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Review

Effects of Amphetamine and Cocaine on Behavior Maintained by Differential Reinforcement of Low-Rate-Response (DRL) Schedule

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Abstract

Although a number of previous review articles cover the effects of psychostimulant drugs on the operant or schedule-controlled behavior, none of those had focused on the effects of amphetamine and cocaine on operant behavior exclusively maintained by differential reinforcement of low-rate response (DRL). This review (a) summarizes research on the psychopharmacology of amphetamines and cocaine that has been conducted using DRL behavior, (b) discusses the potential neural substrates underlying the aforementioned drug-induced behavioral alterations on the basis of the data from lesion studies, and (c) highlights two major behavioral components, behavioral inhibition and temporal control of DRL responding, that are altered by amphetamines and cocaine. Amphetamines and cocaine affect the development and/or performance of DRL behavior in dose related ways that can be differentiated on the basis of the specific types of behavioral alterations. In general, with the moderate but effective doses, these drugs significantly increase the total number of responses and decrease the number of reinforced responses. Although the burst responses with very short inter-response times (IRT's) are more likely increased by these drugs, this aspect of the drugs' effects were found to vary across studies that used different experimental procedures of shaping up or training the subject to perform DRL behavior. Both amphetamine and cocaine produce a leftward shift on the IRT frequency distribution curve compared to vehicle treatment. The effects of amphetamines and cocaine on DRL behavior as reviewed here further highlight the need for additional research to probe neurobehavioral mechanisms that may underlie DRL behavior as manifested by both burst responding and timing the emission of the operant response.

Key Words: operant conditioned behavior, psychopharmacology, timing, behavioral inhibition, rat

Introduction

In addition to having high abuse liability in common, psychostimuant drugs produce significant influences on a variety of affective, cognitive, and sensorimotor processes in the mammalians. Over the last four decades, in human society, as the social cost of abuse of these drugs dramatically increased and as health problems seriously arose, serious concerns about addiction to this class of drugs have led to extensive research to investigate the underlying neurobehavioral mechanisms. There are many other drugs

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or synthetic compounds classified as psychostimulants, but the present review will focus only on amphetamines and cocaine. The use of either amphetamine or cocaine has a long history in human societies for recreational and/or episodic purposes since the last century (52). More recently, amphetamine has also been used for certain medical treatments such as antifatigue, prevention of narcolepsy, amelioration of attention deficit hyperactive disorders (ADHD), and cocaine has been used as a local anesthetic. However, it should be noted that the medical usefulness of either drug is limited due to its addictive potential and toxicity.

Under laboratory conditions, these two drugs are generally categorized as psychomotor stimulants with the fact that the drugs produce hyperactivity in several dimensions of behavior including spontaneous locomotor activity, stereotypy behavior, consummatory motivation related behaviors, and stimulus conditioned behaviors (38, 52, 73, 77). All these behavioral effects are basically dependent on the drugs' properties that increase activity at synapses that use monoamines as neurotransmitters. However, the mechanisms by which they affect these synapses differ (38, 77, 98). For instance, when increasing extracellular dopamine accumulation, amphetamine inhibits the storage of dopamine in synaptic vesicles, whereas cocaine mainly relies on the blockade of dopamine reuptake transporter. Moreover, along with primary focus on the issue of drug addiction and toxicity, extensive data have been accumulated by physiological, pharmacological, biochemical, and pathological studies to elucidate the mechanism of action of amphetamine and cocaine. This work has advanced our understanding of neurobiological bases of addiction for all the drugs of abuse including amphetamines and cocaine (*e.g.* 40, 58, 59). With this advancement, the molecular and cellular mechanisms of actions of these two drugs now have a clearer profile and can be found in other reviews (17, 86, 100).

In contrast to drug reactions at the cellular and molecular levels, the psychotropic and behavioral effects of amphetamines and cocaine can be varied and are dependent on multiple factors (see 32 for *d*-amphetamine). One of those influential factors is related to the fact that most of the behavioral tasks used to study these drugs contain distinct components that require different behavioral features. In the area of psychopharmacology or neuropsychopharmacology, many types of behavioral measurement have been developed and applied to test the effects of psychostimulants, and these behavioral methods have ranged from the non-learned or reflexive behaviors to the leaned or conditioned ones (8, 70, 91, 97). Among the conditioned behavioral tasks, operant behavior has been used to assess the effects of psychoactive drugs (74). The development or performance of operant conditioned behavior critically relies on the schedule of reinforcement (27). Operant responding patterns can be uniquely characterized by different schedules of reinforcement (81). Four different types of operant behaviors are engendered by the four basic schedules of reinforcement including fixed ratio (FR), fixed interval (FI), varied ratio (VR), and varied interval (VI) that produce distinctive behavioral profiles. On each schedule, the animal subject is trained to respond on a manipulandum (*i.e.* lever pressing for the rat) for obtaining reinforcer based on the reinforcement contingency programmed by that schedule with a specific parameter of ratio or time interval. For instance, response rate is generally higher in FR type than in FI type of schedule. And, observed only in FI schedule, the subject tends to make more lever presses in the last quarter of each interval in comparison to those accumulated in the preceding three quarters. Operant conditioning is thus a process by which a behavior can be changed or controlled by the environmental factors. Accordingly, it is possible to manipulate various environmental factors that affect the rate and patterns of lever pressing. Compared to some other behavioral paradigms, such as maze learning, operant behavior tasks provide a relatively more predictable pattern of responding, and this can minimize the significant individual variation in testing. It can then lead to more precise characterization of drugs' behavioral effects. In research emphasizing the neurobiological basis of operant behavior (6, 23), psychopharmacologists have provided substantial insight into behavioral mechanisms underlying the effects of amphetamine and cocaine on these four simple schedules of reinforcement. For instance, according to the rate-dependency hypothesis (19, 20), *d*-amphetamine has been shown to differentially affect operant behaviors with different levels of baseline response rate (*i.e.*, low rates are increased and high rates are decreased). This principle has further supported by the data collected from behavioral tasks other than conventional operant schedule-controlled behaviors such as the locomotor activity and the choice of Y-maze (21). Moreover, the effects of amphetamine or cocaine on operant behaviors based on conventional schedules of reinforcement have been used to test different categories of psychotherapeutic drugs such as antidepressants, anxiolytics, and neuroleptics (also termed as antipsychotics). Some of the drugs classified in the aforementioned categories have been shown to contain selectively-defined actions on specific schedule-controlled behaviors (74). Similarly, it has been argued that psychostimulant drugs can be distinguished on the basis of their different operant effects

on these four simple schedules of reinforcement (33).

These data described above do assist us in understanding the effects of amphetamine and cocaine on the operant behavior with reinforcement contingency upon either the completion of a fixed or variable number of responses or upon the expiration of a fixed or variable time period followed by at least one response. There is a schedule of reinforcement called the differential reinforcement of low-rate response (DRL), which was initially developed from an idea to combine the response ratio and time interval schedules (42). In laboratory animals, operant behavior maintained on the DRL schedule has been characterized as exhibiting temporal regulation as well as behavioral inhibition. Rats trained on this schedule of reinforcement are required to inhibit or withhold lever pressing for a minimum specified period of time in order to obtain a reinforcer. Any premature response leads not only to non-reinforcement consequence but also to re-setting of the time requirement to its full interval. Distinctive behavioral characteristics existed after extensive training on a DRL schedule as compared to those maintained on the aforementioned four reinforcement schedules. Surprisingly, there is no review article focusing on the operant effects of amphetamine and cocaine on DRL behavior. Since the DRL behavioral task has been widely employed in neuroscience and psychopharmacology, a review on the aforementioned topic seemed warranted. Thus, in order to consolidate the results of the studies which bear on the aforementioned topic, this review intends (a) to summarize research on the psychopharmacology of amphetamines and cocaine that have been conducted on the DRL behavior, (b) to discuss the potential neural substrates that underlie the aforementioned drug-induced behavioral alterations on the basis of the data from lesion studies, and (c) to highlight two major behavioral processes, behavioral inhibition and temporal control, being altered by amphetamines and cocaine.

Effects of Amphetamine or Cocaine on DRL Behavior

Two goals can be addressed, in general, for those studies that assessed the effects of amphetamine and cocaine on DRL behavior. The first one, as mentioned above, was to compare the operant response altered by these drugs on simple schedules of reinforcement and DRL schedule that separately represented behaviors with higher and lower response rate. The second goal relates to the use of DRL behavioral measure(s) to screen psychoactive or psychotherapeutic drugs of different classes, and studies in this category frequently included the comparative data on amphetamine or cocaine on this behavioral task (*e.g.* 71, 76). An excellent review by O'Donnell and associates (60) has specifically discussed the hypothesis that antidepressant drugs lead to the improvement of DRL behavior. As mentioned above, the primary objective of the present review is to illustrate the operant behavioral effects or patterns being altered by amphetamine or cocaine on DRL behavior. The independent variables including the doses and administration routs of each drug, the time of drug injection before the commencement of behavioral sessions, as well as the species of the rat are listed in Table 1. Notice that only the studies using rats as subjects are included in the present review. The interval of DRL task, the duration of behavioral session and the type of reinforcer adopted in each study are presented correspondingly along with the drug induced effects on DRL behavioral measures. This information about variables manipulated in psychopharmacological experiments is thought to be useful for understanding any discrepancies between studies. The amphetamine-like drugs addressed in this review include *d*-amphetamine, *dl*-amphetamine, methamphetamine, and methylphenidate. There are twenty two studies regarding to amphetamine-like drugs presented in Table 1, followed by six studies that used cocaine. Sidman (79) first reported the disruptive effects of *dl*-amphetamine on DRL 21-sec behavior with descriptive statistics, and these results have been confirmed with more powerful statistical analyses using multiple measures in both qualitative and quantitative.

Drug Effects on the Reinforced and Non-Reinforced Responses

Accumulated data show that acute treatment with amphetamine, regardless of the type of derivative studied, at moderate doses (0.5~3.0 mg/kg) results in the disruption of DRL behavioral performance by increasing the number of responses and decreasing the number of reinforcers obtained. These results have been consistently observed for operant behavior maintained on a DRL schedule of reinforcement with various interval criteria ranging from 10 sec up to 72 sec (3, 7, 9, 11, 12, 56, 67, 69, 71, 76, 95; see Table 1). However, the results are inconsistent when analyses were made on the responses being classified into more categories than the aforementioned total responses and reinforcements. Despite different terms used, those responses were categorized on the basis of inter-response time (IRT). In these analyses, burst responding or the very premature responses was used to describe responses with relatively short IRT's (*i.e.*, less than 2 sec). A second category of responses have been defined as non burst responses that did not result in reinforcer delivery or simply non-reinforced IRT's. Amphetamine significantly increased this category

Table 1. The dose effects of amphetamines and cocaine on (the performance of) DRL behavior in rats. The studies cited in this table are listed in chronological order. *IP* intraperitoneal, *SC* subcutaneous, *IM* intramuscular, *F* female, *M* male, *B* between-subject dosing design, *W* within subject dosing design, *NS* non-significant effect, IRT inter-response time, LED the least effective dose, ↑ increment, ↓ decrement, ← leftward shift

Doses (mg/kg)	Injection time prior to behavioral session	Strain (sex)	DRL behavior measurement					Reference
			Interval (sec)$^{+}$	Session duration	Reinforcer	Dependent variables	Results (LED)	
d-amphetamine								
0.5, 1.0, 2.0, 4.0 mg/kg (*W*)	15 min (*IP*)	Hooded	15 sec	60 min	food pellet (45 mg)	1) response rate 2) reinforcements	↑ (0.5) ↓ (0.5)	76
0.5, 1.0 mg/kg	30 min (*IP*)	Wistar (*M*)	10 sec	N/A	food pellet (45 mg)	1) burst responses 2) reinforcements	NS ↓ (0.5)	11
11 0.1, 0.32, 1.0, 1.5 mg/kg (*W*)	20 min (*IP*)	Sprague-Dawley (*M*)	20 – 60 sec*	20 min	food pellet (45 mg)	1) total responses 2) non-reinforced responses 3) reinforced responses 4) burst responses 5) IRT distribution	↑ ↑ ↓ ↓ ←	56
0.3, 0.6, 1.25, 2.5 mg/kg (*W*)	30 min (*IP*)	Wistar (*M*)	60 sec	60 min	food pellet (45 mg)	1) responding rate 2) reinforcement frequencies	↑ (1.25) ↓ (2.5)	71
0.5 mg/kg	30 min (*SC*)	Wistar (*M*)	60 sec	60 min	food pellet (45 mg)	1) responses 2) reinforcements 3) efficiency	↑ ↓ ↓	9
0.1, 0.3, 1.0, 2.0, 3.0 mg/kg (*W*)	5 min (*IP*)	CD of Charles River (*M*)	10 – 14 sec*	45 min	food pellet (97 mg)	1) efficiency 2) response rate 3) IRT distribution	↓ (1.0) *NS* ←	95
0.5, 1.0, 2.0, 4.0 mg/kg (*W*)	60 min (*IP*)	Wistar (*M*)	72 sec	60 min	food pellet (45 mg)	1) responses rate 2) reinforcement rate	↑ *NS*	92
0.5, 1.0, 2.0 mg/kg (*W*)	20 min (*IP*)	Sprague-Dawley (*M*)	72 sec	60 min	water	1) responses rate 2) burst responses 3) pause 3) reinforcements 4) burst ratio (BR) 5) peak area (PkA) 6) peak location (PkL)	↑ (0.5) ↑ (1.0) ↑ (0.5) ↓ (0.5) *NS* ↓ (1.0) ↓ (0.5)	67
0.25, 0.5, 1.0, 2.0, 4.0 mg/kg (*W*)	20 min (*IP*)	Sprague-Dawley (*M*)	36 sec	60 min	water	1) total responses 2) reinforcers 3) peak area 4) peak location 5) burst ratio	↑ ↓ ↓ ↓ *NS*	69
1.5 mg/kg	5 min (*IP*)	Sprague-Dawley (*M*)	72 sec	60 min	water (0.025ml)	1) responses 2) reinforcement 3) peak area 4) peak location 5) burst response 6) IRT distribution	↑ ↓ ↓ ↓ *NS* ←	3
0.5, 1.0 mg/kg (*B*)	30 min (*IP*)	Wistar (*M*)	30 sec	30 min	food pellet (45 mg)	1) response rate 2) very premature responses 3) premature responses 4) reinforced responses	↑ (0.5) *NS* ↑ (1.0) ↓ (1.0)	7

Table 1 (Continued)

Doses (mg/kg)	Injection time prior to behavioral session	Strain (sex)	DRL behavior measurement					Reference
			Interval (sec)$^{+}$	Session duration	Reinforcer	Dependent variables	Results (LED)	
0.2, 2.0 mg/kg (*B*)	15 min (*IP*)	Wistar (*M*)	10 sec	15 min	water (0.2 ml)	1) total responses 2) reinforced responses 3) IRT distribution	*NS* ↓ ıмain effects	12
0.1, 0.3, 1.0, 3.0 mg/kg (*W*)	15 min (*IP*)	Long-Evans (*M*)	15 sec	54 min (3 signal & 3 unsignal components)	food pellet (45 mg)	1) response rate 2) deburst IRT 3) time-out intervals 4) reinfrocer number 5) IRT distribution	↑ (1.0) ↓ (1.0) *NS* ↓ (1.0) ←	96
0.1, 0.3, 0.65, 1.0 mg/kg (*W*)	15 min (*IP*)	Sprague-Dawley (*M*)	10 – 14 sec*	~ 50 min	food pellet	1) % accuracy 2) response rate 3) % burst	↓ (1.0) ↑ (1.0) ↑ (1.0)	26
5 mg/kg	^ (*IP*)	Sprague-Dawley (*M*)	30 sec ^^	45 min	food pellet (45 mg)	1) IRT distribution 2) efficiency	↑ (bins of 1, 28, and 29 sec) ↓	63
0.5, 1.0 mg/kg (*W*)	15 min (*IP*)	Wistar (*M*)	10 sec	15 min	water (0.2 ml)	1) total responses 2) reinforced responses 3) non-reinforced responses 4) burst responses 5) peak time 6) peak rate 7) IRT distribution	*NS* ↓ ↑ *NS* ↓ *NS* ←	46
0.1, 0.17, 0.3, 0.56, 1.0 mg/kg (*W*)	10 min (*SC*)	Sprague-Dawley (*M*)	10 sec	30 min	sucrose pellets (45 mg)	1) active lever presses 2) accuracy	↓ (0.56) *NS*	5
1.0 mg/kg	15 min (*IP*)	Sprague-Dawley (*M*)	10 sec	15 min	water (0.04 ml)	1) total responses 2) reinforced responses 3) non-reinforced responses 4) burst responses 5) peak time 6) peak rate 7) IRT distribution	↑ ↓ ↑ *NS* ↓ *NS* ←	14
dl-Amphetamine								
1.5, 3.0 mg/kg (*W*)	5 min (*SC*)	albino	21 sec	120 min	water	1) total responses 2) IRT distribution	↑ # ←	79
Methamphetamine								
0.25, 0.5, 1.0, 2.0, 4.0 mg/kg (*W*)	20 min (*IP*)	Sprague-Dawley (*M*)	36 sec	60 min	Water	1) total responses 2) reinforcers 3) peak area 4) peak location 5) burst ratio	↑ ↓ ↓ ↓ *NS*	69

Table 1 (Continued)

Doses (mg/kg)	Injection time prior to behavioral session	Strain (sex)	DRL behavior measurement					Reference
			Interval (sec)[+]	Session duration	Reinforcer	Dependent variables	Results (LED)	
methamphetamine								
0.3, 1.0, 1.7, 3.0, 5.6 mg/kg (*W*)	10 min (*IP*)	Sprague-Dawley (*M*)	1 – 1.3 sec*	40 min	food pellet (97 mg)	1) accuracy	↓	50
						2) mean IRT	*NS*	
						3) responses rate	*NS*	
			4 – 5.2 sec*			1) accuracy	↓ (1.0)	
						2) mean IRT	↓ (1.0)	
						3) responses rate	*NS*	
			10 – 13 sec*			1) accuracy	↓ (0.3)	
						2) mean IRT	↓ (1.7)	
						3) responses rate	↓ (1.7)	
Methylphenidate								
2.0, 3.25, 4.5, 7.5 mg/kg (*W*)	15 min (*IP*)	Sprague-Dawley (*M*)	10 – 14 sec*	~ 50 min	food pellet	1) % accuracy	↑ (2.0)	26
						2) response rate	↑ (2.0)	
						3) % burst	↑ (2.0)	
Cocaine								
4, 8, 16, 32 (*W*)	15 min (*IP*)	Sprague-Dawley (*M*)	20 sec (45 mg)	60 min	food pellet	1) response rate	↑ (8)	99
						2) reinforcements	↓ (8)	
						3) IRT distribution	←	
0.1, 0.3, 1.0, 3.0, 5.6, 10.0 mg/kg (*W*)	5 min (*IP*)	CD (*M*)	10 – 14 sec*	45 min	food pellet (97 mg)	1) efficiency	↓ (3.0)	95
						2) response rate	*NS*	
						3) IRT distribution	←	
1, 2, 4 (*W*)	0 min (IV)	Sprague-Dawley (*M*)	45 sec	180 min	food pellet (45 mg)	1) total responses	↑ (1)	49 & 93
						2) shorter-response	↑ (1)	
						3) reinforcement	↓ (1)	
						4) IRT distribution	←	
10, 20, 40 (*W*)	0 min (oral)	Sprague-Dawley (*M*)	45 sec	180 min	food pellet (45 mg)	1) total responses	↑	
						2) shorter-response	↑	
						3) reinforcement	↓	
						4) IRT distribution	←	
15 mg/kg	15 min (*IP*)	Sprague-Dawley (*M*)	12 sec	30 min	food pellet	1) total responses	↑	15
						2) burst responses	↑	
						3) peak time	↓	
						4) IRT distribution	←	
1.25, 2.5, 5, 10 mg/kg (*W*)	0 min (*IP*)	Sprague-Dawley (*M*)	20 sec	60 min	water	1) response rate	↑ (5)	84
						2) reinforcements	↓ (1.25)	
						3) IRT (mean, medial, mode)	↓ (1.25)	

+: DRL interval with the limited hold is presented in a time period from the DRL required interval to the maximum time for the availability of accessing the reinforcer.

*: DRL interval extended with a limited hold for responding to access reinforcer.

#: n = 2 and descriptive statistics only

^: administered sub-chronically in 5 days (5 mg/kg each day); DRL test resumed after 2 days of withdrawal (no drug treatment)

^^: nose poke as the operant manipulandum

of responses that correspondingly leads to a leftward shift of the IRT frequency distribution. Moreover, the accuracy or efficiency calculated from the number of reinforced responses divided by total responses was decreased by amphetamines. Not unexpectedly, the effects of cocaine on DRL responding are very similar to those aforementioned for amphetamines. However, because of differences in potency and elimination kinetics, cocaine dose response functions can differ from amphetamine dose-effect functions.

Quantitative Analyses of IRT Frequency Distribution

In addition to the measurement of the aforementioned responses and reinforcement rates, the IRT specified for each response is now recognized as a useful measure when evaluating drug effects on DRL behavioral performance. Amphetamines and cocaine, in general, cause the rat to respond more in shorter IRTs leading to a leftward shift in the IRT frequency distribution. Some of the earlier work presents the IRT data either in a descriptive statistical manner (*e.g.* 9) or qualitative form (*e.g.* 76). Conversely, and reported in more recently, a limited number of studies have reported IRT data using quantitative methods to address IRT frequency distributions altered by amphetamine (46, 50, 67). McClure and McMillan (50) accumulated IRT percentages from the low to high bins and reversed the half part of higher bins to make a sigmoid-like curve for IRT frequency distributions. In this approach to data analysis, the slope and the mean IRT were calculated from the most linear part in the middle of sigmoid curve. Methamphetamine was shown to decrease the mean IRT and slope in a dose-related fashion (50). These two parameters were also reported in a series of studies from the same lab and were confirmed to be sensitive to drug treatment (see 62). With the same rationale as the IRTs-per-opportunity analysis (1), Richards and associates (67) developed a "peak deviation analysis" for quantifying the DRL IRT distribution by three standardized metrics including peak area (PkA), peak location (PkL), and burst ratio (BR). BR represents the burst responses, whereas PkA and PkL quantitatively characterize the de-burst part of responses. The effects of *d*-amphetamine on these three metrics in comparison to those conventional response variables can be seen in Table 1 (see entry for reference 67). Based on the similar ideas of de-burst process and PkA and PkL metrics by Richards and associates (67), this laboratory developed a simpler way to quantify the location of the peak of IRT distribution curve on the de-burst part of responses (46). The peak time and mean peak rate were calculated from the de-burst IRTs, in which a moving average based on four consecutive 1-s bins was applied to smooth the distribution. With a maximum frequency of a 4-s epoch identified, the peak time was the mean value of the IRTs that fell within those four bins. The mean peak rate was then calculated from the summed frequencies of those four bins divided by four. Peak time and peak rate were confirmed to be sensitive to *d*-amphetamine's effects on the timing and motoric components involved in DRL behavior (14, 46). Taken together, while both qualitative and quantitative methods are informative for elucidating IRT data, the latter may more precisely measure drug-induced changes in the IRT distribution curve.

Factors Related to Behavioral Manipulations

Among the dependent variables related to the responses described above, the burst variable was inconsistently affected by amphetamine-like drugs. Although no empirical study has directly probed this inconsistency yet, it could be attributed to several independent variables used in the studies as listed in Table 1. First, from a behavioral perspective, the length of behavioral session set in the DRL task with a specific interval requirement would affect the frequency of reinforcement. For instance, in the normal rat, behavioral performance tends to be poorer at the beginning of the session (more bursts, fewer reinforcers), and performance improves as the 60- min session continues (49, 93). And from 60 to 180 min, while the decrement of bursts ceased, the reinforcements remained at a stabilized level. When cocaine was administered (49, 93), drug-induced behavioral alterations were only apparent in the first hour rather than in the last two hours. These data, thus, indicate that a study applying a longer session for a DRL task may have behavioral measures different from that using a shorter session (*i.e.* 15 min), especially when the response rate is the primary dependent variable in the data analysis. Secondly, another variable affecting DRL performance is the motivational state of the rats (22, 48). Despite the deprivation of food or water widely applied in the operant behavior research, the details of deprivation regimen were rarely stated in the reports of DRL studies. Nevertheless, the use of a within-subject dosing design, which was used in most of the studies reviewed, may help mitigate this potential source of variability across these studies (see Table 1). Third, behavioral history in the form of how the subjects first acquired the operant response (shaping, auto-shaping) or the specific series of progressively more difficult IRT requirements used to establish the final DRL behavior may also explain the inconsistent results apparent between studies. The impact of this factor is more critical in those studies using longer intervals in the DRL task (*i.e.*, > 30 sec). In such as a case, more stages to increase the DRL

interval set for the access of reinforcer are inevitable. Accordingly, the higher the interval of DRL requirement, the greater the amount of training sessions required for reaching stable performance. Fourth, individual differences in gross motor reactivity to the environment may also an influential behavioral factor in DRL studies. Most recently, Stoffel and Cunningham (84) separated rats into high and low responders to a novel environment using locomotor activity as a behavioral measure. They found that higher activity responders had less reinforced responses on DRL 20 sec and DRL 35 sec tasks, whereas the response rate was not affected. These results indicate that the subjects with high reactivity to the novelty are prone to disinhibit their responses with longer IRT for reinforcement on DRL task (but see 5).

Factors Related to Pharmacological Manipulations

Drug dose and route of administration can have markedly different effects on DRL-maintained behavior (32, 47). As shown in Table 1, the doses for *d*-amphetamine administration were variously tested in a range from 0.1 to 4.0 mg/kg, whereas the dose range was from 0.1 to 40 mg/kg for cocaine. In the studies reviewed, routs of administration were: intraperitoneal, intravenous, oral, and subcutaneous. For example, as comparing the effects of cocaine administered *via* intravenous versus oral, dramatic differences were reported for the effects of cocaine on DRL 45 sec task (49, 93). The pre-drug behavioral baseline conditions under which the effects of drug treatment were observed could also be an influential factor. Although it is generally acceptable practice to define baseline stability in terms a limited amount of variability (*e.g.*, 10% variation in the mean) over a certain number of consecutive sessions (*e.g.*, 3), most of the reviewed studies were lax in reporting their stability criteria. DRL behavior is more more easily disrupted than that maintained solely on the ratio or interval schedule, such as FR or FI schedule-controlled behavior. If this information had been provided, it would have been useful for comparing the results from different studies, especially when inconsistencies were appeared.

Except for a few studies testing one single dose, most of the reviewed studies examined multiple doses of amphetamines or cocaine by adopting a within-subject dosing design. Even though these studies were not designed to test psychostimulant induced behavioral sensitization after withdrawal following a specific drug administration regimen (41, 68), it is worthwhile to check the potentially confounding of drug sensitization with assessment of dose effects built up from the repeated injections. It was demonstrated that such a behavioral sensitization can be induced by a lower dose of amphetamine (0.5 mg/kg) in rats pretreated with six injections of 1.5 mg/kg amphetamine intermittently over 3.5 weeks as reported for a DRL 72-s behavior (3). In a recent study using a nose poke rather than the traditional lever press as the operant manipulandum for the rat, a sensitization-like outcome was reported for DRL 30-s behavior (63). In this study, the rat was pretreated with five daily injections of 5 mg/kg of amphetamine and followed by two-day withdrawal significantly increased the total number of nose pokes and decreased the response efficiency by increments for the IRTs of 1 sec, 28 sec, and 29 sec. Together, the number of drug injections, the dosage, and the day(s) in between drug administrations should be taken into account for sensitization effects occurring that may confound estimation of dose effects in within-subject dosing designs.

In terms of acquisition and performance of operant behavior, it should be noted that all the reviewed studies conducted drug evaluation in the performance stage of DRL behavior. The issue being commonly addressed by these studies is to investigate the acute effect of amphetamines or cocaine on DRL behavioral *performance*. How these drugs affect the *acquisition* of DRL behavior is an interesting question but is rarely, if ever, studied.

Effects of Localized Brain Lesions on DRL Behavior

In addition to being an area of experimentation in psychopharmacology, DRL behavior has been investigated from a neurobiological perspective by examining the effects of brain lesions on DRL behavior. Accumulated data indicate that certain brain areas are involved in the DRL behavior, and both acquisition and performance have been studied in this area of research.

The Septo-Hippocampal System

The close anatomical and physiological relationship between the septum and hippocampus has led to the term “septo-hippocampal system”, and this system has received attention as a major area in mediating conditioned behavior including DRL behavior, in the earlier stages of behavioral neuroscience (18). The performance of DRL 20 sec was impaired by hippocampal damage induced by electrolytic lesions (16). With an attention to test the heterogeneity of hippocampal subareas, by using electrolytic lesions, the anteriodorsal rather than the posterior part of the hippocampus was shown to be crucial to the maintenance of DRL 20 sec behavior (39). Electrolytic lesions of medial or lateral septum impair the acqui-

sition of DRL 20 sec behavior, which results were attributed to the disruption of hippocampal theta activity induced in the lesioned subjects (10). However, a subtle decrease of responses on the acquired DRL 20 sec behavior was reported only in the subjects that received hippocampal ablation along with prior intra-septal injection of 6-hydroxydopamine (6-OHDA) in comparison to control subjects with either treatment alone (2). Cytotoxic lesions by ibotenic acid in the hippocampus were shown to impair the acquisition of DRL 18 sec (80). In another study, researchers used the cytotoxin, N-methyl-D-aspartate (NMDA), infused into multiple sites of either the dorsal or the ventral hippocampus to produce a near complete lesion on either part; the results showed that the efficiency of acquiring DRL 18 sec task was attenuated by lesions in either dorsal or ventral lesion groups (4).

The Mesolimbic and Mesocortical Dopamine Systems

In addition to the involvement of septo-hippocampal system in DRL behavioral function, the mesolimbic and/or mesocortical dopamine systems are though to be involved in the control of this behavior. In an earlier study, although the acquisition of a DRL 18 sec was not affected by intra-ventricular 6-OHDA treatment, these 6-OHDA treated subjects showed less response-increasing effect to amphetamine on the DRL task (44). Despite the fact that dopamine and norepinephrine in the brain were significantly depleted by aforementioned 6-OHDA treatment, it was difficult to determine which brain site was specifically affected by 6-OHDA. Electrolytic lesions in the ventral anterior striatum increased responding on a modified DRL 30 sec task (to respond on that DRL task alternatively in two connected operant chambers), but such an effect was not true for the lesion of dorsomedial striatum or prefrontal cortex (57). In that study, the observation of DRL responses increased by direct application of dopamine, *d*-amphetamine, or scopolamine in microgram quantities into the ventral anterior striatum supports the argument for linking brain dopamine and DRL behavior. Bilateral damage to the ventral striatum induced by the excitotoxin ibotenic acid interrupted the acquisition of DRL 20 sec, and these behavioral deficits were reversed by embryonic striatal grafts (66). With an attempt to examine the heterogeneous function of ventral striatum, Pothuizen and associates (65) reported that the selective lesion of the core, but not the shell, subarea in the nucleus accumbens disrupts the acquisition of DRL task on four training phases with 4, 8, 12, and 18 sec as the required intervals. The subjects with the lesions of the core subarea did not meet the DRL criterion measured by the mean response per reward after thirty six daily sessions, whereas the subjects with the lesion of shell subarea acquired the DRL task and performed as well as the controls. These data are compatible with the argument of heterogeneous function of the nucleus accumbens subareas. In regard to the prefrontal areas, unilateral suction lesions of orbito-frontal cortex in the *right* hemisphere were more sensitive to amphetamine-induced response increasing effects on acquiring DRL 20 sec than those lesions done in the *left* hemisphere (43). However, a negative result on the acquisition of DRL tasks over eight intervals from 5 sec to 70 sec was reported in the rat with aspirative lesions of medial frontal cortex (28). A more recent study infused 6-OHDA into the medial prefrontal cortex to selectively deplete dopamine and demonstrated the impairment of the acquisition of DRL 30 sec (82). In this study, the 6-OHDA treated subjects made more responses of shorter IRT and less reinforced responses that correspondingly led to a lower efficiency of DRL responding.

The Cerebellum and Habenula

The cerebellum and the habenula were the other two brain sites that have caught attention to test for their potential of modulating DRL behavior. Based on the fact that the cerebellum is critically involved in temporal processes in the millisecond and perhaps the seconds range (36), the temporal processing on DRL task had then presumed to be affected by cerebellar damage. However, in contrast to this presumption, the acquisition of a DRL 10 sec was intact in the adult rat with the cerebellar stunting induced by prenatal treatment of alpha-difluoromethylornithine (26). The habenula has been thought to serve as a relay between the forebrain and midbrain (87). Recently, it has been argued that the habenula provides continuous monitoring on the mesolimbic dopamine systems such as the striatum (35). If DRL behavior is dopamine dependent, then habenular dysfunction or damage would affect the control of this behavior. Indeed, previous studies demonstrated that the acquisition, but not the performance, of DRL behavior was disrupted by habenular damage induced by electrolytic lesion (24) or habenular catecholamines depletion by 6-OHDA (89).

The Serotoninergic Systems

In addition to brain dopamine, the raphe nucleus and brain serotonin (5-HT) have been suggested to play a role in self-control or behavioral inhibition of motivated behavior. Thus, changes in brain 5-HT are believed to alter DRL behavior. Significant 5-HT depletions in the striatum and hippocampus was in-

duced by local infusion of 5,7-dihydroxytryptamine (5,7-DHT) in either the dorsal or median raphe nucleus (30). And, the results showed that acquisition of DRL 20 sec was impaired by the 5,7-DHT treatment in the median raphe, but not by the lesion in the dorsal raphe. Such behavioral impairment, as shown by increasing total responses, decreasing reinforced responses and mean IRT, and a leftward shift of IRT frequency distribution, was more severe when combined infusions of 5,7-DHT were given in these two sites. The median raphe nucleus is the major afferent input of 5-HT to the hippocampus. Thus, it is inferred that the alterations of DRL behavior induced by the hippocampal 5-HT depletions could be similar to those induced by hippocampal damage (*i.e.*, 39). Compatible evidence showed that 8-OH-DPAT (a 5-HT1a receptor agonist) infused into the medial raphe inhibited the hippocampal 5-HT synthesis leading to the occurrence of DRL behavioral deficits (29). Systemic injection of 8-OH-DPAT also disrupted operant responding on the DRL 10 sec task, and such disruption was also observed for 1-(2,5-dimethoxy-4-indophenyl)-2-aminopropane (DOI) and m-chlorophenyl-biguanide (m-CPBG), 5-HT2 and 5-HT3 agonists respectively (45).

Taken together, the results of above studies indicate that lesions of certain brain areas located in basal forebrain and prefrontal cortex disrupt the establishment and/or maintenance of DRL behavior. All these areas receive afferent inputs projected from the midbrain dopaminergic neuronal cells, although the amount of dopamine released is known to vary across different terminal areas (77). Thus, it is possible that DRL behavioral alterations produced by systemic administration of amphetamines and cocaine are the results of drug actions of increasing dopamine release and/or inhibiting the dopamine re-uptake transporter in these areas (17, 86). In addition to dopaminergic mechanisms, the serotoninergic involvement may not be excluded. DRL behavior has proven useful for identifying neuroanatomical and neurochemical mediators of antidepressant effects on behavior (60). And, most of the antidepressant drugs, specially the selective serotonin reuptake inhibitors (SSRI), are known to affect 5-HT neurotransmissions. However, more work is needed to verify these inferences.

To Probe the Underlying Neurobehavioral Mechanisms

Neurobiological Approach

Based on the previous work described above, it is reasonably presumed that DRL operant responding depends on activation of multiple behavioral processes driven by several brain sites and interconnected circuitry. One way to study what areas of the brain are recruited to mediate DRL behavioral responding is to use the c-Fos immunocytochemistry assay. It is presumed that DRL behavioral is established from behavioral inhibition of the non-reinforced responses to gradually form the temporal process. Accordingly, it is worthwhile to compare the brain distribution of neurons with c-Fos expression in an attempt to correlate different behavioral components involved in DRL behavior with brain loci that may be involved in this complex behavior. A relationship between instrumental learning of lever press and the task-related neurons in the cerebral cortex has been reported by using the aforementioned approach (88). Furthermore, the neurons located in certain brain areas are expected to generate firing patterns as measured neurophysiologically, and the neuronal firing may be correlated with specific behavioral components of DRL behavior. In fact, Young and McNaughton (101) recorded the firing activity of hippocampal neurons in the rat performing on a DRL 15 sec task and revealed three cell clusters that were associated with the functions of timing of the delay, behavioral inhibition, and anticipation of goal responses. This approach may make it possible to delineate the cellular mechanisms of certain brain areas underlying the performance of DRL behavior.

Pharmacological Approach

In terms of pharmacology, the effects of amphetamines and cocaine on DRL behavioral performance are significant as described in the preceding studies. A recent study from this laboratory demonstrated that *d*-amphetamine-induced behavioral changes in the DRL 10 sec task were dose-dependently and partially reversed by dopamine receptor antagonists, SCH23390 and raclopride (14). These results suggest an important role for dopamine in the regulation of DRL-maintained behavior. In considering that all the drugs were administrated systemically (and therefore could reach any part of the brain), it is difficult, from such data, to determine where the attributes of dopaminergic mechanisms are specifically located in the brain. This issue can be dealt by local infusion of dopamine receptor agonists and antagonists in those brain areas involved in DRL behavior as suggested from the lesion work, and to measure how these dopamine receptor manipulations affect DRL-maintained behavior. This research approach would apply to both amphetamine and cocaine. Preliminary data collected in this laboratory showed that the dopamine receptor blockade localized in either the hippocampus or the medial prefrontal cortex partially reversed DRL behavioral deficits induced by *d*-amphetamine (13). In addition, to test the speci-

ficity of dopamine antagonism, serotonin receptor blockade given in a similar manner is also worthy of attention with these direct drug application methods. Conducting experiments with intracranial infusion of amphetamine or cocaine into specific brain area(s) may help reveal the neural substrate(s) for drug induced DRL behavioral deficits. Some of the pertinent brain areas identified by the studies reviewed herein are predicted to be sensitively affected by intracranial amphetamine or cocaine treatment. Such results, if positive, could further verify the role of dopaminergic or serotoninergic receptors by intracranial infusion of selective receptor agonist for either neurotransmitter system. For example, it would be of interest to assess the effects of direct-acting D1 (SKF 81297) or D2 (quinpirole) agonists. Further, in considering the postulated reciprocal relationship between dopamine and glutamate, it is may also be possible to reveal the pharmacological mechanisms of amphetamines and cocaine by testing the effects of glutamate receptor antagonist on DRL behavior. Although there are a few previous studies addressing this issue (34, 72, 75, 83, 85, 90, 94), none of those has investigated the interaction between glutamate-related drugs and amphetamine/cocaine.

Behavioral Approach

In regard to behavioral measurement, conventional operant response data combined with the quantification of IRT frequency distribution have been shown to be useful for providing a better profile to elucidate the performance of DRL behavior. More recently, using a modified operant chamber, Fowler and his associates (31) trained rats on DRL 24 sec or DRL 72 sec and measured the subject's locomotion by setting the chamber on a force-place actometer. The results showed that DRL 24 sec and DRL 72 sec contingencies of reinforcement shaped comparatively low levels of bodily movement. And, the movement was significantly lower for the DRL 72 sec than for the DRL 24 sec schedule. Such a movement profile led the subjects to establish a spatial position away from the operandum before making a reinforced response or non-reinforced response with longer IRT. Further analyses for the distance traveled data over the course of 24 sec and 72 sec intervals preceding reinforcement indicated a temporal gradient of progressively less spatial movement up to 8 sec before a rapidly accelerating increase in movement right before an operant response was made. Moreover, the effects of *d*-amphetamine on these two DRL tasks were verified by abolishing this temporal movement gradient, which led to the impairment of timing process and behavioral inhibition involved. It is useful to test the drug effects by behavioral measures designed in a more delineated and sophisticated manner like this study, which can advance the elucidation of the effects of amphetamines and cocaine on DRL behavior. Additionally, the local infusion of these drugs in specific brain sites would be a preferred method to further identify neural substrates underlying DRL behavioral changes induced by systemic amphetamine or cocaine.

Summary and Conclusions

Although a number of previously published review articles cover the effects of psychoactive drugs on schedule-controlled behavior, none of those had focused solely on the effects of amphetamines and cocaine on the DRL behavior. Amphetamines and cocaine affect the development and/or performance of DRL behavior in certain but varied degrees that depend on dosage. In general, with the moderate doses, these drugs significantly increase the total number of responses and decrease the number of reinforced responses. Although the burst responses with very short IRT are more likely to be increased by these drugs, this aspect of the drugs' effects tend to vary from experiment to experiment, and this variability in findings may be related to different experimental procedures used during lever-press shaping and the subsequent DRL training. Regarding to IRT data which reflect the timing behavior, these drugs tend to produce a leftward shift in the IRT frequency distribution curve. With several recently developed methods, the drug-induced alternation in IRT distribution curve is now quantifiable in a more precise fashion. The effects of amphetamines and cocaine on DRL behavior as reviewed here further highlight the need of additional research to probe neurobehavioral mechanisms potentially underlying DRL behavior.

While initially developed in the experimental psychology, the DRL behavioral task itself has been used in different disciplines of research including physiology, pharmacology, neuropsychology, psychiatry, and neuroscience. Despite investigation conducted with different approaches, timing processes and behavioral inhibition are the two major behavioral components thought to be involved in DRL-maintained behavior. In comparison with other timing tasks, DRL behavior has been shown to be sensitively affected by psychostimulant drugs with the influence on the temporal processing (15, 53). Accordingly, the leftward shift of IRT frequency distribution induced by amphetamines and cocaine could be attributed to the increase of clock-speed effect, which has been argued to be highly relevant to striatal dopamine (54, 55). In addition to the temporal component, behavioral inhibition of the responses with shorter IRT

is essential for the subject to perform DRL behavioral in a relatively efficient manner. That acute injection of amphetamine or cocaine increases premature responding probably reflects a failure of behavioral inhibition. In other words, the subject can not refrain from responding before the elapse of interval set as the requirement for reinforcement in DRL behavior; consequently, the short IRT's can be seen as a form of impulsive behavior (25). Psychostimulant drugs including amphetamines and cocaine have a high addiction liability. Drug addiction is now thought to be related to a loss of self-control in limiting drug intake. Some theories have postulated that inadequate behavioral inhibition be a predictor of drug addiction vulnerability (37, 61). It is then advantageous to use DRL behavioral task for measuring the behavioral inhibition or impulsivity in the case of drug abuse with repeatedly administering amphetamine or cocaine. While the issue of acute effects of amphetamines and cocaine on DRL behavior has been examined by the studies reviewed in this article, the topic regarding how and what DRL behavior would be altered by chronic or sub-chronic treatment of these drugs has not been investigated (but see 63). One interesting issue could also be relevant to the repeated use of these drugs that is the link between drug abuse and stress. Considerable work has indicated that the stress plays a critical role to induce drug taking (64) and drug seeking (78) of psychostimulant drugs. Thus, it is reasonable to suspect that DRL behavior would be influenced by the experimental manipulation of stressor that could interact with amphetamine (12) or cocaine. Further work of systemic examination of the interaction of stress and drugs on DRL behavior is needed to confirm this possibility, especially for the repeated administration of these drugs.

In conclusion, the present paper has endeavored to provide a focused review of the performance of DRL behavior altered by acute treatment of amphetamines and cocaine, as well as a brief review of what brain regions may be involved in the production of the behavior and drugs' effects on it. Based on the studies reviewed here, future work employing neurobiological, pharmacological, or behavioral techniques to elucidate how DRL behavior is acquired and maintained in the normal subject and the individual with psychopathological abnormality (*e.g.* under stress or drug addiction) will provide us a better understanding of the basic processes involved in this behavior including timing and behavioral inhibition.

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