



## Invited review

## Purinergic signalling in brain ischemia



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## ABSTRACT

Ischemia is a multifactorial pathology characterized by different events evolving in the time. After ischemia a primary damage due to the early massive increase of extracellular glutamate is followed by activation of resident immune cells, i.e. microglia, and production or activation of inflammation mediators. Protracted neuroinflammation is now recognized as the predominant mechanism of secondary brain injury progression.

Extracellular concentrations of ATP and adenosine in the brain increase dramatically during ischemia in concentrations able to stimulate their respective specific P2 and P1 receptors. Both ATP P2 and adenosine P1 receptor subtypes exert important roles in ischemia. Although adenosine exerts a clear neuroprotective effect through A<sub>1</sub> receptors during ischemia, the use of selective A<sub>1</sub> agonists is hampered by undesirable peripheral effects. Evidence up to now in literature indicate that A<sub>2A</sub> receptor antagonists provide protection centrally by reducing excitotoxicity, while agonists at A<sub>2A</sub> (and possibly also A<sub>2B</sub>) and A<sub>3</sub> receptors provide protection by controlling massive infiltration and neuroinflammation in the hours and days after brain ischemia.

Among P2X receptors most evidence indicate that P2X7 receptor contribute to the damage induced by the ischemic insult due to intracellular Ca<sup>2+</sup> loading in central cells and facilitation of glutamate release. Antagonism of P2X7 receptors might represent a new treatment to attenuate brain damage and to promote proliferation and maturation of brain immature resident cells that can promote tissue repair following cerebral ischemia. Among P2Y receptors, antagonists of P2Y<sub>12</sub> receptors are of value because of their antiplatelet activity and possibly because of additional anti-inflammatory effects.

Moreover strategies that modify adenosine or ATP concentrations at injury sites might be of value to limit damage after ischemia.

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## Abbreviations

ADA	adenosine deaminase	KO	knock-out
ADAC	adenosine amine congener	LJ529	2-chloro-N(6)-(3-iodobenzyl)-5'-N-methylcarbamoyl-4'-thioadenosine
ADK	adenosine kinase	LPS	lipopolysaccharide
APEC	2-[(2-aminoethylamino)-carbonylethylphenylethylamino]-5'-N-ethylcarboxamidoadenosine	LTP	long-term potentiation
BBG	Brilliant Blue G	L-PIA	N6-(L-2-phenylisopropyl) adenosine
BBB	blood brain barrier	MAPK	mitogen-activated protein kinase
BMDCs	bone marrow derived cells	MCAo	middle cerebral artery occlusion
BDNF	brain-derived neurotrophic factor	2-MeSADP	2-methylthioladenosine 5' diphosphate
BzATP	3'-O-(4-benzoylbenzoyl) adenosine 5'-triphosphate	MRS2500	(1R*,2S*)-4-[2-Iodo-6-(methylamino)-9H-purin-9-yl]-2-(phosphono-oxy)bicyclo[3.1.0] hexane-1-methanol dihydrogen phosphate ester
CHA	cyclohexyladenosine	MRS1220	(N-[9-Chloro-2-(2-furanyl)[1,2,4]-triazolo [1,5-c]quinazolin-5-yl]benzene acetamide)
CNS	central nervous system	MRS2179	N(6) -methyl-2'-deoxyadenosine-3',5'-bisphosphate
CNT	concentrative transporter	MRS1706	N-(4-acetylphenyl)-2-[4-(2,3,6,7-tetrahydro-2,6-dioxo-1,3-dipropyl-1H-purin-8-yl) henoxy]acetamide
CGS15943	9-chloro-2-(2-furanyl)-[1,2,4]triazolo[1,5-c]quinazolin-5-amine	MRS 1754	N-(4-cyanophenyl)-2-[4-(2,3,6,7-tetrahydro-2,6-dioxo-1,3-dipropyl-1H-purin-8-yl)phenoxy]-acetamide
CGS21680	2-p-(2-Carboxyethyl)phenethylamino-5'-Nethylcarboxamidoadenosine hydrochloride	MRS 1523	3-propyl-6-ethyl-5-[(ethylthio)carbonyl]-2-phenyl-4-propyl-3-pyridine carboxylate
Cl-IBMECA	1-[2-Chloro-6[[3-iodophenyl)methyl]amino]-9H-purin-9-yl]-1-deoxy-N-methyl-β-D-ribofuranuronamide]	NGF	nerve growth factor
CADO	2-chloroadenosine	NTPDase	nucleoside triphosphate diphosphohydrolase
CP66713	4-amino [1,2,4] triazolo [4,3a] quinoxalines	OGD	oxygen/glucose deprivation
CPA	N6-cyclopentyladenosine	OPCs	oligodendrocyte progenitors
CCPA	2-chloro-N(6)-cyclopentyladenosine	PLC	phospholipase C
CNT	concentrative nucleoside transporters	PPADS	pyridoxal phosphate-6-azophenyl-2',4'-disulfonic acid
8-CPT	8-cyclo-pentyl theophylline	PKC	protein kinase C
CSC	8-(3-chlorostyryl)caffeine	oxATP	2',3',-dialdehyde ATP
DPCPX	8-Cyclopentyl-1,3-dipropylxanthine	QA	quinolinic acid
e5'-NT	ecto-5'-nucleotidase	RB-2	Reactive Blue 2
ENT	equilibrative nucleoside transporter	R-PIA	R-phenylisopropyl-adenosine
fEPSP	field excitatory postsynaptic potential	SCH58261	5-Amino-7-(2-phenylethyl)-2-(2-furyl)-pyrazolo [4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine
GDNF	glial cell line-derived neurotrophic factor	SVZ	subventricular zone
GLT-1	glutamate transporter-1	TNP-ATP	trinitrophenyl adenosine triphosphate
GPR17	G protein-coupled receptor 17	ZM241385	4-(2-[7-Amino-2-(2-furyl)[1,2,4]triazolo[2,3-a][1,3,5]triazin-5-yl-amino]ethyl)phenol
IB-MECA	N(6)-(3-iodobenzyl)-adenosine-5'-N-methylcarboxamide		
IP3	inositol trisphosphate		

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