REVIEW ARTICLE

Interference of apoptosis in the pathophysiology of subarachnoid hemorrhage

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ABSTRACT

Programmed cell death is crucial for the correct development of the organism and the clearance of harmful cells like tumor cells or autoreactive immune cells. Apoptosis is initiated by the activation of cell death receptors and in most cases it is associated with the activation of the cysteine proteases, which lead to apoptotic cell death. Cells shrink, chromatin clumps and forms a large, sharply demarcated, crescent-shaped or round mass; the nucleus condenses, apoptotic bodies are formed and eventually dead cells are engulfed by a neighboring cell or cleared by phagocytosis. The authors have summarized the most important data concerning apoptosis in subarachnoid hemorrhage that have been issued in the medical literature in the last 20 years.

Key words: Apoptosis, cell death receptors, programmed cell death, subarachnoid hemorrhage

Introduction

Subarachnoid hemorrhage [Figure 1] is associated with high mortality as 14% of patients die before reaching the hospital.[1]

These deaths occur mostly as a result of the initial hemorrhage, and no effective treatment is available for brain injury after the hemorrhage.[2] For survivors, early brain injury caused by the initial hemorrhage and delayed ischemic neurologic deficits due to cerebral vasospasm [Figure 2] are major causes of the subsequent morbidity and mortality.[3]

Although cerebral vasospasm has been studied and treated using a wide array of drugs during the past several decades, the outcome is not improved by the reversal of vasospasm.[4] Early brain injury is considered a prime target for future research and may be also an important factor in preventing symptomatic vasospasm. In this respect, early brain injury may predispose the brain to ischemic injury due to vasospasm. Recent studies showed that apoptosis is involved in the pathogenesis of early brain injury after experimental subarachnoid hemorrhage (SAH) or in a clinical setting.[5,6] Therefore, it is thought that an antiapoptotic treatment can be a therapeutic candidate for early brain injury after SAH.

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Pathophysiology of Early Brain Injury

Most available information about early brain injury after SAH comes from endovascular filament perforation animal models, which show high mortality and acute metabolic changes similar to the clinical settings.[7,8]

Intracranial pressure in this model was increased to 40 mmHg immediately after SAH and then decreased to plateau (15-25 mmHg), whereas cerebral perfusion pressure was decreased to 35-40 mmHg from 70 mmHg, cerebral blood flow was decreased with 20-30% beneath the baseline after SAH induction, and then each of the values were gradually recovered.[9] Interestingly, the mortality rate was 100% when cerebral blood flow was reduced to less than 40% underneath the baseline for 60 min after SAH, while a less augmented cerebral blood flow reduction resulted in a 19% mortality.[10]

Many factors, such as global ischemia,[11] microcirculatory disturbance,[10] and subarachnoid blood toxicity[12] are involved in apoptosis-related mechanisms in early brain injury after SAH, whereas distribution of apoptotic cell death is controversial.[11,13] Although apoptotic cell death was seen in both the cortex and subcortex, neuronal cell death in the

hippocampus, which is related to global ischemia, may depend on intracranial pressure.[6,13]

Blood immediately spreads in the subarachnoid space after SAH, and then the cerebral cortex is covered with a thick blood clot. Hemoglobin is metabolized by neurons and microglia,[14] and the released iron induces apoptosis via lipid peroxidation. Thus, subarachnoid blood clotting, which has been linked to cell injury and oxidative stress,[12] may cause greater apoptotic cell death in the cerebral cortex compared with the subcortex. Apoptotic cell death has been reported to occur in neurons[12,15,16] and endothelial cells[17,18] in early brain injury after SAH. Both these situations may be correlated with brain edema.[19] In this article, we focus on neuronal cell apoptosis, which consists of the intrinsic and extrinsic pathways.[20]

Apoptosis represents the most well-characterized type of programmed cell death. Morphologically, cells typically round up, form blebs, undergo chromatin condensation and nuclear fragmentation. These morphological changes are largely the result of the activation of a set of cell-suicide cysteine proteases referred to as caspases.[21]

The biochemical activation of apoptosis occurs through two general pathways: The intrinsic pathway, which is mediated by the mitochondrial release of cytochrome C and resultant activation of caspase-9; and the extrinsic pathway, originating from the activation of cell surface death receptors such as Fas, resulting in the activation of caspase-8 or -10 (Salvesen and Dixit, 1997). A third general pathway, which is essentially a second intrinsic pathway, originates from the endoplasmic reticulum and also results in the activation of caspase-9.[22] Both extrinsic and intrinsic apoptotic pathways are synthesized in Figure 3.

Intrinsic Mechanisms of Apoptosis and SAH

Caspase-dependent pathway

The intrinsic pathway (mitochondrial pathway), which is mediated by the Bcl-2 family, begins with the increase in outer mitochondrial membrane permeability. This alteration of membrane permeability leads to the leakage of cytochrome C. Cytochrome C is translocated from mitochondria to the cytosolic compartment and interacts with apoptotic proteases, activating factor-1 and forming the apoptosome while leading to caspase-9 activation.

Caspase-9 activates caspase-3, and results in DNA damage.[23] Caspase-3 is well known as one of the effectors of apoptosis, and cleaved caspase-3 is upregulated in the hippocampus and cortex after SAH.[11, 24, 25]

Some reports showed that some protein kinases might directly interact with mitochondrial proteins in cerebral ischemia.

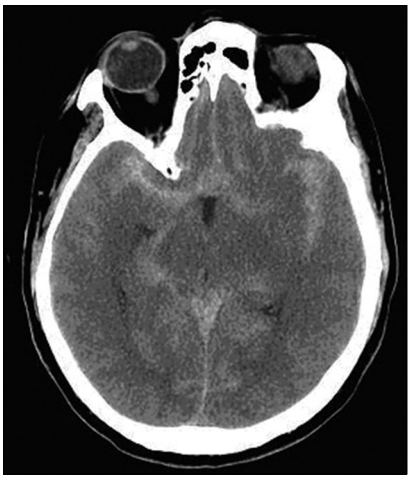

Figure 1: Subarachnoid hemorrhage (CT aspect)

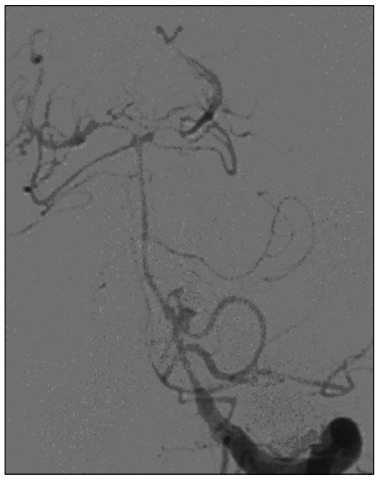

Figure 2: Cerebral vasospasm affecting the basilar artery (DSA)

Their role mainly concentrates on the phosphorylation of pro- and anti-apoptotic proteins (Bad, Bax, Bcl-2, Bcl-xL).[26] Akt (protein kinase B) and mitogen-activated protein kinase (MAPK) were the best studied in early brain injury after SAH. Akt, which is a serine/threonine kinase, is a key anti-apoptotic signaling enzyme positioned downstream of phosphoinositide 3-kinase (PI3K) in a growth factor mediated signaling cascade.

Stimulation of receptor tyrosine kinases or GTP-binding protein-coupled receptors activates Akt via PI3K. Activated Akt modulates many substrates, including Bax, Bad, glycogen synthase kinase-3, apoptosis signal-regulating kinase 1, and caspase-9, which inhibit apoptosis.[27] Akt has also been shown to promote cyclic AMP response element-binding (CREB) protein phosphorylation and lead to Bcl-2 induction.[28] A decrease in Akt activity is responsible for ischemic neuronal cell death. Last but not least, Akt activation is a principal factor in the prevention of apoptosis via the caspase-dependent pathway in cerebral ischemia.[29,30]

Some studies suggested that Akt might be involved in the

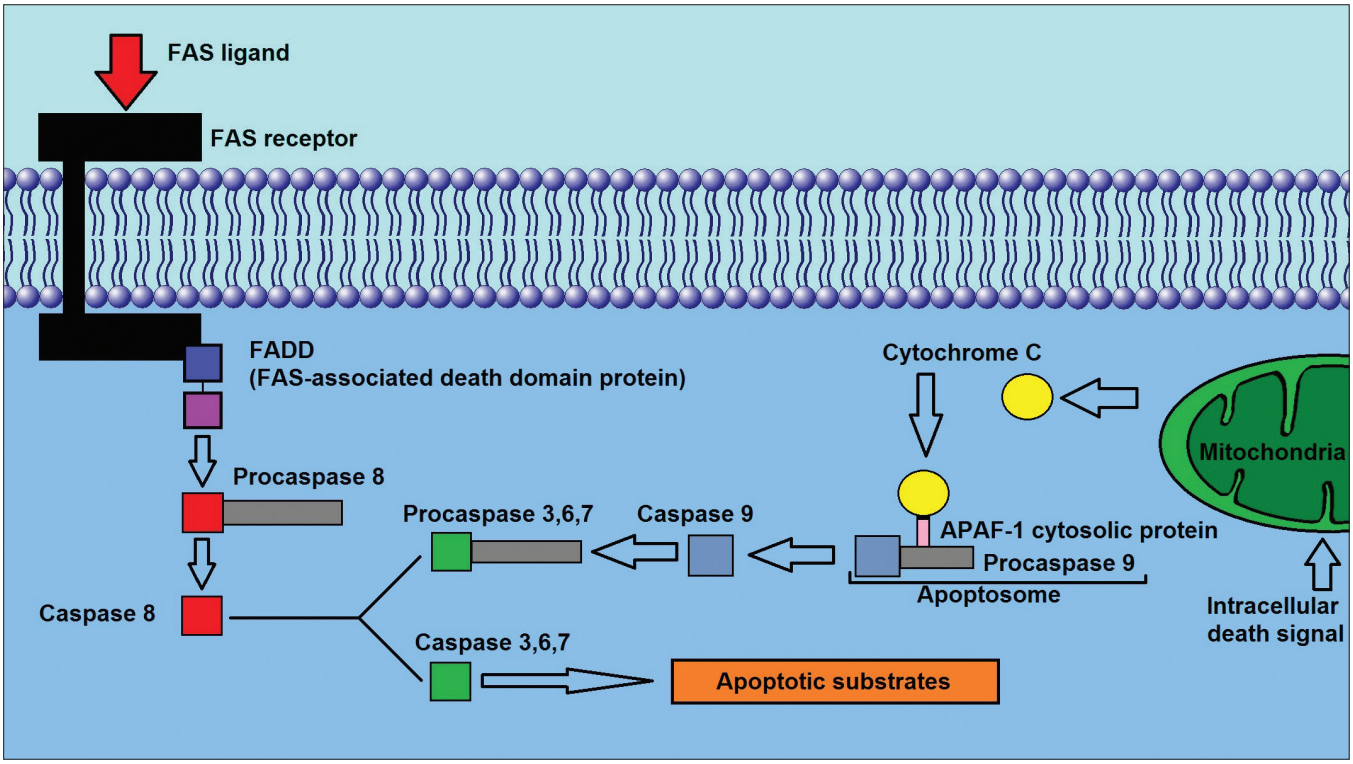

Figure 3: Extrinsic and intrinsic pathways of apoptosis

mechanism for early brain injury after SAH. This conclusion was drawn using a PI3K inhibitor, which prevented phosphorylation of Akt and increased DNA damage.[13,31] Akt activation by overexpression of copper/zinc superoxide-dismutase (SOD1), which is one of the antioxidant enzymes, attenuated early brain injury caused by SAH.[31] The timing of Akt phosphorylation after SAH depended on the damaged brain regions; Akt was rapidly phosphorylated in the cortex, but it took 24 h to phosphorylate Akt in the hippocampus.[13] Because early brain injury after SAH is the most severe in the cortex, it is suggested that Akt phosphorylation depends on the severity of brain injury.[13]

The roles of MAPKs are very important in early brain injury after SAH.[32] MAPK, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38, is involved in the apoptotic responses in cell death during cerebral ischemia.[33] These kinases are activated by various stimuli, e.g. vascular endothelial growth factor (VEGF), oxidative stress, and inflammatory cytokines.[34,35]

After SAH in a perforation model, these kinases were phosphorylated and induced brain edema, continuous high intracranial pressure, and high mortality.[32,36,37] Since ERK is activated in response to growth and differentiation factors and might be part of the survival pathway, whether activation of ERK is protective or detrimental to neurons in cerebral ischemia is controversial.[38] In contrast, JNK and p38 are activated in response to inflammatory cytokines and cellular stress, which were highly elevated in the cerebrospinal fluid and in cerebral arteries after SAH.[39,40] JNK phosphorylates c-Jun, which upregulates apoptotic cascades by inducing expression of the proapoptotic member of Bcl-2 family Hrk/DP5, Bim, and Fas.[41,42]

Phosphorylated JNK and expression of c-Jun were increased after SAH induction and c-Jun mRNA were upregulated in the rat cerebral cortex and hippocampus after SAH.[43,44] p38 activation by TNF-a and IL-1b was associated with neuronal death, and suppression of p38 activation by Bcl-2 suggested that p38 might be involved in apoptosis.[45,46]

Caspase-independent pathway

The caspase-independent component of the intrinsic pathway is carried out by the mitochondria-released apoptosis inducing factor (AIF), endonuclease G and Bcl-2/adenovirus E1B 19 kDa-interacting protein (BNIP3).[47] Apoptosis inducing factor, which is the best studied among them, is normally in the mitochondrial intermembrane space and is translocated to the nucleus by some stimulations, inducing large-scale DNA fragmentation and cell apoptosis, which is independent of caspase activity.[48] Nuclear AIF upregulation was reported in cerebral ischemia,[49] and the translocation might be triggered by poly (ADP-ribose) polymerase activity.[50] There has not been much reported about AIF expression in early brain injury after SAH and it is not clear which compartment of AIF expression increases.[24]

Oxidative stress and early brain injury

It is important to hold the balance between reactive oxygen species (ROS) and antioxidants, which control oxidative stress.

ROS such as superoxide anion, hydrogen peroxide (H_2O_2), and hydroxyl radical (OH-) are generated at low levels and play important roles in signaling pathways.[51]

Under normal conditions, they are regulated by endogenous antioxidants including SOD, glutathione peroxidase, glutathione, and catalase.[52] Overproduction of ROS and/or inactivation of antioxidants cause tissue injury from oxidative damage.[51] Oxidative stress can play important roles in the pathogenesis of early brain injury after SAH.[53] Mitochondria disruption, the production of hydroxyl radicals from extravasated hemoglobin, and disruption of the intrinsic antioxidant systems have all been reported in either experimental or human SAH.[53,54] O_2 production was observed 1 h after SAH, and overexpression of SOD1 inhibited the production and reduced apoptotic cell injury after SAH.[31] The reduction in oxidative stress by SOD1 overexpression attenuated early brain injury after SAH via activation of Akt.[31]

DNA damage

p53 is a tumor suppressor gene involved in the regulation of apoptosis.[55] Responding to cell damage, p53 upregulates pro-apoptotic molecules including Bax, p53-upregulated modulator of apoptosis, and Bid, and downregulates antiapoptotic molecules Bcl-2 and Survivin.[55] p53 is upregulated after an ischemia insult and induces mitochondrial damage and activation of caspases.[56] It was reported that in SAH, p53 is one of the key factors in neuronal cell death. p53 was upregulated both at 24 and 72 h after SAH, and p53 inhibitor decreased brain edema and neuronal cell death.[24,57,58]

Extrinsic pathway of apoptosis

The death receptors, which are located on the cell surface, are involved in the extrinsic apoptosis pathway.[30] The receptor ligands expression, including Fas and tumor necrosis factor (TNF), are upregulated after cerebral ischemia.[59,60] The death receptors can activate caspase-8 or -10, which then directly activate caspase-3 or cause Bid/Bax activation, inducing cytochrome C release.[61] Moreover, forkhead transcriptional factors were activated after cerebral ischemia and then expression of Fas ligand increased, resulting in neuronal cell death.[62]

However, little is known regarding the relationship between early brain injury and death receptors or their ligands, whereas TNF-a was upregulated after SAH.[63]

Therapeutic modalities

For evaluating neuronal apoptosis in early brain injury after SAH, neurological examination should be performed to examine the outcome of neuronal cell injury. These molecular apoptotic pathways in neurons may induce brain edema, neurological deficit, and higher mortality. Previous studies showed that apoptotic-related pathway modulation by treatment could improve the outcome in early brain injury after SAH.

Conclusions

Recent studies have demonstrated the apoptosis mechanism in cerebral ischemia, whereas relatively few have studied the relationship between apoptosis and SAH, especially in early brain injury. It would be very helpful to study the relationship between SAH and another apoptotic mechanism, including autophagy and endoplasmic reticulum stress, which may lead to novel therapies in early brain injury.

Studies regarding early brain injury after SAH are limited, and further studies are needed for the clarification of the exact mechanism. For example, MAPKs, including ERK, JNK, and p38, were reported to induce apoptosis in the brain and cerebral artery after SAH,[32] whereas it has reported that ERK phosphorylation induced a beneficial effect on cerebral vasospasm.[64]

It is suggested that elevated ERK phosphorylation blocks apoptosis by enhancing the antiapoptotic protein Bcl-2 via CREB activation in cerebral ischemia.[38] The opposite effects may depend on the localization in the brain including neurons, glia, and endothelial cells.

In conclusion, apoptosis may play an important role in early brain injury after SAH. Further studies regarding apoptosis may lead to the development of new therapies and the improvement of outcome of SAH patients.

References

1. Huang J, van Gelder JM. The probability of sudden death from rupture of intracranial aneurysms: A meta analysis. Neurosurgery 2002;51:1101-5.
2. O'Hare TH. Subarachnoid hemorrhage: A review. J Emerg Med 1987;5:135-48.
3. Tseng MY, Czosnyka M, Richards H, Pickard JD, Kirkpatrick PJ. Effects of acute treatment with pravastatin on cerebral vasospasm, autoregulation, and delayed ischemic deficits after aneurysmal subarachnoid hemorrhage: A phase II randomized placebo controlled trial. Stroke 2005;36:1627-32.
4. Schievink WI, Riedinger M, Jhutty TK, Simon P. Racial disparities in subarachnoid hemorrhage mortality: Los Angeles County, California, 1985 1998. Neuroepidemiology 2004;23:299-305.
5. Nau R, Haase S, Bunkowski S, Bruck W. Neuronal apoptosis in the dentate gyrus in humans with subarachnoid hemorrhage and cerebral hypoxia. Brain Pathol 2002;12:329-36.
6. Prunell GF, Mathiesen T, Diemer NH, Svendgaard NA. Experimental subarachnoid hemorrhage: Subarachnoid blood volume,mortality rate, neuronal death, cerebral blood flow, and perfusion pressure in three different rat models. Neurosurgery 2003;52:165-75.
7. Bederson JB, Germano IM, Guarino L. Cortical blood flow and cerebral perfusion pressure in a new noncraniotomy model of subarachnoid hemorrhage in the rat. Stroke 1995;26:1086-91.
8. Veelken JA, Laing RJ, Jakubowski J. The Sheffield model of subarachnoid hemorrhage in rats. Stroke 1995;26:1279-83.
9. To¨ro¨k E, Klopotowski M, Trabold R, Thal SC, Plesnila N, Scholler K. Mild hypothermia (33 degrees C) reduces intracranial hypertension and improves functional outcome after subarachnoid hemorrhage in rats. Neurosurgery 2009;65:352-3.
10. Bederson JB, Levy AL, Ding WH, Kahn R, DiPerna CA, Jenkins AL III, *et al*. Acute vasoconstriction after subarachnoid hemor rhage. Neurosurgery 1998;42:352-62.

11. Park S, Yamaguchi M, Zhou C, Calvert JW, Tang J, Zhang JH. Neurovascular protection reduces early brain injury after subarachnoid hemorrhage. Stroke 2004;35:2412-4.
12. Matz PG, Copin JC, Chan PH. Cell death after exposure to subarachnoid hemolysate correlates inversely with expression of CuZn superoxide dismutase. Stroke 2000;31:2450-1.
13. Endo H, Nito C, Kamada H, Yu F, Chan PH. Akt/GSK3beta survival signaling is involved in acute brain injury after subarachnoid hemorrhage in rats. Stroke 2006;37:2140-2.
14. Xi G, Keep RF, Hoff JT. Erythrocytes and delayed brain edema formation following intracerebral hemorrhage in rats. J Neurosurg 1998;89:991-6.
15. Matz PG, Fujimura M, Chan PH. Subarachnoid hemolysate produces DNA fragmentation in a pattern similar to apoptosis in mouse brain. Brain Res 2000;858:312-4.
16. Matz PG, Fujimura M, Lewen A, Morita Fujimura Y, Chan PH. Increased cytochrome c mediated DNA fragmentation and cell death in manganese superoxide dismutase deficient mice after exposure to subarachnoid hemolysate. Stroke 2001;32:506-15.
17. Kimura H, Gules I, Meguro T, Zhang JH. Cytotoxicity of cytokines in cerebral microvascular endothelial cell. Brain Res 2003;990:148-56.
18. Ogihara K, Zubkov AY, Bernanke DH, Lewis AI, Parent AD, Zhang JH. Oxyhemoglobin induced apoptosis in cultured endothelial cells. J Neurosurg 1999;91:459-65.
19. Baza´n NG, Rodrı´guez de Turco EB. Membrane lipids in the pathogenesis of brain edema: Phospholipids and arachidonic acid, the earliest membrane components changed at the onset of ischemia. Adv Neurol 1980;28:197-205.
20. Gules I, Satoh M, Nanda A, Zhang JH. Apoptosis, blood brain barrier, and subarachnoid hemorrhage. Acta Neurochir Suppl 2003;86:483-7.
21. Thornberry NA, Lazebnik Y. Caspases: Enemies within. Science 1998;281:1312-6.
22. Morishima N, Nakanishi K, Takenouchi H, Shibata T, Yasuhiko Y. An endoplasmic reticulum stress-specific caspase cascade in apoptosis. Cytochrome c-independent activation of caspase-9 by caspase-12. J Biol Chem 2002;277:34287-94.
23. Chan PH. Mitochondria and neuronal death/survival signaling pathways in cerebral ischemia. Neurochem Res 2004;29:1943-9.
24. Cheng G, Wei L, Zhi Dan S, Shi Guang Z, Xiang Zhen L. Atorvastatin ameliorates cerebral vasospasm and early brain injury after subarachnoid hemorrhage and inhibits caspase dependent apoptosis pathway. BMC Neurosci 2009;10:1186-9.
25. Yan J, Chen C, Hu Q, Yang X, Lei J, Yang L, *et al*. The role of p53 in brain edema after 24 h of experimental subarachnoid hemorrhage in a rat model. Exp Neurol 2008;214:37-46.
26. Zhang F, Yin W, Chen J. Apoptosis in cerebral ischemia: Executional and regulatory signaling mechanisms. Neurol Res 2004;26:835-45.
27. Hemmings BA. Akt signaling: Linking membrane events to life and death decisions. Science 1997;275:628-30.
28. Pugazhenthi S, Nesterova A, Sable C, Heidenreich KA, Boxer LM, Heasley LE, *et al*. Akt/protein kinase B up regulates Bcl 2 expression through cAMP response element binding protein. J BiolChem 2000;275:10761-6.
29. Hasegawa Y, Hamada J, Morioka M, Yano S, Kawano T, Kai Y, *et al*. Neuroprotective effect of postischemic administration of sodium orthovanadate in rats with transient middle cerebral artery occlusion. J Cereb Blood Flow Metab 2003;23:1040-51.
30. Shioda N, Ishigami T, Han F, Moriguchi S, Shibuya M, Iwabuchi Y, *et al*. Activation of phosphatidylinositol 3 kinase/protein kinase B pathway by a vanadyl compound mediates its neuroprotective effect in mouse brain ischemia. Neuroscience 2007;148:221-9.
31. Endo H, Nito C, Kamada H, Yu F, Chan PH. Reduction in oxidative stress by superoxide dismutase overexpression attenuates acute brain injury after subarachnoid hemorrhage via activation of Akt/glycogen synthase kinase 3beta survival signaling. J Cereb Blood Flow Metab 2007;27:975-82.
32. Kusaka G, Ishikawa M, Nanda A, Granger DN, Zhang JH. Signaling pathways for early brain injury after subarachnoid hemorrhage. J Cereb Blood Flow Metab 2004;24:916-25.
33. Irving EA, Bamford M. Role of mitogen and stress activated kinases in ischemic injury. J Cereb Blood Flow Metab 2002;22:631-47.
34. Chakraborti S, Chakraborti T. Oxidant mediated activation of mitogen activated protein kinases and nuclear transcription factors in the cardiovascular system: A brief overview. Cell Signal 1988;10:675-83.
35. Sugden PH, Clerk A. ''Stress responsive'' mitogen activated protein kinases (c Jun N terminal kinases and p38 mitogen activated protein kinases) in the myocardium. Circ Res 1998;83:345-52.
36. Sozen T, Tsuchiyama R, Hasegawa Y, Suzuki H, Jadhav V, Nishizawa S, *et al*. Role of interleukin 1beta in early brain injury after subarachnoid hemorrhage in mice. Stroke 2009;40:2519-25.
37. Yatsushige H, Ostrowski RP, Tsubokawa T, Colohan A, Zhang JH. Role of c Jun N terminal kinase in early brain injury after subarachnoid hemorrhage. J Neurosci Res 2007;85:1436-48.
38. Sawe N, Steinberg G, Zhao H. Dual roles of theMAPK/ERK1/2 cell signaling pathway after stroke. J Neurosci Res 2008;86:1659-69.
39. Fassbender K, Hodapp B, Rossol S, Bertsch T, Schmeck J, Schu¨tt S, *et al*. Inflammatory cytokines in subarachnoid haemorrhage: Association with abnormal blood flow velocities in basal cerebral arteries. J Neurol Neurosurg Psychiatry 2001;70:534-7.
40. Hirashima Y, Nakamura S, Endo S, Kuwayama N, Naruse Y, Takaku A. Elevation of platelet activating factor, inflammatory cytokines, and coagulation factors in the internal jugular vein of patients with subarachnoid hemorrhage. Neurochem Res 1997;22:1249-55.
41. Kuan CY, Whitmarsh AJ, Yang DD, Liao G, Schloemer AJ, Dong C, *et al*. A critical role of neural specific JNK3 for ischemic apoptosis. Proc Natl Acad Sci USA 2003;100:15184-9.
42. Yuan J, Yankner BA. Apoptosis in the nervous system. Nature 2000;407:802-9.
43. Harada S, Kamiya K, Masago A, Iwata A, Yamada K. Subarachnoid hemorrhage induces c fos, c jun and hsp70 mRNA expression in rat brain. Neuroreport 1997;8:3399-404.
44. Kawamura Y, Yamada K, Masago A, Katano H, Matsumoto T, Mase M. Hypothermia modulates induction of hsp70 and c jun mRNA in the rat brain after subarachnoid hemorrhage. J Neurotrauma 2000; 17:243- 50.
45. Cheng A, Chan SL, Milhavet O, Wang S, Mattson MP. p38 MAP kinase mediates nitric oxide induced apoptosis of neural progenitor cells. J Biol Chem 2001;276:43320-7.
46. Nito C, Kamada H, Endo H, Niizuma K, Myer DJ, Chan PH. Role of the p38 mitogen activated protein kinase/cytosolic phospholi pase A2 signaling pathway in blood brain barrier disruption after focal cerebral ischemia and reperfusion. J Cereb Blood Flow Metab 2008; 28:1686- 96.
47. Elmore S. Apoptosis:A review of programmed cell death. Toxicol Pathol 2007;35:495-516.
48. Cho BB, Toledo Pereyra LH. Caspase independent programmed cell death following ischemic stroke. J Invest Surg 2008;21:141-7.
49. Li X, Nemoto M, Xu Z, Yu SW, Shimoji M, Andrabi SA, *et al*. Influence of duration of focal cerebral ischemia and neuronal nitric oxide synthase on translocation of apoptosis inducing factor to the nucleus. Neuroscience 2007;144:56-65.
50. Yu SW, Wang H, Poitras MF, Coombs C, Bowers WJ, Federoff HJ, *et al*. Mediation of poly(ADP ribose) polymerase 1 dependent cell death by apoptosis inducing factor. Science 2002;297:200-1.
51. Loh KP, Huang SH, De Silva R, Tan BK, Zhu YZ. Oxidative stress: Apoptosis in neuronal injury. Curr Alzheimer Res 2006;3:327-37.
52. Sugawara T, Chan PH. Reactive oxygen radicals and pathogenesis of neuronal death after cerebral ischemia. Antioxid Redox Signal 2003;5:597-607.
53. Ayer RE, Zhang JH. Oxidative stress in subarachnoid haemorrhage: Significance in acute brain injury and vasospasm. Acta Neurochir Suppl 2008;104:33-41.
54. Kaynar MY, Tanriverdi T, Kemerdere R, Atukeren P, Gumustas K. Cerebrospinal fluid superoxide dismutase and serum malondialdehyde levels in patients with aneurysmal subarachnoid hemorrhage: Preliminary results. Neurol Res 2005;27:562-7.
55. Fridman JS, Lowe SW. Control of apoptosis by p53. Oncogene 2003;22:9030-40.
56. Culmsee C, Mattson MP. p53 in neuronal apoptosis. Biochem Biophys Res Commun 2005;331:761-77.

57. Cahill J, Calvert JW, Marcantonio S, Zhang JH. p53 may play an orchestrating role in apoptotic cell death after experimental subarachnoid hemorrhage. Neurosurgery 2007;60:531-45.
58. Gao C, Liu X, Liu W, Shi H, Zhao Z, Chen H, *et al*. Antiapoptotic and neuroprotective effects of Tetramethylpyrazine following subarachnoid hemorrhage in rats. Auton Neurosci 2008;141:22-30.
59. Martin Villalba A, Herr I, Jeremias I, Hahne M, Brandt R, Vogel J, *et al*. CD95 ligand (Fas L/APO 1L) and tumor necrosis factor related apoptosis inducing ligand mediate ischemia induced apoptosis in neurons. J Neurosci 1999;19:3809-17.
60. Rosenbaum DM, Gupta G, D'Amore J, Singh M, Weidenheim K, Zhang H, *et al*. Fas (CD95/APO 1) plays a role in the pathophysiology of focal cerebral ischemia. J Neurosci Res 2000;61:686-92.
61. Yuan J, Horvitz HR. A first insight into the molecular mechanisms of apoptosis. Cell 2004;116:53-6.
62. Kawano T, Morioka M, Yano S, Hamada J, Ushio Y, Miyamoto E, *et al*. Decreased akt activity is associated with activation of forkhead transcription factor after transient forebrain ischemia in gerbil hippocampus. J Cereb Blood Flow Metab 2002;22:926-34.
63. Ma CX, Yin WN, Cai BW, He M, Wu J, Wang JY, *et al*. Activation of TLR4/NF kappaB signaling pathway in early brain injury after subarachnoid hemorrhage. Neurol Res 2008:10:1179-82.
64. Lin CL, Dumont AS, Tsai YJ, Huang JH, Chang KP, Kwan AL, *et al*. 17beta estradiol activates adenosine A(2a) receptor after subarachnoid hemorrhage. J Surg Res 2009;10:3171-2.

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