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Ethanol self-administration in mice under a second-order schedule

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ABSTRACT

Long Fixed-Interval (FI) schedules, particularly second-order schedules, can engender substantial responding before drug or ethanol delivery that is uninfluenced by the direct effects of the drug or ethanol. Thus, these schedules can be used to study the effects of medications upon drug- or ethanol-seeking, uninfluenced by the direct effects of the self-administered drug or ethanol. Long FI second-order schedules are frequently used in primates and occasionally in rats. Under second-order schedules, completion of one response requirement, e.g., a Fixed Ratio 10 (FR10:S), produces a brief stimulus presentation, e.g., a 1-s 80-dB 4-kHZ tone, and this FR10:S serves as the response unit under another schedule, e.g., an FI 1800-s. Thus, the first FR10 completed after 1800 s would result in delivery both of the tone and of reinforcement, e.g., 10 × 0.01 mL 16% (w/v) ethanol. To examine if such schedules could be effectively used in mice, which have advantages in neurobiological and genetic studies, we trained eight C57BL/6J mice to respond under the schedule just described. This schedule maintained substantial responding. The temporal pattern of behavior was typical of an FI schedule with responding accelerating across the interval. We also examined the effects of acute and chronic administration of fluvoxamine on this responding, and these were modest. Finally, we examined responding when alcohol and/or tone deliveries were withheld, and found that extinction occurred most rapidly when both were withheld. This work demonstrates that long FI schedules of ethanol delivery may be useful in studying ethanol seeking in mice.

Introduction

In order to study the neurobiology of addiction and problem drinking, self-administration procedures in which responding changes rapidly as conditions change have been developed. For instance, procedures that allow the assessment of a dose–response curve within a single session (e.g., Zernig, Lewis, & Woods, 1997) or the maximum amount of work that a given dose of drug might maintain within a single session have been developed (e.g., Gilpin & Koob, 2010; Roberts, Loh, & Vickers, 1989). These procedures are quite useful, and many have been extended to the mouse (e.g., Elmer, Pieper, Hamilton, & Wise, 2010), allowing the use of sophisticated neurobiological and genetic tools that are most readily available in the mouse.

As useful as such procedures have been, they have important limitations. These rapid procedures almost always involve repeated drug or alcohol delivery within an experimental session, with responding for the drug or alcohol occurring between deliveries of drug or alcohol. Thus, incidental drug accumulation may impinge upon discriminative and reinforcement processes across the session. Additionally, the self-administered drug may itself elicit behavior that directly affects responding to obtain further drug. Both possibilities complicate the interpretation of the effects of pharmacological, biological, or environmental manipulations on responding that lead to drug or alcohol delivery (see Herling & Woods, 1980). In particular, as Ettenberg (2004) has noted, repeated drug administrations during a session may interfere with identification of processes important to the onset and initiation of drug taking.

Responding that precedes drug or alcohol delivery is of particular interest because behavior that leads to the acquisition of (or opportunity to acquire) drug or alcohol necessarily precedes consumption, and so, this initial seeking behavior represents the starting point in a cascade of events terminating with drug consumption. Thus, drinking or drug taking can be thought of as a chain of behaviors that consists of at least two elements, seeking and consumption. For instance, going to the bar or liquor store precedes

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drinking. The alcohol-seeking behavior that makes up this acquisition phase may itself consist of a number of sub-chains of behaviors, and earlier elements in the chain of behaviors leading to drinking are generally thought to be more effective places to intervene to reduce drinking, and it is the persistence of these earlier elements of the chain that put the problem drinker at continued risk for problem drinking.

Samson, among others, recognized the importance of distinguishing between behaviors that result in access to the opportunity to drink or take drugs (seeking) and the behaviors that result in drug or alcohol consumption (consummatory; see Samson & Czachowski, 2002). Samson, Denning, and Czachowski (2003), for example, required rats to complete 5 to 10 responses to gain access to a sipper tube filled with 10% (v/v) alcohol. The advantage of the procedure is that seeking behavior is uncontaminated by direct effects of the self-administered drug because only one consumption period is allowed per session. A number of studies using this approach support the concept that seeking and consumption of alcohol are governed by distinct processes (e.g., Samson, Sharpe, & Denning, 1999), and highlight the value of such procedures. At the same time, this procedure is limited in that the "seeking" component is very short, resulting in a limited sample of behavior.

Typically, these samples of seeking behavior are usually 30 or fewer than 30 responses. Larger samples of seeking behavior have been maintained in monkeys responding under second-order schedules, particularly schedules that involve long fixed-interval schedules of reinforcement as their primary schedule (e.g., Goldberg, Morse, & Goldberg, 1976). Under such a procedure, every time the monkey completed a fixed number of responses, e.g., 10, a brief stimulus was presented, usually a light (FR10:S), and the first FR10:S completed following 60 min resulted in drug delivery (FI 60 m (FR10:S)). Such schedules can maintain robust responding that is persistent and can increase or decrease in response to various manipulations. Additionally, the brief stimulus presentations may play a role in the maintenance of behavior akin to the role theorized to be played by alcohol- or drug-paired stimuli in problematic drinking or addiction (see Markou et al., 1993). For these reasons, we examined if such a procedure could be developed in the mouse because of the valuable neurobiological and genetic tools that are more easily available in the mouse.

We trained C57BL/6J mice to respond for ethanol under an FI 1800-s (FR10:S) schedule. This schedule is similar to ones that maintain robust and persistent behavior in primates. Further, C57BL/6J mice readily and avidly learn to drink and work for ethanol solutions (Elmer, Meisch, & George, 1986). Once reliable responding was obtained, we examined the effects of acute and chronic fluvoxamine administration on this responding. Fluvoxamine is a specific serotonin reuptake inhibitor (Wong, Bymaster, Reid, & Threlkeld, 1983). We have examined the acute effects of this drug upon responding for ethanol under a variety of schedules in the rat (e.g., Ginsburg, Koek, Javors, & Lamb, 2005; Ginsburg & Lamb, 2006a, 2014; Lamb & Järbe, 2001) and progressive-ratio responding in mice (Lamb & Daws, 2013), and we and others have studied the chronic effects of fluvoxamine or other specific serotonin reuptake inhibitors on responding for ethanol in rats and mice (Ginsburg & Lamb, 2006b; Gulley, McNamara, Barbera, Ritz, & George, 1995). Thus, we had a substantial body of work to which we could compare any effects we might see in the mouse. Finally, we examined the effects of removing contingent ethanol and/or brief stimulus deliveries upon responding maintained by this schedule. This allowed us to examine the persistence of this behavior and the role of the brief stimulus.

Materials and methods

Mice

Eight male C57BL6/J mice purchased from Jackson Laboratories were used in these experiments. Housing was in a temperature- and humidity-controlled vivarium, under a 12-h light/dark cycle (lights on at 6:00 AM). Water was freely available except during experimental sessions. Food was limited to 2.5 g rodent chow provided each day following experimental sessions. In general, food restriction increases longevity, keeps mice at similar weights, and makes development of ethanol self-administration easier. All procedures conducted on the mice were approved by the local institutional animal care and use committee and were in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

Apparatus

Experiments were conducted in 8 mouse operant chambers (Med Associates, St. Albans, VT). Located on either side of the front wall of each chamber were two head-entry detectors with associated dipper mechanisms and yellow LED lights located at the rear of the head-entry detector. The head-entry detector on the left was used in these experiments. The dippers used could hold a volume of 0.01 mL. In addition, chambers had a house light and speaker. Operant chambers were housed inside large fan-equipped sound-attenuating chambers. A white noise generator in the room provided additional masking noise.

Procedure

Mice were initially trained to break the photo beam inside the head-entry detector to earn a dipper presentation of a 20% (w/v) sucrose solution when the house light and the LED in the head-entry detector were lit. The 5-s dipper presentation was accompanied by turning off the house light and the LED and presentation of an 80-dB, 4000-kHZ tone. Initially, session length was 1 h. Over time, session length was reduced to 30 min, 10 beam breaks were required for presentation of the dipper, and the solution was changed from 20% sucrose to 16% (w/v) ethanol by gradually reducing the sucrose concentration and increasing the ethanol concentration (Samson, Tolliver, Pfeffer, Sadeghi, & Haraguchi, 1988). After responding was maintained under this FR10 schedule of ethanol presentations (which took a median of 35 sessions with a range of 27–37 sessions), the schedule was changed to an FI (FR10:S) schedule of ethanol presentation, in which each FR10 completion resulted in a 5-s presentation of the 80-dB, 4-kHZ tone, and the completion of an FR10 after the elapse of the FI resulted in a 5-s tone and dipper presentations. Initially, the FI was 60 s and completion of the schedule requirement resulted in a single dipper presentation with this schedule repeating itself until the 30-min session had expired. Over five sessions the FI length was increased to 1800 s and completion of the schedule requirements resulted in ten 5-s tone-dipper presentations each separated by 2-s periods in which the dipper was lowered to be refilled.

Ethanol

Ethanol solutions were made by diluting 190 proof ethanol (Decon Labs, King of Prussia, PA) with tap water to make up a 16% (w/v) solution.