# 中医肝脏与运动性疲劳关系的理论与实验研究

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# 致　谢

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陈家旭

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# 中文摘要

在运动医学领域，关于运动性疲劳产生的机制以及对它如何进行有效预防和消除的研究，一直是令人瞩目的前沿课题。本研究为国家自然科学基金委重点资助课题（NO. 39430140）分题之一，已开展了以下工作：

**一、理论研究**

中医理论中有着若干关于疲劳的论述，如劳倦伤气，并且很重视五脏、气血、心理与疲劳的关系。中华人民共和国成立以来，在采用中医药消除运动性疲劳方面，已做了大量的工作。根据中医理论，肾主骨，为先天之本；脾主肌肉，为后天之本。运动性疲劳与肌肉、骨骼等有着密切联系。因此，人们长期以来一直采用中医的补肾药物，近年也使用补脾药物来改善运动性疲劳，并取得一定效果。

在中医的脏象学说中，肝脏的功能包括生理及心理，它们与运动、疲劳均有联系：①肝主疏泄，与情绪变化有关；②肝主筋，与肌肉运动能力有关；③肝为罢极之本，与运动性疲劳的产生有关；④肝藏血，是提供运动能量的重要来源；⑤肝协助脾的消化吸收；⑥肝肾都与性腺功能有关。

结合导师提出的“肝脾气化失常为导致运动性疲劳产生”的学说，因此，从中医理论探讨运动性疲劳机制及对运动性疲劳恢复过程中，除了肾、脾之外，对肝脏也应加以关注。理论研究主要从以下7个方面，阐明中医肝脏在运动性疲劳的发生、治疗中的重要地位。

1. 疲劳概念：大量文献资料表明，疲劳是一种主观感受，表现为暂时性的工作能力的下降，经过休息调整能得以恢复。同时，疲

劳的出现也是机体需要休息的信号，以免于损害性病变的发生。广义的疲劳概指任何原因引起的身体不适和工作效率的下降，狭义的疲劳如视觉疲劳、听觉疲劳、腰肌疲劳等。运动性疲劳是运动员这类特殊人群的生理表现，集心身两方面的变化。

2. 古医籍对疲劳的描述：文献表明古籍对疲劳类似的描述有“解体”、“懈怠”、“懈惰”、“体惰”、“四肢沉重”、“四肢劳倦”、“四肢瘫软”、“四肢不用”、“四肢不收”、“四肢缓弱”等。此多为躯体性症状，虽有怠倦疲劳的表现，但多见于其他病证之中，且多以脾虚立论；较之运动性疲劳，以古人类似描述的症状为重，同时心理性疲劳描述较少。

3. 中医对运动性疲劳的病因病机认识：运动员的疲劳主要为体劳与心劳，故认为其病因为：情志不畅，劳役过度。其病机关键在于肝气失于对气血的疏泄，进而引起脏腑功能异常所致。

4. 中医肝脏与运动性疲劳的关系：从肝脏的主要生理功能（肝主疏泄、为罢极之本、肝主筋、肝藏血等）及其与脾肾的关系，主要论述①肝主疏泄与运动性疲劳情绪变化密切相关；②肝主筋与运动性疲劳运动能力大小有关；③肝脾与运动性疲劳能量代谢变化有关；④肝肾与运动性疲劳内分泌变化有关。

5. 肝与运动应激、神经内分泌免疫网络的关系：从应激概念、应激学说、神经内分泌免疫网络的稳态调节，以及中医整体观、肝脾肾现代研究成果，认为运动性疲劳过程中神经内分泌免疫网络的紊乱当首责于肝之疏泄调节失常。

6. 运动性疲劳证候学探讨与鉴别诊断：综合文献报道及临床调查资料，其共同的症状表现有：①情绪变化，如心烦、缺乏耐心、情志抑郁等；②躯体不适，如肌肉酸痛、四肢沉重无力、厌烦训练、渴望休息等；③脾胃症状，如食欲差、食量减少等；④津液的损失，如汗多、口渴、饮水多等。运动性疲劳的根本在于肝的调节功能失常，肝体阴用阳，体阴为物质基础（包括精、气、血等），用阳为功能活动：劳倦太过则肝血、肝阴、肝气暗耗。肝主疏泄，为罢极之本，

运动性疲劳中情绪的异常与肝失疏泄有关，疏泄不及则情志抑郁，郁而化火则心烦、缺乏耐心、易发脾气。肝失疏泄，则气机不畅，而见躯体不适；木不疏土，则运化无力，而见脾胃症状。文中并论述运动性疲劳与过度训练疲劳综合征、慢性疲劳综合征以及中医虚劳、虚损的鉴别诊断。

7. 中医治疗运动性疲劳方药观：针对运动性疲劳的病因病机，认为治疗的关键在于调整肝脏的气化功能，使紊乱的神经内分泌免疫网络复常；同时积极补益气津血，使疲劳康复。并分析了既往从补脾肾论治的理论依据及其局限性。

## 二、实验研究

运动作为一种应激，神经内分泌变化是其基础，在运动与神经肽关系的研究中，涉及较多的是 β－EP、ENK、ACTH、NPY，而 DYN 在运动中的变化尚未见有报道。上述神经肽在血液中的水平与运动的多种因素有关，包括运动强度、运动持续时间、训练水平等。但关于神经肽在运动性疲劳中枢的动态变化及中药复方抗运动性疲劳作用机制的研究尚未见系统的报道。本研究运用放射免疫学、免疫组织化学、原位杂交结合图像分析方法，从血液生化、神经肽蛋白及其前体基因转录、组织与形态超微结构水平，重点研究了中药复方"体复康"对运动性疲劳大鼠相关的神经肽在血和脑组织中动态变化的影响。主要结果如下：

1. 用放射免疫分析法实验表明：慢性运动应激疲劳大鼠血浆 β－EP 较对照组显著下降。末次急性运动应激疲劳大鼠血乳酸于运动后即刻显著高于对照组，与此同时，血浆 DYN $A_{1-13}$ 含量显著下降，而 β－EP、L－ENK 变化不明显；运动结束后的动态变化情况是：30 min 时血乳酸水平下降，3 h 显著下降而恢复至运动前水平，30 min 时血浆 β－EP 继续下降、3 h 恢复，血浆 L－ENK 在 3 h 显著下降而低于运动前水平，血浆 DYN $A_{1-13}$ 在 30 min 时未恢复、在 3 h 恢复至运动前水平。

中药复方"体复康"(由枳壳、黄芪、当归等组成,体现了疏肝柔肝理气、健脾益气养血的理气扶正原则)对慢性运动应激疲劳大鼠血浆 β-EP、L-ENK、DYN $A_{1-13}$ 有一定下调作用。对末次急性运动应激疲劳大鼠血浆 β-EP 于运动后即刻、30 min 均显著上调,对 L-ENK 于运动后30 min仍显著下调,对 DYN $A_{1-13}$ 的调节不明显,对运动后即刻血乳酸有显著清除作用。

2. 用免疫组织化学染色法结合图像分析的结果表明:慢性运动应激疲劳大鼠 NPY 在 PV、DM、VMH 等核团无显著性变化,而末次急性运动应激疲劳大鼠 NPY 于运动后 3 h 在上述核团变化尤为明显。中药复方"体复康"对慢性运动应激疲劳大鼠脑组织上述核团 NPY 调节作用不明显,而对末次急性运动应激疲劳者 NPY 的调节于运动后 3 h 尤为明显,且呈双向调节,即在 PV、DM 核团下调,在 VMH 核团上调。

尾壳核 L-ENK 在慢性运动应激疲劳大鼠显著下降,而在末次运动应激疲劳大鼠则迅速升高;中药复方"体复康"对前者显著上调,对后者则显著下调。大强度运动能使下丘脑 DYN $A_{1-13}$ 水平显著升高,以运动结束后 30 min 最为明显;中药复方"体复康"在疲劳大鼠的恢复过程中,对下丘脑 DYN $A_{1-13}$ 无显著调节作用。

3. 用 POMC 生物素标记的 cRNA 探针原位杂交结合图像分析,实验结果表明:末次急性运动应激疲劳大鼠 POMC 的基因表达在额叶皮层、海马 $CA_1$ 区显著下降(前者于运动结束后 3 h 仍未恢复,后者至运动结束后 30 min 即恢复),在下丘脑则显著增强。中药复方"体复康"对慢性运动应激疲劳大鼠海马 $CA_1$ 区、下丘脑 POMC 的基因表达有显著增强作用,而对额叶皮层 POMC 的基因表达有抑制作用;对于末次急性运动应激疲劳大鼠,该中药复方均能显著增强额叶皮层、海马 $CA_1$ 区与下丘脑 POMC 的基因表达,尤其是运动后 3 h 最为显著

综上所述,本文首次观察了运动性疲劳大鼠及其恢复过程中

相关的神经肽及其前体基因表达在脑组织不同核团和血液中水平的动态变化；同时观察到中药复方“体复康”对它们有重要的调节作用，表现为双向的、呈时相性的动态调节，从而为中医肝脏学说与神经内分泌调节的关系提供了现代科学依据。

关键词：肝（中医） 疏肝理气 中药复方“体复康” 运动性疲劳 应激 β－内啡肽 亮氨酸脑啡肽 强啡肽 $A_{1-13}$ 神经肽 Y 前阿黑皮素 放射免疫法 免疫组织化学 原位杂交

# ABSTRACT

In sport medicine, the research about the mechanism of exercise-induced fatigue (EIF) as well as its prevention, elimination, has been attracting many scholars for a long time. This key project (NO.39430140) was supported by the National Science Foundation Committee of China; the following works has been done.

Part 1. Theoretical Study

There are a lot of viewpoints about fatigue exemplified as qi injured by overworking in traditional Chinese medicine(TCM) basic theory, the relation between the five viscera(Zang), qi, blood, psychology and fatigue was much paid attention. Since the founding of the P.R.C., a lot of works have been done in eliminating EIF, as well as definite effects obtained by adopting TCM, mainly using the theoretical methods such as nourishing spleen or invigorating kidney.

EIF related to the physiological and psychological activities, in visceral manifestation theory of TCM, the liver's function includes the physiology and psychology corresponding to the exercise and fatigue. (1) The liver is in charge of regulating the activity of qi which corresponds to the emotion. (2) The liver is in charge of the

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tendons which is concerned with the ability of muscle exercise. (3) The liver is the root of physical stamina which relates to EIF. (4) The liver stores blood, serving as a reservoir of blood to regulate the circulating blood volume, which is one important originate of energy. (5) The liver can help the spleen to digestion and absorption the essences of food which is one important originate of energy. (6) Both the liver and kidney concern with the sexual hormone.

As combination with the viewpoint of "disturbance in liver qi and spleen qi transformation resulting in EIF" advanced by the tutor, Prof. Yang Weiyi, the paper expounded the prominent position of the liver in the development and treatment of EIF from following 7 aspects.

1. The concept of fatigue: Literatures indicated that fatigue is a subjective feeling, marked by the temporary descending of work efficiency, and could be recover by rest. Meanwhile, fatigue is a signal indicating the body need rest in order to avoid the catastrophe changes. Broadly speaking, fatigue refers to the unwell and the decadence of work efficiency caused by any reasons, while narrow sense of fatigue is such as vision fatigue, auditory fatigue, lumbar muscle fatigue, etc. EIF is the fatigue of athlete, manifested by both mental and bodily fatigue.

2. Descriptions of fatigue in ancient Chinese medicinal literatures: similar descriptions of fatigue appeared in ancient Chinese medicinal literatures, but they were mainly bodily symptoms which emerged in diseases or syndromes (Zheng), and were mainly regarded as spleen deficiency (Pixu). Those similar descriptions were more serious as compared to that of EIF, and with less mental fatigue.

3. Pathogenesis of EIF: Based on the athlete being weary in body and mind, the author considers that the pathogenic factors of

EIF are emotional disorder and overtraining. Its key pathogenesis is that the liver fails to regulate the qi and blood, furthermore affects the functions of the viscera(Zang and fu), then results in EIF.

4. The relationship between the liver and EIF: According to the liver's main physiological functions as well as its relation to the spleen and kidney (the liver has additional partial functions of spleen or kidney), the author regards: (1) The liver being in charge of regulating the activity of qi is associated with the emotional abnormal in EIF. (2) The liver being in charge of the tendons is concerned with the ability of exercise in EIF. (3) The liver and spleen are related to the energy metabolism in EIF. (4) The liver and kidney are corresponding to the neuroendocrine of EIF.

5. The relationship between the liver and stress as well as neuroendocrine-immune network(NEIN): From the concept and theory of stress, homeostasis regulation, and the concept of wholism as well as modern research achievements of the liver, spleen and kidney; the author concludes that the disorder of NEIN in EIF should impute to the abnormal of liver qi.

6. Exploration the syndrome of EIF and its differential diagnosis: As integration of literatures and clinical investigation data, it can be found that the common symptoms are such as emotional disorder, bodily unwell, disturbance of spleen and stomach, the lose of body liquid. The author points out that EIF should be differential diagnose with overtraining fatigue syndrome, chronic fatigue syndrome, "Xulao" or "Xusun" of TCM.

7. Therapeutic method for EIF: The emphasis should focus on adjusting the liver qi with the Chinese drugs which can regulating the flow of qi, meanwhile, immediately nourish qi and blood for the rehabilitation of EIF.

Part 2. Experimental Study

Exercise, as a kind of stress, the change of neuroendorcine is its basis. In the past, many researches have been done about the response of neuropeptides level in blood to the exercise (including sports intensity and duration), such as beta-endorphin, adrenocorticotropic hormone, and neuropeptide Y, etc. But the dynamic change of related neuropeptides in the rat brain of EIF, and effect of TFK on eliminating EIF have not been reported up to now. In this study, radioimmunoassay (RIA), immunohistochemical method (IHC), in situ hybridization (ISH) integrated image pattern analysis, electron microscope were used, in order to explore the effect of TFK on the related neuropeptides and their precursor gene expression in rat brain of EIF. The EIF rat model was done, by using the method of treadmill (with slope of 0 degree) exercise with long term (total 7 weeks) and high intensity (speed from 15 m/min gradually increased to 35 m/min, 20 to 25 min/d duration), The main results are as follows:

1. TFK can significantly down regulate the plasma beta-EP, L-ENK and DYN $A_{1-13}$ levels in chronic fatigue rat. While in the last acute exercise fatigue rat, TFK can obviously up regulate the plasma beta-EP immediately and 30 min post-exercise, still down regulate the plasma L-ENK 30 min post-exercise, no remarkable influnce on the content of plasma DYN $A_{1-13}$ with TFK was observed, and TFK has obviously eliminating effect on the blood lactate immediately post-exercise.

2. In the rats with long term (total 7 weeks) and high intensity exercise (speed from 15 m/min gradually increased to 35 m/min, 20 to 25 min/d duration), at their un-exercise state, NPY was unchanged in paraventricular thalamic (PV), dorsomedial hypothalam-

ic nucleus (DM) and ventromedial hypothalamic nucleus (VMH), but it was changed obviously especially at 3 hours post-exercise after final exercise. NPY was not changed remarkably in the chronic fatigue stress by TFK, but it was double regulated by TFK especially at 3 hours post-exercise in the acute fatigue stress, marked by down-regulating in PV and DM, while up-regulating in VMH.

At their un-exercise state, L-ENK was decreased in caudate-putamen, but it was activated with sharply increased after final exercise. TFK could significantly up regulate the caudate-putamen L-ENK level in chronic fatigue rat brain, while down regulate in the last acute exercise fatigue rat. DYN $A_{1-13}$ in hypothalama could be activated by exercise, especially at 30 minutes post-exercise, but no remarkable influnce on the content of DYN $A_{1-13}$ in hypothalama with TFK was observed.

3. TFK could significantly strengthen POMC mRNA expression in hippocampal $CA_1$ and hypothalama of chronic fatigue rats, while obviously inhibited frontal cortex POMC mRNA expression. In the rats with long term (total 7 weeks) and high intensity exercise (speed from 15 m/min gradually increased to 35 m/min, 20 to 25 min/d duration), after their final exercise, the expression of POMC mRNA was decreased in frontal cortex in which POMC mRNA was not recovery yet at 3 hours post-exercise, and hippocampal $CA_1$ in which POMC mRNA was recovery at 30 minutes post-exercise; but it was increased in hypothalama. To the final acute exercise fatigue rats, TFK could remarkable increase POMC gene expression in hippocampal $CA_1$ and hypothalama as well as frontal cortex.

As mentioned above, the dynamic change of related neuropep-

tides and their precursor gene expression in rat plasma or brain of EIF was first observed. TFK has important effect marked as double (up and down) and time-depending regulation on the related neuropeptides, the results provide modern science basis for the relation between the liver theory and neuroendorcrine.

KEY WORDS: liver (TCM); relieving the depressed liver; TFK recipe; exercise-induced fatigue; stress; beta-endorphin; leucine-enkephalin; dynorphin $A_{1-13}$; neuropeptide Y; proopiomelanocortin; radioimmunoassay; immunohistochemistry; in situ hybridization.

# 英文缩写

| 缩写 | 英文全文 | 中文 |
| --- | --- | --- |
| ACTH | Adrenocorticotropic hormone | 促肾上腺皮质激素 |
| ABC KIT | Avidin-biotin-compound kit | 卵白素生物素复合物试剂盒 |
| ADP | Adenosine diphosphate | 腺苷二磷酸 |
| ANOVA | Analysis of variance | 方差分析 |
| ATP | Adenosine triphosphate | 腺苷三磷酸 |
| BCA | ABranch amino acid | 支链氨基酸 |
| Cpu | Caudate-putamen | 尾壳核 |
| DAB | Diaminobenzidine | 3,3－二氨基联苯胺 |
| DM | Dorsomedial hypothalamic nucleus | 下丘脑背内侧核 |
| DNA | Deoxyribonucleic acid | 脱氧核糖核酸 |
| DYN $A_{1-13}$ | Dynorphin $A_{1-13}$ | 强啡肽 $A_{1-13}$ |
| EDTA | Ethylene diaminetetraacetic acid | 乙二胺四乙酸 |
| EIF | Exercise-induced fatigue | 运动性疲劳 |
| β－EP (β－END) | β－endorphin | β－内啡肽 |
| GABA | γ－aminobutyric acid | γ－氨基丁酸 |
| HPA | Hypothalama-pituitary-adrenal | 下丘脑－垂体－肾上腺 |
| IOD | Integral optical density | 积分光密度 |
| IHC | Immunohistochemistry | 免疫组织化学 |

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