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Monoamine Depletion Attenuates the REM Sleep Deprivation-Induced Increase in Clonidine Response in the Forced Swimming Test

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ASAKURA, W., K. MATSUMOTO, H. OHTA AND H. WATANABE. *Monoamine depletion attenuates the REM sleep deprivation-induced increase in clonidine response in the forced swimming test.* PHARMACOL BIOCHEM BEHAV **49**(1) 79–84, 1994.—Effect of monoamine depletion on the REM sleep (REMs) deprivation-induced increase in clonidine response in the forced swimming test was investigated. Mice were deprived of REMs by the small pedestal method. Clonidine HCl (10–1000 μg/kg, IP), an α_2-adrenoceptor agonist, dose dependently increased swimming activities in group-housed and socially isolated mice used as the control groups. The dose-response relationship shifted to the left following REMs deprivation (ED_{50} values in the group-housed, isolated, and REMs-deprived mice were 250, 200, and 27 μg/kg, respectively). Monoamine depletion, induced by reserpine (5 mg/kg, IP) plus α-methyl-*p*-tyrosine (250 mg/kg, IP), did not produce any changes in the effects of clonidine in the control groups. However, in REMs-deprived mice, monoamine depletion significantly decreased the effect of 100 μg/kg clonidine, but not that of 300 μg/kg clonidine on swimming activity. These results indicate that clonidine-induced increase in swimming activity in the forced swimming test is mainly mediated by postsynaptic α_2-adrenoceptor, and that endogenous noradrenaline in the brain plays an important role in the increase of clonidine response following REMs deprivation treatment. The neuronal mechanism of the increase in clonidine response is discussed.

REM sleep deprivation Forced swimming test Swimming activity Clonidine
α_2-Adrenoceptors Monoamine depletion

RAPID eye movement sleep (REMs) deprivation has been clinically shown to improve certain types of depression in humans [for review, (16)]. In rats, this treatment increases the noradrenaline turnover in the brain (10,12,13,17), and reduces cortical β-adrenoceptor density and cyclic AMP accumulation stimulated by noradrenaline [for review, (14)]. In addition, we have shown that REMs deprivation increases swimming activity in the forced swimming test, and that it reduces the effective doses of clonidine, an α_2-adrenoceptor agonist, on the swimming activity (2). Although α_2-adrenoceptors are located in the pre- and postsynaptic sites in the central nervous system, the antiimmobility effect of clonidine appears to be mediated by stimulation of the postsynaptic α_2-adrenoceptor (5,9). These findings suggest that REMs deprivation induces supersensitivity of postsynaptic α_2-adrenoceptor, resulting in enhancement of the clonidine effect.

To clarify whether presynaptic mechanisms are included in the REMs deprivation-induced increase in the clonidine effect, the present study investigated the effect of monoamine depletion induced by reserpine plus α-methyl-*p*-tyrosine on the clonidine response in the forced swimming test.

METHOD

Animals

Male 5-week-old ddY mice (Japan SLC, Inc., Hamamatsu, Japan) were used in the experiments. The animals were housed in groups of 20–25 per cage (35 × 30 × 16 cm), for at least 1

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week before the start of the experiment, with free access to food and water. Housing conditions were thermostatically maintained at 24 ± 1°C, with a 12L : 12D cycle (lights on: 0730–1930 h).

REM Sleep Deprivation

Mice were deprived of REM sleep (REMs) by the small pedestal (platform) method as described previously (1,2). In brief, a small pedestal (4.5 cm high, 1.8 cm diameter) was fixed at the center of a REMs deprivation chamber (20 × 15 × 21 cm), and was surrounded by water (3.5 cm deep). Mice were placed individually in the chamber, and housed for 48 h with free access to food and water (REMs-deprived mice). Other groups of mice were either housed in groups of four (group-housed mice), or housed individually (isolated mice) in a Plexiglas cage (25 × 18 × 12 cm) during the same period as the REMs deprivation, and were used as the control groups. After the termination of REMs deprivation, each mouse was placed individually in the Plexiglas cage for 3 h, with the exception of those animals used for immediate experimentation.

The Forced Swimming Test

Each mouse was placed individually in a transparent glass cylinder (20 cm high, 8 cm diameter) containing fresh water (25°C, 8 cm deep), and was forced to swim for 15 min (pretest swimming). After a 20-min drying period, the animals were deprived of REMs for 48 h. Immediately after the termination of REMs deprivation or 3 h after a recovery period, the animals were placed in the cylinder for 5 min (test swimming). Clonidine (10, 30, 100, 300, and 1000 μg/kg) was administered 30 min prior to the test swimming. When depleting brain monoamine, reserpine (5 mg/kg) and α-methyl-*p*-tyrosine (250 mg/kg) were injected immediately after the termination of REMs deprivation treatment, and the test swimming was carried out 3 h after reserpine and α-methyl-*p*-tyrosine administrations. Swimming activity during the test swimming was measured using an animal movement analyzing system, Scanet SV-10 (Toyo Sangyo Co., Ltd., Toyama, Japan), as described previously (2). In brief, this system consisted of a rectangular enclosure (40 × 38 cm), the side walls (12 cm) of which were equipped with 144 pairs of photosensors. Each pair of photosensors was set at a height of 8.8 cm above the floor, and was scanned every 0.1 s to detect animal movement. Swimming activity was calculated from the scanning data obtained.

Measurement of Locomotor Activity and Rearing

A Scanet SV-10 system was used to measure locomotor activity and the number of rearings in mice. The photosensors were set at a height of 2.5, and 7.5 cm, above the floor. Three hours after the termination of REMs deprivation each mouse was administered with clonidine (100 μg/kg), and then placed individually in a Plexiglas cage (25 × 18 × 24 cm), which was fixed at the center of the Scanet SV-10 system. Locomotor activity and the number of rearings were measured over a 30-min period. Locomotor activity and the number of rearings were calculated from the scanning data obtained from both series of photosensors.

Brain Monoamine Assay

Immediately after the termination of REMs deprivation treatment mice were administered reserpine (5 mg/kg) and α-methyl-*p*-tyrosine (250 mg/kg). After 3 h, the mice were decapitated. The brain was rapidly removed and washed in ice-cold saline. The parietal cortex, hippocampus, and hypothalamus were dissected on an ice-cold glass plate, and frozen with liquid nitrogen. After weighing, each individual tissue was homogenized in 1 ml ice-cold perchloric acid solution (0.25 M) containing 0.3 mg cysteine, and centrifuged (10,000 × *g*, 4°C) for 10 min. The monoamine concentration in the supernatant was determined by a high performance liquid chromatography system equipped with electrochemical detector (HPLC-ECD) [Coulochem® Electrode Array System, CEAS, Model 5500 (ESA, Inc., Bedford, MA, USA)].

Drugs

The test drugs used were as follows: clonidine HCl (Sigma Chemical Co., St. Louis, MO), DL-α-methyl-*p*-tyrosine methyl ester HCl (Nacalai Tesque Inc., Kyoto, Japan), and reserpine (Apoplone® Inj. 0.5 mg, Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan). Clonidine and α-methyl-*p*-tyrosine were each dissolved in saline. All drugs were intraperitoneally injected using a constant volume (0.01 ml/g body weight).

Statistical Analysis

Data were analyzed by one-way analysis of variance (ANOVA), followed by a two-tailed multiple Student's *t*-test. Differences of $p < 0.05$ were considered significant.

RESULTS

The Effect of 100 μg/kg Clonidine on the Swimming Activity in REMs-Deprived Mice

When tested immediately after the REMs deprivation treatment, a significant increase in the swimming activity following saline administration (basal swimming activity) was observed

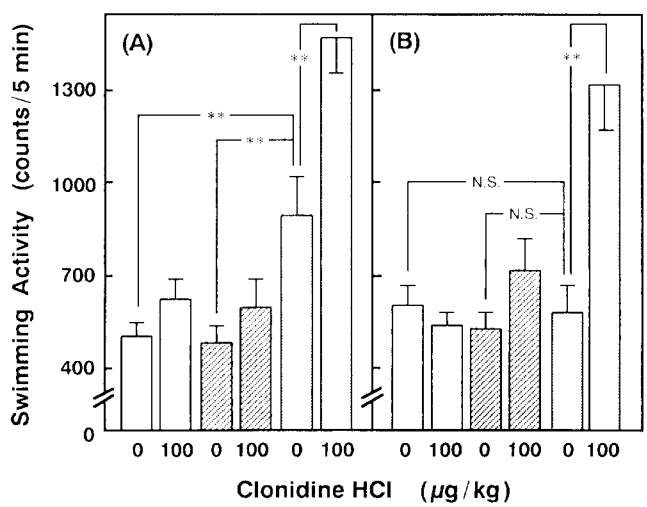

FIG. 1. The effect of clonidine on swimming activity in group-housed, isolated, and REM sleep-deprived mice. Mice were either group housed (open column), socially isolated (hatched column), or deprived of REM sleep (dotted column) for 48 h. Immediately (A) or 3 h (B) after the termination of REM sleep deprivation treatment, swimming activity was measured. Clonidine HCl (100 μg/kg) was administered 30 min before test swimming. Each bar represents the mean ± SEM obtained from 14 or 15 mice. $^{**}p < 0.01$ compared with each group. N.S. = not significant (multiple Student's *t*-test).

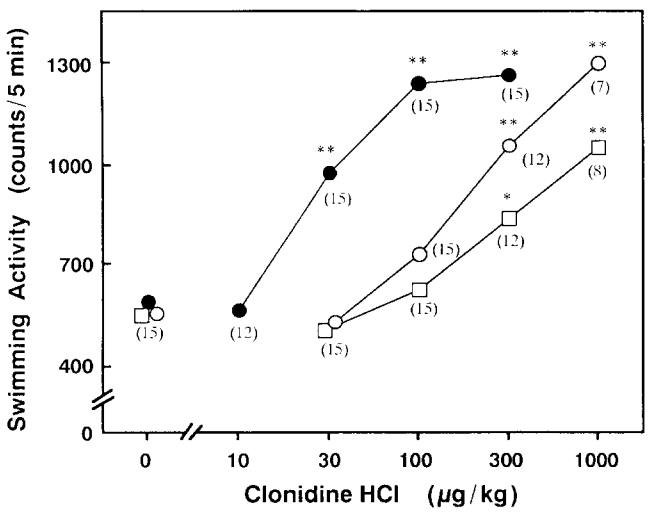

FIG. 2. The dose-response relationship of the clonidine-induced increase in swimming activity in group-housed, isolated, and REM sleep-deprived mice. Mice were either group housed (□), socially isolated (○), or deprived of REM sleep (●). Swimming activity was measured 3 h after the termination of REM sleep deprivation treatment. Clonidine HCl (10–1000 μg/kg) was administered 30 min before the test swimming. Each point represents the mean swimming activity. The number of animals is given in parentheses. *$p < 0.05$, **$p < 0.01$ compared with saline-treated mice (multiple Student's t-test).

in the REMs-deprived mice. Clonidine (100 μg/kg), an α_2-adrenoceptor agonist, further increased swimming activity in the REMs-deprived animals, but there was no increase observed in the control groups treated with the same dose of clonidine [ANOVA value, $F(5, 78) = 18.7$, $p < 0.001$; Fig. 1A]. Three hours after REMs deprivation treatment, the REMs deprivation-induced increase in basal swimming activity returned to the control levels; however, clonidine (100 μg/kg) still markedly increased the swimming activity in REMs-deprived mice [$F(5, 84) = 12.2$, $p < 0.001$; Fig. 1B].

The Dose-Response Relationship of Clonidine-Induced Increase in Swimming Activity

As shown in Fig. 2, when tested 3 h after the REMs deprivation treatment, clonidine (10–1000 μg/kg) dose dependently increased the swimming activity in group-housed and isolated animals [ANOVA values: group-housed, $F(4, 60) = 6.84$, $p < 0.001$; isolated, $F(4, 59) = 8.68$, $p < 0.001$]. The dose-response relationship in isolated mice shifted to the left after REMs deprivation treatment (ED_{50} values calculated from the mean swimming activity of group-housed, isolated, and REMs-deprived mice were 250, 200, and 27 μg/kg, respectively).

*The Effect of Reserpine and α-Methyl-p-*Tyrosine on the Clonidine-Induced Increase in Swimming Activity

Pretreatment with reserpine and α-methyl-p-tyrosine did not affect either the basal swimming activity, nor the effects of clonidine (100 and 300 μg/kg) in group-housed [ANOVA value, $F(5, 84) = 7.04$, $p < 0.001$; Fig. 3A] or isolated animals [$F(5, 84) = 4.13$, $p < 0.005$]; Fig. 3B. However, these agents significantly suppressed the effect of 100 mg/kg clonidine in REMs-deprived mice. The degree of swimming activity induced by 300 mg/kg clonidine was unaltered by the reserpine and α-methyl-p-tyrosine pretreatment [ANOVA value, $F(5, 100) = 5.94$, $p < 0.001$; Fig. 3C].

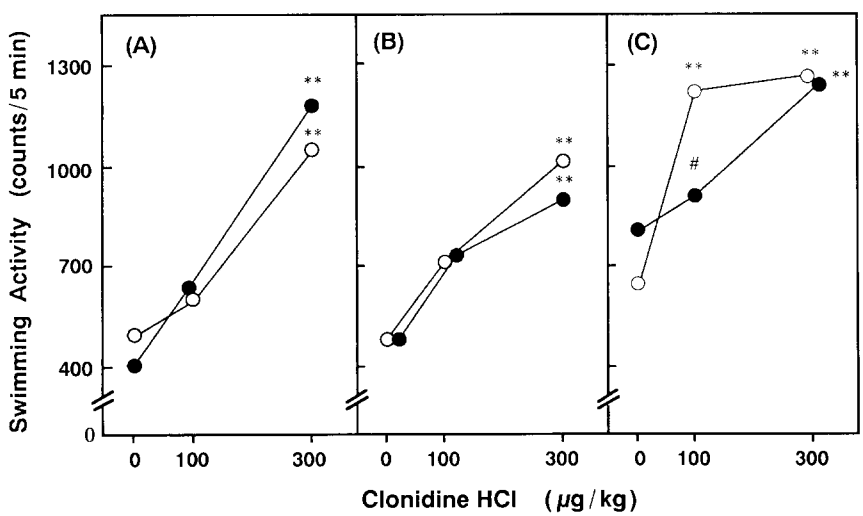

FIG. 3. The effect of monoamine depletion on the clonidine-induced increase in swimming activity. Mice were either group housed (A), socially isolated (B), or deprived of REM sleep (C). Animals were treated with either saline (○) or reserpine plus α-methyl-p-tyrosine (●) immediately after the REM sleep deprivation treatment. The swimming activity was measured 3 h after the REM sleep deprivation treatment. Clonidine HCl (100 and 300 μg/kg) was administered 30 min before the test swimming. Each point represents the mean swimming activity obtained from 15–18 animals. **$p < 0.01$ compared with mice treated with clonidine 0 μg/kg. #$p < 0.05$ compared with animals treated with the respective doses of clonidine (multiple Student's t-test).

TABLE 1

THE EFFECT OF RESERPINE AND α-METHYL-*p*-TYROSINE ON THE BRAIN MONOAMINE CONTENTS

Brain Regions		Treatment	Monoamine Content (μg/g Tissue) Group-Housed	Isolated	REMs-Deprived
Parietal Cortex					
	NA	saline	0.322 ± 0.013	0.348 ± 0.035	0.330 ± 0.019
		reserpine and α-MPT*	0.041 ± 0.018	0.081 ± 0.038	0.030 ± 0.017
	5-HT	saline	0.597 ± 0.093	0.619 ± 0.088	0.720 ± 0.136
		reserpine and α-MPT	0.157 ± 0.032†	0.192 ± 0.063†	0.139 ± 0.035†
Hippocampus					
	NA	saline	0.543 ± 0.045	0.489 ± 0.028	0.510 ± 0.036
		reserpine and α-MPT*	0.079 ± 0.035	0.132 ± 0.062	0.103 ± 0.040
	5-HT	saline	0.451 ± 0.042	0.440 ± 0.059	0.462 ± 0.067
		reserpine and α-MPT	0.083 ± 0.021†	0.097 ± 0.032†	0.062 ± 0.029†
Hypothalamus					
	NA	saline	1.840 ± 0.051	2.014 ± 0.062	2.230 ± 0.072
		reserpine and α-MPT	0.574 ± 0.184†	0.715 ± 0.291†	0.623 ± 0.178†
	5-HT	saline	1.617 ± 0.267	1.900 ± 0.266	2.042 ± 0.255
		reserpine and α-MPT	0.569 ± 0.220†	0.620 ± 0.298†	0.359 ± 0.229†
	DA	saline	0.433 ± 0.033	0.472 ± 0.080	0.511 ± 0.056
		reserpine and α-MPT	0.051 ± 0.023†	0.056 ± 0.028†	0.053 ± 0.035†

Mice were either group-housed, isolated, or deprived of REM sleep (REMs). Mice were pretreated with reserpine (5 mg/kg) and DL-α-methyl-*p*-tyrosine methyl ester HCl (α-MPT, 250 mg/kg) or saline immediately after the REMs deprivation treatment. Each mouse was decapitated 3 h after the administrations. Noradrenaline (NA), serotonin (5-HT), and dopamine (DA) concentrations in each sample were assayed using a HPLC-ECD. Each datum represents the mean value of 5-6 mice, with the SEM indicated.

*Data were not statistically analyzed because noradrenaline levels in some samples were lower than detection limit.

†$p < 0.01$ compared with respective saline control groups (multiple Student's *t*-test).

*The Effect of Reserpine and α-Methyl-*p*-tyrosine on the Brain Monoamine Contents*

REMs deprivation did not change the noradrenaline, serotonin, or dopamine content in the parietal cortex, hippocampus, or hypothalamus. Pretreatment with reserpine and α-methyl-*p*-tyrosine markedly decreased the monoamine contents of several brain regions of REMs-deprived animals to the same levels as those of the control groups treated with these agents (Table 1).

The Effect of Clonidine on Locomotor Activity and Rearing

Clonidine (100 μg/kg) significantly decreased locomotor activity in the group-housed, isolated, and REMs-deprived mice. Clonidine (100 μg/kg) also markedly decreased the number of rearings in the control groups, but had no significant effect on rearings in REMs-deprived mice [ANOVA values: locomotor activity, $F(5, 54) = 6.29$, $p < 0.001$; No. of rearings, $F(5, 54) = 4.97$, $p < 0.001$,; Table 2].

TABLE 2

THE EFFECT OF CLONIDINE ON LOCOMOTOR ACTIVITY AND REARING IN REM SLEEP-DEPRIVED, GROUP-HOUSED, AND ISOLATED MICE

	Locomotor activity (counts/30 min)		No. of Rearings (counts/30 min)	
Clonidine (μg/kg)	0	100	0	100
REMs-deprived	9067 ± 1031	5811 ± 1066*	194 ± 27	122 ± 28^{NS}
Group-housed	7818 ± 1348	3175 ± 708†	148 ± 38	58 ± 21*
Isolated	9686 ± 1176	3890 ± 937†	196 ± 32	60 ± 16†

Clonidine (100 μg/kg) was injected 3 h after the termination of REM sleep (REMs) deprivation. Each value represents the mean locomotor activity, and the number of rearings obtained from 10 mice, with the SEM indicated.

*$p < 0.05$, †$p < 0.01$ compared with the respective saline-treated animals.

^{NS}Not significant (multiple Student's *t*-test).

DISCUSSION

The present results demonstrated that the effect of clonidine, an α_2-adrenoceptor agonist, on swimming activity in the forced swimming test is enhanced by REMs deprivation, and that endogenous noradrenaline in the brain plays an important role in the REMs deprivation-induced enhancement of clonidine response.

As previously reported (2), immediate examination of the mice after REMs deprivation treatment showed that the basal swimming activity in REMs-deprived mice was significantly higher than those in the control groups, and that a dose of clonidine that had no effect on swimming activity in the control groups further increased the comparatively high swimming activity in the REMs-deprived mice. In the present study, we found that this high basal swimming activity in REMs-deprived mice disappeared 3 h after the REMs deprivation treatment, but the stimulatory effect of 100 μg/kg clonidine on the swimming activity in REMs-deprived mice remained unchanged. Furthermore, such an effect of REMs deprivation on the clonidine (100 μg/kg)-induced increase in swimming activity was still observed even when tested 24 h after the REMs deprivation treatment (data not shown). These findings show that the effect of REMs deprivation on the clonidine (100 μg/kg)-induced increase in swimming activity was long lasting, whereas the REMs deprivation-induced increase in basal swimming activity was short lasting. Our previous results demonstrated that the clonidine-induced increase in swimming activity was blocked by an α_2-adrenoceptor antagonist, yohimbine, whereas the REMs deprivation-induced increase in basal swimming activity was not inhibited by adrenoceptor antagonists including yohimbine, nor a noradrenaline synthesis inhibitor, disulfiram (2-4). Therefore, the present data indicate that in immediate examination after the REMs deprivation treatment both nonadrenoceptor and α_2-adrenoceptor mechanisms are involved in the clonidine (100 μg/kg)-induced increase in swimming activity, and that the mediation by nonadrenoceptor mechanism(s) can be eliminated by testing 3 h after the termination of REMs deprivation treatment.

At 3 h after the REMs deprivation treatment, the dose-response relationship for clonidine apparently shifted to the left in REMs-deprived mice, without any contribution from the nonadrenergic mechanism mediating the REMs deprivation treatment-induced increase in swimming activity. Clonidine reportedly stimulates both pre- and postsynaptic α_2-adrenoceptors [for review, (8)] and changes neuronal activities of not only noradrenergic but also serotonergic and dopaminergic systems at similar doses to those used in the present study (6,7,15). On the other hand, Cervo and Samanin (5) and Malinge et al. (9) suggested that clonidine decreases the immobility time in the forced swimming test by activating postsynaptic α_2-adrenoceptors, because the effect of clonidine was blocked by selective α_2-adrenoceptor antagonists but not noradrenaline depletors. The present findings that the dose-response curves of clonidine-induced increase in swimming activity in the control groups did not change following reserpine plus α-methyl-*p*-tyrosine administration, is consistent with their data, and suggest that, at least, neither serotonergic nor dopaminergic systems are involved in the postsynaptic α_2-adrenoceptor-mediated effect of clonidine on swimming activity.

The findings that REMs deprivation increased the clonidine response in the forced swimming test suggest that REMs deprivation may upregulate postsynaptic α_2-adrenoceptors in the brain, resulting in an increase in clonidine effect. However, this does not seems to be the case, because pretreatment with reserpine and α-methyl-*p*-tyrosine altered the clonidine response in REMs-deprived mice. These findings indicate that endogenous noradrenaline plays an important role in the effect of 100 μg/kg clonidine in REMs-deprived mice. On the other hand, monoamine depletion failed to change the effect of 300 μg/kg clonidine in these animals. Taken account of the fact that this dose of clonidine was capable of producing the maximum effect on swimming activity in the forced swimming test, contribution of noradrenaline to the swimming activity enhanced by 300 μg/kg clonidine seems to be little in REMs-deprived mice.

Involvement of noradrenaline in the increase of clonidine response in REMs-deprived mice may be due to the functional change(s) in the presynaptic sites of the central noradrenergic system. In fact, the sedative effect of clonidine (100 μg/kg), which is due to the reduction in noradrenaline outflow via presynaptic α_2-adrenoceptor activation [for review, (8)], was attenuated by REMs deprivation in this study. These results are well consistent with the data of Mogilnicka and Pilc (11), and suggest that the sensitivity of the presynaptic α_2-adrenoceptor is decreased by REMs deprivation. Because presynaptic α_2-adrenoceptor stimulation inhibits release of noradrenaline from the nerve terminal, it is possible that the level of noradrenaline in the synaptic cleft may be higher in REMs-deprived mice than in the control groups. Furthermore, the increase in noradrenaline turnover, which was observed after REMs deprivation (10,12,13,17), may also cause an increase in the transmitter level in the synaptic cleft, and may partly counteract the sedative effect of clonidine. Although exact mechanisms of the REMs deprivation-induced apparent increase in clonidine response in the forced swimming test remain unclear, a speculative explanation is that REMs deprivation-induced functional changes in presynaptic α_2-adrenoceptors may cause excess release of noradrenaline and that postsynaptic α_2-adrenoceptor stimulation by not only clonidine itself but also excessive noradrenaline may result in the apparent increase in the effect of 100 μg/kg clonidine on the swimming activity in REMs-deprived mice.

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