Secondary Neurodegeneration in Remote Regions After Focal Cerebral Infarction
A New Target for Stroke Management?

Jian Zhang, MD, PhD; Yusheng Zhang, MD, PhD; Shihui Xing, MD, PhD; Zhijian Liang, MD, PhD; Jinsheng Zeng, MD, PhD

Cerebral infarction-induced cessation of function in areas of the brain remote from, but connected to, the primary site of damage was termed “diaschisis” by von Monakow. Initially, the concept of diaschisis did not include morphological changes. However, accumulating evidence has shown that histopathologic changes also occur in nonischemic remote brain regions that have synaptic connections with the primary lesion site. For example, after cerebral infarction in the middle cerebral artery (MCA) territory, neuronal death, gliosis, and axonal degeneration have been found in the ipsilateral thalamus, substantia nigra (SN), and distal pyramidal tract, all of which lie outside the MCA territory. This kind of secondary neurodegeneration occurs selectively in such areas several days or weeks after stroke onset, and this can be detected by neuroimaging techniques. For quite a long time, the role of secondary degeneration in stroke recovery has not been well understood. Recently, emerging studies suggest that secondary degeneration is associated with neurological deficits and can predict motor outcome after stroke.

In this review, we aimed to summarize the pathological and neuroimaging evidence of secondary neurodegeneration in the ipsilateral thalamus, SN, and pyramidal tract after MCA infarction and described its potential significance for stroke management. We searched PubMed from 1980 to September 2011, using the terms “cerebral infarction,” “middle cerebral artery,” “Wallerian degeneration,” “anterograde degeneration,” “retrograde degeneration,” and “transneuronal degeneration.” Further articles were identified from the references cited in those articles and through searches of our personal files. The final list of references was selected on the basis of originality and relevance to the topics covered in this review.

Evidence of Secondary Degeneration After Stroke

Postmortem Studies
Data from postmortem studies provide direct evidence of secondary neurodegeneration after focal cerebral infarction (Figure 1). Histopathologic examination at 4 months after MCA infarction revealed a delayed and selective decrease in the neuron density, neuropil rarefaction, and reactive astrogliosis in the ipsilateral thalamus. Different from the pathological features of primary infarction, macrophages were rare in the thalamus. This secondary lesion cannot be explained by insufficient blood supply, and it may reflect retrograde degeneration of the thalamocortical fibers.

The SN is another brain structure that is subjected to secondary degeneration after MCA infarction. Forno reported 10 cases of slight to moderate nerve cell loss in the compact zone of the ipsilateral SN ranging from 6 months to 10 years after massive unilateral infarction of the basal ganglia. One case displayed perineuronal sprouts and paired helical filaments in the ipsilateral SN. The neuronal loss was interpreted as being mainly retrograde degeneration of the nigrostriatal fibers, the perineuronal sprouts as a reaction to partial deafferentation, and the paired helical filaments as either a retrograde or a trans-synaptic reaction.

Additionally, MCA infarction also causes Wallerian degeneration of the distal pyramidal tract. Buss et al investigated temporal changes in the Wallerian degeneration in the spinal cords of patients who died 2 days to 30 years after either cerebral infarction or traumatic spinal cord injury, and they found axonal loss, myelinolysis, and astrocytic reactions. The appearance of these pathological changes is delayed relative to the infarction, starting from the segments close to the lesion site and extending to the distal segments. For example, axonal loss and myelinolysis first appeared in the corticospinal tract of the cervical segment 2 weeks after stroke onset and then progressed to the lumbar segment at 5 weeks. Similarly, no astrocytic reaction was detected in the degenerating corticospinal tract until 4 months after injury. Moreover, activated microglia were found in the descending corticospinal tract at a delayed stage after cerebral infarction. Human leukocyte antigen -DA–positive microglia were detected in the gray matter of the spinal cord contralateral to the infarct within 2 weeks after stroke. As survival time...
progressed from 5 weeks to 4 months, the numbers of human leukocyte antigen-DA–positive microglia decreased in the gray matter but were abundant within the contralateral corticospinal tract. Although the role of these activated microglia in Wallerian degeneration was unclear, they were believed to contribute to removal of the degenerating axons.6,7

Plain CT and Conventional MRI
The neuroimaging features of secondary neurodegeneration have been summarized in the Table. The CT scan revealed atrophy of the thalamus and pyramidal tract at the chronic phase after massive cerebral infarction. Tamura et al16 first reported progressive shrinkage of the ipsilateral thalamus after MCA infarction in 15 (45.5%) of the 33 patients. In the study, the thalamic area gradually decreased starting at 3 months after stroke onset and disappeared thereafter.22 Additionally, a similar evolution of signal changes on T2-weighted and proton density-weighted images. Within 1 month, no abnormalities were found in the ipsilateral basis pedunculi or basis pontis. At 1 to 3 months, a hypointense band was evident in these areas. The low signal then evolved to be hyperintense and stabilized at 3 months after stroke onset. Over the course of 6 to 12 months, shrinkage of the ipsilateral basis pedunculi and basis pontis occurred.20,21 The temporal low signal on T2-weighted and/or proton density-weighted images may result from a transiently increased lipid–protein ratio because of myelin sheath degradation, whereas the high intensity reflected increased water content in the enlarged extracellular spaces.20

Diffusion-Weighted Imaging and Diffusion Tensor Imaging
In a case report study, a transitory diffusion-weighted imaging hyperintense lesion accompanied by a decreased apparent diffusion coefficient value was noted in the ipsilateral SN within 2 weeks after MCA infarction.22 Additionally, a similar evolution of signal change also was detected in the area of pyramidal tract: a high signal on diffusion-weighted imaging and low apparent diffusion coefficient value were evident in the first 2 weeks after stroke onset and disappeared thereafter.23,24 More importantly, recent studies reported that diffusion-weighted imaging hyperintensity or apparent diffusion coefficient map hypointensity in the pyramidal tract was correlated with poor motor outcome, suggesting that a diffusion-weighted imaging signal abnormality in the pyramidal tract is an early predictor of motor recovery after cerebral infarction.9–11

In 2 longitudinal diffusion tensor imaging studies, a significant increase in mean diffusivity was noted in the ipsilateral thalamus 1 to 6 months after MCA infarction, whereas fractional anisotropy (FA) remained unchanged.25,26 The increased mean diffusivity is probably attributable to a progressive loss of cell membranes—the most important barriers of water movement—and the lack of FA changes may be related to the absence of isolated bundles of parallel fibers within the thalamus.25 Consistently, our study using diffusion tensor imaging and proton magnetic resonance spectroscopy revealed a decrease in location of the basis pedunculi shrinkage was determined by the primary infarction site. These results suggest that secondary degeneration can be predicted by the location and extent of the primary ischemic lesions.

In contrast with CT, MRI is more sensitive to secondary degeneration after stroke. A hyperintense area was detected on T2-weighted spin-echo images within the ipsilateral thalamus in 14 (47%) of the 30 patients with embolic cerebral infarction.2 Interestingly, signal abnormality on T2-weighted images varied in different nucleus of the thalamus. A hyperintense signal was detected within the dorsomedial and pulvinar nucleus at 6 weeks after cerebral infarction, whereas a hypointense signal was revealed within the ventral nuclei a few weeks after infarction.18 Besides the thalamus, MRI also can reveal the secondary degeneration in the SN. In patients with striatal infarction, T2-weighted images revealed a hyperintense spot in the ipsilateral SN. This abnormal spot appeared after an average of 14.3 days after the stroke onset and then became less intense 3 months after onset.19 Wallerian degeneration of the pyramidal tract displays an evolution of signal changes on T2-weighted and proton density-weighted images. Within 1 month, no abnormalities were found in the ipsilateral basis pedunculi or basis pontis. At 1 to 3 months, a hypointense band was evident in these areas. The low signal then evolved to be hyperintense and stabilized at 3 months after stroke onset. Over the course of 6 to 12 months, shrinkage of the ipsilateral basis pedunculi and basis pontis occurred.20,21
N-acetylaspartate concentration, a marker for neuronal and axonal integrity and function, in the ipsilateral thalamus after subcortical infarction. Different from the thalamus, the pyramidal tract is composed of parallel fibers. Therefore, a marked reduction in FA values was found in the descending pyramidal tract distal to the primary infarction, accompanied by increased or unaltered mean diffusivity. Interestingly, decreased anisotropy was associated with motor outcome after stroke. Our prospective cohort studies further investigated the association between FA changes in the pyramidal tract above and below the primary infarcts and neurological deficits (Figure 2). The results demonstrated that FA values decreased progressively over 1 to 12 weeks in the pyramidal tract, both proximally and distally to a subcortical cerebral infarct or pontine infarct. Moreover, the percent reductions in FA value were negatively correlated with the percent changes in National Institutes of Health Stroke Scale and the Fugl-Meyer scale.

Potential Therapeutic Targets

Because secondary degeneration occurs several days or weeks after stroke onset and the therapeutic window for such lesions is not as narrow as that of the primary infarction, it is expected that the development of therapies targeting secondary degeneration would enhance brain plasticity and improve functional outcomes. In fact, secondary degeneration after MCA occlusion has been shown in experimental studies (Figure 3), and several potential therapeutic targets have been proposed.

Apoptosis

Morphological features indicative of apoptosis, such as DNA fragmentation, nuclear condensation, and apoptotic bodies, have been observed in the ipsilateral thalamus after focal cerebral infarction in rats. Terminal deoxynucleotidyltransferase-mediated dUTP biotin nick end labeling is a marker of double-strand DNA damage. After MCA occlusion, terminal deoxynucleotidyltransferase-mediated dUTP biotin nick end labeling–positive cells were evident in the ipsilateral ventrobasal thalamus. Interestingly, the terminal deoxynucleotidyltransferase-mediated dUTP biotin nick end labeling–positive cells in the thalamus displayed concurrent apoptotic and necrotic alterations under electron microscopy. Moreover, caspase-3 activity was markedly increased in the terminal deoxynucleotidyltransferase-mediated dUTP biotin nick end labeling–positive cells. Treatment with a caspase inhibitor significantly reduced the number of terminal deoxynucleotidyltransferase-mediated dUTP biotin nick end labeling–positive cells in the ipsilateral thalamus. These findings suggest that apoptosis may be involved in the secondary thalamic degeneration. In addition, the observation that antiapoptotic Bcl-2 expression was reduced in the thal-
amus and that Bcl-2 overexpression in transgenic mice prevented the neuronal loss in the thalamus further supports the possible involvement of apoptosis in secondary degeneration after cerebral infarction.32,33

Inflammatory Reaction
In humans and animals, cytokine upregulation and microglial/astrocytic reactions have been frequently detected before or concurrently with neuronal damage at remote regions after focal cerebral infarction. A recent review of inflammation in a remote area after focal brain lesion has discussed this aspect in detail.8 The inflammatory response seems to be an early event in secondary neurodegeneration. In the ipsilateral thalamus, tumor necrosis factor-α was upregulated 1 day after MCA occlusion, and the microglial/astrocytic reaction was activated after 3 days.34 In contrast, neuronal degeneration was initiated only 4 days after MCA occlusion, and it became evident after 14 days.34,35 Some evidence supports the idea that the inflammatory response may contribute to neuronal damage. Osteopontin, a secretory product of activated macrophages, was reported to be protective against secondary thalamic lesions via antiinflammatory effects.36 Additionally, astrocytic scarring in the spinal cord after cerebral infarction was believed to form an environment that is unfavorable for axonal regeneration.4 Nevertheless, the role of the inflammatory reaction in the neuronal damage at remote regions has not been fully elucidated. It remains unclear whether the inflammatory response is merely a consequence of brain lesions.

Neurotoxic and Neuroinhibitory Factors
Neurotoxic and neuroinhibitory factors also may be involved in secondary lesions after focal cerebral infarction. Retrograde and anterograde degeneration of fibers may cause excitotoxicity in remote regions, leading to neuronal death. For example, the pars reticulata of the SN receives GABAergic inhibitory projections from the striatum and glutamatergic inputs from the subthalamic nucleus.8 Striatal infarction may impair inhibitory afferents to the reticulata of the SN, leading to increased metabolism and neuronal death.35 Consistent with this presumption, treatment with MK-801 (glutamate N-methyl-d-aspartate receptor antagonist) as well as YM872 (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist) can reduce secondary degeneration in the reticulata of the SN after MCA occlusion.37,38
Amyloid-beta (A\(\beta\)), a main constituent of senile plaque in Alzheimer disease, is known to be neurotoxic. In the ipsilateral thalamus, A\(\beta\) accumulated abnormally and aggregated to plaque-like deposits for up to 9 months after MCA occlusion.\(^{39}\) We investigated the association of A\(\beta\) with secondary thalamic damage and found that administration of a functional \(\gamma\)-secretase inhibitor significantly reduced A\(\beta\) deposits and neuronal loss in the thalamus, suggesting that A\(\beta\) deposits may be associated with secondary thalamic damage.\(^{40}\)

In addition to A\(\beta\), Nogo-A, which can inhibit axonal growth, also has been shown to be upregulated within 4 weeks after MCA occlusion.\(^{41}\) The elevation of Nogo-A may be related to enhanced axonal regeneration. Treatment with a Nogo-66 receptor antagonist NEP1–40 can block the effect of Nogo-A and lead to enhanced axonal regeneration and attenuation of neuronal degeneration.\(^{41}\)

**Oxidative Damage**

Oxidative damage to nDNA not only contributes to neuronal damage in the primary infarction but also participates in the pathogenesis of secondary neurodegeneration in remote regions. After focal cerebral infarction, endogenous antioxidant defenses were activated at the remote regions. Increased immunoreactivity of manganese–superoxide dismutase and expression of damage-induced neuronal endopeptidase mRNA was observed in the ipsilateral thalamus after MCA occlusion in rats.\(^{42,43}\) Superoxide dismutases are known to effectively scavenge superoxide radicals and protect neurons from oxidative damage, and damage-induced neuronal endopeptidase can be upregulated in response to neuronal insult and activate superoxide dismutases. Therefore, the elevation of manganese–superoxide dismutase and damage-induced neuronal endopeptidase may reflect increased oxidative stress in the ipsilateral thalamus.

Our study in rats revealed enhanced expression of 8-hydroxy-2′-deoxyguanosine and decreased expression of 8-oxoguanine DNA glycosylase in the ipsilateral thalamus after MCA occlusion, indicating an imbalance between oxidative DNA damage and the base repair activity ratio.\(^{44}\) Furthermore, treatment with ebselen, an antioxidant, significantly attenuated the increased 8-hydroxy-2′-deoxyguanosine expression, ameliorated the decreased 8-oxoguanine DNA glycosylase expression, and reduced the neuronal loss in the ipsilateral thalamus.\(^{44}\)

**Macroautophagy**

Macroautophagy is a lysosomal pathway for the recycling of intracellular organelles and proteins and plays multiple roles in cell homeostasis. It has been suggested that macroautophagy can promote cell survival in chronic brain diseases and can mediate cell death in acute neurological disorders, implicating the effects of macroautophagy are context-dependent.\(^{45}\) We investigated the role of macroautophagy in the secondary thalamic degeneration after cerebral cortical infarction in rats and found that macroautophagy was activated in the ipsilateral thalamic cells.\(^{46,47}\) Furthermore, macroautophagic inhibitor and Beclin-1 knockdown significantly reduced the macroautophagic activation and neuronal loss, suggesting macroautophagy may act in cell death in secondary thalamic degeneration.\(^{46,47}\) To further understand the role of macroautophagy in secondary degeneration, it is necessary to investigate exactly how macroautophagy contributes to cell death and its relationship with other cell death pathways. Interestingly, there is cross-talk between macroautophagy and A\(\beta\) deposits. Inhibition of macroautophagy prevented the A\(\beta\) accumulation and, conversely, reduction of A\(\beta\) suppressed macroautophagy activation.\(^{46,47}\) Future studies are needed to elucidate the underlying mechanisms.

**Future Perspectives**

The findings that neuroprotective agents can reduce the secondary degeneration and associate with functional improvement in animal stroke models are appealing. However, the question we constantly face is whether these effects can be translated into the clinic. Several issues should be considered before entering into clinical trials. First, most of the experimental studies targeting secondary degeneration merely assess the histological outcomes in the remote regions. More experimental studies are needed to evaluate the functional outcomes, which are the primary measures of therapeutic efficacy in clinical trials. Second, the mechanisms involved in the development of secondary degeneration have not been fully elucidated. A better understanding of the underlying mechanisms may help to identify the appropriate therapeutic targets in clinical trials. Third, our recent study has showed that there are neurogenesis and angiogenesis within the ipsilateral thalamus after focal cerebral infarction, suggesting the regeneration is coupled with the damage.\(^{48}\) It also would be interesting and important to investigate the role of neurogenesis and angiogenesis in stroke recovery.

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**Disclosures**

None.

**References**

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단순 CT와 일반 MRI
이차 신경변성의 신경영상학적 형태를 Table에 정리했다.

CT와 MRI는 뇌졸중 이후 이차변성에 좀 더 민감하다.
액전성 뇌경색 환자 30명 중 14명(47%)에서 동측의 시상 내에 고강도음영 영역이 T2강조스캔으로 영상에서 관찰되었다. 
CT와 MRI에 의한 이차변성의 차이점은 다음과 같다.
CT의 경우 이차변성은 ICH 후 3일에서 1주일까지 수술 후 4주까지 정상적으로 보인다.
MRI의 경우 이차변성은 ICH 후 3일에서 1주일까지 수술 후 4주까지 정상적으로 보인다.

추체로의 뇌경색은 T2 강조영상과 양성자 밀도 강조 영상
에서 신호강도의 진행을 보여주다. 1개월 이내에는 동측의 기저핵이나 뇌조직의 일부 이상도 발견되지 않는다. 
뇌경색 발생 이후 1~3개월의 시점에, 다수 영역에 초강도 피사가 나타난다. 
초강도 신호는 정상 영상 및 신호로 보이지 않으며 3개월에 
정상화된다. 6~12개월의 시점에는 동측의 기저핵과 
뇌조직의 이상이 나타나기 시작한다. 

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초의 과료로 인해 일시적으로 저질-단백질이 증가하기 때문으로 생각되고, 고강도 신호는 세포의 공간이 증가함에 따라 수분 함유량이 증가하는 것을 반영하는 것으로 보인다. 20

확산작용성과 확산텐서영상

중대연구에서, 중대뇌 발생 병의 영적 뇌경색 발생 2주 이내에 일시적으로 확산작용성에서 고강도 신호를 보이고 절기 확산 계수는 감소한 영역이 동적 흐름에서 관찰되었다. 22 추가로, 추측영상에서 비슷한 신호 변화의 발전이 관찰되었는데, 뇌졸중 발생 이후 첫 2주까지 확산작용성에서는 고신호강도를 보이면서 절기 확산 계수가 감소한 상태가 나타났다. 이후 사라졌다. 23, 24 좀 더 중요한 것은, 최근의 연구에서 추체로 확산작용성 영역에서 신호가 낮아져게 되면서 절기 확산 계수 지도에서 저강도 신호를 보이는 것이 무반영의 반반 해약과 연관되어 있어, 추체로 확산작용성 신호이상이 뇌경색 이후 운동근 흉부의 초기 예측인자로 제안되고 있다. 25-27

두 개의 확산텐서영상 추적 연구에서, 중대뇌 발생 영적 뇌경색 발생 이후 1~6개월 시점에서, 동측의 시상에서 평균 확산성의 유의한 증가가 관찰되었다. 그 반면 비등방도(fractional anisotropy, FA)는 변화가 없었다. 26, 28 평균 확산성이 증가한 것은 물질과 운동에 중증약한 점을 보이는 세포막의 점진적 소실에 기인하며 FA가 변화하지 않은 것은 아마도 시상 내에 분비된 평행 유도단이 없기 때문에로 생각된다. 23 이와 일관되게, 확산텐서영상과 영상 및 자기공명 분광법을 이용한 저자들의 연구에서, 절단 뇌경색 이후 동측 시상에서 N-acetylaspartate 농도가 감소되었는데, 이는 신경핵, 세포의 활성화와 기능의 표지자이다. 22 시상과와 달리 추체로는 평행한 섬유단백로 이루어져 있다. 그러나, 일자 뇌경색의 원위부의 행성성 추체로에서 FA값의 주목할만한 감소가 나타나며, 평균 확산성은 증가하거나 변화가 없었다. 23, 28 뼈의 한계도, 이방성(anisotropy)이 감소하는 것은 뇌졸중 이후 운동기능의 예후와 연관되어 있었다. 22 저자들의 전향적 코호트 연구에서 일자 뇌경색의 위, 아래의 추체로의 FA 변화와 신경학적 손상의 연관성을 연구웠다(Figure 2). 그 결과 절단 뇌경색이나 뇌교부부의 뇌경색에서, 추체로의 근위부, 원위부 모두 1~12주에 걸쳐 FA값의 점차 감소가 있었다. 또한, FA값의 감소비율은 NIH 뇌졸증척도와 Fugl-Meyer scale의 변화비율과 역의 상관관계를 보였다. 23, 27

<table>
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<td>Plain CT</td>
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ADC indicates apparent diffusion coefficient; CT, computed tomography; DTI, diffusion-tensor imaging; DWI, diffusion-weighted imaging; FA, fractional anisotropy; MCA, middle cerebral artery; MD, mean diffusivity; MRI, magnetic resonance imaging; PDWI, proton density-weighted imaging; T2WI, T2-weighted imaging.
잠재적 치료 목표
이차변성은 뇌졸중 발생 이후 수주에 걸쳐 일어나기 때문에, 이 병변에 대한 치료 시기는 임상 뇌경색 영역에 대한 치료만큼 중요하지 않아서, 이차변성을 대상으로 한 치료방법의 개발은 아마도 뇌의 형성력(plasticity)을 증대시키고, 가능적 예후를 향상시킬 것이다. 사실, 중대뇌졸중 폐색이후의 이차변성은 실험실 연구에서 확인되었고(Figure 3), 여러 개의 치료가능 대상이 제시되어 왔다.

세포사멸(Apoptosis)
세포사멸은 시사하는 형태학적 변화, 즉 DNA 파편화, 핵응축(nuclear condensation), 세포사멸체(apoptotic bodies) 등이 백악서에서 과도적 뇌경색 이후 동측의 시상에서 관찰되었 다. Terminal deoxynucleotidyltransferase-mediated dUTP biotin nick end labeling이 이증상은 DNA 손상의 표지자이다. 중대뇌졸중 폐색 이후, terminal deoxynucleotidyltransferase-mediated dUTP nick end labeling-양성 세포가 뇌졸중의 배측기까지 시상에서 관찰되었다.30,31 홍미로운 점은, 시상에 발현된 terminal deoxynucleotidyltransferase-mediated dUTP biotin nick end labeling-양성 세포를 전자현미경으로 관찰했을 때 세포사멸, 뇌사의 변화를 함께 보인다는 것이다. 게다가 caspase-3 활성도 또한 terminal deoxynucleotidyltransferase-mediated dUTP nick end labeling-양성 세포에서 많이 증가했다. Caspase 억제제를 이용한 치료가 동축의 시상에서 terminal deoxynucleotidyltransferase-mediated dUTP biotin nick end labeling-양성 세포의 수를 감소시켰다.32 이러한 사실은 세포 사멸이 아마도 시상의 이차변성에 관여할 것이라는 것을 시사한다. 또한, antiapoptotic Bcl-2의 발현이 시상에서 감소했고, 유전자변형 생쥐 모델에서 Bcl-2의 과발현이 시상에서의 신경손실을 예방했다. 이 결과 또한 뇌경색 이후 이차변성에 세포사멸 반응이 관여할 가능성을 뒷받침한다.32,33

Figure 3. Amyloid-beta (Aβ) deposits, neuronal loss, and glial activation in the ipsilateral thalamus at 14 days after middle cerebral artery occlusion in rats. A, Aβ immunostaining (star and arrow indicate infarct and Aβ deposits, respectively). NeuN (neuronal marker; B), GFAP (astrocytic marker; C), and OX42 (microglial marker; D) immunostaining, respectively. Scale bars in (A, B) apply to (A–D), respectively.
염증성 반응

인간과 동물에서, 시토카인의 상향 조절과 미세사체소포/성상세포 반응은 국소적 뇌경색 이후 병변과 펌리지 지역에서 나타나는 신경손상과 함께 또는 신경손상 이전에 종종 확인되었다. 국소 뇌뇌증 이후 떨어지지 않는 영역에서의 염증반응에 대한 최근의 평론에서 이러한 면을 자세하게 기술하였다. 염증성 반응은 이차 신경변성에서 조기에 나타나는 것으로 보인다. 동측의 시장에서, 중대뇌동맥 폐쇄 1일 이후에 tumor necrosis factor-α가 상향조정 되었고, 3일 후에 미세사체소포/성상세포 반응이 활성화되었다. 반변에, 신경변성은 중대뇌동맥 폐쇄 4일 후에나 시작되었으며 14일이 지나서야 두려해졌다. 일부 근자들은 염증성 반응이 신경손상에 기여한 것이 라는 생각을 틀바천한다. 활성화된 대식세포의 분비물질은 osteopontin은 항염증작용을 통해서 이차적 시상 병변에 대해 보호효과를 나타내는 것으로 보고되었다. 또한, 뇌경색 이 후 척수의 성상세포흡입(astrocytic scarring)은 축삭 재생에 좋지 않은 환경을 만드는 것으로 생각되고 있다. 그럼에도 불구하고, 일차 병변과 떨어져 있는 지역에서의 신경손상에 대한 염증반응의 역할은 아직 완전히 밝혀지지 않았다. 염증반응이 단지 뇌뇌증의 결과인지 여부는 불명확하다.

신경독성, 신경계열화


산화 독성

DNA의 산화 독성은 아미노 뇌경색의 신경손상에 역할을 할 뿐 아니라, 간隙적으로 떨어져 있는 뇌영역에서의 이차 신경변성의 발생과정에도 참가한다. 국소적 뇌경색 이후, 내인성 산화 방어기제가 간隙적으로 떨어져 있는 뇌영역에서 활성화된다. 백서의 중대뇌동맥 폐쇄 이후 동측의 시상에서 manganese-superoxide dismutase의 변형반응이 증가하고 damage-induced neuronal endop tidase mRNA의 발현이 증가하는 것이 관찰되었다. Superoxide dismutases는 효과적으로 활성산소를 잡고, 산화손상으로부터 신경을 보호한다고 알려져 있으며, damage-induced neuronal endop tidase는 신경세포 손상에 반응해서 상향조절되고, superoxide dismutases를 활성화 시킨다. 그러므로, manganese-super oxide dismutase의 증가와 damage-induced neuronal endop tidases는 동측 시상의 산화 스트레스가 증가한 것을 반영한다.

백서를 이용한 저자들의 연구에서, 중대뇌동맥 폐쇄 이후 동측의 시상에서 8-hydroxy-2′-deoxyguanosine의 발현이 증진되고 8-oxoguanine DNA glycosylase의 발현이 감소했다. 이는 DNS의 산화손상과 염기 치료 활성 비율 간의 불균형을 시사한다. 또한, 항산화제인 ebselen으로 치료 했을 때, 8-hydroxy-2′-deoxyguanosine 발현 증가를 의 미있게 약화시키고, 8-oxoguanine DNA glycosylase 발현의 감소를 개선시켜, 동측 시상의 신경세포 손실을 줄렸다. 자세작용(Macroautophagy)

자세작용은 세포내기관과 단백의 재사용을 위한 유휴소체 경로로 세포 항상성유지에 많은 역할을 한다. 자세작용은 만성 뇌질환에서는 세포 생존을 촉진할 수 있고, 급성 신경학적 질환에서 세포사를 증가할 수 있어서, 어떤 경우와 따라 그 역할이 달라질 수 있다고 알려져 있다. 자세작용은 백서에서 대뇌피질의 뇌경색 이후 시상의 이차변 성에서 자세작용의 역할에 대해 연구했고, 자세작용이 동측 시상의 세포에서 활성화됨을 확인하였다. 자세작용의 억제제를 투여하거나 Beclin-1을 유전적으로 억제 시켰을 때 자세작용 활성화와 신경세포 소실을 유의하게 감소시켰고, 이는 아마도 자세작용이 시상의 이차변성에서 세포사에 역할을 할 것이라는 것을 시사한다. 이차변성에 대한 자세작용의 역할을 좀 더 이해하기 위해서는 자세작용이 어떻게
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Disclosures
None.

References


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**KEY WORDS**: cerebral infarction • secondary neurodegeneration • computed tomography • magnetic resonance imaging • thalamus • pyramidal tract