Stroke Risk in Elderly Individuals: Novel Molecules in Stroke & Therapeutical Targets

Yaşlılarda Strok Riski: Strokta Yeni Moleküller ve Terapötik Hedefler

Ayfer YALÇIN[a]

[a]Biyokimya AD,
Ege Üniversitesi Eczacılık Fakültesi
İZMİR

Yazışma Adresi/*Correspondence:*
Ayfer YALÇIN
Ege Üniversitesi Eczacılık Fakültesi
Biyokimya Anabilim Dalı
Bornova, İZMİR
ayfer.yalcin@ege.edu.tr

ABSTRACT Stroke is one of the leading causes of death and adult disability in industrialized countries. Many risk factors have been identified as the modifiable or non-modifiable causes of stroke including aging. Stroke has a complex pathophysiology and involves oxidative stress, excitotoxicity, apoptosis and inflammation. Molecules related with the mechanisms induced by ischemia and reperfusion such as PPAR, 12/15-LOX, NF-κB, Caspase-3, p53, Bcl-2, PARP-1, APE/Ref-1, TNF-α, CDK5, iNOS and, COX-2 have been evaluated as potential therapeutical targets of stroke. Therefore, the regulation of synthesis of these molecules at mRNA or protein level may be helpful for neuroprotective aims in stroke therapy.

Key Words: Stroke, ischemia/reperfusion, neuroprotection

ÖZET Strok endüstrileşmiş ülkelerde önde gelen ölüm ve yetişkinlerde işgöremezlik nedenlerinden biridir. Strok için modifiye edilebilir veya yaşlanmayı da kapsayan modifiye edilemez bazı risk faktörleri tanımlanmıştır. Strok, oksidatif stres, eksitotoksisite, apoptosis ve inflamasyon olgularını bir arada içeren kompleks bir patofizyolojiye sahiptir. Akut strok tedavisinde kullanılan yaklaşımlardan biri de nöroproteksiyondur. İskemi ve reperfüzyonla indüklenen mekanizmalarla ilişkili moleküller olarak PPAR, 12/15-LOX, NF-κB, Caspase-3, p53, Bcl-2, PARP-1, APE/Ref-1, TNF-α, CDK5, iNOS and COX-2 strok için potansiyel terapötik hedefler olarak değerlendirilmiştir. Bu nedenle, bu moleküllerin mRNA veya protein düzeyinde sentezlerinin düzenlenmesi strok tedavisinde nöroprotektif amaçlar için yardımcı olabilir.

Anahtar Kelimeler: İskemi/reperfüzyon, strok, nöroproteksiyon

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Stroke is one of the leading causes of death and adult disability in industrialized countries. Many risk factors have been identified as the modifiable or non-modifiable causes of stroke. The non-modifiable factors include age, gender, positive family history, ethnicity, previous transient ischemic attack or stroke. The modifiable factors include hypertension, diabetes, smoking, lipid disorders- hypercholestrolemia, alcohol intoxication and physical inactivity.[1-3] The aging process is known to cause specific cardiovascular changes that impair heart and blood vessel function. The higher blood pressure is the greatest risk of developing narrowed arteries which can lead to cardiovascular problems and stroke.

Stroke is a sudden loss of brain function resulting from interference with the blood supply to the central nervous system. Acute stroke can be classified either as

ischemic (80% of stroke cases), which can be further classified to extra-cranial embolism and intracranial thrombosis, or a hemorrhragic stroke (20% of stroke cases), which can be further classified to intracerebral hemorrhage and subarachnoid hemorrhage.[3] The majority of ischemic strokes are due to arterial occlusions, which can rapidly produce a core of infarcted brain tissue surrounded by hypoxic but potentially salvageable tissue, the ischemic penumbra. The goal of therapy is rapid restoration of blood flow with preservation of the ischemic penumbra and minimal neuronal damage. Central nervous system (CNS) damage is occured in stroke as a result of hypoxia. In the penumbra, functional alterations are occured in the neurons and glial cells.[3,4]

Stroke has a complex pathophysiology and involves energy failure, excitotoxicity, spreading depression, elevation of intracellular calcium levels, generation of free radicals, blood-brain barrier (BBB) distruption, inflammation, glial cell contribution, changes in neurotransmitters and neuroactive substances, and apoptosis due to the activation of a sequence of genes and proteins.[4,5] The excessive production of reactive oxygen species (ROS) can cause cellular damage and subsequent cell death, because ROS may oxidize vital cellular components such as membrane lipids, proteins and DNA, and alter several signalling pathways that ultimately promote cellular damage and death during cerebral ischemia and reperfusion. Apoptosis is prominent in the penumbra following stroke. Apoptosis is triggered following cerebral ischemia by various death signals including production of free radicals and tumor necrosis factor, deficiency of growth factor and neurotrophins, DNA damage and p53 induction, and cytochrome c release during mitochondrial injury. Apoptotic mechanisms involve key proteins, such as caspases, apoptosis inducing factor (AIF) and Bcl-2 family proteins During cerebral ischemia, an excessive NMDA-receptor activation (excitotoxicity) may lead to the accumulation of ROS.[1] Glutamate induced excitotoxic stimulation of NMDA receptor and subsequent calcium influx, which activates several intracellular calcium sensitive enzymes, such as nNOS and CaMKs. Expression of various cytokines and adhesion molecules on endothelial cells, promote leukocyte adherence and accumulation thereby initiating the inflammatory response. Further, breakdown of blood brain barrier (BBB) permits neutrophil diapedesis into the ischemic tissue in response to chemokines produced by astrocytes, macrophages, and microglia.[5,6]

Ischemic stroke represents one of the most challenging diseases in translational neurology. Despite considerable efforts made to develop efficacious therapies that prevent damage once a stroke has occured, there are still no established treatments for humans. The only available treatment is intravenous or intra-arterial thrombolysis that is limited to very first hours after the stroke.[7] The major approaches in acute stroke therapy are recanalization, brain hypothermia, usage of pharmaceuticals, and neuroprotection.[4] Neuroprotection is a term used to describe the putative effect of interventions protecting the brain from pathological damage. In occlusive stroke, the concept of neuroprotection involves inhibition of a cascade of pathological molecular events occurring under ischaemia and leading to calcium influx, activation of free radical reactions and cell death.[8] In this presentation, the molecules related with these mechanisms will be discussed as potential therapeutical targets of stroke (Table 1).

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TABLE 1: Potential molecular targets in stroke.

Target	Effect	Reference
PPAR (Peroxisome proliferator-activated receptor-1)	Activation of all PPAR isoforms, especially PPARγ prevent post-ischemic inflammation and neuronal damage	9,11,10
12/15-LOX (12/15-Lipoxygenase)	12/15 LOX knock-out mice are protected in middle cerebral artery occlusion	12
	12/15 LOX inhibitor provided a neuroprotection against ischemic stroke	13
NF-KappaB (Nuclear factor KappaB)	Plays an essential role in the regulation of post-ischemic inflammation	14
	Inhibition of NF-kappaB down regulates apoptotic molecules including p53, cytochrome c and caspase-3.	15
Caspase-3	Caspase inhibitors Z-VAD-fmk, Z-DEVD-fmk, Z-D-DCB offer significant protection against ischemia-induced neuronal apoptosis	16,17,18,19
p53	p53 inhibitor modified stroke-induced endogenous neurogenesis and improved functional recovery in stroke animals	20
Bcl-2	Improved neuronal survival and blocked nuclear AIF translocation when delivered to the infarct margin	21
	Bcl-2 gene therapy reduced numbers of apoptotic cells in the infarct and penumbra area	22
PARP-1 (Poly-ADP-ribose) polymerase-1 enzyme)	PARP-1 gene deletion and PARP-1 inhibitors prevent neuronal death induced by excito toxicity and oxidant stress	23
	PARP-1 inhibition markedly improves cell survival after ischemia reperfusion in brain	17,23,24,25
APE/Ref-1 (Apurinic-apyrimidinic endonuclease-redox factor-1)	Decreases after transient focal cerebral ischemia before the peak of DNA damage	26
	Inhibits the induction of neuronal cell death after transient ischemic stroke in mice by adenoviral vector-mediated increase	27
CDK5 (cyclin dependent kinase-5)	Cdk5 inhibitors are potential neuroprotective strategy for ischemic injury	28
TNF-α (Tumor necrosis factor- α)	TNF- α receptor antagonists or TNF- α processing inhibitors provides a protection in hemorrhagic stroke	29
FLIP(L) (Fas-associated death domain-like interleukin-1-beta-converting enzyme-inhbitory protein)	Protects neurons against in vivo ischemia and in vitro glucose deprivation-induced cell death	30
iNOS (inducible nitric oxide synthase)	Mice lacking iNOS gene and iNOS inhibition shows protection in cerebral ischemia	31,32,33,34
COX-2 (cyclo oxygenase-2)	Loss of iNOS gene and COX-2 inhibition shows reduction in ischemic brain injury and neurological deficits	35
	COX-2 inhibition delays inflammatory events in transient and permanent focal cerebral ischemia	36

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