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# Pretreatments with Tenma and Chotoko extracts on striatal monoamines and lipid peroxides in iron-induced acute epileptic rats

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## Abstract

The present study was undertaken to examine both Tenma (*Gastrodia elata* Bl.) and Chotoko (*Uncaria rhynchophylla* (Miq.) Jacks) extracts, compared with vitamin E, on striatal monoamine levels and lipid peroxides in the iron-induced acute epileptic rats. The results showed that pretreatment with both extracts and vitamin E showed an activating effect on the dopaminergic system, such as early elevations of DA, and its metabolites, DOPAC and HVA. Neither the iron injection nor the pretreatments with the extracts showed an effect on noradrenergic and serotonergic systems. Both extracts, especially the Tenma extract, significantly inhibited the increase of lipid peroxidation in the striatum. These results suggest that the brain dopaminergic system might participate partially in the mechanisms which suppress iron ion induced seizures, while Tenma and Chotoko extracts might increase the inhibitory biogenic amine synthesis, release and metabolism through stimulating the dopaminergic neurons. The finding that Tenma and Chotoko extracts possess the inhibitory effect on lipid peroxidation as that of vitamin E suggests that Tenma and Chotoko extracts may act as antioxidants to prevent the membrane lipid derangements in epileptogenesis.

**Key words** Striatum, monoamines, lipid peroxidation, epileptogenesis, extract, Tenma (*Gastrodia elata* Bl.), Chotoko (*Uncaria rhynchophylla* (Miq.) Jacks).

**Abbreviations** NE, norepinephrine ; DA, dopamine ; DOPAC, dihydroxyphenylacetic acid ; HVA, homovanillic acid ; 5-HT, serotonin ; 5-HIAA, 5-hydroxyindoleacetic acid.

## Introduction

Brain monoamines are etiologically important, and closely related to seizure susceptibility. Both experimental and clinical evidence support the conclusion that the threshold for convulsion is decreased when monoamine levels are low, and conversely, that the threshold is elevated when these levels are high.[1,2]

It is well known that an iron-induced epilepsy model may serve as a clinical model for post-traumatic epilepsy.[3] It has been suggested that monoaminergic neurotransmitters may play some roles in the mechanism of early epilepsy and in the procedure of chronic epileptic focus formation.[3] Production of epileptiform electrographic discharges on iron-induced experimental epilepsy is believed to be mediated by membrane lipid peroxidation initiated by the reactive oxygen species radicals. The formation of lipid peroxidation and of superoxide radicals after iron injection into rat isocortex has been confirmed.[4]

Tenma (*Gastrodia eleta* Bl.) and Chotoko (*Uncaria rhynchophylla* (Miq.) Jacks) are two traditional Chinese herbal drugs that have been used for many years for the treatment of convulsions and epilepsy clinically. Chemical studies have shown that Tenma rhizome contains mainly p-hydroxybenzyl alcohol, and vanillin, also p-hydroxybenzaldehyde, vanillyl alcohol and trace alkaloids[5] ; The major components of the dried climbing hooks and stems of Chotoko are indole alkaloids, such as rhynchophylline, corynoxeine,

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corynantheine, hirsutine and hirsuteine.[6,7] Pharmacological studies have shown that Tenma extract given intravenously increased the threshold for electroshock convulsion and inhibited the occurrence of seizures in experimental epileptic guinea-pigs while given intraperitoneally (i.p.), inhibited the pentylenetetrazol -induced convulsion in mice.[8] The Chotoko extract inhibited the occurrence of seizures in experimental epilepsy in guinea-pigs,[9] and it also showed sedative effects in both rats and mice, as well as showing hypotensive action in dogs, rabbits and rats.[10] However whether the proposed anti-epileptic and anti-convulsive effects were related to the mechanisms of affecting brain biogenic amines and lipid peroxidation has not been clarified yet. In the present study, we examined the effect of the extracts of both Tenma and Chotoko, compared with vitamin E, a well-known antioxidant, on the levels of striatal monoamines with a high performance liquid chromatograph and lipid peroxides with fluorophotometer in the cortical iron injected rats. Although some of these procedures also modify monoamine concentrations, it is possible to observe differences of these monoamines by examining their levels at certain time periods in striatum after the drug administration.

## Materials and Methods

*Animals* : Male adult Sprague-Dawley rats were bought from Charles River Japan Inc., Japan at the age of 7 weeks (body weight 200-230 g) and were used within the following 2 weeks, after allowing 1 week of adaptation to the laboratory.

*Preparation of Tenma and Chotoko extracts :* Tenma (*Gastrodia elata* Bl.) and Chotoko (*Uncaria rhynchophylla* (Miq.) Jacks) are known as Tianma and Gouteng in China. Both extracts were obtained by the methods of water and ethanol extraction, which have been described in detail in our recent publication.[11]

*Drug administration* : Rats were anesthetized with ether and placed in a stereotaxic apparatus. A burr hole was made in the left calvarium 1 mm posterior and 1 mm lateral to the bregma. A 25-gauge needle which was attached to a microsyringer firmly and held in a stereotaxic micromanipulator, was inserted into the cortex to 2.5 mm below the exposed dura. A freshly prepared 100 mM ferric chloride aqueous solution (5 $\mu$l) was injected over a period of 5 minutes. Electrocorticographic recordings were performed to verify the formation of epileptic focus by the evidence of spike activity in an iron injected group.

The iron salt injection operation and the doses used in the pretratment with alpha-tocopherol (which is an established antioxidant and was used for comparison with the two extracts) followed those of Willmore *et al.*.[12,13] The selected doses of the two extracts were based on the results of previous studies.[14,15] Before beginning the intracortical injection, each rat was randomly assigned to one of the five experimental groups, and received 1 ml i.p. injection (30 min before intracortical injection). Group 1, the untreated group, received physiological saline. Group 2 received 0.35 ml / 100 g of a solution containing 625 mg vitamin E/ml (2.19 g/kg) made up to 1 ml with sesame oil. Group 3 received 0.35 ml/100 g, made up to 1 ml with saline of a solution containing 570 mg Tenma extract/ml (2.00 g/kg). Group 4 received 0.35 ml / 100 g of a solution containing 285 mg Chotoko extract/ml, made up to 1 ml with saline (1.00 g/kg) and the sham-operated control group received an injection of 1 ml saline. We omitted another group which should have been given sesame oil as untreated control for the vitamin E treated group, since Willmore *et al.* showed that there was no significant difference between the saline and the sesame oil-treated controls in both lipid peroxide values and edema formation.[16] Upon completion of the intracortical injection, rats were killed by decapitation at the time intervals of 15, 30, 60, 120 and 180 min, respectively. The selected time intervals were based on our electrocorticographic observation that the appearance of the spike discharges induced by iron ions appeared from 15-45 min, and poly spike and ictal patterns were observed starting 70-90 min after iron injection. In addition, lipid peroxides in the injected foci were found to begin increasing from 5 min after intracortical iron injection and to begin attenuating from 120

min[13,17]; monoamines were found to be significantly altered from 120-240 min after iron injection in the brain dialysate samples.[18] After removing the whole brain, the striatum was dissected on an ice plate according to the method described by Glowinski and Iversen,[19] and kept at −80°C until the analyses of monoamines and lipid peroxides.

*Monoamine analysis*: The monoamines were analyzed using high performance liquid chromatography with an electrochemical detector (HPLC-ECD).[20] Briefly, the striatum homogenate was centrifuged at 1550 g for 15 min.. The supernatant was subjected to another centrifugation at 11,000 g for 30 min.. Then, the supernatant was filtered with milliipore of 0.45 μM pore size. The levels of striatal DA, DOPAC, HVA, NE, 5-HT and 5-HIAA were measured by HPLC-ECD (Model ECD-100, Eicom Japan). The mobile phase consisted of 100 mM potassium phosphate buffer (pH 3.1) containing 13% acetonitorile, 770 mg/l sodium octanesulphonate and EDTA, and pumped at 0.8 ml/min.. Peak height and retention times of standard solution were compared with samples and used to calculate the concentrations of constituents. Monoamine levels were expressed against tissue protein levels which were determined using BCA Protein Assay Reagent (Pierce Chemical Company, Rockford, IL.)

*Lipid peroxide analysis*: The thiobarbituric acid reactive substances (TBARS) were measured fluorophotometrically with the method as described by Ohkawa *et al.* and used as the index of levels of lipid peroxidation.[21]

*Statistical analysis*: The statistical significance of the differences between the experimental and control groups was examined by one-way analysis of variance (ANOVA).

## Results

The effects on dopamine and its metabolites of the sham-operated, untreated control and the treated animals are given in Fig 1-3. The animals given injection of iron showed significant increases of DA at 120 min, of DOPAC and HVA at 180 min when compared with the sham-operat-

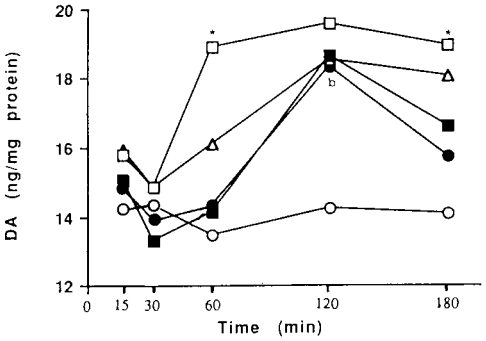


Fig. 1. Pretreatment with vitamin E, Tenma extract, and Chotoko extract on the levels of DA in the striatum of rats, compared with the sham-operated and the untreated control animals. Monoamine levels were measured by HPLC-ECD at 15, 30, 60, 120 and 180 min. after cortical injection of 5 μl of 100 mM $FeCl_3$. Treated animals were administered vitamin E, Tenma and Chotoko extracts by i.p. injection 30 min. before $FeCl_3$ injection, respectively. Each value is mean (ng/mg protein) from five or six animals. SEMs (<8%) were omitted for clarity.
$^b p<0.01$ versus sham-operated group; $^* p<0.05$ versus untreated group examined with one-way ANOVA.

—○— Sham-operated
—●— Untreated
—△— VE-treated
—□— Tenma-treated
—■— Chotoko-treated

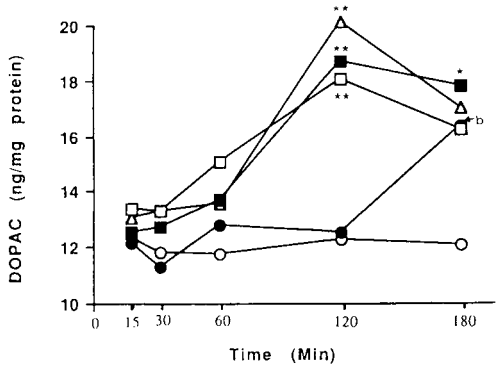


Fig. 2. Pretreatment of vitamin E, Tenma extract and Chotoko extract on the levels of DOPAC in the striatum of rats. The other details are the same as in Fig. 1. $^b p<0.01$ versus sham-operated group; $^* p<0.05$ and $^{**} p<0.01$ versus untreated group examined with one-way ANOVA.

—○— Sham-operated
—●— Untreated
—△— VE-treated
—□— Tenma-treated
—■— Chotoko-treated

ed animals. Both Tenma and Chotoko extracts showed an early increase of DA, DOPAC and HVA in different extents and at different time intervals. DA was increased by the treatment of Tenma extract at 60. 120 and 180 min, but not affected by the treatment of Chotoko extract (Fig. 1.); DOPAC, the major metabolite of DA, was increased by Tenma extract at 60, 120 and 180 min, and by Chotoko extract at 120 and 180 min (Fig. 2). HVA, the final metabolite of DA, was elevated by Tenma extract from 60-180 min, and by Chotoko extract only at 120 and 180 min. (Fig. 3). Vitamin E showed the effects on elevating DA from 120 min, DOPAC at 120 and 180 min, and HVA at 60, 120 and 180 min (Fig. 1-3). The levels of NE, 5-HT and 5-HIAA were neither significantly affected by the iron injection nor by the pretreatments of vitamin E and the two extracts (data were not shown).

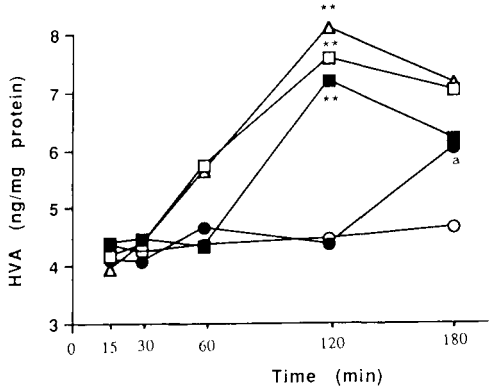


Fig. 3. Pretreatment of vitamin E, Tenma extract and Chotoko extract on the levels of HVA in the striatum of rats. The other details are the same as in Fig. 1. $^{a}p<0.05$ versus sham-operated group ; $^{**}p<0.01$ versus untreated group examined with one-way ANOVA.
—○— Sham-operated
—●— Untreated
—△— VE-treated
—□— Tenma-treated
—■— Chotoko-treated

The fluorescence of striatal TBARS in the sham-operated, untreated control and the treated animals is shown in Table I. Injection of iron showed an increase of TBARS in the striatum from 30 min, reached to peak at 120 min, then decreased slightly, a pattern quite different from that in the iron injected focus, in which, lipid peroxides increased dramatically from 15 min then gradually attenuated.[11] Vitamin E showed inhibitory effect on TBARS levels at 60, 120 and 180 min, whereas Tenma extract, at 30, 60, 120 and 180 min., Chotoko extract, at 60, 120 and 180 min. successively after iron injection, respectively. The treatment with Tenma extract showed the most effective inhibition on the increase of TBARS level in striatum.

Table I Fluorescence of striatal TBARS in treated and untreated rats measured at 15, 30, 60, 120 and 180 minutes after cortical injection of 5 $\mu$l of 100 mM $FeCl_3$. Treated animals were administered vitamin E, Tenma and Chotoko extracts respectively by i.p. injection 30 min before $FeCl_3$ injection.

| Treatment | Time (minutes after iron injection) | | | | |
|---|---|---|---|---|---|
| | 15 | 30 | 60 | 120 | 180 |
| Sham-operated | 42.57±2.93 | 43.24±3.73 | 41.58±4.25 | 42.85±3.55 | 43.08±4.44 |
| Fe (Untreated) | 49.33±4.33 | 80.81±10.98$^{a}$ | 86.68±9.04$^{a}$ | 110.64±12.24$^{b}$ | 80.12±10.02$^{b}$ |
| Fe+VE treated | 51.82±9.03 | 78.76±15.96 | 61.29±10.22* | 71.50±6.10* | 65.52±7.23* |
| Fe+Tenma treated | 47.45±4.99 | 53.89±9.72* | 46.90±4.51** | 50.25±4.87** | 51.18±6.72* |
| Fe+Chotoko Treated | 40.67±2.78 | 64.81±7.80 | 62.77±4.44* | 81.35±13.48* | 71.22±11.24 |

Each value is a mean±SEM (nmol/g protein) of five or six animals. $^{a}p<0.05$ and $^{b}p<0.01$ versus sham-operated group ; $^{*}p<0.05$ and $^{**}p<0.01$ versus untreated group determined with the one-way ANOVA.

## Discussion

Increases in DA, DOPAC and HVA levels and lipid peroxides after cortical iron injection in rat in the present study suggest that the formation of an epileptic focus accompanies the activation of dopaminergic neurons and the neural cellular damages in the brain. These results are consistent with previous reports.[11, 18]

A number of experiments have reported that pharmacologically induced depletion of catecholamines result in an enhancement of susceptibility to seizures.[22] On the other hand, treatment with anticonvulsants could elevate the threshold for convulsion and increase the levels of catecholamines in certain animal models. For example, $CaCl_2$,[23] diazepam,[24] TJ-960,[25] peperine[26] have been proved to affect either catecholaminergic or serotonergic system. We also found that treatment of antioxidants such as EPC-$K_1$, a free radical scavenger, prevented or slowed the occurrence of epileptic discharges induced by iron ions and increased the levels of DOPAC and HVA much earlier than those in controls in striatal dialysates.[27]

In the present study, we found that Tenma and Chotoko extracts, as well as vitamin E, possess the effect on elevating the levels of striatal dopamine or its metabolites examined. Interpretation of these results is further complicated in the present study because both extracts consist of several active components. Anyway, these results suggest that dopaminergic system might participate partially in the mechanisms which suppress iron ion induced seizures, in which Tenma or Chotoko extract might increase dopamine synthesis, release or metabolism. The increased dopamine and its metabolites may exert a suppressive effect on iron-induced convulsion and seizures, because dopamine is well-known to have inhibitory action on the central nervous system. Therefore, altering the biogenic amines in the brain may be partially related to the anticonvulsant action of both Tenma and Chotoko extracts.

The finding that Tenma and Chotoko extracts possess a similar but stronger inhibitory effect on lipid peroxidation as that of vitamin E suggests that Tenma and Chotoko extracts also acted as antioxidants to prevent the membrane lipid derangements, such as neural peroxidation caused by the iron-induced formation of free radicals and powerful oxidants during the development of an epileptic focus. The formation of free radicals and oxidants have been believed to make significant contribution to paroxysmal membrane malfunction in epileptogenesis.[28] The generations of active free radical species have been demontrated with the injection of iron salt into cortex and other methods.[4] The data obtained in this study suggest that peroxidation of neural lipids initiated by the injection of iron salts may have been terminated by free radical scavenging mechanism of both extracts the same as vitamin E.[16, 29, 30] This proposal is in accordance with the newly-found scavenging effects of Tenma and Chotoko extracts on free radicals.[11] It is possible that the activation of dopaminergic neurons may be related to the inhibition of lipid peroxidation both in striatum and also in cortex (the epileptogenic foci), because lipid peroxides, and other toxic metabolites including TBARS, which is from the lipid peroxidation in neuronal and other tissues, are capable of diffusing in tissues and exert damage to structures distant from the primary site of injury. We found that both Tenma and Chotoko extracts were effective in inhibiting the lipid peroxidation in the iron-induced epileptogenic foci of rats.[11] It is also possible that the activation of dopaminergic system is a response to defend the free radical damage during iron epileptogenesis, as we have found that the brain monoamines, including dopamine and its metabolites, are potent free radical scavengers and antioxidants.[31, 32]

In the present experiment, we found that the injection of iron ions, pretreatment with vitamin E, both Tenma and Chotoko extracts only affected the dopaminergic system; this is consistent with the observation that the striatal DA synthesizing system is extremely susceptible to lipid peroxidative processes, such as the process induced by iron ions.[33]

The effects of Tenma and Chotoko on

monoaminergic systems as well as on lipid peroxidation should be contributable to the complexicity of their components. Therefore, it is quite interesting and important to study the effects of their components, the relationship between the structure and the biologic activity of the components, the mechanism of synergistic effect and counteraction of side effects. This is what we are undertaking at present. Vanillin and p-hydroxybenzyl alcohol, two major components of Tenma, have already been found to be potent antioxidants recently (Unpublished data).

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## 和文抄録

天麻及び釣藤鈎エキスの脳の線条体内モノアミンとそれらの代謝物質及び脂質過酸化に対する影響をラットの鉄誘導てんかんモデルを用いて検討した。天麻及び釣藤鈎エキスは，抗酸化剤としてビタミンEのようにドーパミン系を活性化させ，脂質過酸化も抑制した。

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