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A Delayed Onset of Haloperidol Effects on Learned Escape and Avoidance Behavior

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CAREY, R. J. AND S. KENNEY. *A delayed onset of haloperidol effects on learned escape and avoidance behavior.* PHARMACOL BIOCHEM BEHAV **28**(2)203–208, 1987.—The effects of 0.3 mg/kg haloperidol (H) on the acquisition and maintenance of footshock escape behavior of rats in a one meter runway was investigated. In the acquisition phase, a group (N=6) given H before testing (HB) showed severely retarded acquisition and performance of the escape response, as compared with a group (N=6) given H after testing (HA). When the HB and HA treatments were reversed for the groups behavioral performance was initially unaffected. At first, the HA group switched to the HB condition continued to exhibit rapid escape behavior and the HB group switched to the HA treatment continued to have slow escape behavior. Over the course of 8 days of testing, however, the performances of the two groups gradually reversed. After completion of this testing the HB and HA treatments again were switched and the animals were tested for both avoidance and escape behavior. Again, the performance of the animals initially did not change after the treatment switch, but with repeated testing and treatments, the avoidance and escape behavior of the HB group slowed substantially and that of the HA group accelerated markedly. These findings support previous observations that over learned behaviors are much less sensitive to disruption by haloperidol treatment than behaviors which are undergoing learning. The important contribution of the present study was in demonstrating that this insensitivity is a transitional, transient phenomenon and that with chronic treatment and testing, over learned behaviors can be strongly affected by haloperidol. This observation indicates that the study of the effects of haloperidol on over learned behavior may provide a useful animal behavior model to investigate the important clinical issue of delayed onset of efficacy with neuroleptic drugs.

Haloperidol Escape Avoidance Learning Delayed onset

IT is well known that interference with brain dopamine neurotransmission by lesions or neuroleptic drugs can have profound effects upon motoric function [1]. While a substantial influence of dopamine upon motoric behavior is unquestioned, it is less obvious whether dopamine systems are involved in the associative as well as expressive aspects of motor behavior. A variety of recent evidence, however, implicates dopamine and the basal ganglia in sensory-motor processes relevant to learning [15]. In addition, there is an extensive literature involving the use of avoidance and escape conditioning paradigms in which dopamine denervation or neuroleptic drug treatments have been shown to severely impair or prevent the acquisition of aversively motivated behaviors [2, 4, 6–14, 16]. While the implications of these behavioral deficits have been a matter of controversy [7,14], another interesting facet of these studies has been the reliable observation that these dopaminergic manipulations do not interfere with performance if the behavior is acquired prior to treatment [7].

The present study was undertaken to examine the effects of haloperidol on aversively motivated behavior in order to address several issues. One general observation has been that haloperidol impairs avoidance but not escape behavior. Not only are these behaviors distinguished by the presence or absence of the aversive stimulus, but in the conventional test situation the escape behavior occurs reflexively to the aversive stimulus and is an unconditioned response, whereas avoidance is a conditioned behavior. In the present study the escape response required movement down a one meter long alley. With this arrangement the animals must be trained to perform the escape response by successive approximations. Thus, the escape behavior is a learned rather than an unconditioned response. This testing situation permitted an evaluation of the effect of haloperidol on aversively motivated behavior when the escape component was acquired. Influence of haloperidol on the acquisition of this behavioral response would indicate that the drug interfered with the organization of learned behavior rather than affecting selected motivational aspects of aversively motivated behavior (i.e., avoidance versus escape behavior). A second objective of the present study was to assess the apparent insensitivity of trained behaviors to interference by haloperi-

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dol. Previous studies have demonstrated a marked differential between the effects of haloperidol on the acquisition versus performance of learned aversively motivated behavior. Lastly, the study of haloperidol effects on learned responses has been limited to acute treatments. Therefore, the present study examined the effects of chronic haloperidol treatments on performance of a learned aversively motivated escape response.

METHOD

Animals

Eighteen male Sprague-Dawley rats, approximately 500 g were used. The rats were maintained in a room with regulated temperature (72±2°F) and humidity (55±5%), and a 12 hr L-D cycle (6–18 hr L:18–6 hr D). All testing was carried out between 10 and 16 hr.

Apparatus

Escape conditioning was conducted using a black Plexiglas alley with a grid floor. The alley was 100 cm long and 12.5 cm wide. Attached to the alley was a goal box 39×12.5 cm with a Plexiglas floor. Footshock was delivered by a constant current shocker with scrambler (L.V.E. No. 1531). Running speed was recorded with an electronic timer. Flinch-jump testing was carried out in a 20×20×15 cm chamber with a grid floor. The walls and the top were made of clear Plexiglas and a constant current shocker with scrambler was used to deliver the footshock.

Procedure

In this study separate groups of animals receive either 0.3 mg/kg haloperidol (H) (N=12) or lactic acid vehicle (V) (N=6). The H and V treatment groups were further subdivided into subgroups which receive the H or V either before (B), or after (A), testing. HB animals (N=6) receive the H injection one hour before testing and the HA animals were given the H injection one hour after testing. The same injection schedule was used for the V rats. This injection procedure was employed so that H rats could be switched from the B to A condition and vice versa without any change in total drug exposure. Thus, all animals in the H groups received the same number of injections even though their order of injection (B or A) changed several times over the course of experimentation.

Phase 1: Effect of Haloperidol on the Acquisition of Escape Behavior

The escape response was acquired by each animal with the graduated length training method. Initially, 60 cm of the alley was covered by a series of six 10 cm cardboard inserts except for the 40 cm starting section. The rat was placed in this starting section facing in the direction of the goal box and one second later the footshock was delivered. The slight delay in footshock was employed so animals could be placed gently and uniformly on the grid floor and to provide an opportunity to assess anticipatory escape behavior (i.e., avoidance attempts were defined as all four feet outside of the start section before onset of footshock). On the first test trial only 40 cm of the grid floor were exposed. Once an animal made a successful escape response (i.e., less than 60 seconds) 10 additional cm of the grid floor were exposed. This procedure was continued until the animal escaped the complete 100 cm grid floor. If an animal did not make the escape response within 60 sec the shock was terminated and the rat was immediately removed from the apparatus. After an escape response failure, the animal's next trial was conducted with the 40 cm grid and the entire sequence repeated. Initially, the footshock was 0.75 mA but once the escape response to the entire 100 cm alley was acquired, the intensity level was reduced to 0.5 mA for all subsequent tests. With this graduated length training method, all animals learned the escape response within three weeks, with five days per week of training. Once an animal made three successive 100 cm escape responses, it was maintained on this training level until each rat had reached this criterion performance. In this training phase, one half of the H group (N=6) received 0.3 mg/kg haloperidol one hour before testing (HB), and the other half received 0.3 mg/kg haloperidol one hour after testing (HA). Similarly, one half (N=3) of the lactic acid vehicle group was given V one hour before (VB) and the other half received V one hour after testing (VA). The haloperidol was dissolved in warm lactic acid (1 g/ml) and diluted in distilled water to 0.3 mg/ml with a pH of 4.0. The lactic acid solution was prepared in the same concentration.

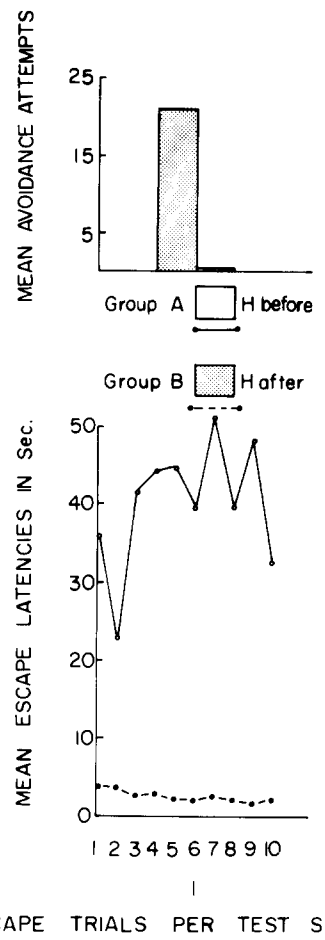

FIG. 1. Mean escape latencies on each of the successive escape trials for rats given 0.3 mg/kg haloperidol (H) one hour before or after testing. The mean number of avoidance attempts made during this test session by each group are displayed in the upper portion of the figure.

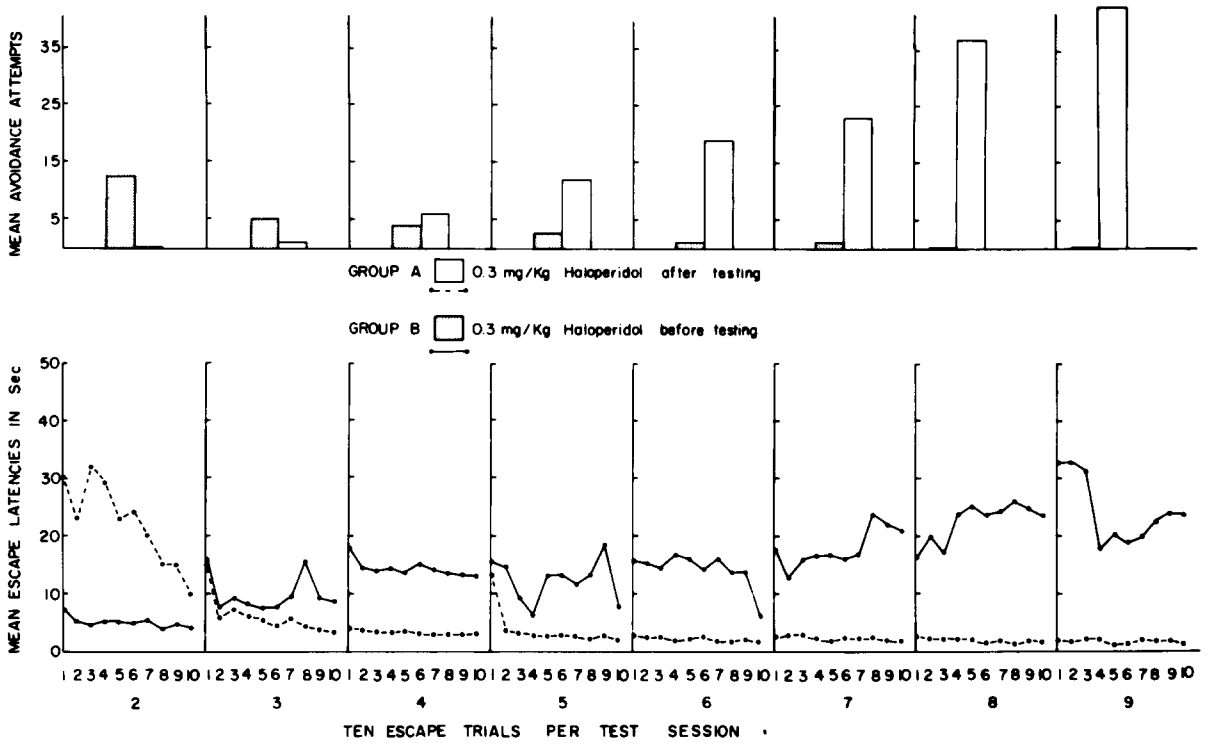

FIG. 2. Mean escape latencies over eight successive test sessions with ten escape trials per session. These results are for phase 2 of testing in which the 0.3 H before versus after treatments are reversed. The mean number of avoidance attempts for each test session are indicated in the upper part of the figure.

Phase 2: Effect of Haloperidol on Escape Behavior Acquired Without Drug

When all animals reached the criterion performance there was an additional test day conducted under the same treatment conditions. On this day each animal received 10 successive escape trials in the 100 cm alley. Failure to complete the escape responses within 60 sec resulted in termination of the shock and removal of the rat from the apparatus. During this testing, anticipatory escape responses were recorded as avoidance attempts since the animal, by running before the onset of the shock, could not completely avoid the shock but only reduced the amount of the alley in which footshock was received. To test for the effect of haloperidol on the learned escape response, the order of H injections for the two H groups was switched (i.e., HB to HA and HA to HB). In order to evaluate performance under more chronic treatment conditions, testing was continued for eight days with 10 successive escape trials daily.

Phase 3: Effect of Haloperidol on Avoidance and Escape Behavior

After completing the 8 days of escape testing (phase two), the haloperidol injection order was reversed again (i.e., HA switched back to HB and HB switched back to HA). There were 10 successive escape trials per test day, but only for three test days. In addition, prior to the start of escape testing on each of the three test days, three additional test trials were conducted. The first of these supplementary test trials was an avoidance test conducted with no footshock, the second was a regular escape trial and the third was another avoidance or non-shock trial. Immediately after the completion of these three trials, each rat was given the 10 successive escape trials. The supplementary three trials, which included 2 avoidance trials, were conducted to assess effects on avoidance behavior before the regular escape testing was conducted.

Flinch-Jump Testing

In order to assess the possible effect of the haloperidol on footshock sensitivity, the rats were tested for footshock sensitivity using the flinch-jump method [18]. The rats were tested twice; once after escape training (phase 1) and again after completion of phase 3. The rats treated with haloperidol and vehicle during the experiment were tested twice in each test; once, without haloperidol or vehicle, and once, one hour following the 0.3 mg/kg haloperidol or vehicle injection with the order of testing counterbalanced. Briefly, each rat was placed in the testing apparatus and given 5 min to adapt. Then, ascending series (0.1 mA increments starting with a 0.1 mA) of footshocks (0.2 sec in duration) were delivered until a flinch response (crouch-flinch-jerk) was detected. Following this test response the shock level was reduced (in 0.1 mA steps) until no response was observed. This procedure was repeated 8 times and the flinch threshold was defined as the mean of the shock levels for the 8 ascending responses and the 8 descending no response determinations. After completion of the flinch response testing, a similar procedure was followed for the jump response, which was defined as any rear paw lifted off the grid floor during shock.

Statistical evaluation of the escape performance was performed using a two-way ANOVA with repeated measures. The 10 escape trials in a session were the repeated measures.

The avoidance attempts were totaled per session and evaluated with independent t-tests between groups. Also, the Flinch-Jump and supplemental escape and avoidance tests in phase 3 were evaluated with t-tests.

RESULTS

In the acquisition phase, all of the vehicle and all of the HA rats acquired the escape response on the first day of training. The rats which received haloperidol before testing, however, showed impaired acquisition and required 8, 10, 11, 12, 14 and 15 days of training respectively to acquire the escape response. It is of interest to note, however, that all three groups initially performed the escape response and performed with similar (not statistically different) response latencies on the first three lengths of the alley. It was only after the alley was lengthened beyond this point (i.e., 70 cm) that the HB group exhibited an impaired performance.

Figure 1 compares the HB versus HA groups on escape performance after the criterion performance level had been achieved. As can be seen in this figure, the HB treatment produced slowed escape responses and a virtual absence of avoidance attempts whereas the HA treatment group exhibited much more rapid escape responding with a substantial number of avoidance attempts. This performance of the HA group was very similar to, and not statistically different from, the vehicle treatment group. The vehicle group maintained this level of performance throughout experimentation. The difference in escape latencies and avoidance attempts between the two haloperidol groups was highly significant statistically ($p<0.01$ escape, and $p<0.01$ avoidance).

Figure 2 shows escape and avoidance behavior when the haloperidol before and after treatments were switched. Initially, switching the drug order had little effect on behavior but, with repeated trials, the performances of the groups gradually reversed. The group which was switched from HA to HB initially displayed rapid escape responses and a substantial number of avoidance attempts but, with repeated testing, the escape responses became increasingly slower and avoidance attempts were eliminated. In contrast, the group switched from HB to HA initially had slow escape responses and made no avoidance attempts but with repeated testing escape responses became rapid and avoidance attempts were made. Reflective of this crossover in behavioral performance, the HB group had significantly faster escape responses ($p<0.01$) and more avoidance attempts than the HA group ($p<0.01$) on the first day of testing shown in Fig. 2; but, over the last five sessions in Fig. 2, the HA group had a statistically significant faster escape response ($p<0.01$) and more avoidance attempts than the HB group ($p<0.01$).

Figure 3 presents the results for the last phase of the experiment in which the haloperidol treatments were switched back to the order used in the acquisition phase. The results shown in Fig. 3 indicate that initially the HA and HB treatments had similar effects but, by the third session, the HB group developed slower escape responses and made fewer avoidance attempts than the HA group ($p<0.01$). It is of primary interest to observe the behavioral performance of the two drug groups in the avoidance tests which were conducted prior to each of the three sets of escape conditioning sessions. As can be seen in Fig. 4, there was a large difference in performance between the two drug groups on these avoidance tests. On the first trial, the HB group displayed a much more rapid avoidance response than the HA group; on the second trial the escape response of the HB group was

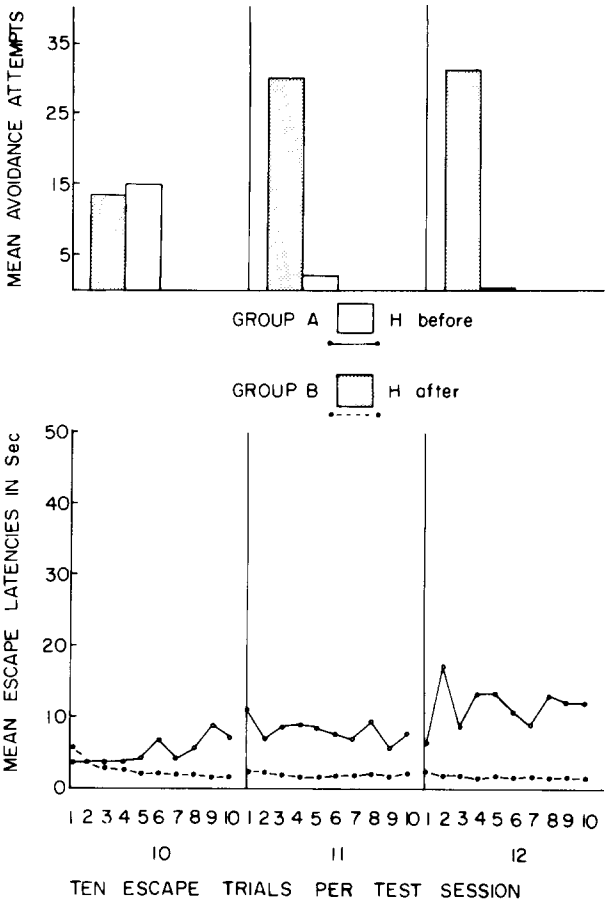

FIG. 3. Mean escape latencies and avoidance attempts in phase three of testing when the 0.3 H before versus after session treatments were reversed from phase two.

also faster than the HA group and by the second avoidance trial both groups performed similarly. By the second test session, however, avoidance and escape performance of the HA and HB groups were reversed and this differential increased even further by the third session so that the HB group was substantially slower than the HA group on both avoidance and escape measures. These findings replicate the findings obtained for escape testing observed after the first switch in treatment but also show that similar effects occurred for avoidance behavior.

While haloperidol had marked effects on escape and avoidance performance, this drug did not have a statistically significant effect on Flinch-Jump thresholds. The mean flinch thresholds were 0.17 ± 0.02 mA with, and 0.18 ± 0.02 mA without haloperidol and the jump thresholds were 0.41 ± 0.08 with, and 0.4 ± 0.06 without haloperidol respectively. The thresholds obtained for the Vehicle groups were similar to and (not statistically different) from the haloperidol groups ($p>0.1$).

DISCUSSION

In the acquisition phase of this study haloperidol severely retarded the acquisition of the escape response. Ostensibly, this finding appears to be in contrast with a number of reports in which haloperidol has been shown to impair

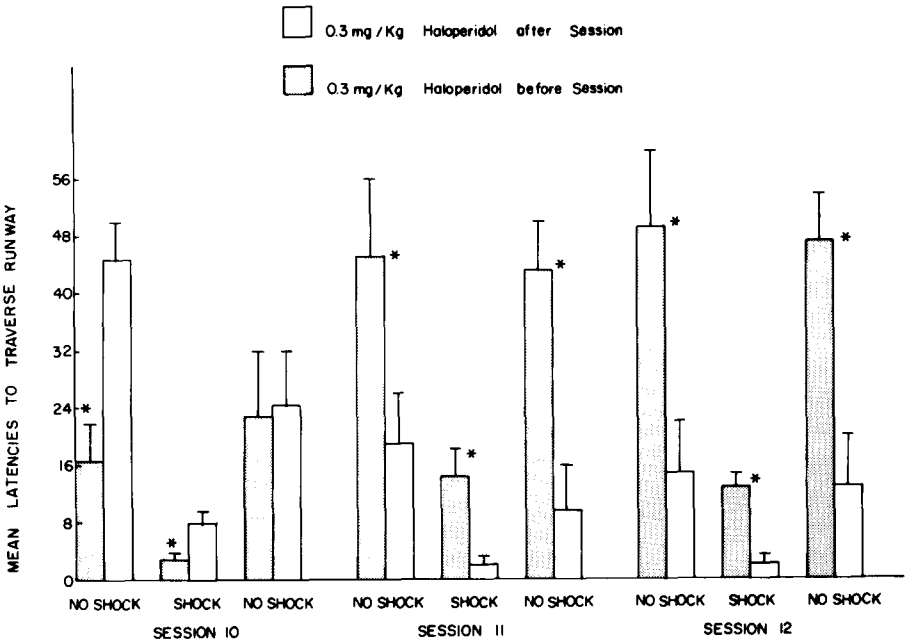

FIG. 4. Means+S.E.M.s of avoidance and escape latencies for the three avoidance-escape-avoidance tests which preceded the ten escape trials in phase three. (*$p<0.01$ t-test comparisons between 0.3 H given before versus after the test session.)

avoidance but not escape behavior [6,12]. In conventional avoidance escape paradigms, however, the escape behavior occurs as an unconditioned response to the footshock. In contrast, in the present study, animals initially do not traverse the meter long alley to escape the footshock and this response must be trained by incremental shaping of increasingly longer and sustained running responses. Thus, the escape response is a learned behavior and in this important sense more related to the learned component of conventional avoidance escape behavior. An important aspect of the present report, therefore, is that it relates the effect of haloperidol to learning a motoric response, rather than to processes inherent in anticipation (i.e., avoidance) or reactions to footshock (i.e., escape).

Another important observation of the present study occurred when the haloperidol before and after treatments were reversed at the end of the acquisition phase. Seemingly, if the behavior were completely under the control of the drug state then the behavioral performances of the two groups should have reversed. In agreement with previous reports [6] the haloperidol after group, which had acquired a rapid escape response, continued to perform at the same level when given haloperidol before testing. Thus, previous learning was effective in overriding the effect of the haloperidol treatment. More interesting were the findings for animals switched from the haloperidol before to the haloperidol after treatment. These animals did not immediately run faster, which would be expected if the haloperidol only induced a response impediment, rather, they initially continued to persist in slow escape behavior. Thus, a dissociation between haloperidol treatment and behavioral performance occurred in both directions. This uncoupling of behavioral performance from drug state indicates that learning, whether acquired under drug or non-drug conditions, can override changes in pharmacological state (i.e., presence or absence of drug).

Perhaps the most important new observation provided from the present report was the change in performance which emerged over successive test sessions following the switch in before and after treatment conditions. While haloperidol before testing initially did not affect escape performance, escape behavior gradually but substantially slowed with repeated testing. This change was mirrored by the development of rapid running in the haloperidol animals which were switched to the after session injection schedule. Thus, performance of the two groups completely reversed and behavior developed which was consistent with the animal's drug state (i.e., slow escape behavior with haloperidol and fast escape behavior without haloperidol). Thus, the apparent insensitivity of over learned behavioral responses to haloperidol which has been observed previously [6] appears to be a transitional and transient phenomenon. When the chronic treatment situation is considered, then haloperidol can have a profound influence on an acquired over learned behavior. It would be of interest to determine if overtrained animals depleted of dopamine by the neurotoxin 6-hydroxydopamine also lose acquired behaviors when given repeated long term testing [13]. This latter aspect is also of interest with regard to the delayed onset of clinical efficacy of haloperidol when it is used as an antipsychotic treatment [7,17]. A delayed onset of efficacy in neuroleptic treatment is observed clinically for both negative effects such as Parkinsonism as well as antipsychotic efficacy. Thus the use of well developed over learned behavioral responses may provide a behavioral model in which delayed onset processes can be studied in experimental animals. This is of considerable importance since animal behavior models which have been applied to the study of chronic neuroleptic treatment have relied on measurement of unconditioned motoric function (e.g., catalepsy) and have only obtained evidence for tolerance or diminished efficacy rather than a delayed onset of efficacy.

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