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Effect of High-tyrosine Diet on Brain Norepinephrine Metabolism in Immobilization-Stressed Rats

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ABSTRACT

S.D.rats were fed with 3.4% tyrosine supplemented diet for 5 days. Tyrosine diet had no effects on brain NE and MHPG-SO4 levels in non-stressed rats. When these animals were given 3 hr-immobilization stress, they responded in a manner that coped better to the stress. This was measured by the increase in brain MHPG-SO4 indicating the increase in norepinephrine turnover by the stressed animals. When rats were stressed, fed basal or high-tyrosine diet, brain tyrosine concentration dropped more than 26% over the non-stress control animals. 3-hr immobilization stress also decreased brain NE levels. However, while the stress resulted in a significant decrease($p<0.05$) of brain NE in basal diet, the decrease was not significant in high-TYR diet group. And as the stress index, serum corticosterone, glucose, and free fatty acid concentrations also were assayed. In this study, it was found that high-TYR diet prevented the stress-induced depletion of brain NE and suppressed the rise in serum corticosterone, glucose, and free fatty acid. These results suggest that high-TYR diet increases the coping ability of body to stress.

KEY WORDS : tyrosine · norepinephrine · stress · MHPG-SO4.

Introduction

It has been generally accepted that stress increases the utilization of brain neurotransmitter and produces the neurochemical changes[1)2)]. During stressful conditions, brain noradrenergic neurons are especially activated[3)]. Thus, norepinephrine(NE) turnover and release are increased and its absolute levels are decreased[4-9)]. Stress-induced depletion of brain stores of neurotransmitter NE is occurred because catecholamine synthesis can not keep pace with the increased amounts of neurotransmitter being released[10)11)]. These results caused the various behavioral deficits involved with stress[8)12-16)]. Therefore one of the factors which protect against the adverse behavioral effects of stress is capacity to produce the neurotransmitter NE.

Under stress, to replenish stocks of NE, individual neurons take up the amino acid tyrosine (TYR) from plasma and convert it biochemically into dopa, then dopamine and finally NE[11)]. TYR is a large neutral amino acid found in a wide variety of common food proteins, and dietary protein is the source of plasma tyrosine. Even though plasma tyrosine concentrations influence on brain tyrosine concentrations in some extent, it

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is the ratio of TYR to its amino acid competitors that determines its rate of entry into the brain because TYR must compete with all the other large neutral amino acids(LNAA ; tryptophan, phenylalanine, leucine, isoleucine and valine) for transport across the blood-brain barrier[10)17-19)].

Many research studies have shown that TYR, given acutely or in the diet, protects rodents from both the neurochemical and the behavioral effects of acute stressors such as immobilization or tail-shock by preventing the depletion of NE in the brain[8)12-15)20)]. That is, TYR supplementation raised plasma TYR, brain TYR, brain NE and physical activity levels. This dietary-biochemical-neural pathway provides strong support for the hypothesis that dietary TYR can aid stress resistance.

The purpose of this study was to examine the effects of TYR diet(using a diet with 3.4% TYR) on brain NE metabolism in immobilized-stressed rats. In addition, it was evaluated whether TYR diet could help stress resistance or coping ability of body and recover more fast from stress. Rats fed the basal diet or high-TYR diet containing 3.4% TYR for five days were divided into three sub-groups ; non-stress group, stress group and recovery group. In each group we measured the levels of serum TYR, brain TYR, brain NE and 3-methoxy-4-hydroxyphenylethyleneglycol sulfate (MHPG-SO4), identified as a useful index in assessing turnover and metabolism of endogenous NE in the rat[21)]. It has been reported that increases in the levels of both plasma corticosterone released from the adrenal cortex in rats and plasma glucose and free fatty acid released by increase of sympathetic nerve activity were sensitive indexes of stress[22-24)]. Therefore, by determining levels of serum glucose and free fatty acid, we examined the relation between brain NE metabolism and these indexes as well as the effect of high-TYR diet on stress resistance.

Materials and Methods

Animals and diets. Weanling male Sprague-Dawley rats were housed 5 per cage and fed pellet diet for nine weeks. After that rats weighing 340–380g were randomized according to body weight into two diet groups. Each group of rats was fed the basal diet or high-TYR diet containing 3.4% TYR(Table 1) for five days. The animals were maintained in a controlled environment(temperature 23± 2℃, light period from 8 : 00 to 20 : 00). Food and water were given ad libitum.

Stress procedure. Two diet groups were divided into three sub-groups : non-stress group, stress group and recovery group. Rats in the latter two groups were stressed by 3-hour immobilization.

Table 1. Ingredient composition of experimental diets

Ingredient	Basal diet	High-TYR diet
	% by weight	
Corn starch	64.8	61.4
Casein	15.0	15.0
Corn oil	10.0	10.0
Cellulose	5.0	5.0
Salt mixture[1)]	4.0	4.0
Vitamin mixture[2)]	1.0	1.0
D,L-Methionine	0.2	0.2
L-Tyrosine	–	3.4

1) Composition of salt mixture, g/kg mixture : CaHPO4 500g, NaCl 74g, K2SO4 52g, Potassium citrate monohydrate 220g, MgO 24g, Maganous carbonate(43–48% Mn) 3.5g, Ferric citrate(16–17% Fe) 6.0g, Zinc carbonate 1.6g, Cupric carbonate(53–55% Cu) 0.3g, KIO3 0.01g, Chromium Potassium Sulfate 0.55g, Na2 SeO3.5H2O 0.01g, Sucrose finely powdered 118.0g.

2) Nutrition Biochemicals, ICN Life Science Group, Cleveland Ohio, Vitamin mixture(–B) : Vitamin A conc.(200,000 units per g) 4.5g, Vitamin D conc.(400,000 units per g) 0.25g, Tocoperol 5.0g, Ascorbic acid 45.0g, Inositol 5.0g, Choline chloride 75.0g, Riboflavin 1.0g, Thiamine hydrochloride 1.0g, Calcium Pantothenate 3.0g, Biotin 0.02g, Folic acid 0.09g, Vitamin B 0.00135g and Starch to 1 Kg.

Animals in stress group were sacrificed by decapitation immediately after exposure to the stress, while rats in recovery group were released from 3-hr immobilization and returned to their home cages to recover for 2 hours prior to sacrifice. During the recovery period, water was available. Non-stressed rats were decapitated without any stress treatment. The decapitations were carried out between 12 : 00 and 13 : 00 hours for non-stress group and between 13 : 00 and 15 : 00 hours for stress and recovery groups.

Biochemical analysis. Immediately after decapitation the brain was removed and weighed. Brain samples were frozen and stored at −25℃ until homogenization and then assayed for tyrosine, NE and MHPG-SO4. Blood was collected from trunk vessels and rapidly centrifuged(500g×15 min). The serum was separated and stored at −25 ℃ until the determination. Serum samples were assayed for corticosterone, glucose and free fatty acid. Tyrosine levels in the brain and the serum were determined fluorometrically by the method of Waalkes and Udenfriend[25]. NE levels in the brain from individual rats were estimated fluorometrically by the method of Shellenberger and Gorden[26]. Also MHPG-SO4 levels were determined according to the fluorometric method of Nagasaki et al.[27] with a slight modification. Serum corticosterone levels were determined by the method of radioimmuno assay. Sensitivity of this test is in the pg range. Serum glucose levels were determined by the enzymatic technique using commercial kits. Free fatty acids levels were determined colorimetrically by the method of Smith[28].

Statistical methods. Data were expressed as the mean± standard deviation of the mean and analyzed statistically by analysis of variance, followed by Duncan's multiple-range test. Significance level for all statistics was set at $P<0.05$.

Results

Pooled serum tyrosine levels are shown in Table 2. High-TYR diet nearly tripled serum tyrosine levels whether or not rats were stressed. Three-hour immobilization stress greatly decreased serum tyrosine levels in both two diet groups. Compared to non-stress groups, stress groups had approximately 41% (basal diet) and 51% (high-TYR dict) decreases of serum tyrosine levels, respectively. Recovery groups had 3.6% (basal diet) and 4.2% (high-TYR diet) decreases of serum tyrosine levels when compared to stress groups.

Both 3-hr immobilization stress and high-TYR

Table 2. Effects of 3hr immobilization and high-tyrosine diet on serum levels of tyrosine in rats*

Treatment	Basal diet	High-TYR diet
	ug/ml	
Non-stress	25.9	90.0
Stress	15.4	44.0
Recovery	14.9	42.2

*Serum samples were pooled in the same group.

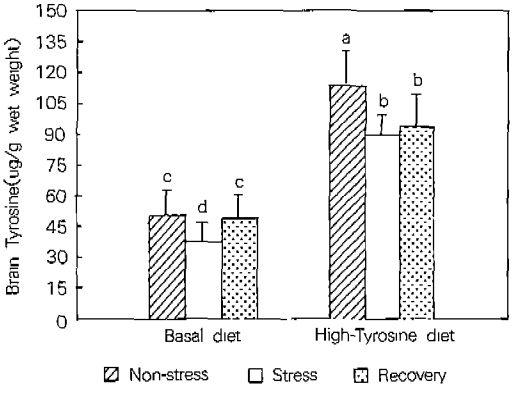

Fig. 1. Effects of 3hr immobilization and high-tyrosine diet on the concentration of tyrosine in rat brain. *Mean± S.E.(n=5−7/group).
*Means with the same letter are not significantly different($P<0.05$) by Duncan's multiple range test.

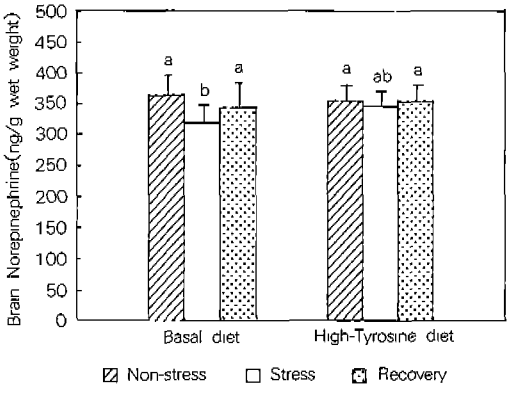

Fig. 2. Effects of 3hr immobilization and high-tyrosine diet on the concentration of norepinephrine in rat brain.
*Mean± S.E.(n=5−7/group).
*Means with the same letter are not significantly different($P<0.05$) by Duncan's multiple range test.

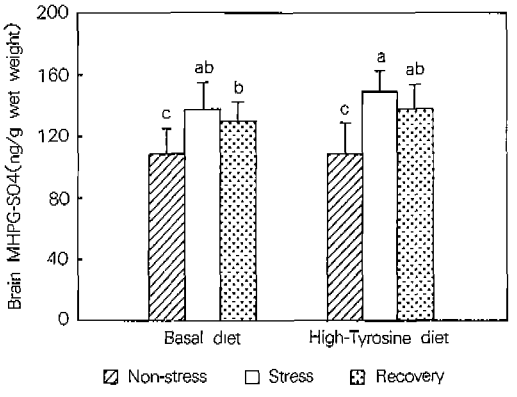

Fig. 3. Effects of 3hr immobilization and high-tyrosine diet on the concentration of MHPG-SO4 in rat brain.
*Mean± S.E.(n=5−7/group).
*Means with the same letter are not significantly different($P<0.05$) by Duncan's multiple range test.

diet had significant effects on brain tyrosine levels (Fig. 1). In all sub-groups, rats fed high-TYR diet had significantly higher($P<0.05$) brain tyrosine levels than rats fed basal diet. However, while high-TYR diet tripled serum tyrosine levels, in brain tyrosine levels, there were nearly double in-

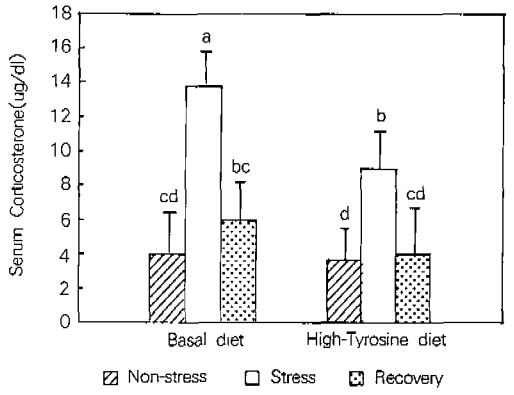

Fig. 4. Effects of 3hr immobilization and high-tyrosine diet on serum levels of corticostertone in rats.
*Mean± S.E.(n=5−7/group).
*Means with the same letter are not significantly different($P<0.05$) by Duncan's multiple range test.

creases. 3-hr immobilization stress significantly decreased($P<0.05$) brain tyrosine levels in both two diet groups. Compared to non-stress groups, stress groups had 29.5% (basal diet) and 26.2% (high-TYR diet) decreases of brain tyrosine levels. After 2hr recovery period, in contrast to serum tyrosine, there were 31.8% (basal diet) and 5.4% (high-TYR diet) increases of brain tyrosine levels. It should be especially noted that increase of brain tyrosine levels in basal diet group was significantly greater than those in high-TYR diet group.

The effects of 3-hr immobilization stress and high-TYR diet on the concentration of brain NE and MHPG-SO4 are shown in Fig. 2−3. High-TYR diet had no effects on brain NE and MHPG-SO4 levels in non-stressed rats. These results indicated that increases of brain tyrosine levels could not be coupled with increases of brain NE levels in normal state. In general, 3-hr immobilization stress decreased brain NE levels. In basal diet group, 3-hr immobilization stress resulted in a significant decrease($P<0.05$) of brain NE. However, in high-TYR diet group, even though rats ex-

posed to 3-hr immobilization stress had slightly lower brain NE levels than non-stressd rats, it was not significantly different. After 2-hr recovery period, brain NE levels nearly increased up to those of non-stressed rats. 3-hr immobilization stress significantly increased($P<0.05$) brain MHPG-SO4 levels in both two diet groups. After 2hr recovery period, rats fed either basal diet or high-TYR diet still had a significantly higher($P<0.05$) brain MHPG-SO4 levels than rats in non-stress group. Rats fed high-TYR diet tended to have slightly higher levels of brain MHPG-SO4 than rats fed basal diet in stress and recovery groups.

Fig. 4 present the effects of 3-hr immobilization stress and high-TYR diet on serum corticosterone levels. 3-hr immobilization stress significantly increased($P<0.05$) serum corticosterone levels in both two diet groups. However, in stress groups, rats fed high-TYR diet had significantly lower serum corticosterone levels than rats fed basal diet. In addition, in recovery groups, rats fed high-TYR diet had the lower levels of serum corticosterone than rats fed basal diet. These results indicated that high-TYR diet could affect serum corticosterone levels in stressed rats. That is, high-TYR diet can suppress the stress-induced rise of serum corticosterone levels.

The effects of 3hr immobilization stress and high-TYR diet on serum levels of glucose and free fatty acid are shown in Table 3. In serum glucose levels, no significant differences were found between two diet groups. 3-hr immobilization stress tended to increase serum glucose levels. However, after 2-hr recovery period, serum glucose levels nearly returned to levels of non-stressed rats. In basal diet group, 3-hr immobilization stress significantly increased($P<0.05$) serum free fatty acid, while in high-TYR diet group, there were no difference between non-stressed rats and stressed rats. Meanwhile, after 2hr recovery period, serum free fatty acid levels returned to basal levels of non-stressed rats. Compared to rats fed basal diet, rats fed high-TYR diet had significantly lower($P<0.05$) levels of serum free fatty acid in all sub-groups.

Discussion

During the experimental period, food intakes of rats fed either basal diet or high-TYR diet were not significantly different(data not shown). As shown in Table 2 and Fig. 1, TYR supplementation greatly increased the levels of serum tyrosine and brain tyrosine, which was in agreement with other report[17]. However, the ranges of increase of serum tyrosine levels were higher than those of brain tyrosine levels. The reason for these results was thought that while serum tyrosine levels were directly affected by the amounts of dietary TYR, brain tyrosine levels were affected by the ratio of tyrosine concentration to other LNAA

Table 3. Effects of 3hr immobilization and high-tyrosine diet on serum levels of glucose and free fatty acid*

Treatment	Glucose		Free fatty acid	
	Basal diet	High-TYR diet	Basal diet	High-TYR diet
	mg/dl		uequiv/l	
Non-stress	151 ± 9^{abc}	135 ± 11^{c}	688 ± 74^{b}	484 ± 163^{c}
Stress	163 ± 10^{a}	155 ± 18^{ab}	1092 ± 120^{a}	533 ± 155^{c}
Recovery	139 ± 23^{bc}	149 ± 8^{abc}	675 ± 156^{b}	472 ± 56^{c}

*All values represent the mean S.E($n=6-7$ per group)
Means with the same letter are not significantly different at $\alpha=0.05$ levels by Duncan's multiple range test.

concentrations rather than serum tyrosine levels. 3-hr immobilization stress greatly decreased the levels of serum tyrosine and brain tyrosine. In serum tyrosine levels(Table 2), while stressed rats had great decreases, rats in recovery groups had slight decreases in both two diet groups when compared to stressed rats. These patterns of reduction of amino acid concentrations suggested that tyrosine, during 3-hr immobilization stress, was used as a precursor of brain NE rather than a merely energy source. During 3-hr immobilization stress, tyrosine was needed in the brain according to the increase of utilization of brain NE so that lots of serum tyrosine were entered into the brain. However, during 2hr recovery period, amounts of tyrosine entering into the brain was greatly decreased due to the decrease of utilization of brain NE so that there was a slight decrease in serum tyrosine levels. On the other hand, the patterns of the changes of brain tyrosine levels, after 3-hr immobilization stress and 2hr recovery period, were shown differently in those of serum tyrosine levels(Fig. 1). In serum tyrosine, recovery groups had slight decreases of levels when compared to stress groups, while in brain tyrosine recovery groups showed significant increases so that the levels of brain tyrosine tended to return to the basal levels of non-stressed rats.

The reason for these results was thought that the rate of influx from blood to brain might have been increased after the exposure to immobilization stress, while utilization of tyrosine as a precursor of brain NE was sharply decreased after the release from the stress. That is, influx of tyrosine into brain exceeded the use for brain NE synthesis so that brain tyrosine levels were increased in recovery groups. On the other hand, in recovery groups, while rats fed basal diet had a significant increase of brain tyrosine concentration, rats fed high-TYR diet had only a slight increase of brain tyrosine levels and were not significantly different in brain tyrosine levels between stress group and recovery group. From these results it could be thought that, in high-TYR group, tyrosine as a precursor for brain NE synthesis was well supplied during stress and recovery period.

As shown in Table 2, Fig. 1 and Fig. 2, tyrosine supplementation(high-TYR diet) greatly increased levels of serum tyrosine and brain tyrosine, while high-TYR diet could not affect the brain levels of NE. This confirms that the tyrosine hydroxylase is normally saturated with its substrate, tyrosine, in brain for NE synthesis. According to Hoskins's report[29], basal tyrosine hydroxylase activity was the same in several areas of the brain. On the other hand, immobilization stress for 3hr resulted in a significant reduction of brain NE and a marked increase in MHPG-SO4 levels. These results show that the enhancement of functional activity of noradrenergic neurons caused by immobilization stress leads to marked acceleration of NE release and turnover and consequently lower NE levels. The enhancement of functional activity of noradrenergic causes the synthesis of brain NE to depend on tyrosine availability because the increased firing causes their enzyme, tyrosine hydroxylase, to become phosphorylated, active form[11][18][30]. Therefore, in these conditions, the supplementation of tyrosine causes these neurons to synthesize more NE so that the levels of brain NE can be increased. From these results, it was thought that high-TYR diet could prevent stress-induced reduction of brain NE. In present study, basal diet group showed the significant difference between non-stress and stress groups. However, in stressed rats, although high-TYR diet group had higher levels of brain NE than basal diet group, the difference was not significant.

Tyrosine supplementation also could not affect brain NE turnover in non-stress group(Fig. 3).

However, in stress and recovery groups, the levels of brain MHPG-SO4 were increased by tyrosine supplementation. Although the elevation of levels was not significant, rats fed high-TYR diet had higher levels of brain MHPG-SO4 than rats fed basal diet in stress and recovery groups. Brain MHPG-SO4 level is a useful index of brain NE turnover[4]. Therefore, these results indicated that when noradrenergic neuron's activity was increased, supplementation of tyrosine causes these neurons to release as well as to synthesize more of their transmitter. It has been known that inhibitory central noradrenergic neural system involved in the inhibition of corticotropin releasing factor(CRF) release exists. Therefore, the reduction of brain NE levels may have resulted in increased release of CRF and consequently increased the activity of hypothalamus-pituitary- adrenal cortex axis[31)32)]. As shown in Fig. 3, recovery groups still had significantly higher levels of brain MHPG-SO4 than non-stress groups with the same dietary treatment. These results indicated that after 2hr period since release from stress,rats had the elevation of brain NE turnover and have been affected by stress.

It was known that stress elevates corticosterone concentrations through central component acting upon hypothalamus-pituitary-adrenal cortex system so that the levels of serum corticosterone are used as a sensitive index of stress[31)]. As shown in Fig. 4, in stress and recovery groups, rats fed high-TYR diet had significantly lower levels of serum corticosterone than rats fed basal diet, indicating that high-TYR diet suppressed the stress-induced rise in serum corticosterone. These results were in good agreement with Reinstein's report [15)].

During stressful conditions, glucose and free fatty acid levels are used as an indirect index indicating the activity of sympathetic nerve. Stress increases the sympathetic nerve activity so that levels of glucose and free fatty acid are increased and are used as an index of stress. As shown in Table 3, 3-hr immobilization stress increased the levels of serum glucose and free fatty acid. In general, rats fed high-TYR diet had lower levels of serum glucose and free fatty acid than rats fed basal diet when exposed to stress.

It is suggested that high-TYR diet can prevent the stress-induced depletion of brain NE and suppress the rise in serum corticosterone,glucose and free fatty acid. Therefore, it may be indicated that high-TYR diet increase the coping ability of body to stress.

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= 국문초록 =

타이로신 보강 식이가 스트레스 상황에서 뇌의 Norepinephrine 대사에 미치는 영향

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타이로신이 보강된 식이가 3시간의 immobilization 스트레스로 인한 뇌의 Norepinephrine 대사 변화에 미치는 영향에 대해 연구하였다. S.D.종 수컷쥐들을 정상식이군, 타이로신 보강식이군(3.4% tyrosine/diet(w/w))으로 나누어 5일간 실험식이로 사육한 후, 이를 각기 비스트레스군, 스트레스군, 회복군으로 세분화하여 실험하였다.

타이로신 보강식이는 혈청과 뇌의 타이로신 농도를 증가시켰으며, 스트레스는 혈청과 뇌의 타이로신 농도와 뇌의 Norepinephrine 함량을 감소시켰다. 뇌의 Norepinephrine 함량의 경우, 정상식이군에서는 그 감소가 현저한 반면, 타이로신 보강 식이군에서는 유의적인 차이가 없었다. 스트레스를 받지 않은 비스트레스군에서는 식이내 타이로신 함량이 뇌의 Norepinephrine와 MHPG-SO4 수준에 영향을 주지 않았다. 그러나 스트레스군에서는 타이로신 보강식이가 스트레스로 인한 뇌의 Norepinephrine 함량 감소를 억제하는 효과를 보였다. 스트레스는 뇌의 MHPG-SO4 함량을 증가시켰으며, 이는 스트레스 상황에서 뇌의 Norepinephrine turnover 증가를 보여준다. 타이로신 보강은 스트레스시 일어나는 혈청내의 포도당, 유리지방산, corticosterone의 농도 증가를 억제하는 효과를 보였다.

본 실험결과에 의하면, 타이로신 보강식이는 스트레스에 대한 체내의 대응력을 증가시키는 것으로 보여진다.