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Prokineticin 2: A Chemokine Swinging Between Neuroprotection and Neurodegeneration

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Abstract

Prokineticin 2 (PK2) and the receptors PKR1 and PKR2 are expressed in several tissues, including the brain. PK2/PKRs signaling are involved in several physiological and cellular processes, such as neurogenesis and chemotaxis of neuroblasts to the olfactory bulb. Neurons, astrocytes, and microglia express PK2 and PKRs and upregulate their expression following injuries to the brain, such as traumatic injury, stroke, or chronic neurodegenerative disorders. The mechanisms controlling PK2 and PKRs expression and the effects of their upregulation on neuroprotection and neurodegeneration are still largely unknown.

Keywords: Prokineticin; PK2; Chemokine; Neurodegeneration

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Description

Prokineticins 1 and 2 (PK1 and PK2) were initially described as potent inducers of gastrointestinal smooth muscle contraction [1]. Their receptors were soon identified as members of the G-protein coupled receptor superfamily [2]. PK1 and PK2 receptors (PKR1 and PKR2) are expressed in many tissues, including the testis, medulla oblongata, skin, skeletal muscle, and several regions of the Central Nervous System (CNS), including the amygdala, hippocampus, frontal lobe, cerebral cortex and fetal brain [3].

The first function of PK2 in the CNS was as an output molecule of the circadian clock because of its rhythmic expression in the suprachiasmatic nucleus [4]. Although the expression of PK2 is rhythmic, the expression of PKR2 in the same region is constitutive [5]. Ng and colleagues described the expression of PK2 in the olfactory bulb (OB) and of PKR1 and PKR2 in the subventricular zone (SVZ) neurogenic niche and the rostral migratory stream of adult mice and proposed the PK2-PKR1/2 axis as relevant for adult neurogenesis [6].

Under physiological conditions, the neural stem cells of the adult mammalian SVZ continuously generate migrating neuroblasts. The neuroblasts leave the SVZ and, using chain migration in the RMS, move towards the OB, detach from the RMS, and are incorporated into the OB layers as interneurons. PK2 knockout mice show decreased OB size, disarranged layer cytoarchitecture, and have neuroblasts accumulated in the RMS. The granular and periglomerular layers are the primary site of PK2 expression in the OB, where the chemokine plays the role of a detachment signal for the arriving neuroblasts [7].

We have previously shown in a traumatic brain injury (TBI) model in mice that PK2 is upregulated at the injury site, while there is significant downregulation in the OB 24 hours post-lesion, followed by expression normalization four days after the injury [8]. Interestingly, Ayari and colleagues had previously described PK2 upregulation in an injury model in zebrafish, with increased proliferation and migration of neuroprogenitors toward the injury site [9].

In a TBI, after the occurrence of the primary lesion caused by the physical trauma, a secondary lesion develops induced by the activation of a cascade of cellular and molecular degenerative mechanisms [10]. The secondary injury is caused by a combination of factors, such as axonal degeneration, cell death, mitochondrial dysfunction, astrocytes and microglia reactivity. Over the years, the use of rodent TBI models revealed that increased proliferation of SVZ neural stem cells, followed by chemoattraction of the migratory neuroblasts to the injury site, are some of the early cellular responses to brain injury [11-13]. Neuroblast migration from the SVZ to the injury site is not common to all types of injury, and it depends on the extent of the damage caused by the initial lesion. Several studies in the literature describe the deviation of migrating neuroblasts from the RMS towards the primary injury site, although it is still debatable if there is a physiological role for this observed cellular event [14,15].

Several soluble factors are produced and secreted at a brain injury site; among them is the chemokine CXCL12, which attracts cells that express one of its receptors, CXCR4. Migrating SVZ-born neuroblasts express CXCR4 and respond to a CXC12 gradient resulting from its upregulation at the TBI site. The chemical

context at a TBI site is made of several cytokines, chemokines, a variety of growth and neurotrophic factors, small molecules released locally by the invading lymphocytes, and the resident microglia and astrocytes. This complex combination of factors seems to be the key to deviate the OB-bound neuroblasts from the RMS to the injury site.

Using primary rat cortical cells neurons, astrocytes, and microglia, Cheng and colleagues showed that reactive oxygen species (ROS), hypoxia, and glutamate could upregulate PK2 mRNA expression in neurons and astrocytes, but not in the microglia [16]. All three cell types express PKR1 and PKR2, neurons express more PKR2 than PKR1, and microglia express more PKR1 mRNA than PKR2. Expression of PK2 by spinal cord astrocytes but not by microglia has also been reported [17].

PK2 functions in response to injury are still under investigation, and apart from its chemotactic effect on PKR-expressing neuroblasts, which could be positive to induce a potential regenerative program, PK2 can also be harmful, as recently reviewed **(Figure 1)** [18].

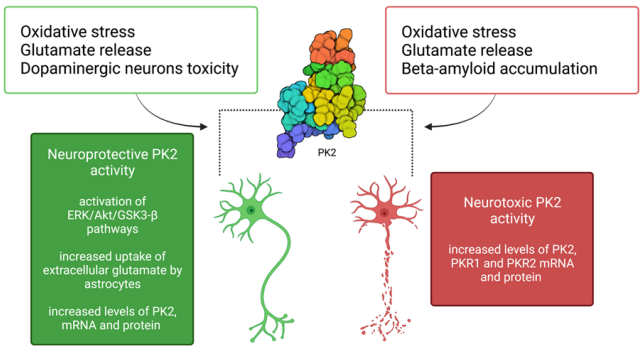

Figure 1: Dual effect of PK2 on neuroprotection and neurodegeneration. (Original figure based on the review by Lattanzi et al.

Overall, TBI disrupts homeostasis of the whole brain, and it affects the synapses, cell-cell signaling, cellular metabolism, and gene expression, to mention a few interferences induced by brain injuries, and PK2 may contribute to neurotoxicity as well as be neuroprotective. The Allen Institute for Brain Science shared a transcriptome dataset of brains from control (no TBI) and TBI cases from a cohort of aged population from the Adult Changes in Thought (ACT) study in which it is possible to search for differentially expressed genes. Searching the database for PK1 and PK2 expression changes, one can observe that PK2 expression is more affected than PK1 expression in four brain regions: parietal neocortex, hippocampus, inferior parietal lobule, and neocortex from the posterior superior temporal gyrus. More studies regarding PK2 expression are needed to evaluate its role in response to injuries and other neurological disorders and investigate its potential as a biomarker for severity and outcome.

PK2 and PKR2 upregulation is also seen in other neurological disorders, including Alzheimer's disease, Parkinson's disease, ischemic stroke. The ubiquitous upregulation of PK2 and PKR2 in these distinct diseases, which present different pathophysiology and distinct cellular and molecular mechanisms, suggests that PK2 may have a controlling role in neuron-astrocyte interactions and may function as an early marker of neuroinflammation [19,20].

So far, PK2, PKR1, and PKR1 have shown to be relevant to several neurological diseases affecting both the central and peripheral nervous systems. Although there is still a lot to know about the mechanisms involved in the control of PK2 and receptors expression, as well as in the role the signaling pathways activated by them, it is clear that this chemokine may be used as a brain injury biomarker and a target for drug development to treat neurodegeneration and neuroinflammation.

Conclusion

Expression levels of PK2, both mRNA and protein, are increased by different types of pathological conditions such as oxidative stress, glutamate release, beta-amyloid accumulation, and dopaminergic neuron death. The role of increased expression of PK2 and PKRs and activation/inactivation of PK2/PKRs signaling pathway in neuroprotection and neurodegeneration is still unclear.

References

1. Li M (2001) Identification of two prokineticin cDNAs: Recombinant proteins potently contract gastrointestinal smooth muscle. Mol Pharmacol. 59: 692-8.
2. Lin D.C (2002) Identification and molecular characterization of two closely related G protein-coupled receptors activated by prokineticins/endocrine gland vascular endothelial growth factor. J Biol Chem. 277: 19276-80.
3. Soga T (2002) Molecular cloning and characterization of prokineticin receptors. Biochim Biophys Acta. 1579: 173-9.
4. Cheng M.Y (2002) Prokineticin 2 transmits the behavioural circadian rhythm of the suprachiasmatic nucleus. Nature. 417: 405-10.
5. Cheng M.Y (2005) Regulation of prokineticin 2 expression by light and the circadian clock. BMC Neurosci. 6: 17.
6. Ng K.L (2005) Dependence of olfactory bulb neurogenesis on prokineticin 2 signaling. Science. 308:1923-7.
7. Doetsch F (1999) Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell. 97: 703-16.
8. Mundim M.V (2019) A new function for Prokineticin 2: Recruitment of SVZ-derived neuroblasts to the injured cortex in a mouse model of traumatic brain injury. Mol Cell Neurosci. 94: 1-10.
9. Ayari B (2010) Prokineticin 2 expression is associated with neural repair of injured adult zebrafish telencephalon. J Neurotrauma. 27: 959-72.
10. Ng S.Y, Lee A.Y.W (2019) Traumatic Brain Injuries: Pathophysiology and Potential Therapeutic Targets. Front Cell Neurosci. 13: 528.
11. Chirumamilla S (2002) Traumatic brain injury induced cell proliferation in the adult mammalian central nervous system. J Neurotrauma. 19: 693-703.

12. Itoh T (2009) The relationship between SDF-1alpha/CXCR4 and neural stem cells appearing in damaged area after traumatic brain injury in rats. Neurol Res. 31: 90-102.

13. Saha B, Peron S, Murray K, Jaber M and Gaillard A (2013) Cortical lesion stimulates adult subventricular zone neural progenitor cell proliferation and migration to the site of injury. Stem Cell Res. 11: 965-77.

14. Gundelach J and Koch M (2018) Redirection of neuroblast migration from the rostral migratory stream into a lesion in the prefrontal cortex of adult rats. Exp Brain Res. 236: 1181-1191.

15. Kokovay E (2010) Adult SVZ lineage cells home to and leave the vascular niche via differential responses to SDF1/CXCR4 signaling. Cell Stem Cell. 7: 163-73.

16. Cheng MY (2012) Prokineticin 2 is an endangering mediator of cerebral ischemic injury. Proc Natl Acad Sci U S A. 109: 5475-80.

17. Guida F (2015) PC1, a non-peptide PKR1-preferring antagonist, reduces pain behavior and spinal neuronal sensitization in neuropathic mice. Pharmacol Res. 91: 36-46.

18. Lattanzi R (2021) The Role of Prokineticin 2 in Oxidative Stress and in Neuropathological Processes. Front Pharmacol. 12: 640441.

19. Caioli S (2017) Prokineticin system modulation as a new target to counteract the amyloid beta toxicity induced by glutamatergic alterations in an in vitro model of Alzheimer's disease. Neuropharmacology. 116: 82-97.

20. Gordon R. (2016) Prokineticin-2 upregulation during neuronal injury mediates a compensatory protective response against dopaminergic neuronal degeneration. Nat Commun. 7: 12932.