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Behavioral and Neurochemical Mechanisms of Opioid–Antidepressant Interactions

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KOVERA, C. A., D. W. SCHAAL, T. THOMPSON, J. B. OVERMIER AND J. CLEARY. *Behavioral and neurochemical mechanisms of opioid-antidepressant interactions.* PHARMACOL BIOCHEM BEHAV **48**(1) 47-52, 1994.— Twelve pigeons key-pecked under a multiple variable interval 15-s, 150-s schedule of food reinforcement. The effects of methadone were studied alone and in combination with chronic daily administration of either imipramine (IMI) or desipramine (DMI). Chronic IMI was also given following reductions in response rates by unsignalled delay-to-reinforcement (UDR). Acute administration of methadone produced dose-dependent reductions in response rates under both schedules of reinforcement. Chronic daily administration of IMI or DMI alone did not result in lasting changes in baseline responding. When administered in combination, chronic daily IMI significantly attenuated the rate-reducing effects of methadone, whereas neither a low nor a high dose of chronic daily DMI was effective. The same dose of chronic daily IMI failed to ameliorate response rate reductions under delayed reinforcement. The behavioral and neurochemical specificity of the antidepressant effect is discussed.

Antidepressant Opioid Imipramine Desipramine Methadone Schedule-controlled behavior Delay-to-reinforcement Pigeons

RECENT research has demonstrated substantial interactions between opioids and tricyclic antidepressant (TCA) drugs. Antidepressants enhance opioid analgesia [e.g., (4,18)], increase opioid withdrawal symptoms (14), increase levels of some opioids in the brain (19), retard opioid tolerance (22), and ameliorate opioid-induced response suppression (5). Many of these interactions are potentially beneficial in pain management and opioid dependency treatment because they allow use of lower opioid doses or reduce undesirable collateral opioid effects.

The neurochemical mechanisms of action for antidepressant–opioid interactions have not been identified (1). Hwang and Wilcox (13) have suggested that norepinephrine (NE) reuptake-blocking properties of tricyclics may be responsible for the enhanced opioid analgesia reported under concurrent morphine–antidepressant treatment. Macenski et. al. (22) have shown that the amelioration of opioid-induced response suppression and blockade of opioid tolerance occurs when subjects are pretreated with doxepin but not with bupropion. Whereas both drugs are effective antidepressants, doxepin appears to exert its action by blocking NE reuptake, and bupropion is a weak inhibitor of dopamine (DA) uptake, with indirect effects on noradrenergic function (12). Although these findings are consistent with the NE hypothesis of opioid–antidepressant interaction, they do not rule out other possibilities because antidepressants are known to have multiple neurotransmitter effects, including actions at histaminic, cholinergic, and serotonergic synapses.

The behavioral mechanism of action of antidepressant effects on opioid-suppressed behavior is also unexplored. It is possible that the ameliorating effect of antidepressants is not specific to opioid-suppressed behavior, but is rather an effect on suppressed behavior in general. Antidepressants may increase reduced behavior by, for example, increasing the efficacy or value of the reinforcer, an explanation suggested by clinical findings that TCA treatment can result in increased preference for certain foods, hyperphagia, and weight gain (3,28). In the studies cited above (5,22) it again may be the case that antidepressants enhance the value of food, and thus increase behavior that produces it. Since response rate reductions under methadone may be based on its ability to decrease the efficacy of other reinforcers (15,26,39), antidepressants may counteract this effect, and increase suppressed

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response rates, by specifically affecting the value of the food reinforcer.

The current study compares effects of combining methadone, an opioid μ-receptor agonist, with the TCAs imipramine (IMI) and desipramine (DMI). IMI, the prototypic tricyclic, interacts with several neurotransmitter systems and has previously been shown to ameliorate methadone-suppressed response rates. Since DMI is a relatively specific NE reuptake blocker (31,33), the role of NE in the amelioration of methadone-suppressed response rates may be assessed. In addition, a nonpharmacological means of suppressing ongoing behavior was used to test the hypothesis that the behavioral mechanism of antidepressant action may be through a general enhancement of suppressed behavior, rather than through a mechanism specific to opioid pharmacology.

METHOD

Subjects

Eleven adult female White Carneaux pigeons (Palmetto Pigeon Plant, Sumter, SC) served as subjects. During nonsession hours, birds were individually housed in cages with 24 h illumination at a constant temperature of 24°C. Whereas water and grit were freely available, birds were maintained at 80% of their free-feeding weights (±10%) by postsession feedings of mixed grain.

Apparatus

Experimental sessions were conducted in four commercially available experimental chambers (BRS/LVE, Laurel, MD). Each chamber was housed in a ventilated, sound-attenuating compartment. Within each chamber was a stimulus panel consisting of three keys and an opening where food could be obtained. Only the center operant key was functional during experimental sessions, and it was transilluminated with an IEE 12 stimulus projector (BRS/LVE model IC-901, 1820 bulb). During operation of the solenoid feeder under reinforcement conditions the overhead house light was extinguished and a light above the feeder illuminated. Experimental conditions and data recording were executed by MED-PC software (Med Associates Inc., East Fairfield, VT) and a Zenith ZW Z286 computer (Zenith, Electronics Corp., St. Joseph, MI) located in an adjacent room.

Procedures

Variable interval reinforcement schedule Birds were initially trained to peck the center key illuminated white. They were then switched to a continuous reinforcement schedule with the center key illuminated red, and each peck resulted in 4 s access to mixed grain. Once birds were responding consistently, the center key color was illuminated green and the contingencies were gradually changed to those of a variable interval 15-s reinforcement schedule (VI 15). Under these conditions, the first peck to occur after intervals of varying length, but with an average duration of 15 s, was reinforced. In the same manner, schedule performance under the red key color was trained by gradually increasing the average delay interval over sessions. Under the final VI value of 150 s (VI 150), the first peck to occur after intervals of varying length, but with an average duration of 150 s, was reinforced. Each reinforcement condition was presented three times per session, with a 10-s blackout interposed between schedule changes. The VI 15 component lasted 5 min at each presentation and the VI 150 component lasted 10 min per presentation. The VI 150 component was longer to insure that at least one reinforcer could be earned during each component. Thus, the terminal reinforcement schedule was a multiple VI 15, VI 150 under green and red colors, respectively, with a total exposure time per session of 15 min and 30 min, respectively. To minimize handling variables and insure precise injection–session intervals birds were placed in the darkened chamber 30 min before the onset of the first reinforcement schedule component (i.e., immediately after injections). Key pecks during dark periods before and during the session had no scheduled consequences. Experimental sessions were conducted daily throughout the experiment. In sum, the multiple VI 15, VI 150 reinforcement schedule allowed assessment of drug effects on relatively low key-peck rates under the VI 150 reinforcement schedule and relatively high rates of response under the VI 15 schedule.

When responding under the multiple VI 15, VI 150 reinforcement schedule showed no trends in excess of criterion (for each bird, 5 consecutive days within ±5 pecks/min of that bird's mean rate for those days), the effects of methadone (0.0, 0.5, 1.5, and 3.0 mg/kg) were assessed for eight birds. For all dose–effect determinations involving methadone, the testing order for doses, including 0.9% saline (1.0 ml/kg), was randomly determined for each bird. At least four days intervened between drug or saline administrations, and at least one saline control injection was given randomly on one of the four days before each drug dose. Following the initial dose–effect determination for methadone, four birds received chronic daily injections of desipramine hydrochloride (6.0 mg/kg/day), and four received chronic daily injections of imipramine hydrochloride (3.0 mg/kg/day). To maintain a more constant blood level, the total daily dose was divided in half and administered twice daily, immediately after the session and 12 h later. Chronic administration of antidepressant continued for at least three weeks and until key-peck rates were stable (three consecutive days within ±5 pecks/min of the mean rate for those days). Dose–effect relationships for methadone were then redetermined in combination with chronic daily DMI or IMI regimens. Following this, daily antidepressant treatment was discontinued and all birds were drug-free for at least three weeks. For birds originally receiving DMI, chronic daily treatment was reinstated at a lower daily dose (3.0 mg/kg/day) for 28 days and dose–effect relationships reestablished in combination with methadone, followed by a three-week drug-free period. A final redetermination of methadone effects occurred after the 28-day drug-free period for all birds.

Unsignalled delay to reinforcement Three birds, not active in any experiment for at least eight months but with previous histories of pecking under delay-to-reinforcement conditions, were retrained to respond under a multiple VI 15, VI 150 reinforcement schedule identical to that described above. When key-peck rates were stable (for each bird, 5 consecutive days within ±5 pecks/min of that bird's mean rate for those days), a 3-s unsignaled delay-to-reinforcement (UDR) was introduced. Under these conditions, feeder operation occurred 3 s after the key peck which satisfied the schedule requirement regardless of the subject's behavior. The array of interval values selected for both VI schedules was adjusted to maintain reinforcement rates comparable to a multiple VI 15, VI 150 reinforcement schedule. Response rates under these conditions decreased and experimental sessions were conducted until key-peck rates had decreased and showed no trends in excess of criterion for 5 consecutive days. All birds then received 3.0

mg/kg/day IMI in divided doses immediately following the session and again 12 h later. After 40 days chronic daily administration of IMI was discontinued. Birds responded under drug-free conditions and a multiple VI 15, VI 150 reinforcement schedule with unsignaled delay for another 28 days before the delay was discontinued and the original multiple VI 15, VI 150 schedule of reinforcement reinstated.

Drug preparation

Methadone hydrochloride (Eli Lilly, Chicago), desipramine hydrochloride (Sigma, St. Louis), and imipramine hydrochloride (Geigy Pharmaceuticals, Ardsley, NY) were dissolved in isotonic saline (0.9%) to obtain a constant injection volume of 1.0 ml/kg. Doses of all drugs are expressed in terms of total salt. All methadone injections (doses 0.0, 0.5, 1.5, and 3.0 mg/kg) were given intramuscularly before the start of the session. Because each session began with 30 min of darkness, the injection-session interval was 30 min. Imipramine HCl (3.0 mg/kg/day) and desipramine HCl (3.0 and 6.0 mg/kg/day) were given in divided doses immediately after the session and 12 h before the session. This regimen minimized acute affects of the antidepressants in combination with methadone and also endeavored to maintain a more constant antidepressant blood level.

Data analysis

The main dependent variable was rate of behavior in responses per minute. When appropriate, data were subjected to repeated-measures analysis of variance (RMANOVA), with planned comparisons of specific means by the method of least squares (Fisher's t_{LSD}). Shifts in methadone dose-effect curves under antidepressant treatment were determined by comparing the exact areas under the curves (AUCs) using a paired sample t test. The AUCs were calculated by summing the trapezoidal areas under the methadone dose-effect curves.

RESULTS

Mean drug-free control response rates under the VI 15 were significantly higher than rates under the VI 150 schedule of reinforcement: RMANOVA $F(3, 9) = 37.6$, $p < .01$; t_{LSD} $p < .05$. Baseline rates did not significantly increase under either schedule during the course of the experiment. Consistent with previous studies, methadone given alone produced significant dose-dependent decreases in response rates under VI 15, RMANOVA $F(7, 21) = 11.0$, $p < .01$, and under VI 150 reinforcement schedules, RMANOVA $F(7, 21) = 5.1$, $p < .01$. Table 1 presents methadone-alone effects under both schedules of reinforcement for initial administration and following discontinuation of the tricyclic treatment. Since determinations of methadone's effects were not significantly different before and after antidepressant treatment, these data were pooled for further analyses and are represented as the methadone-alone functions appropriate for the IMI and DMI groups in Figs. 1 and 2, respectively.

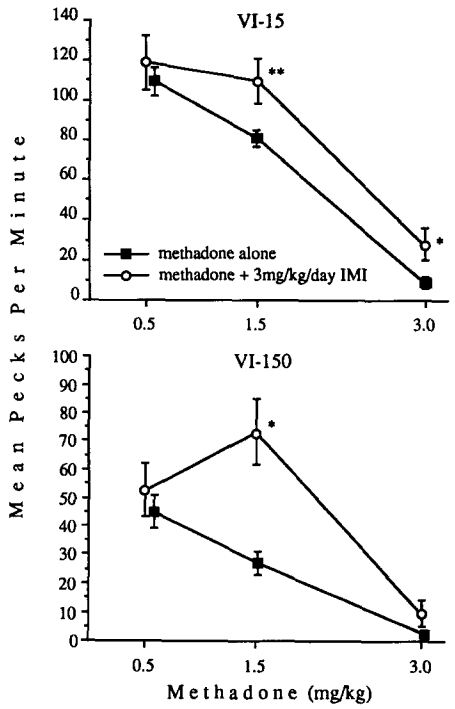

FIG. 1. Effects of methadone alone and in combination with 3.0 mg/kg/day imipramine on key-peck rates for the variable interval (VI) 15-s schedule (top) and the VI 150-s schedule (bottom). Rates represented by methadone alone include the effects of methadone before and after chronic imipramine. Brackets encompass one SEM.

TABLE 1

THE EFFECTS OF METHADONE ALONE FOR IMIPRAMINE AND DESIPRAMINE GROUPS ($N = 8$)

	Initial Determination Responses/min (SEM)		Final Determination Responses/min (SEM)	
Variable interval 15-s				
Mean control	103.8	(21.6)	112.2	(25.0)
0.5 mg/kg methadone	102.8	(19.8)	117.9	(23.4)
1.5 mg/kg methadone	75.9	(15.8)	85.9	(7.9)
3.0 mg/kg methadone	11.6	(10.7)*	7.6	(4.1)*
Variable interval 150-s				
Mean control	49.9	(19.1)	50.2	(20.3)
0.5 mg/kg methadone	43.2	(16.9)	47.0	(18.7)
1.5 mg/kg methadone	26.5	(9.9)*	27.8	(14.0)*
3.0 mg/kg methadone	4.8	(3.4)*	0.6	(0.3)*

*$p < .05$ (Fisher's t_{LSD} one-tailed.

Neither chronic daily administration of IMI nor of DMI produced statistically significant changes in response rates when given alone. Table 2 presents effects of the two antidepressants at the beginning and at the end of the 21-day antidepressant treatment period.

The effects of methadone during chronic daily administration of IMI are compared to methadone given alone in Fig. 1. As expected from previous experiments under these conditions, IMI significantly increased the area under the methadone dose-effect curve (AUC) for both the VI 15 schedule, paired sample one-tailed $t(3) = 6.5$, $p < .01$, and the VI 150 schedule, paired sample one-tailed $t(3) = 2.4$, $p < .05$.

Unlike IMI, the relatively specific NE agonist DMI did not significantly shift methadone dose-effect curves. These relationships are presented in Fig. 2.

The dose of IMI that has repeatedly shown amelioration

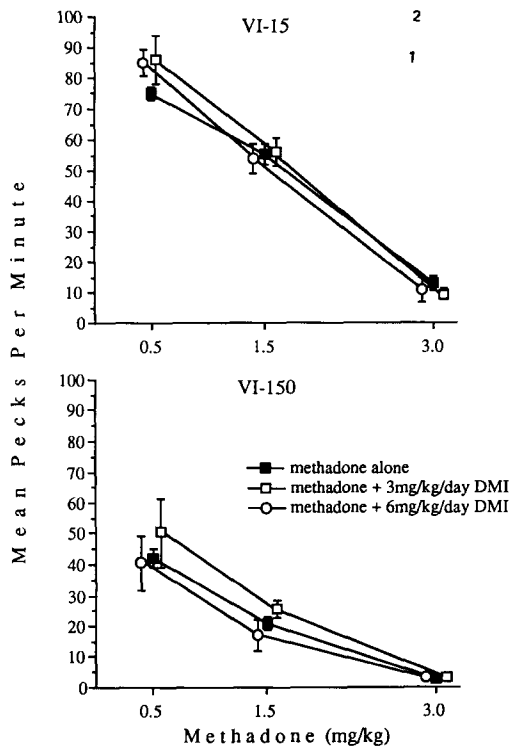

FIG. 2. Effects of methadone alone and in combination with 3.0 and 6.0 mg/kg/day desipramine on key-peck rates for the variable interval (VI) 15-s schedule (top) and the VI 150-s schedule (bottom). Rates represented by methadone alone include the effects of methadone before and after chronic imipramine. Brackets encompass one SEM.

of suppressant effects of methadone on behavior did not affect behavior suppressed by nonpharmacological means (Fig. 3). Imposing a 3-s UDR significantly suppressed response rates under both the VI 15 schedule, RMANOVA $F(4, 8) = 14.6$, $p < .001$, and under the VI 150 schedule, RMANOVA $F(4, 8) = 9.0$, $p < .01$. Chronic administration of IMI did not ameliorate this suppression under either reinforcement schedule.

DISCUSSION

The central focus of the present study was the comparability of two antidepressant drugs with different neurochemical mechanisms of action, imipramine and desipramine, in their ability to alter methadone-induced reductions in behavior. Fundamentally, methadone administered alone resulted in dose-dependent reductions in key-peck rates, an effect consistent with a substantial literature showing reductions in positively reinforced operant behavior by μ-opiate agonists (10,11, 17,24,25,40). Chronic daily IMI treatment ameliorated the reductions in responding due to methadone, an effect that has been previously demonstrated with both IMI (5,22) and doxepin (22). Because these two tricyclics broadly affect several neurotransmitter systems, including NE, DA, 5-hydroxytryptamine (5-HT), acetylcholine (ACh), and histamine, prior experiments have not allowed more specific identification of the neurotransmitter system responsible for the effect. The current study found that in contrast to the broad spectrum tricyclic IMI, the relatively specific NE reuptake blocker DMI had no effect on methadone-reduced behavior. Similarly, bupropion, a tricyclic that produces its effects by action on dopamine receptors and, indirectly, reduction in noradrenergic function, also does not affect opioid-suppressed behavior (22). Together these findings imply that long-term predominant tricyclic blockade of either NE or DA reuptake alone cannot account for the amelioration of opioid-suppressed behavior consistently found under chronic daily IMI or doxepin treatment.

Since the adrenergic system modulates opioid analgesia, opioid brain levels, and the manifestation of opioid withdrawal symptoms, NE and DA systems appeared to be promising candidates for investigation of neurotransmitter specificity in the antidepressant amelioration of opioid-suppressed behavior (41). However, other transmitter systems also hold promise for a neurotransmitter-specific explanation of the effect. For example, differences in anticholinergic properties of the antidepressants so far tested may also account for the presence or lack of effect on responding reduced by methadone. IMI and doxepin have potent and approximately equivalent affinity for muscarinic receptors, but the tricyclics showing no ameliorative effect, bupropion and DMI, have only weak anticholinergic activity (33). Serotonergic (5-HT) systems may also play a role, since a substantial literature indicates that opioid analgesia may be modulated by this system (13,23). It is also possible that the potentially beneficial effect of TCAs on opioid-suppressed behavior may be attributable

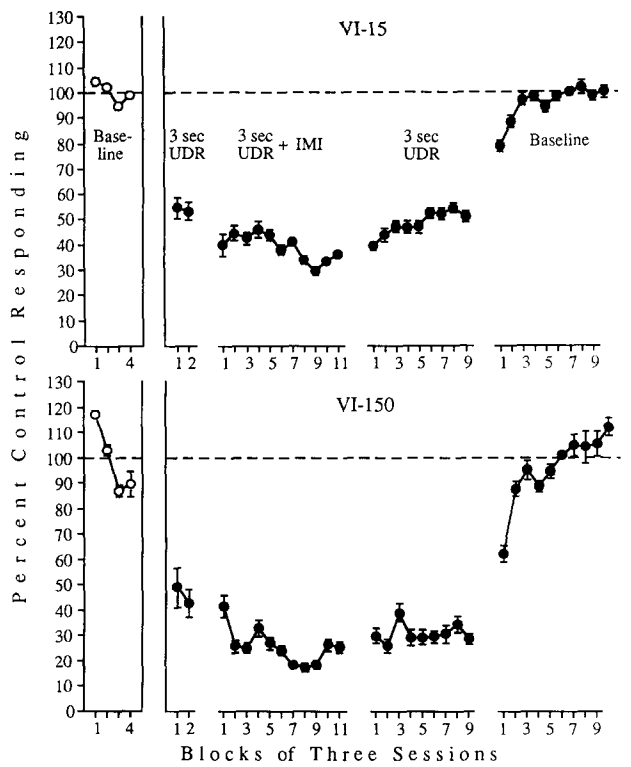

FIG. 3. Mean key-peck rates under consecutive conditions during a multiple variable interval (VI) 15-s (top) and VI 150-s (bottom) schedule of reinforcement. Baseline data are from the 12 days immediately prior to the start of the 3-s unsignalled delay-to-reinforcement (UDR) condition. Data under initial exposure to the 3-s UDR condition are the final 6 of 30 total sessions. IMI = chronic daily imipramine.

TABLE 2

THE EFFECTS OF ANTIDEPRESSANT TREATMENT ALONE FOR 21 DAYS

	Baseline Mean Responses/min (SEM)	Mean of the First Three TCA Days Responses/min (SEM)	Mean of the Final Three TCA Days Responses/min (SEM)
Variable interval 15-s			
3.0 mg/kg/day IMI	106.2 (19.9)	125.5 (14.5)	126.0 (20.7)
3.0 mg/kg/day DMI	76.7 (4.6)	84.2 (8.7)	81.9 (5.9)
6.0 mg/kg/day DMI	75.6 (6.1)	88.9 (5.0)	78.3 (5.3)
Variable interval 150-s			
3.0 mg/kg/day IMI	53.0 (19.5)	60.9 (17.3)	61.5 (21.0)
3.0 mg/kg/day DMI	42.4 (8.0)	53.7 (11.8)	51.9 (13.2)
6.0 mg/kg/day DMI	48.2 (6.6)	61.8 (8.8)	44.9 (11.5)

IMI = imipramine, DMI = desipramine.

to a complex pattern of neurochemical interactions, and not based in a single predominant neurotransmitter system.

The antidepressant effect on methadone-suppressed behavior might be explained behaviorally by a general increase in activity or an increased sensitivity to reinforcement, and not linked directly to the pharmacology of the two drug classes. The present study addressed the possibility that TCA administration might increase all suppressed behaviors in a nonspecific manner by using a nonpharmacological procedure for reducing operant responding maintained under a multiple-VI schedule of food reinforcement. Disruptions in response-reinforcer contiguity were effected by short UDR, which did not affect reinforcement frequency under either VI schedule [see also (16,34,35,37)]. Under these conditions, response rates were reliably and substantially reduced to 50% of baseline by UDR. These reductions were not significantly affected by administration of chronic daily IMI at a dose that consistently has ameliorated behavioral suppression by opioids. This result, combined with other researchers' reported lack of effects of repeated TCA administration on responding reduced under reinforcement manipulations such as extinction and negative contrast (9,21), suggests a pharmacological etiology for the TCA-opioid interaction.

In clinical settings, the antidepressant effects of tricyclic pharmacotherapy are usually delayed two to four weeks after initiation. This fact, together with laboratory investigations reporting different effects under single- versus repeated-administration regimens, have underlined the importance of studying changes consequent to long-term antidepressant administration (8). Several studies have reported that the neurochemical changes following chronic repeated tricyclic administration are markedly different than those of acutely administered drug [e.g., (2,30)]. Behavioral changes following chronic regimens may also be different or even opposite from those obtained under acute treatment [e.g., (20)]. For example, numerous researchers have reported that acute administration of IMI and DMI results in increased operant response rates (6,7,38), an effect that may be related to increases in central NE availability. In contrast, long-term treatment with tricyclic antidepressants often results in no change (5,22) or a decrease in operant rates, as seen for responding under differential reinforcement-of-low-rate (DRL) schedules (36). The results of the present study further support the use of long-term chronic administration models for investigation of behavioral mechanisms of action of the antidepressant drug class.

Clinically, it is unclear to what extent an unadorned pharmacological interaction is responsible for some of the beneficial effects of adjuvant antidepressant treatment in methadone-maintained patients (29). Treatment with antidepressants as an adjunct pharmacotherapy has been reported to alleviate depressive symptoms or improve sense of well-being in methadone-maintained patients (27,43) and in individuals receiving narcotics for chronic pain (32,42). In these cases, beneficial effects appear to be obtained apart from antidepressant activity, or in the absence of depressive symptoms. The present data, along with previous studies (5,22), suggest some portion of the clinically apparent benefits may be related to the pharmacological amelioration of behavior reduced by suppressive effects of opioids. The specific mechanism of the pharmacological interaction does not appear to be attributable to a primary action of acute antidepressant administration, tolerance to effects of methadone, or long-term uptake blockade of primarily DA or NE.

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