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Tolerance to Alcohol: A Critical Yet Understudied Factor in Alcohol Addiction

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Abstract

Alcohol tolerance refers to a lower effect of alcohol with repeated exposure. Although alcohol tolerance has been historically included in diagnostic manuals as one of the key criteria for a diagnosis of alcohol use disorder (AUD), understanding its neurobiological mechanisms has been neglected in preclinical studies. In this mini-review, we provide a theoretical framework for alcohol tolerance. We then briefly describe chronic tolerance, followed by a longer discussion of behavioral and neurobiological aspects that underlie rapid tolerance in rodent models. Glutamate/nitric oxide, γ-aminobutyric acid, opioids, serotonin, dopamine, adenosine, cannabinoids, norepinephrine, vasopressin, neuropeptide Y, neurosteroids, and protein kinase C all modulate rapid tolerance. Most studies have evaluated the ability of pharmacological manipulations to block the development of rapid tolerance, but only a few studies have assessed their ability to reverse already established tolerance. Notably, only a few studies analyzed sex differences. Neglected areas of study include the incorporation of a key element of tolerance that involves opponent process-like neuroadaptations. Compared with alcohol drinking models, models of rapid tolerance are relatively shorter in duration and are temporally defined, which make them suitable for combining with a wide range of classic and modern research tools, such as pharmacology, optogenetics, calcium imaging, *in vivo* electrophysiology, and DREADDs, for in-depth studies of tolerance. We conclude that studies of the neurobiology of alcohol tolerance should be revisited with modern conceptualizations of addiction and modern neurobiological tools. This may contribute to our understanding of AUD and uncover potential targets that can attenuate hazardous alcohol drinking.

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Keywords

ethanol; alcoholism; alcohol use disorder; alcohol dependence; drug addiction; rodent models; preclinical models

Introduction

> "Because I could handle my drinking — or so I thought — and could consume a lot of alcohol without becoming uncontrollably inebriated, I refused to see it as a problem." Buzz Aldrin (lunar module pilot on the 1969 Apollo 11 mission).

Simply defined, alcohol tolerance occurs when the amount of alcohol that is consumed does not change but results in less of an effect or when higher amounts of alcohol are needed to produce the same effect. Diagnostic manuals, such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and *International Classification of Diseases and Related Health Problems* (ICD), have historically included tolerance as one of the criteria for the diagnosis of alcohol use disorder (AUD). The ICD-8 (World Health Organization, 1968) was the first edition that included alcoholism as a clinical syndrome, but it was not until 1979, with the publication of ICD-9 (World Health Organization, 1979), that consideration was specifically given to tolerance, although this criterion was not necessarily mandatory for a clinical diagnosis (i.e., "tolerance may or may not be present"). Tolerance has been included in the clinical assessment of AUD since the 3rd edition of the DSM (American Psychiatric Association, 1980). DSM-5 (American Psychiatric Association, 2013) includes several alcohol tolerance-related questions for AUD, such as, in the past year, have you "Had times when you ended up drinking more, or longer, than you intended?" "Spent a lot of time drinking?" and "Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?" Indeed, one could expand the construct of tolerance to be a key motivational construct in allostatic theories of addiction, in which tolerance to the rewarding effects of a drug or tolerance to the relief effects of a drug (self-medication) engage a form of misregulation, whereby subjects "chase" drug seeking to recapture the previous reinforcement but fail because of tolerance, thus driving further tolerance (Koob and Le Moal, 1997; Koob, 2021).

To this point, greater resistance to alcohol's effects is associated with a faster progression to and greater severity of AUD (Schuckit, 1994). More specifically, low sensitivity or a low response to alcohol intoxication includes subjective feelings and blunted alcohol-related hormonal and electrophysiological measures that are associated with a family history of AUD and the risk of developing alcohol dependence in humans (Schuckit, 2018). Such a low response has heritability estimates of 40–60% in humans (Schuckit, 2018). Animal studies have confirmed a low response to alcohol in some selectively bred alcohol-preferring rodents (Lumeng et al., 1982).

Nevertheless, possibly influenced by claims that tolerance is neither necessary nor sufficient for a diagnosis of AUD (e.g., Goldstein, 1983), the number of preclinical studies on alcohol tolerance has gradually decreased, whereas the number of preclinical studies on alcohol drinking has steadily increased (Figure 1).

There are several reasons why the construct of tolerance has fallen out of neurobiological inquiry. Historically, many studies of tolerance focused on physiological processes and measures that at least superficially have apparently little relevance to the development of addiction or AUD (e.g., locomotor activity and body temperature). Moreover, tolerance appears to be necessary but not sufficient for the development of more debilitating AUD symptoms that have received greater attention and research focus, such as withdrawal, craving, relapse, or the escalation of drinking. Indeed, opponent processes and underlying neuroadaptations (e.g., glucocorticoid receptor and corticotropin-releasing factor (CRF) signaling in the extended amygdala; Vendruscolo and Koob, 2020; Vendruscolo et al., 2015; Tunstall et al., 2017) have been demonstrated to be involved in many of these important AUD constructs and symptoms and not been linked to tolerance. Following this logic, the engagement of negative reinforcement processes would be considered more of an “active” process that drives excessive drinking, whereas tolerance is considered more “passive” and simply permissive in the process by comparison. Nevertheless, there is a burgeoning reawakening of the link between neuroadaptations that are involved in driving the “dark side” of addiction and tolerance that deserve attention (Pietrzykowski et al., 2008; Koob, 2020; Koob, 2021).

We argue that a specific domain of tolerance, reward or hedonic tolerance, reflects underlying neuroadaptive processes that are critically linked to underlying processes of motivational withdrawal, the “dark side” of AUD, and compulsive alcohol seeking and as such are key to understanding AUD.

In this review, we provide a conceptual framework for the neurobiology of alcohol tolerance. We then discuss functional tolerance, in which we briefly describe chronic tolerance to alcohol. We elaborate rapid tolerance to alcohol more comprehensively, including its behavioral and neurobiological aspects and the ways in which it can be modeled in laboratory animals. Our emphasis on rapid tolerance stems from its possible role as a predictor of the development of chronic tolerance (Khanna et al., 1991b; Rustay and Crabbe, 2004) and chronic cross-tolerance to other drugs (Bitrán and Kalant, 1993; Khanna et al., 1991b). Furthermore, “simplistic” experimental procedures that are used to evaluate rapid tolerance can be combined with such techniques as pharmacology, optogenetics, calcium imaging, *in vivo* electrophysiology, and designer receptors exclusively activated by designer drugs (DREADDs) to systematically investigate alcohol tolerance. Although we do not discuss dispositional tolerance that is related to an increase in alcohol metabolism, excellent reviews on this topic have been published (Kalant, 1998; Morato et al., 1996; Riveros-Rosas et al., 1997; Teschke, 2018). Although we do not discuss acute tolerance or acute functional tolerance (i.e., within a single session of alcohol exposure), excellent original and review articles on functional tolerance in humans (e.g., Comley et al., 2020) and preclinical animal models (e.g., Kalant et al., 1998; Tullis et al., 1977; Parker et al., 2020) have been published. We suggest that studies of alcohol sensitivity and tolerance using classic and modern experimental techniques will provide critical information to further understand AUD.

Conceptual Framework for Alcohol Tolerance

In addition to dispositional tolerance (i.e., an increase in metabolism), early studies reported that rodents that were repeatedly exposed to alcohol exhibited tolerance, measured by early recovery from a sedative dose of alcohol while having high brain alcohol levels compared with controls (Levy, 1935). These findings unequivocally indicate the participation of pharmacodynamic mechanisms in alcohol tolerance. Initial hypotheses of tolerance invoked changes in the lower sensitivity of molecular transduction mechanisms, such as second messenger systems, receptor internalization, transcriptional changes, recycling, and structural changes, in the acute effects of alcohol, but this became challenging with alcohol because it has a multitude of targets to exert its acute pharmacological effects (Harris and Koob, 2017). As a result, desensitization plays a role in a wide range of alcohol actions, not simply intoxication, and presumably reverses with the removal of alcohol.

An alternate but key theoretical framework for investigating tolerance that is relevant to intoxication and addiction can be found in opponent-process theory (Solomon and Corbit, 1974). Affective control mechanisms in the brain are hypothesized to serve as an emotional stabilization system that counteracts departures from emotional neutrality or equilibrium, regardless of whether they are aversive or pleasant (Solomon and Corbit, 1974). The initial use of a drug triggers a primary affective process (a positive hedonic process), termed the *a-process*, which has a short time constant. This triggers an opposing *b-process* (an aversive negative emotional state) that responds with a slow rise and slow decay. With repeated drug taking, the *b-process* is strengthened so that it has a faster onset and greater intensity and takes longer to decay (Solomon and Corbit, 1974). Development of the *b-process* reflects the development of hyperkatifeia, defined as an increase in intensity of the constellation of negative emotional or motivational signs and symptoms of withdrawal from drugs of abuse (Shurman et al., 2010), such as dysphoria, anxiety, alexithymia, irritability, sleep disturbances, physical and emotional pain, subjective feelings of unease, and simply not feeling hedonically normal. Hyperkatifeia was formulated as an emotional parallel to hyperalgesia (i.e., greater sensitivity to physical pain) that is observed with repeated opioid and alcohol administration (Edwards et al., 2012; Koob, 2021; Shurman et al., 2010). Masking the *a-process* by a growing *b-process* results in “apparent tolerance” (Colpaert, 1996; Laulin et al., 1999; Park et al., 2015). Colpaert and Fregnac (2001) referred to tolerance as “apparent tolerance” to reflect the observation that with repeated administration, the primary effect of a drug (in their formulation, an opioid analgesic) did not change, but in fact its manifestation was diminished by what they termed “contra-directional second order effects” and what Solomon termed the *b-process* in opponent process theory (Solomon and Corbit, 1974). If the drug does not generate a sufficient *b-process*, then it follows that tolerance does not develop. Hypothetically, a treatment that prevents the *b-process* would block the development of tolerance, although to our knowledge this hypothesis has not been directly tested. From our theoretical hedonic domain perspective, the neuropharmacological blockade of any of the within- or between-system neuroadaptations that are discussed below would have such an action. Thus, based on opponent process theory, tolerance and dependence are inextricably linked. When the hedonic effects of the drug subside and when the *b-process* gets progressively larger over time, more complete tolerance to the initial

euphoric effects of the drug results (Koob and Le Moal, 1997). Thus, we argue that the study of hedonic tolerance to alcohol can be used as a surrogate for understanding AUD.

A framework for tolerance that historically embraced a homeostatic model (Martin, 1968; Solomon and Corbit, 1974) is expanded herein to parallel neuroadaptations that are hypothesized to mediate within-system and between-system changes in the brain that are produced by chronic drug administration (Koob and Bloom, 1988). In a within-system adaptation, repeated alcohol administration would be argued to be the process by which the primary cellular response to the drug within a given neurochemical circuit itself adapts to neutralize the effects of the drug. In a between-system adaptation, repeated alcohol administration recruits circuitry changes whereby other circuits (that generate opposing responses) are activated to oppose overactivity in reward circuits (Koob and Bloom, 1988). The limited data that are available from studies of alcohol tolerance have provided evidence of both within- and between-system neuroadaptations. Clearly, one could theoretically block the development of tolerance by blocking the initial acute neuronal-activating or -inhibiting effects of alcohol before any within- or between-system neuroadaptation occurs. However, one could theoretically also block the development of tolerance if the treatment blocks or reverses the neuroadaptation that is triggered by the acute neuronal-activating or -inhibiting effects of alcohol.

Originally conceptualized as a homeostatic model, accumulating evidence suggests that such opponent process-like within- and between-system neuroadaptations can drive allostatic changes, in which stability is altered but via a new set point (Sterling, 1988). Although beyond the scope of the present mini-review, tolerance should also be considered an intricate part of the allostatic process that drives and perpetuates addiction, particularly regarding the engagement of brain stress systems as part of between-system neuroadaptations (Koob and Bloom, 1988; Koob and Le Moal, 1997).

Thus, for within- and between-system neuroadaptations, alcohol tolerance may also be hypothesized to be prevented by blocking the acute within-system neuroadaptations that contribute to withdrawal. One could argue that within-system neuroadaptations that produce hyperkatifeia and consequently “apparent tolerance” result from actions within a given neurochemical or neural circuit that is associated with the intoxicating effects of alcohol and include changes in molecular events at the receptor level and the actions of downstream effectors, including receptor desensitization/internalization and transcriptional/structural alterations (Cahill et al., 2016). However, tolerance to alcohol could also theoretically result from between-system neuroadaptations that involve the activation of separate neurocircuits that are not directly involved in the intoxicating effects of alcohol and that also contribute to hyperkatifeia that is associated with acute alcohol withdrawal (Koob, 2021). Below we provide an overview of studies of alcohol tolerance that used neuropharmacological tools, and we bridge these findings with the conceptual framework that is outlined above. We emphasize that more studies are needed to establish whether specific neurotransmitter systems and components therein (e.g., different receptor subunits) are functionally involved in within-system neuroadaptations or between-system neuroadaptations. To date, most studies of alcohol tolerance have only investigated within-system neuroadaptations.

Chronic Tolerance to Alcohol

Chronic tolerance is reflected by both an increase in alcohol metabolism (i.e., pharmacokinetic tolerance; Hawkins and Kalant, 1972; Kalant et al., 1971; Riveros-Rosas et al., 1997; Teschke, 2018) and pharmacodynamic tolerance. One example of chronic tolerance is shown in Figure 2. Male mice that were exposed to a binge drinking model for 14 consecutive days developed tolerance to alcohol-induced motor incoordination (Linsenbardt et al., 2011). Male mice that were tested in the 8^{th} drinking session exhibited motor incoordination compared with male alcohol-naive mice. However, mice that were tested following their 15^{th} drinking session exhibited motor performance that was similar to alcohol-naive mice, indicating the development of chronic tolerance. Mice that were chronically exposed to alcohol had blood alcohol levels that were similar to alcohol-naive mice when measured at several timepoints after alcohol administration, indicating that improvements in motor performance were not attributable to an increase in alcohol metabolism (Linsenbardt et al., 2011).

Multiple neurotransmitter systems have been implicated in acute and chronic tolerance. Many of those systems (mainly within-system) overlap with those of rapid tolerance (described below). However, a description of these systems is beyond the scope of the present mini-review.

Rapid Tolerance

Rapid tolerance can be operationally defined as a reduction of alcohol's effects during a second alcohol exposure that occurs 8–24 h after the first exposure (Sharma et al., 2014). Note that according to the opponent process framework that is outlined above, hyperkatifeia (i.e., the negative emotional state that is associated with drug withdrawal) starts with acute withdrawal that is associated with the first administration of a drug (Koob 2020, 2021).

Behavioral and physiological measures that have been shown to reflect rapid tolerance to alcohol include hypothermia, non-rapid-eye-movement sleep promotion, circadian clock phase resetting (e.g., Lindsay et al., 2014; not discussed herein), motor incoordination, and sedation. Critically, rapid tolerance may be a predictor of the development of chronic tolerance (Le and Kiianmaa, 1988; Khanna et al., 1991b; Rustay and Crabbe, 2004) and chronic cross-tolerance to other drugs (Bitrán and Kalant, 1993; Khanna et al., 1991b). In this review, we focus on rodent models of rapid tolerance to alcohol. However, we acknowledge that other animal models, including *Drosophila melanogaster*, have provided valuable information about the genetic and molecular regulation of rapid tolerance to alcohol. For example, some studies have investigated the role of the small guanosine triphosphatase Arf6 (Gonzalez et al., 2018), G-protein receptor kinase 2 (Kang et al., 2020), and BK Ca^{2+}-activated K^+ channels (Krishnan et al., 2016) in regulating alcohol-induced sedation and activity in *Drosophila*.

An intraperitoneal injection of alcohol induced hypothermia in male mice. The hypothermic effect of alcohol was attenuated after a second administration of the same dose 24 h later (Crabbe et al., 1979). Acutely, a higher dose of alcohol causes a greater hypothermic effect, but the same magnitude of rapid tolerance is observed (Figure 3). This effect was evident

when the time between exposures was 24 h but not 48 or 72 h. These findings suggest that, under these conditions, rapid tolerance to hypothermia develops, regardless of the alcohol dose, but only when the second exposure to alcohol occurs within 24 h of the first alcohol exposure.

Sharma et al. (2014) showed that male mice that binge drank alcohol developed rapid tolerance to alcohol-induced increases in non-rapid-eye-movement sleep, measured by electroencephalography and electromyography. Male and female rats exhibited rapid tolerance to alcohol's sedative effect during adolescence on postnatal day 36 and during young adulthood on postnatal day 56, whereas no rapid tolerance was observed in rats on postnatal day 16. On postnatal day 56, males exhibited greater sedation compared with females, but no sex differences in the development of rapid tolerance were observed (Silveri and Spear, 1999). Male rats of three different ages (4, 13, and 25 months) did not differ in rapid tolerance to hypothermia that was induced by alcohol, but 4-month-old rats developed greater rapid tolerance to sedation than the other ages (Chan and York, 1994).

Alcohol sensitivity and rapid tolerance also depend on genetic factors. Male rats that were selectively bred for high alcohol drinking were less sensitive to alcohol-induced sedation, measured by a shorter time to recover from the loss-of-righting reflex, than selectively bred low-alcohol-drinking male rats. This test is commonly performed by treating rodents with a sedative dose of alcohol and placing them in a supine position on a V-shaped platform. The time for the rodents to lose and then regain the righting reflex is used as a measure of sedation. Notably, high-alcohol-drinking rats developed rapid tolerance to the sedative effects of alcohol on day 2, whereas low-alcohol-drinking rats did not (Froehlich and Wand, 1997). These findings suggest that lower sensitivity to alcohol and the development of tolerance may be associated with higher levels of alcohol drinking, similar to observations in humans (Schuckit, 1994). The genetic contribution to rapid tolerance to ataxia was estimated in several inbred strains of mice of both sexes. No sex differences were observed, but the numerous mouse strains exhibited different degrees of tolerance. Moreover, mouse lines that were selected for high and low rapid tolerance exhibited chronic tolerance to alcohol in the same direction, thus providing evidence of a genetic link between rapid tolerance and chronic tolerance to alcohol (Rustay and Crabbe, 2004). Several other studies in male rodents also indicated a genetic component of rapid tolerance (Gallaher et al., 1996; Radcliffe et al., 2013, 2006, 2005).

Rapid cross-tolerance between alcohol and other drugs has also been observed using the tilt-plane test. This method involves gradually inclining a slightly textured plane until the animal is unable to maintain stability and slides from its starting position. The angle at which the animal begins to slide is used as a measure of motor impairment. Pretreatment with alcohol in male rats did not cause rapid cross-tolerance to pentobarbital, but pretreatment with pentobarbital caused rapid cross-tolerance to alcohol (Khanna et al., 1991a). Male rats exhibited rapid cross-tolerance (hypothermia and tilt-plane) to the alcohols n-propanol, n-butanol, and t-butanol. Cross-tolerance with alcohol was also observed with the benzodiazepines chlordiazepoxide, diazepam, oxazepam, and flurazepam and the barbiturates barbital and phenobarbital but not pentobarbital, secobarbital, amobarbital, or thiopental (Khanna et al., 1992b); Khanna et al., 1998). Rapid cross-tolerance between

Δ^9-tetrahydrocannabinol and alcohol has also been reported (da Silva et al., 2001). The cannabinoid CB_1 receptor inverse agonist rimonabant had no effect on alcohol and Δ^9-tetrahydrocannabinol cross-tolerance (da Silva et al., 2001). In another study, an intraperitoneal or intracerebroventricular injection of rimonabant blocked rapid alcohol tolerance in male rats in the tilt-plane test, whereas the CB_1 receptor agonist WIN 55,212–2 facilitated it (Lemos et al., 2007).

Learning factors play a role in rapid alcohol tolerance. In the moving belt test, rats are trained to walk on a belt that moves over a shock grid. If the animal touches the grid, then it receives a mild shock. Motor impairment is reflected by the time that elapses between placing the animal on the moving belt and the shock delivery. Exposing male rats to a single dose of alcohol, followed by intensive intoxicated practice on the moving belt, resulted in tolerance to the motor-impairing effects of a second dose of alcohol that was given 8 or 24 h later. Without such practice during intoxication, however, alcohol tolerance did not develop (Bitrán and Kalant, 1991). Anisomycin blocked the development of rapid tolerance in the moving belt test, suggesting that rapid tolerance requires *de novo* protein synthesis (Bitrán and Kalant, 1993).

Pharmacology of Rapid Tolerance: Within-System Neuroadaptations

The acute reinforcing effects, and by extrapolation “intoxicating” effects, of alcohol are mediated by multiple neurotransmitter systems, including γ-aminobutyric acid (GABA), opioid peptides, dopamine, serotonin, and glutamate (Koob, 2014; Morato and Khanna, 1996). The activation of these neurotransmitter systems that mediate the intoxicating effects of alcohol produced acute within-system neuroadaptations that involve multiple targets. Based on the conceptual framework of within-system neuroadaptations that is outlined above, our review of the literature on rapid tolerance revealed the following systems as potential mediators.

GABA—Although one might hypothesize that GABA receptor agonism/positive allosterism would reduce GABA receptor sensitivity and contribute to alcohol tolerance, data suggest that the effect of GABA receptor agonism/positive allosterism on alcohol tolerance may not necessarily be associated with the sensitivity of GABA receptors but rather interference with alcohol-induced neuroplasticity via a reduction of opponent processes that are engaged by alcohol intoxication.

A classic test of intoxication with alcohol in rodents is a motor measure. The rotarod test utilizes a rotating rod that is raised above a table. Rodents are trained to walk while the rod rotates at a fixed or accelerating speed. The rotations per minute and time at which the animal falls from the rod are recorded. Treatments that disrupt motor coordination, such as alcohol, cause the animal to fall from the rod sooner and at a lower revolution speed.

GABA agonists block the development of rapid tolerance. Muscimol, a $GABA_A$ receptor agonist, blocked alcohol tolerance in the rotarod test (Barbosa and Morato, 2001). Similarly, the $GABA_B$ receptor agonist baclofen blocked rapid tolerance to alcohol, whereas the opposite effect was found with the $GABA_B$ receptor antagonists CGP36742 and CGP56433, which facilitated rapid alcohol tolerance in male mice (Zaleski et al., 2001).

Neurosteroids allosterically modulate $GABA_A$ receptors and provide a means of modulating $GABA_A$ receptor function in studies of tolerance. Isopregnanolone, a positive allosteric modulator of $GABA_A$ receptors, blocked rapid tolerance to the anxiolytic-like effects of alcohol (Debatin and Barbosa, 2006), and epipregnanolone and allotetrahydrodeoxycorticosterone, positive allosteric modulators of $GABA_A$ receptors, blocked the motor-impairing and hypothermic effects of alcohol in male mice (Barbosa and Morato, 2002, 2007). However, pregnenolone sulfate and dehydroepiandrosterone sulfate, negative allosteric modulators of $GABA_A$ receptors, facilitated rapid tolerance to alcohol-induced hypothermia in male mice (Barbosa and Morato, 2002). Pretreatment with pregnenolone sulfate and dehydroepiandrosterone sulfate prevented the inhibitory effect of muscimol on rapid tolerance (Barbosa and Morato, 2001). These findings suggest that GABA receptor agonists or neurosteroids that show the positive allosteric modulation of GABA receptors block the development of rapid tolerance, whereas GABA receptor antagonists or neurosteroids that show the negative allosteric modulation of GABA receptors facilitate rapid tolerance to alcohol, possibly by interfering with alcohol-induced opponent processes.

Endogenous opioid systems—Male rats were pretreated with systemic or intra-nucleus accumbens (NAc) injections of naltrexone or vehicle, followed alcohol or saline administration 30 min later. The rats that received either systemic or intra-NAc (core or shell) injections of naltrexone did not develop rapid tolerance in the tilt-plane test. Naloxonazine, a potent and irreversible μ-opioid receptor antagonist, was administered in the core and shell of the NAc and also blocked the development of rapid tolerance in the tilt-plane test (Varaschin and Morato, 2009).

The second-messenger enzyme protein kinase Cγ is involved in tolerance to opioids (Bailey et al., 2006) and has been shown to be involved in the initial effects of alcohol and development of rapid and chronic tolerance. Male and female C57BL/6J and 129/SvJ mice on a mixed genetic background with a null mutation of protein kinase Cγ did not exhibit rapid tolerance to alcohol's hypothermic or sedative effects. The re-introduction of the null mutation rescued rapid alcohol tolerance in C57BL/6J mice. However, re-introduction of the null mutant in C57BL/6J and 129/SvEvTac mice on a mixed genetic background rescued rapid tolerance to the sedative but not hypothermic effects of alcohol (Bowers et al., 1999, 2000). Sex differences were not analyzed in this study, but these findings indicate a role for protein kinase Cγ in rapid alcohol tolerance, and these effects appear to depend on the genetic background and specific behavioral/physiological measures.

Dopamine and adenosine—Male mice that were pretreated with the dopamine D_1 receptor antagonist SCH23390 but not the D_2 receptor antagonist sulpiride before their first dose of alcohol did not exhibit rapid tolerance in the rotarod test. Adenosine receptors are known to interact with dopamine. Pretreatment with the nonselective adenosine receptor antagonist caffeine and adenosine A_1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine in mice blocked the development of rapid alcohol tolerance in the rotarod test, whereas the A_{2A}-receptor antagonist 4-(2-[7-amino-2-{2-furyl}{1,2,4}triazolo-{2,3-a}{1,3,5}triazin-5-yl-amino]ethyl)phenol did not (Batista et al., 2005). Finally, a cellular prion

protein that alters the dopaminergic system by interfering with dopamine synthesis, content, and receptor density blocked rapid tolerance in female mice in the rotarod test (Rial et al., 2014). These findings suggest that adenosine A_1 receptors and dopamine D_1 receptors may play a role in the development of rapid tolerance.

Serotonin—Following an acute dose of alcohol, extracellular levels of serotonin are significantly higher (Bare et al., 1998) in the nucleus accumbens and ventral hippocampus in male rats. Male Wistar rats developed tolerance to a second dose of 24 h after the first dose, reflected by a decrease in extracellular serotonin levels in the ventral hippocampus (Bare et al., 1998). However, male alcohol-preferring rats exhibited a similar magnitude of the increase in extracellular serotonin levels in the ventral hippocampus following both the first and second doses (Thielen et al., 2002). L-tryptophan is the precursor of 5-hydroxytryptaminne (5-HT; serotonin) and increases 5-HT levels in the brain. Male rats were given L-tryptophan or water by oral gavage for 6 days. On day 7, they were pretreated with L-tryptophan or saline 30 min before receiving the first dose of alcohol or saline. On day 8 (day 2 of alcohol exposure), rats that received chronic L-tryptophan treatment exhibited an increase in rapid tolerance to alcohol in the tilt-plane test. Treatment with (+)MK-801 before L-tryptophan on day 7 dose-dependently attenuated the enhancement of rapid tolerance in the tilt-plane test in rats that were chronically treated with L-tryptophan (Khanna et al., 1994), suggesting an interaction between serotonin and *N*-methyl-D-aspartate (NMDA) receptors during the development of rapid tolerance.

Glutamate and nitric oxide—Khanna et al. (1991b, 1992a, 1992c) tested the effects of different NMDA receptor antagonists on the development of rapid tolerance in male rats in the tilt-plane test. Pretreatment with the NMDA receptor antagonist (+)MK-801 but not the inactive isomer (−)MK-801 blocked the development of rapid tolerance (Khanna et al., 1991b). A similar effect was found with pretreatment with another NMDA receptor antagonist, ketamine (Khanna et al., 1992a). Both (+)MK-801 and ketamine dose-dependently blocked rapid tolerance in the tilt-plane test when they were given before the first exposure to alcohol but not when they were given after the first exposure to alcohol (Khanna et al., 1992a; Khanna et al., 1993a). Additionally, pretreatment with these NMDA receptor antagonists had no effect on the development of rapid tolerance in rats that were only placed on the tilt-plane without actually tilting the plane on day 1 (Khanna et al., 1997).

Male rats that received D-cycloserine, an agonist at the glycine site of NMDA receptors, before alcohol administration exhibited an increase in rapid tolerance in the tilt-plane test, an effect that was blocked by (+)MK-801 (Khanna et al., 1993a). These findings suggest that NMDA receptor antagonists prevent the development but not expression of rapid tolerance, which appears to involve learning mechanisms during practice while intoxicated. Rapid tolerance to sedation was absent in GluN2A knockout mice (Daut et al., 2015). Both (+)MK-801 and ketamine also blocked rapid tolerance and rapid cross-tolerance between alcohol and chlordiazepoxide in the tilt-plane test (Khanna et al., 1992c). D-cycloserine treatment before but not after intoxicated practice in the tilt-plane test that occurred on day 1 facilitated the development of rapid tolerance to a typically subthreshold dose of alcohol (Khanna et al., 1995a).

We found one study that was conducted in only female mice. NMDA receptor antagonism with ketamine or MK-801 dose-dependently reduced the development of rapid tolerance in the rotarod test (Barreto et al., 1998), as was observed in studies on male rats that are described above.

Nitric oxide is a downstream facilitator of NMDA receptor activity. Male rats that were intracerebroventricularly treated with nitric oxide donors developed greater rapid alcohol tolerance in the tilt-plane test (Wazlawik and Morato, 2003). Male rats that received intraperitoneal or intracerebroventricular injections of nitric oxide synthase inhibitors before but not after alcohol administration did not exhibit rapid alcohol tolerance in the tilt-plane test (Khanna et al., 1993b; Khanna et al., 1995b; Wazlawik and Morato, 2002). Nitric oxide synthase inhibitors that were administered before but not after alcohol administration also blocked the enhancement of rapid tolerance by the NMDA receptor agonist cycloserine (Khanna et al., 1995a). Intracerebroventricular administration of the neuronal nitric oxide synthase inhibitor 7-nitroindazole in male rats blocked rapid tolerance, and co-administration of the nitric oxide precursor L-arginine and nitric oxide synthase inhibitor rescued this effect. D-arginine, an inactive isomer of L-arginine, had no effect on rapid tolerance in the tilt-plane test (Wazlawik and Morato, 2002). Mice (sex not specified) that were deficient in the neuronal nitric oxide synthase gene drank more alcohol and were less sensitive to alcohol's sedative effect than wildtype mice, and they did not develop rapid tolerance to alcohol's hypothermic effect (Spanagel et al., 2002). Guanylate cyclase is a mediator of nitric oxide activity. Male rats that were treated with soluble guanylate cyclase inhibitors did not develop rapid tolerance in the tilt-plane test (Wazlawik and Morato, 2003). Collectively, these findings indicate that nitric oxide activity is important for the development of tolerance during alcohol intoxication.

Rial et al. (2009) investigated the role of glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in rapid alcohol tolerance in the rotarod test. Mice that were treated with the AMPA receptor agonist aniracetam before their first exposure to alcohol exhibited improvements in rotarod performance following their second exposure to alcohol 24 h later, indicating the facilitation of rapid tolerance, whereas pretreatment with the AMPA receptor antagonist DNQX on day 1 blocked rapid tolerance on day 2 (Rial et al., 2009).

Pharmacology of Rapid Tolerance: Between-System Neuroadaptations

Neurotransmitter systems that are associated with between-system hyperkatifeia in acute withdrawal represent largely brain stress systems that are localized to the extended amygdala. The activation of these brain stress neurotransmitter systems that respond to the intoxicating effects of alcohol produce between-system neuroadaptations that also contribute to tolerance. Based on the conceptual framework of between-system neuroadaptations that are outlined above, our review of the literature on rapid tolerance revealed the following systems as potential mediators.

Norepinephrine, vasopressin, CRF, and dynorphin—We found one study that reported that the depletion of norepinephrine before alcohol exposure in male mice blocked

rapid tolerance to alcohol's sedative and hypothermic effects (Melchior and Tabakoff, 1981). In a series of studies in the 1970s, De Wied reported the participation of central nervous system actions of the neuropeptide vasopressin in learned behavior (e.g., de Wied, 1976) and opioid and alcohol tolerance, dependence, and self-administration (van Ree and de Wied, 1980). Numerous studies showed that vasopressin facilitated the development of chronic tolerance, and vasopressin receptor antagonists blocked the development of chronic tolerance (Harper et al., 2018; Kalant, 1998). Szabó et al. found that treatment with higher doses of lysine vasopressin before the first alcohol exposure blocked rapid tolerance to alcohol's sedative effects, whereas a lower dose facilitated it (Szabó et al., 1985). A vasopressin analogue that was systemically administered in male mice blocked rapid tolerance to alcohol's hypothermic effects (Crabbe et al., 1979). The authors speculated that vasopressin has a hyperthermic effect *per se* and may act as an antagonist of the hypothermic effect of alcohol. Although the mice were tested in a typical 2-day rapid tolerance experiment, the experiment was repeated weekly, which may have also led to conditioned compensatory hyperthermic responses. We did not find any studies on CRF and rapid tolerance to alcohol.

Injections of nor-binaltorphimine, a κ-opioid receptor antagonist, in the NAc core but not shell also reduced rapid tolerance in the tilt-plane test, whereas naltrindole, a potent and selective δ-opioid receptor antagonist, had no effect (Varaschin and Morato, 2009).

Neuropeptide Y—Alcohol treatment produced an anxiolytic-like response in male rats in the elevated plus maze and induced molecular effects that increased the expression of neuropeptide Y (NPY) in the central and medial nuclei of the amygdala. However, rats that received the same dose of alcohol 24 h later did not exhibit these behavioral or neuropharmacological effects. Pharmacological treatments via G9a-mediated epigenetic mechanisms increased NPY expression in the amygdala and reversed rapid tolerance to the anxiolytic-effects of alcohol (Berkel et al., 2019; Sakharkar et al., 2012).

Oxytocin—Oxytocin is another stress-related peptide that is involved in alcohol-related behaviors in dependent rodents and humans (Pedersen, 2017; Tunstall et al., 2019) and has long been implicated in the development of chronic alcohol tolerance (Szabó et al., 1985; van Ree and de Wied, 1980). The systemic administration of oxytocin (Szabó et al., 1985) or its C-terminal fragments (Aoun et al., 2017; Vendruscolo et al., 2015) before alcohol exposure blocked the development of rapid tolerance to the hypothermic effects of alcohol in male mice.

Conclusions

Rapid tolerance to alcohol is a well-established model of some of the earliest neuroadaptations to alcohol that may be hypothesized to set up a cascade of further neuroadaptations that are associated with acute withdrawal, which in turn evolve into profound neurocircuitry alterations that further drive moderate to severe AUD (Koob and Harris, 2017). Despite being a key and common component of the diagnosis of AUD, a clear etiological feature of AUD, and one of the more prominent conceptual rationales for studying of addiction, studies of the neurobiological bases of tolerance have been

largely neglected in the past 40 years. Future studies should focus on areas of research that have been relatively neglected to date, namely measures that are more directly related to hedonic responses, the genetic and epigenetic basis of tolerance, sex differences, and between-system neuroadaptations. Many alcohol tolerance models are relatively simple, and the effects can be temporally defined. Such models may be combined with classic and modern experimental tools, such as pharmacology, optogenetics, DREADDs, calcium imaging, and *in vivo* electrophysiology, to systematically study neurobiological aspects that underlie alcohol tolerance. Additionally, very little is known about region-, pathway-, and cell type-specific effects on rapid tolerance and the many neurotransmitter systems that are involved in this process. Such studies will contribute substantially to our understanding of AUD and potentially reveal new targets for the diagnosis, prevention, and treatment of AUD.

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Highlights

- Tolerance is a diagnostic criterion for alcohol use disorder.
- Alcohol tolerance has been neglected in preclinical research.
- Understanding alcohol tolerance may contribute to the treatment of alcohol use disorder.

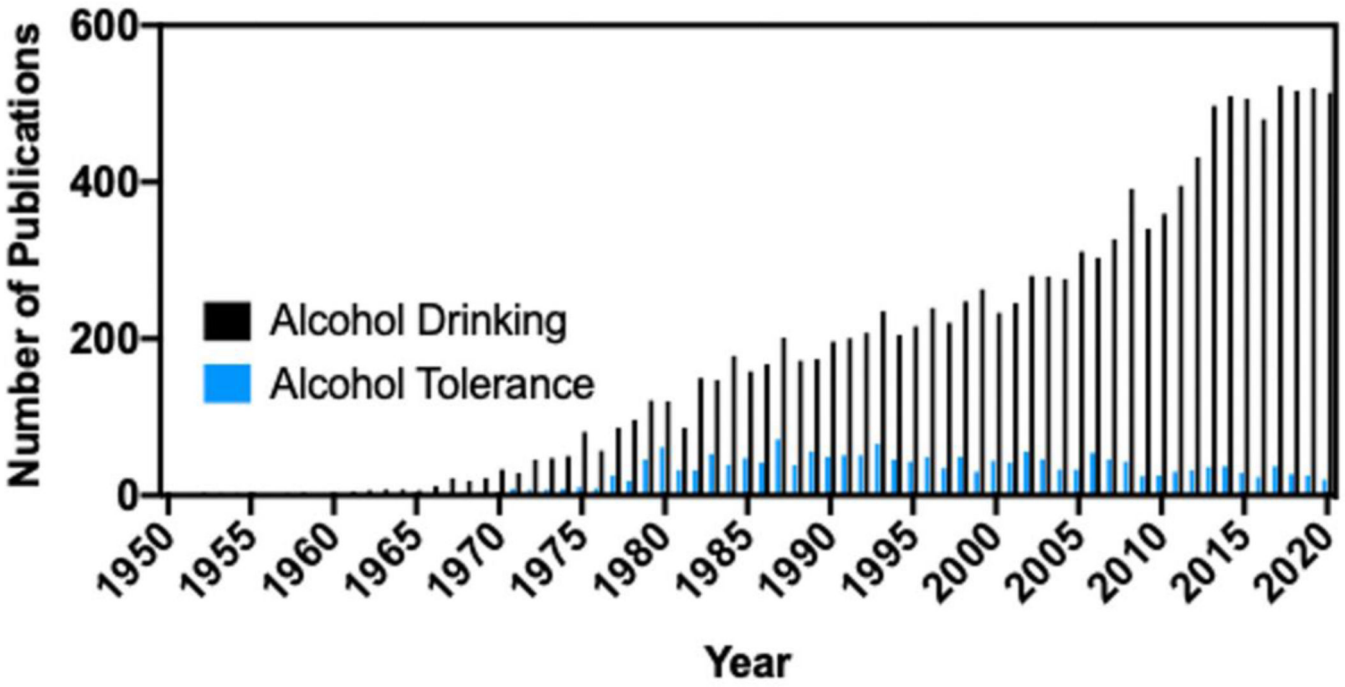

Figure 1. PubMed results of articles published between 1960 and 2020 referencing alcohol tolerance or alcohol drinking in rodents.

PubMed was searched on December 31st, 2020. The following search terms for alcohol tolerance (blue bars) and alcohol drinking (black bars) were used: (alcohol[ti] OR ethanol[ti]) AND (tolerance[tw] OR tolerant[tw]) AND (rat[tw] OR rats[tw] OR mice[tw] OR mouse[tw]). Search terms for alcohol drinking (black bars): (alcohol[ti] OR ethanol[ti]) AND (drinking[tw] OR "self-administer"[tw] OR "self-administered"[tw] OR "self-administers"[tw] OR "self-administration"[tw] OR consume[tw] OR consumed[tw] OR consumes[tw] OR consumption[tw]) AND (rat[tw] OR rats[tw] OR mice[tw] OR mouse[tw]). The search yielded a total of 1,882 articles for tolerance and 12,847 articles for drinking.

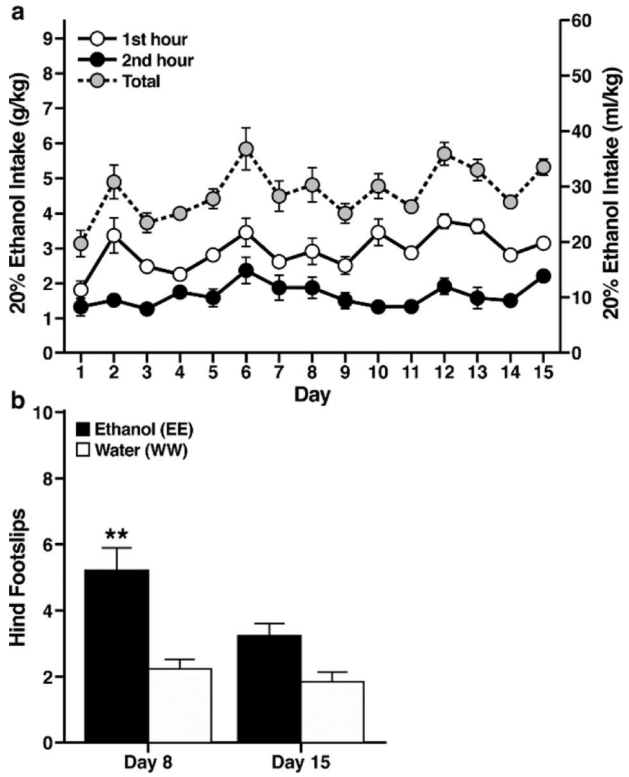

Figure 2. Alcohol consumption and motor coordination in mice.

(a) Alcohol intake (g/kg in 2 h) in mice in the drinking-in-the-dark paradigm, in which mice could drink from a single bottle that contained 20% alcohol (v/v) 3 h into their dark phase. A separate cohort of mice received water instead of alcohol and served as controls (water intake not shown). (b) Motor coordination in the balance beam test, which consisted of a long and narrow wood block that was elevated above the floor. After training the mice to traverse the wood block, they were tested immediately after the 8^{th} and 15^{th} drinking-in-the-dark sessions. Mice that were exposed to drinking-in-the-dark exhibited motor incoordination during the 8^{th} session but not during the 1^{5th} session compared with the mice that drank water only. Modified from Linsenbardt et al. (2011), with permission.

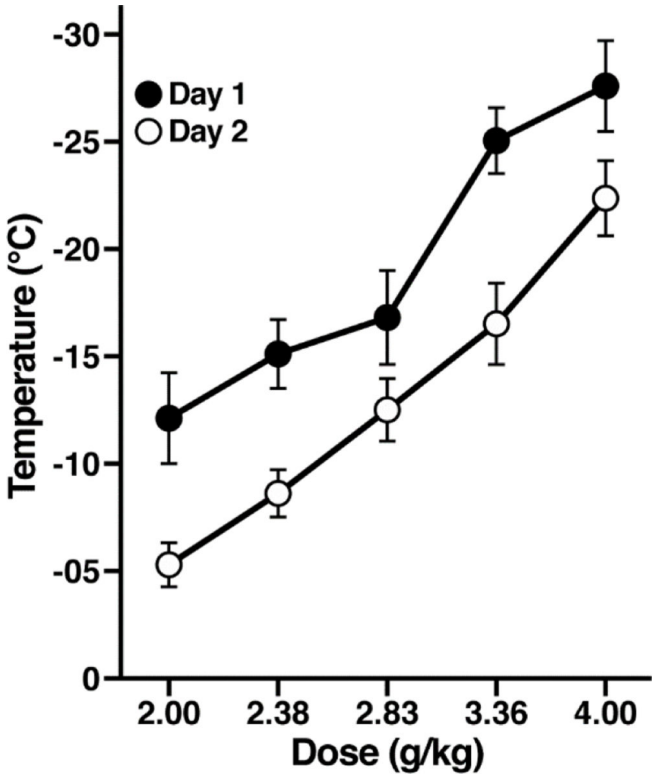

Figure 3. Dose-response curve for alcohol-induced hypothermia and the development of rapid tolerance.

Alcohol dose-dependently produced hypothermia in mice, an effect that decreased, regardless of dose, when the mice were tested with the same doses on day 2. Taken with permission from (Crabbe et al., 1979).