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Applications of schedule-induced polydipsia in rodents for the study of an excessive ethanol intake phenotype

Matthew M. Ford*

Division of Neuroscience, Oregon National Primate Research Center, Oregon Health & Science University, L-584, 505 NW 185th Avenue, Beaverton, OR 97006, USA

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ABSTRACT

Schedule-induced polydipsia (SIP) is generated by subjecting a highly motivated animal to a sub-optimal rate of food reinforcement while also providing access to a fluid. SIP is one of several adjunctive (or displacement) behaviors that are expressed in an exaggerated form that is deemed 'excessive.' This feature makes SIP an attractive model for studying an excessive ethanol drinking phenotype in rodents. Multiple experimental variables are crucial for the full manifestation of adjunctive drinking, including the degree of food deprivation, the inter-pellet interval selected, and the size of the food reward offered. Although these variables were extensively studied and optimized for water polydipsia in rats, a similarly customized approach to ethanol SIP and application of the procedure in mice have largely been curtailed in favor of the default variable values historically used for water SIP in rats. Further, ethanol SIP also requires careful consideration of variables such as taste and ethanol concentration. Investigation of the stress axis and neurochemical systems such as dopamine and serotonin in mediating adjunctive drinking stemmed from two leading hypotheses regarding the underlying mechanisms of SIP generation: 1) SIP as a coping strategy to mitigate stress associated with the aversive environmental condition, and 2) SIP as a displacement of reward in a highly motivated animal. Ethanol SIP is a powerful model of excessive intake because it can generate an ethanol-dependent state and sustain frequent and intoxicating levels of blood ethanol with voluntary oral consumption. The required food deprivation and the loss of the excessive drinking phenotype following removal of the generator schedule are the two main limitations of the model. Future utility of ethanol SIP will be enhanced by more fully dissecting the underlying hormonal and neurochemical mechanisms and optimizing experimental variables for ethanol SIP on a per species and strain basis.

Introduction

The term 'poly-dipsia' is of Greek origin and translates as 'much thirst.' Polydipsia (excessive water intake) is clinically observed as an initial symptom of diabetes insipidus (Moeller, Rittig, & Fenton, 2013) and is observed occasionally in psychotic patients with schizophrenia or related mental illness (Goldman, 2010; Moreno & Flores, 2012). Experimentally, Lester (1961) was the first investigator to document schedule-induced polydipsia (SIP) in rats provided access to ethanol, and this represented a rapid translation from seminal work published by Falk (1961) regarding SIP with water earlier that same year. These investigators discovered that rats will consume excessive quantities of fluid amounting to either half their body weight or 10-fold baseline levels in 3 h if food-restricted and placed under a schedule of intermittent food reinforcement. In a typical SIP experiment, subjects are food-restricted to 80–90% of their free-feeding body weight, and then are placed into an operant chamber for daily sessions of 30–180 min in duration. The operant chambers minimally contain a fluid source and a food pellet dispenser and receptacle (see Fig. 1). Key to the generation of polydipsia is the schedule of intermittent food delivery, which is often referred to as the 'generator schedule.' Historically, multiple types of interval schedules have been used, including fixed interval (FI), variable interval (VI), and fixed time (FT). The FI and VI schedules require animals to press a lever for food access. For example, following a 1-min or an on-average 1-min interval, respectively, the first lever response is reinforced and then another 1-min delay is imposed before the subject is again eligible for reinforcement, and so on. When an animal is under schedule control (see Acquisition of SIP and demonstration of schedule control section below), bursts of fluid intake occur immediately after each pellet delivery and this culminates in the consumption of large volumes throughout the session. The earliest investigations with SIP employed a variable interval 1-min (VI-1) schedule

* Corresponding author. Tel.: +1 503 614 3716; fax: +1 503 690 5384.
E-mail address: fordma@ohsu.edu.

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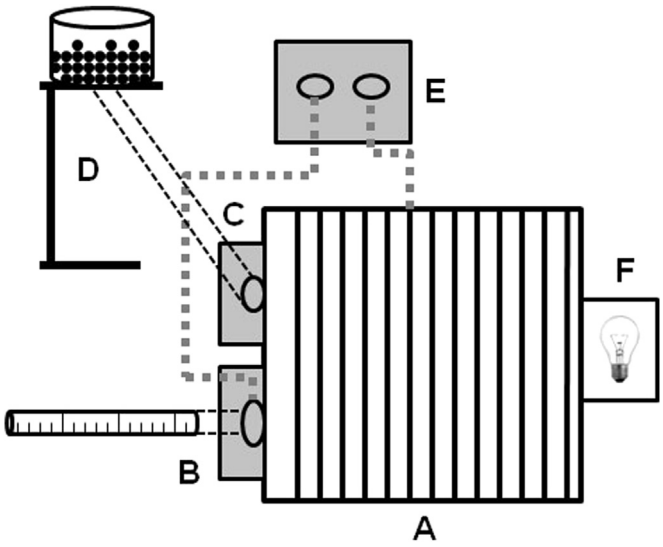

Fig. 1. Apparatus for schedule-induced polydipsia procedure. The operant chamber configuration in our laboratory includes a stainless-steel rod floor (A), graduated drinking sipper attached to a stationary mount (B), food receptacle (C), food pellet dispenser (D), lickometer circuit (E) with electrical connections (dotted gray lines) to metal sipper and rod floor, and house light (F). Apparatus is positioned within a sound-attenuating cabinet and a fan is used to ventilate the chamber and mask external noise. Iterations to this configuration and its components are discussed in the text.

(Falk, 1961; Lester, 1961). However, this response contingency was later found not to be a crucial factor for the manifestation of SIP in its fully exaggerated form (Falk, 1969), and most contemporary applications omit response requirements from the procedure and allow pellets to be delivered automatically according to an FT interval (notice absence of lever in Fig. 1).

SIP is classified as an adjunctive (or displacement) behavior along with other scheduled-induced behaviors such as aggression, escape, wheel running, and air licking (see Falk, 1971 for review). By definition, adjunctive behaviors are excessive in nature and are purportedly derived from thwarting conditions (sub-optimal food reinforcement rate) that dramatically increase the probability of the animal engaging in other possibilities within the environmental context provided, and this exerted effort is viewed as both evolutionarily advantageous and successful adaptation (Armstrong, 1950; Falk, 1971). Because of its key feature of excessiveness, the phenomenon of adjunctive drinking has been tailored to address excessive ethanol intake to model alcoholism in humans. Multiple comprehensive reviews of adjunctive behavior (Falk, 1971, 1998; Wallace & Singer, 1976), polydipsia for the study of pathologic behavior (Moreno & Flores, 2012), and the implementation of SIP to study excessive ethanol consumption (Falk & Samson, 1975; Falk & Tang, 1988; Falk, Zhang, Chen, & Lau, 1994; Meisch, 1975; Meisch & Thompson, 1972; Mello, 1975) have been previously published, and the current review does not attempt to exhaustively replicate these earlier efforts. This work strives to identify crucial features of SIP in rodents that have culminated from decades of investigation and to specifically outline procedural aspects of significance that pertain to the examination of excessive ethanol intake in rats and mice. In reviewing the literature, it was apparent that ethanol SIP studies in rodents have largely retained the procedural parameters that were initially characterized for the investigation of water SIP in rats. The optimization of these experimental variables to account for species differences (rats versus mice) and fluid properties (water versus ethanol) will likely enhance the future utility of ethanol SIP as a model of excessive intake. Identification and discussion of these key procedural variables are presented next.

Distinguishing features and experimental variables of SIP procedure that engender excessive ethanol drinking

Food deprivation

Since a strong feeding response is required to keep animals actively engaged during schedule exposure, food deprivation is a necessary prerequisite for the manifestation of polydipsia. Falk (1969) explored the relationship between adjunctive water drinking and level of food deprivation in one of his early seminal experiments characterizing the SIP phenomenon. In brief, rats were maintained at 80% of their free-feeding body weight under a 1.5-min interval schedule until water SIP fully developed, and then over a 3-week period the animals were permitted to slowly gain weight to approximately 105%. No appreciable difference in water intake was observed as rats surpassed 90%, but between 90% and 105% a linear decline in adjunctive drinking was observed. Although these findings were later recapitulated for water SIP in gerbils placed under an FT 3-min schedule (Porter, 1983), a comparable evaluation of food deprivation level and ethanol SIP has yet to be determined. This ends up being more than just an academic exercise, as it is not known whether the caloric value of ethanol would appreciably influence the relationship between these two variables (see additional discussion in Advantages and limitations of ethanol SIP section below).

It is unclear from the food deprivation study mentioned above (Falk, 1969) whether restriction to 80% was necessary for acquisition of adjunctive drinking, though 90% was apparently sufficient for maintenance of behavior in its exaggerated form. In the vast majority of water and ethanol SIP applications it is standard practice for rodents to be maintained at 80–85% of their free-feeding body weight. The pertinent question is whether this degree of deprivation is necessary. The answer may be dependent upon the interval schedule selected (see below), because a more frequent delivery of pellets (i.e., 0.5 min) may require a greater level of deprivation to keep subjects vigilant and engaged in adjunctive drinking throughout a session. A simple measure of vigilance is whether or not animals consume all of the pellets that are delivered, and engagement can be assessed by whether drinking occurs after each pellet delivery (see 'schedule control' below). This point is illustrated by some of our recent work with male C57BL/6 and DBA/2 mice that were restricted to 90% of their free-feeding body weight and then serially examined for ethanol SIP with FT intervals ranging from 0.5 to 20 min during 1-h sessions. Mice were provided access to 5% v/v ethanol for 10 sessions at each FT interval, and food pellets remaining in the chamber at the conclusion of each session were tallied. The percentage of pellets consumed during the 10th and final session at each FT interval per strain is shown in Fig. 2 (see legend for additional details). A two-way repeated measures ANOVA detected significant main effects of strain [$F(1,9) = 9.69$; $p < 0.05$] and interval [$F(1,9) = 182.63$; $p < 0.001$] as well as a strain × interval interaction [$F(9,81) = 3.68$; $p < 0.001$] for the percentage of pellets consumed. The percentage of pellets consumed was significantly greater than baseline (FT-0) values with 1-min and longer intervals in both strains (all p's < 0.001). Both strains consumed approximately 100% of pellets offered when under FT intervals of 2-min and longer. Thus, in our hands a deprivation of 90% was sufficient to maintain vigilance in mice under an FT-2 schedule. This is consistent with the observation that ethanol drinking was under strong schedule control with intervals of 2-min and greater, as indicated by licking after each pellet delivery (Ford, Steele, McCracken, Finn, & Grant, 2013; also see Fig. 4B below). Ideally, food restriction should be adjusted to the least degree that is necessary to sustain a fully developed polydipsia.