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Anti-migraine and anti-depression activities of Tianshu capsule by mediating Monoamine oxidase

Xiaoping Sun[1], Fangfang Zhu[1], Jun Zhou, Xiujuan Chang, Liang Li, Hanfei Hu, Zhenzhong Wang, Wei Xiao*

State Key Laboratory of New-tech for Chinese Medicine Pharmaceutical Process, Jiangsu Lianyungang 222001, China

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ABSTRACT

Background: Tianshu capsule(TSC)is a Chinese patent medicine. It's widely used to treat migraine clinically in China.

Aim of the study: In the present study, we investigated anti-migraine and anti-depression activities of TSC using in vivo animal models together with in vitro studies to investigate the mechanism of action.

Materials and methods: Nitroglycerin (NTG) -induced migraine rat model, rat was given a subcutaneous injection of the NTG suspension (10 mg/kg) once a week for 5 weeks. Behavioral observation was carried out and brain tissues were sampled to determine levels of 5-hydroxytryptamine (5-HT), dopamine (DA), norepinephrine (NE), monoamine oxidase A (MAO-A), monoamine oxidase B (MAO-B) and tyrosine hydroxylase (TH) by ELISA, in order to evaluate the effect of TSC on migraine progression. Tail suspension test and forced swim test were carried in order to evaluate the effect of TSC on depression progression.

Results: TSC treatments decreased scratch head times significantly in a rat migraine model. Meanwhile, TSC suppressed activities of MAO-A and MAO-B, up-regulated 5-HT, DA and NE expressions in brain tissues. Tail suspension test showed a decrease of immobility time in TSC groups. Furthermore, TSC increased climb times, up-regulated activities of 5-HT, DA and NE in forced swim test mice. Additionally, TSC could attenuate the reduction of 5-HT, DA and NE induced by corticosterone in primary neuronal cells.

Conclusion: TSC could effectively prevent depression, one of the most frequent comorbidities in migraine. It may provide a new target for treating migraine.

1. Introduction

Migraine is the most common disease, which can bring considerable burden to health care systems around the world. Its symptoms include one side or bilateral headaches, often accompanied with nausea, vomiting or visual disturbances. Studies show that 6.5% of men and 18.2% of women suffer from migraine. Most patients are women at the age of 20–40 [1]. However, migraine sufferers still have no effective and widely applicable drug treatment methods [2].

Currently, migraines have some drug treatments, including nonspecific and relatively specific medications [3,4]. The nonspecific drugs like non-steroidal antiinflammatory drugs (NSAIDs) are effective, such as aspirin and acetaminophen. But their applications are often accompanied with side-effects on gastrointestinal tract. The nonspecific agents, opioids, may be useful for some migraine patient [5]. The use of these drugs is limited because of the risk of drug abuse or addiction [6]. Therefore, developing more effective and safe anti-migraine agents is still a pressing task.

Migraine is always accompanied with other neuropsychiatric disorders. One of the most common comorbidities is depression. It's a very common, recurring mental illness, which affects human life from every aspect [7]. Depression is one of the major causes of disability in the world, which imposes a heavy burden on society, with a lifetime of risk [8]. About 50% of people with depression suffer from severe migraines. It suggested a bidirectional relationship between migraine and depression [9,10]. However, the relationship is complicated and the pathogenesis has not been determined. The fact that some biological pathways, e.g., the serotonergic and dopaminergic systems, affect depression and migraine, which suggests that disturbances of these systems may increase the incidence of these disorders [11,12].

Monoamine oxidases (MAOs) catalyze the oxidative deamination of monoamines, including the monoamine neurotransmitters 5-HT, NE,

* Corresponding author at: Jiangsu. Kanion Pharmaceutical Co. Ltd., China.
E-mail address: xw_kanion@163.com (W. Xiao).
[1] These authors contributed equally to this work.

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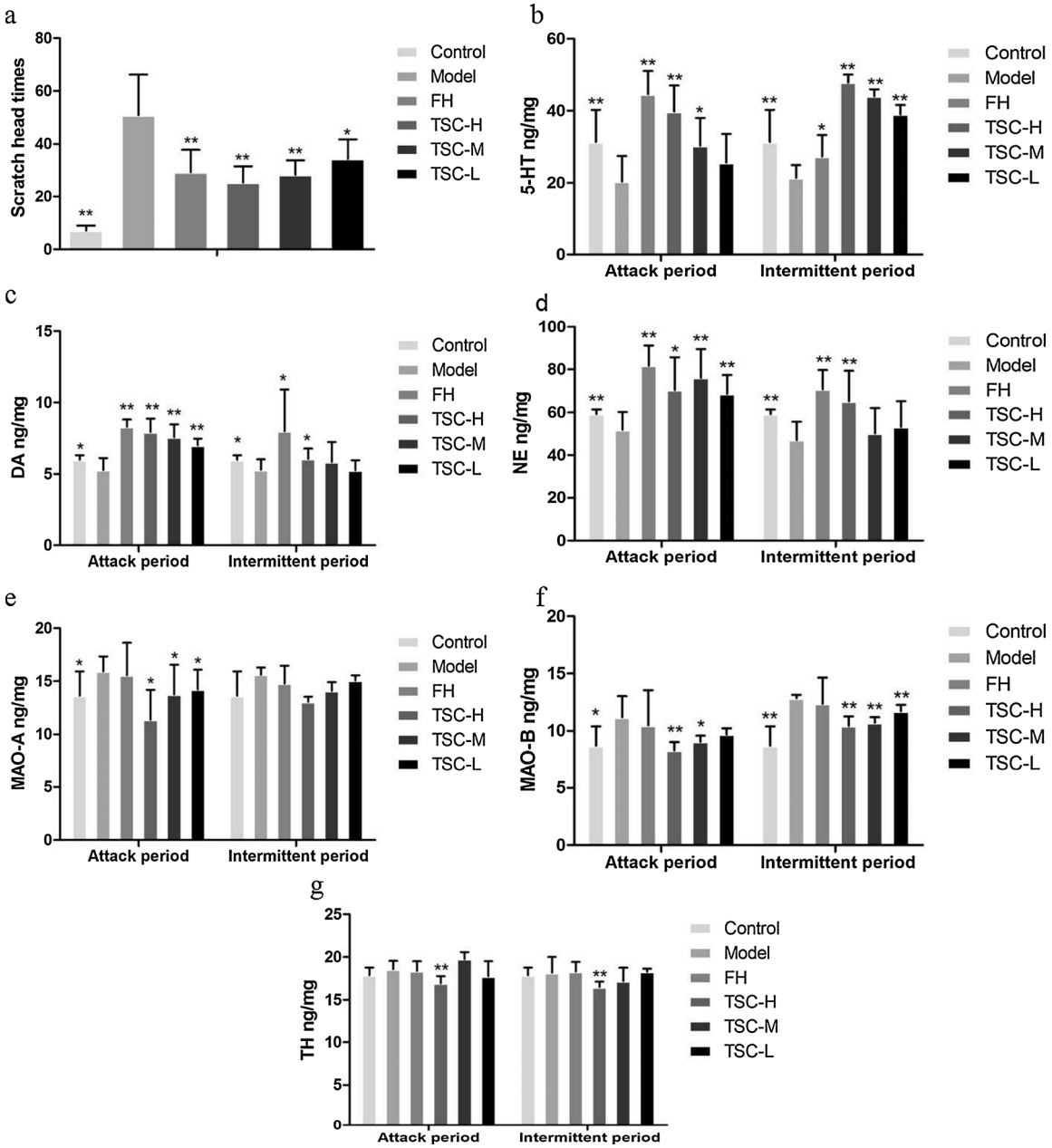

Fig. 1. Effect of TSC on the Nitroglycerin-induced migraine rat model. (a) Scratch head times of NTG induced migraine rats. (b) The content of 5-HT in rats brain tissue. (c) The content of DA in rats brain tissue. (d) The content of NE in rats brain tissue. (e) The content of MAO-A in rats brain tissue. (f) The content of MAO-B in rats brain tissue. (g) The content of TH in rats brain tissue. Values are worked out by means ± SEM (n = 6). **, $p < 0.01$; *, $p < 0.05$; compared with the model group.

DA, melatonin and so on [13]. Abnormal expressions of MAOs in humans are associated with depression, schizophrenia, migraines, and other diseases [14]. Selective inhibition of MAO-A may increase the levels of neurotransmitter in CNS and exert anti-depression activity [15].

Herbal formulae are characterized as multiple herbs, constituents and targets. They have been recognized as having a clinical effect on migraine. Tianshu capsule (Kanion pharmaceutical, Lianyungang, Jiangsu, China) is an effective Chinese patent medicine which is widely used to treat migraine in China. It is developed from Da Chuan Xiong Fang, which is well-known and extensively used as traditional decoction for the treatment of migraine. It first appeared in Xuan Ming Lun Fang, a famous formula book written by Wansu Liu who lived in Jin Dynasty. It also can be traced back to Song Dynasty, a classic prescription in medical ancient book Sheng Ji Zong Lu. Tianshu capsule is composed of two herbs, *Ligusticum striatum* DC and *Gastrodia* in the mass ratio of 4:1. Among them, herb R. *Ligusticum striatum* DC has been used to promote blood circulation, expel wind and alleviate pain [17]. It has hemodynamic and analgesic effects. So it is treated as a monarch in the TSC formula. Another herb, *Gastrodia*, has effect of calming liver, extinguishing wind and alleviating pain. It is used as auxiliary drug to ameliorate migraine because of its sedative, anti-convulsant and anti-vertigo effect [18]. In modern medicine, its anti-migraine effect has been definitely confirmed. Nowadays, TSC has been used in treating different types of headache [19]. Interestingly, TSC could effectively control the headache and relieve the patient's suffering without obvious side effects [20]. Now it has been recorded in Pharmacopoeia of the People's Republic of China (Edition 2010), due to its function of a clinical effect on migraine.