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The role of PKD1 in brain injury: ROS detoxification and neuroprotection.

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Introduction: Oxidative stress is a major pathophysiological mediator of degenerative processes in many neurodegenerative diseases. It is an early event produced during excitotoxicity and is one of the main causes of neuronal damage. It has been described that Protein Kinase D1 (PKD1) is activated by oxidative stress and regulate detoxification of free radicals in tumor cells. However, the role of PKD1 in brain injury associated with excitotoxicity and oxidative stress damage has not yet been explored.

Methods: We analyze the activity of PKD1 using in vitro and in vivo models of neuronal damage, as well as human ischemic stroke samples. In addition, and through the use of pharmacological inhibitors, lentiviral silencing and neuronal conditional knockout mice we study the role of this kinase in the pro-survival oxidative stress detoxification pathway and the regulation of their activity in these processes.

Results: We find that excitotoxicity provokes an inactivation of neuronal PKD1 and as a consequence there is a decline of IKK/NF-κB survival cascade and an increase in reactive oxygen species. We identify the first molecular mechanism involved in PKD1 inactivation, caused in excitotoxicity by the action of phosphatases not identified so far. Consistent with these results, we demonstrate that the elimination of PKD1 in murine models increases neuronal damage after ischemic stroke and the neurospecific expression of dephosphorylation-resistant active PKD1 prevents kainic acid-induced neuronal death in vitro and in vivo.

Conclusions: Our data support that the loss of neuronal PKD1 activity is detrimental for neuronal survival and ROS-detoxification and suggest that this kinase could be a promising target for treatment of excitotoxic brain damage associated to acute and chronic neurodegeneration.

Keywords: Excitotoxicity, oxidative stress, neuronal death, stroke, PKD1
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