

Connexin 43 hemichannels and pannexin-1 channels contribute to the α -synuclein-induced dysfunction and death of astrocytes

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Diverse studies have suggested that cytoplasmic inclusions of misfolded α -synuclein in neuronal and glial cells are main pathological features of different α -synucleinopathies, including Parkinson's disease and dementia with Lewy bodies. Up to now, most studies have focused on the effects of α -synuclein on neurons, whereas the possible alterations of astrocyte functions and neuron-glia crosstalk have received minor attention. Recent evidence indicates that cellular signaling mediated by hemichannels and pannexons is critical for astroglial function and dysfunction. These channels constitute a diffusional route of communication between the cytosol and the extracellular space and during pathological scenarios they may lead to homeostatic disturbances linked to the pathogenesis and progression of different diseases. Here, we found that α -synuclein enhances the opening of connexin 43 (Cx43) hemichannels and pannexin-1 (Panx1) channels in mouse cortical astrocytes. This response was linked to the activation of cytokines, the p38 MAP kinase, the inducible nitric oxide synthase, cyclooxygenase 2, intracellular free Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$), and purinergic and glutamatergic signaling. Relevantly, the α -synuclein-induced opening of hemichannels and pannexons resulted in alterations in $[\text{Ca}^{2+}]_i$ dynamics, nitric oxide (NO) production, gliotransmitter release, mitochondrial morphology, and astrocyte survival. We propose that α -synuclein-mediated

opening of astroglial Cx43 hemichannels and Panx1 channels might constitute a novel mechanism involved in the pathogenesis and progression of α -synucleinopathies. © 2019 Wiley Periodicals, Inc.

connexin

glia

neuroinflammation

pannexin

α -synucleinopathies

alpha synuclein

brain protein

connexin 43

cyclooxygenase 2

ethidium

glutamic acid

inducible nitric oxide synthase

mitogen activated protein kinase p38

nitric oxide

pannexin 1

unclassified drug

agents interacting with transmitter, hormone or drug receptors

alpha synuclein

calcium channel

connexin 43

cytokine

gap junction protein

GJA1 protein, mouse

nerve protein

nitric oxide

Panx1 protein, mouse

small interfering RNA

Snca protein, mouse

animal experiment

Article

astrocyte

brain cortex

calcium cell level

cell death

cell survival

controlled study

glutamatergic synapse

nonhuman

priority journal

animal

astrocyte

biosynthesis

cell communication

cell culture

genetics

metabolism

mitochondrion

mouse

pathology

ultrastructure

alpha-Synuclein

Animals

Astrocytes

Calcium Channels

Cell Communication

Cell Death

Cells, Cultured

Connexin 43

Connexins

Cytokines

Mice

Mitochondria

Nerve Tissue Proteins

Neurotransmitter Agents

Nitric Oxide

RNA, Small Interfering