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The involvement of σ receptors in the choice reaction performance deficits induced by phencyclidine

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Abstract

The present study investigated the effects of phencyclidine (PCP) on choice reaction in a 3-choice serial reaction time task for studying attentional function. PCP (3.2 mg/kg) significantly delayed choice reaction time and reduced choice accuracy. A novel σ receptor antagonist *N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]-ethylamine monohydrochloride (NE-100) at 3.2 mg/kg, and 1-(cyclopropylmethyl)-4-[2′-(4″-fluorophenyl)-2′-oxoethyl]piperidine HBr (DuP734) at 1.0–3.2 mg/kg, but not 4-[2′-(4″-cyanophenyl)-2′-oxoethyl]-1-(cyclopropylmethyl)piperidine (XJ448), antagonized both the delayed choice reaction time and the decreased choice accuracy elicited by PCP administration. The antagonism induced by NE-100 was blocked by the σ receptor agonist (+)-*N*-allylnormetazocine HCl [(+)-SKF10,047]. These findings indicated that PCP (3.2 mg/kg) significantly induced attention deficit in a 3-choice serial reaction time task, and that this process may be mediated by σ receptors.

Keywords: Choice reaction time; Attention; σ Receptor; Phencyclidine

1. Introduction

The psychotomimetic drug phencyclidine (PCP) has two binding sites, a σ binding site and a PCP binding site (Walker et al., 1990). Sigma binding sites have been found in cortical and limbic structures in human postmortem brains, and their distribution differs from that of PCP sites (Shibuya et al., 1992; Monnet, 1993). Tam et al. (1991, 1992) reported that DuP734, a σ receptor antagonist, antagonized the rotational behavior induced by PCP in rats. NE-100 is a novel compound with selective and potent affinity for the σ binding site. The head-weaving behavior and cognitive dysfunction induced by PCP was dose dependently antagonized by NE-100 in rats (Okuyama et al., 1993; Ogawa et al., 1994). These findings suggest that the behavioral effects of PCP are mediated by σ receptors.

Attentional and information processing abnormalities have been noted frequently in schizophrenic patients (Jones et al., 1991; Erlenmeyer-Kimling et al., 1993; Braff et al., 1992; Posner and Petersen, 1990). Administration of PCP induces disturbance in attention uniquely similar to that observed in schizophrenia (Rosenbaum et al., 1959; Cohen et al., 1961). However, there has been little investigation of the effect of PCP on attentional function, using animal experiments. In the present study, we examined the influence of PCP on attentional performance in a 3-choice serial reaction time task in rats. Furthermore, we investigated whether attentional performance deficits produced by PCP are mediated by σ receptors by using several σ receptor ligands.

2. Materials and methods

2.1. Animals

Seven to nine-week-old male rats of the Wistar Strain (Nippon SLC) were used. During the experiment, food was limited to 10–15 g a day so that body weight could be maintained at approximately 80% of free-feeding weight. Water was provided ad libitum. The rats were housed in groups of three per cage under a constant temperature (23 ± 2°C) on a 12-h light-dark cycle (light period 07:00–19:00).

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2.2. Apparatus

The apparatus (26 cm length × 25 cm width × 24 cm high) had 3-retractable levers and a signal lamp over each lever. The levers were 3.5 cm apart and at a height of 6.5 cm from the grid floor. Food pellets (45 mg), which served as a positive reinforcement, were dispensed in the pellet feeder mounted at a height of 0.5 cm from the floor. The house light was located on the ceiling above the levers. The 3-lever operant apparatus was situated in a light-and sound-attenuating box. The experiments were carried out using a personal computer (NEC, PC-9801RX) and digital I/0 interface (Neuroscience INC, Japan).

2.3. Procedure

The animals were first trained to obtain food pellets by pressing any lever. Once the animals were consistently pressing a lever for the food reward, they were introduced to the experimental schedule. The beginning of the experiment was signaled by illumination of the house light. Immediately, the three levers (A, B and C) appeared simultaneously and one of the signal lamps was turned on (signal lamp A in Fig. 1). If the rat pressed the lever with the signal lamp on (lever A; correct lever) 3 consecutive times (FR3) within 60 s, it received one food pellet (45 mg) as a positive reinforcement automatically from the food dispenser and the three levers were then retracted behind the wall. However, if the rat pressed one of the levers with the signal lamp off (lever B and C in Fig. 1) 3 consecutive times, it did not receive a food pellet. Once again the levers were retracted. After a fixed inter-trial interval (20 s), the levers appeared again and a specific signal lamp was turned on (lever B in Fig. 1) for the next trial. The house light remained on throughout the experimental period. Rats were trained using one session (15 trials) per day. The order of exhibiting of signal lamps was randomized by a computer according to 8 different programs. Each signal lamp was presented 5 times in random order for a total of 15 consecutive trials. The following were recorded for each rat during each trial: (1) the time required for an animal to press any lever (choice reaction time; s), (2) choice accuracy (number of correct lever pressing/number of total lever pressing × 100; %), and (3) response rate (number of lever pressing/min). The criterion for learning was as follows: less than 35 s summed across the 15 trials for the choice reaction time and more than 14 correct responses (14 reinforcements). Once the rats had achieved this criterion throughout three consecutive sessions, they were used in the drug test session.

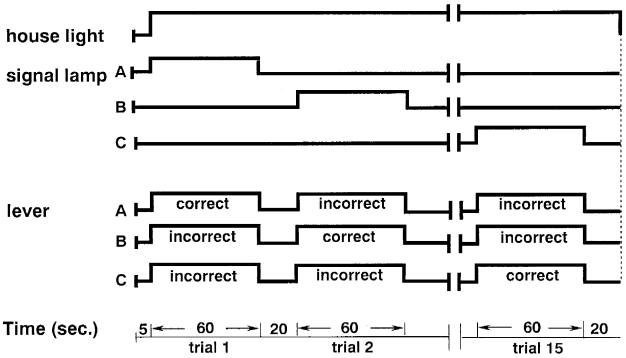

Fig. 1. The experimental schedule of the 3-choice serial reaction time task. (A) Left lever or signal lamp; (B) central lever or signal lamp; (C) right lever or signal lamp.

2.4. Drugs and treatment

The drugs used in this study were phencyclidine (PCP), *N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]-ethylamine monohydrochloride (NE-100; Taisho Pharmaceutical), 1-(cyclopropylmethyl)-4-[2′-(4″-fluorophenyl)-2′-oxoethyl] piperidine HBr (DuP734), 4-[2′-(4″-cyanophenyl)-2′-oxoethyl]-1-(cyclopropyl- methyl)piperidine (XJ448) and (+)-*N*-allylnormetazocine HCl ((+)-SKF10,047; Research Biochemical). PCP and (+)-SKF10,047 were dissolved in 0.9% saline and administered i.p. at a volume of 1 ml/kg of body weight at 30 min and 40 min before the test session, respectively. NE-100, DuP734 and XJ448 were dissolved in distilled water and administered at a volume of 1 ml/kg of body weight at 40 min before the test session.

2.5. Data analysis

The significance of the difference between groups was determined using a one-way analysis of variance (ANOVA) followed by Dunnett's test.

3. Results

Table 1 shows the effects of PCP on choice reaction in a 3-choice serial reaction time task. Although PCP 1.0

Table 1
Effect of PCP on choice reaction in a 3-choice serial reaction time task

Drug	mg/kg (*n*)	CRT (s)	Choice accuracy (%)	Correct response	Total response
Saline	– (8)	26.2 ± 1.1	96.0 ± 1.1	44.3 ± 0.5	46.1 ± 0.5
PCP	1.0 (5)	50.0 ± 15.0	91.9 ± 3.0	43.8 ± 0.7	47.8 ± 1.1
PCP	3.2 (8)	378.7 ± 39.0 [a]	62.7 ± 5.3 [a]	28.0 ± 2.2 [a]	45.6 ± 3.1

PCP was administered i.p. 30 min before the test session. Data represent the means ± S.E. Abbreviations: *n* = number of animals; CRT = choice reaction time (s) summed across 15 trials in a session; choice accuracy (%) = number of correct lever-pressings/total lever-pressings × 100; correct response = number of correct lever-pressings; total response = number of total lever-pressings. [a] $P < 0.01$ vs. saline.

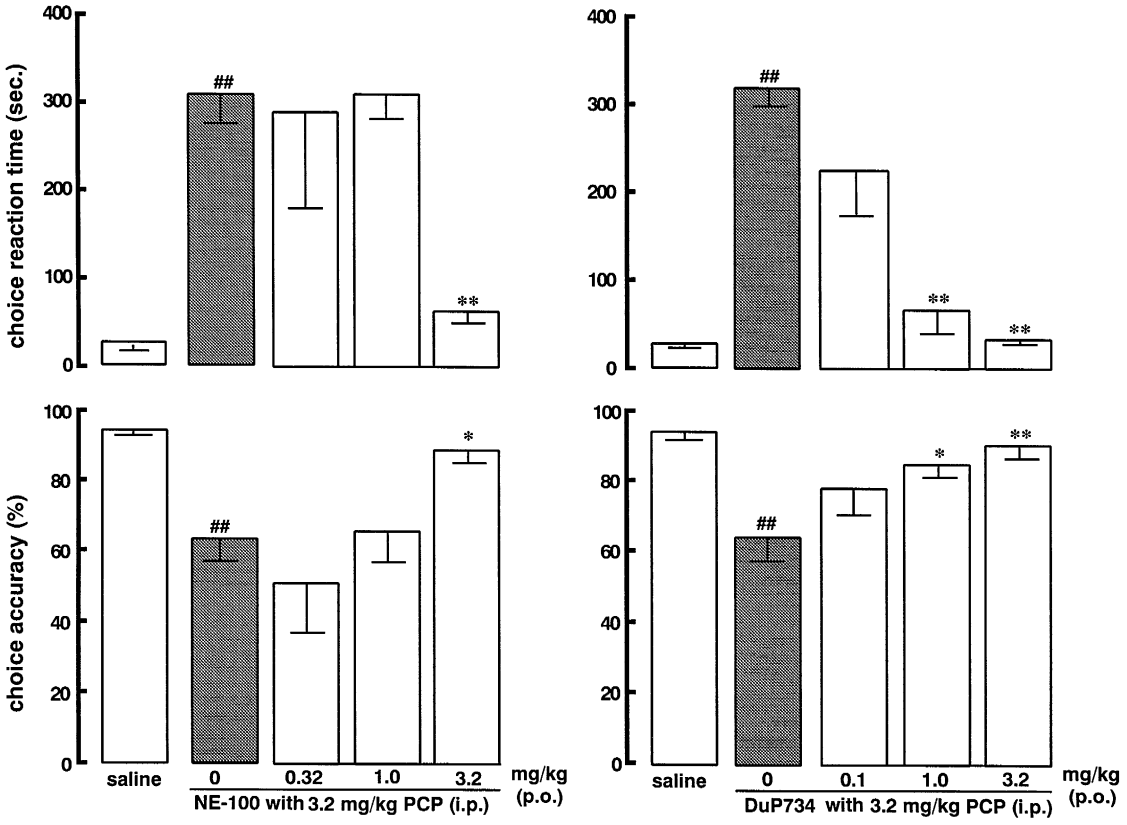

Fig. 2. Effects of NE-100 and DuP734 on delayed choice reaction time and decreased choice accuracy induced by PCP. The upper vertical axis indicates choice reaction time (s), while the bottom indicates choice accuracy (%). NE-100 and DuP734 were administered (p.o.) 10 min before injection of PCP. * $P < 0.05$, ** $P < 0.01$ vs. PCP 3.2 mg/kg, $^{\#\#}$ $P < 0.01$ vs. saline.

mg/kg had no effect, PCP 3.2 mg/kg produced a significant delay in choice reaction time in comparison to the saline group ($F(2,18) = 58.81$, $P < 0.01$). Choice accuracy was also significantly decreased by PCP 3.2 mg/kg ($F(2,18) = 27.34$, $P < 0.01$). PCP at this dose induced a significant decrease in correct lever-pressing ($F(2,18) = 45.82$, $P < 0.01$) without affecting the total number of lever pressings.

Pretreatment with the novel σ receptor antagonist NE-100, dose dependently antagonized the choice reaction performance deficits induced by PCP (Fig. 2, left panel). NE-100 at a dose of 3.2 mg/kg, without affecting choice

Table 2
Effects of SKF10,047, NE-100 and DuP734 on choice reaction in a 3-choice serial reaction time task

Drug	mg/kg (*n*)	CRT (s)	Choice accuracy (%)	Correct response	Total response
Saline	– (8)	25.5 ± 0.8	96.8 ± 1.7	44.5 ± 0.5	46.0 ± 0.5
SKF10,047	3.2 (7)	22.5 ± 2.8	98.5 ± 1.6	45.0 ± 0.0	45.8 ± 0.8
	10 (7)	24.2 ± 2.3	97.0 ± 2.4	45.0 ± 0.0	46.5 ± 1.2
	18 (7)	30.3 ± 2.0	97.4 ± 1.3	43.7 ± 0.9	44.9 ± 0.4
	32 (6)	329.6 ± 47.9 [a]	67.2 ± 5.4 [a]	27.8 ± 3.4 [a]	41.4 ± 5.7
NE-100	0.32 (6)	27.9 ± 0.6	99.4 ± 0.4	45.0 ± 0.0	45.4 ± 0.2
	1.0 (8)	28.3 ± 0.5	99.1 ± 0.5	44.6 ± 0.4	45.3 ± 0.3
	3.2 (8)	29.1 ± 0.5	98.4 ± 0.6	44.3 ± 0.5	45.0 ± 0.4
DuP734	0.1 (6)	26.8 ± 0.7	98.9 ± 0.5	45.0 ± 0.0	45.5 ± 0.2
	1.0 (7)	27.6 ± 0.7	98.5 ± 0.8	44.5 ± 0.5	44.6 ± 0.4
	3.2 (7)	28.7 ± 0.4	98.7 ± 0.7	44.1 ± 0.6	44.1 ± 0.6

SKF10,047, NE-100 and DuP734 were administered i.p. or p.o. 30 min before the test session. Data represent the means ± S.E. Abbreviations: *n* = number of animals; CRT = choice reaction time (s) summed across 15 trials in a session; choice accuracy (%) = number of correct lever-pressings/total lever-pressings × 100; correct response = number of correct lever-pressings; total response = number of total lever-pressings. [a] $P < 0.01$ vs. saline.

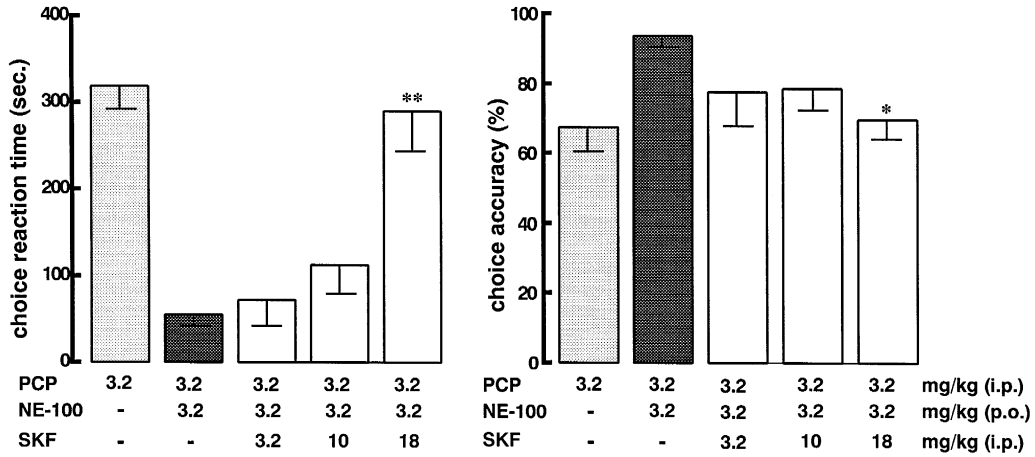

Fig. 3. Effect of SKF10,047 on NE-100-induced antagonism in choice reaction performance induced by PCP. Co-administration of NE-100 (p.o.) and SKF10,047 (i.p.) performed 10 min before injection of PCP. * $P < 0.05$, ** $P < 0.01$ vs. PCP 3.2 mg/kg + NE-100 3.2 mg/kg.

reaction performance (Table 2), significantly blocked both the PCP-induced delay in choice reaction time ($F(3,14) = 10.79$, $P < 0.01$) and decrease in choice accuracy ($F(3,14) = 5.14$, $P < 0.05$). NE-100 also significantly increased the incidence of correct lever-pressing ($F(3,14) = 9.44$, $P < 0.01$) compared with PCP at 3.2 mg/kg. Another σ receptor antagonist, DuP734 (0.1–3.2 mg/kg), alone did not affect choice reaction (Table 2). Pretreatment with DuP734 completely reversed the impairments in choice reaction performance in PCP-treated rats (Fig. 2, right panel). DuP734, at doses of 1.0–3.2 mg/kg, significantly inhibited both the PCP-induced delay in choice reaction time ($F(3,18) = 13.59$, $P < 0.01$) and the decrease in choice accuracy ($F(3,18) = 3.89$, $P < 0.05$). Also, DuP734 significantly increased the incidence of correct lever-pressing ($F(3,18) = 5.99$, $P < 0.01$) compared with PCP (3.2 mg/kg).

The σ receptor agonist (+)-SKF10,047, at doses of 3.2–10 mg/kg, did not attenuate the antagonistic effects of NE-100 on the PCP-induced impairments in choice reaction. However, (+)-SKF10,047 at a dose of 18 mg/kg, without affecting choice reaction (Table 2), significantly attenuated the antagonism induced by NE-100 in PCP-treated rats (Fig. 3). SKF10,047 (18 mg/kg) reversed the antagonistic effects of NE-100 on the PCP-induced delay in choice reaction time ($F(3,17) = 10.91$, $P < 0.01$) and decrease in choice accuracy ($F(3,17) = 5.0$, $P < 0.05$).

Another σ receptor antagonist, XJ448, at doses of 1.0–10 mg/kg, did not improve the impairment of choice reaction performance in PCP-treated rats (Table 3).

4. Discussion

Phencyclidine is a powerful psychotropic drug that can induce a behavioral state with some similarities to schizophrenia. In normal volunteers, administration of PCP produces a selective attention deficit similar to that observed in schizophrenia (Bakker and Amini, 1961). Okuyama et al. (1994) reported that PCP injection (i.m.) reduced attention in rhesus monkeys with decreased or no response to exogenous stimuli (sound and touch). In the

Table 3
The antagonism of XJ448 on choice reaction performance deficits induced by PCP

Drug	mg/kg (*n*)	CRT (s)	Choice accuracy (%)	Correct response	Total response
Saline	– (8)	25.2 ± 1.6	96.0 ± 1.1	43.8 ± 0.7	48.2 ± 1.0
+ XJ448	1.0 (7)	28.1 ± 0.6	98.7 ± 0.9	41.1 ± 0.6	44.7 ± 0.2
+ XJ448	3.2 (7)	28.0 ± 0.7	98.2 ± 0.7	44.0 ± 0.6	45.0 ± 0.4
+ XJ448	10 (7)	127.9 ± 14.0	83.6 ± 2.1	32.0 ± 1.5	38.3 ± 1.8
PCP alone	3.2 (8)	353.0 ± 38.8 [a]	70.7 ± 5.3 [a]	29.0 ± 3.2 [a]	41.0 ± 6.0
+ XJ448	1.0 (7)	365.3 ± 46.5 [a]	67.6 ± 4.8 [a]	25.7 ± 4.2 [a]	38.0 ± 7.5
+ XJ448	3.2 (7)	306.5 ± 51.9 [a]	70.0 ± 5.9 [a]	24.5 ± 3.7 [a]	35.0 ± 11.0
+ XJ448	10 (7)	643.4 ± 71.3 [a]	60.4 ± 8.1 [a]	15.8 ± 3.1 [a]	26.2 ± 1.2 [a]

PCP (3.2 mg/kg) was administered i.p. 30 min before the test session. XJ448 was administered p.o. 10 min before injection of PCP. Data represent the means ± S.E. Abbreviations: *n* = number of animals; CRT = choice reaction time (s) summed across 15 trials in a session; choice accuracy (%) = number of correct lever-pressings/total lever-pressings × 100; correct response = number of correct lever-pressings; total response = number of total lever-pressings. [a] $P < 0.01$ vs. saline.

present study, using a new 3-lever operant apparatus for studying attentional function, PCP was found to produce an attention deficit in rats, as indicated by a delayed choice reaction time and a decreased choice accuracy. The attention deficit induced by PCP was improved by NE-100 and DuP734. NE-100 and DuP734 alone did not affect choice reaction, and no significant changes in motor activity were observed. Okuyama et al. (1993) also reported that NE-100 has no effect on spontaneous locomotor activity in mice. PCP has both a σ receptor binding site and a PCP receptor binding site. NE-100 has high affinity (IC_{50} value = 4.2 nM) for the σ receptor, but low affinity (IC_{50} value > 10 000 nM) for PCP receptors, as well as for dopamine D_1 receptors, dopamine D_2 receptors, 5-HT_{1A} receptors, and 5-HT_2 receptors (Okuyama et al., 1993). DuP734 also has a strong affinity (IC_{50} value = 2.4 nM) for σ receptors, but weak affinity (IC_{50} value > 10 000 nM) for dopamine D_1 receptors, 5-HT_{1A} receptors and PCP receptors (Tam et al., 1992; Okuyama et al., 1993). Thus, NE-100 and DuP734 are novel compounds with selective and high affinity for σ receptors. Furthermore, the NE-100-induced antagonism of the PCP-induced attention deficit was blocked by SKF10,047. It is known that SKF10,047 shows high affinity (K_d value = 13 nM) for σ receptors, but low affinity (K_d value = 430 nM) for PCP receptors (Zhou et al., 1991). These findings suggested that the attention deficit induced by PCP in rats as well as the antagonism produced by NE-100 and DuP734 are mediated by σ receptors. The head-weaving behavior and cognitive dysfunction induced by PCP was also antagonized by NE-100 in rats (Okuyama et al., 1993; Ogawa et al., 1994). Sigma binding sites have been proposed to have two subtypes, termed σ_1 and σ_2 receptors (Quirion et al., 1992). In saturation binding studies, the affinity profile of ligands displacing [^{3}H](+)-pentazocine was consistent with the labeling of σ_1 recognition sites: haloperidol > (+)-pentazocine > (+)-SKF10,047 > (+)-3-PPP (Zabetian et al., 1994). Chaki et al. (1994) reported that NE-100 inhibited [^{3}H](+)-pentazocine binding to σ_1 binding sites. DuP734 is also a high-affinity ligand for the σ_1 binding site, which is labeled by [^{3}H] (+)-SKF10,047 (Tam et al., 1992). Based on these results, the antagonism induced by NE-100 or DuP734 of PCP-induced attention deficits may be mediated by σ_1 receptors. These findings indicate that the effects of PCP, including the induction of psychotic behavior, are mediated by specific interactions with σ receptors. PCP induces a psychotomimetic state that closely resembles schizophrenia. Weissman et al. (1991) reported the selective loss of cerebral cortical σ sites in schizophrenia. σ receptors have been found in cortical and limbic structures in human postmortem brain (Weissman et al., 1988). Thus, σ receptor ligands may be useful in the treatment of schizophrenia.

The σ receptor antagonist XJ448 did not improve the attention deficit induced by PCP. In rat brain membranes, competition binding experiments showed that the order of potency of displace bound [^{3}H](+)-3-PPP was DuP734 (IC_{50} value = 2.4 nM) > NE-100 (IC_{50} value = 4.2 nM) > XJ448 (IC_{50} value = 16.5 nM) (Okuyama et al., 1993). These findings indicate that the affinity of NE-100 or DuP734 for σ receptors was 4–8 times that of XJ448. In our experiments, the order of potency of the antagonism of the attention deficit induced by PCP was DuP734 > NE-100 > XJ448. Therefore, the reason XJ448 had no effect in improving the attention deficit may be due to its lower affinity for σ receptors compared to NE-100 and DuP734. However, the 10 mg/kg dose of XJ448 dose had a tendency to impair choice reaction time performance and to facilitate PCP-induced attention deficit. Judging from this, XJ448 may be a partial agonist.

In conclusion, PCP significantly produced attention deficit in rats in a 3-choice serial reaction time task, and this process may be mediated by σ receptors.

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