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THE ROLE OF APOPTOSIS IN THE EARLY BRAIN INJURY AFTER SUBARACHNOID HEMORRHAGE

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Резюме. *Данная работа направлена на установление взаимосвязи между процессами, происходящими в период ранней травмы мозга после субарахноидального кровоизлияния, и явлением апоптоза как запрограммированной гибели клеток в соответствующих условиях. В работе предприняты попытки прогнозирования влияния одного процесса на другой, а также оценка осведомлённости студентов в данной теме.*

Ключевые слова: *апоптоз, субарахноидальное кровоизлияние, травма мозга.*

Resume. *This work aims to establish the relationship between processes during early brain injury after subarachnoid hemorrhage and the phenomenon of apoptosis as programmed cell death in the appropriate conditions. We tried to predict the effects of one process to another, as well as to evaluate the understanding of this problem among students.*

Keywords: *apoptosis, subarachnoid hemorrhage, brain trauma.*

Topicality: Apoptosis is essential for correct development of the human organism. Programmed cell death is initiated by the activation of specific receptors and in most cases it is associated with the activation of cysteine proteases. In this way molecular apoptotic pathways in neurons may induce brain edema, neurological deficit, and higher mortality rate. In general, apoptosis may play an important role in early brain injury after subarachnoid hemorrhage (SAH) and it is thought that an antiapoptotic treatment can be a nice therapeutic candidate which may lead to the improvement of outcome for these patients.

Objective: to describe and analyze the interrelationships between apoptosis and the condition of early brain injury caused by subarachnoid hemorrhage.

Tasks:

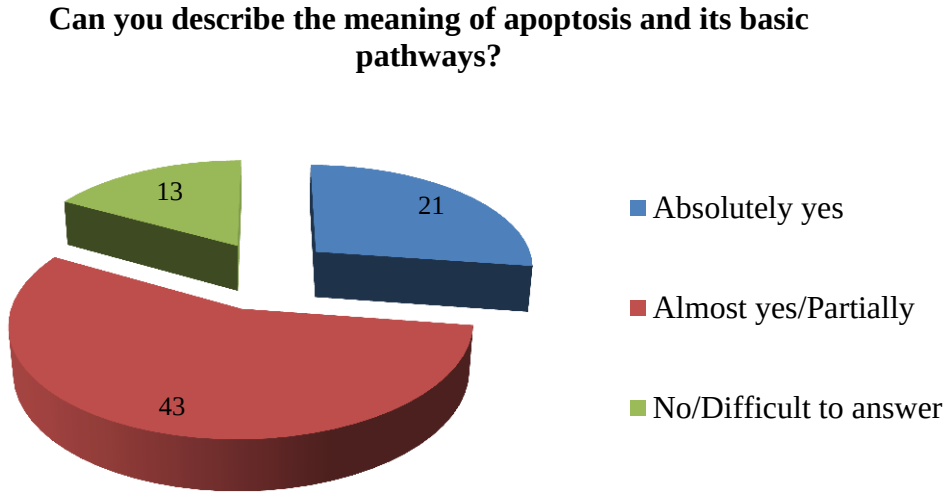
1. To conduct a social survey
2. To analyze the topical literature

Material and methods. The analysis of the topical literature for the last 9 years; a topical social survey among 77 4-6-year BSMU students (7 students from each faculty; 2 students – 4^{th} course, 2 students – 5^{th} course, 3 students – 6^{th} course).

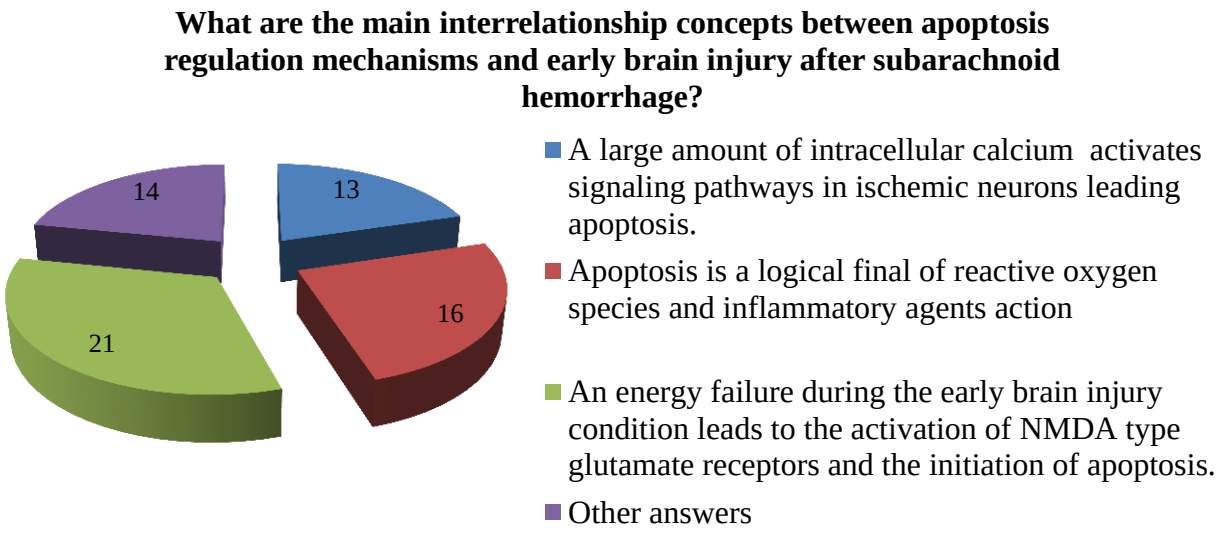
Results and discussion. The social survey was conducted among BSMU students in order to establish the current awareness and understanding of the interrelationships between early brain injury after subarachnoid hemorrhage and apoptosis. For this, they were asked three questions: one on general knowledge of the subject of apoptosis, the second on the in-depth knowledge of the apoptosis regulation, the third question was to make them free to predict the possible development of the situation in the field of antiapoptosis treatment. The following questions were asked:

1. Can you describe the meaning of apoptosis and its basic pathways?
2. What are the main interrelationship concepts between apoptosis regulation mechanisms and early brain injury after subarachnoid hemorrhage?
3. What is the best way of antiapoptotic treatment of early brain injury after subarachnoid hemorrhage you can offer?

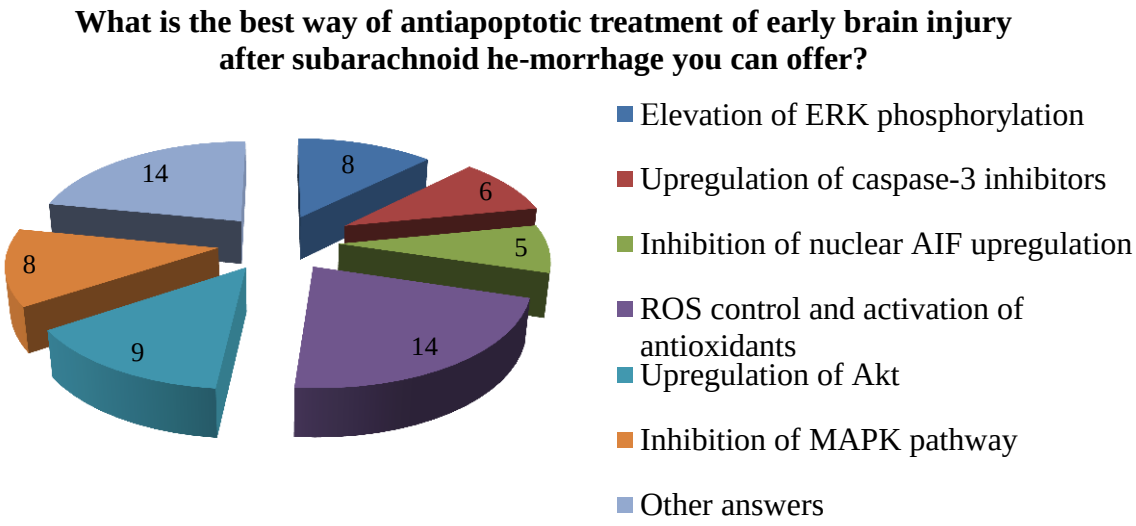
The results of this survey are presented in the form of diagrams (pictures 1, 2, 3).



Picture №1 – Results of the social survey (question 1).



Picture №2 – Results of the social survey (question 2) (64 participants, who answered «Absolutely yes» and «Almost yes» on the 1st question)



Picture №3 – Results of the social survey (question 3)

After this we turned to the scientific literature and medical journals (2007-2015) to understand the results of the survey and achieve the original goal.

Subarachnoid hemorrhage (SAH) is one of the types of intracerebral hemorrhage and denotes the presence of blood within the subarachnoid space between the pial and arachnoid membranes. It occurs in situations like head trauma, rupture of the cerebral aneurysm etc. SAH has a high mortality rate because 14% of patients die before reaching the hospital. These deaths occur mostly due to initial hemorrhage. For survivors, early brain injury caused by the initial hemorrhage and delayed ischemic neurologic deficits due to vasospasm are major causes of the subsequent mortality.

Although cerebral vasospasm after initial hemorrhage has been treated using a wide array of drugs, the outcome is not improved by the reversal of vasospasm. In this respect, early brain injury is considered a prime target for future research may predispose the brain to ischemic injury due to vasospasm. Recent studies show that exactly apoptosis is involved in the pathogenesis of early brain injury.

Early brain injury results from the action of multiple pathogenic factors. The ischemic cascade is triggered by a sudden and severe reduction in cerebral blood flow. Ischemic neurons release large amounts of the neurotransmitter glutamate that activates glutamate receptors, especially the NMDA type. It leads to an increase in intracellular calcium, which activates signaling pathways responsible for cellular and molecular events leading apoptosis.

Many factors are involved in apoptosis in early brain injury after SAH, whereas distribution of apoptotic cell death is controversial. Although apoptotic cell death was seen in both the cortex and subcortex, neuronal cell death in the hippocampus may depend on intracranial pressure.

Blood spreads in the subarachnoid space and cover the cerebral cortex with a thick

blood clot. The iron from metabolized hemoglobin induces apoptosis via lipid peroxidation. Thus, SAH blood clotting may cause greater apoptotic cell death in the cortex compared with the subcortex.

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.

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. 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.

The intrinsic pathway, which is mediated by the Bcl-2 family, begins with the increase in outer mitochondrial membrane permeability. This leads to the leakage of cytochrome C which 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. 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.

Some protein kinases might directly interact with mitochondrial proteins in cerebral ischemia. Their role mainly concentrates on the phosphorylation of pro- and anti-apoptotic proteins. Akt and mitogen-activated protein kinase (MAPK) were the best studied in early brain injury after SAH.

Akt is a key antiapoptotic signal. Activated Akt modulates Bax, Bad, glycogen synthase kinase-3, apoptosis signal-regulating kinase 1, and caspase-9, which inhibit apoptosis. Akt activation is a principal factor in the prevention of apoptosis via the caspase-dependent pathway. Preventing the phosphorylation of Akt increases DNA damage. Akt activation by overexpression of superoxide-dismutase in turn attenuated early brain injury caused by SAH.

MAPK, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38, is involved in the apoptotic responses. They induce brain edema, continuous high intracranial pressure, and high mortality. ERK is activated in response to growth and differentiation factors and might be part of the survival pathway. In contrast, JNK and p38 are activated in response to inflammatory cytokines and cellular stress. JNK upregulates apoptotic cascades by inducing expression of the proapoptotic member of Bcl-2 family; it increases after SAH induction.

The caspase-independent pathway is carried out by the mitochondria-released apoptosis inducing factor (AIF), endonuclease G and Bcl-2/adenovirus E1B 19 kDa-interacting protein (BNIP3). AIF, which is the best studied among them, is normally in the

mitochondrial intermembrane space and is translocated to the nucleus caspase-independently by some stimulations (large-scale DNA fragmentation, apoptosis). Nuclear AIF upregulation was reported in cerebral ischemia but there has not been much reported about AIF expression in early brain injury and it is not clear which compartment of AIF expression increases.

The death receptors, which are located on the cell surface, are involved in the extrinsic apoptosis pathway. The receptor ligands expression, including Fas and tumor necrosis factor (TNF), are upregulated after cerebral ischemia. The death receptors can activate caspase-8 or -10, which then directly activate caspase-3 or cause Bid/Bax activation, inducing cytochrome C release. Moreover, forkhead transcriptional factors can be activated too after cerebral ischemia and then increase the expression of Fas ligand. Little is known regarding the relationship between early brain injury and death receptors or their ligands, whereas TNF-a was upregulated after SAH.

Conclusions:

1. The social survey shows that 17% of students can't give the correct response about the nature of apoptosis. The opinion of remaining people regarding questions 2 and 3 about regulation mechanisms and antiapoptotic therapy was divided about equally with a small proportion of the original single responses denoted as "Other answers". This implies (together with theoretical information) either the possibility of any of these answers to be correct or the possibility of multiple correct answers or even the stages of one process.
2. 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.
3. 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, whereas it has reported that ERK phosphorylation induced a beneficial effect on cerebral vasospasm. It is suggested that elevated ERK phosphorylation blocks apoptosis by enhancing the antiapoptotic protein Bcl-2 via CREB activation in cerebral ischemia.

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.

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