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Alcohol and violence: neuropeptidergic modulation of monoamine systems

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Abstract

Neurobiological processes underlying the epidemiologically-established link between alcohol and several types of social, aggressive, and violent behavior remain poorly understood. Acute low doses of alcohol, as well as withdrawal from long-term alcohol use, may lead to escalated aggressive behavior in a subset of individuals. An urgent task will be to disentangle the host of interacting genetic and environmental risk factors in individuals that are predisposed to engage in escalated aggressive behavior. The modulation of 5-hydroxytryptamine impulse flow by gamma-aminobutyric acid (GABA) and glutamate, acting via distinct ionotropic and metabotropic receptor subtypes in the dorsal raphe nucleus during alcohol consumption, is of critical significance in the suppression and escalation of aggressive behavior. In anticipation and reaction to aggressive behavior, neuropeptides such as corticotropin-releasing factor, neuropeptide Y, opioid peptides, and vasopressin interact with monoamines, GABA, and glutamate to attenuate and amplify aggressive behavior in alcohol-consuming individuals. These neuromodulators represent novel molecular targets for intervention that await clinical validation. Intermittent episodes of brief social defeat during aggressive confrontations are sufficient to cause long-lasting neuroadaptations that can lead to the escalation of alcohol consumption.

Keywords

violence; aggression; alcohol; GABA; glutamate; serotonin

Alcohol has been linked to at least half of all violent assaults, cases of child abuse, and other incidents of domestic violence as well as homicides and murders.[1–3] This association has persisted over several decades and extends across most regions of the world. While the consumption of alcohol features prominently in many celebratory and salient events in social life, it is the anti-social, destructive nature of alcohol's effects that is of profound concern to the criminal justice system, and as a public health problem.[4,5] Surprisingly, the

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neurobiological processes underlying the link between alcohol and social, aggressive and violent behavior remain poorly understood, and there is no effective clinical treatment for violence induced or heightened by alcohol.

Initially, this review highlights several fundamental and essential pharmacological features of the link between alcohol and aggression, ranging from the acute effects to the effects of withdrawal after long-term use. Next, we consider the reinforcing actions of aggression and alcohol, both acting on neural circuits in mesolimbic monoaminergic systems. Furthermore, this review links alcohol and aggression to a postulated deficiency in brain serotonin and will outline the different serotonin subsystems and their receptor subtypes. Serotonin (5-hydroxytryptamine, 5-HT) and other canonical monoaminergic pathways are modulated by gamma-aminobutyric acid (GABA) and glutamate, and these excitatory and inhibitory amino acids are critical sites of action for alcohol to escalate aggressive behavior. Finally, we consider some of the prominent neuropeptides and neuroactive steroids and their modulatory action on alcohol and aggression.

There are several new conclusions about the neurobiological processes that mediate the effects of alcohol on aggressive behaviour

1. Significant aggression-heightening effects are evident after acute, low alcohol doses as well as during withdrawal from long-term alcohol use; alcohol may lead to the distortion of social signals from benign to threatening.
2. A significant subset of individuals engages in alcohol-heightened aggression, while most alcohol-consuming individuals do not exhibit significant changes in aggressive behavior.
3. Subsystems of 5-HT neurons originating in the dorsal raphe nuclei and maturing during specific critical periods appear to contribute to the emergence of aggressive behavior.
4. The modulation of 5-HT impulse flow by GABA and glutamate, acting via distinct ionotropic and metabotropic receptor subtypes is of critical significance in the suppression and escalation of aggressive behavior.
5. In anticipation and reaction to aggressive behavior, neuropeptides such as corticotropin-releasing factor (CRF), neuropeptide Y (NPY), opioid peptides, and vasopressin interact with monoamines, GABA, and glutamate to attenuate and amplify aggressive behavior. These neuromodulators represent novel targets for intervention and await clinical validation.
6. Intermittent episodes of brief social defeat during aggressive confrontations are sufficient to cause long-lasting neuroadaptations that lead to the escalation of alcohol consumption. Activation of the CRF system is necessary for this social stress-induced escalation of alcohol consumption.

Epidemiological background

A consistent series of epidemiological and criminal statistics documents the association between alcohol and violent crimes starting in the 1950s and extending to the present;[6–11]

Table 1. Clinical diagnoses distinguish among instrumental, calculating, pre-meditated, and proactive “cold” aggressive acts on the one hand, and hostile, affective, impulsive and reactive “hot” aggression on the other.[12–14] Alcohol profoundly exacerbates the latter subtypes of aggression. Important features of the epidemiological data link alcohol and several major types of violent behavior ranging from homicides, sexual assaults, rapes, and child abuse to other physical assaults. This link is large in magnitude and costly to the individual, family, and society.[15–18] In addition to the pervasive escalation of many types of impulsive and reactive violent acts, possibly due to the myopic perception of threatening stimuli,[19] some epidemiological data point to geographic hot spots and epidemics of the alcohol-violence link.[20] Rather than proposing a neurogenetic deterministic account of the genesis of alcohol-heightened aggressive behavior, this evidence points to several risk factors that may interact with the social context.[21,22]

Discovery of ethanol’s action on discrete receptors in the brain: 1980–1990

A major shift in research on neural sites and mechanisms of ethanol and by implication on the aggressogenic effects of ethanol, began in the 1980s, when the focus on the disordering effects of alcohol was redirected from the lipid component of cell membranes to the action of ethanol on protein components in neuronal membranes.[23] This latter action was identified at several ionotropic receptors at millimolar concentrations which were more relevant to the excitatory effects of ethanol (Fig. 1).

$GABA_A$ receptors were among the first ionotropic receptors shown to increase chloride ion (Cl)-flux as a result of action by 20–100 mM ethanol, and this effect was blocked by $GABA_A$ antagonists.[24–27] $GABA_A$ receptors are pentameric ligand-gated ion channel complexes composed of at least 16 subunits, with two alpha and beta subunits plus either a gamma or delta subunit being the most typical compositions for receptors in the mammalian central nervous system (CNS).[28] With the aid of molecular genetic techniques, it appears feasible to learn which subunits need to be expressed in specific brain regions for alcohol to achieve specific behavioral effects. For example, $GABA_A$ receptors which contain a delta subunit instead of a gamma subunit are sensitive to concentrations of ethanol that are in the mild to moderately intoxicating range,[29,30] but see Ref. 31.

While ethanol has enhancing effects on GABAergic synapses, it has the opposite effect on glutamatergic signaling. Ethanol at concentrations of 10–25 mM inhibits NMDA glutamate receptors.[32–35] Intoxicating doses of ethanol can reduce glutamatergic neurotransmission in the nucleus accumbens[36] and amygdala.[37]

N-Methyl-D-aspartic acid receptors (NMDAR) are tetrameric ligand-gated ion channel complexes composed of two GluN1 subunits and two GluN2 (A, B, C, or D) subunits; GluN3 (A and B) subunits reduce ligand sensitivity and Ca^{2+} permeability.[38,39] As with the $GABA_A$ receptor, many NMDAR subunit combinations are responsive to ethanol. The recombinant approach has demonstrated that GluN1 is required, but then it is the fundamental obligatory NMDAR subunit.[40] Of the four isoforms of GluN2 subunit, ethanol can inhibit recombinant GluN1/GluN2A and GluN1/GluN2B NMDA receptors, and those containing GluN2B have been found to be the most sensitive to ethanol in HEK cells, but

not *Xenopus oocyte* expression systems.[41–45] Ethanol sensitivity is lower if the recombinant receptors contain GluN2C or GluN2D subunits instead of GluN2A or 2B.[46] The conditional knock-out approach suggests that GluN2B subunits play an important role in ethanol's effects on NMDARs in the bed nucleus of the stria terminalis.[47] In addition, acute low concentrations of ethanol alter NMDA subunit trafficking and can result in a selective internalization of GluN2A subunits, as well as a change in the GluN2A/GluN2B ratio.[48]

Ethanol can also increase neural activity in the VTA and increase dopamine (DA) release in the nucleus accumbens, potentially indicative of the rewarding effects of this drug[49–52] (see below). These effects appear to be mediated by ethanol's actions on GABAergic and glutamatergic neurons, and in part by ethanol's effects on other ion channels, including G protein–gated inwardly rectifying K^+ channels (GIRK)[53,54] and other intracellular signaling pathways.[55]

Similarly, ethanol increases 5-HT release in the nucleus accumbens,[56–58] and this effect may play a role in modulating DA release in this nucleus.[59] Some of the effects of ethanol on serotonergic neurotransmission, like those on DA, appear to be indirect.[60] However, ethanol does directly potentiate 5-HT_3 receptors,[61,62] and these receptors, as well some other 5-HT subtypes, may be important in alcohol abuse.[63–67] Genetic differences in serotonergic systems across individuals may also explain some of the differences in alcohol intake and abuse[68] (see below).

Recently, the action of alcohol in the DRN has been explored using electrophysiological techniques. DRN inhibitory transmission is particularly sensitive to ethanol, and this is mediated primarily by synaptic $GABA_A$ receptors and secondarily by glycine receptors.[69] In mice previously exposed to chronic intermittent ethanol vapor there was increased DRN excitability during withdrawal[70] and decreased spontaneous inhibitory transmission in DRN-containing brain slices from these animals. Further, bath application of ethanol enhanced the frequency of miniature inhibitory postsynaptic currents (mIPSCs) in DRN neurons in slices from ethanol-withdrawn mice, but not ethanol-naive mice.[70] Chronic, voluntary ethanol intake through intermittent access to two-bottle choice in Sprague-Dawley rats and C57BL/6J mice also can lead to functional DRN changes.[71,72] Repeated binge drinking during adolescence specifically decreased expression of 5-HT-related genes and of genes encoding the $GABA_A$ receptor $\alpha 2$, $\alpha 3$, and $\alpha 5$ subunits in the DRN.[73] However, this contrasts with a recent clinical study demonstrating that adult alcoholics have greater tryptophan hydroxylase 2 mRNA and protein in the DRN, compared to nonpsychiatric controls.[74] Taken together, these results suggest that ethanol can cause alterations in DRN signaling, both after acute and chronic exposure.

Basic pharmacology of alcohol and aggression

It has been challenging to determine the exact amount of alcohol circulating in the blood, and the amount acting on pivotal target sites in the brain, of human perpetrators or victims of violence. Instead, estimates rely on retrospective analysis of events that occurred at varying times in the past and involve questionable recall. It is even rarer to learn about precise blood levels of alcohol at the time of apprehension of an alcohol-intoxicated perpetrator or victim

of aggressive acts or both. In the absence of such data, experimental studies with human subjects, and preclinical studies in animal models, supply important information on the basic pharmacology of alcohol on aggressive behavior, although experimental work on intensely violent acts is ethically unacceptable. We have developed preclinical methods to study escalated aggression after oral consumption of alcohol in a significant subgroup of individual mice, rats, and monkeys.[16,75–77]

Acute exposure to alcohol results in a biphasic dose- and time-dependent relationship between alcohol and most of its behavioral, physiological, and neurochemical effects, among them aggressive behavior.[78] The level of circulating alcohol is systematically related to the rate and intensity of aggressive behavior in several experimental models. Low doses of alcohol on the ascending limb of the dose-effect curve result in increased aggressive behavior, whereas high doses decrease this behavior as part of its sedative effects in humans, non-human primates, and rodents (Fig. 2). [79–83] For example, resident mice or rats that were administered ethanol by gavage showed peak escalation of attack bites and sideways threats at the 1.0 g/kg dose. Similarly, when outbred Swiss mice were conditioned to self-administer fixed doses of ethanol prior to confronting an intruder opponent, they engaged in peak levels of aggressive behavior at the 1.0 g/kg dose.[16,84] In a methodological refinement, outbred Swiss mice self-administered droplets of 6% w/v ethanol voluntarily. After accumulating 1.0 g/kg ethanol within 5 minutes, they confronted an intruder opponent and engaged in significantly escalated aggressive behavior. Detailed quantitative analysis of alcohol-heightened aggressive behavior revealed that resident rats fail to terminate aggressive bouts.[80]

Aside from increasing the rate of aggressive behavior, self-administered ethanol also intensifies aggressive acts, based on detailed analysis of the wounds. Among the key criteria for modeling pathological aggression in experimental animals are the lack of threats preceding injurious attacks and the indiscriminate targets for inflicting bodily harm.[85,86] Slow-motion video analysis reveals that alcohol self-administering resident mice or rats aim their attack bites at vulnerable parts of the intruder's body such as the ventrum and face[87] (Newman *et al*. in prep; Fig 3).

Epidemiological and clinical studies primarily focus on recurrent violent incidents in individuals experiencing repeated alcohol intoxication.[88] It is well-established that half of alcohol-dependent males who cycle through bouts of intoxication and withdrawal commit violent acts.[89–92] Recently, an experimental protocol was developed to identify peak aggressive behavior in laboratory mice concurrent with glutamatergic convulsive phenomena in withdrawal from two months of intermittent access to 20% ethanol (w/v).[77] With increasing length of intermittent access to alcohol, a larger proportion of mice began to engage in aggressive behavior when withdrawing from alcohol (Fig. 4).

While the evidence from preclinical studies is valuable, being based on systematic and controlled drug manipulations and measurements, it is limited by important differences in patterns of voluntary alcohol consumption, alcohol uptake, distribution and metabolism, and neurochemical targets. Animal species differ considerably with regard to the fate of alcohol in the body and the brain, and to the morphological and functional characteristics of the

neural sites of action for alcohol.[23] When translating preclinical data to the human condition, it is essential to scale doses and time of peak effect across species very carefully.[23]

Individual differences in ethanol and aggression

Individuals differ markedly as to whether the consumption of a given dose of alcohol will escalate aggressive and violent behavior.[93] Reliable and predictive genetic, physiological, or behavioral markers remain elusive, making it difficult to identify individuals with a predisposition for heightened aggressive and violent behavior in the early phase of ethanol action or during withdrawal. Retrospective clinical studies have associated polymorphisms in individuals with a propensity to engage in escalated aggressive and violent behavior. For example, genotyping the *BDNF* gene polymorphism, G196A, revealed that Japanese alcoholics with violent tendencies were more likely to be homozygous for the A allele compared to non-violent individuals.[94] In a Swedish sample of adolescents with alcohol-related problem behaviors, a short variant of gene encoding MAO-A was detected, particularly when the youngsters grew up in abusive families.[95] Longitudinal studies with a focus on childhood abuse and continuing through adolescence into early adulthood would be particularly informative in identifying interactions between developmental and genetic risk factors that engender alcohol-related violence.

Preclinical studies with mice, rats, and monkeys identify subgroups of individuals for whom a moderate dose of alcohol reliably escalates aggressive behavior, whereas most others do not show this effect[16] (Fig. 5). This variability in laboratory rats and mice has led to our distinction between alcohol-heightened aggressors (AHA) and alcohol-non-heightened aggressors (ANA) on account of the persistent, large increase in injurious attack behaviors after every exposure to a moderate 1 g/kg dose of ethanol.[76,80,81] So far, these subtypes have been characterized in terms of pharmacological sensitivity with serotonergic, GABAergic, and glutamatergic compounds.[76,84,96–102] In rhesus monkeys, intense consumption of alcohol leads to long bursts of impulsive aggressive behavior primarily in those individuals with a history of social isolation early in life.[103] It will be most instructive to identify biomarkers that predict whether an individual will engage in alcohol-heightened aggressive behavior.

Victims of aggression: escalated alcohol consumption as a result of social stress

While the aggressogenic effects of alcohol continue to be the focus of clinical and basic research with animal models,[16,104] a critical role of alcohol emerges in the individual who is not the perpetrator, but the target of aggressive acts. Early preclinical studies have demonstrated how administration of ethanol to mice, rats, or monkeys alters their behavior in confrontations with an aggressive opponent.[105–107] The higher the dose of alcohol in the intruder mouse or rat or the subordinate monkey, the more frequently these individuals provoked attacks and threats. The perception and production of social signals and pheromones contribute to the escalation of aggressive interactions. The analysis of social cues and the interpretation and integration of these cues promises to reveal how alcohol

alters provocative signals, and the response to these signals. Giancola[19] proposes that distorted perceptions of social signals—a type of myopia— emerge as a key determinant of alcohol-escalated aggressive behavior.

When exposed to repeated episodes of aggression and displaying salient characteristics of social stress, individuals who are the target of attacks or threats can undergo neural adaptations that cause them to consume large amounts of alcohol and to exhibit signs of increased motivation for alcohol.[108,109] There is considerable debate about the impact of different types of environmental stressors on alcohol consumption.[110–113] In order to capture the well-documented and often reiterated link between stress and alcoholic drinking in humans, several preclinical efforts have focused on social stress.[114] One approach focuses on continuous subordination stress that extends over several weeks and months in mice, rats, and monkeys. Low-ranking squirrel monkeys or macaques consume more alcohol than high-ranking individuals.[115,116] Several studies report increases in consumption of alcohol at concentrations ranging from 2–20% v/v in socially subordinate members of a group of mice or rats.[117,118] Even though these increases in intake relative to non-stressed controls are statistically significant, they are usually insufficient to produce either intoxication or dependence.

A second approach in animal models involves repeated acute episodes of social defeat stress that result in escalated alcohol drinking.[119–122] When corticotropin releasing factor receptor 1 (CRF-R1) gene knock-out mice bred onto an outbred CD-1 background were subjected to brief episodes of social defeat stress on three consecutive days, they began to consume ~3 g/kg/day of 8% alcohol (v/v), compared to the 1 g/kg/day pre-stress baseline.[119] This increase manifested itself only after a three-week interval between the social stress experience and the alcohol consumption. More recently, a series of studies identified the parameters of social defeat stress that induced escalated alcohol consumption in mice without any restriction in fluid intake and engendered a preference for alcohol relative to concurrently available water. Brief episodes of social defeat stress every day or every other day were sufficient to escalate consumption of 20% unsweetened alcohol (w/v) up to 15 g/kg/day in CFW mice and up to 30 g/kg/day in C57BL/6J mice (Fig. 6).[77,120] Several features of these latter studies are noteworthy: the escalated alcohol intake began after several weeks without stress and continued in the absence of any further exposure to social stress, suggesting the induction of an enduring neuroadaptation. Pharmacological antagonism and genetic deletion experiments implicate the CRF system in the induction and expression of the neuroadaptations that result from exposure to brief episodes of social defeat stress and eventually lead to persistently escalated alcohol consumption (see below).

Alcohol-heightened aggression as a source of satisfaction and pleasure: Mesocorticolimbic circuits

More than 50 years ago John Paul Scott[123] recognized that “aggression not only produces dangers which must be avoided, but pleasures which can be enjoyed.” Among the causative factors for alcohol-heightened aggression are the rarely-investigated neural mechanisms mediating the rewarding effects of aggressive behavior.[124–128] By contrast, the neural mechanisms for the rewarding effects of alcohol consumption are more adequately

characterized. Many facets of alcohol's reinforcing effects have been examined in a range of species and conditions.[50,129–134] Individuals may prefer alcohol over other commodities, seek out the opportunity to self-administer ethanol, exert themselves to obtain alcohol, or resist the negative consequences of alcohol consumption. All of these behaviors are based on neural interactions in mesencephalic–limbic–cortical loops. These circuits include sensory components, and most alcohol is consumed in flavored concoctions; alcohol solutions affect neural circuits that regulate ingestive homeostasis of intra- and extracellular fluids and calories; most importantly, the pharmacological actions of alcohol on targets in the mesocortical and mesolimbic monoaminergic pathways appear to be necessary for its reinforcing effects. While an "alcohol receptor" has not been discovered, several ionophoric receptors in GABAergic, glutamatergic, and monoaminergic neurons are the targets of millimolar concentrations of alcohol, as previously mentioned.[23] Alcohol's reinforcing effects depend on the integrity of dopaminergic neurons in the VTA that are modulated by GABAergic and glutamatergic afferents, and that project to the core and shell of the nucleus accumbens, as well as to the medial prefrontal cortex.[135] These basic networks of monoamines—excitatory and inhibitory amino acids subserving the reinforcing effects of alcohol—are modulated by a large number of neuropeptides.[132,136]

To what extent do the neural mechanisms mediating alcohol's reinforcing effects overlap or interact with those that are responsible for aggressive and violent acts, which in themselves function as reinforcers? So far, only a few candidate neural mechanisms have been explored in experimental models that identify aggressive acts as reinforcers. Positive allosteric modulation by benzodiazepines and allopregnanolone of the $GABA_A$ receptor has proven effective in escalating the rate of responding that was reinforced by the opportunity to engage in aggressive behavior.[124,137] As the opportunity for aggressive behavior approached, the rate of responding accelerated and plasma levels of corticosterone were elevated; and corticosterone elevations appeared to be required for responding that is motivated by the opportunity to engage in aggressive behavior and for the escalated aggression (Fig. 7).[137] It is likely that the allosterically- modulated $GABA_A$ receptors are altering DA and 5-HT impulse flow.

Direct antagonism of DA receptor subtypes reduces the rate of responding that is reinforced by the opportunity to engage in aggressive behavior; microinjections of low doses of DA D1- or D2-like receptor antagonists into the nucleus accumbens (NAcc) preferentially reduced the behavioral effort to gain access to an aggressive confrontation.[128] It appears reasonable to suggest that alcohol-heightened aggressive behavior may require intact DA activity in the mesolimbic pathway, particularly in view of heightened release of DA in the NAcc in rats that consume alcohol and subsequently engage in escalated aggressive Recently-developed optogenetic methods promise to differentiate the aggression-specific DA cells from those that mediate other motivated behavior and motor functions.

Escalated aggressive behavior with pathological features is evident in mouse and rat strains that are selectively bred for high aggression.[139] So far, the reinforcing nature of pathological aggression can only be inferred from the short-latency, high-frequency, and high-intensity of persistent and injurious attacks;[127] more definitive information will have to be obtained from a formal analysis of the contingencies between pathologically escalated aggressive

behavior and its consequences. Most evidence for neurobiological mechanisms mediating pathologically escalated aggressive behavior has focused on tonic brain 5-HT activity and on 5-HT autoreceptors.[140] In prefrontal cortex, increased 5-HT has been detected when escalated aggressive behavior is initiated, whereas termination of aggressive bouts and return to tonic levels of 5-HT is associated with reduced neural activity in the serotonergic soma of raphe cells.[98,141] The extent to which alcohol's violence- and aggression-heightening effects depend on serotonergic activity has been studied both in clinical and preclinical models for several decades.

The 5-HT-alcohol link: from the deficiency hypothesis to discrete subsystems

No other neurotransmitter has been more intensively investigated than 5-HT when characterizing neural mechanisms of violence and aggression,[98,140,142–144] including the link between alcohol and aggression.[104,145–148] Historically, the most frequently reiterated hypothesis attributed a predisposition for violent behavior to a deficiency in 5-HT in alcohol-consuming individuals, supported primarily by post-mortem assays of tissue samples or lumbar CSF.

Shortly after the discovery of 5-HT in the brain, the calming role of this biogenic amine was highlighted,[149] and then extended to aggressive individuals.[150] Consistent evidence in many species, ranging from invertebrates, fish, and rodents to non-human primates and humans, documents an effective reduction in aggressive behavior after treatment with drugs that target 5-HT_{1A} or 5-$HT_{2A/C}$ receptor subtypes and transporter sites.[140,151–153] Conversely, monkeys and humans with the short allele of the serotonin transporter polymorphism (5HTTLPR) are characterized by heightened aggressive behavior.[154,155] However, like clinically-employed pharmacotherapeutic treatments with potent anti-aggressive effects (including anti-psychotics, β-adrenergic blockers, steroid derivatives, and benzodiazepines), nearly all of the 5-HT_{1A} receptor agonists, 5-HT_{2A} receptor antagonists, and selective serotonin reuptake inhibitors (SSRIs) decrease aggressive behavior in dose ranges that have problematic side-effect profiles.[156] Agonists of 5-HT_{1B} receptors appear to result in behaviorally more selective anti-aggressive effects in experimental studies with mice and humans.[76,102,157–159]

Research on the anatomical sites of action for alcohol's effects on escalated aggression has focused on the regions within the prefrontal cortex, amygdala, septum, and hypothalamus.[148,156] Imaging studies in patients with intermittent explosive disorder show deficient activation of medial prefrontal cortex concurrent with heightened activity in the amygdaloid complex.[160–162] The same regions are activated by acute alcohol intake, as indicated by converging evidence from several methodologies. Expression of immediate early genes in laboratory rodents that engage in escalated aggressive behavior identify several interconnected brain regions along the center of the neuraxis, ranging from the periaqueductal grey to the ventral tegmentum, hypothalamus, preoptic area, septum, amygdala, and prefrontal cortex.[141,153,163–165] Expression of 5-HT receptor subtypes is reduced in prefrontal cortex of those individual mice who engage consistently in alcohol-heightened aggression relative to those who do not.[99]

Intracerebral microinjection studies localized the neural pathway projecting from the DRN to the striatum and prefrontal cortex as pivotal in the actions of 5-HT_{1A} and 5-HT_{1B} receptors. Activation of these subtypes at the 5-HT_{1A} somatodendritic autoreceptors, as well as pre- and post-synaptic 5-HT_{1A} and 5-HT_{1B} receptors, effectively reduced alcohol-heightened aggressive behavior in mice and rats.[98,101,166,167] Studies with muscimol microinjections suggest that escalated aggression as a result of alcohol consumption involves GABAergic modulation of 5-HT in the DRN.[98] A role of glutamatergic modulation of 5-HT impulse flow to the mPFC in alcohol-heightened aggression is indicated by effects of memantine and ketamine in AHA mice (Newman *et al*. in prep). An emerging hypothesis regarding the mechanism for alcohol-heightened aggression focuses on subpopulations of 5-HT projections to the forebrain and their modulation by specific GABA and glutamate receptors.

Alcohol-heightened aggression and GABA

A great deal of attention has been paid to the effects of alcohol on GABA receptors for several reasons. As discussed below, alcohol can allosterically modulate $GABA_A$ receptors but a number of effects of alcohol on the brain and behavior are similar to those of more specific drugs that act relatively specifically on $GABA_A$ receptors. For example, the sedative and hypnotic effects of alcohol are similar to those of barbiturates and benzodiazepines, and both of these classes of drugs also act on $GABA_A$ receptors as positive allosteric modulators. In addition, chronic exposure to alcohol alters the expression of $GABA_A$ receptor subunits,[168–171] although the expression of these subunits appears to depend on the pattern and dose of alcohol, as well as whether withdrawal occurs.

$GABA_A$ receptors

Alcohol can increase aggressive behavior not only in people but in a number of laboratory animal species. However, the magnitude of this effect varies across individuals[80,172]. We have been investigating the likely bases for individual differences in sensitivity to the pro-aggressive effects of alcohol in laboratory rodents and it is quite clear is that alcohol generally has biphasic effects on aggressive behavior (see below). Although these drugs can be pro-aggressive in some individuals,[173,174] higher doses of benzodiazepines and $GABA_A$ agonists in conjunction with neuroleptics have an inhibitory effect, and so are often used to sedate violent patients.[175–177]

Benzodiazepines can act as positive modulators of $GABA_A$ receptors, but not all $GABA_A$ receptors have a benzodiazepine binding site. Benzodiazepine action requires that the $GABA_A$ receptor include a $\gamma 2$ subunit as well as α and β and subunits.[178–180] However, there is debate as to which α subunit of the $GABA_A$ receptor is necessary for the benzodiazepine to exert sedative, anxiolytic, amnestic, or anticonvulsive effects or to lead to abuse.[181] We have examined whether $GABA_A$ receptor subunit composition might also influence the effect of alcohol on aggressive behavior. We have found that benzodiazepine antagonists which preferentially act on $GABA_A$ receptors with $\alpha 1$ subunits can reduce the pro-aggressive effects of alcohol in mice.[84] In addition, point mutations to the genes encoding $\alpha 1$ (H101R) or $\alpha 2$ (H101R), but not $\alpha 3$ (H126R) subunits in mice can block the aggression-heightening effects of midazolam (Newman *et al*. 2015).[182] These findings may

be useful in the eventual development of therapies to specifically reduce the association between alcohol and violence.

Direct agonists of $GABA_A$ receptors, such as musicmol, can also influence aggressive behavior. Much of the early research on the effects of muscimol on aggressive behavior in laboratory rodents reported inhibitory effects.[183–186] However, when microinjected into the DRN of male mice, 0.006 nmol of muscimol potentiated aggressive behavior.[98,187] Importantly, this effect only occurred in mice that showed alcohol-heightened aggression.[98] In addition, muscimol microinjections were behaviorally ineffective if they missed the DRN. This suggests that the DRN may be a particularly important site in the link between $GABA_A$ receptors and the effects of alcohol on aggression.

Another tool that has been employed to study the possible link between alcohol- heightened aggression and $GABA_A$ receptors is the neuroactive steroid allopregnanolone (ALLO), produced both in the brain and peripherally and the most potent positive modulator of $GABA_A$ receptors known.[188–193] Disrupted ALLO is associated with depression, stress, and anxiety.[194] Alcohol can increase ALLO levels in laboratory rodents and altered brain concentrations of ALLO might be a mechanism through which alcohol exerts behavioral effects such as sedation, anxiolysis, and analgesia. Likewise, some pharmacological effects of alcohol may be caused by alcohol-induced increases in ALLO synthesis.[195,196] Forced-swim stress elevates ALLO in the brain,[197] and decrements in its biosynthesis, specifically in the basolateral amygdala, can affect aggressive behavior.[198, 199] We have seen that moderate doses of ALLO increase aggressive behavior and this effect occurs primarily in the subset of mice that previously have been classified as alcohol-heightened aggressors.[200] When tested in combination with alcohol, ALLO shifted the alcohol dose-response curve to the left. In addition, higher doses of ALLO, like higher doses of alcohol, inhibit aggressive behavior. That finding is similar to ALLO reducing the frequency of attacks in isolation-enhanced aggression.[201] This neurosteroid appears to be stress-responsive and plays a major role in regulating the hypothalamic–pituitary–adrenal (HPA) axis.[202] It is possible that individual differences in ALLO may influence stress resilience. It will be important to tease apart the specific neural mechanisms for how alcohol and ALLO affect escalated aggressive behavior.

$GABA_B$ receptors

In addition to the ionotropic $GABA_A$ receptor, GABA actions are also mediated by the metabotropic G-protein coupled $GABA_B$ receptor. The $GABA_B$ receptor agonist baclofen has received some attention as a possible treatment for alcohol dependence,[132,203,204] although some studies have not found it to be significantly better than placebo.[205] Baclofen also has been reported to reduce the severity of alcohol withdrawal symptoms in patients.[203,206,207] In rats, baclofen usually reduces aggressive behavior.[185,208,209] However, our research demonstrates that systemically administered baclofen can actually have a biphasic dose-effect on aggression in male mice.[210] Microinjection of baclofen into the DRN can specifically increase aggressive behavior.[98,187] However, that effect does not depend on alcohol and occurs in mice independent of whether they are alcohol-heightened aggressors.

Alcohol-heightened aggression and glutamate NMDA receptor

The rationale for considering glutamate and its receptors as relevant to the mechanisms mediating alcohol-heightened aggressive behavior derives from the discovery that alcohol (5–50 mM) antagonizes NMDARs, possibly via the GluN1-glycine site.[34,211–214] A post-mortem analysis of hippocampal tissue from alcoholics and cocaine addicts revealed upregulation of *GRIN2B* (gene for GluN2B) in all individuals and specific upregulation of *GRIN2D* (gene for GluN2D) in alcoholics.[215,216] In addition, *GRIN2A* polymorphisms may be associated with disruptions in aversion learning and may predict the development of an alcohol use disorder.[217,218] Polymorphisms of *GRIN2B* may serve as an indicator for the effectiveness of acamprosate in the treatment of alcohol use disorders.[219] Preclinical investigations point to the importance of NMDARs in species-typical social behavior. Heterozygous deletion of the GluN1 subunit renders the receptor insensitive to the crucial co-agonist, glycine and thereby reduces the proportion of functional NMDARs.[220] GluN1 hypomorphic mice consume more alcohol and spend less time in social interactions relative to their genetically unaltered counterparts.[220,221] Pharmacological blockade of NMDAR can similarly dysregulate social and agonistic behavior. When mice consume a modest dose of alcohol (1 g/kg) and are treated with the uncompetitive NMDAR antagonist memantine their aggressive behavior toward a submissive male conspecific escalates.[96] Furthermore, when alcohol-dependent mice are challenged with a moderate dose of memantine (5 mg/kg) during withdrawal from access to alcohol following 8 weeks of access, their aggressive behavior escalates (Fig. 9).[77] Collectively, these findings point to the genetically or pharmacologically suppressed NMDAR as pivotal in behavioral dysregulation as indicated by increased alcohol self-administration, more intense social anxiety-like behavior, and escalated aggressive behavior.

Conversely, several findings point to the therapeutic value of NMDAR antagonists as suggested by the anti-craving effects of acamprosate, memantine, and neramexane (MRZ 2/579) in rats.[222,223] Additionally, treatment with the uncompetitive antagonist MK-801 (dizocilpine) can increase social interactions between adolescent rats, suggesting reduced social anxiety.[224] Importantly, in patients diagnosed with alcohol use disorders, memantine and ketamine treatments reduce both cravings for alcohol and alcohol consumption.[225–227]

These divergent interactions between alcohol and NMDAR antagonists may depend on the expression of the GluN2 subunit. Receptors containing GluN2A or GluN2B are more sensitive to the inhibitory action of alcohol and exhibit regionally specific expression patterns.[228] GluN2A-containing NMDARs are expressed throughout the CNS of rats, while GluN2B subunits are localized preferentially in the forebrain, specifically in the prelimbic and orbital regions of the prefrontal cortex.[229] Glutamatergic pyramidal cells within these prefrontal cortical areas are activated during aggressive encounters in rats.[230] Excitatory inputs, particularly from the PFC to the DRN may facilitate the initiation and termination of aggressive behavior.[231] We hypothesize that dysregulation of cortical inhibition of GluN1/GluN2B-containing NMDA receptors may result in alcohol-induced social disinhibition and escalated aggression. Individual differences in GluN2 subunit expression may determine the behavioral effects of drugs such as ethanol and memantine in interaction with an individual’s predisposition for aggressive behavior and other psychopathologies.[232]

Alcohol-heightened aggression and neuropeptides: CRF and opioid peptides

Stress-related neuropeptide systems have been implicated in alcohol-related behaviors, most prominently CRF and urocortin, NPY, nociception/orphanin, and neurokinin.[233] These and other neuropeptides have been implicated in the regulation and dysregulation of social behaviors, especially vasopressin, oxytocin, and substance P.[234–236] Most of the evidence points to a significant role of CRF and opioid peptides in the modulation of alcohol-related aggression.

Corticotropin-releasing factor

CRF is the initial link in the cascade of neural, endocrine, and behavioral responses to stressful stimuli,[237,238] especially those related to pro-social and conflict situations.[239,240] CRF biphasically modulates aggression in various species,[241,242] with low doses increasing and high doses decreasing agonistic behaviors in rats.[243] Further, most CRF-R1 antagonists effectively reduce aggression in socially organized species.[244–246] One way CRF-R1 antagonism prevents alcohol-heightened aggression is, in part, its facilitation of 5-HT impulse flow from the DRN to the mPFC.[247] The mPFC has emerged as a critical site through which alcohol-induced impairments can contribute to emotional outbursts and violence.[126,248] Alcoholic, impulsive offenders[249] and perpetrators of domestic violence[250] are characterized by dysregulated CRF levels compared to healthy controls. Enhanced aggression, compared to species-typical aggression, may recruit stress-related circuits resulting in a loss of inhibitory control.

Opioid peptides

Brain opioid peptides acting on mu, delta, or kappa opioid receptors (MOR, DOR, KOR) are critically involved in the regulation of social behaviors and mood disorders.[251,252] Increased aggression after acute opiates has been documented in several species such as fish,[253–255] cats,[256] pigs,[257] crickets,[258] and mice,[259] which implicate endogenous opioids in social conflict. By contrast, opioid antagonists reduce alcohol-heightened aggression primarily in some individuals, possibly with a distinctive pattern of expression for genes encoding MOR, DOR and KOR.[260–262] Research is limited for alcohol-heightened aggression, but alcohol interferes with endogenous opioid mechanisms, including the acute release of β-endorphin.[263] We hypothesize that endorphins acting on MOR are of particular relevance to alcohol-heightened aggression, and represent important targets for intervention. Social conflict activates antinociception through opioid mechanisms.[261,264,265] Opioid receptor activation in aggressive encounters may lead to exaggerated responses to threatening environmental stimuli. Naltrexone can reduce self-injurious behavior,[266] so the prominent interaction between alcohol and endogenous opioids may enable opioid antagonists to suppress alcohol-related aggression.

Future agenda

One of the urgent tasks will be to characterize the individuals who are predisposed to engage in alcohol-heightened aggressive behavior. To disentangle the host of interacting genetic and environmental risk factors will require a concerted effort at every level of analysis.

In preclinical studies, novel neurobiological tools such as optogenetic stimulation and inhibition of chemically specific cell groups in discrete nodes of neural microcircuits promise to characterize effective targets of intervention to attenuate alcohol-heightened aggressive behavior.

Novel molecular targets in the neural microcircuits for escalated aggressive behavior are likely to emerge from studies with neuropeptidergic modulation of GABA and glutamate cells that stimulate or inhibit monoaminergic pathways. Alternatively, it will be useful to explore steroid systems and endocannabinoids for their role in alcohol-heightened aggression.

The validity of experimental models of alcohol-heightened aggression derives from their potentially injurious and harmful nature. The ethical dilemma of on the one hand studying alcohol-escalated aggressive behavior in experimental models and on the other hand following the principle of harm reduction will require careful and thorough examination in each case.

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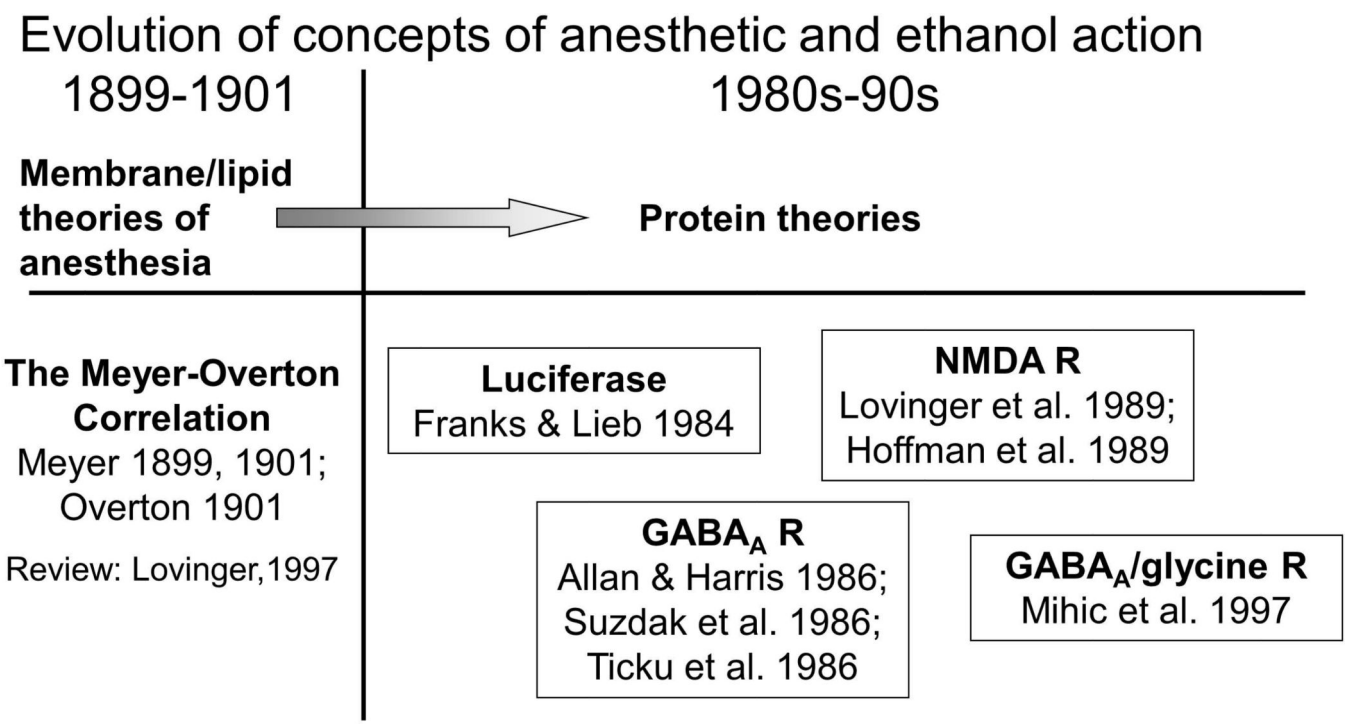

Figure 1.
Theories of ethanol action at the cellular level. Adapted from Dunwiddie 2001;[267] works cited.[26,27,32,34,268–274]

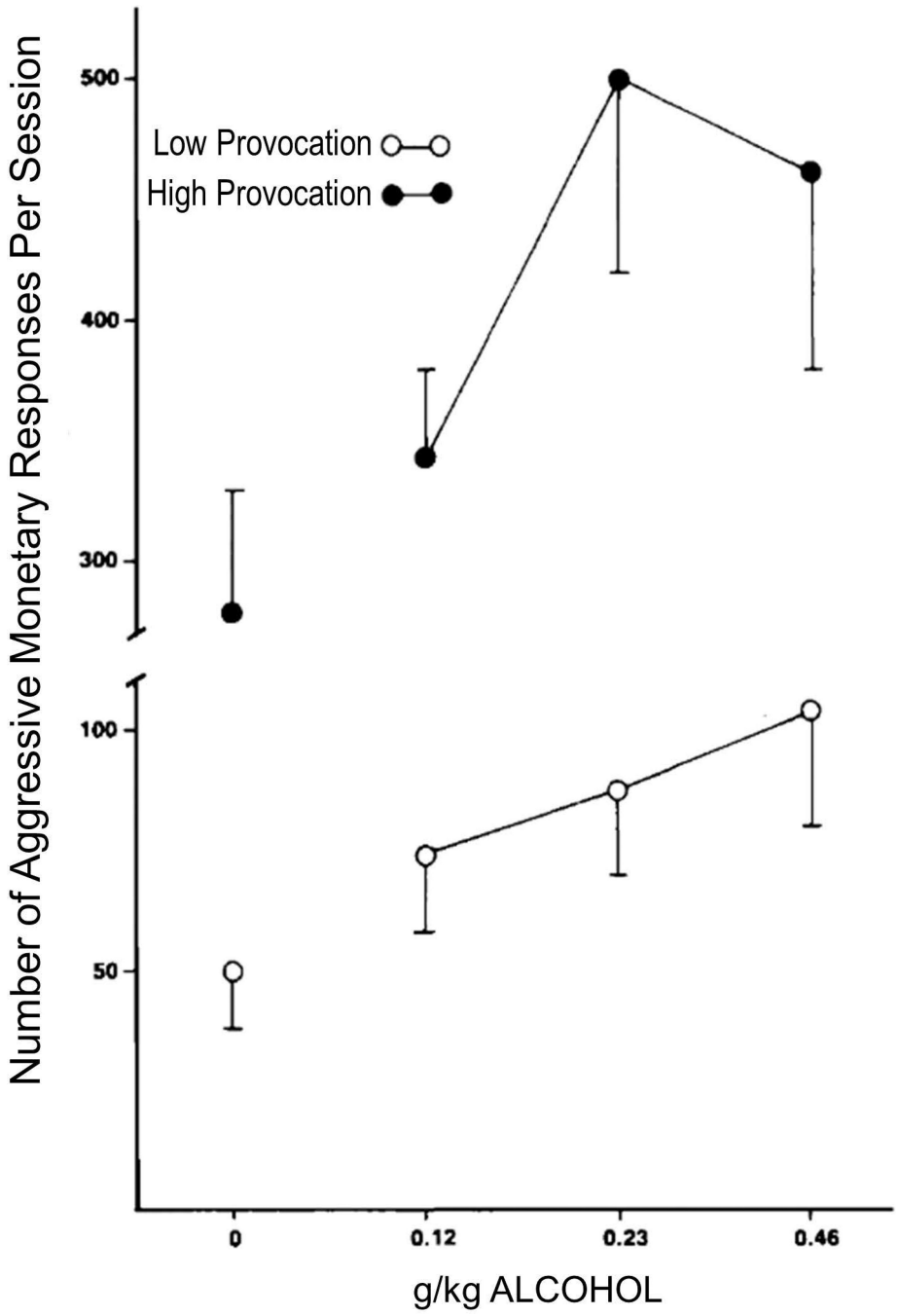

Figure 2.

Number of aggressive monetary subtraction responses per session after the administration of placebo or 3 different doses of alcohol. Data points represent means of 4 subjects each in the low- and high-provocation conditions, and vertical lines are ±1 SEM. From Cherek, *et al.*[79]

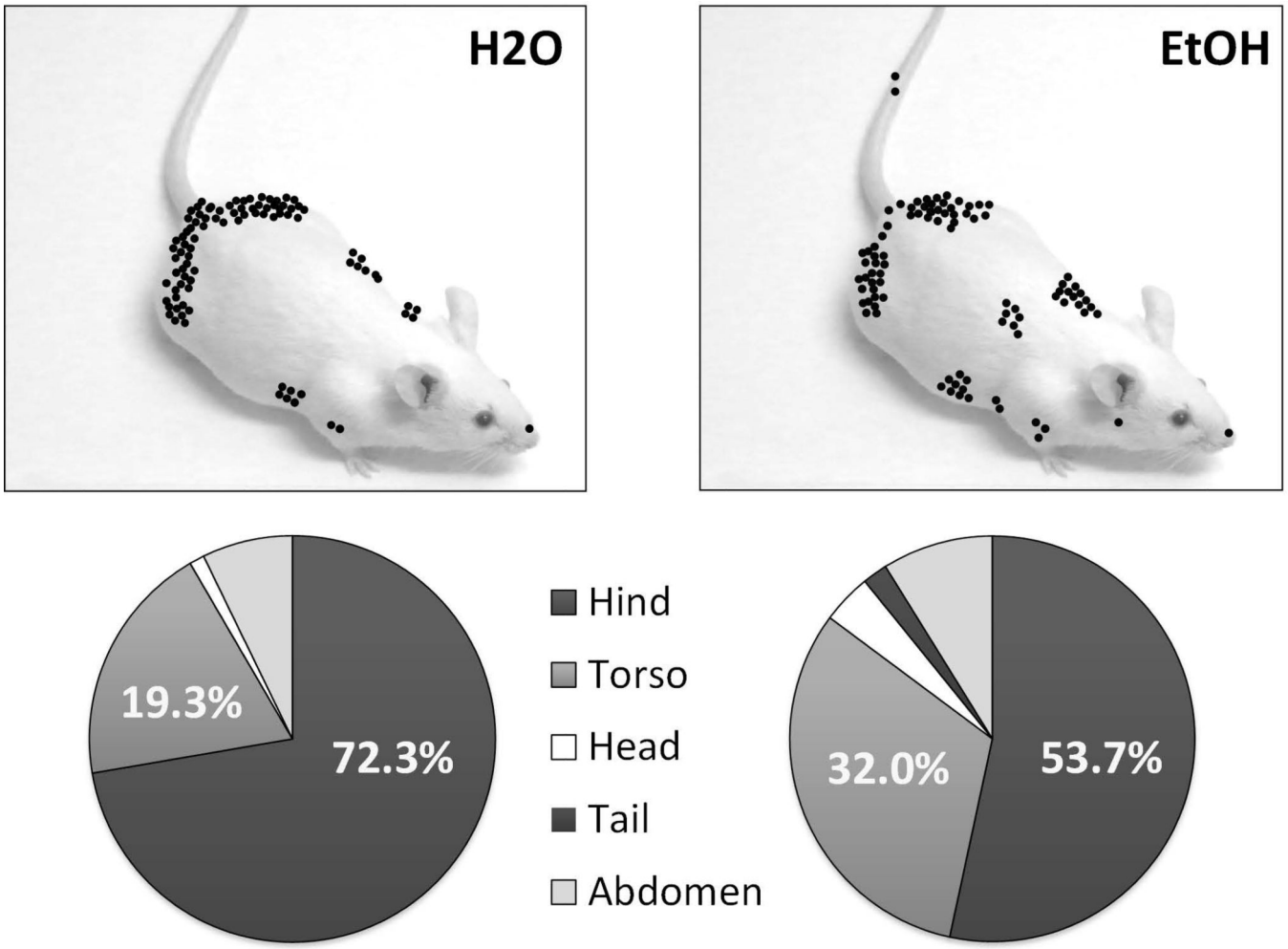

Figure 3.
Target areas of bites inflicted by resident mice after oral self-administration of water (left) or 1 g/kg ethanol (right). From Newman, *et al*. in preparation.

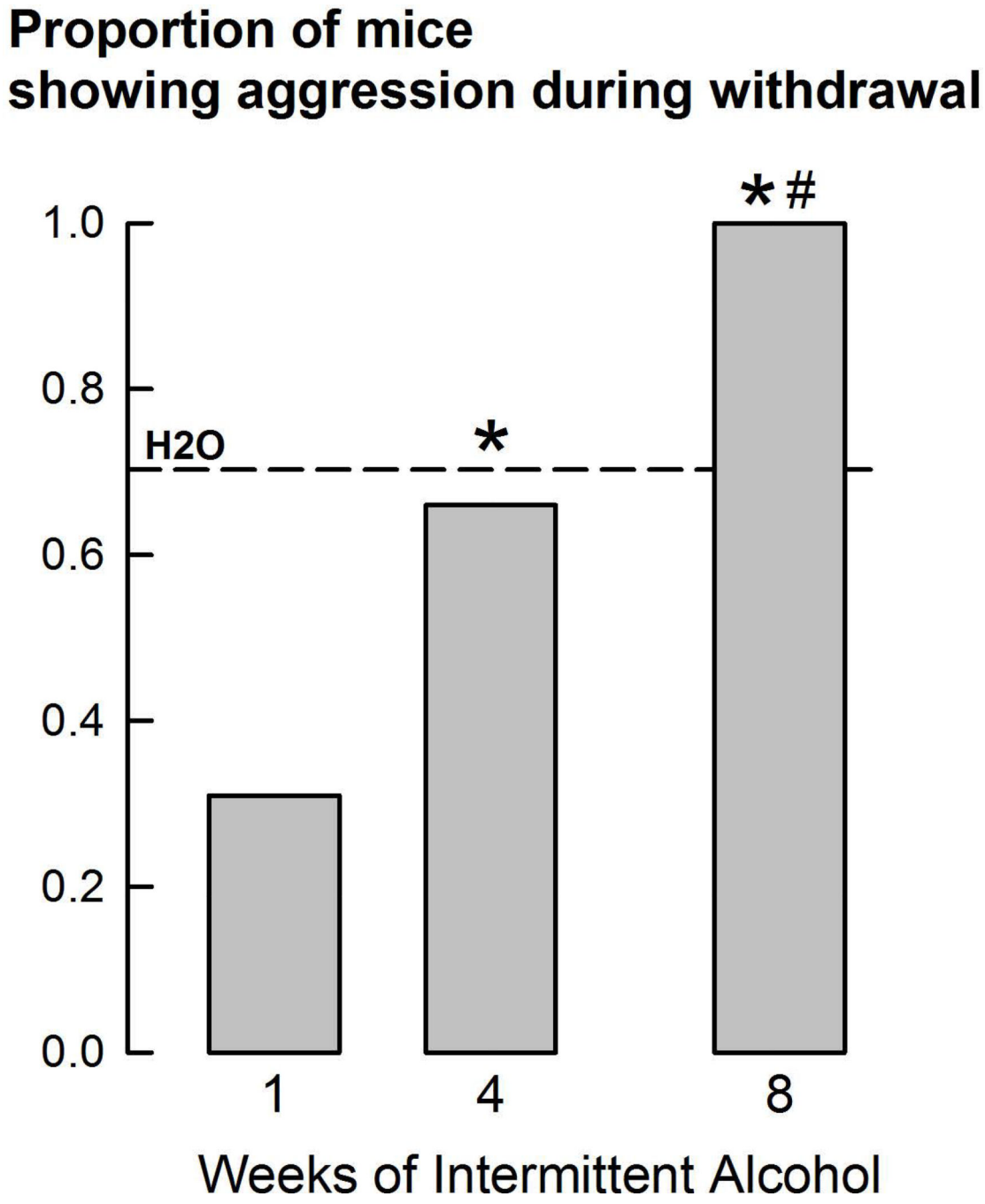

Figure 4.

Proportion of mice showing aggression during 8 hour withdrawal from intermittent alcohol access after 1, 4, or 8 weeks of exposure. The dashed line represents the average of water drinkers across age-matched groups. *$P < 0.05$ vs. wk 1; $^{\#}P < 0.05$ vs. H_2O. From Hwa, *et al.*[77]

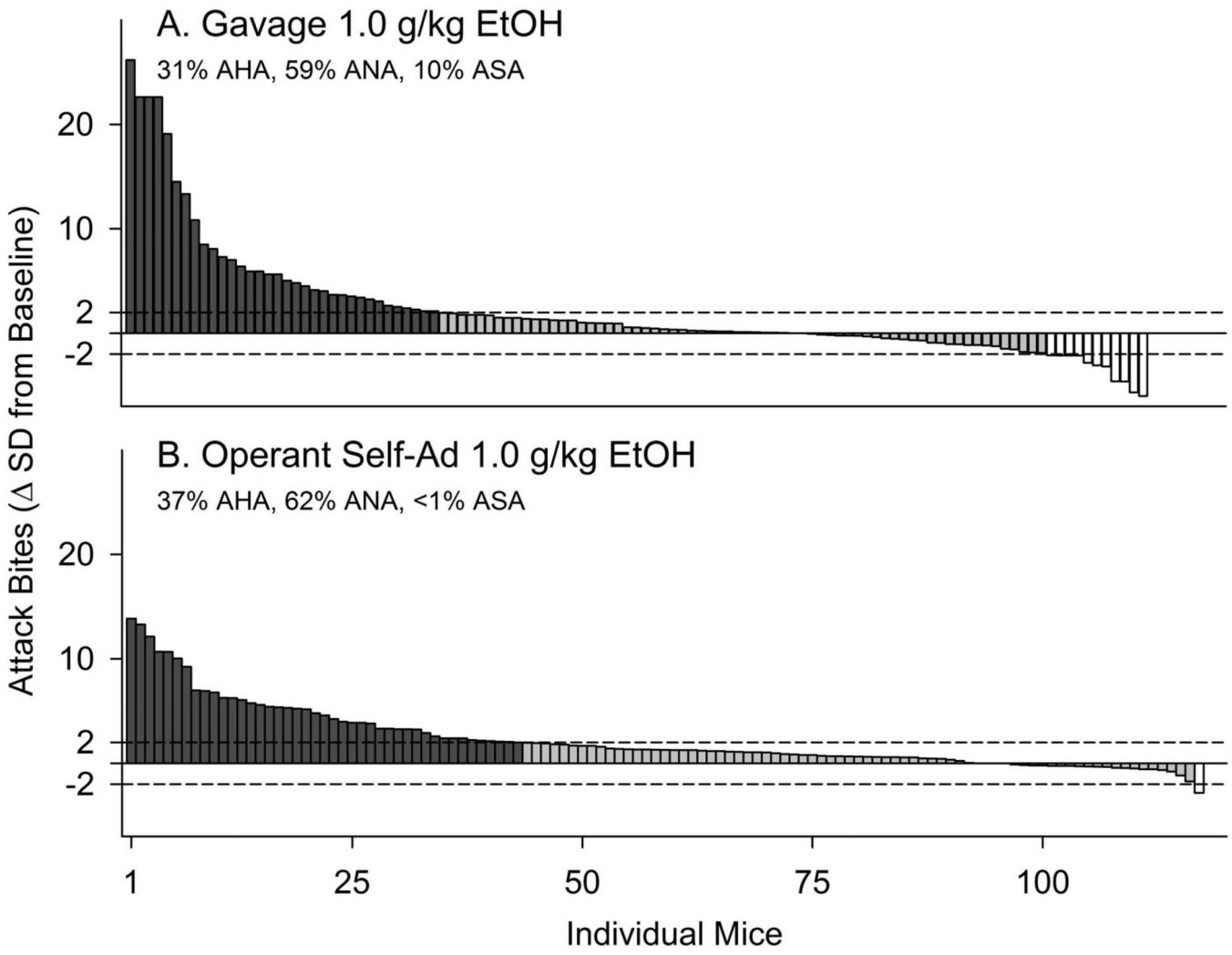

Figure 5.

Histogram representing the proportion and individual magnitude of alcohol-heightened aggression after gavage (A) or operant self-administration (B) of 1.0 g/kg alcohol. Dark vertical bars represent outbred CFW mice whose average frequency of attack bites after 1 g/kg alcohol exceeds their baseline levels of aggression by >2 SD (alcohol-heightened aggression, or AHA). Gray vertical bars represent mice whose aggressive behavior is not significantly altered by 1 g/kg alcohol (alcohol non-heightened aggression, or ANA), and white vertical bars represent mice whose aggressive behavior after 1 g/kg alcohol is reduced by >2 SD (alcohol-suppressed aggression, or ASA). Dotted horizontal lines represent a 95% confidence interval, ±2 SD from average baseline. From Miczek, *et al*.[86]

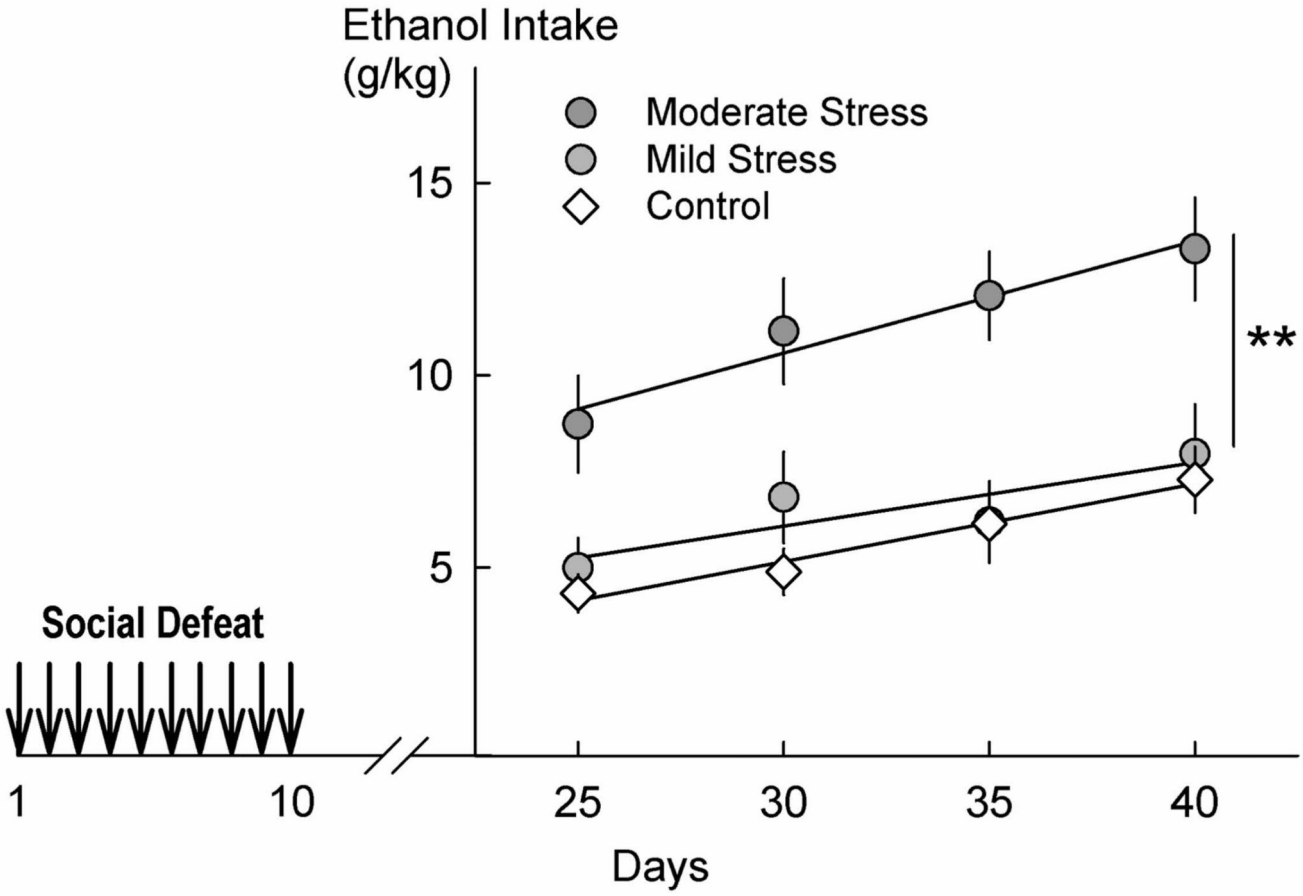

Figure 6.

Twenty percent ethanol intake (g/kg/day) during continuous access two-bottle choice over the course of 20 days, starting 10 days after moderate (n = 39) or mild (n = 19) social defeat stress (control, n = 29). Data points are 5-day averages ±SEM beginning on the day indicated (i.e., 25 signifies days 25–29); $^{**}P < 0.001$ compared to controls. From Norman, *et al.*[120]

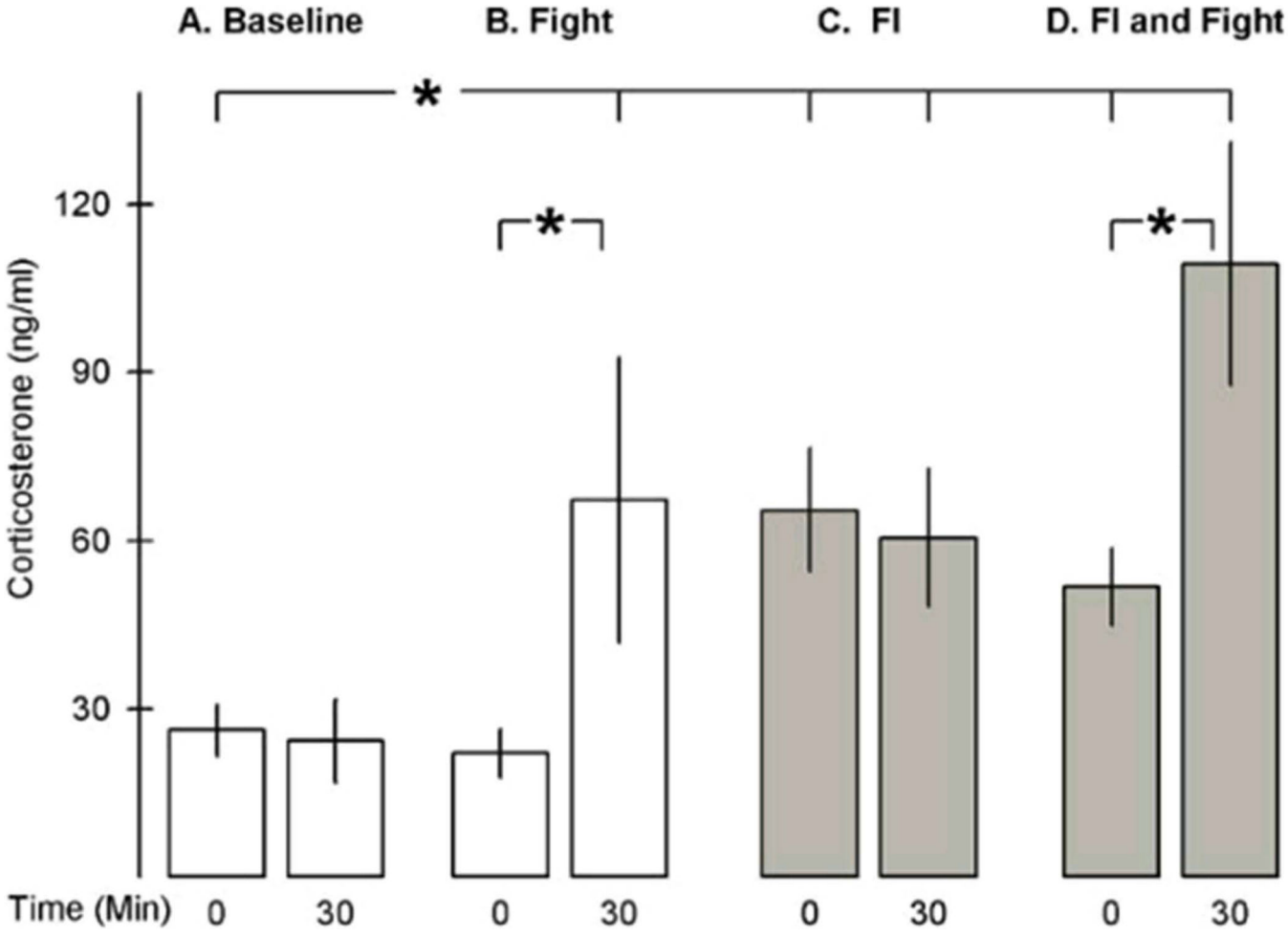

Figure 7.

The effects of fixed interval schedule of reinforcement (FI) performance and fighting on corticosterone levels. Mean plasma corticosterone levels (ng/ml) are shown from resident mice immediately or 30 min after four different events. (A) Baseline corticosterone levels at the time of day when mice are conditioned to respond on an FI10 schedule; (B) levels after a brief attack flurry; (C) levels after completing the FI, but when no fight has occurred; and (D) levels after completing the FI and engaging in a brief fight. The open bars represent corticosterone levels when the mice have not responded on the FI10, and the filled gray bars represent levels after completion of the FI10. Vertical lines indicate ± 1 SEM; *$P < 0.05$. From Fish, *et al.*[137]

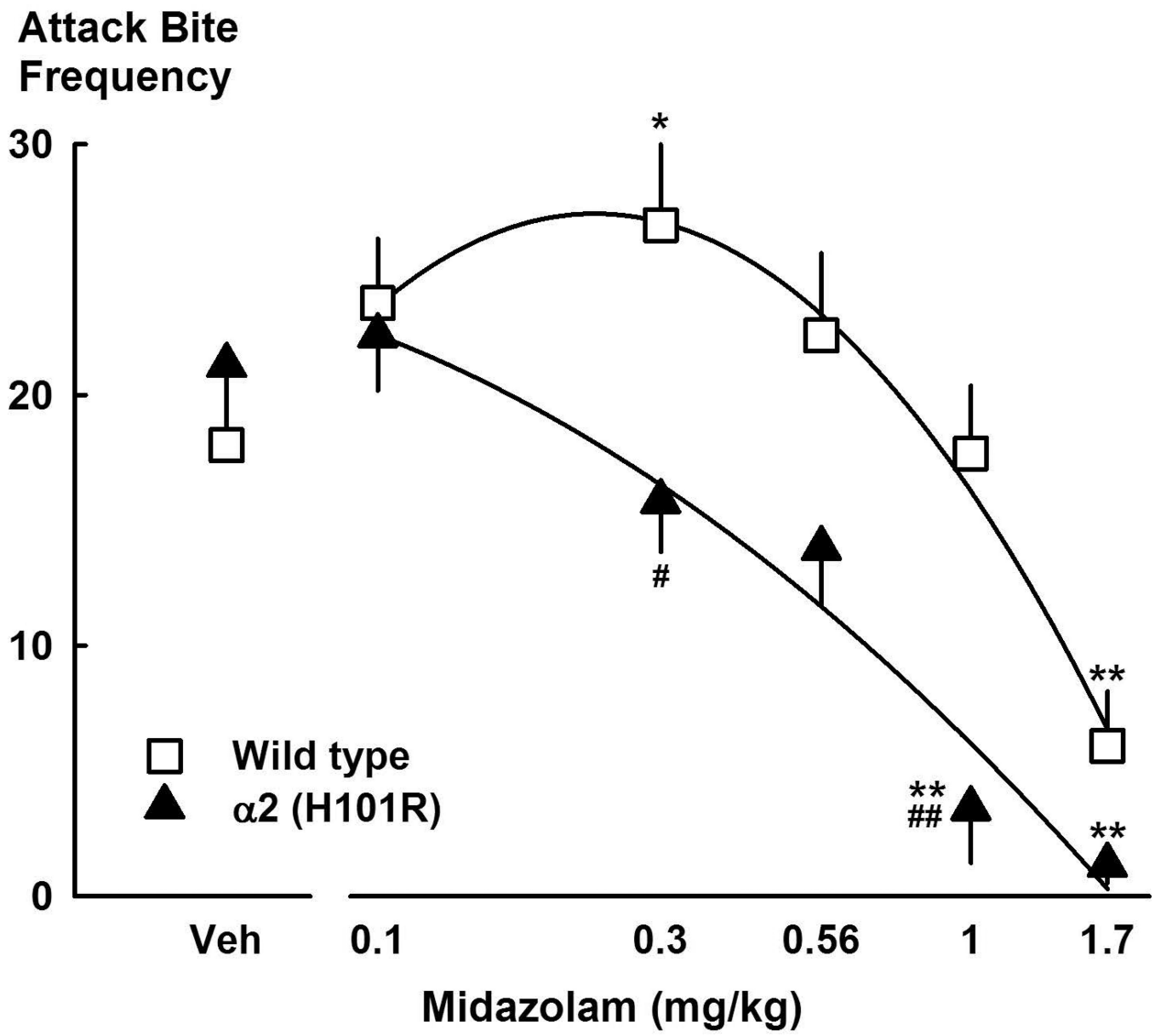

Figure 8.

Attack bite frequencies in a novel environment following systemic midazolam treatment of wild-type C57BL6/J and benzodiazepine-insensitive *Gabra2* (H101R) point-mutated mice. Values are means ± SEM; $^{*}P < 0.05$, $^{**}P < 0.01$ compared to vehicle; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ compared to wild type. From Newman, *et al.*[182]

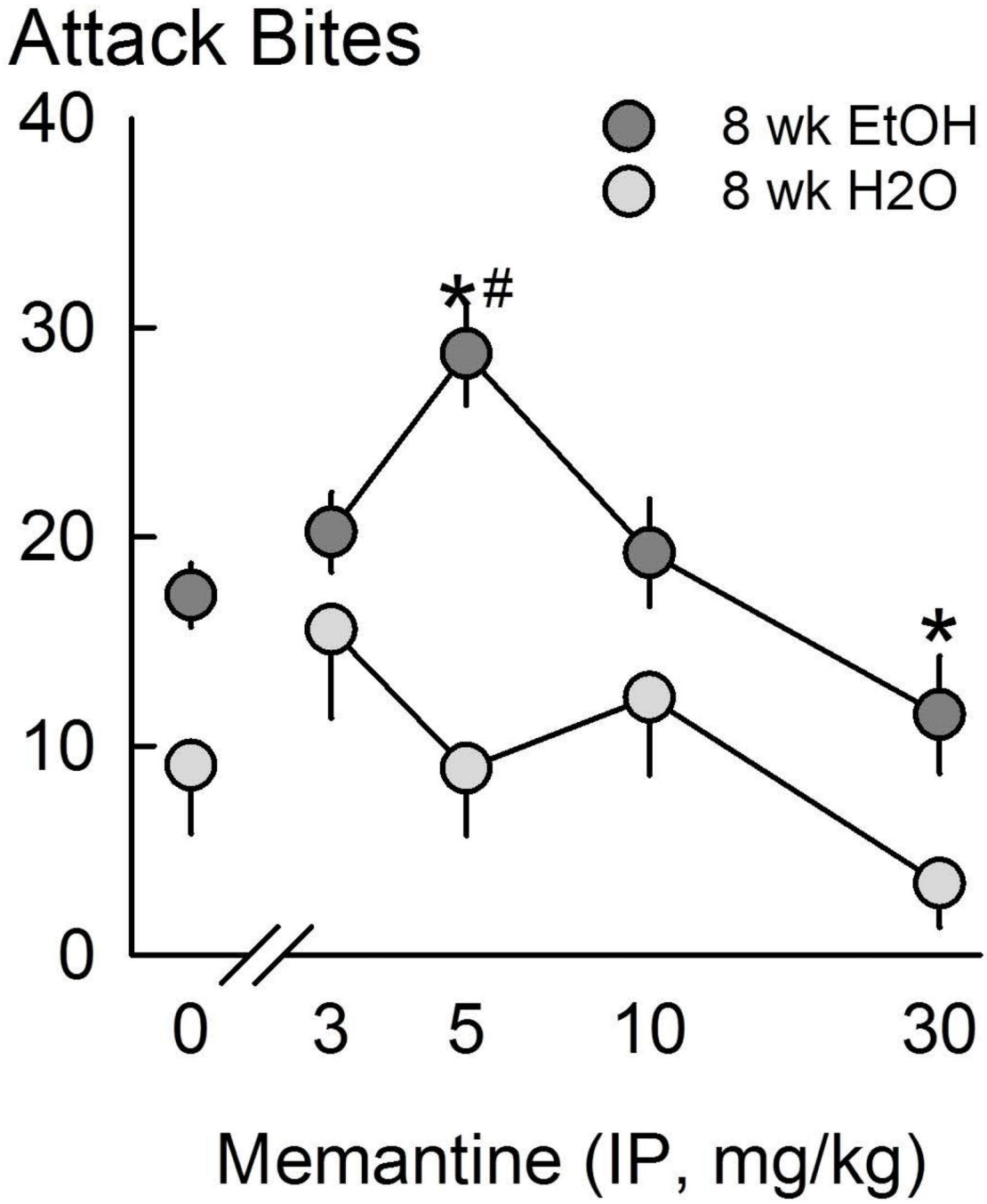

Figure 9.

Attack bites during 6–8 h withdrawal from 8 weeks of intermittent alcohol access after treatment with the NMDA receptor antagonist memantine (0–30 mg/kg, i.p.). Black dots represent alcohol drinkers and white dots represent water drinkers. Values are means ± SEM; **P* < 0.05 vs. vehicle; $^{\#}P$ < 0.05 vs. H2O. From Hwa, *et al.*[77]

Table 1

Estimates of association between alcohol consumption and homicide rates, hazardous drinking pattern score and estimated fraction of homicides attributable to alcohol consumption (from Rossow and Bye, 2013[3])

Author(s)	Country/area, period	Parameter estimate (SE)	Level of hazardous drinking pattern	Attributable fraction (AF)
Rossow (2001)[274]	North Europe, 1950–1995	0.124 (0.038)	High	0.50
Rossow (2001)	Central Europe, 1950–1995	0.085 (0.023)	Medium	0.55
Rossow (2001)	South Europe, 1950–1995	0.055 (0.017)	Low	0.61
Rossow (2004)[275]	Canada, Ontario, 1950–1995	0.093 (0.040)	Medium	0.58
Rossow (2004)	Canada, Quebec, 1950–1995	–0.030 (0.077) ns	Low	na
Bye (2008)[276]	Belarus and Russia, 1959–2004	0.072 (0.016)	Very high	0.57
Bye (2008)	Former Czechoslovakia, 1953–1989	0.117 (0.067)	Medium	0.73
Landberg and Norström (2011)[277]	United States, 1950–2002	0.094 (0.044)	Medium	0.57
Landberg and Norström (2011)	Russia, 1959–1998	0.081 (0.015)	Very high	0.73
Norström (2011)[278]	United States, 1950–2002, dry	0.035 (0.047) ns	Low	na
Norström (2011)	United States, 1950–2002, moderate	0.071 (0.037)	Medium	0.51
Norström (2011)	United States, 1950–2002, wet	0.174 (0.045)	High	0.80
Ramstedt (2011)[11]	Australia, 1950–2003	0.075 (0.028)	Medium	0.56

ns, not significant; na, not applicable.