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Dual role of mitochondria in producing melatonin and driving GPCR signaling to block cytochrome c release and modulation of cerebral ischemic injury

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Introduction

G-protein coupled receptors (GPCRs) are classically characterized as cell surface receptors transmitting extracellular signals into cells.

Methods

Mitochondrial purification and evaluation, MCAO

Results

Here we show that central components of a GPCR signaling system constituted of the melatonin type 1 receptor (MT1), its associated G protein, and ß-arrestins are on and within neuronal mitochondria. We discovered that the ligand, melatonin, is exclusively synthetized in the mitochondrial matrix and activates the mitochondrial MT1 signal transduction pathway inhibiting stress mediated cytochrome c release and caspase activation. These findings coupled to our observation that mitochondrial MT1 overexpression reduces ischemic brain injury in mice delineate a novel mitochondrial GPCR mechanism contributing to the neuroprotective action of melatonin.

Conclusions

We propose a new term “automitocrine”, analogous to autocrine when a similar phenomenon occurs at the cellular level, to describe this unexpected intracellular organelle ligand-receptor pathway that opens a new research avenue investigating mitochondrial GPCR biology, with particular importance to both the ageing process of well as acute (i.e. cerebral ischemia, TBI) and chronic (i.e. ALS, Huntington’s disease) neurodegenerative diseases.

Learning Objectives

Understand mechanisms of endogenous melatonin-mediated protection

References

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