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Adaptations underlying the development of excessive alcohol intake in selectively bred mice

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Abstract

This commentary discusses the important contributions of the article in this issue by Matson and colleagues entitled “Selectively bred crossed high-alcohol-preferring mice drink to intoxication and develop functional tolerance, but not locomotor sensitization during free-choice ethanol access” as well as providing comparison to studies on other drugs of abuse. In their study, Matson et al. report that mice derived by crossing different lines selectively bred for high alcohol intake exhibit initial alcohol intakes associated with motor impairment followed by marked escalation of consumption and tolerance to the effects of alcohol on motor coordination. In contrast, no evidence of pharmacokinetic tolerance or sensitization of alcohol-induced locomotion was observed. These results demonstrate that the cHAP mice constitute an appropriate model for the study of excessive drinking which is produced by escalated alcohol intake and functional changes leading to excessive intoxication. Future work should assess adaptations in motivational processes and subjective effects of alcohol as well as the potential genetic and epigenetic bases of escalated alcohol intake.

Keywords

Alcohol; Escalation; Tolerance; Sensitization

Beyond sporadic binge drinking which has recently been recognized as a major health concern for a wide range of individuals, there remains the dramatic impact of extensive, excessive drinking on the health of a smaller number of individuals. Indeed, greater than three quarters of alcoholic beverages sold in the US are consumed by less than a quarter of drinkers (Dawson, 2000) and alcoholics drink to levels of intoxication (200 mg/dl; e.g. Mello & Mendelson, 1970) that are in great excess of the limits of “binge drinking” as defined by National Institute on Alcohol Abuse and Alcoholism (NIAAA). Such consumption is highly detrimental not only through chronic use but also in the more immediate term as evidenced by, for example, high blood ethanol concentrations (BECs) in emergency rooms and driving fatalities. Understanding why individuals drink to dangerous levels, particularly in a chronic fashion, is critical to the development of successful management strategies of their condition.

Animal models are invaluable for determining why individuals drink to excess because of their ability to dissect the impact of subject variables (e.g. alcohol, stress, and social histories, heritability, etc.) and acute situational variables on alcohol intake. Studies in primates are consistent with epidemiological data with a subpopulation becoming “excessive

drinkers”, consuming alcohol in sprees, and achieving BECs in excess of 200 mg/dl (e.g. Grant et al., 2008; Vivian et al 2001), however, these studies are not well suited to detailed elucidation of the nature of individual differences due to their resource intensive nature. Conversely, rodent models (for a recent review see e.g. Becker, 2013) are highly appropriate for large scale, causative studies designed to understand individual variability but, unfortunately, rodents have typically failed to achieve BECs at levels comparable to those of alcoholics. In fact, most rodent models aim to achieve intoxication equivalent to legal intoxication limits (i.e. 80 mg/dl) or NIAAA binge drinking definitions. Although such rodent models are useful for examining the cause and consequences of “heavy” or “binge” drinking they do not appear to recapitulate “excessive drinking” as exhibited by alcoholics.

The study by Matson, Kasten, Boehm, and Grahame in this issue extends recent work by their group on a rodent strain that exhibits excessive alcohol drinking with intakes producing BECs comparable with those of alcoholics. By combining lines of mice selected for high alcohol intake, they have generated a strain with substantially higher intake and BECs than those achieved in other rodent models. Indeed, alcohol-experienced cHAP mice consume on average around 25 g/kg/day and achieve BECs of 200 mg/dl with some individuals reaching BECs of 400 mg/dl. In the present study, they demonstrate that cHAP mice spontaneously drink to a level of intoxication at which motor function is impaired and obtain BECs meeting criteria for binge drinking (averaging around 100 mg/dl), usually during the first session of alcohol exposure. Further, they show that cHAP mice with chronic access to alcohol under two-bottle choice exhibit rapid escalation of alcohol intake starting at approximately 17 mg/kg/day to achieve intakes of around 25 g/kg/day within about 1 week and these levels of intake persist throughout the experiment (Figure 2A). This observed pattern of drinking demonstrate that cHAP mice initially exhibit relatively high intake, achieving BECs comparable to the commonly employed C57BL/6J mice, but the cHAP mice exhibit pronounced self-administration induced escalation during continued alcohol access. A pattern of self-administration induced escalation of intake is important to studying the development of excessive intake because drug-induced plasticity is critically dependent upon the nature of exposure. Specifically, it has been well documented that active self-administration of psychostimulants and opiates induces plasticity that is distinct from that which is observed following passive exposure on molecular, neurochemical, and behavioral measures (e.g. Kippin et al., 2006; LeBlanc et al., 2013; Lecca et al., 2007a; b; Lominac et al., 2012; Stefanski et al, 1999). Accordingly, the cHAP mice offer a novel model to study alcohol-induced escalation of alcohol intake in a fashion analogous to that experienced by alcoholics.

Matson et al. (this issue) also examine plasticity in physiological and behavioral measures that are associated with escalation of alcohol intake in cHAP mice. In two experiments, they observe that cHAP mice with three weeks of alcohol intake exhibit robust and substantial escalation but do not exhibit differences in BECs following an alcohol challenge relative to alcohol-naïve mice indicating that escalation is not associated with pharmacokinetic tolerance. This observation is generally consistent with their prior findings that escalated alcohol intake in cHAP mice is associated with achieving higher BECs. Together these findings have two important implications. First, escalated alcohol intake is not due to a need for increased intake to achieve the same level of intoxication but is actually associated with higher intoxication.

That is the mice get more “drunk”. Second, escalated alcohol intake is due to functional changes, presumably in the nervous system, that permit higher intoxication. To address the nature of the functional changes associated with escalated alcohol consumption, Matson et al. assessed the potential development of tolerance and sensitization to the effect of alcohol of motor coordination and locomotor activity levels. A balance beam task was employed to

measure alcohol impairment of motor coordination and cHAP mice allowed alcohol access quickly developed tolerance on this task, despite exhibiting equivalent BECs as alcohol-naïve mice. Interestingly, the development of tolerance to alcohol motor impairment closely paralleled the development of escalation of alcohol intake suggesting that the two processes may share common biological bases. Conversely, cHAP mice failed to exhibit evidence of sensitized alcohol-induced locomotion following escalation development. These findings support the contention that escalation of alcohol intake is associated with motor tolerance but not locomotor sensitization, however, the nature of the relations between these behavioral processes is not entirely clear. Specifically, the lack of locomotor sensitization does not imply that other types of responses to alcohol are not sensitized and the presence of tolerance to motor impairment does not indicate that other types of responses to alcohol are diminished nor do these findings provide a clear indication of the type(s) of adaptation(s) mediating the escalation of alcohol intake.

Drugs, including alcohol, have multiple effects at the behavioral and molecular levels which undergo dynamic plasticity in an independent fashion. Along these lines, it is difficult to assess if the development of tolerance to the motor impairment is functionally related to the acquisition of escalated drinking. Intuitively, if an individual is too intoxicated to perform the motor requirements necessary to obtain further alcohol then tolerance development to the effect of alcohol on motor coordination may be an antecedent to escalation. Conversely, the concurrent development of two adaptations (i.e. tolerance to motor impairing effects of alcohol and intake escalation) is suggestive of a causal relation but certainly not conclusive.

Along this line, it will be very informative to study potential changes in the subjective properties of alcohol that accompany escalation of alcohol intake. Subjective effects of alcohol (and other stimuli) can be measured by the place conditioning procedure in which one distinctive environment is repeatedly paired with alcohol exposure while another environment is paired with a neutral, control manipulation and the resulting preference or aversion for the alcohol-paired environment indexes the magnitude and valence of the subjective properties of alcohol exposure. Indeed, alcohol has been shown to have both rewarding and aversive properties that can be dissociated (e.g. Cunningham et al., 2003) and the balance of these properties likely determines the levels of alcohol seeking and/or intake. Moreover, given that adaptations to drug effects develop independently, tolerance to one effect of a drug may actually enhance a different effect. In this case, the development of tolerance to the aversive properties would be expected to increase alcohol intake which may appear as sensitization to its rewarding properties. Selective induction of alterations to the rewarding and aversive properties of cocaine has been recently argued to be a critical aspect of changes in cocaine-seeking behavior (e.g. Su et al., 2012) and similar changes may accompany and, potentially mediate, escalation of alcohol intake. For instance, in addition to changes to the effects of alcohol on motor function, escalation is likely to be accompanied by changes in its rewarding properties with shifts in the dose-response curve for conditioned place preferences to potentially the left (reflecting reward tolerance) as well to potentially upward (reflecting reward sensitization). As such, further addressing the relation between tolerance and sensitization to the rewarding effects of alcohol that develops during escalation are necessary to more completely understand the associated adaptations.

In addition to characterizing changes in the motor and subjective effects of alcohol, it will also be important to examine of the adaptations in motivational processes that are associated with escalation of alcohol intake. Some theories of drug and alcohol addiction (for a general review see e.g. Badiani et al., 2011) posit that changes in the motivational properties of the drug or drug-related stimuli are critical to the addiction process as for example in the highly influential incentive salience sensitization theory of addiction (e.g. Berridge et al., 2009). Although locomotor sensitization may co-occur at the same time and be mediated in part by

the same mechanism(s) as incentive salience sensitization, the two processes are not identical. Similar to the current demonstration of dissociation between alcohol intake escalation and sensitization of alcohol-induced locomotion observed in cHAP mice, the escalation of cocaine intake or cocaine-induced reinstatement observed following prolonged daily access has also been dissociated from the sensitization of cocaine-induced locomotion (Ahmed & Cador, 2006; Ben-Shahar et al., 2004; Kippin et al., 2006; see however, Ferrario et al., 2005). Moreover, escalated cocaine intake has repeatedly been shown to be associated with incentive salience sensitization as measured by enhanced drug-seeking behavior and motivational adaptations (for a recent review, see Ahmed, 2012). Together, the findings from the cocaine literature and those of Matson et al (this issue) indicate that the mechanisms underlying cocaine and alcohol intake escalation are likely to involve motivational processes and, thus, it will be highly informative to determine how a history of alcohol exposure changes these processes in cHAP mice.

More generally, the creation of a mouse strain that achieves clinically-relevant levels of intoxication solely through alcohol exposure allows for the analyses of subject factors constituting vulnerability to excessive alcohol intake. Inbred strains have long been essential tools for studying the role of genetics in disease vulnerability and it will be intriguing to see if cHAP mice possess gene variation(s) similar to those observed in human alcoholic populations as well this model will be useful to determine if such genetic differences mediate the adaptations underlying escalation of alcohol intake. However, this model may also be of use in examining the biological bases of vulnerability beyond differences in nucleotide sequence of DNA. There is a growing appreciation that environmental factors can have a contribution to inheritance in the vulnerability to a number of disorders. In fact, strain differences in behavior are mediated in part by environmental factors as demonstrated by embryo transfer and cross-fostering experiments (e.g. Francis et al., 2003). Further, parental intake of drugs of abuse, including alcohol, even outside of the gestational period, produces trans-generational effects mediated by epigenetic mechanisms (for a recent review see Vassoler et al., 2013). Given that the development of the cHAP mouse strain involved alcohol exposure prior to selective breeding, it is of interest to examine both the potential genetic and epigenetic bases of the plasticity supporting their escalation of alcohol intake.

In summary, the cHAP mice constitute a promising model of excessive alcohol intake with high potential relevance to alcoholism. These mice exhibit high levels of initial alcohol consumption, escalation of alcohol intake induced by self-administration, and achieve levels of intoxication similar to those of alcoholics. In particular, the determination of the bases of the functional adaptations mediating escalation of alcohol intake will give insight into the neural pathology associated with alcohol addiction.

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