Psychoneuroendocrinology (2013) 38, 2598—2610

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The relationship between adjunctive drinking, blood ethanol concentration and plasma corticosterone across fixed-time intervals of food delivery in two inbred mouse strains

Matthew M. Ford [a,b,*], Andrea M. Steele [a], Aubrey D. McCracken [a], Deborah A. Finn [a,c], Kathleen A. Grant [a,b]

[a] Department of Behavioral Neuroscience, Oregon Health and Science University, Portland, OR, USA
[b] Division of Neuroscience, Oregon National Primate Research Center, Oregon Health and Science University, Beaverton, OR, USA
[c] Department of Research, Veterans Affairs Medical Center, Portland, OR, USA

Received 21 December 2012; received in revised form 21 May 2013; accepted 7 June 2013

KEYWORDS
Schedule-induced polydipsia;
Adjunctive behavior;
Excessive alcohol consumption;
Blood ethanol concentration;
Drinking patterns;
Stress;
HPA axis;
Corticosteroid;
C57BL/6 mice;
DBA/2 mice

Summary Schedules of intermittent food delivery induce excessive fluid intake, termed schedule-induced polydipsia (SIP), and hypothalamic—pituitary—adrenal (HPA) axis activation is important for the expression and maintenance of this adjunctive behavior. Previous work has focused on examining the relationship between water intake and plasma corticosterone (CORT) in rats at a single or a limited range of fixed time (FT) intervals. However, little remains known regarding SIP and the corresponding stress response (1) across the bitonic function that epitomizes adjunctive behavior, (2) when ethanol is the available fluid, and (3) when a species other than rat or multiple strains are studied. Here we report the findings from ethanol-preferring C57BL/6J (B6) and non-preferring DBA/2J (D2) mice serially exposed to progressively larger FT intervals (0 → 60 min) and given access to either water or a 5% (v/v) ethanol solution. Following 2 weeks of experience with each schedule, blood samples were collected at the conclusion of the last 60-min session to evaluate CORT and the blood ethanol concentration (BEC) achieved. While both strains exhibited a bitonic function of ethanol intake and BEC that peaked at or near a 5-min interval, only D2 mice showed a similar response with water. In contrast, CORT levels rose monotonically with incremental increases in the FT interval regardless of the strain examined or

* Corresponding author at: Division of Neuroscience, Oregon National Primate Research Center (L-584), Oregon Health and Science University, 505 NW 185th Avenue, Beaverton, OR 97006, USA. Tel.: +1 503 614 3716; fax: +1 503 690 5384.
E-mail address: fordma@ohsu.edu (M.M. Ford).

0306-4530/$ — see front matter
http://dx.doi.org/10.1016/j.psyneuen.2013.06.011

fluid type offered, indicating that glucocorticoid release likely reflects the aversive aspects of increasing intervals between reinforcement rather than engagement in adjunctive behavior. These findings also caution against the use of a single intensity stressor to evaluate the relationship between stress and ethanol intake, as the magnitude of stress appears to affect ethanol consumption in a non-linear fashion.

1. Introduction

Schedule-induced (adjunctive) drinking occurs when fluid is available and small quantities of food are delivered intermittently at fixed time (FT) intervals that constitute suboptimal reinforcement magnitude for the animal (Falk, 1961, 1984). The term polydipsia refers to the excessive nature of adjunctive drinking; consumption of twofold or greater volume under scheduled conditions versus baseline intake (Falk, 1971). One characteristic of adjunctive behavior is a bitonic function between the amount of behavior generated and the interval length between scheduled food pellet deliveries. If the rate of food presentation is frequent or rare, then adjunctive behavior is not generated. In contrast, intervals falling between these extremes (termed the 'effective range') generate excessive levels of behavior (Falk, 1971). Regarding schedule-induced polydipsia (SIP), earlier work in rats demonstrated incremental increases in water intake during schedule exposure with intervals between 5 s and 3 min in duration, followed by a progressive decline in consumption with larger intervals up to 8 min (Falk, 1966, 1969; Flory, 1971). More contemporary applications of SIP with ethanol or sweetener (sucrose or saccharin) solutions in rats and mice have largely adopted the practice of investigating only a single interval schedule, usually an interval between 30 s and 2 min (as this approximates the maximal polydipsic response historically observed with water). However, similar parametric analyses of the bitonic function with fluids other than water and within a species other than rat have yet to be conducted. Given that ethanol can serve as a reinforcer, exhibits an anxiolytic profile, and results in intoxication when consumed in excessive quantities, it is likely that important differences in the polydipsic response given ethanol to drink versus water exist.

The effective range of pellet delivery for SIP has been related to an increase in hypothalamic—pituitary—adrenal (HPA) axis activity. For example, in rats it is well established that the schedule conditions that induce adjunctive behaviors also activate the HPA axis (Brett and Levine, 1979, 1981; Dantzer et al., 1988; Dantzer and Mormède, 1981; López-Grancha et al., 2006; Mittleman et al., 1988; Tazi et al., 1986). The increase in HPA activity is thought to reflect an enhanced arousal and vigilance as well as "conflict" in motivational forces upon behavior that are associated with obtaining intermittent reinforcement (Dantzer and Mormède, 1981; Falk, 1971, 1977). Specifically, under conditions that induce adjunctive behavior, there are heightened circulating levels of adrenal hormones such as corticosterone (CORT), the catecholamines epinephrine and norepinephrine (Brett and Levine, 1979, 1981; Dantzer et al., 1988; López-Grancha et al., 2006; Mittleman et al., 1988; Tazi et al., 1986), and the pituitary hormones prolactin (Dantzer et al., 1988) and adrenocorticotropic hormone (ACTH; Helms et al., 2012). In general, the elevations in these hormones persist as long as the schedule is in effect and the animal is not given the opportunity to escape (Dantzer et al., 1988; Tazi et al., 1986; López-Grancha et al., 2006). Acquisition of water SIP over successive sessions was reduced in rats following either adrenalectomy or administration of the CORT synthesis inhibitor metyrapone, but was restored in adrenalectomized rats that received CORT replacement (Levine and Levine, 1989; Mittleman et al., 1992). Further, elevations in plasma CORT over baseline (massed-feeding) conditions were observed in conjunction with an interval schedule associated with the generation of water SIP in rats, but not following exposure to an ineffective schedule (López-Grancha et al., 2006). Collectively, these observations suggest that stress-response mediators like CORT are integral to the development and maintenance of excessive drinking in SIP procedures. However, it is not known if CORT is correlated with adjunctive drinking across the entire bitonic function of interval schedules.

While experimental variables (intermittent schedule, level of food deprivation, etc.) play prominent roles in the generation of adjunctive behavior, it is clear that genetic background also exerts influence. First, earlier examinations of SIP in outbred rat lines yielded large individual differences in responsiveness, with only some subjects demonstrating excessive water intake when under a fixed interval schedule (Dantzer et al., 1988; López-Grancha et al., 2008; Mittleman et al., 1988; Moreno and Flores, 2012). Second, comparisons between strains (DeCarolis et al., 2003; Mittleman et al., 2003) and selected lines (Gilpin et al., 2008; Moreno et al., 2010) of rodents have identified significant divergence in the expression of water and ethanol polydipsia when tested at either a single interval or a limited range of intervals. However, the presence or absence of strain differences in SIP responsiveness may be reliant upon the interval schedule chosen for investigation. For instance, one study found no strain difference between C57BL/6 (B6) and DBA/2 (D2) mice in the expression of water polydipsia under a 1 min interval schedule (Mittleman et al., 2003) whereas a second study reported a pronounced difference when a 2.5 min interval was implemented (Symons and Sprott, 1976). Again, a more complete examination of the entire bitonic function in these inbred mouse strains may help reconcile the disparity between these earlier observations. Further, concomitant measurement of plasma CORT would help determine whether differences in stress axis responsiveness to interval schedules are associated with between-strain variability in expression of adjunctive drinking.

Thus, the goals of the current work were to identify the FT interval associated with the greatest amount of drinking, assess whether this peak FT is specific to the fluid type offered (5% (v/v) ethanol versus water) or the mouse strain examined (ethanol-preferring B6 versus ethanol-avoiding D2