Equal response rates maintained by concurrent drug and nondrug reinforcers: a design for treatment evaluation

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During daily 3-h sessions, four rhesus monkeys had concurrent access to 16% alcohol (w/v) and saccharin. A response occurred when a monkey made mouth contact with the metal spout and thereby completed a drinkometer circuit. The liquids were available under concurrent nonindependent fixed-ratio 32 schedules. With these schedules, responses on the right spout decremented both the right and left fixed-ratio counters and vice versa. Responding was well maintained by both alcohol and saccharin. Increases in saccharin concentration produced increases in saccharin responding to the point that saccharin responding exceeded alcohol responding. Responses per saccharin delivery were also a direct function of the saccharin concentration. In contrast, responses per alcohol delivery generally decreased as the saccharin concentration became greater. Changeover or switching responses were also a direct function of the saccharin concentration. Relative reinforcing effects of each combination of liquid pairs were measured for each monkey. For all monkeys, it was possible to establish equal rates of responding for both reinforcers and frequent switching between reinforcers. The balanced responding can serve as a baseline for the evaluation of potential treatments that may alter relative reinforcing effects. *Behavioural Pharmacology* 31: 458–464 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Ideally a medication for treating drug abuse would act selectively by decreasing or eliminating an abused drug's reinforcing effects. However, drug-reinforced responding can also be decreased by less desirable nonselective effects including sedation and motor impairment. A number of approaches have been developed to measure relative selectivity.

One preclinical method to evaluate nonselective effects is to measure the medication's effects on behaviors such as motor activity, open field locomotion, or responding on an inactive lever. Doses of the candidate medication are then chosen for further study that have minimal actions on these nonspecific measures.

A more direct approach to examining nonselective effects is to study a medication's effects on operant behavior maintained by a nondrug reinforcer such as saccharin. For example, the effects of lorcaserin on sucrose-reinforced responding were studied in one group of rats and the effects on cocaine-reinforced responding were studied in another group of rats (Cunningham *et al.*, 2011). Lorcaserin suppressed responding reinforced by sucrose and by cocaine. Greater medication effects on drug rather than sucrose responding would be the desired outcome (i.e. decreased self-administration or drug seeking).

Another approach is to use a within-subject design to measure operant behavior maintained by another reinforcer such as food. For example, alternating daily sessions of cocaine and food availability have been used (Negus and Mello, 2003). Greater effects of a medication on food-reinforced responding suggest that its actions are not selective. A related design is to use within session components of drug self-administration, preceded and followed by segments of food (Woolverton and Virus, 1989).

Use of a multiple schedule also permits a within-subject design. Drug and another reinforcer such as food are scheduled within the same session rather than in different sessions, and they are available in separate components that alternate. This design has been used in a number of studies (e.g. Caine and Koob, 1994; Ginsburg and Lamb, 2014; Kangiser *et al.*, 2018)

Another design is to record responding when both a drug and nondrug reinforcer such as food are concurrently scheduled. The effects of a candidate medication can be studied on both response rate and choice behavior (Banks

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and Negus, 2017a). The time course of a medication's actions will be the same for both reinforcers since they are concurrently available. Importantly, when both reinforcers are present, the additional measurement of choice is possible (Moerke *et al.*, 2017; Maguire and France, 2018). However, to get balanced numbers of drug and food reinforcers, it has often been necessary to use one schedule size for food and another schedule size for drug (Banks and Negus, 2017b). Use of different schedule sizes may hinder interpretations of changes in relative reinforcing effects.

The aim of the present study was to evaluate baselines of responding maintained under concurrent nonindependent fixed-ratio (nFR) schedules as a tool for measuring treatment-specific effects. A baseline was established with equal schedule requirements for the nondrug and drug reinforcers and with equal response rates maintained by the concurrently available drug and nondrug reinforcers. Such a baseline would indicate that the two reinforcers have equivalent magnitudes of reinforcing effects, thereby providing balanced baselines for the study of potential therapies.

Comparable reinforcing effects were obtained by adjusting a saccharin concentration across sessions until saccharin maintained the same rates as the drug reinforcer. Frequent switching between the concurrent schedules was achieved by using concurrent nFR schedules of the same size (Meisch and Gomez, 2016). Under such schedules, responses on either operandum result in progress toward completion of both the right and left ratio requirements. Nonindependent ratio schedules result in frequent switching between sides as responding increases the probability of reinforcer delivery on both sides, rather than just one. The response requirement on a side is not reset until a delivery is collected on that side.

Concurrent nonindependent ratio schedules were first described by Shull and Pliskoff (1971); however, the significance and implications of these schedules were described in studies by MacDonall (1988, 1998, 1999). He noted that these schedules are the formal and functional equivalent of concurrent VI VI schedules. These concurrent nonindependent ratio schedules have been used in several drug self-administration studies. Unlike concurrent interval schedules, pausing does not alter the number of responses required per reinforcer delivery, however, like concurrent interval schedules relative rates of responding match relative drug intake (Meisch and Spiga, 1998; Meisch and Gomez, 2013, 2016). Moreover, the number of responses emitted per delivery becomes a dependent measure of 'price paid' for the reinforcer. Thus, data obtained in this context can also be analyzed in the framework of behavioral economics.

Methods

Subjects

The subjects were four adult male rhesus monkeys (*Macaca mulatta*). Three had more than 8 years of experience with oral drug self-administration (Crash, JoJo, and Raja), and one (Lucas) had 2 years of experience. Their behavior had been reinforced under standard (independent) concurrent FR FR schedules and under nonindependent concurrent FR FR schedules (Meisch and Gomez, 2013, 2016). Crash had experience with responding reinforced by alcohol, methadone, and cocaine, Jojo with alcohol and cocaine, Raja with alcohol and methadone, and Lucas with alcohol. Due to their histories, it was not necessary to establish alcohol as a reinforcer.

The monkeys were individually housed in their chambers in a climate-controlled room (22.8ºC) with a 12-h light-dark cycle (lights on at 07:00 h). Water was provided ad libitum via attached water bottles for 19 h during the intersession period. They were maintained at 85–90% of their optimal weights by feeding a daily, measured quantity of commercial chow (High Protein Monkey Diet 5045; Lab Diet, St. Louis, Missouri, USA), fresh fruit, and vegetables. At the start of the study, their weights were as follows: Crash, 10.3, Jojo, 12.8, Raja, 10.7 and Lucas, 9.0 kg.

Each monkey's optimum weight was determined by two veterinarians familiar with the monkeys and was based on individual monkey's health and body condition (cf. Pugh *et al.* 1999). The food allotment maintained stable weights for the duration of the study. Food restriction is known to increase drug self-administration (Carroll and Meisch, 1984) and reinforcing effects of drugs (Kliner and Meisch, 1989; Carr, 2002). Food restriction also protects against obesity (Meisch and Lemaire, 1988), lengthens median life span, and benefits general health (Mattison *et al.*, 2007; Kemnitz, 2011). Animal care followed the guidelines of the Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council (2011), and all procedures were approved by the Institutional Animal Use and Care Committee of The University of Texas Health Science Center at Houston (UTHealth) and conducted at AAALAC-l-accredited facilities.

Apparatus

The monkeys were individually housed 24 h a day in primate cages, which also served as the experimental chambers. Two brass spouts protruded 2 cm into the cage, and each was connected to a liquid delivery system. Mouth contact with the spout served as the response and was detected by completion of a drinkometer circuit. For further details see Meisch and Gomez (2016). The programming of experimental events and the recording of behavior utilized a Dell computer (Round Rock, Texas, USA), MED-PC software, and Med Associates Inc. (St. Albans, Vermont, USA) interface equipment. This equipment was in a room near the rooms containing the experimental chambers.

Procedure

The initial sequence of experimental conditions was similar for each monkey. Across all conditions, 16% (w/v)

alcohol was held constant. Alcohol was alternately available from one of the two spouts. At the opposite spout, blocks of sessions were obtained with the reservoir either (1) empty, (2) containing the water vehicle, or (3) containing an ascending series of saccharin concentrations in mg/ml: 0.06, 0.12, 0.24, 0.48, etc. The saccharin concentration was increased across sessions until saccharin responding clearly exceeded alcohol responding. For two monkeys, additional concentrations were then examined to extend the range studied: Jojo 0.03 mg/ml; and Lucas, 0.015 and 0.03 mg/ml.

Prior to the session

Some of each solution was drained through the tubing leading from the reservoir to ensure that the appropriate solution was present on the first delivery of the session. Liquid volumes were measured after flushing to obtain the exact volume in the reservoirs at each session's onset. One hour before each session, the water bottle attached to the side of the cage was removed.

Sessions

Experimental sessions were 3 h in length (from 11:00 to 14:00) and were conducted 7 days per week. During sessions, the green stimulus light above each spout blinked at a rate of 10 Hz. Identical discriminative stimuli were used for both spouts to control for responding that might result from dissimilar exteroceptive stimuli. Each mouth contact with a spout illuminated the green-lensed pair of spout lights for the duration of the response. Liquid delivery was contingent upon making spout-contact responses. The final response in the nFR 32 requirement initiated the liquid flow. For each liquid delivery, the solenoid-operated valve was opened for approximately 150 ms, allowing approximately 0.65 ml of liquid to pass through the spout and into the monkey's mouth. To reduce the influence on responding that might occur due to a monkey's preference for a particular spout, the location of alcohol and concurrent liquid were alternated between spouts each session.

Each condition remained in effect until six consecutive sessions of stable behavior were obtained. Stability was judged by visual determination of the absence of upward or downward trends in numbers of responses and liquid deliveries.

Feeding Schedule

One hour after the end of a session, the monkeys were fed, and a water bottle was reattached to the side of each cage. Water was thus available continuously for 19 h.

Liquids

Alcohol solutions (w/v) were made by diluting an appropriate amount of 95% (v/v) alcohol approximately 20 h before the start of the session. Saccharin solutions were prepared by diluting an appropriate amount of stock solution (1.92 mg/ml) 2 hours before the session. The alcohol and sodium saccharin solutions were at room temperature at the start of each session.

Data analysis

The mean numbers of responses, responses per liquid delivery, changeover responses, and liquid deliveries were calculated across the last six stable sessions of each condition. A standard error was computed for each mean.

Results

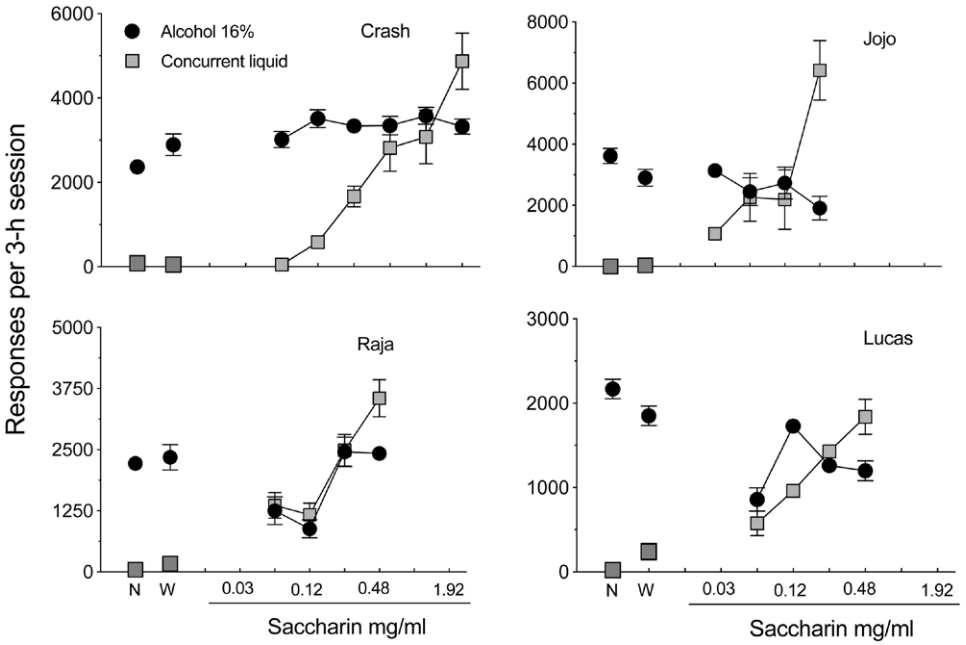
Figure 1 shows responses per session for 16% (w/v) alcohol and the concurrently available liquid. When 16% alcohol was available from one reservoir and nothing was available from the second reservoir, few responses were made on the spout connected to the empty reservoir, despite identical stimulus and schedule conditions and daily alternation of the spout dispensing alcohol (Fig. 1). However, high rates of responding occurred on the spout delivering alcohol. When water was placed in the second reservoir, response rates on the spout delivering water rose slightly for two monkeys (Raja and Lucas) and did not change for the other two (Crash and Jojo). In all cases, alcohol responses were far greater than for the vehicle (water) thereby confirming that 16% alcohol functioned as a reinforcer for all monkeys (Fig. 1).

As the saccharin concentration became greater, response rates increased until they were greater than rates maintained by alcohol (Fig. 1). An exception was Raja for whom the second concentration studied (0.12 mg/ml) maintained lower rates than the first concentration (0.06 mg/ml). Importantly, it was possible to identify a saccharin concentration that yielded response rates approximately equal to response rates maintained by 16% alcohol. Under identical concurrent schedules, equal response rates reflect equal magnitudes of reinforcing effects. This behavioral context provides an optimal condition to examine therapeutic interventions for alcohol and other drugs of abuse.

Figure 1 also depicts the number of alcohol responses at each concentration of concurrently presented saccharin. Across the four monkeys, there was no consistent effect of saccharin concentration on alcohol responding. A comparison at the lowest and highest saccharin concentration for each monkey reveals that alcohol responding either increased (Raja and Lucas), decreased (Jojo), or showed little change (Crash).

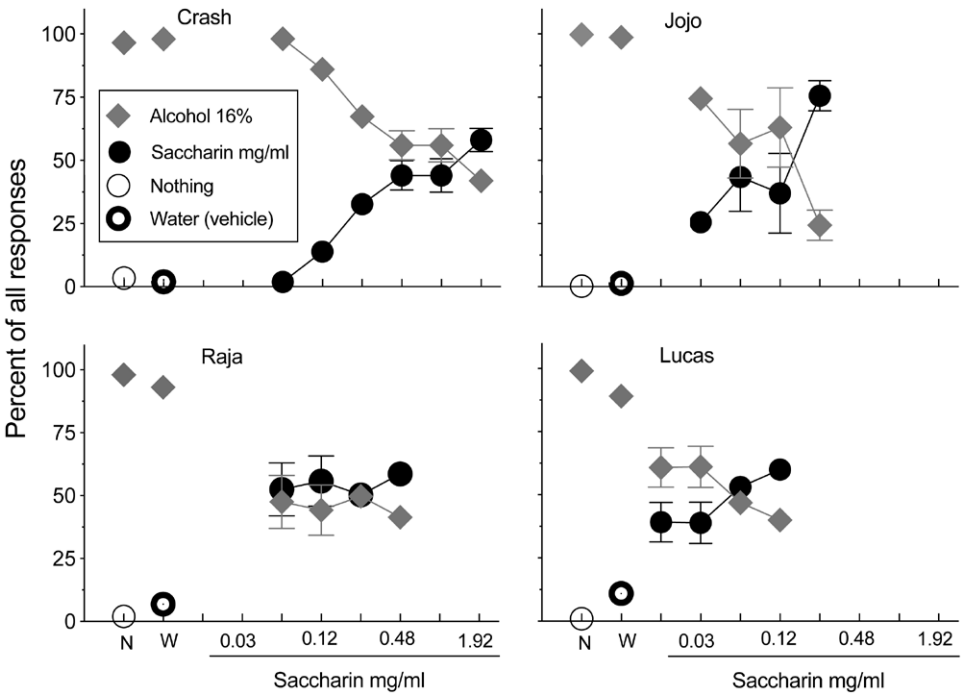
In general, relative rates of responding maintained by saccharin were a direct function of the saccharin concentration (Fig. 2). For all monkeys, saccharin maintained higher response rates than water except for the lowest concentration studied with Crash. The higher rates were most apparent for Crash and least for Raja. With all monkeys, at the highest saccharin concentration rates exceeded 50% of total responding.

Fig. 1



Responses per 3-h sessions for 16% alcohol and a concurrent liquid. Each point is a mean from six consecutive sessions of stable behavior; brackets indicate the SEM. Note the different scales of the ordinates. As the concentration of saccharin increased, saccharin responses increased until they exceeded alcohol responses. Across the four monkeys, alcohol responses did not systematically vary as a function of the saccharin concentration. Responses on the spout that delivered water or no liquid (empty reservoir) were low in number and far less than responses that delivered alcohol.

Fig. 2



Responses for the concurrent liquids are shown as a percentage of total responses per session. Each point is a mean from six consecutive sessions of stable behavior; brackets indicate the SEM and absence of brackets indicates that they fell within the area occupied by the symbol. In general, values for saccharin increased as the saccharin responses increased and values for 16% alcohol decreased. When the reservoir contained water or no liquid almost all responding occurred on the spout delivering alcohol.

Figure 3 shows the mean number of responses per delivery for 16% alcohol and the concurrent fluid: nothing (empty reservoir), water (vehicle), or saccharin. When the opposite reservoir was empty or contained water, responses reinforced by 16% alcohol were far greater than responses on the opposite spout (Fig. 3). When the opposite reservoir contained saccharin, responses per delivery of saccharin generally were a direct function of the saccharin concentration. This relation was clearest for monkey Crash and least for monkey Raja. For all monkeys, responses per delivery for saccharin were greatest and also above alcohol values at the highest saccharin concentration studied. In contrast, responses per alcohol delivery generally decreased with increases in the saccharin concentration. Again, this pattern was seen most clearly with the monkey Crash and least with the monkey Raja. Responses per delivery can be described as the price paid for that delivery with price paid being a dependent variable.

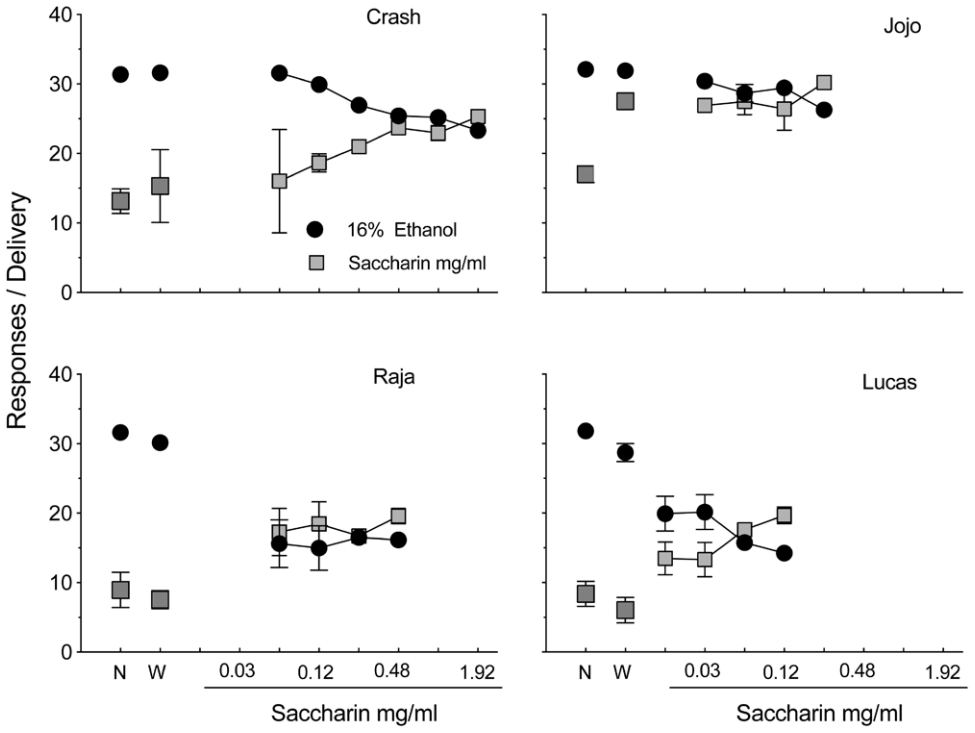
Figure 4 depicts the number of changeover responses or switches between spouts. In general, changeover responses were a direct function of the saccharin concentration. Since the alcohol concentration was constant at 16%, the rise in changeover responses and saccharin-reinforced responses is consistent with a concentration-dependent increase in saccharin's reinforcing effects.

Discussion

As saccharin concentration increased, response rates increased until they were greater than rates maintained by alcohol. Note that each monkey had a long history of alcohol self-administration. Importantly, it was possible to identify a saccharin concentration that yielded response rates approximately equal to response rates sustained by 16% alcohol. Under identical size concurrent schedules, equal response rates are consistent with equal magnitudes of reinforcing effects. The direct relation between saccharin concentration and response rate is similar to the results of a study with rhesus monkeys where increases in saccharin concentration also resulted in increases in response rate when saccharin was concurrently available with pentobarbital (Macenski *et al.*, 1993)

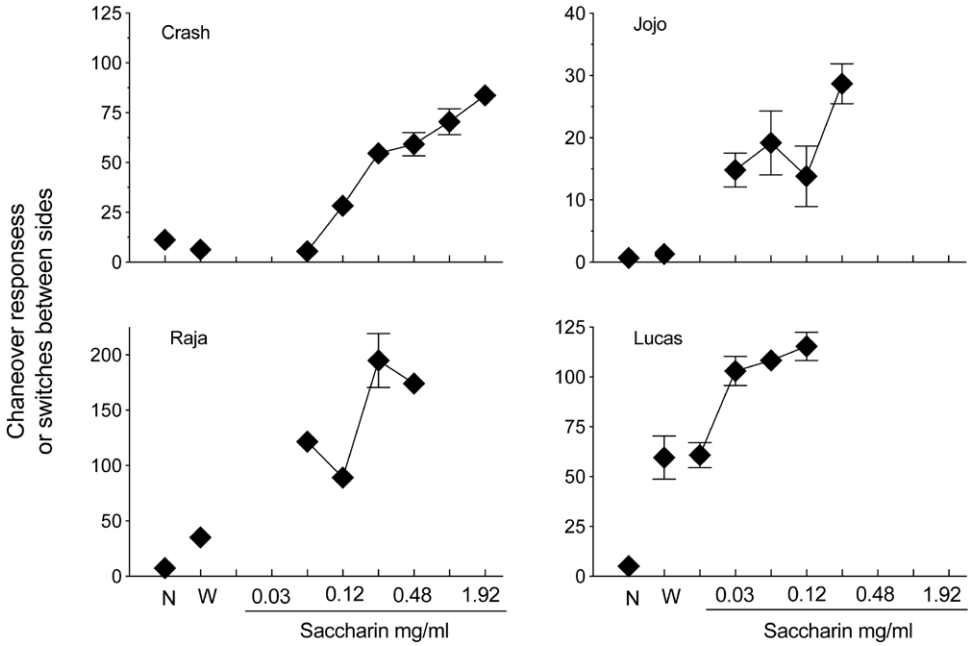
Nonindependent ratio schedules yield the additional dependent variable of responses per delivery, that is, price paid. Responses per saccharin delivery tended to increase as saccharin concentration became greater.

Fig. 3



Responses per liquid delivery are shown across a series of saccharin concentrations and for conditions when either the water vehicle or an empty reservoir was the alternative to 16% alcohol. Each point is a mean from six consecutive sessions of stable behavior; brackets indicate the SEM and absence of brackets indicates that they fell within the area occupied by the symbol. In general, as the saccharin concentration increased, the number of responses per saccharin delivery increased and the number for alcohol decreased. Responses per alcohol delivery exceeded the number for water and for no delivery of a liquid (empty reservoir). The elevated values for Jojo reflect are due to low numbers of water or empty deliveries.

Fig. 4



Changeover or switching responses are shown across increasing saccharin concentrations and for conditions when either the water vehicle or an empty reservoir was the alternative to 16% alcohol. Each point is a mean from six consecutive sessions of stable behavior; brackets indicate the SEM and absence of brackets indicates that they fell within the area occupied by the symbol. Note the different scales of the ordinates. In general, as the saccharin concentration increased, the number of changeover or switching responses rose. When one reservoir contained 16% alcohol and the other reservoir contained the water vehicle or nothing, changeover or switching responses were low.

However, responses per alcohol delivery diminished for three of the four monkeys. The degree of decrease varied among the monkeys. For all monkeys, responses per alcohol delivery were lower at the three highest saccharin concentrations than when water was present (Fig. 2). Under the nonindependent FR schedules, a decrease in responses per delivery reflects an increase of changeover responses, since changeover responses result in a decrement in the number of responses required per reinforcer delivery. Thus, responding reflects the maximizing of intake of both reinforcers and the minimizing of responses per delivery.

Frequent changeover responses also result in both reinforcers being received over the same time intervals. Consequently, the effects of any potential medication would act within the same periods on responding maintained by each reinforcer. Thus, the effects of a candidate therapeutic medication would not differ due to one reinforcer being consumed over one time interval and the other reinforcer being consumed over another time interval. An outcome is improved measurement of the selectivity of a candidate therapeutic on responding maintained by each reinforcer.

It is possible to use drug reinforcers other than alcohol and to use concurrent reinforcers that other than saccharin. Thus, the type of baseline illustrated in the present study is not restricted to alcohol and saccharin solutions. Nonindependent ratio schedules are not limited to using monkeys as subjects since the schedules have been used with pigeons (Shull and Pliskoff, 1971) and rats (MacDonall, 1988, 1998). These schedules would also be appropriate for used with human participants.

In many studies with concurrent access to both a drug and nondrug reinforcer, the nondrug reinforcer 'competes' with the drug reinforcer and thereby decreases drug intake. In contrast in the present study, a nondrug reinforcer can potentially increase drug intake since responding maintained by the nondrug reinforcer can decrease the response requirement for the drug reinforcer, and vice versa.

Ideally, a baseline of concurrent behavior would have the following features: (1) equal schedule sizes, (2) equal preference for each reinforcer, reflecting equivalent reinforcing effects, (3) frequent choice of each reinforcer, so that contact is made with each reinforcer, and (4) similar time course of consuming the drug and nondrug reinforcers, so that the temporal effects of any treatment are comparable for both reinforcers. In the present study, it was also possible to reverse reinforcer locations each session to balance for any potential side preferences. Both reinforcers were liquids dispensed by the same delivery systems, and the topographies of ingestion were the

same. This preparation minimizes potential confounding variables and affords clearer interpretations of outcomes with regard to the relative reinforcing effects of two different compounds. Its utility is that (1) pausing does not decrease the schedule requirement as it does in interval schedules, (2) changeover responses are increased since responses required per delivery decreases, and (3) the dependent variable of price paid or responses emitted per reinforcer delivery can be measured.

Conclusion

With the use of concurrent nonindependent nFR 32 nFR 32 schedules, it was possible to establish approximately equal response rates maintained by 16% alcohol and saccharin, as well as similar time courses of intake, and obtain frequent switching between the two reinforcers. The baselines generated can serve to evaluate relative selectivity of potential therapeutic drugs and behavioral interventions.

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Conflicts of interest

There are no conflicts of interest.

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