HHS Public Access

Author manuscript

Alcohol Clin Exp Res. Author manuscript; available in PMC 2021 April 01.

Published in final edited form as:

Alcohol Clin Exp Res. 2020 April ; 44(4): 806–813. doi:10.1111/acer.14307.

Timing eclipses amount: The critical importance of intermittency in alcohol exposure effects

Linda Patia Spear

Behavioral Neuroscience program, Department of Psychology and Developmental Exposure Alcohol Research Center, Binghamton University, Binghamton, NY 13902-6000

Abstract

Frequency and duration of ethanol (EtOH) exposures influence the consequences of those experiences, with evidence building from basic science studies in rats and mice that intermittent alcohol access (IAA) typically produces a greater escalation of EtOH intake than more continuous alcohol access (CAA). IAA also better simulates human use patterns where alcohol levels typically clear from the body between periods of use. A variety of mechanisms have been proposed to contribute to the enhanced intake of EtOH induced by IAA, including a possible attenuation in the aversive effects of EtOH, although further studies are needed to address this and other possibilities. Neural differences include indications of an IAA-associated increase in NR2B receptors that is not evident with CAA; although little studied, alterations in other neural and neurotransmitter systems are evident as well. Many gaps in understanding of IAA/CAA effects remain. Further work is needed to characterize neural mechanisms underlying these effects, consequences of IAA/CAA on EtOH effects beyond intake, and the impact of stress and environmental variables on these differences. IAA/CAA studies to date have also largely been limited to males and to adult animals and hence more studies examining IAA/CAA across sex and age are needed. Such additional work is essential to determine unique contributors to IAA-induced elevations in EtOH intake that may provide important insights for development of new prevention/intervention strategies for heavy alcohol use and abuse.

Keywords

intermittent intake; frequency of exposure; rat; mice

Evidence from animal studies is mounting that exposure frequency exerts an important influence on the consequences of repeated ethanol (EtOH) exposure, with periodic, intermittent access to alcohol (IAA) inducing elevations in EtOH drinking that are often more pronounced than when animals are given continuous alcohol access (CAA) (e.g., O'Dell et al, 2004; Simms et al, 2008; Hwa et al, 2015; Spoelder et al, 2015; Kimbrough et al, 2017). The goal of this mini-review is to summarize these studies comparing EtOH intake (and other measures where possible) under CAA and IAA conditions, and consider possible contributors to the intake differences associated with these conditions.

lspear@binghamton.edu.

Frequency of reinforcement is known to play an important role in the motivation for a reinforcer. As but one example, in operant situations, reinforcers received intermittently are slower to extinguish than reinforcers that are continuously reinforced (e.g. Chan & Harris, 2017). Exposure frequency has also been shown to exert major influences on escalation of drug intake, a phenomenon particularly well studied with stimulant drugs. For instance, Allain and associates (2015) cited evidence for the importance of intermittency (as well as the rapidity of the rise in psychostimulant levels) for inducing sensitization and increasing motivation to escalate drug use over time, concluding that frequency and speed may be more important than overall amount of drug exposure per se for inducing long-term, addictive-like effects. Indeed, intermittent access, though typically resulting in less overall drug exposure, characteristically induces more sensitization and greater escalation of intake of drugs such as cocaine than more continuous access procedures (e.g. Kawa et al, 2016). In such studies of exposure frequency effects, the emphasis has largely been on psychostimulants (e.g., Kawa et al, 2019), although in early work, Post (1980) reviewed evidence showing sensitization with intermittent exposure to a variety of drugs, with tolerance more likely to emerge upon continuous exposure.

Intermittent access is one of the procedures that have been used as a strategy to elevate EtOH consumption in rodents (see Becker, 2013). This emphasis on IAA has been based in part on recognition that this exposure model better emulates the episodic nature of human EtOH use than CAA, given that EtOH consumption in humans is typically characterized by complete EtOH clearance between periods of re-exposure. As but one example, a NIAAA-funded consortium tasked with using animal models to assess effects of chronic adolescent EtOH exposure on later neurobehavioral function targeted IAA models tor examination due to greater comparability to human patterns of use (see Crews et al, 2019).

The enhancing effects of intermittency on EtOH consumption were first reported 45+ years ago (Wayner et al, 1972; Wise, 1973), with a dozen or so research groups now having reported intermittency-related elevations in EtOH intake over more continuous access (see Table 1). However, intermittency per se often does not induce dependency although (as discussed later) some procedures, including extended months of IAA access, have produced signs of dependency in some cases (Hopf et al,2010; Spoelder et al, 2017). Another strategy of particular interest is the drinking-in-the dark (DID) procedure where animals are given 2–4 hrs. of access to EtOH (either alone or with water access as well) typically beginning several hrs after the onset of the dark cycle (e.g., Rhodes et al, 2005; Lesscher et,al, 2010; Wilcox et al, 2014; Chen et al, 2015). Repeated DID access to EtOH has been shown to be sufficient to induce signs of dependency (e.g., inflexible and indifferent EtOH drinking) in some instances (Lesscher et al, 2010). While DID has proved very useful as a model of IAA that produces high exposure levels, there is no seemingly comparable CAA comparison group. Hence, DID studies will not be a focus of this mini-review which has the goal of comparing and contrasting the effects of IAA and CAA per se on EtOH intake and other measures. Such IAA/CAA comparisons are needed to determine whether IAA effects are a function of amount of prior EtOH exposure or a function of intermittency per se – issues critical for assessing potential contributors to and consequences of intermittency for elevated EtOH use and potential later problematic use.

Evidence for intermittency effects on EtOH consumption:

The results of studies comparing the effects of IAA and CAA on intake are summarized in Table 1. Most of these articles used voluntary 2 bottle choice (2BC) procedures either provided every other day (for IAA) or continuously (CAA). In all of these instances (except in one case where IAA and CAA were not directly compared – Priddy et al, 2017), intake of the IAA animals was significantly greater than that of CAA animals). Two studies used a within-subject design, with subjects receiving 2BC access via CAA prior to IAA (Sinclair, 1979; Priddy et al, 2017); although these findings were consistent with cross-sectional studies, it is possible that exposure time-course could have contributed to these sequential effects. Greater intake in IAA than CAA rats was also evident in a study using much shorter, ~ 30 min. daily test sessions where the insertion of a sipper tube was provided and withdrawn during 25 short sipper tube access periods (IAA-like) or was given continuously (CAA-like) during the session (Tomie et al, 2006). While most studies have used voluntary EtOH access procedures, a study using intermittent forced vapor exposure provided on a 14 hr on/10 hr off schedule for 4 weeks was also found to induce greater EtOH consumption than when the vapor was provided continuously for 2 weeks (O'Dell et al, 2004). A notable exception to studies finding IAA/CAA differences was one negative finding where there were no notable differences between mice allowed EtOH access via DID for 4 hr. daily (more CAA-like) or only on M,W,F (more reminiscent of IAA procedures) (Crabbe et al, 2012).

IAA/CAA effects on intake have been seen in both rats (10 of the studies listed in Table 1) and mice (5 of the 6 listed studies). Typically, animals were singly housed, with males and adults being examined. Exceptions include a study by Osterndorff-Kahanek et al, (2013) where only females were examined and work by Mendelez (2011) that examined both adolescent and adult mice and observed more pronounced IAA/CAA intake differences in adolescents. C57BL/6J (C57) mice and Wistar (W) rats have been the most frequently used in IAA/CAA intake studies, although other strains and lines have been used as well (see Table 1).

In studies comparing animals of different strains or lines, some strain- or line-specific outcomes have been reported (e.g., Rossenwasser et al, 2013). For example, Simms et al (2008), gave IAA rats free access to 20% EtOH on Mondays, Wednesdays, and Fridays and CAA rats access continuously and reported greater EtOH consumption in IAA than CAA animals in both Long-Evans (LE) and W rats, but not notably in EtOH-preferring (P) rats. There is also, however, some data suggesting the converse – i.e., that higher drinking lines or rodents selected for high drinking may show greater IAA/CAA intake effects than their lower drinking counterparts (Sinclair, 1979; Spoelder et al, 2015). Thus, despite some genetic differences in observed effects, collectively the available data provide compelling evidence that EtOH intake of animals on an IAA schedule is generally greater than on a CAA schedule across a variety of circumstances. It bears emphasizing, however, that intermittency effects are not inevitable, with the magnitude of the increases in EtOH intake (Rosenwasser et al, 2013) and whether such increases are evident at all (e.g., Sinclair, 1979; Simms et al, 2008; Crabbe et al, 2012) influenced by genotype and other factors, including prior stressor exposure (Hwa et al,2015).

Moreover, it should be noted that the 2BC procedure often used in these studies does not typically induce signs of dependency. Intriguingly, however, under some circumstances – especially when IAA access was provided for an extended period of time, signs of loss of control over intake have been reported when indexed for example via physical signs of withdrawal, higher progressive ratio breakpoints for EtOH, attenuated sensitivity to quinine adulteration or reduced conditioned suppression of EtOH seeking -- e.g., see Vendruscolo & Roberts, 2014). For example, there are reports of signs of dependency emerging after extended (3–4 months) but not shorter (1.5–2 months) periods of intermittent access (Hopf et al,2010; Spoelder et al, 2017). In both the Spoelder et al (2017) study and in work by Augier and colleagues (2018), specific subgroups of rats were chosen for study based either on those that drank moderate levels of EtOH (Spoelder et al, 2017) or that chose to continue to self-administer EtOH at the expense of an alternative, highly rewarding reinforcer (Angier et al, 2018). Although these studies used orally self-administered EtOH, more typically, studies modeling various aspects of dependency have used forced exposure via repeated vapor or EtOH in the diet (e.g., see Gilpin et al, 2009), with Griffin et al (2009) finding that only vapor inhalation procedures resulting in sustained blood alcohol levels of >175 mg% were sufficient to escalate drinking. In addition to vapor models involving forced exposure, de Guglielmo and colleagues (2017) recently developed a voluntary vapor exposure model where clear signs of dependency emerged in rats allowed to intermittently self-administer EtOH on a schedule that escalated over time. Given that studies of dependency using vapor models have focused on intermittent exposure alone, they will not be discussed further in this mini-review comparing IAA and CAA effects.

Possible mechanisms underlying the enhanced EtOH intake induced by IAA relative to CAA models:

Arousal.

In one of the first articles to report intake comparisons between animals given IAA or CAA, Wayner and colleagues (1972) observed greater EtOH intake with intermittency; this effect, however, was also evident with quinine and saccharin. Increased saccharin consumption after intermittent exposure in rats was also reported by Pinel & Huang (1976). Intermittency-associated increases were hypothesized by Wayner et al (1972) to be a function of deprivation-induced increases in arousal, given that similar elevations were also sometimes seen following periodic periods of food or water deprivation. Other researchers have reported, however, that increases in intake following intermittent exposure are specific to EtOH and not evident with other substances (e.g., sucaryl: Sinclair & Senter, 1968; saccharin: O'Dell et al, 2004) – such findings do not support a simple arousal hypothesis.

Sensitization/incentive-salience and the EtOH deprivation effect (ADE).

Sensitization has been studied most often with stimulants where intermittency has been reported to increase incentive salience and potentially elevate later addiction-related behavior. Sensitization, however, is highly unlikely to play a necessary role in the elevated intake in IAA animals given that EtOH intermittency effects are evident in both rats and mice whereas sensitization to EtOH is characteristic only of mice and not rats (e.g., Masur et

al, 1986; although see Hoshaw & Lewis, 2001, for a rare report of EtOH sensitization in male Sprague-Dawley (SD) rats).

ADE is an increase in voluntary intake of EtOH after a period of EtOH deprivation following a relatively long interval (weeks to months) of EtOH exposure. This effect is unlikely to contribute to IAA and CAA differences due to the long period of pre-deprivation access required to induce the ADE, the transient nature of the increase observed, and the emergence of this effect with both intermittent and continuous EtOH exposures (Sinclair, 1979; Sinclair & Senter, 1968).

Acute withdrawal precipitated alterations and kindling.

Abstinence from a drug can result in an increase in reward threshold that may be evident even following initial drug exposure and which has been viewed as a sign of acute withdrawal; this increase in affective/hedonic withdrawal can elevate subsequent use and builds over repeated exposures (see Koob, 2015, for review). Like other drugs of abuse, this response also emerges with repeated episodes of withdrawal from EtOH (Schulteis & Liu, 2006), with this escalation of withdrawal symptoms (e.g., induction of negative affect and induction of seizures) postulated to be akin to those produced by “kindling” (e.g., Ballenger & Post, 1978; Breese et al, 2005). Kindling, however, is unlikely to be related to IAA/CAA 2BC intake differences given that kindling is associated with chronic repeated exposure and withdrawal from high levels of ETOH that are not characteristic of EtOH intake in 2BC studies. The timing of kindling and IAA is also different. Kindling after EtOH exposure greatest after approximately 24 hour separations between exposures whereas IAA effects are not restricted to this timing, with much shorter (Tomie et al, 2006) as well as longer EtOH-free periods inducing IAA-related increases in intake (see Table 1).

Possible conditioning effects, including attenuated conditioned taste aversions (CTA).

Tomie and colleagues (2006) used intermittent or continuous access to a sipper tube containing EtOH, and discussed a number of possible learning-based explanations for the greater intake in the intermittent access rats, including Pavlovian autoshaping, schedule-induced polydipsia and other schedule-induction procedures (see also Becker, 2013, for review of these and other models). In a study examining EtOH CTAs in male C3H mice exposed to EtOH via vapor either continuously for 64 hours or intermittently (4 sessions of 16 hours separated by 8 hours), attenuated sensitivity to the aversive effects of EtOH was found to be more pronounced in intermittent than continuously exposed mice (Diaz-Granados & Graham, 2007). They suggested that such attenuated aversive effects could permit/encourage the increases in EtOH preference/consumption seen with IAA. Consistent with this interpretation, a recent study by Crabbe and colleagues (2019) found that animals bred for high levels of drinking-in-the-dark (HDID) were less sensitive to the aversive effects of EtOH, results leading the authors to suggest that HDID mice may drink more EtOH in part due to an attenuation in their genetic sensitivity to EtOH’s aversive effects (Crabbe et al, 2019).

Potential Neurobiological contributors to IAA/CAA differences

While a diversity of studies has examined neural changes associated with repeated EtOH exposure (e.g., see Becker, 2013, for review), few have included comparable IAA/CAA groups for examination. In the studies that have included such comparisons, the most prevalent neural differences seen between IAA and CAA animals are in the glutamate/NMDA system. Indeed, alterations in glutamate neurotransmission have been consistently associated with the transition from moderate to heavy drinking, with a shift from metabotrophic to glutamate NMDA receptor-mediated effects and increases in **NR2B receptors** especially emphasized (see Goodwani et al, 2017, for discussion). Acamprosate, a drug with complex mechanisms of action that likely include serving as a partial glutamate antagonist and GABA agonist (but with actions on other systems as well), was reported to decrease drinking under intermitttent but not continuous conditions (Simms et al, 2008). Likewise, intermittent but not continuous vapor exposure was reported to increase temporal summation of NMDAR-mediated EPSCs in C57 male mice that was associated with an increase in NR2B-containing NMDARs in the ventral portion of the bed nucleus of the stria terminalis (vBNST), concluding that multiple withdrawals were necessary to induce sensitization of these vBNST receptors (Kash et al, 2009). Cell culture studies have also revealed effects of IAA on the NMDA receptor system. In cultured cells, NR2B receptor expression was increased after IAA more so than CAA, with less pronounced effects on GABAA receptors (Rani & Ticku, 2006). In other cell culture work, Reynolds and colleagues found that an NMDA antagonist blocked withdrawal-related IAA-induced neurotoxicity while having no effect in cultures of CAA animals (Reynolds et al, 2015).

IAA/CAA differences have been reported with other neurotransmitter systems as well. Different patterns of gene expression have been reported between female C57 mice exposed to IAA versus CAA in networks involving **dopamine (DA)**-related genes (e.g. DRD1; DRD2), although similar changes were also sometimes evident in females exposed only to lipopolysaccharide-induced immune activation (Osterndorff-Kahanek et al, 2013). A **CRF1** antagonist infused into the ventral tegmental nucleus or the dorsal raphe decreased EtOH intake in C57 male mice given IAA (2 bottle choice access every other day for 4 weeks), with no drug effect in CAA mice (Hwa et al, 2015; 2016). Work by Logrip et al (2015) focused on differences in **BDNF** mRNA expression after dissimilar patterns of EtOH access, with CAA-like daily, continuous 2 bottle-access to EtOH for 4 weeks (consumption that generated EtOH intakes < 80 mg%) increasing BDNF levels in dl-striatum and decreasing EtOH drinking. In contrast,6 weeks of daily 4 hour limited access periods (reminiscent of IAA) that induced blood EtOH levels >80 mg% and elevated EtOH self-administration was found to decrease BDNF mRNA levels in medial prefrontal cortex but had no effect in dorsal striatum. The differing effects of IAA and CAA in this study, of course, could be related at least in part to amount or frequency of exposure rather than intermittency per se. The **opiate** antagonist naltrexone was reported to suppress drinking in C57 mice when the drug was infused into the dorsal (but not medial) raphe of IAA but not CAA animals (Hwa et al, 2016).

A couple of other studies have focused on regions of the nervous system differentially affected by IAA and CAA. Lundqvist and colleagues (1994) gave male W rats IAA (3 g/kg

EtOH intraperitoneally 2 times/day for ~ 1 month) or CAA (20% EtOH in drinking water [1 bottle only available] for ~ 1 month). In this study, only rats exposed to IAA exhibited a reduction in number of synapses in the CA3 region of the **hippocampus (HPC)**, even though total EtOH exposure was greater in the CAA than IAA group (Lundqvist et al, 1994). Of course, interpretation of these data in terms of IAA/CAA differences is complicated by the different routes of EtOH exposure used between the groups. A cell culture study also observed alterations in HPC neurotoxicity in IAA but not CAA preparations, effects blocked by an NMDA antagonist (Reynolds et al, 2015). Riikonen and colleagues (1999) used M,T,Th,F (IAA) or continuous (CAA) access to 1 bottle containing EtOH, and observed a decrease in **sympathetic neurons** in the superior cervical ganglia after IAA but not CAA.

Conclusions and Implications

The evidence is compelling that intermittent exposure to EtOH often induces greater increases in EtOH intake and more pronounced neural alterations than relatively continuous exposure. These effects are seen in both rats and mice of a variety of strains/lines and have been most typically studied using 2BC procedures. A variety of neural differences have been reported, with the most definitive evidence to date in terms of alterations in the glutamate/NMDAR system, particularly with regard to greater expression of the NR2B NMDA receptor subunit that has been consistently observed in intermittently relative to continuously exposed animals.

There are numerous gaps in our current understanding of IAA/CAA effects:

Few studies have compared IAA and CAA on behaviors other than intake.

Pohorecky and Roberts (1991) used intermittent (3 days on; 3 days off) or continuous intragastric infusions and observed that male, singly housed Sprague-Dawley rats given IAA exhibited less tolerance but greater withdrawal from EtOH than CAA. As discussed earlier, Diaz-Granados & Graham (2007) reported that intermittent forced vapor exposure to EtOH during adolescence resulted in greater attenuation of EtOH CTA than when vapor exposure was given continuously. Crabbe et al (2019) observed that high drinking in the dark (HDID) mice were less sensitive to the aversive effects of EtOH than mice from the founder stock that were not selected for high drinking. It is possible that these reports of attenuated CTA could be related to the increases in NMDA receptors associated with intermittent administration given that Bienkowski et al (1998) observed an inverse relationship between EtOH CTA and NR2B receptor activation.

In terms of non-EtOH challenge effects, social interaction deficits were reported by Wills et al (1999) after an IAA pattern of dietary exposure to EtOH (5 days on; 2 off – repeated 3 times) but not CAA (diet for 15 days continuously) in both adolescent- and adult-exposed rats, with the deficits lasting longer after adolescent exposure. Potential cognitive differences between consequences of IAA and CAA can be gleaned by comparing two studies conducted by the Savage group (Fernandez et al, 2016; 2017). Although similar, but not identical measures were used across studies, comparisons across these two publications support the suggestion that effects of CAA (continuous forced exposure in drinking water) (Fernandez et al, 2016) may be less pronounced than IAA (intragastric EtOH on a 2 day on,

2 day off schedule) (Fernandez et al, 2017) on learning and behavioral flexibility. These contrasting findings could, of course, be related in part to the different routes of EtOH administration, time of year, or other potential alterations rather than pattern of exposure per se, and hence interpretations drawn from comparing these two studies should be tempered accordingly.

More work is needed exploring mechanisms underlying IAA/CAA effects.

Studies exploring molecular, cellular and neuroanatomical alterations in specific brain regions are of particular importance. Little is known about the relative peak blood EtOH levels reached with these two types of exposure frequencies and whether this could potentially contribute to observed effects.

The study of consequences of IAA/CAA on EtOH effects beyond intake is limited.

One critical question that has been little explored is the extent to which differences between the effects of IAA versus CAA extend beyond measures of EtOH intake. As discussed above, this has begun to be explored, but the critical question of whether IAA might potentiate intake via attenuating undesired effects of EtOH (see CTA discussion above) and/or via increasing EtOH's rewarding effects (and the neural substrates of these effects) remains to be investigated systematically.

Stressors, housing, and other environmental variables have not typically been considered.

Effects of potentially critical variables such as housing have not been systematically explored, with the most common procedure used in IAA/CAA studies being 2BC access conducted in singly housed animals (see Table 1). The latter is likely due in large part to the greater ease of single housing for monitoring ethanol consumption in individual animals, but limits interpretability to isolated animals.

Focus of the studies to date has been on males.

With few exceptions, studies examining IAA/CAA effects in rats and mice have been conducted in males. One exception is the study by Osterndorff-Kahanek et al (2013) mentioned earlier where only female mice were used. There is also a recent study where both male and female SD and W rats were compared for EtOH intake under IAA and CAA conditions (Priddy et al, 2017). As is often the case, EtOH intake of females was found to be greater than that of males – an effect evident in both strains with voluntary home cage access drinking and uninfluenced by estrous cycle. However, when work (i.e., lever pressing) was required for EtOH access, intake differences across sex were no longer evident. Crabbe et al (2012) examined both male and female, group-housed C57 and HDID mice in a DID study and found few IAA and CAA differences in either strain or sex.

Investigation of IAA/CAA in other than adult animals is limited.

Few articles have explored possible age-dependency of IAA/CAA effects, although intermittency has been suggested to be important in fetal exposure studies (see Lundqvist et al, 1994, for discussion) and intermittency effects have been reported to be more pronounced in adolescent than adult C57 mice (Melendez, 2011). There is also some initial evidence that

consequences of IAA and CAA may differ in the aged brain from that of the adult brain (Reynolds et al, 2015). Clearly more work examining the expression of intermittency effects throughout the lifespan is warranted.

Collectively, future studies examining these little explored areas would help determine contributors to intermittency-related escalations in EtOH intake exposure and their potential consequences for later problematic EtOH use/abuse. Such insights could be of considerable value in the development of new prevention and intervention strategies.

Acknowledgements

Preparation of this MS was supported by the National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health under Award Numbers **P50AA017823** and **U01AA19972-NADIA Project**. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

Allain F, Minogianis E-A, Roberts DCS, Samaha A-N (2015) How fast and how often: the pharmacokinetics of drug use are decisive in addiction. Neurosci Biobehav Rev 56:166–79. [PubMed: 26116543]

Augier E, Barbier E, Dulman RS, Licheri V, Augier G, Domi E, Barchiesi R, Farris S, Natt D, Mayfield D, Aldermark L, Heilig M (2018) A molecular mechanism for choosing alcohol over an alternative reward. Science 360:1321–1326. [PubMed: 29930131]

Ballenger JC, Post RM (1978) Kindling as a model for alcohol withdrawal symptoms. Brit J Psychiat 133:1–14.

Becker HC (2013) Animal models of excessive alcohol consumption in rodents. Curr Topics Behav Neurosci 13:355–77.

Bienkowski P, Koros E, Piasecki J, Kostowski W (1998) Prior exposure to MK-801 sensitizes rats to ethanol-induced conditioned taste aversion. Alcohol Alcoholism 33(2):116–120. [PubMed: 9566472]

Breese GR, Overstreet DH, Knapp DK (2005) Conceptual framework for the etiology of alcoholism: a “kindling”/stress hypothesis. Psychopharmacology (Berl) 178(4):367–380. [PubMed: 15765253]

Chan CKJ, Harris JA (2017) Extinction of Pavlovian conditioning: the influence of trial number and reinforcement history. Behav Processes 131(Pt 1):19–25.

Chen H, Donghong He MS, Lasek AW (2015) Repeated binge drinking increases perineuronal nets in the insular cortex, Alcohol Clin Exp Res 39(10):1930–1938. [PubMed: 26332441]

Crabbe JC, Harkness JH, Spence SE, Huang LC, Metten P (2012) Intermittent availability of ethanol does not always lead to elevated drinking in mice. Alcohol Alcoholism 47(5):509–17. [PubMed: 22717273]

Crabbe JC, Savarese AM, Ozburn AR, Schlumbohm JP, Spence SE, Hack WR (2019) Ethanol conditioned taste aversion in high drinking in the dark mice. Brain Sci 9(1):1–15.

Crews FT, Robinson DL, Chandler LJ, Ehlers CL, Mulholland PJ, Pandey SC, Rodd ZA, Spear LP, Swartzwelder HS, Vetereno RP (2019) Mechanisms of persistent neurobiological changes following adolescent alcohol exposure: NADIA Consortium findings. Alcohol Clin Exp Res 43(9):1806–22. [PubMed: 31335972]

de Guglielmo G, Kallupi M, Cole MD, George O (2017) Voluntary induction and maintenance of alcohol depepdence in rats using alcohol vapor self-administration. Psychopharmacology (Berl) 234(13):2009–2018. [PubMed: 28342089]

Diaz-Granados JL, Graham DL (2007) The effects of continuous and intermittent ethanol exposure in adolescence on the aversive properties of ethanol during adulthood. Alcohol Clin Exp Res 31(12):2020–27. [PubMed: 18034694]

Fernandez GM, Lew BJ, Vedder LC, Savage LM (2017) Chronic intermittent ethanol exposure leads to alterations in brain-derived neurotrophic factor within the frontal cortex and impaired behavioral flexibility in both adolescent and adult rats. Neuroscience 348:324–34. [PubMed: 28257889]

Fernandez GM, Stewart WN, Savage LM (2016) Chronic drinking during adolescence predisposes the adult rat for continued heavy drinking: neurotrophin and behavioral adaptation after long-term, continuous ethanol exposure. PLoS One 11(3):e0149987. [PubMed: 26930631]

Gilpin NW, Smith AD, Cole M, Weiss F, Koob GF, Richardson R (2009) Operant behavior and alcohol levels in blood and brain of alcohol-dependent rats. Alcohol Clin Exp Pres, 33(12);2113–2123.

Griffin WC III, Lopez MF, Becker HC (2009) Intensity and duration of chronic ethanol exposure is critical for subsequent escalation of voluntary ethanol drinking in mice. Alcohol Clin Exp Res 33(11):1893–1900. [PubMed: 19673744]

Goodwani S, Saternos H, Alasmari F, Sari Y (2017) Metabotropic and lonotropic glutamate receptors as potential targets for the treatment of alcohol use disorder. Neurosci Biobehav Rev 77:14–31. [PubMed: 28242339]

Hopf FW, Chang S-J, Sparta DR, Bowers MS, Bonci A (2010) Motivation for alcohol becomes resistant to quinine adulteration after 3–4 months of intermittent alcohol self-administration. Alcohol Clin Exp Res 34(9)1565–1573. [PubMed: 20586757]

Hwa LS, Chu A, Levinson SA, Kayyali TM, DeBold JK, Miczek KA (2011) Persistent escalation of alcohol drinking in C57BL/6J mice with intermittent access to 20% ethanol. Alcohol Clin Exp Res 35(11):1938–1947. [PubMed: 21631540]

Hwa L, Holly EN, DeBold JF, Miczek KA (2015) Social stress-escalated intermittent alcohol drinking: modulation by CRF-R1 in the ventral tegmental area and accumbal dopamine in mice. Psychopharmacology (Berl) 233(4):681–90. [PubMed: 26576941]

Hwa L, Shimamato A, Kayyall T, Norman KJ, Valentine RJ, DeBold JF, Miczek KA (2016) Dissociation of mu opioid receptor and CRF-R1 antagonist effects on escalated ethanol consumption and mPFC serotonin in C57BL/6J mice. Addict Biol 21(1):111–24. [PubMed: 25262980]

Hoshaw BA, Lewis MJ (2001) Behavioral sensitization to ethanol in rats: evidence from the Sprague-Dawley strain. Pharmacol Biochem Behav 68:685–90. [PubMed: 11526965]

Kash TL, Baucum AJ II, Conrad KL, Colbran RJ, Winder DG (2009) Alcohol exposure alters NMDAR function in the bed nucleus of the stria terminalis. Neuropsychopharmacology 34(11):2420–29. [PubMed: 19553918]

Kawa AB, Allain F, Robinson TE, Samaha A-N (2019) The transition to cocaine addiction: the importance of pharmacokinetics for preclinical models. Psychopharmacology 236: 1145–57. [PubMed: 30820634]

Kawa AB, Bentzley BS, Robinson TE (2016) Less is more: prolonged intermittent access cocaine self-administration produces incentive-sensitization and addiction-like behavior. Psychopharmacology 233:3587–3602. [PubMed: 27481050]

Kimbrough A, Kim S, Cole M, Brennan M, George O (2017) Intermittent access to ethanol drinking facilitates the transition to excessive drinking after chronic intermittent ethanol vapor exposure. Alcohol Clin Exp Res 41(8):1502–09. [PubMed: 28679148]

Koob GF (2015) The dark side of emotion: the addiction perspective. Eur J Pharmacol 753:73–87. [PubMed: 25583178]

Lesscher HM, van Kerhof LW, Vanderschuren LJ (2010) Inflexible and indifferent alcohol drinking in male mice. Alcohol Clin Exp Res 34(7):1219–1225. [PubMed: 20477770]

Logrip ML, Barak S, Warnault V, Ron D (2015) Corticostriatal BDNF and alcohol addiction. Brain Res 1628:60–67. [PubMed: 25801118]

Lundquist C, Volk B, Knoth R, Alling C (1994) Long-term effects of intermittent versus continuous ethanol exposure on hippocampal synapses of the rat. Acta Neuropathol 87:242–49. [PubMed: 8009956]

Masur J, Oliveira de Souza ML, Zwicker AP (1986) The excitatory effect of ethanol: absence in rats, no tolerance and increased sensitivity in mice. Pharmacol Biochem Behav 24(5): 1225–28. [PubMed: 3725828]

Melendez RI (2011) Intermittent (every-other-day) drinking induces rapid escalation of ethanol intake and preference in adolescent and adult C57BL/6J mice. Alcohol Clin Exp Res 35(4):652–58. [PubMed: 21223302]

O'Dell LE, Roberts AJ, Smith RT, Koob GF (2004) Enhanced alcohol self-administration after intermittent versus continuous alcohol vapor exposure. Alcohol Clin Exp Res 28(11):1676–82. [PubMed: 15547454]

Osterndroff-Kahanek E, Ponomarev I, Blednov YA, Harris RA (2013) Gene expression in brain and liver produced by three different regimens of alcohol consumption in mice: comparison with immune activation. PloS One 8(3):e59870. [PubMed: 23555817]

Pinel JP, Huang E (1976) Effects of periodic withdrawal on ethanol and saccharin selection in rats. Physiol Behav 16(6):693–98. [PubMed: 981364]

Pohorecky LA, Roberts P (1991) Development of tolerance to and physical dependence on ethanol: daily versus repeated cycles treatment with ethanol. Alcohol Clin Exp Res 15(5):824–33. [PubMed: 1755516]

Post RM (1980) Intermittent versus continuous stimulation: effect of time interval on the development of sensitization or tolerance. Life Sciences 26:1275–82. [PubMed: 6991841]

Priddy BM, Carmack SA, Thomas LC, Vendruscolo JC, Koob GF, Vendruscolo LF (2017) Sex, strain, and estrous cycle influences on alcohol drinking in rats. Pharmacol Biochem Behav 152:61–67. [PubMed: 27498303]

Rani CS, Ticku MK (2006) Comparison of chronic ethanol and chronic intermittent ethanol treatments on the expression of GABA(A) and NMDA receptor subunits. Alcohol 38(2):89–97. [PubMed: 16839855]

Reynolds AR, Barry JN, Sharrett-Field L, Prendergast MA (2015) Ethanol withdrawal is required to produce persisting N-methyl-D-aspartate receptor-dependent hippocampal cytotoxicity during chronic intermittent ethanol exposure. Alcohol 49(3):219–27. [PubMed: 25746220]

Riikonen J, Jaatinen P, Karjala K, Rintala J, Porsti I, Wu X, Erikkson CJ, Hervonen A (1999) Effects of continuous versus intermittent ethanol exposure on rat sympathetic neurons. Alcohol Clin Exp Res 23(7):1245–50. [PubMed: 10443993]

Rhodes JS, Best K, Belknap JK, Finn DA, Crabbe JC (2005) Evaluation of a simple model of ethanol drinking to intoxication in C57BL/6J mice. Physiol Behav 84:53–63. [PubMed: 15642607]

Rossenwasser AM, Fixaris MC, Crabbe JC, Brooks PC, Ascheid S (2013) Escalation of intake under intermittent ethanol access in diverse mouse genotypes. Addict Biol 18(3):496–507. [PubMed: 22862671]

Schulteis G, Liu J (2006) Brain reward deficits accompany withdrawal (hangover) from acute ethanol in rats. Alcohol 39(1):21–8. [PubMed: 16938626]

Pohorecky JA, Steensland P, Medina B, Abernathy KE, Chandler LJ, Wise R, Bartlett SE (2008) Intermittent access to 20% ethanol induces high ethanol consumption in Long-Evans and Wistar rats. Alcohol Clin Exp Res 32(10):1816–23. [PubMed: 18671810]

Sinclair JD (1979) Alcohol-deprivation effect in rats genetically selected for their ethanol preference. Pharmacol Biochem Behav 10(4):597–602. [PubMed: 572554]

Sinclair JD, Senter BJ (1968) Development of an alcohol-deprivation effect in rats. Q J Stud Alcohol 29(4):863–67. [PubMed: 5705408]

Spoelder M, Hesseling P, Baars AM, Lozeman-van't Klooster, Rotte MD, Vanderschuren LJMJ, Lesscher HMB (2015) Individual variation in alcohol intake predicts reinforcement, motivation, and compulsive alcohol use in rats. Alcohol Clin Exp Res 39(12):2427–37. [PubMed: 26745576]

Spoelder M, Pol S, Janssen BSG, Baars AM, Vanderschuren LJMJ, Lesscher HMB (2017) Loss of control over alcohol seeking in rats depends on individual vulnerability and duration of alcohol consumption experience. Behav Pharmacol 28(5):334–344. [PubMed: 28418943]

Tomie A, Miller WC, Dranoff E, Pohorecky LA (2006) Intermittent presentations of ethanol sipper tube induce ethanol drinking in rats. Alcohol Alcohol 41(3):225–30. [PubMed: 16476763]

Vendruscolo LF, Roberts AJ (2014) Operant alcohol self-administration in dependent rats: focus on the vapor model. Alcohol 48(3):277–286. [PubMed: 24290310]

Wayner MJ, Greenberg I, Tartaglione R, Nolley D, Fraley S, Cott A (1972) A new factor affecting the consumption of ethyl alcohol and other sapid fluids. Physiol Behav 8:345–62. [PubMed: 4665346]

Wilcox MV, Cuzon Carlson VC, Sherazee N, Sprow GM, Bock R, Thiele TE, Lovinger DM, Alvarez VA (2014) Repeated binge-like ethanol drinking alters ethanol drinking patterns and depresses striatal GABAergic transmission. Neuropsychopharmacology, 39:579–594.

Wills TA, Knapp DJ, Overstreet DH, Breese GR (2009) Sensitization, duration, and pharmacological blockade of anxiety-like behavior following repeated ethanol withdrawal in adolescent and adult rats. Alcohol Clin Exp Res 33(3):455–63. [PubMed: 19120055]

Wise RA (1973) Voluntary ethanol intake in rats following exposure to ethanol on various schedules. Psychopharmacology (Berl) 29:203–10.

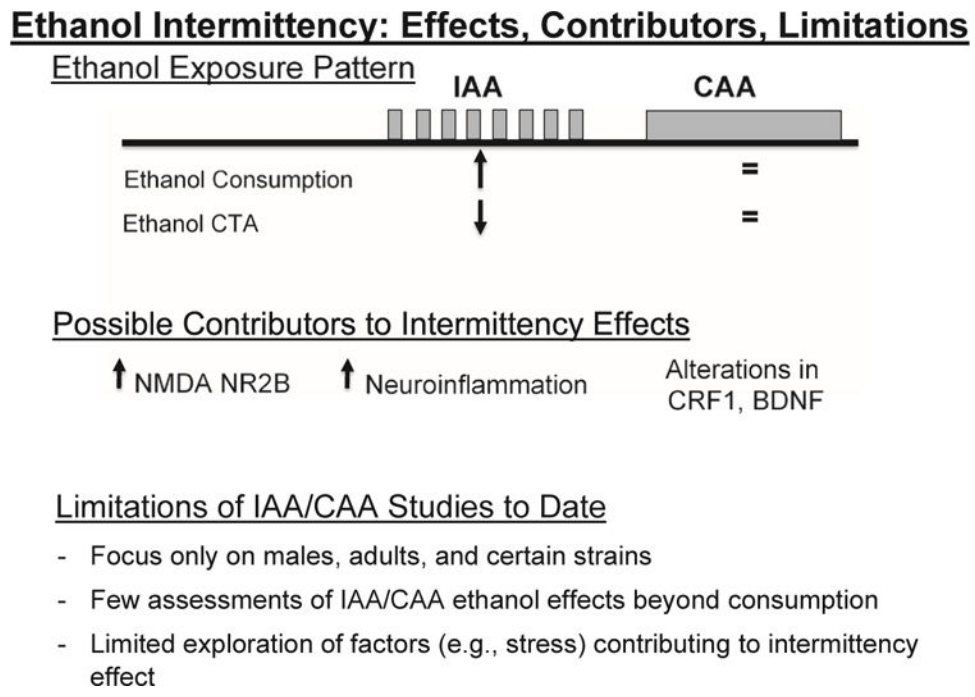

Figure 1:
Intake data—IAA versus CAA.

Table 1.

Comparison of levels of Alcohol Intake under Intermittent (IAA) and Continuous (CAA) Access Conditions

Author(s)	IAA Model	CAA Model	Route: light/ dark	Strain/species	Sex/housing	Intake Findings
Crabbe et al (2012)	4 hr DID M,W,F	4 hr DID daily	dark	C57 + HDID mice	M/F group	Mostly no IAA/CAA diff, although modest IAA drinking increase in C57
Hopf et al (2010)	M,W,F 2BC	cont 2BC	n.a.	Wistar rats	M indiv	IAA>CAA intake
Hwa et al (2011)	EOD 2BC	cont 2BC	n.a.	C57 mice	M/F indiv	IAA>CAA intake and preference
Hwa et al (2015)	EOD 2BC	cont 2BC	n.a.	C57 mice	M indiv	IAA>CAA intake and preference; exacerbated by stress
Kimbrough et al (2017)	M,W,F 2BC	cont 2BC	n.a.	Wistar rats	M ?(prob indiv)	IAA>CAA intake
Melendez (2011)	EOD 2BC	cont 2BC	n.a.	C57 mice	M indiv (adoles. & adult)	IAA>CAA intake and preference; adolesc.>adults
Osterndorff-Kahanek et al (2013)	EOD 2BC	cont 2BC	n.a.	C57 mice	F indiv	IAA>CAA intake
Pinel & Huang (1976)	EOD 2BC	cont 2BC	n.a.	Black hooded rats	M indiv	IAA>CAA intake (but also seen with saccharin)
Priddy et al (2017) *	*EOD 2BC (after 25 days cont) + vapor to induce dependence*	*cont 2BC followed by <EOD*	*n.a.*	*Long-Evans and Wistar rats*	*M/F indiv*	*No direct IAA/CAA comparisons*
Simms et al (2008)	EOD 2BC	cont 2BC	n.a.	LE, Wistar, P rats	M indiv	IAA>CAA intake- LE and W rats; little effect P rats
Sinclair (1979) *	*2BC EOD*	*2BC cont for 18 days, then IAA switch*	n.a.	AA/ANA rats	M indiv	AA: IAA>CAA intake; ANA: no intake increase
Spoelder et al (2015)	2BC: 7hr/day M,W,F	cont 2BC	IAA - dark; CAA - n.a.	Listar hooded rats screened for high and low drinkers	M indiv	High drinkers only: IAA>CAA intake + preference
Rossenwasser et al, (2013)	1 or 3 days/wk 2BC	cont 2BC	n.a.	6 different strains of mice	M indiv	IAA>CAA intake & preference but magnit. of effect varied w/genotype
Tomie et al, (2006)	25 trials sipper tube access in 30 min. daily	30 min cont access to EtOH sipper tube daily	Sipper tube; light	LE rats	?sex indiv	IAA>CAA during ~ 30 min daily sessions
Wise (1993)	EOD (1 or 2 bottle)	cont home cage (1 or 2 bottle)	n.a.	Wistar rats	M indiv	IAA>CAA intake & preference

* Italic indicate sequential, within subject study

Alcohol Clin Exp Res. Author manuscript; available in PMC 2021 April 01.

Abbreviations:
2BC – two bottle choice; EOD – every other day; cont -- continuous