Microglial Activation and Inhibition: Implications for Neurodegeneration

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Abstract

Accumulating evidence over the past 20 years has indicated that the brain has an endogenous immune system, mediated at the local level predominantly by microglial cells. The primary role of an inflammatory response is to protect the host against a foreign stimulus, remove damaged cells and to initiate repair and regeneration of damaged tissue. However, it has become increasingly evident that this inflammatory response, in addition to its role in host defence and repair, can exert detrimental effects in the central nervous system (CNS). Neuroinflammation, as this response is now commonly known, has been implicated in the pathogenesis of many neurodegenerative diseases. Microglia, the resident macrophage of the brain, play a central role in sustaining this inflammatory response through the release of pro-inflammatory and potentially cytotoxic mediators. Hypothermia is neuroprotective, and these properties are thought to be mediated, in part, by the suppression of microglial activation.

The BV-2 microglial cell line was used to investigate the mechanisms involved in the activation and inhibition of microglia. Lipopolysaccharide (LPS)-induced activation of BV-2 cells led to the up-regulation of inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2, the release of inflammatory mediators such as nitric oxide (NO), prostaglandin (PG)-E_2, interleukin (IL)-6 and tumour necrosis factor (TNF)-α, and a change to a phagocytic phenotype. This response was mediated by the initiation of signal transduction pathways that culminated in transcription and translation of the inflammatory genes. Hypothermia (33°C) caused complete suppression of iNOS and NO whilst displaying little or no effect on IL-6 and TNF-α respectively. In contrast, LPS-induced COX-2 expression and PGE_2 release was super-induced in response to hypothermia. A co-culture model of neuroinflammation was developed to investigate microglial-neuronal interactions. LPS/interferon (IFN)-γ activated BV-2 cells required direct contact with SK-N-SH neuroblastoma cells to elicit a cytotoxic phenotype. Hypothermia and the selective iNOS inhibitor *S*-methylisothiourea (*S*-MT) protected against this BV-2-induced SK-N-SH cell death, strongly implicating NO as the major candidate molecule in microglial-induced neuronal cell death.

Thus, microglial activation sustains the chronic inflammatory response in the CNS and in doing so contributes to further neuronal death. Inhibition of the detrimental facets of microglial activation may provide some protection against neurodegeneration.

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Abbreviations

Aβ	β-amyloid
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
AP-1	Activator protein-1
APOE	Apolipoprotein E
APP	Amyloid precursor protein
ATF	Activating transcription factor
BBB	Blood-brain barrier
BrdU	5-bromo-2'-deoxyuridine
CD	Cluster of differentiation
C/EBP	CCAAT-enhancer binding proteins
CNS	Central nervous system
CO_2	Carbon dioxide
COX	Cyclooxygenase
CRE	CREB response element
CREB	cAMP response element binding protein
CSF	Cerebrospinal fluid
DMSO	Dimethylsulphoxide
DNA	Deoxyribonucleic acid
eNOS	Endothelial nitric oxide synthase
EP	Prostaglandin E_2 receptor
ERK1/2	Extracellular signal-regulated kinase
FAD	Flavin adenine dinucleotide
FMN	Flavin mononucleotide
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GFAP	Glial fibrillary acidic protein
H_2O_2	Hydrogen peroxide
HD	Huntington's disease
HLA	Human leukocyte antigen
6-OHDA	6-hydroxydopamine
4-HNE	4-hydroxynonenal
HOCl	Hypochlorous acid
ICAM-1	Intracellular adhesion molecule
ICC	Immunocytochemistry
IFN	Interferon
IFNR	IFN-γ receptor
IKK	IκB kinase
IL	Interleukin
IL-6R	Interleukin-6 receptor

iNOS	inducible nitric oxide synthase
IRAK	IL-1-receptor-associated kinase
IRF	Interferon regulatory factor
JIP	JNK-interacting protein
JNK	c-Jun N-terminal kinase
LPB	LPS-binding protein
LPS	Lipopolysaccharide
MAC	Membrane attack complex
MAPK	Mitogen-activated protein kinase
MCAO	middle cerebral artery occlusion
MEK1/2	MAPK/ERK kinase
MHC	Major histocompatibility complex
MPO	Myeloperoxidase
MPP^+	1-methyl-4-phenylpyridinium
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NADPH	Nicotinamide adenine dinucleotide phosphate
NF-κB	Nuclear factor-κB
NFT	Neurofibrillary tangle
NMDA	N-methyl-D-aspartate
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NO_2	Nitrogen dioxide
NOS	Nitric oxide synthase
NSAID	Non-steroidal anti-inflammatory drug
O_2^-	Superoxide
OH^-	Hydroxyl radical
$ONOO^-$	Peroxynitrite
PAMP	Pathogen-associated molecular patterns
PCNA	Proliferating cell nuclear antigen
PD	Parkinson's disease
PDZ	Post-synaptic density-95/discs large/zonula occludens-1
PET	polyethylene terephthalate
PG	Prostaglandin
15d-PGJ_2	15-deoxy-$\Delta^{12,14}$-PGJ_2
PHF	Paired helical filament
PKC	Protein kinase C
PMA	Phorbol 12-myristrate 13-acetate
PPAR	Peroxisome proliferator-activated receptor
RNS	Reactive nitrogen species
ROS	Reactive oxygen species

RT-PCR	Reverse transcription-polymerase chain reaction
sIL-6R	Soluble interleukin-6 receptor
S-MT	*S*-methylisothiourea
SNpc	Substantia nigra pars compacta
SRE	Serum response element
STAT	Signal transducers and activators of transcription
TCF	Ternary complex factor
TGF	Transforming growth factor
TIR	Toll/interleukin-1 receptor
TLR	Toll-like receptor
TNF	Tumour necrosis factor
TNFR1	p55 TNF receptor
TNFR2	p75 TNF receptor
TRAF6	TNF-receptor-associated factor