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Translational dynamics of alcohol tolerance of preclinical models and human laboratory studies

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Abstract

Increasing sensitivity due to alcohol intake has been explored using molecular and cellular mechanisms of sensitization, adaptive biobehavioral changes, and through negative experiences of altered function during withdrawal. However, within both a preclinical and human laboratory setting, little has been elucidated towards understanding the neural substrates of decreased sensitivity to alcohol effects, i.e. alcohol tolerance. More paradigms assessing alcohol tolerance are needed. Tolerance can be assessed through both self-reported response (subjective) and observed measurements (objective). Therefore, sensitivity to alcohol is an exploitable variable that can be utilized to disentangle the diverse alcohol use disorder (AUD) phenotypical profile. This literature review focuses on preclinical models and human laboratory studies to evaluate alcohol tolerance and its modulating factors. Increased understanding of alcohol tolerance has the potential to reduce gaps between preclinical models and human laboratory studies to better evaluate the development of alcohol-related biobehavioral responses. Furthermore, alcohol tolerance can be used as an AUD phenotypic variable in randomized clinical trials (RCTs) designed for developing AUD therapies.

Keywords

Alcohol use disorder; tolerance; human laboratory studies; preclinical models; translational research

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1. Introduction

The desire to consume and the capacity to metabolize alcohol extends deep into human history. Roughly 9000 years ago, humans learned to ferment foods (Schrago, Menezes, Moreira, Pissinatti, & Seuanez, 2012; Steiper & Young, 2006), however, the most ancient form of alcohol dehydrogenase class IV (ADH4), the enzyme in the digestive tract that is capable of metabolizing alcohol, was found in *hominoid* lineage as far back as 70 million years ago (Carrigan et al., 2015).

Increased sensitivity to alcohol has been explored using multiple approaches, including molecular and cellular mechanisms of sensitization (Hoek & Pastorino, 2004), adaptive alcohol-related bio-behavioral changes, and through negative experiences of altered function during withdrawal (Gilpin & Koob, 2008). However, there is limited research aimed at understanding the neural substrates of the decreased sensitivity to alcohol's effects (i.e. alcohol tolerance) within a preclinical and human laboratory setting.

Measuring alcohol tolerance is a complex task, due to the fact that it can be differentiated in a variety of ways; for review see: (Kalant, 1998). For example, *metabolic tolerance* results from the induction of alcohol within metabolizing enzymes resulting in changes in the pharmacokinetic profiles (Ryan et al., 1985). *Acute tolerance* refers to tolerance developed during the alcohol administration procedure (within session), *chronic tolerance* is reached through multiple or prolonged alcohol exposures (between sessions), and *rapid tolerance* is described as the process that occurs after a second alcohol exposure followed by complete clearance of the first dose during which, the second dose is given between 8–24 hours after the initial dose (Khanna, Chau, & Shah, 1996).

Observations conducted on dogs one hundred years ago, revealed a more pronounced alcohol-induced ataxia on the alcohol ascending limb compared to the descending limb (Mellanby, 1919). Decades later, Wistar rats, after a single administration of alcohol (1.0–2.8 g/kg dose), portrayed significant motor function impairment for a given blood level on the falling (descending) compared to the rising (ascending) limb of the blood alcohol curve (LeBlanc, Kalant, & Gibbins, 1975). Interestingly, one of the first models for alcohol use disorder (AUD) was based upon the fact that, after alcohol withdrawal, rats who were injected with alcohol were much less responsive to subsequent injection of alcohol compared to control rats who were previously exposed only to water (Cicero, Snider, Perez, & Swanson, 1971). This early model demonstrated that it is possible to test the classic criteria signifying AUD by evaluating physical dependence and tolerance to alcohol. In humans, tolerance can be assessed by both self-reported responses and objective measurements. As such, it represents an exploitable variable in the field of alcohol research. Alcohol tolerance can be utilized towards understanding the complex AUD phenotype and developing novel pharmacotherapies (Haass-Koffler & Perciballi, 2020).

2. Functional, metabolic and cross tolerance

Tolerance to alcohol can result from pharmacodynamic and/or pharmacokinetic effects. Pharmacodynamic (or functional) tolerance refers to neurobiological and/or neurochemical

adaptations that reduce functional impairment (i.e. cognitive and motor). In addition to CNS adaptation, chronic alcohol consumption leads to metabolic adaptation, which is characterized by an increase in alcohol metabolism and rate of blood alcohol clearance in individuals without liver disease (Cederbaum, 2012). In brief, the disposition of alcohol (as for any other xenobiotic) is characterized by four criteria: absorption, distribution, metabolism and excretion (ADME); for extensive review see: (Jones, 2019). Metabolic tolerance refers to changes in alcohol pharmacokinetic effects due to changes in metabolism and elimination (B. Tabakoff, Cornell, & Hoffman, 1986).

First pass metabolism of alcohol occurs in the stomach and liver (Lim et al., 1993). A small part portion of ingested alcohol undergoes oxidation in the stomach and will not enter into the systemic circulation (Cederbaum, 2012). The liver is primarily responsible for the rate of enzymatic oxidation during first pass metabolism (Swift, 2003), however, it is import to know that first pass metabolism of alcohol is determined by the speed of gastric emptying (Oneta et al., 1998).

Some of the suggested mechanisms leading to metabolic tolerance to alcohol includes induction of alcohol dehydrogenase (ADH), induction of cytochrome P450 2E1 (CYP2E1), increased re-oxidation of nicotinamide adenine dinucleotide (NADH) by mitochondria, increased cytokines, and hypoxia of hepatocytes (origin of alcohol toxicity) (Cederbaum, 2012). Also, alteration of alcohol elimination rates may contribute to the development of metabolic tolerance. The major enzyme for metabolizing alcohol, hepatic alcohol dehydrogenase, produces acetaldehyde (and NADH) which is further oxidized to acetate. Chronic alcohol consumption decreases acetaldehyde oxidation, either due to decreased aldehyde dehydrogenase 2 Family Member (ALDH2) activity or impaired mitochondrial function. As a result, metabolic adaptation, characterized by elevated circulating levels of acetaldehyde, observed in individuals with AUD may result in an increased production and or decreased removal of acetaldehyde. Additionally, oxidation of alcohol by CYP2E1 are induced by alcohol and represent additional pathways to eliminate alcohol especially at high concentrations. Other potential mechanisms underlying metabolic tolerance are extensively reviewed in (Cederbaum, 2012).

The contribution of the elimination rates impact on the development of metabolic tolerance is based on several biochemical processes and is supported by preclinical studies. For example, studies evaluating alcohol elimination rates comparing Wistar and alcohol preferring P rats on chronic free-choice drinking and forced alcohol feeding, showed that all the alcohol preferring P rats exposed to alcohol by either free-choice or forced-feeding exhibited increased alcohol elimination rates (Lumeng & Li, 1986).

Metabolic tolerance has also been evaluated in flies. In *Drosophila*, alcohol metabolizing enzyme alcohol dehydrogenase, ADH, is characterized by variation between the two alleles Adh^F (more active) and Adh^S, (less active). Larvae with a deficiency of the *ADH* gene are very sensitive to alcohol toxicity (David, Bocquet, Arens, & Fouillet, 1976), however, there was not a phenotypic difference in alcohol-induced sedation within locomotor activity when compared to wild-type controls (Singh & Heberlein, 2000).

In addition to functional and metabolic tolerance, alcohol tolerance can be assed via cross-tolerance, which depends on similarities in the pharmacological profile of alcohol and other drugs, such as sedatives (e.g. barbiturates) and anxiolytics (e.g. benzodiazepines). Cross-tolerance appears to follow the trajectory of functional rather than metabolic tolerance; for extensive review see: (B. Tabakoff et al., 1986). First, the changes in ADH activity would not be expected to produce metabolic cross-tolerance to other drugs (Koivula & Lindros, 1975). Additionally, studies in rats consuming alcohol and barbiturates found that the development of tolerance and impairments in motor control tasks were characterized by unaltered phenobarbital elimination from the serum, suggesting that cross-tolerance was due to CNS adaptations (Lau, Tang, & Falk, 1981). Studies with alcohol and benzodiazepines (chlordiazepoxide) reported a partial and short-lasting development of tolerance, suggesting different neuronal pathways between the drugs (Chan, Schanley, Aleo, & Leong, 1985).

3. Alcohol tolerance in *Drosophila melanogaster*

Previous research using flies have described tolerance through alcohol's impact on the development of larvae and adult fly survival (Guarnieri & Heberlein, 2003; Kaun, Devineni, & Heberlein, 2012). Adult *Drosophila melanogaster* are a particularly useful model to elucidate mechanisms of alcohol tolerance since they do not have changes in enzymatic ADH levels after developing rapid tolerance (Geer et al., 1988). The short life cycle of a fly may also help to evaluate the development from rapid tolerance to chronic tolerance without the variability introduced by metabolic changes.

Studies with *Drosophila melanogaster* have contributed to our understanding of alcohol-related behaviors in other preclinical models and humans, suggesting that alcohol tolerance may be conserved across evolution (Petruccelli & Kaun, 2019). One of the most astounding discoveries of alcohol tolerance using *Drosophila melanogaster* models involves the role of stress in alcohol-related behaviors. The development of alcohol tolerance in flies relies on two distinct molecular pathways. The first pathway involves the octopamine system (an organic chemical in invertebrates that is related to vertebrates' noradrenaline), which is specific to the development of chronic alcohol tolerance. Flies with a mutation in the *Tbh* gene (the encoding tyramine β-hydroxylase enzyme that converts tyramine to octopamine) developed reduced tolerance compared to wildtype flies even after a single sedating alcohol pre-exposure; for review see: (Monastirioti, 1999).

The other pathway is related to the newly discovered *hangover* gene which encodes a large nuclear zinc-finger protein required for cellular stress response (Scholz, Franz, & Heberlein, 2005). After heat shock (stress-induction), flies with the *hangover* mutation developed rapid tolerance to alcohol, i.e. instead of exhibiting a sedating effect during alcohol pre-exposure, they expressed tolerant behavior as if they had previously been exposed to alcohol. Additional data examining stress-tolerant outcomes was tested using flies bred specifically for alcohol resistance. Similar to the flies with the *hangover* mutation, flies bred for alcohol tolerance exhibited increased resistance to stressors (heat shock, desiccation and chemicals) (Cohan & Hoffmann, 1986). As the flies became tolerant to stressors, they began to show greater resistance during alcohol exposure (Hoffmann & Parsons, 1989).

Additional neurotransmitters tested in flies have also portrayed similar effects in vertebrates. For example, the γ-aminobutyric acid (GABA) B antagonist CGP54626 has shown to decrease sedation in flies (Dzitoyeva, Dimitrijevic, & Manev, 2003). Similar responses have been observed in alcohol-mediated behavior within rat models (Maccioni & Colombo, 2009).

Among the preclinical models used to test alcohol tolerance, the *Drosophila melanogaster* offers numerous advantages recently explored in greater context. The fly mushroom body is comprised of a neuropil structure required for processing memories and learning; for review see: (Petruccelli & Kaun, 2019) that have been involved in not only alcohol-induced hyperactivity (King et al., 2011), but also in alcohol tolerance (Engel et al., 2016). This work suggests that flies regulate alcohol tolerance, a form of behavioral plasticity, via conserved signal transduction pathways by anchoring signaling molecules to the plasma membrane in proximity to the actin cytoskeleton (Parkhurst et al., 2018).

4. Alcohol tolerance in rodent models

Alcohol tolerance has been evaluated in rodent models (Erwin & Deitrich, 1996; Ponomarev & Crabbe, 2002). Behaviorally, high drinking rats have consistently demonstrated a greater degree of tolerance to alcohol's intoxicating effects; for review see: (Kalant, 1998). One of the original studies on acute alcohol tolerance in rodent models was conducted by simultaneous measurements of arterial blood and brain alcohol level in male Wistar rats. This study demonstrated that the brain alcohol level is in equilibrium with the arterial alcohol level (LeBlanc et al., 1975). These results were also confirmed later in human studies that evaluated the effects of alcohol on pharmacokinetic profiles within breath alcohol concentration (BrAC), and venous and arterial blood concentrations after oral consumption (Martin, Moll, Schmid, & Dettli, 1984). This study demonstrated that, during the absorption process, BrAC follows the trajectory of arterial blood. Due to this trajectory, BrAC levels are a more accurate prediction of arterial blood concentrations compared to venous blood alcohol levels. However, during elimination, BrAC, and arterial and venous blood follow similar trajectories.

A more systematic approach to evaluate alcohol tolerance was initiated with the development of the Alko Alcohol (AA) and Alko Nonalcohol (ANA) rat lines by the ALKO, the State Alcohol Monopoly of Finland (K. Eriksson, 1971). After the development of the AA and ANA rat lines, alcohol tolerant (AT) and alcohol nontolerant (ANT) rats were selectively bred to measure acute and chronic tolerance (Kalervo Eriksson & Rusi, 1981). Both lines have been utilized to elucidate mechanisms that affect alcohol-induced motor impairment. The AT rats show decreased sensitivity to alcohol induced motor impairment on a tilting plane over a wide range of alcohol doses, without difference in other behavioral measures for alcohol sensitivity. Consistently, the AA rats portrayed increased rapid and chronic tolerance to alcohol-induced hypothermia, and exhibited a more profound effect in motor impairment and sleep patterns than the ANA rats (Le & Kiianmaa, 1988).

A second generation of rodents with the same phenotype were bred and tested for ataxia, loss of righting reflex (LORR), and blood ethanol concentration at regain of the righting

reflex (BECRRR) at the University of Colorado Alcohol Research Center (Radcliffe et al., 2004). Ataxia was measured on the inclined plane at 5 and 30 minutes after an intraperitoneal alcohol dose of 2 g/kg. The AT rats developed acute tolerance compared to NAT rats. In addition, LORR and BECRRR, following an alcohol dose of 3.5 g/kg, were tested as a proxy of acute alcohol tolerance. The AT rats had a significantly higher BECRRR compared to the NAT rats. There was however, no difference in LORR (Radcliffe et al., 2004).

Later, a study tested the hypothesis that the larger voluntary alcohol intake of the AA strain might be due not only to a stronger innate (genetically linked) tolerance to alcohol, but may also be linked to a greater likelihood of developing tolerance after chronic alcohol exposure (Nikander & Pekkanen, 1977). After chronic alcohol administration, both strains increased their tolerance, but the AA rats exhibited higher rates of tolerance compared to the ANA rats (Nikander & Pekkanen, 1977). Overall, the alcohol-preferring rats (P rats) develop tolerance to alcohol more quickly, and are less sensitive to the sedative-hypnotic effects of alcohol compared with non-preferring animals; for extensive review see: (McBride & Li, 1998). Motor impairment (tilt-plane) and hypothermia tests were adopted to characterize the differences between rapid alcohol tolerance and chronic alcohol tolerance. A series of experiments with control rats (those who were not exposed to alcohol or the apparatus) demonstrated similarities between the mechanisms of rapid and chronic tolerance (Khanna et al., 1996).

The development of alcohol tolerance as a way of detecting persistent rapid changes in the effects felt due to alcohol were demonstrated in male Swiss mice (Crabbe, Rigter, Uijlen, & Strijbos, 1979). Research utilizing hypothermia as a measure of alcohol physical dependence (Ritzmann & Tabakoff, 1976), demonstrated that mice develop tolerance to the hypothermic effects of a single alcohol injection upon administration of an equivalent dose 24 hours prior to the initial administration. Blood alcohol concentration did not differ in tolerant and nontolerant mice, and tolerance was present within 10 minutes of the second alcohol injection; this phenomenon was later termed rapid tolerance, a measure that is unique to the previously coined term *metabolic* tolerance (Crabbe et al., 1979).

The effect of stress on acute alcohol tolerance was also tested in mice using yohimbine, an α2 receptor blocker. Yohimbine was able to antagonize acute tolerance in mice during the rolling test drum, suggesting that α2 receptors may play an important role in mediating acute alcohol tolerance (Edwards, Schabinsky, Jackson, Starmer, & Jenkins, 1983). In addition, the intraventricular administration of 6-hydroxydopamine, a neurotoxic for noradrenergic and dopaminergic neurons, in mice prior to chronic exposure to alcohol prevented the development of acute tolerance (B Tabakoff & Ritzmann, 1977). These findings suggest that the role of the noradrenergic system plays a role in the development of acute tolerance, and can provide key neurobiological mechanisms signifying underlying acute tolerance. This insight, along with knowledge of the role of the noradrenaline analogue octopamine in rapid alcohol tolerance among flies, as reviewed above, confirms the role of this noradrenergic system in tolerance-related mechanisms.

In rodent models, the role of the neurotransmitter, neuromodulator and neuroendocrine systems in the context of alcohol tolerance have been predominately focused on acute and rapid tolerance. For example, the original AT rat lines exhibited a higher capacity to develop acute tolerance with dysregulation of the noradrenergic and GABAergic systems (Kiianmaa & Hellevuo, 1990). Within the GABA-ergic system, studies in male Swiss mice showed that the GABAB agonist baclofen is capable of blocking rapid tolerance, while GABAB antagonists (CCGP36742 and CGP56433) facilitate the development of rapid tolerance in a dose dependent manner (Zaleski, Nunes Filho, Lemos, & Morato, 2001). Actions due to alcohol exposure at the GABAA receptor are also influenced by endogenous neuroactive steroids. A pharmacological study showed that pretreatment with pregnenolone (a neurosteroid) among female mice significantly facilitated the development of rapid tolerance (Barbosa & Morato, 2001) and the stimulatory action of pregnenolone was reversed by the inhibitory action of muscimol (a GABAA agonist). Rodent studies focusing on the GABA-ergic system reveled potential links between neurosteroids and the development of tolerance. However, neurosteroid studies have cast mixed results, as they can block or facilitate chronic tolerance (within a time span of 2–5 days). In the rota-rod apparatus, the impairing effect of alcohol occurred on the fifth day of treatment of epipregnanolone (an endogenous steroid that acts as a negative allosteric modulator of the GABAA receptor and reverses the effect of allopregnanolone). This effect was enhanced by pretreatment with pregnenolone (endogenous steroid and precursor of most steroid hormones), on the second day (Barbosa & Morato, 2000).

The role of the opioid system in the development of rapid tolerance has been evaluated using pharmacological probes in male Wistar rats (Varaschin, Wazlawik, & Morato, 2005) by infusion of selective μ- (naloxonazine), δ- (naltrindole), and κ- (nor-binaltorphimine) opioid antagonists in the core and shell of the nucleus accumbens. The results of this study suggest that μ-opioid receptors in both the shell and core of the nucleus accumbens participate in the modulation of rapid tolerance to alcohol. However, it is also possible that the κ-opioid played a role in this development, but this role has been limited to the accumbens' core (Varaschin & Morato, 2009).

The role of the N-methyl-D-aspartate (NMDA) system on rapid alcohol tolerance was tested by intraperitoneal injection of the active isomer (+) of the NMDA antagonists MK-801(dizocilpine) and ketamine in Swiss female mice. Administration of (+)MK-801 and ketamine blocked the development of rapid tolerance as measured in the tilt-plane apparatus (Barreto, Lemos, & Morato, 1998).

There is a large body of preclinical research that supports the role of oxytocin in alcohol tolerance; for extensive review see: (Pedersen, 2017). Oxytocin administered (intraperitoneally in mice and subcutaneous in rats) 10 min to 2 hours before each alcohol daily dose over 3 to 5 days significantly inhibited tolerance formation as measured by hypothermia and sedation (Jodogne, Tirelli, Klingbiel, & Legros, 1991; Puciklowski, Kostowski, & Trzaskowska, 1985; Szabó, Kovács, Székeli, & Telegdy, 1985).

Finally, conflicting results on motor impairment and anticonvulsant effects due to alcohol intake have suggested differences among both sexes and between male and female hormones when assessing alcohol tolerance in rats (Koirala, Alele, & Devaud, 2008).

5. Alcohol tolerance in *Rhesus macaques*

Research examining alcohol tolerance in nonhuman primates allows scientists to dose and evaluate behaviors indicative of alcohol response in a preclinical model very similar to human tendencies. Primates' large brains have allowed researchers to utilize magnetic resonance spectroscopy (MRS) to detect decreases in brain membrane alcohol partitioning as a way to measure the development of alcohol tolerance (Kaufman et al., 1994).

Innate sensitivity and the use of different doses prompts investigation of both rapid tolerance (Kalant, 1993; Khanna et al., 1996) and sensitization to the acute effects of alcohol (Schwandt, Higley, Suomi, Heilig, & Barr, 2008). As observed in mice with hypothermia (Crabbe et al., 1979), *Rhesus macaques* ataxic behavior decreased from dose one to dose two, while locomotor stimulation increased between doses. This change in behavior was independent of blood alcohol concentrations and was not associated with the amount of time between doses (roughly 5–30 days occurred between alcohol administration) (Schwandt et al., 2008). Results from this work suggest that *Rhesus macaques* are capable of developing rapid tolerance to motor impairing and locomotor sensitization. A factor analysis showed that the behavioral response (exhibited through the development of rapid tolerance) was evident within a single dose of alcohol, and rapid tolerance may persist for some time following the first alcohol dose (Schwandt et al., 2008). Studies in rodents have cast similar results. Locomotor sensitization in mice lasts 30 to 60 days (Fish, DeBold, & Miczek, 2002; Lessov & Phillips, 1998) and rapid tolerance in alcohol preferring P rats persists for 10 days (Gatto et al., 1987).

Rhesus macaques, have a long period of adolescence (similar to human populations) as such, they offer opportunities to evaluate alcohol-related phenotypes during youth; for review see: (Schwandt et al., 2010). Furthermore, *Rhesus macaques* studies can extend evaluation of the genetic variations associated with alcohol tolerance in a controlled laboratory setting without introduction of additional environmental variables. In humans, decreased sensitivity to alcohol has been demonstrated as a predictor of AUD, and variations in the gene-linked polymorphic region of the serotonin transporter (*5-HTTLPR*) have been associated with neuronal mechanisms responsible for alcohol tolerance (Hinckers et al., 2006; Turker et al., 1998). *Rhesus macaques* homozygous for the *rh5-HTTLPR*, showed a decreased sensitivity to the ataxic and sedating effects of alcohol after being intoxicated by intravenous administration of alcohol (with doses of 2.2 g/kg for males and 2.0 g/kg for females): this 21-basepair length variation has been detected within the transcriptional control region in human beings (Barr et al., 2003). However, the phenotypic expression of this genotype is environmentally dependent since peer-reared adolescent animals predicted lower intoxication scores compared to mother-reared animals (Barr et al., 2003).

6. Alcohol tolerance in human laboratory studies

Human studies measuring subjective responses to alcohol have greatly contributed to our understanding of the development of acute alcohol tolerance (Trim, Schuckit, & Smith, 2009). However, the concept of subjective response is not novel since it was previously evaluated as a clinical predictor of AUD risk (Schuckit & Smith, 1996). The development of AUD paradigms to evaluate acute alcohol tolerance have risen from multiple models with inclusion of both subjective and objective measures, for review see (Haass-Koffler & Perciballi, 2020). Those paradigms have been based on the low level response model (LLR), which focuses on the hypothesis that individuals who are less responsive to the sedative effects of alcohol are at greater risk of developing AUD (Schuckit, 1994), and the differentiator model, which evaluates behavioral responses during alcohol's biphasic effects (Newlin & Thomson, 1990).

Intravenous alcohol administration paradigms have been utilized to evaluate alcohol tolerance. These paradigms allow for a highly controlled alcohol concentration procedure, and can limit the effects felt due to variability in pharmacokinetics (Ramchandani, Bolane, Li, & O'Connor, 1999). Intravenous alcohol paradigms (which bypass absorption and first pass metabolism) focus on pharmacokinetic principles, and allow researchers to examine short and long term tolerance within human laboratory studies through a quantitative approach by controlling for BrAC exposure over the entire procedure (Ramchandani et al., 2006). Recent intravenous alcohol administration studies evaluating the role of hangovers post alcohol consumption have demonstrated that individuals who are heavier drinkers display signs of chronic tolerance more frequently than those who consume less, suggesting that a direct relationship between hangovers, tolerance development, and alcohol consumption may exist (Vatsalya, Stangl, Schmidt, & Ramchandani, 2018).

Another important paradigm to consider when translating preclinical models to human laboratory studies is the environment (Ciccocioppo, 2012). Additionally, within clinical research, it has been observed that a novel drinking environment may elucidate a more stimulating experience compared to a familiar place (Plebani et al., 2012). The development of a bar-like laboratory has provided an additional setting to determine predictors of alcohol-related behavior where many variables can be controlled in a more naturalistic environment compared to the typical "sterile" clinical laboratory setting (Fox et al., 2012; Haass-Koffler et al., 2017; Haass-Koffler, Leggio, Davidson, & Swift, 2015; Kenna et al., 2016; Thomas, Bacon, Sinha, Uhart, & Adinoff, 2012). Additionally, mechanisms that impact knowledge acquisition play a critical role in impaired behavior (Vogel-Sprott, 1979). Accordingly, pre-drug cues determine conditioned preparatory responses to counteract the substance's effects leading to tolerance (Poulos & Cappell, 1991; Siegel, 1989). As such, it is important to acknowledge that individuals tend to lose inhibition when drinking in unfamiliar places when assessing tolerance within a laboratory setting. In fact, alcohol tolerance can facilitate a drinker's ability to anticipate the effects of alcohol. This aspect of human alcohol tolerance suggests that tolerance is not a static state, but it is subject to environmental stimuli (Ostling & Fillmore, 2010).

Ecological Momentary Assessment (EMA) sampling (Shiffman, Stone, & Hufford, 2008) has the advantage of assessing alcohol-related behaviors in real time within a natural environment. However, while the EMA real time assessments may have numerous advantages, compared to retrospective calendar methods utilized to assess drinking outcomes (Morgenstern, Kuerbis, & Muench, 2014), the EMA has some limitations. EMA data is collected in the absence of the experimenter therefore, may lack objectivity when assessing alcohol tolerance.

The rate at which an individual's blood alcohol concentration rises should be taken into consideration in order to understand the intra-individual differences in acute tolerance in the laboratory setting. Greater psychomotor impairment occurs on the ascending limb while a reduced impairment is observed on the descending limb. For example, with a faster rise in blood alcohol concentration, there is a consequent increase in psychomotor impairment (Mark T Fillmore, Vogel-Sprott, & Research, 1998). Thus, the rate at which blood alcohol concentration rises may predict impaired behavior, rather than the blood alcohol concentration value previously detected. Intravenous alcohol administration techniques have great relevance to the concept of assessing acute alcohol tolerance and the rate at which alcohol concentration changes. The control of many variables provide consistent exposure rates during the alcohol biphasic profile (Ramchandani et al., 1999) to assess Mellanby differences in motor control, cognition and memory between the ascending and descending limbs (Mellanby, 1919).

Sex should be considered when measuring alcohol tolerance within the laboratory setting. It is well known that pharmacokinetically, women metabolize (Kwo et al., 1998; Li, Beard, Orr, Kwo, & Ramchandani, 1998) alcohol differently than men. Women reached significantly higher peak blood alcohol concentrations than men when alcohol was administered based on individual body weight, however, there was no difference detected between the sexes when alcohol was administered based on total body water (Goist & Sutker, 1985). Unfortunately, limited research on the effects of sex hormones on alcohol tolerance and behavioral response has been conducted (Mumenthaler, Taylor, O'Hara, & Yesavage, 1999).

Additional intra-variabilities affecting measurements of alcohol tolerance have been explored among human subjects. For example, nicotine may impact the biphasic effects of alcohol, such as, enhancing its positive effects (e.g., stimulation) (Kouri, McCarthy, Faust, & Lukas, 2004) and diminishing its sedative effects (Perkins et al., 1994). This is an important aspect considering that smoking is highly prevalent among individuals with AUD (Kalman, Morissette, & George, 2005).

Finally, little is known about the mechanisms that re-establish control following impaired behavior. Both the diminishing and stimulating aspects of behavioral control appear to be affected by alcohol (M. T. Fillmore, Marczinski, & Bowman, 2005). Interestingly, acute alcohol tolerance seems to develop within impaired activation but not with impaired inhibition (Fillmore, Marczinski et al. 2005). Evidence of acute excitatory responses, but not of inhibitory responses suggests some degree of independence between these two

mechanisms of control (Logan, 1994; Logan & Cowan, 1984). Further studies are needed to better understand the mechanisms underlying recovery of behavioral control.

7. Conclusion

It has long been established that the positive reinforcing effects of alcohol during initial alcohol consumption, followed by chronic alcohol exposure, result in neuroadaptations that can eventually lead to transient and prolonged neuroplasticity that contributes to the development of AUD; for review see: (Koob & Le Moal, 2008). This change in brain biochemistry has been observed via the signaling of neurotransmitters, receptor proteins, and neuronal connectivity; for review see: (Kalivas & O'Brien, 2008). To date, most of the literature on preclinical models used for measuring alcohol tolerance is not only scarce, but outdated, however, different preclinical models employed to test alcohol tolerance have offered diverse advantages.

The *Drosophila melanogaster* models have demonstrated that there are two independent cellular pathways that affect rapid and chronic tolerance; one pathway involves the octopamine (leading to rapid tolerance) and the other pathway is independent of octopamine signaling (leading to chronic tolerance) (Scholz et al., 2005), suggesting that stress plays different roles in the development of alcohol tolerance. One of the most important studies on alcohol tolerance in rodent models resulted from simultaneous measurements in rat arterial blood and brain levels (LeBlanc et al., 1975). This study elucidates the equilibrium process of the arterio-venous differences in alcohol concentration.

The long adolescent period of the *Rhesus Macaques* has offered an opportunity to evaluate alcohol-effects comparable to human adolescence, a time often deemed the age at which humans may begin developing alcohol tolerance (Schwandt et al., 2010). Due to the lack of data available, early literature on rodent models has revealed limitations in assessing sex differences among alcohol tolerance. GABAA receptors are influenced by endogenous neuroactive steroids affecting different alcohol rates between the sexes (Barbosa & Morato, 2001). As such, sensitization to GABAA by allosteric compounds (e.g. benzodiazepines) have been shown to influence (through the role of cross-tolerance) alcohol use disorder; GABAA sensitization may represent an exploitable variable utilized to study gender and sex hormone differences in the molecular effects of alcohol on the development of tolerance (Grobin, Matthews, Devaud, & Morrow, 1998). Furthermore, to our knowledge, limited work regarding this topic has been conducted in humans (Mumenthaler et al., 1999).

Human bar laboratory studies offer the advantage of testing alcohol tolerance in a more naturalistic setting rather than the typical "sterile" clinical laboratory setting; however, non-bar laboratory challenge paradigms examining tolerance and sensitization to alcohol have and will continue to be significant contributors to the study of tolerance.

In conclusion, both preclinical models and human studies offer opportunities to study the pharmacokinetic effects of tolerance (alterations of alcohol metabolism) and pharmacodynamic effects of alcohol tolerance (CNS adaptation) that often lead to alcohol related diseases (Cederbaum, 2012). Alcohol tolerance is a complex measure, but may

represent one additional variable that can be utilized to expand understanding of the diverse AUD phenotypical profile and prompt development of new medications to treat alcohol use disorder.

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References

Barbosa AD, & Morato GS (2000). Effect of epipregnanolone and pregnenolone sulfate on chronic tolerance to ethanol. Pharmacol Biochem Behav, 67(3), 459–464. doi:10.1016/s0091-3057(00)00372-5 [PubMed: 11164072]

Barbosa AD, & Morato GS (2001). Influence of neurosteroids on the development of rapid tolerance to ethanol in mice. Eur J Pharmacol, 431(2), 179–188. doi:10.1016/s0014-2999(01)01337-1 [PubMed: 11728424]

Barr CS, Newman TK, Becker ML, Champoux M, Lesch KP, Suomi SJ, … Higley JD (2003). Serotonin transporter gene variation is associated with alcohol sensitivity in rhesus macaques exposed to early-life stress. Alcohol Clin Exp Res, 27(5), 812–817. doi:10.1097/01.ALC.0000067976.62827.ED [PubMed: 12766626]

Barreto PS, Lemos T, & Morato GS (1998). NMDA-receptor antagonists block the development of rapid tolerance to ethanol in mice. Addict Biol, 3(1), 55–64. doi:10.1080/13556219872344 [PubMed: 26736080]

Carrigan MA, Uryasev O, Frye CB, Eckman BL, Myers CR, Hurley TD, & Benner SA (2015). Hominids adapted to metabolize ethanol long before human-directed fermentation. Proc Natl Acad Sci U S A, 112(2), 458–463. doi:10.1073/pnas.1404167111 [PubMed: 25453080]

Cederbaum AI (2012). Alcohol metabolism. Clin Liver Dis, 16(4), 667–685. doi:10.1016/j.cld.2012.08.002 [PubMed: 23101976]

Chan AW, Schanley DL, Aleo MD, & Leong FW (1985). Cross-tolerance between ethanol and chlordiazepoxide. Alcohol, 2(2), 209–213. [PubMed: 4015844]

Ciccocioppo R (2012). Genetically selected alcohol preferring rats to model human alcoholism Behavioral Neurobiology of Alcohol Addiction (pp. 251–269): Springer.

Cicero TJ, Snider SR, Perez VJ, & Swanson LW (1971). Physical dependence on and tolerance to alcohol in the rat. Physiol Behav, 6(2), 191–198. doi:10.1016/0031-9384(71)90088-6 [PubMed: 5166470]

Cohan FM, & Hoffmann AA (1986). Genetic divergence under uniform selection. II. Different responses to selection for knockdown resistance to ethanol among Drosophila melanogaster populations and their replicate lines. Genetics, 114(1), 145–164. [PubMed: 3095180]

Crabbe JC, Rigter H, Uijlen J, & Strijbos C (1979). Rapid development of tolerance to the hypothermic effect of ethanol in mice. J Pharmacol Exp Ther, 208(1), 128–133. [PubMed: 759607]

David JR, Bocquet C, Arens MF, & Fouillet P (1976). Biological role of alcohol dehydrogenase in the tolerance of Drosophila melanogaster to aliphatic alochols: utilization of an ADH-null mutant. Biochem Genet, 14(11–12), 989–997. [PubMed: 828053]

Dzitoyeva S, Dimitrijevic N, & Manev H (2003). Gamma-aminobutyric acid B receptor 1 mediates behavior-impairing actions of alcohol in Drosophila: adult RNA interference and pharmacological evidence. Proc Natl Acad Sci U S A, 100(9), 5485–5490. doi:10.1073/pnas.0830111100 [PubMed: 12692303]

Edwards F, Schabinsky V, Jackson D, Starmer G, & Jenkins OJP (1983). Involvement of catecholamines in acute tolerance to ethanol in mice. 79(2–3), 246–250.

Engel GL, Marella S, Kaun KR, Wu J, Adhikari P, Kong EC, & Wolf FW (2016). Sir2/Sirt1 Links Acute Inebriation to Presynaptic Changes and the Development of Alcohol Tolerance, Preference, and Reward. J Neurosci, 36(19), 5241–5251. doi:10.1523/JNEUROSCI.0499-16.2016 [PubMed: 27170122]

Eriksson K (1971). Rat strains specially selected for their voluntary alcohol consumption. Ann Med Exp Biol Fenn, 49(2), 67–72. [PubMed: 5106239]

Eriksson K, & Rusi M (1981). Finnish selection studies on alcohol-related behaviors: General outline. Development of animal models as pharmacogenetic tools, 6.

Erwin VG, & Deitrich RA (1996). Genetic selection and characterization of mouse lines for acute functional tolerance to ethanol. J Pharmacol Exp Ther, 279(3), 1310–1317. [PubMed: 8968355]

Fillmore MT, Marczinski CA, & Bowman AM (2005). Acute tolerance to alcohol effects on inhibitory and activational mechanisms of behavioral control. J Stud Alcohol, 66(5), 663–672. [PubMed: 16331852]

Fillmore MT, Vogel-Sprott MJAC, & Research E (1998). Behavioral impairment under alcohol: cognitive and pharmacokinetic factors. 22(7), 1476–1482.

Fish EW, DeBold JF, & Miczek KA (2002). Repeated alcohol: behavioral sensitization and alcohol-heightened aggression in mice. Psychopharmacology (Berl), 160(1), 39–48. doi:10.1007/s00213-001-0934-9 [PubMed: 11862372]

Fox HC, Anderson GM, Tuit K, Hansen J, Kimmerling A, Siedlarz KM, … Sinha R (2012). Prazosin effects on stress- and cue-induced craving and stress response in alcohol-dependent individuals: preliminary findings. Alcohol Clin Exp Res, 36(2), 351–360. doi:10.1111/j.1530-0277.2011.01628.x [PubMed: 21919922]

Gatto GJ, Murphy JM, Waller MB, McBride WJ, Lumeng L, & Li TK (1987). Persistence of tolerance to a single dose of ethanol in the selectively-bred alcohol-preferring P rat. Pharmacol Biochem Behav, 28(1), 105–110. doi:10.1016/0091-3057(87)90020-7 [PubMed: 3659101]

Geer BW, McKechnie SW, Bentley MM, Oakeshott JG, Quinn EM, & Langevin ML (1988). Induction of alcohol dehydrogenase by ethanol in Drosophila melanogaster. J Nutr, 118(3), 398–407. doi:10.1093/jn/118.3.398 [PubMed: 3127555]

Gilpin NW, & Koob GF (2008). Neurobiology of alcohol dependence: focus on motivational mechanisms. Alcohol Research & Health, 31(3), 185. [PubMed: 19881886]

Goist KC Jr., & Sutker PB (1985). Acute alcohol intoxication and body composition in women and men. Pharmacol Biochem Behav, 22(5), 811–814. doi:10.1016/0091-3057(85)90532-5 [PubMed: 4011640]

Grobin AC, Matthews DB, Devaud LL, & Morrow AL (1998). The role of GABA(A) receptors in the acute and chronic effects of ethanol. Psychopharmacology (Berl), 139(1–2), 2–19. doi:10.1007/s002130050685 [PubMed: 9768538]

Guarnieri DJ, & Heberlein U (2003). Drosophila melanogaster, a genetic model system for alcohol research. Int Rev Neurobiol, 54, 199–228. [PubMed: 12785288]

Haass-Koffler CL, Goodyear K, Zywiak WH, Magill M, Eltinge SE, Wallace PM, … Leggio L (2017). Higher pretreatment blood pressure is associated with greater alcohol drinking reduction in alcohol-dependent individuals treated with doxazosin. Drug Alcohol Depend, 177, 23–28. doi:10.1016/j.drugalcdep.2017.03.016 [PubMed: 28551590]

Haass-Koffler CL, Leggio L, Davidson D, & Swift RM (2015). Effects of idazoxan on alcohol pharmacokinetics and intoxication: a preliminary human laboratory study. Alcohol Clin Exp Res, 39(4), 594–602. doi:10.1111/acer.12658 [PubMed: 25833022]

Haass-Koffler CL, & Perciballi R (2020). Alcohol Tolerance in Human Laboratory Studies for Development of Medications to treat Alcohol Use Disorder. Alcohol Alcohol. doi:10.1093/alcalc/agz103

Hinckers AS, Laucht M, Schmidt MH, Mann KF, Schumann G, Schuckit MA, & Heinz A (2006). Low level of response to alcohol as associated with serotonin transporter genotype and high alcohol intake in adolescents. Biological psychiatry, 60(3), 282–287. [PubMed: 16497275]

Hoek JB, & Pastorino JG (2004). Cellular signaling mechanisms in alcohol-induced liver damage. Paper presented at the Seminars in liver disease.

Hoffmann AA, & Parsons PA (1989). Selection for increased desiccation resistance in Drosophila melanogaster: additive genetic control and correlated responses for other stresses. Genetics, 122(4), 837–845. [PubMed: 2503423]

Jodogne C, Tirelli E, Klingbiel P, & Legros J-J (1991). Oxytocin attenuates tolerance not only to the hypothermic but also to the myorelaxant and akinesic effects of ethanol in mice. Pharmacology Biochemistry and Behavior, 40(2), 261–265.

Jones AW (2019). Alcohol, its absorption, distribution, metabolism, and excretion in the body and pharmacokinetic calculations. Wiley Interdisciplinary Reviews: Forensic Science, 1(5), e1340.

Kalant H (1998). Research on tolerance: what can we learn from history? Alcohol Clin Exp Res, 22(1), 67–76. doi:10.1111/j.1530-0277.1998.tb03618.x [PubMed: 9514287]

Kalivas PW, & O'Brien C (2008). Drug addiction as a pathology of staged neuroplasticity. Neuropsychopharmacology, 33(1), 166–180. doi:10.1038/sj.npp.1301564 [PubMed: 17805308]

Kalman D, Morissette SB, & George TP (2005). Co-Morbidity of Smoking in Patients with Psychiatric and Substance Use Disorders. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions, 14(2), 106–123. doi:10.1080/10550490590924728

Kaufman MJ, Chiu T-M, Mendelson JH, Woods BT, Mello NK, Lukas SE, … Wighton LG (1994). In vivo proton magnetic resonance spectroscopy of alcohol in rhesus monkey brain. Magnetic resonance imaging, 12(8), 1245–1253. [PubMed: 7854030]

Kaun KR, Devineni AV, & Heberlein U (2012). Drosophila melanogaster as a model to study drug addiction. Hum Genet, 131(6), 959–975. doi:10.1007/s00439-012-1146-6 [PubMed: 22350798]

Kenna GA, Haass-Koffler CL, Zywiak WH, Edwards SM, Brickley MB, Swift RM, & Leggio L (2016). Role of the alpha1 blocker doxazosin in alcoholism: a proof-of-concept randomized controlled trial. Addict Biol, 21(4), 904–914. doi:10.1111/adb.12275 [PubMed: 26037245]

Khanna JM, Chau A, & Shah G (1996). Characterization of the Phenomenon of rapid tolerance to ethanol. Alcohol, 13(6), 621–628. [PubMed: 8949959]

Kiianmaa K, & Hellevuo K (1990). The alcohol tolerant and alcohol nontolerant rat lines selected for differential sensitivity to ethanol: a tool to study mechanisms of the actions of ethanol. Ann Med, 22(4), 283–287. [PubMed: 2248764]

King I, Tsai LT, Pflanz R, Voigt A, Lee S, Jackle H, … Heberlein U (2011). Drosophila tao controls mushroom body development and ethanol-stimulated behavior through par-1. J Neurosci, 31(3), 1139–1148. doi:10.1523/JNEUROSCI.4416-10.2011 [PubMed: 21248138]

Koirala B, Alele PE, & Devaud LL (2008). Influence of hormonal status on behavioral responses to an acute ethanol challenge during ethanol withdrawal in male and female rats. Pharmacol Biochem Behav, 90(4), 691–700. doi:10.1016/j.pbb.2008.05.013 [PubMed: 18603287]

Koivula T, & Lindros KO (1975). Effects of long-term ethanol treatment on aldehyde and alcohol dehydrogenase activities in rat liver. Biochemical pharmacology, 24(21), 1937–1942. [PubMed: 1212243]

Koob GF, & Le Moal M (2008). Review. Neurobiological mechanisms for opponent motivational processes in addiction. Philos Trans R Soc Lond B Biol Sci, 363(1507), 3113–3123. doi:10.1098/rstb.2008.0094 [PubMed: 18653439]

Kouri EM, McCarthy EM, Faust AH, & Lukas SE (2004). Pretreatment with transdermal nicotine enhances some of ethanol's acute effects in men. Drug Alcohol Depend, 75(1), 55–65. doi:10.1016/j.drugalcdep.2004.01.011 [PubMed: 15225889]

Kwo PY, Ramchandani VA, O'Connor S, Amann D, Carr LG, Sandrasegaran K, … Li TK (1998). Gender differences in alcohol metabolism: relationship to liver volume and effect of adjusting for body mass. Gastroenterology, 115(6), 1552–1557. doi:10.1016/s0016-5085(98)70035-6 [PubMed: 9834284]

Lau CE, Tang M, & Falk JL (1981). Cross-tolerance to phenobarbital following chronic ethanol polydipsia. Pharmacology Biochemistry and Behavior, 15(3), 471–475.

Le AD, & Kiianmaa K (1988). Characteristics of ethanol tolerance in alcohol drinking (AA) and alcohol avoiding (ANA) rats. Psychopharmacology (Berl), 94(4), 479–483. doi:10.1007/bf00212841 [PubMed: 3131793]

LeBlanc AE, Kalant H, & Gibbins RJ (1975). Acute tolerance to ethanol in the rat. Psychopharmacologia, 41(1), 43–46. [PubMed: 1124268]

Lessov CN, & Phillips TJ (1998). Duration of sensitization to the locomotor stimulant effects of ethanol in mice. Psychopharmacology (Berl), 135(4), 374–382. doi:10.1007/s002130050525 [PubMed: 9539262]

Li TK, Beard JD, Orr WE, Kwo PY, & Ramchandani VA (1998). Gender and ethnic differences in alcohol metabolism. Alcoholism: Clinical and Experimental Research, 22(3), 771–772.

Lim RT Jr., Gentry RT, Ito D, Yokoyama H, Baraona E, & Lieber CS (1993). First-pass metabolism of ethanol is predominantly gastric. Alcohol Clin Exp Res, 17(6), 1337–1344. doi:10.1111/j.1530-0277.1993.tb05250.x [PubMed: 8116851]

Logan GD (1994). On the ability to inhibit thought and action: A users' guide to the stop signal paradigm.

Logan GD, & Cowan W. B. J. P. r. (1984). On the ability to inhibit thought and action: A theory of an act of control. 91(3), 295.

Lumeng L, & Li TK (1986). The development of metabolic tolerance in the alcohol-preferring P rats: comparison of forced and free-choice drinking of ethanol. Pharmacol Biochem Behav, 25(5), 1013–1020. doi:10.1016/0091-3057(86)90079-1 [PubMed: 3786353]

Maccioni P, & Colombo G (2009). Role of the GABA(B) receptor in alcohol-seeking and drinking behavior. Alcohol, 43(7), 555–558. doi:10.1016/j.alcohol.2009.09.030 [PubMed: 19913200]

Martin E, Moll W, Schmid P, & Dettli L (1984). The pharmacokinetics of alcohol in human breath, venous and arterial blood after oral ingestion. Eur J Clin Pharmacol, 26(5), 619–626. doi:10.1007/bf00543496 [PubMed: 6468479]

McBride WJ, & Li TK (1998). Animal models of alcoholism: neurobiology of high alcohol-drinking behavior in rodents. Crit Rev Neurobiol, 12(4), 339–369. [PubMed: 10348615]

Mellanby E (1919). Alcohol: its absorption into and disappearance from the blood under different conditions: The University Press.

Monastirioti M (1999). Biogenic amine systems in the fruit fly Drosophila melanogaster. Microsc Res Tech, 45(2), 106–121. doi:10.1002/(SICI)1097-0029(19990415)45:2<106::AID-JEMT5>3.0.CO;2-3 [PubMed: 10332728]

Morgenstern J, Kuerbis A, & Muench F (2014). Ecological Momentary Assessment and Alcohol Use Disorder Treatment. Alcohol Res, 36(1), 101–109. [PubMed: 26259004]

Mumenthaler MS, Taylor JL, O'Hara R, & Yesavage JA (1999). Gender differences in moderate drinking effects. Alcohol Res Health, 23(1), 55–64. [PubMed: 10890798]

Newlin DB, & Thomson JB (1990). Alcohol challenge with sons of alcoholics: a critical review and analysis. Psychol Bull, 108(3), 383–402. doi:10.1037/0033-2909.108.3.383 [PubMed: 2270234]

Nikander P, & Pekkanen L (1977). An inborn alcohol tolerance in alcohol-preferring rats. The lack of relationship between tolerance to ethanol and the brain microsomal (Na+K+) ATPase activity. Psychopharmacology (Berl), 51(3), 219–223. doi:10.1007/bf00431628 [PubMed: 139633]

Oneta CM, Simanowski UA, Martinez M, Allali-Hassani A, Pares X, Homann N, … Seitz HK (1998). First pass metabolism of ethanol is strikingly influenced by the speed of gastric emptying. Gut, 43(5), 612–619. doi:10.1136/gut.43.5.612 [PubMed: 9824340]

Ostling EW, & Fillmore MT (2010). Tolerance to the impairing effects of alcohol on the inhibition and activation of behavior. Psychopharmacology (Berl), 212(4), 465–473. doi:10.1007/s00213-010-1972-y [PubMed: 20686751]

Parkhurst SJ, Adhikari P, Navarrete JS, Legendre A, Manansala M, & Wolf FW (2018). Perineurial Barrier Glia Physically Respond to Alcohol in an Akap200-Dependent Manner to Promote Tolerance. Cell Rep, 22(7), 1647–1656. doi:10.1016/j.celrep.2018.01.049 [PubMed: 29444420]

Pedersen CA (2017). Oxytocin, tolerance, and the dark side of addiction International review of neurobiology (Vol. 136, pp. 239–274): Elsevier. [PubMed: 29056153]

Perkins KA, Sexton JE, Stiller RL, Fonte C, DiMarco A, Goettler J, & Scierka A (1994). Subjective and cardiovascular responses to nicotine combined with caffeine during rest and casual activity. Psychopharmacology, 113(3), 438–444. doi:10.1007/bf02245220 [PubMed: 7862856]

Petruccelli E, & Kaun KR (2019). Insights from intoxicated Drosophila. Alcohol, 74, 21–27. doi:10.1016/j.alcohol.2018.03.004 [PubMed: 29980341]

Plebani JG, Ray LA, Morean ME, Corbin WR, MacKillop J, Amlung M, & King AC (2012). Human laboratory paradigms in alcohol research. Alcoholism: Clinical and Experimental Research, 36(6), 972–983.

Ponomarev I, & Crabbe JC (2002). A novel method to assess initial sensitivity and acute functional tolerance to hypnotic effects of ethanol. J Pharmacol Exp Ther, 302(1), 257–263. doi:10.1124/jpet.302.1.257 [PubMed: 12065725]

Poulos CX, & Cappell H. J. P. r. (1991). Homeostatic theory of drug tolerance: a general model of physiological adaptation. 98(3), 390.

Puciklowski O, Kostowski W, & Trzaskowska E (1985). The effect of oxytocin and fragment (MIF-I) on the development of tolerance to hypothermic and hypnotic action of ethanol in the rat. Peptides, 6(1), 7–10.

Radcliffe RA, Hoffmann SE, Deng XS, Asperi W, Fay T, Bludeau P, … Deitrich RA (2004). Behavioral characterization of alcohol-tolerant and alcohol-nontolerant rat lines and an f(2) generation. Behav Genet, 34(4), 453–463. doi:10.1023/B:BEGE.0000023650.32243.39 [PubMed: 15082942]

Ramchandani VA, Bolane J, Li TK, & O'Connor S (1999). A physiologically-based pharmacokinetic (PBPK) model for alcohol facilitates rapid BrAC clamping. Alcohol Clin Exp Res, 23(4), 617–623. [PubMed: 10235297]

Ramchandani VA, O'Connor S, Neumark Y, Zimmermann US, Morzorati SL, & de Wit H (2006). The alcohol clamp: applications, challenges, and new directions--an RSA 2004 symposium summary. Alcohol Clin Exp Res, 30(1), 155–164. doi:10.1111/j.1530-0277.2006.00017.x [PubMed: 16433744]

Ritzmann RF, & Tabakoff B (1976). Body temperature in mice: a quantitative measure of alcohol tolerance and physical dependence. J Pharmacol Exp Ther, 199(1), 158–170. [PubMed: 988176]

Ryan D, Ramanathan L, Iida S, Thomas P, Haniu M, Shively J, … Levin W (1985). Characterization of a major form of rat hepatic microsomal cytochrome P-450 induced by isoniazid. Journal of Biological Chemistry, 260(10), 6385–6393. [PubMed: 3997827]

Scholz H, Franz M, & Heberlein U (2005). The hangover gene defines a stress pathway required for ethanol tolerance development. Nature, 436(7052), 845–847. doi:10.1038/nature03864 [PubMed: 16094367]

Schrago CG, Menezes AN, Moreira MA, Pissinatti A, & Seuanez HN (2012). Chronology of deep nodes in the neotropical primate phylogeny: insights from mitochondrial genomes. PLoS One, 7(12), e51699. doi:10.1371/journal.pone.0051699 [PubMed: 23272145]

Schuckit MA (1994). Low level of response to alcohol as a predictor of future alcoholism. Am J Psychiatry, 151(2), 184–189. doi:10.1176/ajp.151.2.184 [PubMed: 8296886]

Schuckit MA, & Smith TL (1996). An 8-year follow-up of 450 sons of alcoholic and control subjects. Arch Gen Psychiatry, 53(3), 202–210. doi:10.1001/archpsyc.1996.01830030020005 [PubMed: 8611056]

Schwandt ML, Higley JD, Suomi SJ, Heilig M, & Barr CS (2008). Rapid tolerance and locomotor sensitization in ethanol-naive adolescent rhesus macaques. Alcohol Clin Exp Res, 32(7), 1217–1228. doi:10.1111/j.1530-0277.2008.00676.x [PubMed: 18482160]

Schwandt ML, Lindell SG, Chen S, Higley JD, Suomi SJ, Heilig M, & Barr CS (2010). Alcohol response and consumption in adolescent rhesus macaques: life history and genetic influences. Alcohol, 44(1), 67–80. doi:10.1016/j.alcohol.2009.09.034 [PubMed: 20113875]

Shiffman S, Stone AA, & Hufford MR (2008). Ecological momentary assessment. Annu Rev Clin Psychol, 4, 1–32. doi:10.1146/annurev.clinpsy.3.022806.091415 [PubMed: 18509902]

Siegel S (1989). Pharmacological conditioning and drug effects Psychoactive drugs (pp. 115–180): Springer.

Singh CM, & Heberlein U (2000). Genetic control of acute ethanol-induced behaviors in Drosophila. Alcohol Clin Exp Res, 24(8), 1127–1136. [PubMed: 10968649]

Steiper ME, & Young NM (2006). Primate molecular divergence dates. Mol Phylogenet Evol, 41(2), 384–394. doi:10.1016/j.ympev.2006.05.021 [PubMed: 16815047]

Swift R (2003). Direct measurement of alcohol and its metabolites. Addiction, 98 Suppl 2, 73–80. [PubMed: 14984244]

Szabó G, Kovács GL, Székeli S, & Telegdy G (1985). The effects of neurohypophyseal hormones on tolerance to the hypothermic effect of ethanol. Alcohol, 2(4), 567–574. [PubMed: 4026981]

Tabakoff B, Cornell N, & Hoffman PL (1986). Alcohol tolerance. Ann Emerg Med, 15(9), 1005–1012. doi:10.1016/s0196-0644(86)80119-6 [PubMed: 3526989]

Tabakoff B, & Ritzmann RF (1977). The effects of 6-hydroxydopamine on tolerance to and dependence on ethanol. 203(2), 319–331.

Thomas S, Bacon AK, Sinha R, Uhart M, & Adinoff B (2012). Clinical laboratory stressors used to study alcohol-stress relationships. Alcohol Res, 34(4), 459–467. [PubMed: 23584112]

Trim RS, Schuckit MA, & Smith TL (2009). The relationships of the level of response to alcohol and additional characteristics to alcohol use disorders across adulthood: a discrete-time survival analysis. Alcohol Clin Exp Res, 33(9), 1562–1570. doi:10.1111/j.1530-0277.2009.00984.x [PubMed: 19485971]

Turker T, Sodmann R, Goebel U, Jatzke S, Knapp M, Lesch KP, … Stober G (1998). High ethanol tolerance in young adults is associated with the low-activity variant of the promoter of the human serotonin transporter gene. Neurosci Lett, 248(3), 147–150. doi:10.1016/s0304-3940(98)00347-4 [PubMed: 9654330]

Varaschin RK, & Morato GS (2009). Selective mu- and kappa-opioid receptor antagonists administered into the nucleus accumbens interfere with rapid tolerance to ethanol in rats. Psychopharmacology (Berl), 206(1), 85–96. doi:10.1007/s00213-009-1582-8 [PubMed: 19506836]

Varaschin RK, Wazlawik E, & Morato GS (2005). Systemic and intra-accumbens microinjections of naltrexone interfere with tolerance to ethanol in rats. Psychopharmacology (Berl), 182(3), 366–374. doi:10.1007/s00213-005-0095-3 [PubMed: 16025314]

Vatsalya V, Stangl BL, Schmidt VY, & Ramchandani VA (2018). Characterization of hangover following intravenous alcohol exposure in social drinkers: methodological and clinical implications. Addict Biol, 23(1), 493–502. doi:10.1111/adb.12469 [PubMed: 27860050]

Vogel-Sprott MDJP (1979). Acute recovery and tolerance to low doses of alcohol: Differences in cognitive and motor skill performance. 61(3), 287–291. doi:10.1007/bf00432274

Zaleski MJ, Nunes Filho JR, Lemos T, & Morato GS (2001). GABA(B) receptors play a role in the development of tolerance to ethanol in mice. Psychopharmacology (Berl), 153(4), 415–424. doi:10.1007/s002130000581 [PubMed: 11243488]

Public Significance Statements

This review article focuses on the translational efforts utilized to understand the neural substrates that affect decreased sensitivity to the effects of alcohol, i.e. alcohol tolerance. The field of alcohol research requires enhanced translational efforts to develop paradigms that can be utilized to elucidate the diverse alcohol use disorder phenotypical profile.