An increase in the cerebral infarction area during fatigue is mediated by IL-6 through an induction of fibrinogen synthesis

Hong Lei,\(^1\) Jian Xu,\(^{1,\#}\) Li-Juan Cheng,\(^1\) Qi Guo,\(^1\) An-Mei Deng,\(^2\) Yong-Shen Li\(^*\)

\(^1\)Institute for Drug and Instrument Control of Beijing Military Area Command, Beijing, China. \(^2\)Second Military Medical University, Chang Hai Hospital, Department of Laboratory Medicine, Shanghai, China.

**OBJECTIVES:** Our study aimed to investigate the impact of fatigue on the severity of stroke and to explore the underlying mechanisms.

**METHODS:** Fatigued male rats underwent middle cerebral artery occlusion and the infarcted brain area was determined. Then, coagulation parameters were assessed in the fatigued group and a control group. In addition, the level of fibrinogen was determined in rats deprived of sleep for various numbers of days. To study whether interleukin-6 was involved in fibrinogen synthesis during fatigue, we also measured levels of interleukin-6 in rats deprived of sleep for various numbers of days. Furthermore, brain injury by middle cerebral artery occlusion was measured in wild-type mice, interleukin-6\(^{-/-}\) mice and wild-type mice treated with bezafibrate.

**RESULTS:** More severe cerebral infarction was observed in the fatigued rats, resulting in an infarct ratio of 23.4%. The infarct ratio was significantly increased in the fatigued rats compared with that in the control group (8%, \(p<0.05\)). The level of fibrinogen was increased significantly in the fatigued rats compared with that in the control group. In addition, a marked reduction in fibrinogen level was observed in the fatigued interleukin-6\(^{-/-}\) mice compared to their wild-type counterparts, whereas no difference was observed between fatigued wild-type mice and interleukin-6\(^{-/-}\) rats treated with recombinant human interleukin-6. The reduction in brain injury due to middle cerebral artery occlusion during fatigue was observed in interleukin-6\(^{-/-}\) mice and wild-type mice treated with bezafibrate.

**CONCLUSION:** Fatigue could increase stroke severity and was associated with the interleukin-6-induced expression of fibrinogen.

**KEYWORDS:** Fibrinogen IL-6; Fatigue; Stroke; Middle Cerebral Artery Occlusion.

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**INTRODUCTION**

Fatigue has been found to be prevalent in the general population, and it is an important symptom of mental and stress-related health complaints (1-3). The high prevalence of this condition in the general population has led to a growing interest in the influence of clinical and sociodemographic factors on the level of fatigue experienced by individuals (4,5).

In previous studies, fatigue was shown to be strongly associated with bad mental health states, impaired functioning and a variety of long-term illnesses; it is also a central symptom in many diseases, such as ischemic heart disease, cancer and depression (6-10). It has been reported that fatigue is the most common prodromal symptom before acute myocardial infarction, and preinfarction fatigue could contribute to early left ventricular dysfunction (11,12). In addition, fatigue is also a common symptom following a stroke (13,14). Numerous studies have confirmed that severe fatigue after stroke usually predicts a bad prognosis and an increased risk of recurrent stroke (15,16). However, few studies have examined the influence of fatigue on the severity of acute ischemic events, such as acute ischemic stroke. Therefore, our study aimed to investigate the impact of fatigue on the severity of stroke and to explore the underlying mechanisms.
MATERIALS AND METHODS

Animals
Rats and mice were housed in a controlled environment and provided access to standard rodent chow and water. The animal care practices were in compliance with Chinese regulations on the protection of animals used for experimental and other scientific purposes.

Experimental groups
To study the effects of fatigue on the cerebral infarction area, two groups of Sprague-Dawley rats were assigned randomly to control and fatigued groups. To study whether IL-6 was involved in the synthesis of fibrinogen during fatigue, rats and mice were randomly assigned to four groups and six groups, respectively. Each group of rats was deprived of sleep for a different length of time: no sleep deprivation (control), sleep deprivation for one day (F1), sleep deprivation for three days (F3) and sleep deprivation for five days (F5). The six groups of mice included wild-type mice, fatigued wild-type mice, IL-6−/− mice, fatigued IL-6−/− mice, IL-6−/− mice treated with IL-6 and fatigued IL-6−/− mice treated with IL-6. To study whether the decreased expression of fibrinogen could affect the infarction area, three groups of mice were tested: a fatigued group, a fatigued IL-6−/− group and a fatigued group treated with bezafibrate. All of the studies included six rats or mice per group.

Fatigue model
Male Sprague-Dawley rats were deprived of rest for five consecutive days in a cage filled with water to a height of 1.5 cm, as described previously (18). The cage was 485x350x200 mm, and there was a heater placed underneath it to keep the water warm. Under these conditions, the rats were unable to assume a resting position while avoiding the water, and they progressively grew fatigued.

MCAO model and evaluation of infarcted area
After fatigue treatment (five days of sleep deprivation), male Sprague-Dawley rats underwent the MCAO procedure described by Longa et al. (17). Briefly, the rats were anesthetized with ketamine and xylazine, and the left common carotid artery was exposed. Then, the external carotid artery and its branches were isolated and coagulated. A 3-0 Nylon suture with a blunted tip was inserted into the internal carotid artery through the external carotid artery stump and then advanced to the anterior cerebral artery to occlude the middle cerebral artery (MCA). The skin was then sutured, and the rats were allowed to awaken. Twenty-four hours after the operations, the rats were sacrificed, and coronal sections of the brain (2 mm thick) were cut and immersed in a 2% solution of 2,3,7-triphenyltetrazolium chloride. The stained slices were then fixed by immersion in phosphate-buffered 4% paraformaldehyde. The infarcted area and hemispheric area of each section were traced and measured using an image-analysis system (a Macintosh computer running the public domain National Institutes of Health Image program, written by Wayne Rasband and available on the Internet). The percentage of infarction (infarct ratio) was calculated by dividing the infarcted area by the total area of the ipsilateral hemisphere.

Measurement of coagulation parameters
Blood samples were obtained from the rats via a nonheparinized venous catheter in the femoral vein. APTT, PT and TT (Taiyang Biotechnology Company, Shanghai, China) were measured automatically from clotting tests using commercial reagents, and the test results were reported in seconds. The default settings for the minimal/maximal measuring times for APTT and TT were 3/120 sec and 13/240 sec, respectively. Fibrinogen was detected using Claus’s method with a human plasma calibration standard provided by the manufacturer.

Measurements of IL-6 in serum and CSF
The levels of IL-6 in the serum/CSF were measured using commercially available ELISA kits (IL-6, Fuji Lebio, Tokyo, Japan). The kit had a sensitivity limit of 4 pg/ml, and no detectable IL-6 was found in sera from control mice or IL-6 knockout mice.

Animal treatment
Male IL-6−/− mice, weighing 18-22 g, were kept on a 12-h day/night rhythm with free access to water and standard rodent chow. The animals were injected daily with 0.02 μg of rhIL-6/g body weight in a 0.9% NaCl solution containing 0.1% mouse serum albumin (MSA) or with only the 0.9% NaCl/0.1% MSA solution at the start of sleep deprivation, and the treatment lasted five days.

Bezafibrate was suspended in 1% methylcellulose solution and administered at a dose of 10 mg/kg/day orally at the start of sleep deprivation and the treatment lasted five days. The same amount of methylcellulose vehicle solution was also administered orally as a control.

CSF and tissue samples
After five days of sleep deprivation, the fatigued rats were anesthetized with 350 mg/kg ip chloral hydrate, and CSF (60-100 μl) was drawn from the cisterna magna using a glass capillary with a tip of approximately 300 μm in size. The surgery was performed carefully to avoid blood contamination. The CSF was then prepared for an IL-6 enzyme-linked immunosorbent assay (ELISA).

The brain samples were placed in sterile PBS containing a protease inhibitor cocktail (0.2 mM 4-[2-aminoethyl]benzenesulfonyl fluoride, HCl [AEBSF], 1 μg/ml aprotinin, 1 mM benzamidine, 1 mM EDTA, 10 μg/ml leupeptin and 10 μg/ml of pepstatin) and then homogenized and centrifuged (10000 g, 30 min, 4°C). Subsequently, the supernatant was removed and stored at -70°C. All of the samples were assayed for immunoreactive IL-6 using a validated rat-specific ELISA kit (IL-6, Fuji Lebio, Tokyo, Japan). Briefly, total brain samples were added to wells and incubated for two hours. Then, the conjugate was added and incubated for another two hours. After washing five times, the substrate solution was added and incubated for 30 minutes. Finally, the stop solution was added and measurements were obtained at 450 nm.

RESULTS

Effects of fatigue on the cerebral infarction area
To study the impact of fatigue on the severity of stroke, we compared the cerebral infarction area between the fatigued and control groups. Figure 1A presents representative results of the effects of MCA occlusion on infarction size in both groups: the control group and the fatigued
group (rats deprived of sleep for five consecutive days). Coronal sections were obtained by cutting brain slices at distances of 2, 4, 6, 8 and 10 mm from the rostral extremity of the frontal cortex. The white-colored areas represent the infarction regions in these sections. Figure 1B shows the percentage of infarction area in rats that underwent MCAO. More severe cerebral infarction was observed in the fatigued rats and the infarct ratio was 23.4%. The infarct ratio was significantly increased in the fatigued rats compared with that in the control group (8%, \( p < 0.05 \)).

Coagulation parameter changes in rat plasma during fatigue

Figure 2A shows the plasma changes in PT, APTT and TT in the fatigued and control groups. None of these parameters showed significant changes in the fatigued rats compared with those of the control group. Figure 2B shows the plasma changes in fibrinogen in the fatigued and control groups. The level of fibrinogen increased significantly in the fatigued rats compared with that in the control group.

Involvement of IL-6 in fibrinogen synthesis during fatigue

As shown in Figure 3A, the plasma fibrinogen level showed slight changes in rats deprived of sleep for one day (F1 group) compared with that in the control group (401.7 mg/dl vs. 417.9 mg/dl). Furthermore, the level was significantly increased in rats deprived of sleep for three days (F3 group); in that group, the fibrinogen level was 532.5 mg/dl. The fibrinogen concentration reached a maximum value in rats deprived of sleep for five consecutive days (F5 group), with a fibrinogen level of 793.1 mg/dl.

To study whether IL-6 was involved in fibrinogen synthesis during fatigue, we also measured the levels of IL-6 in rats deprived of sleep for various time intervals. As shown in Figure 3B, the serum IL-6 level started to increase in the F1 group, rose gradually in the F3 group and reached a peak in the F5 group. The levels of serum IL-6 were 301.6 pg/ml, 438.4 pg/ml and 1004.6 pg/ml, respectively (the level of IL-6 in the control mice was 212.6 pg/ml, as shown in Figure 3A). As indicated by Figure 3C, the levels
of IL-6 in serum were significantly increased in fatigued rats, consistent with our previous results, and no detectable IL-6 was observed in the IL-6 knockout mice. To identify whether IL-6 was involved in fibrinogen synthesis, IL-6 knockout mice were included in the subsequent studies. Consistent with the previous results, the level of fibrinogen increased significantly in fatigued wild-type mice. The IL-6⁻/⁻ mice showed significantly increased fibrinogen levels compared to the wild-type mice, but the fibrinogen levels in the fatigued IL-6⁻/⁻ mice were not as high as those in the fatigued wild-type mice, suggesting that the elevation of fibrinogen levels during fatigue was at least partially attenuated in the IL-6⁻/⁻ mice (Figure 3D, wild-type: 402 mg/dl and 797.9 mg/dl; IL-6⁻/⁻: 383 mg/dl and 593 mg/dl). At the same time, treating IL-6⁻/⁻ mice with recombinant human IL-6 (Pharma Technology, Hannover, Lower Saxony, Germany) greatly increased the levels of fibrinogen compared with those in the untreated IL-6⁻/⁻ mice (fibrinogen: 593 mg/dl and 745.4 mg/dl, respectively).

Measurements of cerebral infarction area in fatigued mice

The fatigued mice that underwent sleep deprivation were divided into three groups: 1) fatigued wild-type mice; 2) fatigued IL-6-knockout mice; and 3) fatigued wild-type mice treated with bezafibrate. As shown in Figure 4, compared to wild-type animals, the IL-6⁻/⁻ mice displayed significantly less brain injury after MCAO procedures, demonstrated by the decreased infarction area. At the same time, treating wild-type mice with bezafibrate, which decreased the fibrinogen levels, also provided protection from MCAO-induced brain injury.

**DISCUSSION**

Our results revealed that fatigued rats experienced significantly more brain injury after MCAO compared to their wild-type counterparts. In this study, we used the animal model of fatigue established by Tanaka et al. Although this model was created to study central fatigue, the swimming time of the fatigued rats also decreased sharply. When kept in water, the animals were unable to assume a resting position or sleep soundly as they attempted to avoid the water. Notably, sleep deprivation caused a wide range of neuropsychological and homeostatic changes that could not be ascribed to simple fatigue (19,20). Most of these alterations due to sleep deprivation could have interfered with the cerebral response to ischemic stress. Therefore, we compared brain infarction area in rats
performing an acute exercise protocol. In this model of fatigue, the rats were allowed to run until exhaustion, which was defined as the point at which the rats failed to escape the shock grid and had to be repositioned manually to the front of the treadmill on three consecutive occasions (21). This acute exhaustive exercise did not cause neuropsychological or homeostatic changes and could be considered to represent simple fatigue. Subsequent results revealed that the infarction area also increased significantly in rats after performing exhaustive exercise (Supplemental Figure 1). These results indicated that fatigue, whether physical or mental, aggregated the brain injury induced by MCAO.

Fibrinogen is acute-phase protein, and it serves as a nonspecific marker of inflammatory disease (22). It also has important hemostatic properties due to its effects on platelet aggregation and endothelial function. Fibrinogen is a major determinant of plasma viscosity. High levels of fibrinogen in the plasma might reduce blood flow and predispose to thrombosis. High levels of fibrinogen have been associated with an increased risk of cardiovascular disease and stroke (23,24). In our studies, we found that the level of fibrinogen increased significantly in fatigued rats. Whether increased levels of fibrinogen reflected active involvement in the pathogenesis of stroke severity during fatigue or were merely a nonspecific marker of inflammatory disease was not clear. Bezafibrate, a classic lipid-lowering drug, was used to lower plasma fibrinogen concentrations as well (25). In this study, we treated fatigued mice with bezafibrate to lower the fibrinogen levels (data not shown) and then submitted these mice to MCAO surgery. The bezafibrate-treated mice showed significantly decreased brain infarction areas compared to the control mice, indicating that fibrinogen was involved in the pathogenesis of stroke severity.

IL-6 is a multifunctional cytokine. Numerous studies have found IL-6-responsive elements in the fibrinogen gene promoter (26). IL-6 and its receptor were involved in fibrinogen synthesis (27). To determine whether elevated fibrinogen levels during fatigue were mediated by IL-6, we first measured the levels of IL-6 in fatigued rats and then examined the fibrinogen concentrations in IL-6-/- mice and wild-type controls. A significant increase in IL-6 levels was observed in the serum of fatigued rats. Because the fatigue model we examined in this study was a mental model, we also measured the levels of IL-6 in the cerebral spinal fluid (CSF) and brain tissue. Fatigue increased the expression of IL-6 in the CSF and brain as well (Supplemental Figures 2A and 2B). Consistent with previous results, fatigue increased the expression of fibrinogen in the wild-type controls. A marked reduction in fibrinogen levels was seen in the fatigued IL-6-/- mice compared to their wild-type counterparts, whereas no...
mice treated with recombinant human IL-6. The reduction in brain injury caused by MCAO during fatigue in IL-6−/− mice suggested that the lack of IL-6 protected against MCAO-induced brain injury. In conclusion, our results explained why fatigue subjects were more prone to severe brain injury induced by MCAO than were control subjects, and IL-6 might serve as a biological marker for fatigue in our fatigue model.

Supplemental Figure 2 - Level of IL-6 in CSF and brain tissue. Supplemental figure 2A and 2B show the changes of IL-6 in CSF and brain of rats from different groups. The white column represents the control group. The black column represents the fatigue group (F5; deprived of sleep for five days). The level of IL-6 increased significantly in CSF of fatigue rats when compared with that in control group (771.6 ± 74.2 pg/ml vs. 72.6 ± 10.6 pg/ml). The level of IL-6 increased significantly in brain of fatigue rats when compared with that in control group (775.2 ± 73.6 pg/mg protein vs. 18.3 ± 3.5 pg/mg protein).

The difference was seen between fatigued wild-type mice and IL-6−/− mice treated with recombinant human IL-6. The reduction in brain injury caused by MCAO during fatigue in IL-6−/− mice suggested that the lack of IL-6 protected against MCAO-induced brain injury. In conclusion, our results explained why fatigue subjects were more prone to severe brain injury induced by MCAO than were control subjects, and IL-6 might serve as a biological marker for fatigue in our fatigue model. To the best of our knowledge, fatigue has typically been considered to be a subjective symptom, and no specific marker has been identified to measure it. People usually underestimate the importance of unusual fatigue, although it might be associated with sudden death due to coronary heart disease or stroke. Our studies demonstrated that progressively increasing levels of IL-6 during fatigue constitute a dangerous signal because they lead to increased expression of fibrinogen, which would eventually aggregate ischemic disease or stroke. Our results explained why fatigued subjects were more prone to severe brain injury induced by MCAO than were control subjects, and IL-6 might serve as a biological marker for fatigue in our fatigue model.

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Author Contributions
Lei H designed the experiments, detected the levels of fibrinogen and wrote the manuscript. Xu J drew the cerebral spinal fluid and measured the levels of IL-6. Cheng IJ performed the middle cerebral artery occlusion operation. Guo Q and Deng AM supervised the project. Li YS revised the manuscript.

References
1. Sluiter JK, de Croon EM, Meijman TF, Frings-Dresen MHW. Need for recovery from work related fatigue and its role in the development and prediction of subjective health complaints. Occup Environ Med. 2003;60(Suppl 1):s62-70, http://dx.doi.org/10.1136/oem.60.suppl_1.s62.
2. Janssen N, Kant IJ, Swaen PPM, Schroë CAP. Fatigue as a predictor of sickness absence: results from the Maastricht cohort study on fatigue at work. Occup Environ Med. 2003;60(Suppl 1):s71-6, http://dx.doi.org/10.1136/oem.60.suppl_1.s71.
3. Andrea H, Kant IJ, Beurskens AJHM, Metsemakers JFM, van Schayck CP. Associations between fatigue attributes and fatigue, health, and psychosocial work characteristics: a study among employees visiting a physician with fatigue. Occup Environ Med. 2003;60(Suppl 1):s99-110, http://dx.doi.org/10.1136/oem.60.suppl_1.s99.
4. Riegel B, Ratcliffe SJ, Sayers SL, Potashnik S, Buck HG, Jurkovicz C, et al. Determinants of excessive daytime sleepiness and fatigue in adults with heart failure. Clin Nurs Res. 2012;21(3):271-93, http://dx.doi.org/10.1177/1054773811419842.
5. Taylor RR, Jason LA, Jahn SC. Chronic fatigue and sociodemographic characteristics as predictors of psychiatric disorders in a community-based sample. Psychosom Med. 2003;65(5):896-901, http://dx.doi.org/10.1016/S0033-3174(03)00122-0.
6. Ekmann A, Oder M, Avlund K. The Predictive Value of Fatigue for Nonfatal Ischemic Heart Disease and All-Cause Mortality. Psychosom Med. 2012;74(5):464-70, http://dx.doi.org/10.1016/j.psych.2012.02.004.
7. Smith ORF, Pedersen SS, Domburg RTV, Denollet J. Symptoms of fatigue and depression in ischemic heart disease are driven by personality characteristics rather than disease stage: a comparison of CAD and CHF patients. Eur J Cardiovasc Prev Rehabil. 2008;15(5):583-8, http://dx.doi.org/10.1097/HJR.0b013e32830e78e7.
8. Grossman P, Deuring G, Garland SN, Campbell TS, Carlson LE. Patterns of objective physical functioning and perception of mood and fatigue in posttreatment breast cancer patients and healthy controls: an ambulatory psychophysiological investigation. Psychosom Med. 2008;70(7):819-28, http://dx.doi.org/10.1097/PSY.0b013e3181318061.
9. Brønborg W, Aili-Exvainte Y. Update on Psychotropic Medications for Cancer-Related Fatigue. J Natl Compr Canc Netw. 2007;5(10):1081-91.
10. Westhoff G, Dorner T, Zink A. Fatigue and depression predict physician visits and work disability in women with primary Sjögren’s syndrome: results from a cohort study, Rheumatology (Oxford). 2012;51(2):262-9, http://dx.doi.org/10.1093/rheumatology/ker208.
11. Bethell HJN. Fatigue as a prodromal symptom of myocardial infarct. Circulation. 2004;109(22):e311, http://dx.doi.org/10.1161/01.CIR.0000129347.00233.C8.
12. Johansson I, Karlson BW, Granvist G, Brink E. Disturbed sleep, fatigue, anxiety and depression in myocardial infarction patients. Eur J Cardiovasc Nurs. 2010;9(3):175-80.
13. Winward C, Sackley C, Metha Z, Rothwell PM. A population-based study of the prevalence of fatigue after transient ischemic attack and minor stroke. Stroke. 2009;40(3):757-61, http://dx.doi.org/10.1161/STROKEAHA.108.527101.
14. Zedlitz AMEE, Fasotti L, Geurts ACH. Post-stroke fatigue: a treatment protocol that is being evaluated. Clinical Rehabilitation. 2011;25(6):487-500, http://dx.doi.org/10.1177/0269215510391285.
15. Glader EL, Stegmayr B, Asplund K. Poststroke Fatigue: A 2-year follow-up study of stroke patients in Sweden. Stroke. 2002;33(5):1327-33, http://dx.doi.org/10.1161/01.STR.0000014244.28711.D6.
16. Prevalence and Predictors of 6-Month Fatigue in Patients With Ischemic Stroke: A population-based stroke incidence study in Auckland, New Zealand, 2002-2003. Stroke. 2012;43(10):2604-9.
17. Krakowsky M, Rogatsky G, Zarchin N, Mayevsky A. Effect of hyperbaric oxygen therapy on survival after global cerebral ischemia in rats. Surg Neurol. 1998;49(4):412-6, http://dx.doi.org/10.1016/S0090-3019(97)00195-X.
18. Tanaka M, Nakamura F, Mizokawa S, Matsumura A, Nozaki S, Watanabe Y. Establishment and assessment of a rat model of fatigue. Neurosci Lett. 2003;352(3):159-62, http://dx.doi.org/10.1016/j.neulet.2003.08.051.
19. Gajar N, Yoo SS, Hu P, Walker MP. Sleep Deprivation Amplifies Reactivity of Brain Reward Networks, Biasing the Appraisal of Positive Emotional Experiences. J. Neurosci. 2011;31(12):4466-74, http://dx.doi.org/10.1523/JNEUROSCI.3220-10.2011.
20. Kopp C, Longordo F, Nicholson JR, Liuhi A. Insufficient Sleep Reversibly Alters Bidirectional Synaptic Plasticity and NMDA Receptor Function. J Neurosci. 2006;26(48):12456-65, http://dx.doi.org/10.1523/JNEUROSCI.2702-06.2006.
21. Malaguti M, Angeloni C, Garatachea N, Baldini M, Leoncini E, Collado PS, et al. Sulforaphane treatment protects skeletal muscle against damage induced by exhaustive exercise in rats. J Appl Physiol. 2009;107(4):1028-36, http://dx.doi.org/10.1152/japplphysiol.00293.2009.
22. Sabeti S, Exner M, Mlekusch W, Amighi J, Quehenberger P, Rumpold H, et al. Prognostic impact of fibrinogen in carotid atherosclerosis: nonspecific indicator of inflammation or independent predictor of disease progression? Stroke. 2005;36(7):1400-4, http://dx.doi.org/10.1161/01.STR.0000169931.96670.fc.
23. Thompson SG, Fechttrup C, Squire E, Heyse U, Breithardt G, van de Loo JCW, et al. Antithrombin iii and fibrinogen as predictors of cardiac events in patients with angina pectoris. Arterioscler Thromb Vasc Biol. 1996;16(3):357-62, http://dx.doi.org/10.1161/01.ATV.16.3.357.
24. Chuang SY, Bai CH, Chen WH, Lien LM, Pan WH. Fibrinogen independently predicts the development of ischemic stroke in a Taiwanese Population: CVDFACTS Study. Stroke. 2009;40(5):1578-84, http://dx.doi.org/10.1161/STROKEAHA.108.540492.
25. Sinzinger H, Pirich C, Kondor P, Etti H. Atherogenic risk reduction in patients with dyslipidemia comparison between bezafibrate and lovastatin. Eur Heart J. 1995;16(11):1491-501.
26. Ray A. A SAF binding site in the promoter region of human γ-fibrinogen gene functions as an il-6 response Element. J Immunol. 2000;165(6):3411-7, http://dx.doi.org/10.4049/jimmunol.165.6.3411.
27. Ōhta S, Okazaki M, Maruyama M, Oguchi K. Involvement of IL-6 and IL-6 receptor in fibrinogen synthesis in the liver of triton wr-1339-induced hyperlipidemic rats. In Vivo. 2004;18(2):203-12.