicing. PKL, PKR, PKM1 and PKM2 are four main isoforms found in mammals of which two latter are most relevant to the central nervous system (Foster *et al*., 2022). While PM1 is constitutively expressed in catabolic tissue with high ATP demand, supporting continuous energy production, PM2 displays distinguishing regulatory specification under stress conditions. This occurs via the conversion of glycolytic intermediates into the biosynthetic processes in order to exert a protective effect (Patel *et al*., 2021; Rajala & Rajala, 2024).

The region of expression of PK isoforms in the brain determines their functional properties. PKM1 is highly detected in neural cells of the cortex and hippocampus, where ATP consumption for their synaptic activity is critical. On the contrary, PKM2 is a more dynamic enzyme and overexpressed under stress conditions such as hypoxia, ischemia and oxidative stress. The results of in vivo studies have revealed that PK activity substantially varies across different brain regions, highlighting the essential role of structural specificity of this enzyme in metabolic processes (Cui *et al*., 2024).

Apart from the metabolic role of PK, non-glycolytic functions of this enzyme are more documented particularly important for neural plasticity and survival. It has been shown that PKM2 can translocate into the nucleus and modulate gene expressions involved in angiogenesis and survival by interacting the function of transcription factors. Also, nuclear PKM2 can affect the structure of chromatin and further gene expression by phosphorylating histone protein. These unique activities propose that PK isoforms mediate an integrative link between the metabolic status and transcriptional function of neurons. Animal studies have also documented the key role of PK in the fate of neural cells. Sha et al. (2024) have addressed that there is direct connection between PKM2 and

pyroptic cell death in hipocapmus during a hypoxic-ischemic brain injury demonstrating the role of metabolic enzymes in inflammation-related cell death cascades.

Glycolytic metabolism has also been in relation with cellular processes of learning and memory. Ion pump and cycling of the synaptic vesicles which are vital for neural activities require rapid mobilization of ATP. In this context, PK directly regulates ATP availability in the presynaptic terminals by governing glycolytic flux. It has been shown that PK prohibition disturbs long-term potentiation in hippocampal slices, while elevated activation of PK maintains synaptic efficiency and resilience in metabolic stress conditions (Jha *et al*., 2016). These findings illuminate the robust association between PK activity and the cognitive processes.

3. Hypoxia/ischemia and PK activity

Hypoxia is among the most extensively investigated environmental stress factors that can significantly alter brain metabolism. The effect of hypoxia on glycolytic enzymes including PK has frequently been addressed in experimental studies. In vivo studies in neonatal, perinatal and adult rodents reveal that PK function is sensitive to oxygen deprivation with activity being either upsurged or plummeted based on the intensity and duration of the hypoxic stress. Early findings in 1984 showed that intermittent normobaric hypoxia induces a noticeable change in the glycolytic enzyme activity of rat brain, particularly PK in comparison with the normal control (Dagani *et al*., 1984). The heterogeneous vulnerability of the enzyme activity proposed differential regional susceptibility. Likewise, other studies have demonstrated that prenatal hypoxia results in persistent alteration of PK enzymes in the developing brain (Al-Hasan *et al*., 2014). Neonatal hypoxia has grabbed attention since immature brain is principally sensitive to oxygen deficit. A rapid decline of cortex and hippocampal PK activity has been shown in hypoxia-exposed neonates (Anderson, 2004). This subsequently led to a noticeable metabolic failure in pryoptosis in immature neurons. Also, long-lasting effects of hypoxia which results in persistent metabolic reprogramming has been addressed in postnatal life On the other hand, adult animals often show compensatory responses. It has been revealed that intermittent hypoxia exposure increases PK activity in the medulla oblongata, suggesting a metabolic adaptation process in control centers of the respiratory system. Controversial results have been obtained in other brain regions after hypoxia insult underscoring the flexibility of adult brain in mediating PK function in a region-specific manner (Adeva-Andany *et al*., 2014).

In addition to differences in the developmental stages, hypoxia severity and exposure length influence PK activity. An acute severe hypoxia prohibits PK function, while and adaptive upregulation might be observed after exposure a chronic hypoxia. Enhanced PK activity and a subsequent glycolytic flux has been observed in rats exposed to chronic hypoxia. On the contrarary, acute ischemia-hypoxia has resulted in a downward trend of PK expression, leading to energy collapse and vulnerebility of nueral cells (Jha *et al*., 2016).

The interchange of PK isoforms also play a pivotal role in animal responses to hypoxia. While neural cells principally express PKM1, hypoxia significantly increases PKM2 expression. It has been documented that hypoxic insult augments the expression of PKM2 in the hippocampal region, while PKM1 isoform is downregulated, suggesting a switch towards a more flexible type that can deal with less ATP-efficient glycolysis (Israelsen & Vander Heiden, 2015). This isoform shift has been considered as an adaptive

mechanism to support cellular survival but not energy producing pathways (Lunt *et al*., 2015).

In vivo studies further have addressed the connection between PK activity and functional consequence. Diminished PK activity in hypoxia-exposed neonates has been correlated with disturbed synaptic plasticity and learning shortfalls in later life. It has been shown that early-life hypoxia exposure results in long-lasting disturbances in hippocampal long-term potentiation in consistence with persistent decrement of PK activity. Notably, simultaneous exposure to environmental insults triggers PK alterations. Prenatal hypoxia exposure in combination with postnatal stress factors such as environmental toxin and malnutrition induces a higher extend of PK downregulation proposing a synergistic susceptibility of brain metabolism (Jha *et al*., 2016).

Hypoxia-related responses of PK in the brain is tightly connected with a network of molecular mechanisms in relation to energy metabolism, oxidative equilibrium and cell fate pathways. Hypoxia-inducible factor-1 alpha (HIF-1α) serves as key transcription factor that mediates cellular adaptation to oxygen fall. In a normoxic environment, HIF-1α is rapidly degraded, while hypoxic condition can stabilize the protein and further nuclear translocation leads to the expression of genes responsible for glycolysis, angiogenesis and survival (Zhang *et al*., 2025). PKM2 is an important target of HIF-1α under hypoxia which shifts cellular metabolism into anaerobic glycolysis pathway (Zhang *et al*., 2024). HIF-1α affects PK in a both developmentally and regionally specific manner. Hypoxia induces a more HIF-1α accumulation in the cortex and hippocampus of neonatal and perinatal brains which is in association with a significant plunge of PKM1 activity. This can provide a metabolic flexibility for neural cells under low oxygen circumstances; however, persistent hypoxia can terminate in energy deficits. In the brainstem of adults rats, the stabilization of HIF-1α has been associated with increased activity of total PK, indicating the ATP demand of neural cells in vital autonomic tasks (Zhang *et al*., 2025). It has been shown that cerebral ischemia can augment HIF-1α expression (Gao *et al*., 2022). In addition, the hypoxic condition can prohibit the propyl hydroxylation of HIF-1α resulting in the degradation of the proteasome and stabilization HIF-1α activity (Selak *et al*., 2005). The dimerization of HIF-1α with HIF-1β induces the transcription of PKM gene by recruiting the hypoxia response element site of the PKM (Liu *et al*., 2021). The resultant HIF-1α-PKM2 complex can upsurge the nuclear translocation of PKM2 in its dimer type (Gao *et al*., 2022). Subsequently, the direct interaction of PKM2 with HIF-1α subunit potentiates the transactivation of HIF-1 target genes (Liu *et al*., 2021). Additionally, HIF-1α-associated PKM gene transcription could be activated by the activity of the phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin(mTOR) signaling pathway (Sun *et al*., 2011; Iqbal *et al*., 2013). Moreover, the AMP-activated protein kinase (AMPK)/mTOR signaling pathway can upregulate HIF-1α leading to the elevated levels of PKM2 protein (Wang *et al*., 2018). Although this signaling cascade connects PKM2 to hypoxic-ischemic conditions, the inhibitory function of phosphatase and tensin homolog (PTEN) towards mTOR pathway can in turn reduce PKM2 expression (Liu & Zhou, 2023). In another pathway, the epidermal growth factor receptor can modulate nuclear factor kappa enhancer binding protein (NF-κB)-dependent expression of PKM2 (Yang *et al*., 2012). This occurs via the binding of activated NF-κB to promotor of PKM gene and further activation of the transcription process. Also, activated NF-κB can affect the upregulation of PKM2 by stimulation of HIF-1α expression in an upward trend (Jia *et al*., 2022).

It has been demonstrated that hypoxia/ischemia-related neural apoptosis could be also mediated by PK. Studies have shown that PKM2 silencing can increase the expression of Bcl-2 and downregulate Bax and thus reduce Bax: Bcl-2 ration in hyperglycemia and 6-hydroxydopamine-treated PC-12 cells (Zhao *et al*., 2023). Numerous investigations have addressed the modulatory role of PKM2 on the inactivation of phosphorylated PI3K/AKT that contributes to the apoptotic machinery in different brain damages such as hypoxic-ischemic encephalopathy, traumatic brain injury and anesthesia-associated apoptosis of hippocampal neurons (Wu *et al*., 2019; Fang *et al*., 2023). On the contrary, PKM2 silencing can improve apoptosis in these problems. This phenomenon is different from how PKM2 promotes the proliferation of tumor cells though the PI3K/AKT signaling pathway (Wang *et al*., 2017; Zhang *et al*., 2024). Figure 1 represents the schematic role of PK in neural cells-exposed to hypoxia/ischemia.

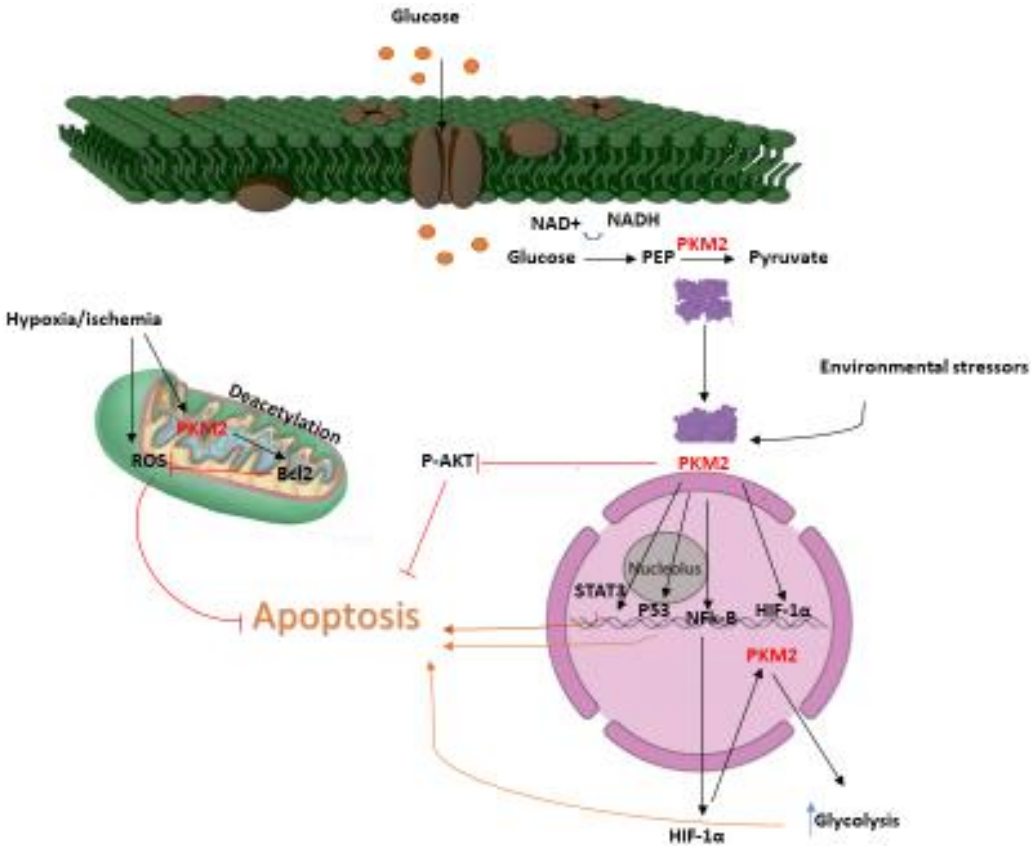

Figure 1. The role of PK in neural cells-exposed to hypoxia/ischemia.

Under physiological circumstances, cytoplasmic PKM2 is in its tetramer form. Upon the exposure to different stimuli, PKM2 dissociates into dimers and translocates to the nucleus. HIF-1α directly increases the expression of PKM2. In the nucleus, PKM2 - HIF-1α, triggers promote IL-1β release. Moreover, PKM2 phosphorylates STAT3 to enhance the extent of the inflammatory response and further apoptosis. PKM2 also is contributes to apoptosis modulation. As a result of hypoxia ischemia mitochondrial PKM2 is deacetylated and inhibits Bcl2 degradation, which then blocks oxidative stress-induced apoptosis. PKM2 induces p-AKT the inactivation of p-AKT in nerve cells, which then influences apoptosis. Additionally, Nuclear PKM2 can activate HIF-1α, STAT3 or block P53, which then regulates the transcription of inflammatory and apoptotic genes.

Ischemia has been attributed to oxidative hazards and disturbances in microtubules of the hippocampus (Kang *et al*., 2020, 2022). Peroxidation of membrane lipids produce 4-hydroxynoneal, a highly reactive α,β-unsaturated aldehyde in neurodegenerative diseases (Pillon *et al*., 2012; Mihalas *et al*., 2017). The activation of NADPH oxidase increase ROS formation in degenerating neurons post ischemia and 4-hydroxynoneal could be detected as a biomarker of oxidative damage. The deletion of PKM2 in astrocytes prohibits ATP delivery to neurons after ischemia leading to escalated mitochondrial injury and elevated ROS formation, which in turn exacerbate neuronal degeneration (Hua *et al*., 2008). In spite of the crucial role microtubules in the growth, differentiation and plasticity of neural cells, they seem to be among the most sensitive cytoskeletal proteins subsequent to an ischemic insult (Kühn *et al*., 2005). PKM2 gene deletion has been associated increased oxidative stress and microtubule disruption in the hippocampus following a brain ischemia (Kang *et al*., 2023).

4. EMF exposure and PK activity in the brain

Non-ionizing electromagnetic fields (EMF) have been considered as environmental stressors that can alter brain metabolism and the glycolytic signaling including PK. Exposure to EMF, in particular at radiofrequency ranges is increasingly observed in our everyday life. *In vivo* studies have shown that EMF can affect the brain in all developmental stages specially interfering with the functionality and plasticity-related processes in association with energy metabolism. Diminished PK activity of the hippocampal and cortex regions has been observed in neonates exposed to EMF daily. This was accompanied by reduced ATP generation (Zhang *et al*., 2025). The suppression of PK activity results in ROS formation and disturbed growth of neural cells. Therefore, it could be considered that EMF can serve as a metabolic stress factor in early developmental stages. Also, a persistent reduction of PK activity which results in long-term metabolic effects has been detected when EMF exposure spans late gestational days. In adults animals, PK activity shows a decline in cortical neurons simultaneous with moderate increment in brainstem (Jha *et al*., 2016). Moreover, EMF-mediated changes in PK activity are associated with the dose and duration of exposure. For instance, longer constant exposure has led to a stronger effect in comparison with intermittent exposure. It has been shown that combined exposure to EMF and other stress-inducing factors can show a synergistic effect. Concurrent exposure to EMF and hypoxia decrease the activity of PK to a higher extent compared to each of them alone. Further modulation of PK enzyme influences neural plasticity, connectivity and neurotransmitter release which are all ATP-dependent processes. Similar to hypoxia, EMF exposure can have different effects on PK isoforms. It has been shown that a relative increment of PKM2 expression is observed in EMF-exposed neonates, whereas PKM1 shows a reduced activity (Rashidova, 2021). EMF can change the functionality of neurons by modulating PK activity. Impaired long-term potentiation and memory declines ha has been observed in neonates exposed to EMF with a further suppression pf PK (Lin *et al*., 2016). However, adult animals preserve their cognitive function in spite of PK modulation.

Different molecular mechanisms in connection with brain metabolism and PK activity which could be easily affected by EMF. It has been reported that EMF can increase ROS formation, mediate HIF-1α activity, induce PK isoform switches and correlate with cell death pathways. In this context, oxidative stress is the chief regulator of EMF-induces PK alterations. EMF-exposed neonatal and adult rats have shown

augmented ROS formation associated with plummeted PK activity and energy deprivation in hippocampus and cortex neurons. Oxidative stress can change the conformational and catalytic properties of PK enzyme by oxidizing cysteine residues. Moreover, the use of antioxidant has partially improved PK functionality, indicating the central role of oxidative damage in EMF-related metabolic disturbances. In addition, ROS can result it elevated expression of PKM2 by stabilizing HIF-1α). It has been demonstrated that EMF exposure enhances HIF-1α accumulation and upregulates PKM2 in hippocampal, while PKM1 expression is diminished (Zhang *et al*., 2024).

EMF can also influence the PDH/PDK axis in which elevated PDK activity is connected with EMF-mediated PKM2 upregulation. This process in turn prohibits PDH activity, restricts mitochondrial oxidation of pyruvate and increases lactate production. Rashidova et al. (2021) reported that the exposure of rats in 3, 6 and 24-month old age to EMF resulted in different activity of PK in the cortex and subcortex brain regions; increased at 10 $\mu W/cm^2$, while reduced at 30 $\mu W/cm^2$. Also, PK activity was lower at 10 $\mu W/cm^2$ compared to 30 $\mu W/cm^2$ in mitochondrial subcellular fractions. However, different intensities of PK did not change PK activity in cytosolic subcellular fractions. These findings indicate that increased PK activity might reflect a metabolic adaptation in order to protect cellular components against the harmful effects of EMF (Rashidova, 2021).

It has been demonstrated that light-related oxidative damage in mice retinal cone cells substantially drops when PKM2 inhibitors are administrated. This might be correlated with the increased expression of pentose phosphate pathway in turn (Zhu *et al*., 2021). Diminished activity of PKM2 though S-nitrosation or its blockade promotes substrate flow through the pentose phosphate pathway to generate reducing agents including NADH and reduced glutathione (GSH) that can protect against oxidative injuries (Siragusa *et al*., 2019; Wang *et al*., 2020; Zhu *et al*., 2021). The slower activity of PKM2 compared to PKM1, paves the way for an anabolic energy pathway (pentose phosphate) instead of the glycolytic pathways that ultimately provides reducing equivalents to protects cells (Zhang *et al*., 2019; Magadum *et al*., 2020).

PK can influence other signaling pathways such as nuclear factor-erythroid-2-related factor 2 (Nrf2) as the main mediator of cytoprotective responses against ROS (Zhu *et al*., 2014). It has been shown that PKM2 can bind to Nrf2 and enable the nuclear entry of Nrf2 in HT-22 hippocampal neurons. Nrf2-PKM2 complex can further mediate mitochondrial glutathione peroxidase 4 transcription (Ren *et al*., 2023). Also, trans-activation of Nrf2 by the PKM2 can increase the expression of glutamate-cysteine ligase in astrocytes, which is a GSH-synthetized rate limiting enzyme. This in turn combats with the increment of oxidative stress (Wei *et al*., 2020). Additionally, dimerized PKM2 can form Nrf2-antioxidant response element (ARE) complex boosting the expression of Nrf2-related antioxidant production with neuroprotecting effects (Ding *et al*., 2022).

5. Conclusion and Future Directions

Prior research demonstrates that PK as the central regulator of glycolysis has a fundamental role in brain physiology. PK is highly sensitive to environmental factors such as hypoxia, ischemia and EMF. In this context, PK activity can interfere with several signaling pathways altering metabolic pathways and cell fate decisions. While PKM1 isoform mainly leads glycolytic pathways, the function of PKM2 is associated with compensatory mechanisms protecting the neural cells and preserving synaptic plasticity

and energy production. Therefore, PK serves not only as a valued biomarker of neural damage but also could be a promising therapeutic target for future intervention strategies. Nevertheless, critical research gaps, including the necessity of investigating the combined effects of stressors, cell-type-specific mechanisms and therapeutic options in experimental models remain to be addressed.

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