# Guanosine promotes neuroprotection via potassium channels (BK) and activation of the PI 3-kinase/AKT pathway

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Guanine derivates (GD) have been implicated in many extracellular effects, such as modulation of glutamate transmission and neuroprotection against excitotoxic insults. GD are spontaneously released to the extracellular space from cultured astrocytes and during oxygen-glucose deprivation (OGD). The aim of this study was to evaluate the involvement of potassium channels and the PI3-K pathway in the mechanisms related to the neuroprotective role of Guanosine (GUO) in rat hippocampal slices submitted to OGD. The addition of GUO (100 µM) to hippocampal slices submitted to 15 minutes of OGD followed by 2 hours of reperfusion was neuroprotective. The presence of $K^+$ channel blockers, glibenclamide (20µM) and apamine (300nM) revealed that the neuroprotective effect of GUO was not dependent on the ATP-sensitive $K^+$ channel and the small conductance $Ca^{2+}$-activated $K^+$ channels. The presence of charybdotoxin (100nM), a big conductance $Ca^{2+}$- activated $K^+$ channel (BK) blocker, blocked the neuroprotective effect of GUO. The hippocampal slices submitted to 15 minutes of OGD followed by 2 hours of reperfusion showed a significantly reduction of glutamate uptake. The addition of GUO in the reperfusion period blocked the reduction of glutamate uptake. This GUO effect was inhibited when hippocampal slices were preincubated with charybdotoxin or wortmanin (1µM, PI3-K inhibitor) at the reperfusion period. GUO promotes an increased phosphorylation of AKT protein, however the presence of charybdotoxin reverted such effect. In conclusion, the neuroprotective effect of GUO involves augmentation of glutamate uptake, which is modulated by BK channels and activation of PI3-K pathway. GUO-induced increased expression of phospho-AKT resulted in neuroprotection.

Keywords: Guanosine, neuroprotection, oxygen-glucose deprivation, potassium channel

Supported by:CAPES, CNPq