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Different Effects of 5-HT Receptor Agonists on Operant Response in Rats Under DRL 10-s and DRL 30-s Schedules

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ABSTRACT

5-hydroxytryptamine (5-HT) is thought to be involved in a wide range of behavioral functions. Based on binding evidence, 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT), 1-(2,5-dimethoxy-4-indophenyl)-2-aminopropane (DOI), and m-chloro-phenyl-biguanide (m-CPBG) are selective 5-HT1a, 5-HT2, and 5-HT3 receptor agonists, respectively. The present study examined the effects of these 5-HT receptor agonists on operant behavior maintained on the differential reinforcement for low rate response 10-second (DRL 10-s) and 30-second (DRL 30-s) schedules of reinforcement. Water-deprived rats were trained to press a lever in response to DRL 10-s and DRL 30-s schedules. After a stable baseline was set, each subject was then repeatedly challenged using one drug with different doses through peripheral administration. The dose ranges were 0.025, 0.05, and 0.1 mg/kg (SC) for 8-OH-DPAT; 0.5, 1, and 2 mg/kg (SC) for DOI; and 1, 3 and 9 mg/kg (IP) for m-CPBG. The overall results of the present work indicate that distinct profiles of operant response on DRL 10-s and DRL 30-s schedules were produced by 8-OH-DPAT, DOI, and m-CPBG, based on quantitative and qualitative data analyses. All three 5-HT receptor agonists caused the number of responses to the DRL 10-s schedule to decrease significantly in a dose-related fashion. The operant performance on the DRL 10-s schedule was more sensitive to drug treatment than was that on the DRL 30-s schedule. Analyses of inter-response time (IRT) distributions revealed that different time bins were shifted by each of these three agents. The current data indicate that 8-OH-DPAT, DOI, and m-CPBG can significantly alter operant response maintained on a DRL schedule. The distinct operant performance for each drug is believed to be derived from drug activation of its own specific 5-HT subtype receptors.

Key Words: differential reinforcement of low rate, 8-OH-DPAT, DOI, m-CPBG, operant behavior, inter-response times

I. Introduction

Interest in the psychobiological functions of serotonin, also known as 5-hydroxytryptamine (5-HT), has increased steadily since multiple (at least 15) subtypes of 5-HT receptors were characterized (Humphrey *et al*., 1993; Saxena, 1995). It is assumed that drugs activating different 5-HT subtype receptors should produce distinguishable effects on behavioral functions similar to those found in binding assays. While studies using *in vitro* biochemical assay have recently led to great advances in characterizing heterogeneous subtypes of 5-HT receptors, the search for correspondingly consistent behavioral functions associated with 5-HT receptors has so far been limited. By mainly testing drug effects on reflexive types of behavior, previous works on psychopharmacology revealed that a range of behavioral responses can be attributed the functions derived from different subtypes of 5-HT receptors. For instance, a selective 5-HT1a receptor agonist, 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT), increased food intake in satiated rats (Dourish *et al*., 1986), and induced a number of reflexive behaviors in rats including: rotational response to asymmetric lesion of 5-HT neurons (Blackburn *et al*., 1984), tail flicks (Millan *et al*., 1991), lower lip retraction (Berendsen *et al*., 1989), and the well known '5-HT behavioral syndrome' (Jacobs, 1976). In regard to 1-(2,5-dimethoxy-4-indophenyl)-2-aminopropane (DOI), this 5-HT2 receptor agonist can enhance the magnitude of the acoustic startle reflex to different degrees (Svensson and Ahlenius, 1983). While behavioral measurements or tasks can generally be classified into unlearned (reflexive) and learned (conditioned) domains in psychopharmacology, 5-HT receptor agonists have rarely been tested in studies on learned types of behavior (i.e., operant conditioned) in comparison with agonists that have been tested in studies on the reflexive types of behavior. It is, thus, important to investigate drug effects on both reflexive and learned behaviors in order to obtain a gross profile of behavior reaction to 5-HT receptor agonists. Nevertheless, several studies employing drug discrimination procedures have revealed that some of the selective 5-HT receptor agonists contain their own stimulus properties. Likewise, animals are able to discriminate 8-OH-DPAT from other agents that are selectively activating on other 5-HT receptor subtypes, such as TFMPP and MCPP (for 5-HT1b and 5-HT1c subtypes) or DOI (for 5-HT2 subtype) (Cunningham

et al., 1987; Lucki, 1988). Although an operant conditioning process is known to be involved in drug discrimination, little is known about the effects of 5-HT receptor agonists on operant behavior maintained based on traditional schedules of reinforcement.

There is a growing body of evidence for the involvement of 5-HT in the regulation of positively reinforced operant behavior. However, most of these data were collected by examining the lesion effects of 5-HT related pathways in the brain on operant behaviors (Fletcher, 1993, 1995; Wogar *et al*., 1991, 1993). Other researchers have used a choice procedures involving small immediate and large delayed reinforcers, and argued that 5-HT participates in the process of behavioral inhibition (Bizot *et al*., 1999; Evenden and Ryan, 1999; Ho *et al*., 1999; Soubrie, 1986). Operant behavior maintained on a schedule of differential reinforcement of low-rate response (DRL) enables the assessment of the subject's ability to inhibit response (Kramer and Rilling, 1970). That is, a subject maintained on a DRL schedule must inhibit response for a minimum specified period of time in order to obtain the reinforcer. Thus, DRL behavior was employed in the present study to evaluate the effects of 5-HT receptor agonists on operant behavior. Two levels of the temporal requirement, DRL 10-s and DRL 30-s, in this schedule were further tested in the present work since behavioral profiles induced by these two DRL schedules were assumed to exhibit different degrees of sensitivity to drug challenge. The present study aimed to examine the operant effects of 5-HT receptor agonists on DRL 10-s and DRL 30-s schedules. The agonists were chosen in order to probe three 5-HT receptor subtypes, including 5-HT1a receptors by 8-OH-DPAT, 5-HT2 receptors by DOI, and 5-HT3 receptors by m-chloro-phenylbiguanide (m-CPBG).

II. Methods

1. Subjects

The subjects were male Sprague-Dawley rats, averaging approximately 250 g in body weight upon receipt from the National Laboratory of the Animal Breeding and Research Center. After 10 days of adaptation with food and water *ad libitum*, the rats were maintained on a water deprivation regimen in which they were allowed 5 min of access to tap water in the home cage no less than 30 minutes after the end of each daily session. The rats were monitored and kept at 85 percent of their pre-experimental body weight. Food pellets were continuously available in each home cage. Training and/or test sessions were administered daily in the same time period during the light portion of the vivarium's 12/12 hr light-dark cycle.

2. Drugs

The 5-HT receptor agonists, 8-OH-DPAT HBr, DOI HCl, and m-CPBG HCl, were purchased from Research Biomedicals Inc. (Natick, MA, U.S.A.). Drugs were freshly prepared with normal saline on the day of use. The doses and administration routes were 0.025, 0.05, and 0.1 mg/kg for 8-OH-DPAT (SC); 0.5, 1.0, and 2.0 mg/kg for DOI (SC); 1, 3, and 9 mg/kg for m-CPBG (IP). The injections were all conducted 30 min before the start of each operant session and kept at a volume of 1 ml per 1 kg of body weight. Doses of these three drugs are expressed as the salt.

3. Apparatus

Operant responses were measured in 4 chambers located in a room separate from the animal colony. All the chambers were serviced using a microcomputer. The interior dimensions of each chamber were 20 cm by 25 cm by 30 cm. Aluminum panels formed the front and back walls, and clear plexiglas comprised the remaining sides and top. Stainless steel bars (diameter 5 mm) set 8 mm apart provided flooring. Each chamber was equipped with a press lever 4 cm above the floor positioned 4 cm from the right corner of the front panel. A liquid dispenser was set outside of the front panel. The reinforcer (water) delivery mechanism contained 0.04 ml of water for each presentation. The water was delivered into a receiving dish located at the center of the front panel and 4 cm above the floor. Each chamber was illuminated by a small light bulb located 10 cm above the floor and positioned 5 cm from the left corner of the front panel. The chamber was enclosed in a plywood box with a fan to provide necessary ventilation and white noise. The contingencies for each schedule of reinforcement were programmed and compiled using a commercial kit, Medstate Notation (MED Associate Inc., East Fairfield, VT, U.S.A.).

4. Procedure

One week of adjustment to water deprivation was provided before each rat was trained in the operant chamber. All the animals were manually shaped to press a lever after one session of magazine training. Magazine training consisted of 30 min of exposure to a variable interval 1 min schedule. Then, the animals were put on a continuous reinforcement (CRF) schedule for 5 sessions, in which every lever press was reinforced. Each daily session lasted 15 min from this stage to DRL 10-s. Acquisition of response under the CRF schedule was judged to be initiation of operant behavior. The rats were subsequently placed on the DRL 5-s schedule. The lever presses were reinforced only if at least 5 sec had elapsed since the previous response made during this DRL schedule. Any response emitted less than 5 sec after the previous one was not reinforced, and the temporal requirement of 5 sec was reset. After 6 sessions of DRL 5-s training, the rats were trained to respond on the DRL 10-s schedule. There were 15 sessions of DRL 10-s training before the rats could perform reliably on

the DRL 10-s schedule. The baseline criterion for determining a stable DRL 10-s behavior was less than 10 percent variation in the response rate for three consecutive ses-sions. Subsequently, the rats were randomly assigned to three groups (n = 8 each) to receive drug treatments of 8-OH-DPAT, DOI, and m-CPBG. Only one drug treatment was conducted for each rat with repeated injections made via peripheral administration. The drug effects for each treatment were evaluated over a period of 10 days that included of 3 vehicle-injection (V), 3 drug-injection (D), and 4 intervening no injection (I) days. The order was arranged as V-D-I-I-V-D-I-I-V-D. The doses for each drug were given in a counterbalanced way over three drug injection (D) days. Following completion of the dose response tests on the DRL 10-s schedule, the rats were trained to respond on the DRL 20-s schedule for 10 sessions followed by DRL 30-s training. A total of 66 daily sessions was required to achieve stable response on DRL 30-s. Subsequently, the aforementioned dose response test was conducted on DRL 30-s behavior. Each subject received the same drug treatment from the phase of DRL 10-s to DRL 30-s. Two points regarding the DRL 30-s training process need to be addressed. The session time for the DRL 30-s schedule was increased from 15 min to 20 min due to the longer duration needed to obtain a reinforcer. The final number of rats in each group subjected to enter the dose response test for DRL 30-s was six, since two rats in each group did not respond well when the training phase shifted from DRL 20-s to DRL 30-s.

5. Data Analysis

The operant behavior was examined based in the following variables: the number of responses, the number of reinforcers, and the inter-response time (IRT). The dose response effect for each dependent variable was determined by means of one-way analysis of variance (ANOVA). The frequencies of IRT distributions for each drug were plotted for both DRL 10-s and DRL 30-s with different bin times, 2.5 sec and 3 sec, respectively. The overall IRT distribution was analyzed by means of two-way ANOVA with two repeated factors of the bin and drug injection. In each bin of the graph, the frequencies of the vehicle bar and drug bar were statistically examined by means of paired t-tests. In all cases, the results were considered significant at $p < 0.05$.

III. Results

1. Responses and Reinforcers

The numbers of responses and reinforcers of both DRL behaviors under 8-OH-DPAT, DOI, and m-CPBG treatments are presented in Figs. 1 – 3, respectively. In each figure, those DRL 10-s data are on the left and those of DRL 30-s are on the right. For each DRL behavior, the response variable is

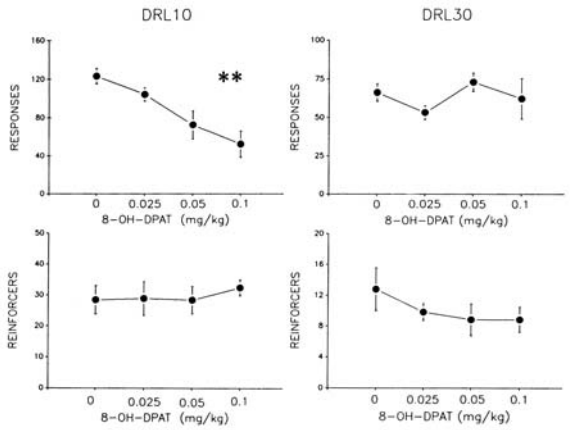


Fig. 1. Dose effects for the indicated dependent variables under treatment of 8-OH-DPAT on the DRL 10-s and DRL 30-s schedule controlled behaviors (brackets denote the upper and lower 1 s.e.m.); ** $p < 0.01$ significant dose effect (one-way ANOVA).

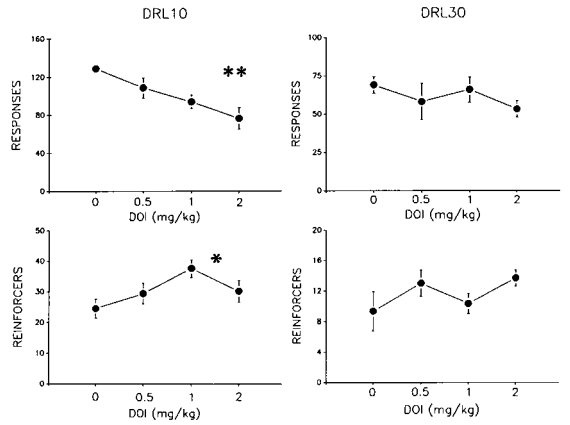


Fig. 2. Dose effects for the indicated dependent variables under treatment of DOI on the DRL 10-s and DRL 30-s schedule controlled behaviors (brackets denote the upper and lower 1 s.e.m.) ; ** $p < 0.01$, * $p < 0.05$ significant dose effect (one-way ANOVA).

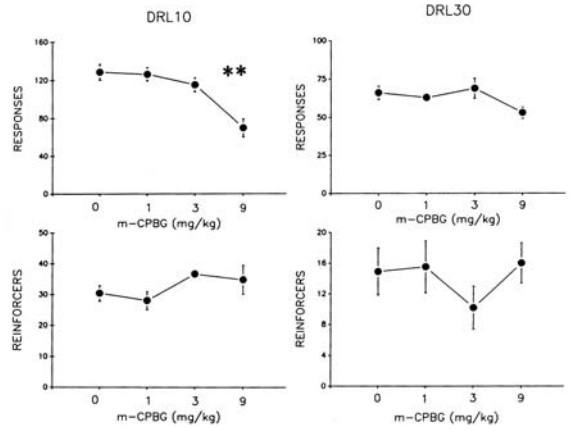


Fig. 3. Dose effects for the indicated dependent variables under treatment of m-CPBG on the DRL 10-s and DRL 30-s schedule controlled behaviors (brackets denote the upper and lower 1 s.e.m.) ; ** $p < 0.01$ significant dose effect (one-way ANOVA).

shown in the upper panel, whereas the reinforcer variable is shown in the lower panel. As noted previously, the responses emitted and the reinforcers earned were significantly fewer under the DRL 30-s schedule than under the DRL 10-s schedule after baseline training ($p < 0.05$). Figure 1 presents the effects of 8-OH-DPAT on the DRL schedule controlled behaviors. Only the responses of DRL 10-s behavior were significantly decreased by 8-OH-DPAT in a dose related manner, $F(3,21) = 9.971$, $p < 0.01$. The dose curves shown in the other three graphs were not significantly detected by ANOVA's. The data of DRL schedule controlled behaviors under DOI treatments are shown in Fig. 2. DOI significantly decreased the responses, $F(3,21) = 11.192$, $p < 0.01$, and increased the reinforcers of DRL 10-s behavior, $F(3,21) = 3.865$, $p < 0.05$. In contrast to these profound effects on DRL 10-s behavior, DOI did not significantly alter the operant performance of either dependent variable on DRL 30-s behavior. Figure 3 presents the effects of m-CPBG on the DRL schedule controlled behaviors. m-CPBG significantly decreased the responses of DRL 10-s behavior, $F(3,21) = 19.631$, $p < 0.01$. None of the other three dose curves was significantly affected by m-CPBG.

2. IRT Analyses

IRT analysis results for both DRL behaviors under three drug treatments are presented in Figs. 4 – 9. Each figure contains three graphs representing each of the three dose treatments with its corresponding vehicle injection for a specific drug, and the data contained in each of these figures were separately analyzed using 2-way repeated ANOVA. Details of these ANOVA results are presented in Table 1. The IRT data of DRL 10-s behavior are presented in Figs. 4 – 6 in the following order of drug treatment of 8-OH-DPAT, DOI, and m-CPBG. As generally revealed by the ANOVA results, the bin effects and the bin by drug interactions were significantly affected by most of the dosing treatments for all three drugs ($p < 0.05$). None of statistical tests on the main drug effects were significantly revealed from ANOVA's for all three drug treatments at various doses. These results indicated that the overall IRT distribution of DRL 10-s performance was generated by different frequencies of IRT's. Furthermore, the drug treatment used to produce significant alteration of the IRT distribution depended upon the specific dosing and on the given bin. Regarding the results of t-tests conducted to analyze the IRT data of DRL 10-s behavior, significant differences between the drug and its corresponding vehicle bars are described by the bin numbers for specific doses in the followings: (1) for 8-OH-DPAT treatment as shown in Fig. 4, bins 1, 2, 3, and 4 for 0.025 mg/kg and bins 1 and 4 for 0.05 mg/kg; (2) for DOI treatment as shown in Fig. 5, bins 1, 3, and 5 for 0.5 mg/kg, all 5 bins for 1 mg/kg, and bins 1, 2, 3, and 4 for 2 mg/kg; and (3) for m-CPBG treatment as shown in Fig. 6, bins 2 and 5 for 3 mg/kg, bins 1, 3, and 4 for 9 mg/kg.

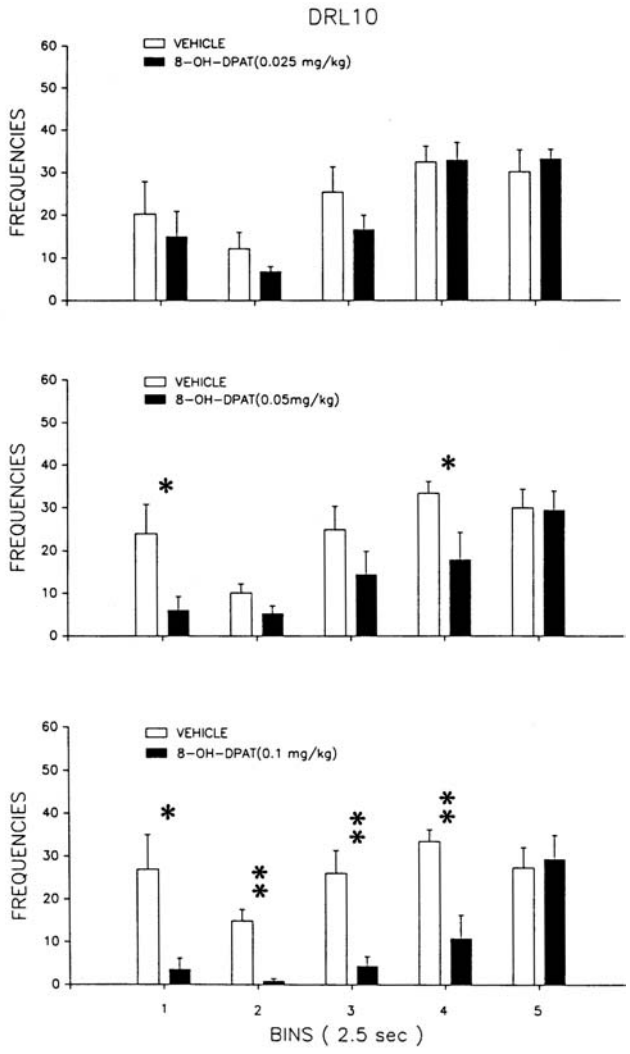


Fig. 4. Comparison of the IRT distribution of responses (means ± 1 s.e.m.) made on the DRL 10-s schedule of reinforcement after 8-OH-DPAT administration of 0.025 mg/kg (top), 0.05 mg/kg (middle), and 0.1 mg/kg (bottom). Each vehicle corresponds to a specific dose injection. The last IRT bin includes all responses with IRT's greater than 10 sec. (** $p < 0.01$, * $p < 0.05$ compared with the appropriate vehicle control)

The IRT data of DRL 30-s behavior are presented in Figs. 7 – 9 in the order of drug treatments 8-OH-DPAT, DOI, and m-CPBG. Similar to the aforementioned IRT data for DRL 10-s, most of the statistical tests on bin effects and bin-by-drug interactions were significantly detected by ANOVA's for these IRT data of DRL 30-s. Again, statistical tests on the main drug effects did not reveal any significant effects for all drug treatments at various doses. Details of these ANOVA results are given in Table 1. Regarding the results of t-tests for each paired bars in the IRT data of DRL 30-s behavior, only the paired bars of bin 9 under the treatment with 0.05 mg/kg of 8-OH-DPAT were significantly different, $p < 0.01$, as shown in Fig. 7. As shown in Figs. 8 and 9, none of the

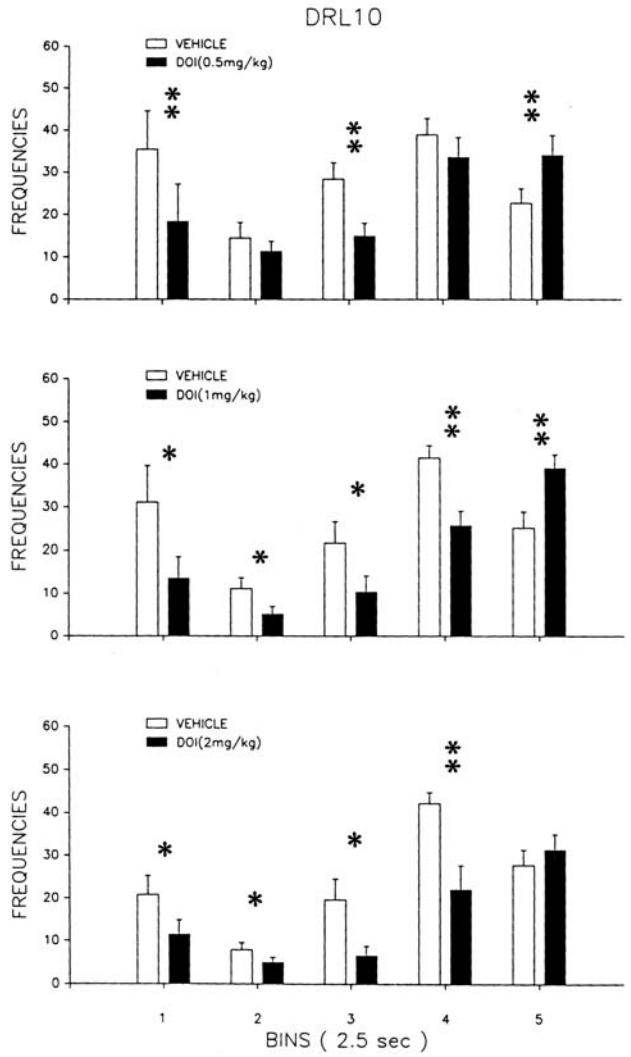


Fig. 5. Comparison of the IRT distribution of responses (means ± 1 s.e.m.) made on the DRL 10-s schedule of reinforcement after DOI administration of 0.5 mg/kg (top), 1 mg/kg (middle), and 2 mg/kg (bottom). Each vehicle corresponds to a specific dose injection. The last IRT bin includes all responses with IRT's greater than 10 sec. (** $p < 0.01$, * $p < 0.05$ compared with the appropriate vehicle control)

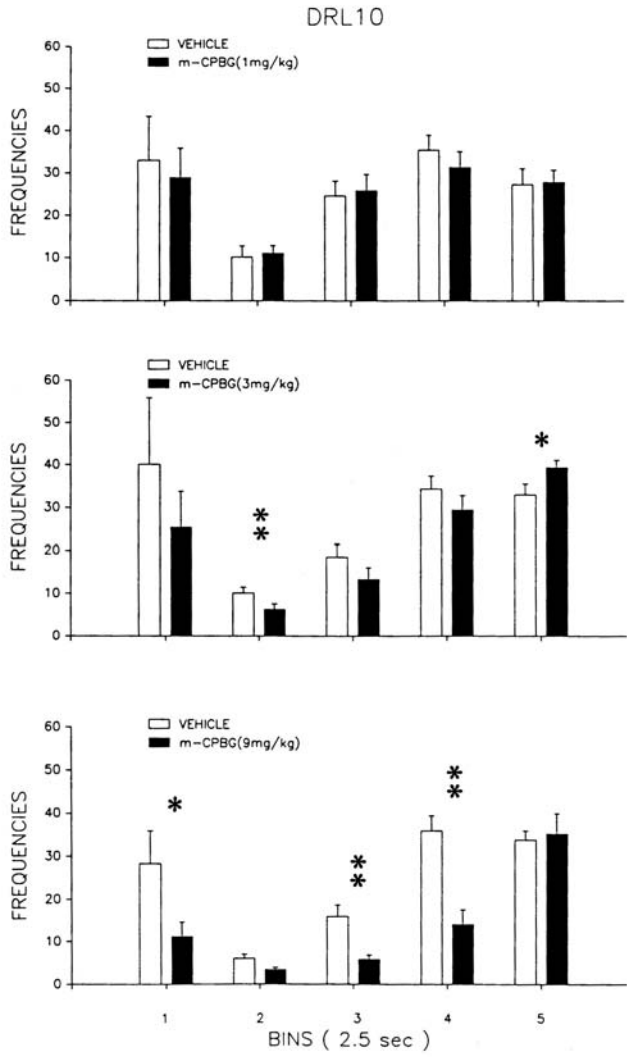


Fig. 6. Comparison of the IRT distribution of responses (means ± 1 s.e.m.) made on the DRL 10-s schedule of reinforcement after m-CPBG administration of 1 mg/kg (top), 3 mg/kg (middle), and 9 mg/kg (bottom). Each vehicle corresponds to a specific dose injection. The last IRT bin includes all responses with IRT's greater than 10 sec. (** $p < 0.01$, * $p < 0.05$ compared with the appropriate vehicle control)

eleven bins in each graph representing a specific dose treatment of both DOI and m-CPBG for IRT distributions of DRL 30-s were significantly different.

IV. Discussion

The overall results of the present work indicate that distinct profiles of operant response on the DRL 10-s and DRL 30-s schedules were produced by 8-OH-DPAT, DOI, and m-CPBG based on quantitative and qualitative data analyses. All three 5-HT receptor agonists significantly decreased the number of responses on the DRL 10-s schedule in a dose-related fashion. The operant performance on the DRL 10-s schedule was more sensitive to drug treatment than was that on the DRL 30-s schedule. Thus, the DRL 30-s behavior showed a higher resistance to drug treatment in comparison to the DRL 10-s behavior. The analyses of IRT distributions detected the DRL behavioral shifts mostly through alteration of the short burst bin and the reinforced bin under drug treatment.

That the 5-HT receptor agonists produced dose-related decrements in DRL 10-s response indicates the involvement of 5-HT in the maintenance of operant behavior. In contrast to the lack of reports in the past on direct effects of DOI and m-CPBG on operant behavior, 8-OH-DPAT has recently been demonstrated to disrupt operant response on various schedules of reinforcement. Consistent with the present study employing the DRL behavioral paradigm, a previous work evalu-

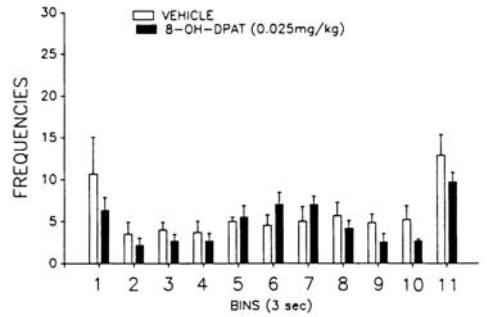
Table 1. A Summary of ANOVA's for the IRT Distributions of the DRL 10-s and DRL 30-s Behaviors under Drug Treatments of 8-OH-DPAT, DOI and m-CPBG

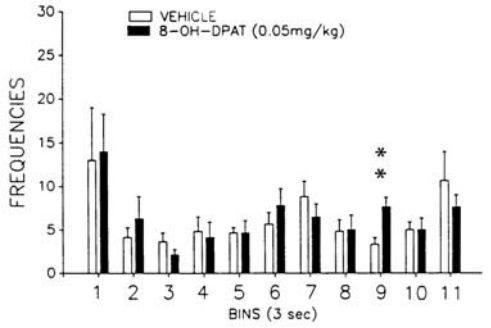
	Bin	Drug	Bin by Drug
DRL 10-s			
8-OH-DPAT			
0.025	F(4,28) = 8.243 **	F(1,7) = 0.144	F(4,28) = 8.428 **
0.05	F(4,28) = 4.663 **	F(1,7) = 0.964	F(4,28) = 5.302 **
0.1	F(4,28) = 4.992 **	F(1,7) = 0.62	F(4,28) = 2.922 *
DOI			
0.5	F(4,28) = 6.134 **	F(1,7) = 3.048	F(4,28) = 1.91
1	F(4,28) = 9.665 **	F(1,7) = 1.621	F(4,28) = 6.365 **
2	F(4,28) =13.966**	F(1,7) = 0.44	F(4,28) = 10.626**
m-CPBG			
1	F(4,28) = 2.027	F(1,7) = 0.013	F(4,28) = 3.756 **
3	F(4,28) = 5.303 **	F(1,7) = 0.228	F(4,28) = 2.531
9	F(4,28) =10.723**	F(1,7) = 0.078	F(4,28) = 16.224**
DRL 30-s			
8-OH-DPAT			
0.025	F(10,50) = 2.841**	F(1,5) = 0.919	F(10,50) = 3.556**
0.05	F(10,50) = 2.093*	F(1,5) = 3.657	F(10,50) = 1.829
0.1	F(10,50) = 1.373	F(1,5) = 0.509	F(10,50) = 3.124**
DOI			
0.5	F(10,50) = 2.036*	F(1,5) = 1.872	F(10,50) = 2.599*
1	F(10,50) = 3.915**	F(1,5) = 0.026	F(10,50) = 2.538*
2	F(10,50) = 3.509**	F(1,5) = 0.328	F(10,50) = 3.879**
m-CPBG			
1	F(10,50) = 5.016**	F(1,5) = 0.18	F(10,50) = 7.857**
3	F(10,50) = 4.125**	F(1,5) = 2.788	F(10,50) = 5.222**
9	F(10,50) = 6.039**	F(1,5) = 3.93	F(10,50) = 7.642**

Note: ** as $p < 0.01$; * as $p < 0.05$; the dose unit of mg/kg represented for each drug.

ating chronic effects of 8-OH-DPAT showed acute decrement of responses on the DRL 20-s behavior at the first day of drug administration with effective doses of 0.1 and 1.0 mg/kg administered via the subcutaneous (SC) route (Evenden *et al*., 1995). The response decrement induced by 8-OH-DPAT was also reported from a study using a stringent DRL 72-s schedule of water reinforcement (Marek *et al*., 1989). Regarding schedules of reinforcement other than those of the DRL type, Shukla *et al*. (1989) reported that operant response on a fixed-ratio 40 (FR40) schedule was inhibited by 8-OH-DPAT injected (SC) at an effective dose of 0.05 mg/kg. Similarly, operant response on a fixed-interval 60 sec (FI 60) schedule was significantly suppressed by 8-OH-DPAT (SC) at doses greater than 0.1 mg/kg (Evenden *et al*., 1995). Based on these data, it is likely that operant response suppressed by systemic injection of 8-OH-DPAT within the present dose range occurs due to drug action on the 5-HT1a receptors of the brain. One previous work examined the effects of local infusion of 8-OH-DPAT into two subareas of the raphe nucleus on DRL 20-s behavior (Fletcher, 1994). In that study, microinjection of 8-OH-DPAT into the medial raphe, but not the dorsal raphe, disrupted the DRL 20-s behavior by increasing the number of responses and decreasing the number of reinforcers, leading to a significant drop in the efficiency rate. Given that the performance of DRL behavior was disturbed, the response rates of DRL responding were changed in opposite direction following systemic and intracranial injection of 8-OH-DPAT. More work needs to be done to understand this difference. A potential direction for further research may be to compare the effects of 8-OH-DPAT on pre- and post-synaptic 5-HT1a receptors.

One of the major findings of this study is the marked difference in drug induced behavioral alteration between DRL 10-s and DRL 30-s. While the operant response of DRL 10-s was significantly affected by drugs administered in the present work, that of DRL 30-s was almost unchanged following drug treatment. Why DRL 30-s response seems to show higher resistance to drug actions deserves to discuss based on the following two points. First, from the perspective of operant behavior, DRL 30-s response can be characterized by the operant performance under a higher degree of partial reinforcement in comparing to DRL 10-s response. It is known that partially reinforced behavior is unlikely to be extinguished (Skinner, 1938). It might be true that operant performance under a higher degree of partial reinforcement is more resistant to being extinguished than is that under a lower degree of partial reinforcement (i.e., DRL 30-s vs. DRL 10-s). Although we did not manipulate the traditional extinction process of omitting reinforcers to directly test this assumption, the drug effect itself on the operant response can be recognized as an obstacle to access for the reinforcer which may then explain the less degree of changes in DRL 30-s response after drug





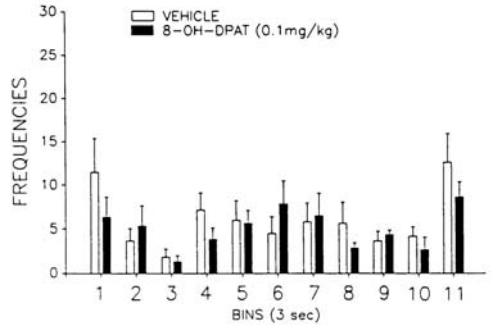
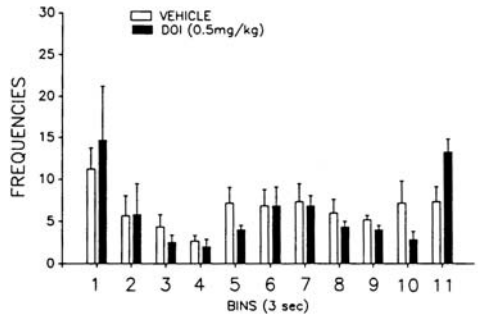
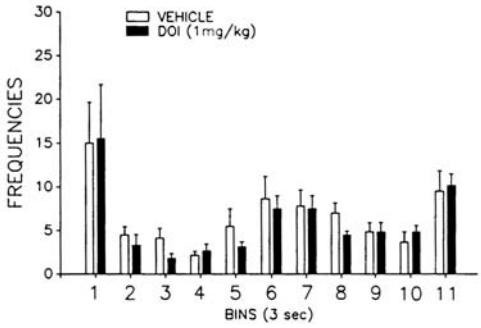


Fig. 7. Comparison of the IRT distribution of responses (means ± 1 s.e.m.) made on the DRL 30-s schedule of reinforcement after 8-OH-DPAT administration of 0.025 mg/kg (top), 0.05 mg/kg (middle), and 0.1 mg/kg (bottom). Each vehicle corresponds to a specific dose injection. The last IRT bin includes all responses with IRT's greater than 30 sec. (** $p < 0.01$ compared with the appropriate vehicle control)





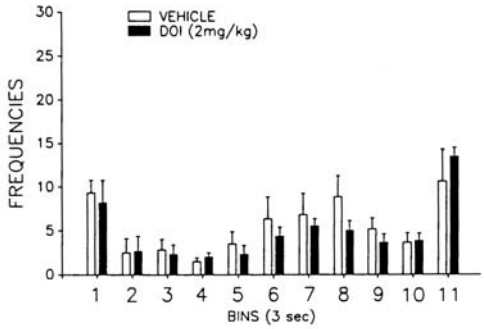


Fig. 8. Comparison of the IRT distribution of responses (means ± 1 s.e.m.) made on the DRL 30-s schedule of reinforcement after DOI administration of 0.5 mg/kg (top), 1 mg/kg (middle), and 2 mg/kg (bottom). Each vehicle corresponds to a specific dose injection. The last IRT bin includes all responses with IRT's greater than 30 sec.

treatment. Also, in the present procedure, the subject was trained to perform on DRL 30-s with quite a number of sessions extended after DRL 10-s. Such an extended training experience may cause the DRL 30-s response to be more resistant to experimental manipulation including drugs. Second, considering the tolerance that develops in response to repeated administration of a drug, one might argue that the reduced drug effect on DRL 30-s response observed in the present work was a result of tolerance. Although 8-OH-DPAT induced tolerance in response to operant behavioral deficits has been reported by Evenden *et al.* (1995), it is unlikely that this was the case in the present work. In contrast to the procedure with continuous injection used in that study and others to develop drug tolerance, the subjects in the present work were injected intermittently within either DRL phase. Furthermore, there were 66 sessions separated in the two DRL phases. Even though the drug was given repeatedly in this work, any drug induced tolerance can be neglected for such an intermittent and separated arrangement of drug administration. Thus, in comparison to DRL 10-s, the DRL 30-s behavior containing the less influence produced by the 5-HT receptor agonists tested in the present work may be resulted from its higher degree of resistance to extinction, rather than to tolerance potentially induced by repeated injections of drugs.

Regarding the reinforcer measurement data, it may be thought that, in general, the number of reinforcers under drug treatments should be correlated with the number of responses for operant behaviors. This may be true for operant behavior maintained under fixed types of reinforcerment schedules

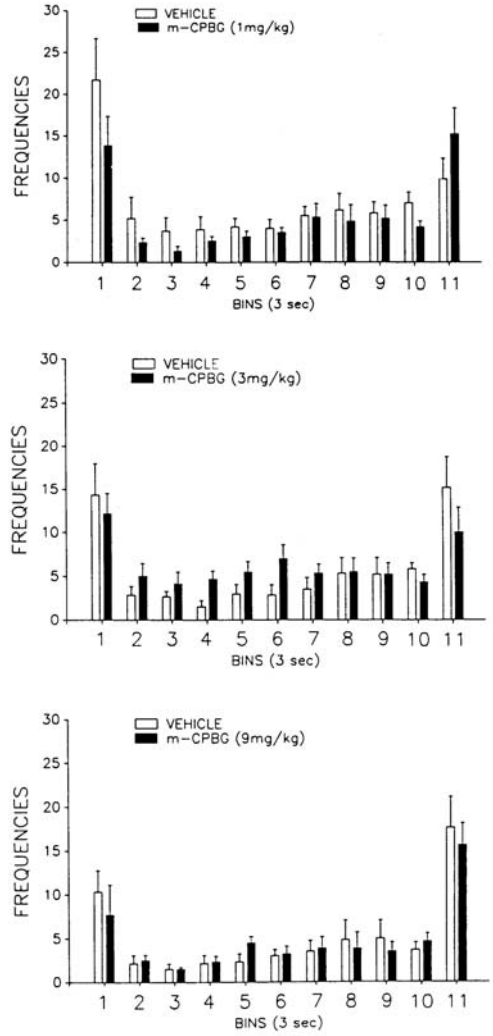


Fig. 9. Comparison of the IRT distribution of responses (means ± 1 s.e.m.) made on the DRL 30-s schedule of reinforcement after m-CPBG administration of 1 mg/kg (top), 3 mg/kg (middle), and 9 mg/kg (bottom). Each vehicle corresponds to a specific dose injection. The last IRT bin includes all responses with IRT's greater than 30 sec.

(Fowler, 1987; Sanger, 1989). This kind of correlation did not appear for DRL behaviors treated with of 5-HT receptor agonists in the present study. In terms of dose challenges on both the DRL 10-s and DRL 30-s schedules, the subject's ability to respond correctly after certain periods of time elapsed for obtaining reinforcer seemed not to be affected by treatment with 5-HT receptor agonists here. The results shown in the dose curves of reinforcers for all three 5-HT agents on either DRL schedule are flattened, in general. However, an exception is the significant increase in the number of reinforcers at the treatment of DOI with 1 mg/kg on DRL 10-s responding. L.S. Seiden and his associates (Marek *et al*., 1989; Richards *et al*., 1994; Seiden *et al*., 1985) addressed that the reduction of the number of responses after injecting 5-HT related drug to cause the increased number of reinforcers is due to the probability increased for rat to press less levers to get more reinforcers. They found this operant characteristic by examining the effects of several 5-HT agonists (*e.g*., gepirone) and antidepressants (*e.g*., fluoxetine) on DRL 72-sec response. This argument may be congruent for aforementioned effects of DOI. However, this may not have been the general case in the present work. It is also important to consider that the temporal requirement for the subject to earn reinforcer in the present work was obviously much shorter than 72 sec. Moreover, a previous work reported that both responses and reinforcers of DRL 20-s were decreased by systemic injection of 8-OH-DPAT (Evenden *et al*., 1995). Together, all these data strongly indicate that these two dependent variables measured for the quantitative aspect of operant behavior following drug treatment are not necessarily correlated with each other. In other words, they are not redundant for each other.

In addition to the analyses of operant data of responses and reinforcers, the evaluation of the IRT data collected from the operant sessions is demonstrated to be useful. For DRL 10-s response, its IRT distribution is significantly illustrated by those higher frequencies located on (1) the first bin with burst response, (2) the bins just before and after the criteria of 10 sec, and (3) in the middle between the very short bursting bin and the one set for criteria. Generally, the shifts in the IRT distributions on DRL 10-s were dose dependent. For each dose of a drug, the patterns of the IRT distribution of DRL 10-s response were not similar, which was confirmed by ANOVA results suggesting that significant interaction between the bin and the drug injection. Also, distinctive profiles of IRT distributions were observed from drug to drug. For instance, although the short burst bins of DRL 10-s were affected by all three agents, the reinforced bin were varied by drug treatment. This supports the idea that behavior can be distinctively changed by drugs acting on different receptors (i.e., 5-HT subtypes).

In conclusion, the present work found that 8-OH-DPAT, DOI, and m-CPBG can significantly alter operant response maintained on DRL schedules. However, the profiles of operant response on the DRL 10-s and DRL 30-s schedules were differentially affected by these drugs both quantitatively and qualitatively. The difference in the operant performance for each drug is believed to be due to drug activation of specific 5-HT subtype receptors.

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五羥色胺素受體的顯效劑影響大白鼠操作式制約行爲在DRL 10秒及DRL 30秒爲增強程序之反應的相異效果

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摘　要

五羥色胺素（即血清素）被認爲參與很多的行爲功能，利用受體結合之生物化學檢驗技術的研究結果已對五羥色胺素次級受體有更嚴謹的區分界定，一些新的專屬作用於五羥色胺素次級受體的顯效劑亦被發展出來。基於瞭解它們對學習制約行爲的影響作用，本研究利用安排增強物在時間向度上不同（10 秒及 30 秒）強化低頻反應程序所訓練出的 DRL 類型操作式學習行爲（DRL 10-s 及 DRL 30-s），檢視其受三種作用於不同的五羥色胺素次級受體之顯效劑的影響效果。實驗受試爲經過日常飲水剝奪的大白鼠，利用傳統的斯金納操作式學習箱配合微電腦監控箱內環境及收集反應訊號。受試經過初期漸近式的塑形，當它們學會操作按箱內的壓桿反應器之後，每一隻受試繼續學習 DRL 10-s 和 DRL 30-s 增強物安排的情境。在它們學會所指定的操作式學習行爲且很穩定的反應之後，每隻大白鼠便接受一種特定之五羥色胺素受體顯效劑測試。每種藥劑均採用週邊重覆注射並比較控制液及多種劑量之藥效。測試劑量如下：8-OH-DPAT 爲 0.025, 0.05 及 0.1 毫克／公斤（皮下注射）， DOI 爲 0.5, 1 及 2 毫克／公斤（皮下注射），m-CPBG 爲 1, 3 及 9 毫克／公斤（腹腔注射）。實驗結果用量與質的資料分析明顯指出三種五羥色胺素受體顯效劑對操作式學習行爲均有不同的影響效果：就反應次數及增強物次數而言，三種藥物均顯著的減抑反應次數，但藥物干擾 DRL 10-s 的效果顯然大於 DRL 30-s。利用兩個反應區間所佔時間（IRT）的次數分佈圖，結果顯示藥物對不同時距的 IRT 反應有不等的影響效果。綜合而論，本研究所測試的三種五羥色胺素次級受體顯效劑對 DRL 操作式學習行爲有明顯的影響效果，但其響程度則依不同藥物及 DRL 類型操作式學習行爲的時間要求程序而有所差異。這些藥物影響行爲的作用，本文認爲是來自藥物激活不同之五羥色胺素次級受體所致。