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Contribution of tumor necrosis factor alpha to the pathogenesis of stroke

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Tumor necrosis factor alpha (TNF-alpha) is a protein of a cellular origin belonging to a group of proinflammatory cytokines. A rapid overproduction of TNF-alpha in a cerebral post-ischemic inflammatory response leads to the stimulation of adhesive molecules expression with subsequent accumulation of leukocytes in the ischemic focus, which is preceded by their adhesion and migration. The TNF-alpha proinflammatory activity results mainly in extending the area of the brain infarct, which brings about negative clinical implications. Being the final morphological effect of ischemic stroke, TNF-alpha appears also to contribute to neuronal necrosis by its involvement in the process of apoptosis as well as in the death of neurons. The present study describes and discusses mainly the contribution of TNF-alpha to the formation of ischemic focus in the brain.

key words: tumor necrosis factor alpha (TNF-alpha), proinflammatory cytokines, stroke

INTRODUCTION

The key phenomenon contributing to the ischemic stroke is endothelial transformation altering hemostatic and immunologic balance towards the prothrombotic and proinflammatory state [46]. The advance of inflammatory response induced by cerebral ischemia and reperfusion leads to leukocyte migration to the ischemic focus of the brain with a subsequent leukocyte accumulation. This, in turn, exacerbates cerebral damage by microvessel occlusion, vasomotor reactivity impairment, oxygen free radical formation, the release of both cytotoxic enzymes and cytokines and chemokines [10]. Recent research in cerebral ischemia on animal models and initial studies on humans indicate a significant contribution of cytokines — mainly proinflammatory ones — to the sequence of inflammatory response which influences the morphology of cerebral damage [15,26,34].

Cytokines are pleiotropic transmitters of cellular origin that may affect target cells or cause an autocrine effect during intercellular communication. Cytokines are free glycoproteins deprived of immunoglobulin properties that act in a non-enzymatic manner and whose activity is modulated by specific receptors found on the cell surfaces [1,7]. In the intact brain there is a very small amount of cytokines. However, those cytokines, which may be synthesized after damage to cerebral structures and also those ones that co-operate with other inflammatory agents, are called proinflammatory cytokines. The above-mentioned damage may be due to multietiological factors such as cerebrovascular diseases, severe cerebrocranial traumas, or inflammation [26,34,47,48,60].

The group of proinflammatory cytokines is represented mainly by tumor necrosis factor alpha (TNF-alpha) as well as by interleukin-1 beta (IL-1 beta), interleukin-6 (IL-6), interleukin-8 (IL-8) and by interferon-gamma [44,57,58,64].

In humans the gene for TNF-alpha is situated in a short branch of the 6th chromosome within the genes of the main tissue compatibility system. TNF-

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alpha precursor appears on a mother cell surface as transmembrane protein that is released to the environment due to proteinase activity. Biologically active TNF-alpha occurs in the form of non-covalently connected trimmers [20].

So far, the best-known pathophysiological effect of TNF-alpha activity is cytotoxicity. Such result is achieved due to TNF-alpha causing haemorrhagic necrosis of some neoplastic cell lines by apoptosis, i.e. programmed cell death, possibly by activating endogenic nucleases [49,50]. TNF-alpha is a cytokine produced mainly by macrophages, monocytes, T and B lymphocytes, neutrophils, mast cells and keratinocytes [31].

EARLY TNF-ALPHA EXPRESSION IN CEREBRAL ISCHEMIA

Recent research carried on animal models and human material collected at autopsy allowed TNF-alpha identification in the ischemic brain in microglial, astroglial and ependymal cells, in macrophages, and in neurons both in ischemic focus and penumbric region [21,37,60,61,67].

Brain ischemia induces a very rapid and dramatic increase in TNF-alpha synthesis, which is reflected by the following data: Buttini et al. [8] showed mRNA TNF-alpha expression in the ischemic region within 0.5 h after onset of a focal ischemia; Feuerstein et al. [15], Liu et al. [37] and Wang et al. [64] noticed mRNA TNF-alpha expression with a slight delay, i.e. within 1 h; moreover, Uno et al. [63] reported TNF-alpha expression in the brain at 1.5 hrs, and Gong et al. [21] — 3 hrs following focal ischemia.

The period of sustained TNF-alpha expression in the ischemic brain is 24 hrs by Gong et al. [21] with its maximum between 6 and 12 hrs. Buttini et al. [8] and Feuerstein et al. [15] reported TNF-alpha mRNA expression during 1–2 days following focal cerebral ischemia. Wang et al. [64] showed increased TNF-alpha mRNA expression for up to 2 days. However, Liu et al. [37] noticed TNF-alpha mRNA overexpression significantly longer, i.e. until the 5th day following focal brain ischemia.

The above studies performed on experimental animal models prove the occurrence of an increased TNF-alpha expression as early as in the first few hours of brain ischemia and determine the duration of this phenomenon for one to a few days. The difference in the duration observed by different authors may be due to the pleiotropism of this cytokine the property of which may also be responsible for various results obtained in vitro and in vivo as well as in clinical studies.

Both Fassbender et al. [13] and Elneihoum et al. [12] studying the levels of inflammatory mediators in serum of patients with ischemic stroke did not show statistically relevant TNF-alpha concentration increase between the 4th hour and the 7th day of the disease. Ferrarese et al. [14] reported a high and statistically relevantly increased TNF-alpha release from stimulated blood cells between the 1st–2nd and the 90th day after the stroke. They concluded that cerebral ischemia induces a prolonged activation of TNF-alpha production in blood cells of peripheral blood in humans. Tarkowski et al. [58] studying cytokine levels in cerebrospinal fluid in patients with stroke observed increased TNF-alpha concentrations only in cases of ischemic damage located in white matter of the brain. Recently we have studied TNF-alpha levels in cerebrospinal fluid and serum in 30 patients with stroke within 24 hours after the onset of neurological signs. All studied patients suffered first incidence of the stroke in their lives and brain infarct affected only white matter. The findings revealed statistically relevant higher TNF-alpha concentrations in cerebrospinal fluid and serum in stroke patients in comparison to the control group. The data of our study suggest the overproduction of TNF-alpha during the first twenty-four hours of stroke [69].

THE INVOLVEMENT OF TNF-ALPHA IN STROKE PATHOPHYSIOLOGIC MECHANISM

Contribution of TNF-alpha to ischemic stroke is basically derived from its proinflammatory activity that is manifested mainly by induction of upregulation of the mRNA expression such adhesion molecules as intercellular adhesion molecule-1 (ICAM-1), endothelial-leukocyte adhesion molecule-1 (ELAM-1) and E-selectin [28,30,32,53,65]. This phenomenon is an integral part of inflammatory reaction in the post-ischemic brain as adhesive molecules are responsible for adhesion and migration of leukocytes to ischemic areas [32,65,70]. Infiltration of leukocytes to ischemic focus is a key morphological element of an intracerebral inflammatory reaction induced by a vasogenic process. Such a reaction consists of cellular presentation (neutrophils followed by monocytes) that is preceded by mediator activity, where proinflammatory cytokines, chemokines and adhesive molecules — including integrins — are particularly active [16,19,33].

Another phenomenon fundamental to the cerebral ischemic process is damage to the blood-brain

barrier. TNF-alpha, being a hydrophilic peptide, is unable to cross the blood-brain barrier without bonding to a membrane receptor. Nevertheless, TNF-alpha is able to damage the barrier and its expression detected in the ischemic brain is suggestive of both its intrathecal synthesis in the central nervous system and pathogenic contribution of haematogenic TNF-alpha [18,21,51,67]. Previously mentioned ICAM-1 activation induced by TNF-alpha on the surface of cerebral vessels endothelial cells shows its significant role in adhesion crucial for crossing the blood-brain barrier [30]. In the ischemic brain TNF-alpha has been found both in the astrocyte end-feet and in ependymal cells which suggests the involvement of this cytokine in the blood-brain barrier damage mechanism [21]. Moreover, TNF-alpha expression following cerebral ischemia precedes increased blood-brain barrier permeability [67]. Uno's et al. [63] observation concerning pathophysiological changes sequence in cerebral ischemia seems to be of significance here. This author — like many other researchers [8,60,61] — was observing TNF-alpha expression in microglial cells. Nevertheless, he emphasizes the subsequent TNF-alpha presence in astroglia that implies a two-stage TNF-alpha expression as well as likelihood of cytokine network activation in the post-ischemic brain. This activation is caused by an early TNF-alpha production in microglia and leads to TNF-alpha synthesis by astrocytes.

Research has also shown TNF-alpha expression of the ischemic brain in macrophages at different states of activation [8,15,60]. These data correlate with Hallenbeck's et al. [25] reporting an increase in TNF-alpha synthesis as a result of exogenic lipopolysaccharide administration known to be a very strong macrophageal stimulator. Moreover, Chlamydial and human heat shock protein 60 (HSP 60) induce TNF-alpha production by macrophages and in this way may promote atherogenesis [35].

Moreover, TNF-alpha increases capillary permeability, activates endothelium and produces a significant neutrophil adherence and accumulation in capillaries and small blood vessels. Also, early expression of TNF-alpha in ischemic neurons precedes leukocyte infiltration to the ischemic area and appears to facilitate the influx of inflammatory cells [37]. TNF-alpha causes local microvascular injury in the form of pericapillary edema and leukocyte adhesion to cerebral capillaries [17]. Last of all, TNF-alpha exacerbates ischemic brain injury and increases infarct size by several mechanisms, including thrombus formation, release of endothelin-1 and nitric oxide — the potent vasoactive agents, promotion of leukocyte adhesion and infiltration, blood-brain barrier breakdown and tissue swelling [3,15,17,37,38].

THE RELATIONSHIP BETWEEN TNF-ALPHA AND CHEMOKINES IN STROKE

Regarding the pathogenesis of the ischemic brain damage, the TNF-alpha and chemokines relations are of special value.

Chemokines are a superfamily of inflammatory cytokines and they have been shown to chemoattract and activate different leukocyte populations [68].

TNF-alpha stimulates release of three best-known beta chemokines — which can play a significant role in inflammatory processes within the brain — i.e. macrophage inflammatory protein-1 alpha (MIP-1 alpha), macrophage inflammatory protein-1 beta (MIP-1 beta) and monocyte chemotactic protein-1 (MCP-1) from human foetal microglial cell and astrocyte cultures [45]. Macrophage inflammatory protein-1 (MIP-1) is implicated in the inflammatory reaction of the brain in response to ischemia [22]. MIP-1 alpha mRNA was induced by middle cerebral artery occlusion with the peak of expression at 4–6 hrs after the onset of occlusion, and the signals of MIP-1 alpha mRNA were observed in the ischemic core and in the penumbra in microglia/macrophages of the rat brain after focal cerebral ischemia [56]. Here, it may be worth adding that anti-tumor necrosis factor alpha antibody prevented MCP-1 release [11].

Astrocytes constitute a part of the blood-brain barrier. Chemokine expression by astrocytes may contribute to leukocyte infiltration within the central nervous system during inflammation. TNF-alpha induces mRNAs expression of such beta chemokines as MCP-1 and MIP-1 beta in rat astrocytes. Transforming growth factor-beta 1 (TGF-beta 1) and interleukin-10 (IL-10) down-regulate MCP-1 mRNA expression induced by TNF-alpha. On the other hand IL-10, but not TGF-beta 1, inhibits MIP-1 beta mRNA expression induced by TNF-alpha. The results of this in vitro study suggest that TNF-alpha as a proinflammatory cytokine can induce these astrocyte-derived beta-family chemokine mRNAs expressions, whereas regulatory cytokines, such as TGF-beta 1 and IL-10 down-regulate them [23].

THE ROLE OF THE LOCALIZED SHWARTZMAN PHENOMENON IN THE DEVELOPMENT OF STROKE IN RELATION TO TNF-ALPHA

Hallenbeck [27] and Siren et al. [54,55] have been interested in the potential relationship between the localized Shwartzman phenomenon and acute stroke. The essence of this phenomenon is that vessel segments exposed to TNF-alpha and interleukin-1 (IL-1) [40] become activated and prepared in such a way that the occurrence of an additional provocative step causes local thrombosis. The provocative step involves activation of the coagulation system or inflammation with activation of a complement [41]. Most likely a mechanism similar to the Shwartzman phenomenon operates in the genesis of stroke; a vessel segment periodically exposed to effective levels of the cytokines TNF-alpha and IL-1 would be brought into a state in which its endothelium would be activated [6,43], and the vessel segment could be considered prepared and ready to be triggered for a period of hours. This way, during this critical interval, the coagulation or complement system should become activated (the provocative stimulus) and the prepared vessel segment could undergo thrombosis.

Hallenbeck et al. [24] showed that various stroke risk factors effectively prepared the brainstem vasculature of rats for a localized Shwartzman reaction. Rats with hypertension, hypertension and genetic stroke predisposition, of advanced age, and streptozotocin-induced diabetes reacted with a significantly higher incidence of strokes than rats devoid of such stroke risk factors. In further studies Hallenbeck [27] demonstrated that the stroke risk factor, hypertension, is associated with preparation of brain vessels to thrombosis, increased perivascular monocyte and macrophage accumulation, increased stimulated TNF-alpha release from blood vessels and brain cells, and increased response of cerebral microvessel endothelial cells to TNF-alpha and IL-1.

Studies reported that risk factors for stroke prepare brainstem tissue for a localized Shwartzman reaction, including the development of ischemia and the production of TNF-alpha after a provocative dose of lipopolysaccharide. Moreover, these studies indicated that rats with stroke risk factors, such as hypertension and advanced age, respond to lipopolysaccharide with a more exuberant production of TNF-alpha and platelet activating factor than young and normotensive rats. These findings are consistent with the hypothesis that perivascular cells are capable of exaggerated signalling of endothelium through cytokines such as TNF-alpha in animals with stroke risk factors. The effect of such signaling might be to prepare the endothelial local vascular segment for thrombosis in accordance with the local Shwartzman reaction paradigm [54,55].

It might be worth noticing that TNF-alpha, platelet activating factor and IL-1 together participate in leukocyte accumulation and subsequent activation. This mechanism contributes to the extension of the infarct area and destruction of the microvasculature sustained by the central nervous system after cerebral reperfusion [33]. Moreover, it must be emphasized that TNF-alpha activity causes the fall in nitric oxide synthase that may lead to the spread of ischemic focus volume by the reduction of vasodilating mechanism [62]. On the other hand, though, TNF-alpha induces vasodilation [52]. These antagonistic vasogenic effects performed by TNF-alpha may be connected with interactions between ischemia-induced sequence of inflammatory changes together with cerebral reperfusion and the progress of pathomorphological lesions in an ischemic area of the brain.

INHIBITION OF TNF-ALPHA REDUCES BRAIN INFARCT VOLUME

The TNF-alpha synthesis or activity inhibitors may decrease infiltration of leukocytes to ischemic area of the brain thus reducing the infarct volume [15]. Inhibition of TNF-alpha involves blocking of TNF-alpha with specific antibodies or soluble TNF receptor I (sTNF-RI) and other neuroprotective agents like dexanabinol, MK 801, dexamethasone and CNI-1493.

Monoclonal neutralizing anti-TNF-alpha antibody administered intracerebroventricularly (or into the brain cortex [39]) in the experimental animals with middle cerebral artery occlusion significantly decreases focal ischemic brain injury [3,66].

sTNF-RI in higher concentrations is a natural inhibitor of endogenous TNF-alpha. Thus, administered intracerebroventricularly also reduced brain infarction [3]. sTNF-RI linked to polyethylene glycol (TNFbp) produced a significant reduction in the cortical infarct volume [42]. Plasma soluble tumor necrosis factor receptor protein-1 (sTNFR-1) levels are increased after acute cerebral ischemia and related to both intraplatelet cGMP and cAMP (which mediates the effects of vasodilatory and platelet antiaggregatory factors such as nitric oxide and prostacyclin, respectively) levels, indicating chronic inflammatory activity connected with late protective endothelial activation [2].

Dexanabinol (HU-211), a synthetic cannabinoid, is a noncompetitive N-methyl-D-aspartate antagonist with antioxidating and anti-TNF-alpha properties. Dexanabinol significantly decreases brain infarct volume and significantly lowers TNF-alpha levels [36].

Both MK 801, a noncompetitive NMDA receptor antagonist and dexamethasone reduced TNF production and decreased brain infarct volume [5].

CNI-1493, tetravalent guanylhydrazone compound effectively inhibited endogenous brain TNF synthesis and significantly reduced brain infarct volume. It seems very important that specific antibodies anti-TNF and CNI-1493 were each cerebroprotective when given within a clinically relevant time for up to 2 hrs after the onset of ischemia. These findings suggest that inhibiting TNF with CNI-1493 (just by systemic administration) may be beneficial in the future treatment of stroke [39].

Moreover, the finding that brain ischemia triggers inflammation in the brain with its rapid onset and progress over many hours after stroke and its contribution to the increase of infarct size brings about the search of selective inhibitors for specific inflammatory mediators. Inhibition of the mitogen-activated protein kinase (MAPK) cascade via cytokine suppressive anti-inflammatory drugs blocks the production of TNF-alpha [4].

Catania and Lipton [9] mention that alpha-melanocyte stimulating hormone (alpha-MSH) is a neuropeptide which exerts an anti-inflammatory activity via direct actions on peripheral host cells, descending neurogenic anti-inflammatory pathways stemming from central nervous system melanocortin receptors, and local actions on receptors that control inflammation within the brain. Respecting the latter influence there are reports that alpha-MSH inhibits TNF-alpha. alpha-MSH administered systemically modulates disturbances of auditory evoked potentials induced by ischemia/reperfusion of the brain in the posterior circulation. Such influences of the peptide may occur through inhibition of inflammatory factors produced by glia, namely alpha-MSH modulate TNF-alpha produced both by activated murine microglia and human astrocytes. Because glia can secrete alpha-MSH and express melanocortin receptors, they may, like peripheral macrophages, contain autocrine regulatory circuits based on the peptide and thus alpha-MSH modulated inflammation in the brain by acting on local melanocortin receptors.

TNF-ALPHA CONTRIBUTES TO APOPTOSIS IN STROKE

Programmed cell death, or apoptosis, may contribute to a neuronal death that accompanies stroke [59]. Recently, Herr et al. [29] have indirectly shown that in cerebral ischemia TNF-alpha may contribute to cytotoxicity through apoptosis, and to cell necrosis. Well, middle cerebral artery occlusion in rats leads to increased synthesis of ceramide in ischemic brain.

Ceramide is a key mediator of apoptosis that is also involved in a stroke-induced death. Synthetic C2-ceramide causes increased expression of TNF-alpha and induces both necrosis and apoptosis in the ischemic brain.

Control of factors regulating apoptosis may lead to a decreased brain damage in stroke.

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