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Review

Conflation of cocaine seeking and cocaine taking responses in IV self-administration experiments in rats: Methodological and interpretational considerations

David C.S. Roberts*, Amanda Gabriele, Benjamin A. Zimmer

Department of Physiology and Pharmacology, Wake Forest Health Sciences, Winston-Salem, NC 27101, USA

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ABSTRACT

IV drug self-administration is a special case of an operant task. In most operant experiments, the instrumental response that completes the schedule requirement is separate and distinct from the consumptive response (e.g. eating or drinking) that follows the delivery of the reinforcing stimulus. In most IV self-administration studies drug seeking and drug taking responses are conflated. The instrumental lever press or nose poke is also a consumptive response. The conflation of these two response classes has important implications for interpretation of the data as they are differentially regulated by dose and price. The types of pharmacological pretreatments that affect appetitive responses are not necessarily the same as those that affect consumptive responses suggesting that the neurobiology of the two response classes are to some extent controlled by different mechanisms. This review discusses how schedules of reinforcement and behavioral economic analyses can be used to assess the regulation of drug seeking and drug taking separately. New methods are described that allow the examination of appetitive or consumptive responding in isolation and provide subjects with greater control over the self-administered dose. These procedures provide novel insights into the regulation of drug intake. Cocaine intake patterns that result in large, intermittent spikes in cocaine levels are shown to produce increases in appetitive responding (i.e. drug seeking). The mechanisms that control drug intake should be considered distinct from appetitive and motivational processes and should be taken into consideration in future IV self-administration studies.

Contents

* Corresponding author at: Department of Physiology and Pharmacology, Wake Forest University Health Sciences, Medical Center Boulevard, Winston-Salem, NC 27101, USA. Tel.: +1 336 716 8697; fax: +1 336 716 8501.
E-mail address: dcsrobts@wakehealth.edu (D.C.S. Roberts).

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1. Introduction

The addiction process is an interaction between patterns of drug taking and subsequent drug seeking. With cocaine, and presumably all drugs, particular patterns of consumption emerge over time (such as binge-abstinence cycles), and it is assumed that these patterns make drug seeking more likely (Epstein and Preston, 2010; Epstein et al., 2009; Gawin, 1991; Levin et al., 1993, 1996; Myers et al., 1995; Preston et al., 2009). The theme of this review will be that the neural systems that underlie drug taking and drug seeking are to some extent dissociable and that different procedures must be used to isolate the factors that control these two classes of behavior. We will use the term "drug seeking" to describe the behaviors involved in obtaining access to a drug. For human drug users this entails behaviors involved in the search for and acquisition of the drug. In preclinical IV self-administration experiments, the seeking behavior generally takes the form of a lever response or a nose poke. We will use the term "drug taking" to refer to behaviors involved in the act of drug ingestion. In the clinical population, the "taking" response could take many forms depending on the substance. For cigarettes, it would be the act of smoking and for alcohol it would be the act of drinking. Cocaine taking could involve snorting, smoking or intravenous injection. In cocaine self-administration studies in rats however, the taking response is typically the same lever press or nose poke as the appetitive response. This review will discuss the implications of having two very different classes of behavior being represented by the same instrumental response and how this might pose problems for interpretation. Behavioral strategies for studying drug taking and drug seeking separately will be described.

The distinction between drug taking and drug seeking can be viewed in the larger context of consummatory and appetitive behaviors.[1] The work of Dr. Ann Kelley, to whom this review is dedicated, illustrates the utility of distinguishing between appetitive and consummatory behaviors by demonstrating that they have different anatomical and neurochemical substrates. The pharmacological influences on free feeding are different from those that affect the instrumental response for the attainment of food. For example, injections of glutamate antagonists or GABA agonists into the shell of the nucleus accumbens was shown to increase food intake in tests with free-feeding; however, these same manipulations had no effect on food-reinforced operant responding (Hanlon et al., 2004; Zhang et al., 2003). In contrast, depletion of dopamine in the accumbens decreased responding on a progressive ratio (PR) task for food, but had no effect on intake under free-feeding conditions (Aberman and Salamone, 1999). Similarly, facilitation of dopamine signaling (via intra-accumbal amphetamine injections) dramatically increased PR responding for a food reinforcer, but had no effect on food intake (Bakshi and Kelley, 1991; Zhang et al., 2003). Just as the mechanisms that regulate food intake are different than those that plan for their attainment, it appears that the mechanisms that serve to regulate drug intake can be dissociated from those that influence drug seeking (Gan et al., 2010; Nicola and Deadwyler, 2000; Pettit and Justice, 1989). Therefore it becomes increasingly important to distinguish these classes of behavior in our animal models.

2. The study of drug seeking and drug consumption: clinical and preclinical strategies

With human subjects it is relatively straightforward to separate the study of drug consumption from appetitive behaviors. Drug ingestion can be studied by giving the subject free access to drug and investigating the physiological processes that regulate intake. For example, patterns of tobacco smoking are assessed by giving access to cigarettes and measuring puff size and frequency (Woodward and Tunstall-Pedoe, 1993; Ashton et al., 1979; Agué, 1973). Similarly, the clinical alcohol field allows access to alcoholic beverages and examines the patterns of consumption. These studies show that differences in consumption patterns can distinguish alcoholics from non-alcoholic individuals (Schaefer et al., 1971; Sobell et al., 1972) and predict impairment on cognitive and behavioral tasks (Bernosky-Smith et al., 2012).

It must be emphasized, however, that the rate of drug intake when the drug is freely available is not necessarily predictive of how much energy a subject will expend to gain access to the drug. A good clinical example was offered by Schuster (1973). Groups of hospital patients who had been detoxified from heroin were assigned to receive codeine, pentazocine or placebo. Subjects could receive their drug simply by reporting to the nursing station every 4 h. Both codeine and pentazocine were requested at high rates. After patients were discharged, they were allowed to come back as out-patients for their medication. Only the patients in the codeine group continued to return. When response cost was minimal, the consumption of codeine and pentazocine were the same. However, when the response cost was increased – by time, bus fare and effort to return to the clinic – drug seeking for the two drugs was clearly different. To be clear, ad libitum drug consumption does not necessarily predict drug seeking, and cost may be an effective way to dissociate these behaviors.

Appetitive responding for drugs of abuse has been investigated in clinical settings using operant procedures traditionally used in preclinical studies (Comer et al., 2008). For example, various schedules of reinforcement have been used with human subjects to control access to a cigarette that can be smoked at a preferred rate (Griffiths et al., 1976) or unit doses of alcohol (10 cc) that can be combined to create larger doses (Mendelson and Mello, 1966). Similarly, a PR procedure has been used with human cocaine users to control access to cocaine powder, a mirror and a razor blade (Stoops et al., 2010). The rate and pattern of intra-nasal cocaine use is under the subject's control.

The use of operant procedures to asses IV self-administration in rats differs from both the clinical operant experiments for drugs mentioned above, as well as typical animal operant experiments for non-drug reinforcers such as food in one important respect; there is no separate consumption phase. The procedures developed by the pioneering work of Weeks (1962) and other early investigators (Deneau et al., 1969; Goldberg et al., 1971; Hoffmeister et al., 1970; Thompson and Pickens, 1970; Wilson et al., 1971) created a special case of an operant experiment (see Wise, 1987). Normally there

[1] The terms "appetitive" and "consummatory" appear to have quite different meanings that have evolved over time. For example, in the alcohol literature, the terms appetitive and consummatory have been used synonymously with drug seeking and drug taking (Czachowski and Samson, 1999; Samson and Czachowski, 2003; Sharpe and Samson, 2001). However, other authors might point to the early work of Craig (1918) and infer a completely different meaning. Craig sought to explain the termination of instinctual behavior following the presentation of an "appeted" stimulus. In his view, a consummatory act is the last act in a series that results in satisfaction or satiety. The terminology has evolved with the study of motivated behavior. Two distinct phases are defined: an appetitive phase characterized by arousal, exploration, instrumental responding, and flexible approach behavior directed toward obtaining a goal; and a consummatory phase that results in cessation of the approach behavior and is characterized by interactions with the goal object that are typically highly stereotyped patterns of repetitive movements (e.g. chewing, swallowing, licking, drinking) (Berridge, 2004; Craig, 1918; Kelley et al., 2005). In cases where the goal involves an ingestible object (e.g. food or water) the consummatory phase involves consumption of the goal. However, the consummatory phase can proceed with no consumption at all (e.g. sex). That is the consummatory phase reflects the consummation of the appetitive phase behavior which may or may not involve consuming the goal object. For the purposes of this review, we will use the word "consummatory" to mean the terminal action in an appetitive sequence. In order to avoid confusion, we will use "consumptive" and "ingestive" to refer to any behaviors involved in intake of a commodity such as cocaine, food or alcohol.

Table 1
Comparison of the effects of various treatments on cocaine self-administration.

Treatment	PR break-point	FR1 rate	Reference
Higher unit doses	↑	↓	Depoortere et al. (1993); Roberts et al. (1989b)
DA (D1) antagonist SCH 23390	↓	↑	Depoortere et al. (1993); Hubner and Moreton (1991)
DA (D2) antagonist spiperone	↓	↑	Hubner and Moreton (1991)
DA atypical antagonist clozapine	↑	↓	Loh et al. (1992); Roberts and Vickers (1984)
Haloperidol decanoate	↓	↑	Richardson et al. (1994); Roberts et al. (1989b)
Flupenthixol decanoate	↓	↑	Richardson et al. (1994)
6-OHDA lesions	↓	↓	Koob et al. (1987); Roberts et al. (1977)
Intrastriatal SCH 23390	NC	↑	McGregor and Roberts (1995)
Ibotenic acid lesions	↓	↓	Hubner and Koob (1990)
5,7-DHT lesions	↑	NC	Loh and Roberts (1990); Roberts et al. (1994)
Estrous phase	↑	NC	Roberts et al. (1989a)
Fluoxetine	↓	↓	Carroll et al. (1990); Richardson and Roberts (1991)
DS 121	↓	↓	Smith et al. (1995)
Tryptophan	↓	↓ or NC	Carroll et al. (1990); McGregor et al. (1993)
Selective breeding for depression	↓	NC	Lin et al. (2012)
Baclofen	↓	↓ or NC	Brebner et al. (2000); Campbell et al. (1999); Roberts et al. (1996); Shoaib et al. (1998)
Orexin antagonist (SB 334867)	↓	NC	Aston-Jones et al. (2009); Borgland et al. (2009); España et al. (2010); Smith et al. (2009)

Summary of the effects of various treatments on responding for cocaine under progressive ratio (PR) or fixed ratio (FR) schedules of reinforcement. The primary dependent measure for progressive ratio schedules is break point (BP) and for fixed ratio schedules is rate of responding. The upper section illustrates that the effects of many dopaminergic manipulations on BP are inversely related to their effects on rate of drug intake. The lower section lists reports showing that BP and rate of drug intake are not necessarily related. Some treatments can affect one dependent measure (sometimes dramatically) without affecting the other. Updated from Richardson and Roberts (1996).
NC = no change.

is what is referred to as an instrumental-consummatory response chaining. The appetitive phase is separated from the phase in which the reward is ingested. In the most common case of food reward, the appetitive response is a lever press; after completion of the response requirement the reinforcing stimulus is presented and the subject then has the opportunity to consume the reward (or not). There is a distinct period during which the subject engages in behaviors specific to the particular reinforcing stimulus being used (i.e. licking, chewing and swallowing). Importantly, these consumptive behaviors are separate and distinct from the operant response. That is, there are instrumental responses (lever pressing) and consumptive responses (eating and drinking). However, Wise et al. (1977) has argued that IV self-administration procedures are a special case of an operant task in that the lever-press is not only an instrumental response involved in drug seeking but also a consummatory response (i.e. a terminal act in the goal-directed sequence). The lever press immediately prior to the drug injection is a drug taking response since it results in the automatic delivery of drug directly into the venous system. There is no separation between the consumptive and appetitive response.

It is critical to distinguish the appetitive responding from the act of drug consumption because the rules that govern these two classes of behavior appear to be quite different. The clearest example is that reducing the unit dose has opposite effects on consumption and appetitive behaviors. To use a real life example, if a bartender were to dilute a customer's whiskey it would be predicted that the patron would compensate by drinking proportionally more; however it would also be predicted that he or she would be less satisfied and pay less for the drink. Thus, the regulatory influences on ad libitum drug consumption are often opposite to those involved in assessing its worth.

This distinction between regulation of ad libitum consumption and behavioral price can be seen in dose-response studies using schedules with high or low behavioral cost. When schedules of reinforcement with high response requirements are used, there is a dose-dependent increase in rate of responding (Depoortere et al., 1993; Goldberg, 1973; Li et al., 1994; Spear and Katz, 1991) resulting in an ascending dose-response curve. These data are explained well by operant theory and are consistent with other measures of reinforcing efficacy. Higher doses are chosen over smaller doses in choice studies (Johanson and Schuster, 1975; Llewellyn et al., 1976; Lynch et al., 1998; Ward et al., 2005) and support higher breakpoints on a PR schedule (Richardson and Roberts, 1996). By contrast, data from self-administration studies using fixed ratio (FR1) schedules show quite different dose-response profiles. Early studies demonstrated quite clearly that rate of drug intake is inversely related to dose (Pickens and Thompson, 1968; Dougherty and Pickens, 1973); larger unit doses produced longer post-reinforcement pauses in responding. The contrasting shapes of the dose-effect curves (descending vs ascending) is accounted for by the idea that responding on an FR1 is entirely related to drug consumption whereas other higher order schedules, (i.e. those more typical of the operant literature) are influenced by appetitive processes.

Note that the degree to which lever responding reflects appetitive behavior or regulation of drug intake depends on the experimental situation and the schedule of reinforcement. Rats undergoing extinction or reinstatement testing (for review see Epstein et al., 2006; Kalivas and McFarland, 2003; Shaham et al., 2003) would be immune from the consumptive influence since the drug is never offered during the session. Since no drug is self-administered, every lever press or nose poke is an uncontaminated appetitive response. However, in most other IV self-administration experiments drug seeking and drug taking behaviors are conflated to some degree although the extent of this confound can vary over a wide range. With higher order schedules of reinforcement that generate high rates of responding the distinction between drug seeking and drug taking is only slightly contaminated. While virtually every response could be considered appetitive and would be expected to conform to operant principles, only the final response before an injection is a consumptive act. The opposite end of this continuum is an FR1 schedule which provides ad libitum access to cocaine. In this case, essentially all of the responses can be considered an act of drug consumption.

The clearest evidence that cocaine taking and cocaine seeking are different classes of behavior is that the types of drugs that modulate cocaine consumption are different from those that modulate appetitive responding (Table 1). These results parallel the work of Ann Kelley and colleagues on feeding behavior discussed above. The top portion of Table 1 illustrates experimental manipulations that produce opposite effects on responding under FR1 and PR schedules. As discussed previously, reducing

the unit dose produces decreases in breakpoints and increases in FR1 response rates. Similarly, pretreatment with DA receptor antagonists decreases breakpoints and increases FR1 response rates in keeping with the interpretation that neuroleptics produce an effect analogous to a reduction in dose (Yokel and Wise, 1975; De Wit and Wise, 1977). There is a consistent and predictable effect on drug seeking and drug taking with pretreatment of drugs that affect the DA system. Treatments that increase drug intake result in reduced appetitive responding and vice versa. With other manipulations, however, the relationship between appetitive and consumptive responding becomes more complicated. The lower portion of Table 1 shows examples of treatments that affect PR breakpoint and FR1 rate in the same direction or, in some cases, one measure might be affected and not the other. A physiological, rather than pharmacological, example is the effect of the female reproductive cycle. PR breakpoints are increased by 100% during estrus compared to other phases of the estrous cycle yet there is no discernible effect on the rate of intake on an FR1 (Roberts et al., 1987, 1989a; Lynch, 2008). The most parsimonious explanation for these discordant results is that appetitive responding (as measured by PR) and ad libitum drug consumption (as measured by FR1) are regulated by different (but in some cases overlapping) mechanisms.

Above it was emphasized that the schedule of reinforcement was a critical factor in whether appetitive responding or regulation of drug intake was the major determinant of the response rate. It was argued that ad libitum drug consumption on an FR1 appears to be regulated differently from responding on schedules requiring higher response output. The dissociation between the two classes of behavior seems to be effectively captured by manipulation of response cost or "price".

Behavioral economics (Hursh, 1991; Hursh and Silberberg, 2008; Hursh and Winger, 1995) provides a useful framework for studying the interaction between drug seeking and drug taking. The manner in which consumption varies as a function of price is the essence of the demand curve. There are two ways to increase the behavioral price of the drug. One way is to raise the response requirement as illustrated above with a PR schedule. Alternatively, a decrease in the unit dose on an FR1 schedule would have the effect of increasing the price per mg of drug. For example, a dose of 0.1 mg/kg/inj would "cost" 10 responses/mg; one tenth of this dose (0.01 mg/kg/inj) would cost 100 responses/mg.

Fig. 1 shows data from a within-session threshold procedure in which a descending series of eleven unit doses (FR1) were offered in 10 min bins, resulting in a progressively greater response cost over time. As shown in the cumulative record (Fig. 1A), responding increased every 10 min as the available cocaine dose decreased until a threshold dose (Bin 8) was reached. These data are replotted in Fig. 1B to demonstrate that a relatively stable rate of cocaine intake was established during the first part of the session. The level of cocaine consumption unconstrained by price (Q_0) was 0.61 mg/10 min bin. Later in the session, as the behavioral cost increased, the response rate of the animal began to be affected. The maximal price paid (P_{max}) for cocaine was determined by assessing the unit price at which maximal responding occurred. In this example, P_{max} was determined to be 133.9 resp/mg which corresponded to the apex of the price-response function (Fig. 1C). Note that the two dependent measures provided by the behavioral economic analysis are directly related to appetitive responding (P_{max}) and drug consumption unconstrained by price (Q_0).

Oleson et al. (2011) has shown that P_{max} and Q_0 are differentially sensitive to pharmacological pretreatments. Table 2 summarizes the effects of haloperidol, amphetamine, fluoxetine and baclofen on P_{max} and Q_0. Specifically, the dopamine receptor antagonist haloperidol increased Q_0 (i.e. cocaine consumption unconstrained by price) but decreased P_{max}. In contrast, the indirect dopamine agonist d-amphetamine increased the price paid for cocaine but had no effect on Q_0. The serotonin uptake inhibitor fluoxetine decreased consumption and price paid. Baclofen, a $GABA_B$ receptor agonist, selectively decreased price paid for cocaine. These results reveal that cocaine consumption (unconstrained by price) and P_{max} are differentially sensitive to various classes of drug, suggesting that neurobiological substrates of consumption and price paid involve separate mechanisms.

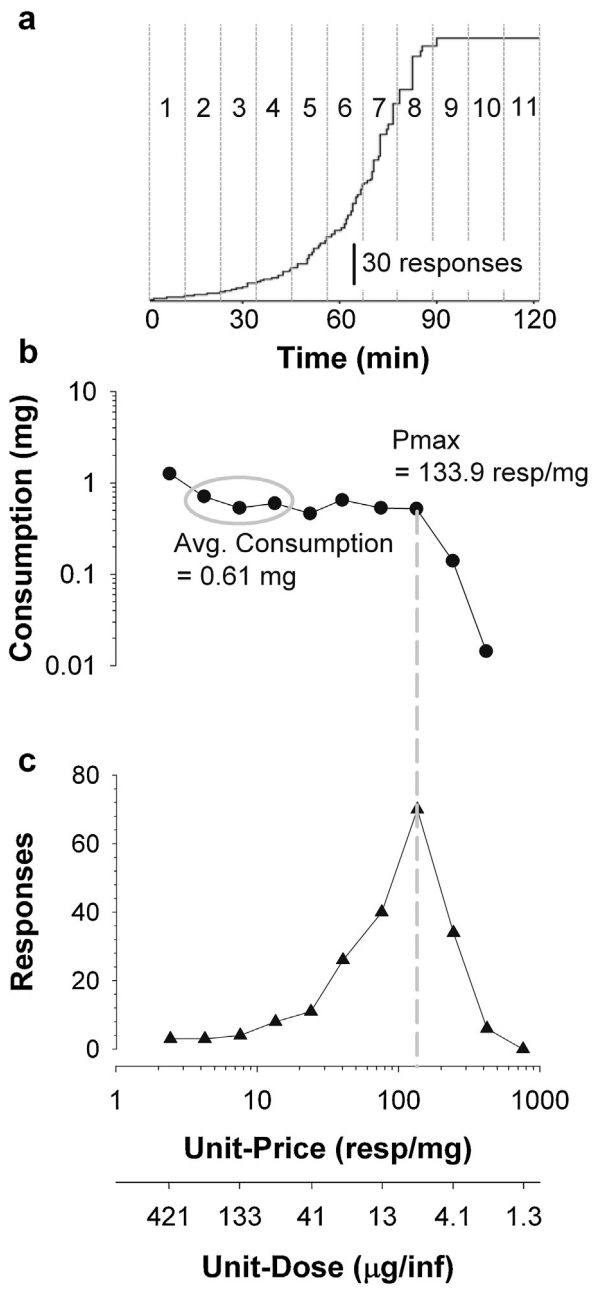

Fig. 1. Representative within-session threshold data and explanation of behavioral economics measures. (A) A cumulative record from one animal responding in a single within-session threshold procedure is shown. Note that the available unit-injection dose (lower *x*-axis) decreases across eleven consecutive 10 min bins. (B) The same animal's data are replotted to show cocaine consumption (mg/10 min bin) as a function of unit price (upper *x*-axis). Mean cocaine consumption (0.61 mg; gray ellipse) is calculated by averaging intake across bins 2–4. (C) The same animal's data are replotted to show responding (responses/10 min bin) as a function of unit price. The maximal price paid (P_{max}; 133.9 resp/mg) can be distinguished by assessing the apex of the price response function. Note that P_{max} also corresponds to the final unit price at which cocaine consumption is maintained in 1B (adapted from Oleson et al., 2011).

Table 2
Differential effects on P_{max} and Q_0 of various pharmacological pretreatments.

	P_{max}	Q_0
Haloperidol	↓	↑
Amphetamine	↑	n.c.
Fluoxetine	↓	↓
Baclofen	↓	n.c.

Summary of the effects of various treatments on maximal price paid for cocaine (P_{max}) and cocaine consumption when response cost is minimal (Q_0) on a within-session threshold procedure.

3. Regulation of cocaine consumption

3.1. Regulation of cocaine intake on an FR1 schedule

As discussed above, operant behavior is conflated in typical IV drug self-administration studies, and depending on the contingencies the observed behavior may conform to consumptive or appetitive principles. This section will focus on procedures that appear to be primarily driven by principles of drug consumption. First we will describe results from studies using the FR1 schedule of reinforcement examining consumption regulation. Second, we will introduce a new self-administration procedure that provides the animal with greater control over the size of each dose.

The FR1 schedule of reinforcement offers access to cocaine with a very low response cost, and therefore results from this schedule have been very useful in advancing our understanding of the regulation of cocaine consumption. It has been noted many times that self-administration behavior under an FR1 schedule of reinforcement produces a remarkably stable rate of cocaine intake, and that this rate is inversely related to the size of the unit dose (Pettit and Justice, 1991; Pickens and Thompson, 1968; Wilson et al., 1971). That is, the highest rates of responding are seen at the lowest unit doses. There has been some discussion as to whether there is an ascending limb to this curve (Mello and Negus, 1996; Zittel-Lazarini et al., 2007). However, there is growing consensus that the initial jump in the dose-response curve could be considered a threshold dose (i.e. responding is all or nothing) after which the injection rate decreases with increasing doses (Tsibulsky and Norman, 1999; Wise et al., 1995; Zittel-Lazarini et al., 2007; but see Flory and Woods, 2003).

These FR1 studies have led to the development of a hypothesis that the rates and patterns of cocaine self-administration on an FR1 schedule reflect a titration phenomenon. It has been observed that brain levels of drug are maintained within a relatively narrow range during FR1 self-administration sessions (Yokel and Pickens, 1974; Wise et al., 1995; Tsibulsky and Norman, 1999; Ranaldi et al., 1999). The hypothesis reached from these studies is that satiety mechanisms are triggered when cocaine concentrations reach a certain level. This satiety titration hypothesis fits well with long-standing behavioral observations. At the beginning of a typical session, several unit doses are quickly self-administered, suggestive of a "loading" phase where brain levels are quickly elevated above a satiety threshold; subsequently a "maintenance" phase occurs during which consistent post-infusion pauses are observed that maintain brain levels above this threshold (Carelli and Deadwyler, 1996; Pickens and Thompson, 1968; Wilson et al., 1971; Wise et al., 1995). Mathematical estimates of brain levels have helped illustrate this idea. The temporal pattern of cocaine infusions can be used to calculate brain-cocaine concentrations at any point during a self-administration session (as described by Pan et al., 1991). The equations have been used by several labs to examine the relationship between estimated drug levels and behavioral (Shou et al., 2006; Samaha et al., 2002; Zimmer et al., 2011, 2012a, b), electrophysiological (Nicola and Deadwyler, 2000; Peoples and Cavanaugh, 2003; Peoples et al., 2004, 2007) and neurochemical responses (Wise et al., 1995; Hermans et al., 2008; Stuber et al., 2005a, b). Fig. 3A and B (Fig. 3 is discussed in greater detail in Section 4) shows the estimated levels of cocaine during an FR1 session. The modeling clearly illustrates the rapid loading phase (within the first few minutes) and the oscillating levels within a relatively tight range during the maintenance phase.

While there appears to be a consensus on the general idea of drug titration (although see Panlilio et al., 2003), there is some debate about the specific mechanism involved. One possibility (Katz, 1989; Lynch and Carroll, 2001; Pickens and Thompson, 1968; Rose and Corrigall, 1997; Wilson et al., 1971) is that the titration range is determined by an upper aversive boundary, such that animals maintain brain levels below some ceiling to avoid punishing effects. This hypothesis is certainly plausible given findings that cocaine can produce avoidance behavior (DeVries and Pert, 1998; Ettenberg and Geist, 1991, 1993) as well as conditioned taste aversions (Booth et al., 1977; Goudie et al., 1978) suggesting it has anxiogenic properties. If aversive properties were primarily responsible for the regularity of responding then it would be predicted that rats should choose a frequent small dose over a larger one (Ranaldi et al., 1999). However, this prediction is not supported; animals consistently choose larger doses over small ones (Johanson and Schuster, 1975; Llewellyn et al., 1976; Lynch et al., 1998; Ward et al., 2005) suggesting that aversive properties are not likely to be the most important contribution to the observed regularity of inter-injection intervals.

3.2. Using a hold-down procedure to study cocaine consumption

Human drug users interact with and have precise control over their drugs when they consume them. However, in IV self-administration procedures using an FR1 schedule with a fixed unit dose, animals do not have this opportunity. Completion of the response requirement results in an automatic infusion of a pre-selected dose. In this section we will highlight key findings from a new procedure recently developed that gives animals control over the size of the dose essentially making it a dependent measure. This procedure has provided some key insights into regulation of intake within a session that would otherwise be impossible to measure.

The original impetus to give animals control over the dose size came from observations that human drug users are able to manipulate dose and frequency in dynamic ways. Nicotine smokers regulate their intake throughout the day by adjusting factors such as puff rate and puff size (Ashton et al., 1979; McMorrow and Foxx, 1983; DeGrandpre et al., 1992). Similarly, drinkers regulate their alcohol intake by adjusting dose size (e.g. small sips or large gulps) and frequency (Schaefer et al., 1971; Sobell et al., 1972; Bernosky-Smith et al., 2012). This is in stark contrast to normal rodent self-administration studies in which dose is an independent variable, fixed by the experimenter. Since rats have no control over the injection dose size they adjust the time between injections, which is the only titration strategy available to them.

To address this, Morgan et al. (2009) made a simple and elegant modification of the contingencies to give animals dynamic control over drug intake in an unprecedented way. In this procedure, termed "hold down", the duration of time the lever was pressed down directly determined the volume of drug injected. That is, when the lever was pressed down, the pump turned on, and when the lever was released, the pump turned off. Using this procedure for self-administration resulted in similar total intake rates as an FR1 schedule suggesting that rats successfully consumed cocaine using the hold down procedure. It was observed that the majority

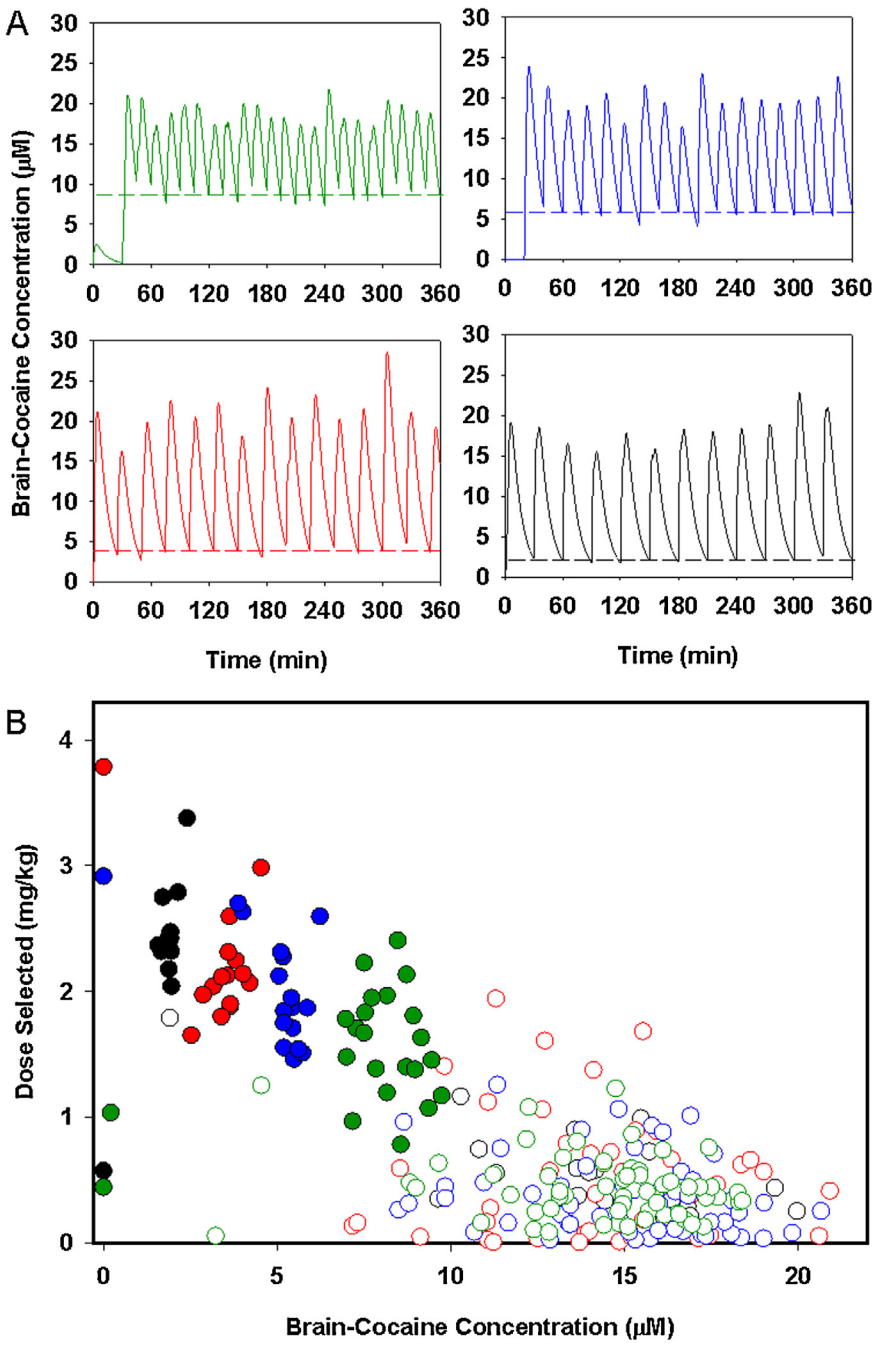

Fig. 2. Current brain levels of cocaine predict subsequent dose. Data from a representative animal during four 6-h sessions consisting of alternating 5 min access period to the hold down lever and timeout periods of varying length. (A) The calculated brain-cocaine concentration during a session with a 10 min (top left, green), 15 min (top right, blue), 20 min (bottom left, red), or 25 min (bottom right, black) timeout period. Dashed lines emphasize how far brain-cocaine levels declined following each timeout period. (B) The relationship between brain-cocaine concentration and subsequent doses animals self-administered. Data points are from the same sessions illustrated in panel A. Colors represent a 10, 15, 20, or 25 min timeout period (green, blue, red, or black, respectively). Closed circles represent the first dose of a 5-min access period, and open circles represent a dose self-administered within the remainder of the period. From Zimmer et al. (2011). (For interpretation of the references to color in the text, the reader is referred to the web version of the article.)

of selected doses[2] (Zimmer et al., 2011, 2012a) appeared to fall well within a range (0.5–1.0 mg/kg/inj) commonly reported in typical self-administration studies (Caine and Koob, 1994; Ito et al., 2002; Liu et al., 2005a; Pettit and Justice, 1991; Quadros and Miczek, 2009). However, a number of the doses selected were surprisingly large (~4 mg/kg). The observation that rats would self-administer a dose of 4 mg/kg in ~20 s is, to our knowledge, unprecedented. These large doses were always selected at the beginning of a session (Zimmer et al., 2011). Thus, there appeared to be *two* categories of doses within the same session – very large ones associated with the "loading" phase and the remaining much smaller ones associated with the "maintenance" phase. These findings would not have been possible using fixed, experimenter-selected doses.

[2] In this review, the hold down "dose" refers to the total amount of drug self-administered within a cluster using a 1 s criterion. That is, any response occurring within 1 s of the end of the previous response is accumulated. A pause of 1 s would denote the start of the next cluster (Zimmer et al., 2012a).

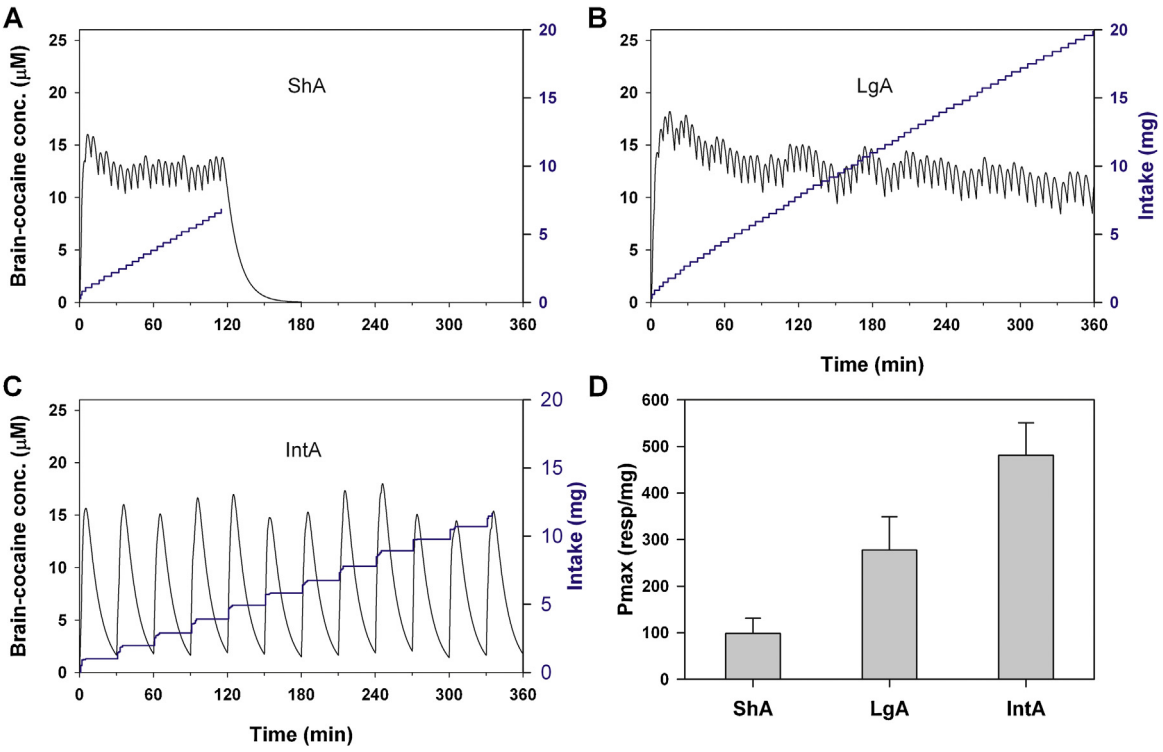

Fig. 3. (A–C) Intake and estimated brain levels of cocaine for representative animals tested using three distinct self-administration procedures. Each panel shows the modeled brain levels of cocaine (left axis, black) and cumulative intake (right axis, blue) throughout a session for an individual rat self-administering for cocaine on a ShA (A), LgA (B), or IntA (C) procedure. (D) Behavioral economic analysis of data obtained from the within-session threshold procedure. The P_{max} value was calculated for all animals as the price (responses/mg of cocaine) animals reached before responding dropped off. Bars represent average (±SEM) P_{max} values for each group. Adapted from Zimmer et al. (2012b). (For interpretation of the references to color in the text, the reader is referred to the web version of the article.)

The hold down procedure also provided a unique opportunity to examine the factors that were involved in the selection of the large, "loading" doses. Zimmer et al. (2011) introduced a series of timeout periods (10–25 min) throughout daily 6-h sessions. This manipulation forced estimated brain-levels of cocaine to decrease by predictable amounts before access to cocaine was reinitiated (Fig. 2). Because the animal could control the size of each dose, once access was resumed the subject could self-administer a loading dose of any size. This procedure, in effect, produced a session with multiple loading phases resulting in repeated "spiking" brain levels. Results showed that larger doses–again, sometimes as large as 4 mg/kg – were self-administered when estimated brain levels of cocaine were very low, whereas much smaller doses were self-administered when levels were higher. It appears that the size of large, loading doses can be accounted for by current estimates of brain cocaine levels as evidenced by the highly significant negative correlation ($r = -0.77$) shown in Fig. 2B (Zimmer et al., 2011). These data show that during the loading phase the dose is inversely related to the current brain levels of cocaine and suggest that the self-administered dose closely matched the amount necessary to elevate drug levels into a theoretically preferred range.

The dynamic control over dose size that the hold down procedure provides also allows a sophisticated investigation of factors that regulate the smaller, maintenance doses. Zimmer et al. (2012a) examined whether the size of the self-administered dose and the delay in responding (post-infusion pause) interacted in the control of drug intake. The concentration of cocaine was changed across daily sessions during which rats self-administered cocaine using a hold down procedure. The total pump-time self-administered decreased in a near proportional manner to the change in cocaine concentration, and the size of each self-administered dose was highly correlated with the subsequent, *but not previous*, inter-dose interval (Zimmer et al., 2012a). Thus the size of each dose self-administered determined how long the animal waited for the next infusion.

In summary, results from experiments using a hold down procedure to change dose size into a dependent measure have yielded three primary insights that could not have been examined using fixed unit doses of cocaine. First, rats will rapidly self-administer unprecedented doses of cocaine (4 mg/kg). Second, the "preferred" dose can change dramatically within a session depending on brain cocaine levels. Third, the self-administered dose is tightly correlated with the inter-infusion interval. These data corroborate the titration hypothesis and add to our understanding of the mechanisms regulating cocaine consumption. Results from studies using hold down procedures have demonstrated that, when given the opportunity to dynamically control the dose size, rats are surprisingly accurate at pharmacologically maintaining cocaine levels within a preferred range.

4. Interaction between consumption and appetitive behaviors

Our premise is that the addiction process is an interaction between patterns of drug taking and subsequent drug seeking. To this point we have argued that appetitive and consumptive behaviors are regulated by distinct neurobiological mechanisms and that they should be considered separately in order to evaluate how each contributes to self-administration behavior. A different question, however, is how the two types of behaviors interact. That is, what patterns of drug taking are more likely to accelerate future drug seeking? Identifying the access conditions that alter the subsequent motivation to seek drugs is fundamental to understanding the addiction process. A number of access parameters that produce unique consumption patterns have been shown to produce

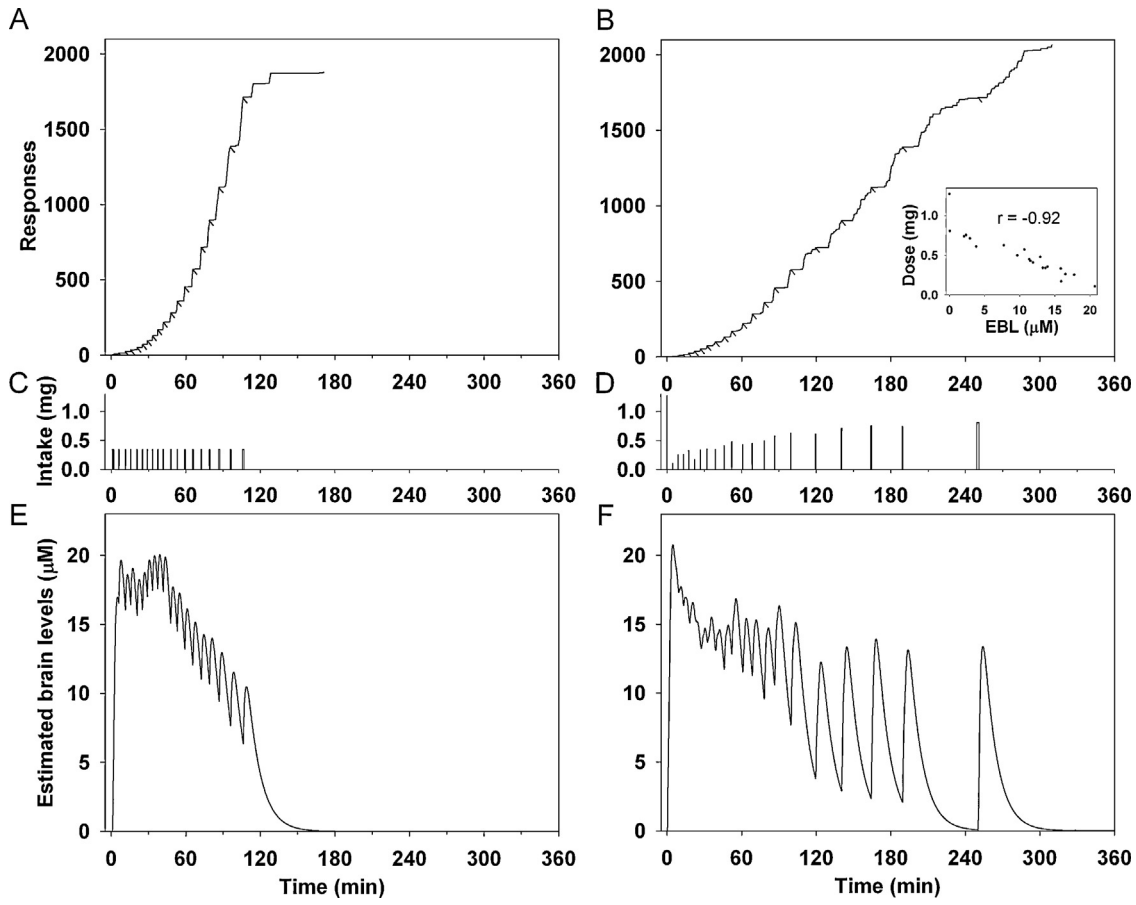

Fig. 4. Comparison of responding and intake for representative rats self-administering on a 1-lever (left panels) or 2-lever (right panels) PR schedule of reinforcement. (A and B) Cumulative responses are plotted for representative animals. Each tick mark represents the completion of a ratio. (C and D) Corresponding intake (mg) self-administered following each ratio completion during the same sessions represented in panels A and B. Note that completion of each ratio on the 1-lever PR schedule resulted in a fixed, unit dose (0.34 mg, panel C), whereas on the 2-lever schedule a separate drug lever provided 5 min access during which no limitations were placed on intake (D). (E and F) Estimated brain levels are shown for the 1-lever (E) or 2-lever (F) sessions. Inset correlation between dose and estimated brain levels (EBL) on the data from panel D. Correlation coefficient was −0.92.

changes in subsequent appetitive behavior, such as increased access (Ahmed and Koob, 1998, 1999), abstinence (Grimm et al., 2001; Pickens et al., 2011), speed of injection (Liu et al., 2005b; Wakabayashi et al., 2010), and intermittency (Morgan et al., 2002; Morgan and Roberts, 2004).

As discussed above, results using hold down procedures have demonstrated that rats will self-administer repeated spikes of cocaine when intermittency is introduced into the session and will maintain high, constant levels in sessions with no timeout periods. Recent work has examined the effects of these different consumption phenomena on subsequent appetitive responding (Zimmer et al., 2012b). Animals self-administered cocaine under short access (ShA) or long access (LgA) conditions (as described by Ahmed and Koob, 1998, 1999, 2004) as a measure of sustaining high levels of intake (for 2 or 6 h respectively – Fig. 3A and B). A third group self-administered under intermittent access (IntA) conditions, which consisted of repeating 5 min access and 25 min timeout periods (see Fig. 3C). This contingency did not allow drug levels to be sustained and instead produced spiking cocaine levels. Fig. 3C illustrates that each 5 min access period produced a spike in estimated cocaine levels that was almost completely cleared during the 25 min timeout period. Each group subsequently self-administered cocaine in a within-session threshold schedule (as discussed in detail in Section 2). As expected, behavioral economic analysis revealed that P_{max} values for LgA subjects were significantly increased compared to ShA rats, confirming previous data demonstrating that LgA increases motivated responding for cocaine (Paterson and Markou, 2003; Mantsch et al., 2008; Wee et al., 2008) (Fig. 3D). The IntA group showed significantly higher P_{max} values relative to both LgA and ShA animals (Fig. 3D). It should be emphasized that the total amount of cocaine self-administered did not predict the resulting differences in appetitive responding since LgA animals had by far the highest intake rates and IntA and ShA intake was not significantly different (Zimmer et al., 2012b). These data suggest that the experience of repeated spiking cocaine intake leads to increased drug seeking relative to a history of sustained cocaine intake.

IntA and LgA procedures may offer models of two different phases of the addiction process. LgA can be thought to model binge-like behavior which results in prolonged and sustained drug levels. The IntA procedure illustrates that discrete intoxicating effects (that produce rapid and high drug levels) are able to change subsequent drug seeking. This may be important for understanding the neuroadaptations responsible during the early transition from recreational to habitual drug use.

In summary, different daily consumptive patterns of cocaine can have very different effects on subsequent appetitive behaviors. High sustained levels of drug intake do not appear to be necessary to produce an increase in subsequent appetitive behavior.

5. Separating appetitive and consumptive behaviors with a two lever task

In this review we have argued that characterizing the factors at work in cocaine self-administration experiments necessarily

involves an assessment of consumptive and appetitive responding. This is essential as these two classes of behavior are differentially regulated, sometimes in opposite ways (see Table 1). However, as we have stated above, most self-administration paradigms conflate appetitive and consumptive responding in a single operant response, and we have discussed interpretations that take this conflation into consideration. However, another strategy is to separate appetitive and consumptive responding entirely. Below we will discuss strategies that distinguish the relative involvement of appetitive and consumptive behaviors using two responses or levers operants within the same behavioral paradigm.

Our work builds on a considerable background literature in which drug seeking and drug taking are procedurally separated. In the alcohol field, for example, Czachowski and Samson (1999) introduced a method to investigate the mechanisms that mediate ethanol-seeking versus ethanol consumption. A PR schedule controlled access to a 20 min period of alcohol availability. The procedure allowed for the assessment of appetitive (number of lever presses) and consumption (number of licks and intake volume) behaviors. Separating the seeking and taking components has been applied to IV self-administration procedures as well. A variety of schedules have been used (e.g. random interval, FR, PR) with the drug seeking lever controlling access to the drug taking lever (Economidou et al., 2009; Vanderschuren and Everitt, 2004; Pelloux et al., 2007; Olmstead et al., 2000, 2001; Gancarz et al., 2012). In some cases, the drug taking component has included the opportunity to self-administer a single injection (Economidou et al., 2009; Vanderschuren and Everitt, 2004; Pelloux et al., 2007; Olmstead et al., 2000, 2001), or in others has provide access to a 2 h session on an FR1 schedule (Gancarz et al., 2012). Note that the consumptive component typically involves an FR1 schedule and fixed unit doses. Because of the insights into consumption obtained from experiments using the hold down procedure (see Section 3.2), we have recently attempted to apply this technique to the consumptive phase of a two lever seeking-taking procedure. Thus changes in the self-administered dose could be monitored throughout the session (Fig. 4). This two lever progressive ratio (2L-PR) procedure has allowed us the unique opportunity to assess appetitive responding for a self-selected dose in the rat.

Because the 2L-PR paradigm procedurally separates the two phases of behavior, results have yielded an uncontaminated assessment of consumptive and appetitive responding for cocaine. In regard to consumption, we have demonstrated that the dose animals self-administer changes dramatically within a 2L-PR procedure (Fig. 4). At the beginning of the session, the animal self-administers an extremely high dose (sometimes as high as 4–5 mg/kg). Subsequent dose are small and the animal is able to maintain brain cocaine levels while the response requirement is low. However, as the response requirement to complete each ratio increases, and therefore the time between each drug access period increases, animals begin to take increasingly higher doses (Fig. 4, panel D and F). This change in dose throughout the session directly correlates with estimated brain levels (Fig. 4, panel B inset) again confirming results from our previous hold down procedures (Zimmer et al., 2011, 2012a). That animals can manipulate dose size to compensate for the increasing time to complete each ratio means that animals can continue appetitive responding even when estimated cocaine levels are essentially zero (see Fig. 4F). This stands in stark contrast to the traditional PR procedure using unit doses, where the animal eventually is unable to maintain a preferred brain cocaine level regardless of effort (Fig. 4, panel E; Nicola and Deadwyler, 2000). Therefore, results from 2L-PR procedures represent a far more pure assessment of appetitive responding without the typical conflation of consumption levels.

In summary, since the size of the dose self-administered at any point during the session depends largely on the amount of cocaine already on board, it is likely that the most preferred or most reinforcing dose of cocaine might fluctuate according to the brain levels at any particular moment. Thus, using the 2L-PR procedure to separate appetitive and consumptive behaviors has allowed for the discovery that the dose that the animal is working for changes throughout the session.

6. Concluding remarks

This review has drawn attention to the mechanisms that control drug intake and highlighted how different patterns of consumption can feed forward in the addiction process to influence subsequent drug seeking. We wish to re-emphasize that, while there may be overlap, the mechanisms that control drug intake should be considered distinct from appetitive and motivational processes.

Conflict of interest

None.

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