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Combined and sequential effects of alcohol and methamphetamine in animal models

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Abstract

Comorbid drug use, often alcohol with other drugs, poses significant health and societal concerns. Methamphetamine is among the illicit drugs most often co-used with alcohol. The current review examines the animal literature for impacts of comorbid alcohol and methamphetamine exposure. We found evidence for additive or synergistic effects of combined or sequential exposure on behavior and physiology. Dopaminergic, serotonergic, and glutamatergic systems are all impacted by combined exposure to alcohol and methamphetamine and cyclooxygenase-2 activity plays an important role in their combined neurotoxic effects. Adverse consequences of comorbid exposure include altered brain development with prenatal exposure, impaired learning and memory, motor deficits, gastrotoxicity, hepatotoxicity, and augmented intake under some conditions. Given high susceptibility to drug experimentation in adolescence, studies of co-exposure during the adolescent period and of how adolescent exposure to one drug impacts later use or sensitivity to the other drug should be a priority. Further, to gain traction on prevention and treatment, additional research to identify motivational and neurobiological drivers and consequences of comorbid use is needed.

Keywords

alcohol use disorder; addiction; amphetamine; comorbid drug use; ethanol; neurotoxicity; substance use disorder

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DECLARATION OF COMPETING INTEREST

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1 INTRODUCTION

Concurrent or sequential use of more than one addictive drug is common among individuals developing or suffering from a substance use disorder (SUD). Comorbid use of two or more addictive substances may intensify drug-related physical and mental health consequences, negatively impacting SUD treatment success (Connor et al., 2014; Karjalainen et al., 2017; Wang et al., 2017). Alcohol is arguably the most common addictive substance co-used with illicit drugs, although nicotine co-use is also prominent (Kedia et al., 2007; Midanik et al., 2007; Moeller et al., 2018; Myers and Kelly, 2006). Individuals seeking treatment for alcohol use disorder (AUD) often have a comorbid SUD (Kedia et al., 2007; Substance Abuse and Mental Health Services Administration, 2014a), and alcohol-related hospital admissions frequently involve the use of other drugs (Substance Abuse and Mental Health Services Administration, 2014b; World Health Organization, 2018). Among illicit substances with strong addiction potential, stimulants including amphetamines are widely used, only second to marijuana (World Drug Report, 2019). From survey data collected about three years ago, the global prevalence of amphetamine-type stimulant use among adults aged 15–64 was estimated at 0.6% (~29 million people; World Drug Report, 2019), and there were 6.6 million estimated cases of amphetamine-type stimulant dependence globally in 2015 (Peacock et al., 2018).

Methamphetamine (MA) is the most common clandestinely and illegally manufactured amphetamine-type stimulant in the world, and shifts in the illicit stimulant market have expanded MA use (World Drug Report, 2016, 2019). In a prospective study of young adult MA users who completed surveys at baseline, and 12 and 30 months later, 84–90% indicated that they consumed alcohol during their most recent episode of MA use (Leslie et al., 2017). Furthermore, simultaneous alcohol and MA use increased the odds of MA-related aggression and hostility by about three-fold compared to MA use alone. A DSM-IV diagnosis of lifetime MA dependence and MA use within the last 18 months was associated with a more extensive history of alcohol use in comparison to the alcohol use of non-dependent MA users (Saloner et al., 2019). Given the increasing and pervasive use of MA with alcohol and the potential for heightened adverse consequences, compared to the use of only one of these drugs, it is important to consider why co-use occurs and what the consequences may be. Human studies that directly examine physiological or behavioral effects of combined alcohol and MA are rare. We are aware of two. Kirkpatrick et al. (2012) administered a MA capsule and then an alcoholic drink to a group of individuals who reported alcohol use in the past month and amphetamine use in the past year. Consistent with a similar laboratory investigation conducted almost two decades earlier (Mendelson et al., 1995), the combination of alcohol and MA resulted in greater increases in heart rate and subjective ratings of good drug effect, compared to alcohol or MA administered alone. However, alcohol co-administration attenuated MA-induced sleep disruptions, and MA co-administration reduced feelings of alcohol intoxication and alcohol-induced performance deficits in a divided attention task, providing some clues to motivations for their co-use.

Understandably, the animal literature directly addressing alcohol (ethanol; EtOH) and MA co-exposure is richer than the human literature. Two recent reviews summarized some of the EtOH interactions with a number of commonly used stimulant and depressant drugs

(Althobaiti and Sari, 2016; Singh, 2019). The current review focuses specifically on EtOH and MA, and examines the animal literature with the goals of identifying motivations for EtOH and MA co-use, outcomes of co-exposure, and areas that would benefit from additional research. The animal studies offer control over amount and pattern of drug exposure and certain animal models can provide information about genetic susceptibility to co-use and to deleterious outcomes. Because amphetamine is a major MA metabolite that shares mechanisms of action with MA, alcohol interactions with amphetamine are also discussed. Finally, we consider the potential differential impacts of sequential vs. simultaneous drug exposure on the findings. The questions addressed by these patterns of exposure are somewhat different. Simultaneous drug studies address whether the drugs have additive, opposing, or synergistic effects; whereas sequential studies address whether neural impacts of exposure to the first drug play a role in effects of the subsequent drug. Overall, the literature indicates intensified deleterious effects of comorbid use, compared to effects of each drug alone, under both patterns of exposure.

2 BEHAVIOR

For the behavioral studies not focused on genetic commonalities, experiment details and outcomes are summarized in Table 1. Studies using genetic models are detailed in Table 2.

2.1 Motor

EtOH and MA each have motor effects that could motivate or inhibit continued use. EtOH is typically classified as a sedative-hypnotic and a logical prediction is that EtOH would reduce the excitatory effect of MA. However, EtOH and MA each can dose- and time-dependently increase and decrease locomotor behavior, traits in animals that have been studied as models of human drug euphoria/stimulation and sedation/stereotypy, respectively (Dudek et al., 1994; Erickson and Kochhar, 1985; Kamens et al., 2005; Kitanaka et al., 2007; 2010; 2014; Milesi-Hallé et al., 2005; Phillips and Dudek, 1991; Scaplen et al., 2019; Singh et al., 2012; Wolf et al., 2002; Yates et al., 2007). Reward pathway activation, including increased dopaminergic pathway activity, plays a role in the stimulant effects of both drugs, and is hypothesized to motivate further use; long-term dysregulation of these pathways plays a role in craving and relapse (Camarini and Pautassi, 2016; de Wit and Phillips, 2012; McCreary et al., 2015; Robinson and Berridge, 2008; Wise and Bozarth, 1987). Depressant effects are more likely to inhibit further use, and drug motor effects can complicate interpretation of other behavioral outcomes. For example, animals may reduce operant responding for a reward because the drug impacts motivation for the reward or alternatively, because it interferes with the ability to perform the operant response. In humans, sensitivity to drug stimulation and depression have been considered as potential predictors of future use or abuse (Boyd and Corbin, 2018; Boyd et al., 2016; de Wit and Phillips, 2012; King et al., 2019; Schuckit, 2018). For both drugs, sensitization of the stimulant and stereotypic effects may occur with repeated administration (for reviews, see Phillips et al., 2011; Robinson and Berridge, 1993, 2000; Steketee and Kalivas, 2011), reflecting neuroadaptations that may further impact probability of use (Camarini and Pautassi, 2016; Robinson and Berridge, 2008). But what is known about effects of combined administration?

2.1.1 Simultaneous MA and EtOH exposure—Most studies addressing the effects of EtOH and (meth)amphetamine on motor performance, when administered together or in close succession, have examined locomotor behavior (e.g., level of activity determined by photocell beam breaks, sometimes converted to distance traveled); an occasional study has examined motor coordination (e.g., latency to remain on a rotarod). When Swiss-Cox mice were treated with EtOH alone or in combination with amphetamine just before placement on a rotarod, the dose-dependent impairment induced by EtOH was not intensified or abrogated by several doses of amphetamine (Maickel and Nash, 1986). However, when EtOH and MA were administered in quick succession to ddY mice, EtOH inhibited the stimulation of locomotor behavior induced by lower doses of MA, and enhanced stimulatory effects of higher MA doses (Kohda et al., 1986). A similar attenuating effect of EtOH co-administration on the low dose stimulating effect of amphetamine was found in Long-Evans rats (Hamida et al., 2008). Finally, MA treatment attenuated EtOH-associated reductions in activity in a study using alcohol-preferring P rats in which voluntary EtOH drinking was first established and then continued during MA treatment (Althobaiti et al., 2019).

Overall, the outcomes of studies examining the effect of EtOH exposure on (meth)amphetamine stimulation suggest that EtOH can reduce lower dose, but may actually enhance higher dose, stimulatory effects. MA may attenuate depressant effects of EtOH. These combined effects could be conceptualized as shifts in the dose-response curve induced by two drugs that share dopaminergic actions, which are known to underlie the stimulant effects of addictive drugs (Beckstead and Phillips, 2009; Di Chiara and Imperato, 1988; Ferragud et al., 2014; Meyer et al., 2009). Considering data indicating that the combination of higher drug-induced stimulation and lower sedation predict higher risk for continued use (de Wit and Phillips; 2012; King et al., 2019; Schuckit, 2018), this mixture of outcomes could set the stage for further combined use.

2.1.2 Sequential MA and EtOH exposure—Sequential drug studies address drug-induced changes that have the potential to alter the subsequent effect of a second drug. One study offered Sprague-Dawley rats access to intermittent voluntary EtOH drinking and then administered saline or MA in a “binge regimen” known to induce neurotoxicity (Fantegrossi et al., 2008; Grace et al., 2010; O’Callaghan and Miller, 1994). When motor function was measured on a rotarod a week later, dysfunction was observed only in rats exposed to both EtOH and MA (Blaker et al., 2019b). More common in the motor literature have been studies that have examined the effects of prior EtOH drinking on later locomotor stimulant response to (meth)amphetamine. TO mice maintained on an EtOH liquid diet for about three weeks exhibited heightened locomotor stimulation to amphetamine, compared to non-EtOH controls, when the mice were tested six days and two months after EtOH withdrawal, but not one day after (Manley and Little, 1997). C57BL/6J (B6) mice with a history of binge-level EtOH drinking later exhibited heightened stimulation to a higher MA dose, but not lower doses, compared to water drinking controls (Tschumi et al., 2020). Two additional studies in B6 mice, one in males (Fultz and Szumlinski, 2018) and the other in females (Sern et al., 2020), found no significant effect of prior EtOH drinking on stimulant response to a low dose of MA. However, although these mice had a similar history of binge-level EtOH drinking to those tested by Tschumi et al. (2020), effects of a higher MA dose comparable

to that tested by Tschumi et al. (2020) were not evaluated. Wistar rats given an EtOH solution as their sole source of fluid for eight weeks exhibited an exaggerated stimulant response to amphetamine one day later (Lograno et al., 1993). However, up to 24 days of EtOH liquid diet consumption by Hooded Lister rats did not alter their stimulant response to amphetamine measured five days later (Ripley et al., 2002). Clearly, these EtOH drinking studies had large differences in methodology, species and strain that could explain disparate findings. However, it is also clear that EtOH drinking can result in changes in sensitivity to the locomotor stimulant effects of (meth)amphetamine. In another approach, Albino Swiss Webster mice were treated daily by injection with EtOH and then classified as insensitive or sensitive to locomotor stimulation, based on activity scores after the last treatment. When later challenged with MA, the EtOH-sensitive group exhibited more stimulation than a saline pre-exposed control group, whereas the EtOH-insensitive group did not differ from the other two groups (Abrahao et al., 2009). These data provide an additional potential explanation for variation in the impact of prior EtOH exposure on (meth)amphetamine-induced stimulation, namely differential sensitivity to EtOH stimulation. However, when Albino Swiss Webster mice were given repeated MA treatments and then classified as sensitive or insensitive to MA stimulation, they did not differ in locomotor response to EtOH (Abrahao et al., 2009).

Prior drug exposure in the studies just summarized occurred during adulthood. Several studies have examined the impacts of early life exposure. Sprague-Dawley or Long Evans rats exposed to EtOH via maternal EtOH drinking (throughout gestation and lactation) exhibited increased sensitivity to stimulant effects of amphetamine in adulthood (Barbier et al., 2008; 2009). EtOH exposure only during gestation produced long-lasting sensitization to the motor stimulating effects of repeated amphetamine in Sprague-Dawley rats, compared to non-EtOH pre-exposed controls (Uban et al., 2015). Thus, again, there are several examples of EtOH pre-exposure effects on sensitivity to the locomotor stimulant effects of (meth)amphetamine. Given the involvement of dopaminergic processes within reward pathways in sensitivity to drug stimulant effects, these outcomes suggest neuroadaptations that could impact the probability of further drug use.

2.1.3 Genetic models—Although there are many studies that have addressed shared mechanisms underlying the stimulant and sensitizing effects of EtOH, MA and other drugs of abuse (Broadbent et al., 2005; Camarini and Pautassi, 2016; Ferragud et al., 2014; Nestby et al., 1997; Phillips and Shen, 1996; Robinson and Berridge, 2008; Wearne and Cornish, 2019; Wise and Bozarth, 1987), an important question is whether genetically-determined sensitivity to the effects of one of the two drugs confers sensitivity to the other drug. Perhaps the most directly relevant studies to address the question of shared genetic influence are those examining MA sensitivity in lines bred for EtOH sensitivity and vice versa. The FAST and SLOW lines of mice were bred for differential sensitivity to the stimulant effects of EtOH (Phillips et al., 1991) and were tested for amphetamine or MA stimulation in several selection generations. Data were inconsistent in earlier generations of selection, but in later generations, FAST mice exhibited greater sensitivity to the stimulant effects of MA (Bergstrom et al., 2003; Phillips et al., 1992). In another selection study, mouse lines were bred for low vs. high stimulant response to acute MA and tested for EtOH sensitivity. The high MA stimulation line exhibited more EtOH-induced stimulation than the low MA

stimulation line (Kamens et al., 2006). The overall evidence from these studies is for some shared genetic influence on sensitivity to EtOH- and MA-induced stimulation, consistent with evidence that there are mutual neurobiological processes through which stimulation and changes in stimulation with repeated exposure are induced by these two drugs (Broadbent et al., 2005; Camarini and Pautassi, 2016; Ferragud et al., 2014; Nestby et al., 1997; Phillips and Shen, 1996; Robinson and Berridge, 2008; Wearne and Cornish, 2019).

The potential relationship between differences in EtOH preference and amphetamine locomotor sensitivity have also been examined. Two studies reported that rats bred for higher EtOH preference were less sensitive than non-preferring rats to the motor stimulating effects of amphetamine (D'Aquila et al., 2002; McKinzie et al., 2002), whereas one found the opposite relationship (Fahlke et al., 1995). In the Fahlke et al. (1995) study, selectively bred rat lines were not used. Rather, Wistar rats were first categorized as high or low preference based on their EtOH preference during a three-week period of two-bottle choice EtOH vs. water drinking. Selected line differences depend on genetic variation upon which selective breeding capitalizes, whereas differences in phenotype in a genetically heterogeneous stock, like the Wistar rats, could have a genetic or environmental source (or both). As a result, outcomes could be quite different when asking a question about the correlation between two traits. In the case of selected lines, a significant correlation between the selection trait and another trait would be interpreted as indicating that the two traits have shared genetic influence. In a heterogeneous stock, a significant correlation could be impacted by both genetic and environmental variation among individuals. In addition, the amphetamine stimulation studies in the selected lines were performed using EtOH-naïve rats, whereas the Fahlke et al. (1995) study assessed amphetamine stimulation after a three-week EtOH washout period.

2.2 Consumption and operant self-administration

2.2.1 MA effects on EtOH intake—Effects of prior MA exposure on subsequent EtOH consumption were examined in several free-choice studies and at least one operant study. In B6 mice administered a neurotoxic regimen of MA, two-bottle choice EtOH intake and preference were greater than in saline-treated controls (Gutierrez-Lopez et al., 2010). Similar results were obtained for the effects of prior amphetamine treatment on subsequent two-bottle choice EtOH intake in rats (Fahlke et al., 1994; Ruiz et al., 2018). In the Gutierrez-Lopez et al. (2010) study, MA-induced changes in the endocannabinoid system corresponded with increases in EtOH intake and preference, and the MA-induced increases were not found after treatment with the cannabinoid 1 receptor antagonist, AM251. Furthermore, in another study in which B6 mice were given limited 2 h/day access to MA in water as their sole source of fluid, subsequent intake of EtOH was increased, specifically from the highest of four concentrations of EtOH that were simultaneously offered, compared to a water control (Fultz et al., 2017). However, when MA was operantly self-administered, subsequent two-bottle choice EtOH intake and preference were not significantly altered in P rats (Winkler et al., 2018). Therefore, in the majority of studies, prior (meth)amphetamine exposure increased subsequent EtOH intake in both mice and rats.

2.2.2 EtOH effects on MA intake—Several studies have measured effects of prior EtOH exposure on subsequent MA consumption. Two studies assessed effects on oral MA intake under non-operant conditions. In selectively bred MA high drinking (MAHDR) mice, a prior history of two-bottle choice EtOH consumption had no impact on subsequent two-bottle choice MA intake, when compared to the MA intake of EtOH-naïve mice (Stafford et al., 2020). However, when B6 mice were given 2 h/day limited access to EtOH solutions as their sole source of fluid and then tested in a three-bottle choice procedure, with simultaneous access to EtOH, MA, and an EtOH+MA mixture, mice with a history of EtOH consumption had greater total MA intake (Fultz et al., 2017). This increased MA intake may reflect an increase in sensitivity to MA reward, as subsequent studies found that B6 mice with an EtOH drinking history, under the same conditions, exhibited potentiation of MA-conditioned place preference (Fultz and Szumlinski, 2018; Sern et al., 2020). The contrasting results between the MAHDR and B6 studies may be related to their natural avidities for MA vs. EtOH (discussed in section 2.2.3). However, it is also important to note that the MAHDR study measured two-bottle water vs. MA choice, whereas the B6 study offered MA and EtOH simultaneously without a water choice.

For the effect of EtOH consumption on subsequent operant MA self-administration, outcomes are also mixed. Adult mice of a B6 by 129X1/SvJ inbred strain cross were first allowed to consume water or EtOH and then operant oral MA self-administration was assessed under an escalating schedule of reinforcement. MA intake was either not impacted or reduced in the EtOH compared to water control group, depending upon the reinforcement schedule (Fultz et al., 2017). A subsequent operant MA dose-response study generated for increasing concentrations of MA also found that the mice with a prior history of EtOH consumption consumed less MA, compared to water controls, particularly at the highest MA concentration (Fultz et al., 2017). Intragastric EtOH given during adolescence did not impact later IV amphetamine self-administration measured in adult Wistar rats (Granholm et al., 2015). In contrast, Sprague-Dawley rats prenatally exposed to EtOH had increased IV amphetamine self-administration under a progressive ratio schedule of reinforcement (Wang et al., 2019), but only for a low 0.02 mg/kg/infusion dose and not the higher 0.1 mg/kg/infusion dose, which was the initial dose used by Granholm et al. (2015). Thus, the effect of EtOH exposure on subsequent operant (meth)amphetamine self-administration may depend on work effort (reinforcement schedule) and on when EtOH exposure occurs (prenatally vs. during adolescence/adulthood).

Overall, the effect of prior EtOH exposure on (meth)amphetamine intake appears to be small. One important factor to consider in these studies is the amount of EtOH exposure. Prior EtOH exposure increased non-operant MA intake in B6, but not MAHDR mice; however, MAHDR mice consumed ~1–3 g EtOH/kg/day, compared to ~6–7 g EtOH/kg/day for B6 mice. The amount of EtOH consumed by MAHDR mice may not have been high enough to impact subsequent MA intake. Prior EtOH exposure during the prenatal period enhanced acquisition of IV amphetamine self-administration in rats, but EtOH exposure during adolescence did not. EtOH exposure during adulthood did not impact subsequent oral MA self-administration in mice. Although, effects could be most profound when EtOH exposure occurs during an early developmental period, the increase was found only for a

low dose, which reduces the significance. Another important consideration is the potential impact of route of (meth)amphetamine self-administration. The oral route is subject to first pass metabolic effects and delay of reinforcement. However, the general outcome was little impact of prior EtOH exposure on subsequent (meth)amphetamine intake, regardless of route (IV vs. oral).

2.2.3. Concurrent EtOH and MA effects—A study in P rats examined the effect of MA administered IP during a place conditioning procedure on concurrent EtOH consumption. Rats first consumed EtOH or water, and then MA-induced place conditioning was initiated while EtOH access was maintained in the home cage. Compared to intake at baseline and on saline-conditioning days, on MA days, EtOH intake was initially reduced and then gradually recovered (Althobaiti et al., 2019). Winkler et al. (2018) reported a series of studies in P rats. In the first study, P rats were given home-cage access to water and EtOH, and then daily access to IV saline or MA self-administration. During the self-administration sessions, home-cage EtOH access was continued. They found reduced concurrent EtOH intake and preference in the MA group, compared to the saline control. Next, when MA self-administration sessions occurred prior to EtOH drinking and were continued during the EtOH access phase, there was an initial reduction and then recovery of EtOH intake and preference in the MA group, compared to the saline control; however, there was no impact on sucrose intake in a similar study in which sucrose was substituted for EtOH. Finally, when EtOH drinking was introduced prior to MA self-administration, and then self-administration was examined in the absence of further EtOH access, MA self-administration was increased, compared to baseline and to that of water-drinking controls. However, this higher level of MA self-administration did not persist when the schedule of reinforcement was increased from fixed ratio 1 to fixed ratio 5, nor was there a lasting effect when rats were subsequently tested under a progressive ratio schedule of reinforcement. Overall, MA initially reduced EtOH intake that ultimately recovered, and EtOH enhanced acquisition of MA self-administration under low work effort, but not did not impact maintenance or motivation for MA self-administration.

The studies just described measured oral EtOH intake and IV MA self-administration. Fultz et al. (2017) measured the intake of both drugs via the oral route. When male B6 mice were given simultaneous access to EtOH, MA, and an EtOH+MA mixture, preference for the EtOH+MA solution was greater than for either the EtOH or MA alone solution, and preference for the EtOH solution was greater than for the MA solution. In addition, mice consumed more MA from the EtOH+MA than from the MA alone solution and there was a strong trend for higher EtOH intake from the EtOH+MA, compared to the EtOH alone solution (Fultz et al., 2017). A similar study in male MAHDR mice found largely opposite results (Stafford et al., 2020). Thus, MAHDR mice exhibited a strong preference for the MA solution over both the EtOH and EtOH+MA solutions, and consumed more MA from the MA alone solution. The amount of EtOH consumed was comparable for the EtOH and EtOH+MA solutions. Female mice were not tested by Fultz et al. (2017), but when Stafford et al. (2020) tested female MAHDR mice alongside males, unlike the greater preference for the MA alone solution observed in males, no preference differences were found in females;

thus, females consumed comparable amounts of EtOH and MA from the single vs. admixed solutions.

Stafford et al. (2020) also examined intake in independent groups of MAHDR mice offered water vs. EtOH, water vs. MA, or water vs. EtOH+MA. There were no sex differences and EtOH consumption was similar in mice given access to water vs. EtOH+MA or water vs. EtOH alone. However, mice offered water vs. EtOH+MA consumed less MA than mice offered water vs. MA alone. Thus, regardless of whether MAHDR mice were offered just one of the three drug solutions or all three at once, MA consumption was reduced when mixed with EtOH. The one exception was for female mice offered all three solutions simultaneously. Females appeared to be resistant to the attenuation of MA intake by EtOH adulteration of the MA solution.

Natural drug avidity is important to consider when interpreting these results. MAHDR mice were bred for high MA consumption (Hitzemann et al., 2019; Shabani et al., 2011; Wheeler et al., 2009), whereas B6 mice are MA-avoiding (Eastwood and Phillips, 2014) and EtOH-preferring (Belknap et al., 1993; Yoneyama et al., 2008). A two-bottle choice water vs. EtOH study in MAHDR mice, recorded EtOH consumption amounts of ~1–3 g/kg/day (Stafford et al., 2020), which are much lower than the typical amounts of 3–16 g/kg/day consumed by B6 mice at the same EtOH concentrations under similar choice conditions (e.g., Belknap et al., 1993; Yoneyama et al., 2008). There were also some procedural differences that could have impacted the results. Fultz et al. (2017) offered a choice between 20% EtOH, 10 mg/L MA, and the mixture during three daily 2-h sessions. Stafford et al. (2020) offered a choice between EtOH at increasing concentrations (3, 6, and 10%), 20 mg/L MA, and the mixture of 20 mg/L MA with each EtOH concentration for four days each, during 18-h sessions. The 18-h access condition is consistent with prior data collected in the MAHDR model and Stafford et al. (2020) reported that MA intake is greater when 6-h withdrawal periods occur between access trials.

2.2.4 Genetic models—Finally, with regard to the potential for shared genetic contributors to MA and EtOH intake, there is virtually no literature. For example, a significant genetic correlation between MA and EtOH intake in selected lines would support shared genetic influence; but no data have been published comparing the MAHDR and MALDR lines for EtOH consumption or comparing lines bred for EtOH consumption or preference for MA intake. In mice selectively bred for high (HMACT) vs. low (LMACT) sensitivity to the locomotor stimulant effects of MA, low MA sensitivity was associated with greater EtOH consumption (Kamens et al., 2006) as well as greater MA intake (Kamens et al., 2005); see Table 2. This single study suggests that genetic factors that influence sensitivity to the stimulant effects of MA also contribute to EtOH intake and MA intake, but additional investigation is needed to determine if there is shared genetic influence on EtOH and MA intake.

2.3 Affective behaviors, learning, and memory

Results and experimental details from the few studies that have examined combined effects of EtOH and MA on affective behaviors, learning, and memory are described in Table 1.

In some cases, co-exposure to EtOH and MA has a more extreme impact, compared to exposure to just one of these drugs. For example, repeated co-administration of EtOH and MA produced anxiogenic effects in BALB/c mice not observed after exposure to either drug alone. These mice had EtOH as their sole source of fluid in combination with daily injections of an EtOH and MA mixture, and made fewer entries and spent less time in the open arms of an elevated plus maze the following day, compared to drug-naïve mice. Mice exposed to either EtOH or MA alone did not differ from drug-naïve mice (Chuang et al., 2011). Adolescent Long Evans rats with a history of prior exposure to EtOH, MA or both displayed increased anxiety-like behavior, compared to a saline control, when tested about two weeks after a drug-free period (Loxton and Canales, 2017). Further, when effects of these adolescent drug exposures were examined on radial arm maze reference and working memory, all three drug groups exhibited comparable reference memory deficits, but a significant working memory deficit was found only in the drug co-exposure group. In another study, spatial memory was examined in Wistar rats one day or two weeks after repeated treatment with MA, EtOH, or their combination given during adulthood, and impaired spatial memory was found after MA alone, but not EtOH alone, with the MA effect exacerbated by EtOH co-exposure (Vaghef et al., 2014). Finally, in adult Sprague-Dawley rats, MA-associated deficits in avoidance learning were amplified by EtOH in a wheel running shock-avoidance test (Yamamura et al., 1992).

Overall, the existing data indicate that EtOH and MA co-administration adversely impacts affective behaviors, learning, and memory to an extent greater than each drug alone. However, missing from the literature are studies examining potential effects of sequential exposure and shared genetic contributions to these effects.

3 PHYSIOLOGY

3.1 Pharmacokinetics

Some behavioral or neurobiological outcomes of EtOH and MA co-use or co-addiction may be consequences of alterations of the pharmacokinetics of one drug by the other or by pre-existing differences in pharmacodynamics (e.g., a faster rate of MA metabolism could impact the effect of combined EtOH and MA or amount of drug use). Table 3 describes the existing studies and results, which indicate that simultaneous EtOH exposure affects MA pharmacokinetics. For example, Sprague-Dawley rats were first offered water or EtOH as their sole source of fluid for four weeks, and then MA was administered daily for five or 14 additional water or EtOH access days. Samples examined after the final MA treatment found higher levels of MA and its metabolite, amphetamine, in blood and in several organs including the brain, in the EtOH group compared to the water control. The MA absorption rate was increased by EtOH, but the distribution of MA in body tissues and fluids was not impacted (Liang et al., 2012). Similarly, in white rabbits, simultaneous administration of MA and EtOH via oral gavage accelerated MA absorption and rate of metabolism of MA to amphetamine, but there was no significant impact on MA distribution (Li et al., 2014).

On the other hand, MA does not appear to impact EtOH pharmacokinetics (Liang et al., 2012; Gutierrez-Lopez et al., 2010). The kinetics of EtOH are dependent on concentration (Cederbaum, 2012). At very low concentrations, EtOH elimination is a first-

order process. However, when alcohol dehydrogenase (ADH) becomes saturated, EtOH elimination becomes a zero-order process, occurring at a constant rate. This may present a unique challenge in studying the impact of prior or simultaneous MA exposure on EtOH pharmacokinetics, as observations of MA-induced changes may not be possible when the EtOH metabolic process is saturated.

There do not appear to be studies addressing genetic susceptibility to EtOH effects on MA pharmacokinetics, but we found a single paper that examined the potential impact of genetic susceptibility to an effect of MA on EtOH pharmacokinetics (Kamens et al., 2006). Mice with no drug exposure history, selectively bred for high vs. low sensitivity to the locomotor stimulant effects of MA, were tested for EtOH clearance rate. Mice from the low MA stimulation line had a significant, but small (0.1 mg/ml/h), increase in EtOH clearance rate compared to the high MA stimulation line, and this difference was found for a 2, but not 4 g/kg dose of EtOH. These data suggest a small impact of differential genetic susceptibility to MA stimulation on EtOH pharmacokinetics, but clearly, additional research is needed in this area.

Overall, the existing data indicate that EtOH exposure could increase MA absorption and metabolism. Both EtOH and MA are metabolized by cytochrome P450s (Dostalek et al., 2008; Guengerich and Avadhani, 2018) and they could compete for the same P450 isoenzymes. Although data have not appeared in the literature examining this, the increased formation of some MDMA metabolites found in rat hepatocyte cultures after combined EtOH and MDMA exposure appears to have been partially mediated by the cytochrome P450 isoenzymes CYP3A and CYP2E1 (Pontesa et al., 2010). Another consideration is that MA was administered into the highly vascularized peritoneal cavity in the Liang et al. (2012) study, and, at lower concentrations, EtOH is a vasodilator (Howes and Reid, 1986) and could have increased MA absorption through this action. Blood alcohol levels obtained from EtOH drinking rats in that study were ~9 mg/dl, which would be considered low, although these levels likely waxed and waned. EtOH-induced increases in MA absorption and rate of metabolism could impact MA euphoria, reward and use, although the direction of effects will require additional study.

3.2 Thermal effects

Hyperthermia produced by MA is associated with toxicity and lethality (Matsumoto et al., 2014). Though the basis for MA-induced hyperthermia is not fully known, activation of non-shivering thermogenesis in brown adipose tissue and sympathetic norepinephrine are known to contribute (Sanchez-Alavez, 2020). MA can also lower body temperature (Harkness et al., 2015; Miner et al., 2017; Myles et al., 2008), which is a typical effect of EtOH (Tanaka et al., 2010; Watson et al., 2020). Thus, in combination, the thermal effects of EtOH and MA could be opposing, additive or potentially synergistic, depending on dose and pattern of administration. Existing studies examining the thermal effects of sequential and combined EtOH and MA are few (see Table 3). A prior history of EtOH exposure does not appear to impact the hyperthermic effect of MA in rodents. Wistar rats with a history of saline or EtOH administration via oral gavage did not differ in thermal response to MA measured the following day after the last binge regimen MA injection (Althobaiti et al.,

2016). Similarly, studies in Sprague-Dawley rats found that, compared to water drinking, a history of intermittent two-bottle choice EtOH drinking had no effect on MA binge regimen-induced hyperthermia measured the next day (Blaker and Yamamoto, 2018; Blaker et al., 2019b). However, there is one study in albino mice that found blockade of the hyperthermic effect of MA by pretreatment with EtOH 30 min before MA (Ageel and Ginawi, 1985). Thus, a history of prior EtOH exposure may not impact MA-induced hyperthermia, but EtOH pretreatment or perhaps co-administration may protect against the hyperthermic effect of MA. Additional studies are needed to further characterize the impact of EtOH on the thermal effects of MA, given the potentially detrimental effects of hyperthermia on brain functioning, and that human alcohol use could be driven, in part, to reduce body temperature elevation by MA. We were able to locate only one study that examined the effect of MA on the hypothermic effect of EtOH. Pretreatment with MA 30 min before EtOH attenuated EtOH-induced hypothermia in albino mice (Ageel and Ginawi, 1985).

Some data suggest that sensitivity to hypothermic drug effects (the lowering of body temperature) may attenuate voluntary drug intake (Harkness et al., 2015; Mootz et al., 2020). Mice that voluntarily consume lower amounts of morphine (Eastwood and Phillips, 2014) exhibit relatively greater sensitivity to morphine-induced hypothermia (Mootz et al., 2020). In addition, the MALDR mice, bred for low MA intake, exhibit stronger MA-induced hypothermia, compared to the MAHDR mice, bred for high MA intake (Harkness et al., 2015). Higher sensitivity to MA-induced hypothermia corresponds with low MA intake across other genetic models as well (Reed et al., 2018), and is impacted by the trace amine-associated receptor 1 (*Taar1*) gene, which also impacts MA intake (Stafford et al., 2019). Although there could be a causative relationship between these two traits, such that experiencing a hypothermic drug effect (the lowering of body temperature) attenuates voluntary drug intake (see discussion in Harkness et al., 2015; Mootz et al., 2020), it is also possible that common genetic factors impacting the two traits present the appearance of a functional relationship. The MALDR and MAHDR mice do not differ in sensitivity to EtOH-induced hypothermia (Harkness et al., 2015), nor do mice bred for high vs. low sensitivity to EtOH-induced hypothermia differ in thermal response to amphetamine (Feller and Crabbe, 1991). These data suggest that disparate mechanisms are involved in MA- and EtOH-induced hypothermia. Thus, *Taar1* appears to play a significant role in MA-induced hypothermia, whereas serotonergic systems have commonly, though not exclusively, been implicated in EtOH-induced hypothermia (Feller et al., 1993; Popova and Ivanova, 2002; Tanaka et al., 2010).

4 NEUROBIOLOGICAL MECHANISMS AND NEUROTOXIC EFFECTS

Much of the existing evidence indicates that EtOH and MA have additive or supra-additive (synergistic) effects at the behavioral and physiological level, depending on the timing of their exposures, doses, and how they are administered. These effects are somewhat predictable, based on unique and some overlapping neurochemical and neuropharmacological profiles. For example, both drugs acutely alter the activity of some of the same neurotransmitter systems (i.e., glutamate, dopamine (DA), gamma-aminobutyric acid (GABA), and serotonin (5-HT)). Moreover, EtOH and MA target some of the same neurotransporters, ion channels, and genes, as well as act on the liver and gut. While

additive/synergistic effects of EtOH and MA are often observed, opposing effects have occasionally occurred. Regardless, relatively little is known about the neurochemical underpinnings following co-exposure to EtOH and MA that mediate behavior and other possible negative outcomes such as hepatotoxicity, gastrotoxicity, and neurotoxicity.

The existing data regarding the effects of simultaneous and sequential EtOH and MA exposure on neurobiological processes, and in some cases, corresponding behavioral effects, are described in 4.1 – 4.3 and in Table 4. Studies specifically examining neurotoxic effects are described in 4.4 – 4.7.

4.1 Effects of EtOH and MA on monoaminergic systems

Nucleus accumbens (NAc) DA uptake (Budygin et al., 2007; Carroll et al., 2006; Karkhanis et al., 2015) and DA transporter (DAT) levels (Healey et al., 2008) are increased in response to EtOH exposure in rodents, a result consistent with the increase in striatal DAT availability associated with prior heavy EtOH drinking in humans (Cosgrove et al., 2009). Because MA acts on DAT to cause the efflux of DA, increased DAT availability associated with EtOH exposure could lead to augmented acute MA-induced DA release. But, in contrast to that expectation, episodic binge-like EtOH exposure of Wistar rats during adolescence reduced evoked DA release in the dorsal striatum in response to amphetamine in adulthood, in comparison to EtOH-naïve rats (Granholm et al., 2015). This effect of EtOH on amphetamine-induced DA release did not correspond with changes in amphetamine self-administration, which was not altered by prior EtOH exposure. Further, prenatal EtOH exposure did not alter the effect of amphetamine treatment on DA levels in the striatum of three-month old Wistar rats (Nowak et al., 2006). Although these results could indicate that the effect of EtOH on amphetamine-induced DA release is dependent on developmental period of exposure, more data are needed.

The vesicular monoamine transporter (VMAT2) is another potential substrate for the combined acute effects of EtOH and MA. EtOH alone increases VMAT2 gene expression in mice (Darlington et al., 2014) and MA acts on VMAT2 to cause the efflux of DA by disrupting vesicular packaging (Nickell et al., 2014). Therefore, increased VMAT2 availability resulting from EtOH pre-exposure could enhance acute MA-induced DA release. Prior EtOH consumption also can alter MA-induced changes in midbrain DA neuron activity. Thus, increases in midbrain D2 receptor-mediated inhibitory postsynaptic current amplitude induced by MA was blunted in B6 mice with a history of EtOH drinking during adulthood, compared to water drinking mice (Tschumi et al., 2020). Such a reduction in depression of DA activity may result in greater DA release from nerve terminals in projection regions, such as the NAc. The EtOH-associated blunting occurred only when a higher concentration of MA was applied, a concentration proposed to affect VMAT2, whereas the ineffective lower MA concentration was one that acts only at DAT. Tschumi et al. (2020) also examined MA-induced locomotor stimulation, which was increased by a history of EtOH drinking for a higher, but not lower, dose of MA. EtOH-associated attenuation of increases in midbrain D2 receptor-mediated inhibitory postsynaptic current amplitude corresponded with EtOH-induced increases in MA stimulation at higher doses. It is possible that the EtOH-induced reduction in the inhibitory effect of MA resulted in

increased sensitivity to MA stimulation, but additional studies are needed to confirm a causative link.

In contrast to Tschumi et al. (2020), prenatal EtOH exposure of Sprague-Dawley rats enhanced sensitivity to amphetamine-induced reductions in ventral tegmental area DA neuron firing rates measured in adulthood (Xu and Shen, 2001). This could have been due to heightened sensitivity of somatodendritic DA autoreceptors in the ventral tegmental area after prenatal EtOH exposure, observed in a previous study in Long Evans rats (Shen et al., 1995). Interestingly, Shen et al. (1995) also found that chronic postnatal amphetamine exposure reversed this effect of prenatal EtOH exposure, restoring sensitivity of DA autoreceptors to normal. Overall, EtOH attenuated the acute depressive effects of MA when EtOH exposure occurred during adulthood and MA responses were recorded from midbrain slices, whereas the acute depressive effects of amphetamine were enhanced by prenatal EtOH exposure when recorded in unanesthetized rats. In addition, the enhancing effect of prenatal EtOH on amphetamine-induced depression of midbrain DA neuron activity was reversed after chronic amphetamine exposure, suggesting that tolerance to the enhancing effect of EtOH developed over time.

Less studied has been the impact of MA on the monoaminergic effects of EtOH. Local application of EtOH depressed the activity of all cerebellar Purkinje neurons measured in anesthetized Sprague-Dawley rats. MA co-application had a weak potentiating effect (<10% increase) in half of the neurons studied. However, after systemic administration of prazocin, an α-adrenergic receptor antagonist, MA significantly potentiated EtOH-induced neural depression in 88% of the neurons studied (Wang et al, 1995). Further, when noradrenergic neurons were chemically lesioned, the depressant effects of EtOH were unaltered, but the enhancement of EtOH-induced Purkinje neuron depression by MA was potentiated (Wang et al., 1995). Together, these data support an inhibitory role of noradrenergic mechanisms and α-adrenergic receptors on MA potentiation of the depressant EtOH effect.

A few studies have examined (meth)amphetamine-induced DA release in lines of rats selectively bred for high vs. low EtOH preference (See Table 2). Bifone et al. (2019) compared Marchigian Sardinian alcohol-preferring rats to non-selected genetically heterogeneous Wistar rats that serve as their control line (Colombo et al., 2006) and found a greater increase in extracellular DA in response to amphetamine in the NAc shell in the high preference rats. Using magnetic resonance imaging, this study also detected increased functional reactivity in the NAc shell of the alcohol-preferring rats in response to amphetamine, compared to Wistar rats. Nishiguchi et al. (2010) compared high alcohol preference (HAP) and low alcohol preference (LAP) rats for striatal DA levels after treatment with MA and found that intracerebroventricular pretreatment with the D1 receptor antagonist SCH23390 augmented the effect of MA in HAP but not LAP rats. These studies indicate that the dopaminergic response to MA is related to genetically-determined differences in EtOH preference.

4.2 Effects of EtOH and MA on GABAergic systems

The role of GABA transmission and GABA receptors in the pharmacological and addictive effects of EtOH (Augier et al, 2018; Maccioni and Colombo, 2009) and of GABA

receptors and transporters as treatment targets for AUD are well known (Fairbanks et al., 2020; McColl and Piquette-Miller, 2020; Phillips and Reed, 2014). In addition, GABA interneurons in the prefrontal cortex, which interact with the mesolimbic DA system through inhibition of excitatory prefrontal cortical projections, play a role in the effects of (meth)amphetamine. The GABA system is a proposed target for the treatment of MA use disorder (Rose and Grant, 2008; Wearne and Cornish, 2019). Changes in GABA after EtOH or MA are also at the intersection of DA and glutamate transmission in the mesolimbic system and basal ganglia (Mark et al., 2004; 2007; Matuszewich and Yamamoto, 1999; Williams et al., 2018), which could affect addictive behavior. Despite the findings that GABA transmission has a role in effects of EtOH and MA alone and has been a target for therapeutic intervention for both EtOH and MA use disorder, there have not been reports of findings for potential GABAergic mechanisms underlying co-use or co-exposure effects for EtOH and MA.

4.3 Effects of EtOH and MA on glutamatergic systems

EtOH and MA independently increase glutamate transmission (Nash and Yamamoto, 1993; Roberto and Varodayan, 2017). Glutamate-regulating NMDA and AMPA receptors expressed on D1 receptor-expressing medium spiny neurons in the NAc and DA neurons in the ventral tegmental area attenuate relapse-like EtOH intake, as demonstrated in site- and time-specific conditional mutant mice lacking GluN1 or GluA1 receptor subunits (Eisenhardt et al., 2015). Further, MAHDR mice that have high genetic risk for MA intake and voluntarily consume binge-level amounts of MA, exhibit greater extracellular glutamate levels in response to acute MA administration, compared to low risk, low intake, MALDR mice (Szumlinski et al., 2017). Changes in extracellular glutamate and glutamate transporter levels have been examined in response to sequential EtOH and MA exposure. In Sprague-Dawley rats, two-bottle choice intermittent EtOH drinking prior to binge regimen MA treatment augmented the increase in striatal extracellular glutamate induced by MA alone. EtOH exposure alone did not impact glutamate levels compared to saline (Blaker et al., 2019a). The potential mechanism underlying this synergistic increase in glutamate appears to have been an EtOH drinking-induced reduction in the glutamate aspartate transporter (GLAST), which was quantified one day after EtOH drinking ended in a separate group of MA-naïve rats. The glutamate transporter subtype 1 (GLT-1) was not impacted by EtOH drinking. However, the findings related to the subtype of glutamate transporter may be dependent on rat strain. Whereas EtOH drinking decreased GLAST, but not GLT-1 in Sprague-Dawley rats (Blaker et al., 2019a), the sequential exposure to EtOH by gavage followed by the MA binge regimen in Wistar rats additively decreased GLT-1, but not GLAST expression in the NAc, dorsal striatum, and hippocampus, when measured 48 h after MA treatment (Alshehri et al., 2017; Althobaiti et al., 2016). These studies also examined the effect of ceftriaxone, a β-lactam antibiotic known to increase the expression of glutamate transporters. Ceftriaxone administered during EtOH drinking alone was sufficient to not only block the EtOH-induced increases in basal extracellular striatal glutamate concentrations, but also the augmented increase in glutamate produced by MA (Blaker et al., 2019a). In another study, ceftriaxone blocked the decreases in GLT-1 associated with EtOH drinking and reduced EtOH intake in P rats (Das et al., 2015). Ceftriaxone administered after MA treatment rescued GLT-1 expression in Wistar rats with

and without a history of EtOH consumption (Alshehri et al., 2017; Althobaiti et al., 2016). Regardless of the rat strain-associated differences in the effects of EtOH on glutamate transporters, these studies indicate that glutamate transporters and extracellular glutamate work in concert to contribute to the combined neurochemical effects of EtOH and MA. The roles of glutamate receptors have yet to be studied.

4.4 Neurotoxic effects of combined EtOH and MA on dopaminergic systems

The neurotoxicity of either EtOH or MA exposure is well documented, but neurotoxicity induced by sequential exposure is less understood. Long-term depletions of monoamine content are suggestive of nerve terminal degeneration, and thus, used as a marker of neurotoxicity. A study in Sprague-Dawley rats examined neurotoxic effects of exposure to two-bottle choice intermittent EtOH drinking or EtOH by gavage, followed by the MA binge regimen. In both cases, prior EtOH exposure led to exacerbated long-term MA-induced depletions of DA in the striatum, but no changes were observed after EtOH exposure alone (Blaker and Yamamoto, 2018). Further, higher amounts of voluntary EtOH intake produced greater decreases in DA in response to neurotoxic MA exposure (Figure 1). This is the only study we found that reported correlations between level of EtOH intake and effects of MA. Given that large individual differences often occur in EtOH drinking procedures during intermittent two-bottle choice EtOH drinking (e.g., Blaker et al., 2019a), future studies should assess such quantitative relationships. It is also notable that even though blood EtOH concentrations were much lower on the last EtOH drinking day compared to after the last EtOH gavage (70.9±1.9 mg% vs. 146.3±2.2 mg%, respectively), exacerbated MA-induced DA depletions were similar for the two methods of exposure (Blaker and Yamamoto, 2018). There may be a certain threshold of EtOH exposure that is required to impact MA neurotoxicity, which was met for both routes of administration. Although similar results were observed, blood EtOH concentration achieved is important to consider in future studies, and may be informative with regard to the threshold required to impact the effects of MA.

The long-term depletions of striatal DA after sequential exposure to EtOH and MA were due to glutamate and calcium/calpain-dependent excitotoxicity, preceded by augmented increases in extracellular glutamate, and dependent on cyclooxygenase 2 (COX-2) during EtOH drinking (Blaker and Yamamoto, 2018; Blaker et al., 2019a). As discussed above, glutamate transporters have a role in the combined glutamatergic effects of EtOH and MA (Alshehri et al., 2017; Althobaiti et al., 2016). Enhanced downregulation of GLT-1, which is responsible for regulating extracellular glutamate levels, may lead to an excess in extracellular glutamate, resulting in excitotoxicity. Although increases in tissue content of glutamate were not observed in a procedure that employed EtOH gavage in Wistar rats (Almalki et al., 2018), increases in extracellular glutamate and calcium mediated proteolysis and excitotoxicity were observed in Sprague-Dawley rats that voluntarily drank EtOH (Blaker et al., 2019a).

The toxicity to DA terminals in the striatum after serial exposure to EtOH and MA extended to the loss of tyrosine hydroxylase-positive neurons in the substantia nigra pars compacta (SNc) that was not present after voluntary EtOH drinking alone or MA exposure alone

(Blaker et al., 2019b). This effect corresponded with motor dysfunction specific to serial exposure, suggesting the EtOH-induced exacerbation of MA neurotoxicity may underlie motor dysfunction. Blaker et al. (2019b) concluded that tyrosine hydroxylase-positive cell loss in the SNc was due to an increase in COX-2 activity during EtOH drinking, because the COX-2 inhibitor, nimesulide, given during EtOH drinking, blocked the loss of these DA neurons and the accompanying motor dysfunction, and also blocked caspase-3 and microglial activation in the SNc found after exposure to MA. Inhibition of COX-2 also protects against MPTP-induced DA cell death through a reduction in reactive oxygen species and DA quinones (Chae et al., 2008; Hastings, 1995; Świątkiewicz et al., 2013). It remains unknown how co-exposure to EtOH and MA induces COX-2 in or near DA cells specifically, but it could be due to the auto-oxidation of DA and quinone formation (Asanuma et al., 2003; Barzilai et al., 2001) causing a feed-forward mechanism.

The enhanced neurotoxicity following serial exposure to EtOH and MA suggests a confluence of glutamate-mediated excitotoxicity, inflammation, and ion channel expression that mediates damage to DA neurons. EtOH alters multiple ion channels (Crews et al., 1996), including the L-type calcium channel CaV1.2 (Uhrig et al., 2017) and GIRK channels (Cannady et al., 2018; Mayfield et al., 2015) to affect neuronal excitability. These effects of EtOH occur in parallel with upregulated expression of the *CACNA1C* gene and increases in the number of L-type Ca^{2+} channels in response to in vitro MA exposure of human SH-SY5Y dopaminergic cells (Andres et al., 2015). Nevertheless, it remains unknown if there are additive or supra-additive effects on the expression of L-type calcium channels following co-exposure that may explain the calcium-mediated excitotoxity and apoptosis to DA neurons.

There are studies in which EtOH pre-exposure did not exacerbate MA-induced neurotoxicity. For example, increased striatal DA depletions by EtOH were not found in a study of C57BL/6N mice provided with an EtOH solution as their sole source of fluid, and then treated with the MA binge regimen, when measures were taken 72 h after MA treatment (Ali and Bondy, 2010). However, the concentration of EtOH offered was only 2%, compared to the 10 to 20% concentrations typically used in drinking studies of B6 mice, and average EtOH consumption was only 2.7 g/kg/day. That said, a study in which Wistar rats were sequentially exposed to 6 g/kg bolus doses of EtOH by gavage for seven days immediately followed by the MA binge regimen also did not find a significant effect of EtOH pre-exposure on striatal DA levels, when measured 48 h after MA treatment (Almalki et al., 2018). However, it is important to note that EtOH alone in that study produced a large increase in striatal DA and there was no significant effect of MA alone on DA levels (Almalki et al., 2018).

Rather than sequential exposure, some studies have examined neurotoxic effects of co-exposure. Sprague-Dawley rats were repeatedly administered escalating doses of EtOH and/or escalating doses of MA (Yamamura et al., 1992). Striatal DA levels were depleted by MA, whereas co-administration with EtOH appeared to mitigate MA-induced DA depletion; however, the effect of EtOH was not statistically significant. In the hippocampus, EtOH alone decreased DA, MA alone increased DA, and the combination appeared to mitigate each of these independent effects. There were no significant effects of drug treatment on

DA levels in the cortex. This investigation found amplified MA-associated learning deficits in the EtOH co-administration group, however they did not correspond with any of the dopaminergic impacts. In B6 mice, EtOH delivered in close proximity to an MA binge regimen also attenuated MA-induced striatal DA depletions (Yu et al., 2002). In contrast, when BALB/c mice were given EtOH as their sole source of fluid in combination with repeated daily injections of an EtOH and MA mixture, there was no significant effect of EtOH or MA exposure, alone or in combination, on striatal or prefrontal cortex DA levels (Chuang et al., 2011). In the Chuang et al. (2011) study, co-administration of EtOH and MA had anxiogenic effects that were not observed in response to either drug alone and did not correspond with changes in DA levels in the striatum or prefrontal cortex.

Results are mixed. It appears likely that the combined neurotoxic effects of EtOH and MA on the DA system are dependent on species and/or strain, as well as procedural differences, such as timing of exposure (sequential vs. concurrent), dose, length of drug exposure, or timing of DA measurements after drug treatment. However, overall, prior EtOH exposure enhanced MA-induced dopaminergic neurotoxicity in several studies, but simultaneous EtOH exposure mitigated MA-induced DA depletions.

4.5 Neurotoxic effects of combined EtOH and MA on serotoninergic systems

Several of the studies discussed above also examined 5-HT neurotoxicity under the same treatment conditions. Similar to effects on MA-induced DA levels, prior EtOH exposure enhanced MA-induced 5-HT depletions, whereas EtOH co-administration had the opposite or no effect. Thus, intermittent two-bottle choice EtOH drinking followed by MA binge regimen treatment exacerbated long-term MA-induced depletions of 5-HT in the striatum, with no changes observed after EtOH exposure alone (Blaker and Yamamoto, 2018). Higher levels of voluntary EtOH intake produced greater decreases in 5-HT after neurotoxic MA exposure (Figure 1). When MA and EtOH were given independently or co-administered, MA reduced 5-HT levels to a greater extent than EtOH alone, and EtOH co-administration rescued MA-induced depletions to the level of EtOH alone in the hippocampus and striatum; EtOH also reversed MA-induced cortical 5-HT depletions (Yamamura et al., 1992). Shock avoidance learning measured by Yamamura et al. (1992) was negatively impacted by MA, and EtOH amplified the MA-induced learning deficits. Thus, the outcomes for cognitive function were not aligned with the 5-HT outcomes in this study. In another study, no effect of EtOH or MA, alone or in combination, on striatal or prefrontal cortex 5-HT levels were found (Chuang et al., 2011), and Almalki et al. (2018) found no prior EtOH exposure effect on MA-induced hippocampal or striatal 5-HT depletions.

4.6 Other neurotoxic effects of combined EtOH and MA

Chuang et al. (2011) measured potential toxicity to neurons and glia, and the impact of drug treatments on cell proliferation in several brain regions. NeuN was used as a neural marker, GFAP as a glial marker, and BrdU as a marker of proliferation. The number of NeuN-positive cells in the dentate gyrus was reduced by combined EtOH and MA exposure, but not by either drug alone. The dentate gyrus has been implicated in anxiety-like behaviors (Weeden et al., 2015), and anxiogenic effects corresponded with the treatment outcomes (Chuang et al., 2011). In the amygdala, the NeuN-positive cell count was reduced to the

same extent after treatment with each drug alone and their combination. In the striatum and prefrontal cortex, there were no significant drug effects on NeuN-positive cell counts. For glial toxicity, significant reductions in the number of GFAP-positive cells in the striatum, dentate gyrus, and amygdala were comparable for EtOH, MA and combined drug groups, whereas there were no significant effects in the prefrontal cortex. Finally, with regard to cell proliferation, the number of BrdU-positive cells was equivalently decreased by EtOH, MA, and their combination in the subventricular zone and dentate gyrus. Overall, only neuronal toxicity in the dentate gyrus was uniquely altered by EtOH and MA co-exposure, compared to either drug alone, and anxiogenic behavioral outcomes aligned with this result.

Microglia may also play a role in EtOH and/or MA neurotoxicity. When RNA sequencing was used to identify gene expression differences in striatal isolated microglia from saline vs. binge MA-treated rats, COX-2-driven prostaglandin synthesis was associated with differential expression between the two treatment groups (Kays and Yamamoto, 2019). When EtOH drinking was followed by binge MA, changes in microglial morphology were found in the SNc that were distinct from those in EtOH drinking or MA treatment alone groups (Blaker et al., 2019b). Microglia mediate EtOH-induced inflammatory responses in the brain (Henriques et al., 2018). That exposure to EtOH and MA caused exaggerated changes in microglial morphology (Blaker et al., 2019b) suggests important roles for microglia and inflammation in the interactions between the drugs. Overall, the damage to DA terminals in the striatum and DA cell bodies in the SNc reveals novel neurotoxicity mediated by microglia, glutamate excitotoxicity, and inflammation that is different from what is observed after either drug alone. Loss of motor control has been documented in extreme cases of AUD and MA users are three times more likely to be diagnosed with Parkinson’s disease (Curtin et al., 2015; Granado et al., 2013; Lappin et al., 2018). Co-abuse of EtOH and MA may produce inflammation that enhances the vulnerability to calcium-mediated excitotoxicity and results in motor deficits or early onset Parkinson’s disease.

There is also evidence that structural abnormalities in the brain are produced by combined EtOH and MA exposure. Hippocampal neurogenesis during adulthood was altered in Long Evans rats that had been exposed for five days during adolescence to EtOH and MA by gavage. Persistent working memory deficits were observed for combined exposure that were not observed for either drug alone (Loxton and Canales, 2017). Some data in human studies also suggest effects with the potential for long-term cognitive impacts. Thus, prenatal exposure to alcohol and/or MA resulted in fMRI abnormalities in frontostriatal connectivity of children such that frontal brain regions that project to the putamen had increased connectivity, whereas connectivity for those that project to the caudate were decreased (Roussotte et al., 2011). Frontal cortex thickness was reduced in adults with comorbid amphetamine dependence and heavy alcohol use, compared to controls or those who used either drug alone (Lawyer et al., 2010). Taken together, the combination of alcohol and (meth)amphetamine produces additive and supra-additive changes in brain structure and neurochemistry that may underlie some behavioral and cognitive changes associated with the co-abuse of these drugs.

4.7 Peripheral organ effects and their relation to neurotoxicity

Acute and chronic alcohol use can result in alcoholic fatty liver disease (hepatic steatosis and cirrhosis; Dugum and McCullough, 2015) characterized by inflammation and loss of liver function, respectively. In contrast, little is known about the adverse effects of MA on the liver, although damage to the liver and other organs has been observed (Ago et al., 2006; Halpin et al., 2013; Kamijo et al., 2002; Smith and Fischer, 1970; Wijetunga et al., 2003). MA-induced hepatotoxicity increases plasma ammonia occurring after either EtOH drinking (Lockwood et al., 1979) or exposure to the MA binge regimen (Halpin and Yamamoto, 2012). Plasma ammonia is normally broken down in the gut and converted to urea in the liver, the latter being compromised with a loss of hepatic function. Consequently, hepatotoxicity causes ammonia to accumulate in the systemic circulation. Hyperammonemia has been identified as a contributor to the long-term depletions of DA and 5-HT in brains after MA exposure (Felipo and Butterworth, 2002; Halpin and Yamamoto, 2012; Halpin et al., 2013; Halpin et al., 2014), highlighting the importance of the liver as a contributing factor to drug-induced neurotoxicity. In addition, alcoholic liver cirrhosis can have a negative impact on the brain and produce hepatic encephalopathy (Davis and Bajaj, 2018). As a consequence of hepatotoxicity, increased levels of blood and brain ammonia can increase glutamate within the brain and contribute to DA depletions (Halpin and Yamamoto, 2012). Based on these similarities, a recent study in Wistar rats examined the impact of exposure to EtOH in combination with MA and found hepatoxicity through pro-inflammatory and oxidative stress mechanisms (de Carvalho et al., 2018). The consequences of hepatotoxicity and elevated ammonia on the brain after EtOH and MA co-exposure remain to be fully determined.

EtOH consumption also affects the gastrointestinal (GI) tract and produces inflammation and oxidative stress via production of pro-inflammatory cytokines (Fleming et al., 2001). Oxidative stress caused by EtOH metabolism within the epithelial cells that line the lumen of the GI tract stimulates inflammation and GI barrier breakdown via degradation of the tight junction proteins lining the gut mucosa (Elamin et al., 2014). The GI-blood barrier functions under normal circumstances to prevent harmful microorganisms such as endotoxin (i.e., lipopolysaccharide; LPS) from exiting the GI tract and entering the circulation, where endotoxin can induce inflammation throughout the body (Qin and Crews, 2012). Thus, EtOH can cause inflammation via breakdown of the GI-blood barrier through oxidative stress and by increasing para-cellular translocation of bacteria from the gut into the circulation (Leclercq et al., 2012; Mathurin et al., 2000).

MA also causes systemic inflammation through increases in pro-inflammatory chemokines in the peripheral circulation of both rodents and humans (Loftis et al., 2011). The systemic inflammation is reflected by pro-inflammatory cytokines (e.g., IL-1β) caused by LPS leaking from the gut into the circulation. The increases in circulating inflammatory mediators could result in GI damage evidenced by ischemic colitis, ulcers, and necrosis in individuals with high levels of MA use (Anderson et al., 2018; Brannan et al., 2004; Johnson and Berenson, 1991; Prendergast et al., 2014; Zou et al., 2018) that further exacerbate inflammation. Consequently, peripheral inflammatory mediators can enter the brain parenchyma and induce neuroinflammation (Banks, 2005; Engelhardt et al., 2016;

Louveau et al., 2015). Thus, any injury to the gut that promotes GI barrier breakdown and inflammation could potentiate a neuroinflammatory state (Banks, 2005). Along these lines, EtOH produced increases in LPS in the serum and brain as well as COX-2 in the brain of Sprague-Dawley rats (Blaker and Yamamoto, 2018). It remains to be determined if the increase in LPS could be exacerbated by MA-induced liver damage. The significance of the increases in LPS and COX-2 within the brain and the neurotoxicity to DA neurons could be responsible for microglia activation produced by exposure to both EtOH and MA (Blaker et al., 2019b). Overall, these findings support the gut as a target for therapeutic intervention (Leclercq et al., 2012) and support a role for peripheral organ effects of EtOH and MA on the brain (de Timary et al., 2017).

4.8 Blood brain barrier

The blood-brain barrier (BBB) is at the interface between the periphery and the brain, and serves as a protective barrier to the influx of pathogens into the brain. MA can increase the permeability of the BBB through the same mechanisms that mediate MA-induced damage to monoaminergic nerve terminals (Abbott, 2000; Kousik et al., 2012; Ramirez et al., 2009). In addition to COX-2-mediated damage to DA neurons following the combination of EtOH and MA (Blaker et al., 2019b), COX-2 has been implicated in BBB disruption and is increased in response to MA in rodents (Kita et al., 2000; Thomas and Kuhn, 2005). EtOH also causes dysfunction and increases permeability of the BBB of humans (Pratt et al., 1990) and rodents (Rosengren and Persson, 1979) by the same inflammatory and oxidative stress mechanisms that mediate MA-induced damage to the BBB (Northrop and Yamamoto, 2012). Little if anything is known about the effects of combined exposure to EtOH and MA on the BBB. Because LPS is mainly derived from the gut and augments EtOH drinking-induced BBB permeability (Singh et al., 2007), it is probable that the peripheral pro-inflammatory and pro-oxidant effects of EtOH drinking (Haorah et al., 2007; Le Moine et al., 1995; Mathurin et al., 2000) would exacerbate the pro-inflammatory effects of MA (Northrop and Yamamoto, 2015). Thus, increased permeability of the BBB by the co-use of EtOH and MA may have broad and significant consequences manifesting as cognitive decline, learning and memory deficits, dementia, and enhanced vulnerability to other disease states such as HIV (Swan, 1997) and Hepatitis C (Letendre et al., 2007), which are comorbid with drug use disorders.

5 CONCLUSIONS AND FUTURE DIRECTIONS

We have reviewed the evidence from animal studies examining the frequency, motivation, and consequences of combined or sequential alcohol and MA exposure. Human studies examining rates and patterns of alcohol and MA co-use and co-addiction indicate that there are high rates of simultaneous and sequential alcohol use with MA both in individuals with and in those without a MA use disorder diagnosis; many of these people have a comorbid AUD (Brecht et al., 2007; 2008; Herbeck et al., 2013; Wang et al., 2017). Not surprisingly, there are negative impacts of co-use on treatment outcomes. Many clinical studies do not report the exact timing, frequency, or quantities of alcohol and MA use, making the impact of such factors difficult to ascertain. We have chosen to examine the animal literature in detail, because alcohol and drug history can be controlled and manipulated, increasing the

ability to draw specific conclusions. Figure 2 summarizes the strength of current knowledge for combined effects of alcohol and MA on behavior, neurobiology and toxicity, based on the animal literature.

Animal studies have provided valuable insights into the combined and sequential behavioral effects of EtOH and MA. Many have found prior exposure or co-exposure effects of EtOH on MA-induced motor, consummatory, affective, and cognitive effects, and vice versa. Existing studies also indicate that there may be shared genetic influences on EtOH and MA-related behaviors. Although observed effects may appear inconsistent, there has been considerable variation across studies in species, strain, dosage, drug exposure timing and duration, method of drug exposure, and time of testing relative to drug exposure. Thus, the effect of EtOH on MA-induced locomotor stimulation depended on MA dose (Fultz and Szumlinski, 2018; Kohda et al., 1986; Sern et al., 2020; Tschumi et al., 2020); the effect of prior MA exposure on EtOH intake depended on method of MA administration, and vice versa (Fultz et al., 2017; Gutierrez-Lopez et al., 2010; Winkler et al., 2018); intake and preference when the two drugs were offered together was driven by which drug was most preferred when offered alone (Fultz et al., 2017; Stafford et al., 2020); and the impact of exposure to one drug on response to the other depended upon developmental period (Granholm et al., 2015; Nowak et al., 2006; Tschumi et al., 2020; Wang et al., 2019; Xu and Shen, 2001). It is not surprising that such factors could impact outcomes, and variation among individuals and between populations should be expected. Some studies have included dose and time considerations in their research designs, and it would be beneficial to systematically study these and other factors, such as genetic contributions to the effects of combined EtOH and MA, in future studies.

In their recent reviews of alcohol use with a number of stimulant drugs, Althobaiti and Sari (2016) and Singh (2019) proposed that combining alcohol and stimulants could (1) potentiate euphoria/pleasure; (2) attenuate adverse subjective effects; (3) have negative consequences on the brain and behavior, such as decreases in antioxidant enzymes, neurotransmitter depletions, augmented withdrawal, and learning and memory disruption; and (4) alter pharmacokinetics. We found supportive evidence for some of these proposed outcomes, but also identified gaps in the literature that suggest potential research directions that could shed more light on motivation for and consequences of EtOH and MA co-use. Human studies in which alcohol and MA have been administered are rare, but the existing research findings raise the possibility that co-use increases euphoric and pleasurable drug effects (e.g., subjective ratings of good drug effect), while decreasing adverse effects (e.g., performance deficits, sleep disruptions, sedation), which could increase motivation for combined use (Kirkpatrick et al., 2012; Mendelson et al., 1995). Although the animal studies of combined EtOH and MA effects have used some measures of behavioral and cognitive performance, lacking are studies of how combined effects on sedation or stimulation might be related to co-use. There is some evidence for reduced MA-induced sleep disruption by alcohol in human studies (Kirkpatrick et al., 2012), but although sleep disruption has been an area of interest in both EtOH and MA research (e.g., Andersen et al., 2009; Sharma et al., 2018), combined effects of EtOH and MA have not been a focus. Pharmacokinetic, pharmacodynamic, neurochemical and peripheral organ effects appear to be relevant to the impact of combined EtOH and MA, but more studies are needed to fully elucidate

the additive, synergistic and opposing effects of EtOH and MA on biological mechanisms contributing to co-use.

The majority of the studies examining the consequences of EtOH and MA co-exposure on monoaminergic and glutamatergic systems reveal additive or synergistic effects of EtOH and MA on neurotransmitter release, neuronal activity, and transporter expression. Combined effects on other neurotransmitter systems that are known to be independently impacted by EtOH and MA, such as the GABAergic system, have yet to be examined. There is also a dearth of information about behavioral correlates of the pharmacodynamic and neurochemical effects of EtOH and MA co-exposure and a lack of direct studies of mechanisms that could provide evidence of casual relationships. Examples include a study that implicated the D2 receptor in the effect of EtOH on MA-induced locomotor stimulation (Tschumi et al., 2020), and one that implicated the endocannabinoid system in the effect of MA on EtOH intake (Gutierrez-Lopez et al., 2010).

Also lacking are studies addressing EtOH and MA co-exposure effects on the consequence of drug withdrawal and likelihood of relapse. Such studies may provide insight into factors underlying the poor treatment outcomes associated with EtOH and MA co-use and co-addiction (e.g., Mutter and Ali, 2019; Tan et al., 2019; Wang et al., 2017). In addition, sex differences in the response to combined or sequential EtOH and MA exposure are grossly understudied in animal models. The vast majority of the animal studies described in this review were conducted in males only (see Tables 1–4). There is an abundance of evidence demonstrating sex differences in response to many addictive drugs including EtOH and MA (Becker and Koob, 2016), making it important to conduct experiments examining the effects of combined EtOH and MA in both sexes. Further, the existing studies that have considered developmental period in drug co-exposure effects support potential augmentation of adverse effects with early exposure. This literature is limited and cross-sectional studies are needed to fully disclose the importance of age of exposure.

Finally, critically important is the potential for EtOH and MA co-use to exacerbate the neurotoxicity associated with chronic use of each drug individually. Relative to independent neurotoxic effects of EtOH and MA, neurotoxic consequences of co-exposure have been minimally explored. That said, a number of studies do indicate that serial exposure to EtOH and MA has additive or synergistic neurotoxic effects. Amplified neurotoxicity could result in more severe consequences on cognition, reward processing and risk for psychiatric disorders (e.g., anxiety, depression) than experienced with either drug alone. Several studies indicate that motor dysfunction, anxiety-like behaviors, and learning and memory deficits measured subsequent to exposure are exacerbated by combined EtOH and MA exposure. Such outcomes could increase the probability of continued use to reduce or avoid adverse effects, increase the probability of relapse, and predict poor treatment success. The overall result may be increased motivation for further use, with the potential for long-term consequences on mental and physical health. More systematic research is needed that examines the impact of EtOH and MA co-exposure on sensitivity to motivational effects of these drugs and subsequent drug seeking and taking.

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REFERENCES

Abbott NJ, 2000. Inflammatory mediators and modulation of blood-brain barrier permeability. Cell Mol Neurobiol 20, 131–147 doi:10.1023/a:1007074420772 [PubMed: 10696506]

Abrahao KP, Quadros IM, Souza-Formigoni ML, 2009. Individual differences to repeated ethanol administration may predict locomotor response to other drugs, and vice versa. Behav Brain Res 197, 404–410 doi:10.1016/j.bbr.2008.10.009 [PubMed: 18984011]

Ageel AM, Ginawi OT, 1985. Effects of methamphetamine and methyldopa on ethanol induced hypothermia in mice. Jpn J Pharmacol 37, 137–142 doi:10.1254/jjp.37.137 [PubMed: 3999469]

Ago M, Ago K, Hara K, Kashimura S, Ogata M, 2006. Toxicological and histopathological analysis of a patient who died nine days after a single intravenous dose of methamphetamine: a case report. Leg Med (Tokyo) 8, 235–239 doi:10.1016/j.legalmed.2006.03.002 [PubMed: 16793314]

Ali SF, Bondy SC, 2010. Red wine but not ethanol at low doses can protect against the toxicity of methamphetamine. Brain Res 1346, 247–250 doi:10.1016/j.brainres.2010.05.058 [PubMed: 20510887]

Almalki AH, Das SC, Alshehri FS, Althobaiti YS, Sari Y, 2018. Effects of sequential ethanol exposure and repeated high-dose methamphetamine on striatal and hippocampal dopamine, serotonin and glutamate tissue content in Wistar rats. Neuroscience Letters 665, 61–66 doi:10.1016/j.neulet.2017.11.043 [PubMed: 29174641]

Alshehri FS, Althobaiti YS, Sari Y, 2017. Effects of administered ethanol and methamphetamine on glial glutamate transporters in rat striatum and hippocampus. J Mol Neurosci 61, 343–350 doi:10.1007/s12031-016-0859-8 [PubMed: 27888396]

Althobaiti YS, Sari Y, 2016. Alcohol interactions with psychostimulants: an overview of animal and human studies. J Addict Res Ther 7 doi:10.4172/2155-6105.1000281

Althobaiti YS, Alshehri FS, Almalki AH, Sari Y, 2016. Effects of ceftriaxone on glial glutamate transporters in wistar rats administered sequential ethanol and methamphetamine. Front Neurosci 10, 427 doi:10.3389/fnins.2016.00427 [PubMed: 27713684]

Althobaiti YS, Alshehri FS, Hakami AY, Hammad AM, Sari Y, 2019. Effects of clavulanic acid treatment on reinstatement to methamphetamine, glial glutamate transporters, and mGluR 2/3 expression in P rats exposed to ethanol. J Mol Neurosci 67, 1–15 doi:10.1007/s12031-018-1194-z [PubMed: 30471010]

Anderson JE, Brown IE, Olson KA, Iverson K, Cocanour CS, Galante J, 2018. Nonocclusive mesenteric ischemia in patients with methamphetamine use. J Trauma Acute Care Surg 84, 885–892 doi:10.1097/TA.0000000000001855 [PubMed: 29462085]

Anderson ML, Margis R, Frey BN, Giglio LM, Kapczinski F, Tufik S, 2009. Electrophysiological correlates of sleep disturbance induced by acute and chronic administration of D-amphetamine. Brain Res 1249, 162–172 doi: 10.1016/j.brainres.2008.10.023 [PubMed: 18992721]

Andres MA, Cooke IM, Bellinger FP, Berry MJ, Zaporteza MM, Rueli RH, Barayuga SM, Chang L, 2015. Methamphetamine acutely inhibits voltage-gated calcium channels but chronically up-regulates L-type channels. J Neurochem 134, 56–65. doi:10.1111/jnc.13104 [PubMed: 25807982]

Asanuma M, Tsuji T, Miyazaki I, Miyoshi K, Ogawa N, 2003. Methamphetamine-induced neurotoxicity in mouse brain is attenuated by ketoprofen, a non-steroidal anti-inflammatory drug. Neurosci Lett 352, 13–16 doi:10.1016/j.neulet.2003.08.015 [PubMed: 14615038]

Augier E, Barbier E, Dulman RS, 2018. A molecular mechanism for choosing alcohol over an alternative reward. Science 360, 1321–1326 doi:10.1126/science.aao1157 [PubMed: 29930131]

Banks WA, 2005. Blood-brain barrier transport of cytokines: a mechanism for neuropathology. Curr Pharm Des 11, 973–984 doi:10.2174/1381612053381684 [PubMed: 15777248]

Barbier E, Houchi H, Warnault V, Pierrefiche O, Daoust M, Naassila M, 2009. Effects of prenatal and postnatal maternal ethanol on offspring response to alcohol and psychostimulants in long evans rats. Neuroscience 161, 427–440 doi:10.1016/j.neuroscience.2009.03.076 [PubMed: 19348874]

Barbier E, Pierrefiche O, Vaudry D, Vaudry H, Daoust M, Naassila M, 2008. Long-term alterations in vulnerability to addiction to drugs of abuse and in brain gene expression after early life ethanol exposure. Neuropharmacology 55, 1199–1211 doi:10.1016/j.neuropharm.2008.07.030 [PubMed: 18713641]

Barzilai A, Melamed E, Shirvan A, 2001. Is there a rationale for neuroprotection against dopamine toxicity in Parkinson's disease? Cellular and Mol Neurobiol 21, 215–235 doi:10.1023/a:1010991020245

Becker JB, Koob GF, 2016. Sex differences in animal models: focus on addiction. Pharmacol Rev 68, 242–263 doi:10.1124/pr.115.011163 [PubMed: 26772794]

Beckstead MJ, Phillips TJ, 2009, Mice selectively bred for high- or low-alcohol-induced locomotion exhibit differences in dopamine neuron function. J Pharmacol Exp Ther 329, 342–349 doi:10.1124/jpet.108.146316 [PubMed: 19122113]

Belknap JK, Crabbe JC, Young ER, 1993. Voluntary consumption of ethanol in 15 inbred mouse strains. Psychopharmacology (Berl) 112, 503–510 doi:10.1007/BF02244901 [PubMed: 7871064]

Bergstrom HC, Palmer AA, Wood RD, Burkhart-Kasch S, McKinnon CS, Phillips TJ, 2003. Reverse selection for differential response to the locomotor stimulant effects of ethanol provides evidence for pleiotropic genetic influence on locomotor response to other drugs of abuse. Alcohol Clin Exp Res 27, 1535–1547 doi:10.1097/01.ALC.0000091226.18969.B9 [PubMed: 14574223]

Bifone A, Gozzi A, Cippitelli A, Matzeu A, Domi E, Li H, Scuppa G, Cannella N, Ubaldi M, Weiss F, Ciccocioppo R, 2019. phMRI, neurochemical and behavioural responses to psychostimulants distinguishing genetically selected alcohol-preferring from genetically heterogenous rats. Addiction Biology 24, 981–993 doi:10.1111/adb.12671 [PubMed: 30328656]

Blaker AL, Moore ER, Yamamoto BK, 2019a. Serial exposure to ethanol drinking and methamphetamine enhances glutamate excitotoxicity. J Neurochem 151, 749–763 doi:10.1111/jnc.14861 [PubMed: 31478210]

Blaker AL, Rodriguez EA, Yamamoto BK, 2019b. Neurotoxicity to dopamine neurons after the serial exposure to alcohol and methamphetamine: Protection by COX-2 antagonism. Brain Behav Immun 81, 317–328 doi:10.1016/j.bbi.2019.06.028 [PubMed: 31228610]

Blaker AL, Yamamoto BK, 2018. Methamphetamine-Induced brain injury and alcohol drinking. J Neuroimmune Pharmacol 13, 53–63 doi:10.1007/s11481-017-9764-3 [PubMed: 28856500]

Boyd SJ, Corbin WR, 2018. Faster alcohol metabolism is associated with increased stimulation and within session consumption. Exp Clin Psychopharmacol 26, 168–176 doi:10.1037/pha0000176 [PubMed: 29355349]

Boyd SJ, Schacht JP, Prisciandaro JJ, Voronin K, Anton RF, 2016. Alcohol-Induced stimulation mediates the effect of a GABRA2 SNP on alcohol self-administrated among alcohol-dependent individuals. Alcohol and Alcoholism 51, 549–554 doi:10.1093/alcalc/agw024 [PubMed: 27117237]

Brannan TA, Soundararajan S, Houghton BL, 2004. Methamphetamine associated shock with intestinal infarction. MedGenMed 6, 6

Brecht ML, Greenwell L, Anglin MD, 2007. Substance use pathways to methamphetamine use among treated users. Addict Behav 32, 24–38 doi:10.1016/j.addbeh.2006.03.017 [PubMed: 16675150]

Brecht ML, Huang D, Evans E, Hser YI, 2008. Polydrug use and implications for longitudinal research: ten-year trajectories for heroin, cocaine, and methamphetamine users. Drug Alcohol Depend 96, 193–201 doi:10.1016/j.drugalcdep.2008.01.021 [PubMed: 18329825]

Broadbent J, Kampmueller KM, Koonse SA, 2005. Role of dopamine in behavioral sensitization to ethanol in DBA/2J mice. Alcohol 35, 137–148 doi:10.1016/j.alcohol.2005.03.006 [PubMed: 15963427]

Budygin EA, Oleson EB, Mathews TA, Läck AK, Diaz MR, McCool BA, Jones SR, 2007. Effects of chronic alcohol exposure on dopamine uptake in rat nucleus accumbens and caudate putamen. Psychopharmacology (Berl) 193, 495–501 doi:10.1007/s00213-007-0812-1 [PubMed: 17492432]

Camarini R, Pautassi RM, 2016. Behavioral sensitization to ethanol: Neural basis and factors that influence its acquisition and expression. Brain Res Bull 125, 53–78 doi:10.1016/j.brainresbull.2016.04.006 [PubMed: 27093941]

Cannady R, Rinker JA, Nimitvilai S, Woodward JJ, Mulholland PJ, 2018. Chronic alcohol, intrinsic excitability, and potassium channels: Neuroadaptations and drinking behavior. Handb Exp Pharmacol 248, 311–343 doi:10.1007/164_2017_90 [PubMed: 29374839]

Carroll MR, Rodd ZA, Murphy JM, Simon JR, 2006. Chronic ethanol consumption increases dopamine uptake in the nucleus accumbens of high alcohol drinking rats. Alcohol 40, 103–109 doi:10.1016/j.alcohol.2006.10.003 [PubMed: 17307646]

Cederbaum AI, 2012. Alcohol metabolism. Clinics in liver disease 16, 667–685 doi:10.1016/j.cld.2012.08.002 [PubMed: 23101976]

Chae SW, Kang BY, Hwang O, Choi HJ, 2008. Cyclooxygenase-2 is involved in oxidative damage and alpha-synuclein accumulation in dopaminergic cells. Neuroscience Letters 436, 205–209 doi:10.1016/j.neulet.2008.03.031 [PubMed: 18403118]

Chuang JY, Chang WT, Cherng CG, Kao GS, ali L, 2011. Repeated co-administrations of alcohol- and methamphetamine-produced anxiogenic effect could be associated with the neurotoxicity in the dentate gyrus. J Neural Transm (Vienna) 118, 1559–1569 doi:10.1007/s00702-011-0645-2 [PubMed: 21499940]

Colombo G, Lobina C, Carai MA, Gessa GL, 2006. Phenotypic characterization of genetically selected Sardinian alcohol-preferring (sP) and -non-preferring (sNP) rats. Addict Biol 1, 324–338 doi:10.1111/j.1369-1600.2006.00031.x

Connor JP, Gullo MJ, White A, Kelly AB, 2014. Polysubstance use: diagnostic challenges, patterns of use and health. Curr Opin Psychiatry 27, 269–275 doi:10.1097/YCO.0000000000000069 [PubMed: 24852056]

Cosgrove KP, Krantzler E, Frohlich EB, Stiklus S, Pittman B, Tamagnan GD, Baldwin RM, Bois F, Seibyl JP, Krystal JH, O'Malley SS, Staley JK, 2009. Dopamine and serotonin transporter availability during acute alcohol withdrawal: effects of comorbid tobacco smoking. Neuropsychopharmacology 34, 2218–2226 10.1038/npp.2009.49 [PubMed: 19440191]

Crews FT, Morrow AL, Criswell H, Breese G, 1996. Effects of ethanol on ion channels. Int Rev Neurobiol 39, 283–367 doi:10.1016/s0074-7742(08)60670-4 [PubMed: 8894851]

Curtin K, Fleckenstein AE, Robison RJ, Crookston MJ, Smith KR, Hanson GR, 2015. Methamphetamine/amphetamine abuse and risk of Parkinson's disease in Utah: a population-based assessment. Drug Alcohol Depend 146, 30–38. doi: 10.1016/j.drugalcdep.2014.10.027 [PubMed: 25479916]

D'Aquila PS, Peana AT, Tanda O, Serra G, 2002. Different sensitivity to the motor-stimulating effect of amphetamine in Sardinian alcohol-preferring and non-preferring rats. Eur J Pharmacol 435, 67–71 doi:10.1016/s0014-2999(01)01531-x [PubMed: 11790379]

Darlington TM, McCarthy RD, Cox RJ, Ehringer MA, 2014. Mesolimbic transcriptional response to hedonic substitution of voluntary exercise and voluntary ethanol consumption. Behav Brain Res 259, 313–320 doi:10.1016/j.bbr.2013.11.001 [PubMed: 24239693]

Das SC, Yamamoto BK, Hristov AM, Sari Y, 2015. Ceftriaxone attenuates ethanol drinking and restores extracellular glutamate concentration through normalization of GLT-1 in nucleus accumbens of male alcohol-preferring rats. Neuropharmacology 97, 67–74. doi:10.1016/j.neuropharm.2015.05.009 [PubMed: 26002627]

Davis BC, Bajaj JS, 2018. Effects of alcohol on the brain in cirrhosis: Beyond hepatic encephalopathy. Alcohol Clin Exp Res 42, 660–667 doi: 10.1111/acer.13605 [PubMed: 29417604]

de Carvalho TG, Garcia VB, de Araujo, Gasparotto H.dS., Silva H, Guerra GCB, Miguel EC, Leitao R.F.deC., Costa D.V.deS., Cruz LJ, Chan AB, Junior R.F.deA., 2018. Spherical neutral gold nanoparticles improve anti-inflammatory response, oxidative stress and fibrosis in alcohol-methamphetamine-induced liver injury in rats. Int J Pharm 548, 1–14 doi: 10.1016/j.ijpharm.2018.06.008 [PubMed: 29886101]

de Timary P, Stärkel P, Delzenne NM, Leclercq S, 2017. A role for the peripheral immune system in the development of alcohol use disorders? Neuropharmacology 122,148–160 doi:10.1016/j.neuropharm.2017.04.013 [PubMed: 28400259]

de Wit H, Phillips TJ, 2012. Do initial responses to drugs predict future use or abuse? Neurosci Biobehav Rev 36, 1565–1576 doi:10.1016/j.neubiorev.2012.04.005 [PubMed: 22542906]

Di Chiara G, Imperato A, 1988, Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 85, 5274–5278 doi: 10.1073/pnas.85.14.5274 [PubMed: 2899326]

Dostalek M, Jurica J, Pistovcakova J, Hanesova M, Tomandl J, Linhart I, Sulcova A, 2007. Effect of methamphetamine on cytochrome P450 activity. Xenobiotica 37, 1355–1366 doi: 10.1080/00498250701652877 [PubMed: 17922362]

Dudek BC, Tritto T, Underwood KA, 1994. Genetic influences on locomotor activating effects of ethanol and sodium pentobarbital. Pharmacol Biochem Behav 48, 593–600 doi:10.1016/0091-3057(94)90319-0 [PubMed: 7938111]

Dugum M, McCullough A, 2015. Diagnosis and management of alcoholic liver disease J Clin Transl Hepatol 3,109–116 doi:10.14218/JCTH.2015.00008 [PubMed: 26356792]

Eastwood EC, Phillips TJ, 2014. Opioid sensitivity in mice selectively bred to consume or not consume methamphetamine. Addict Biol 19, 370–379 doi:10.1111/adb.12003 [PubMed: 23145527]

Eisenhardt M, Leixner S, Luján R, Spanagel R, Bilbao A, 2015. Glutamate receptors within the mesolimbic dopamine system mediate alcohol relapse behavior. J Neurosci 35, 15523–15538 doi:10.1523/JNEUROSCI.2970-15.2015 [PubMed: 26609150]

Elamin E, Masclee A, Troost F, Pieters H-J, Keszthelyi D, Alekas K, Dekker J, Jonkers D, 2014. Ethanol impairs intestinal barrier function in humans through mitogen activated protein kinase signaling: a combined in vivo and in vitro approach. PLoS One 9, e107421 doi:10.1371/journal.pone.0107421 [PubMed: 25226407]

Engelhardt B, Carare RO, Bechmann I, Flugel A, Laman JD, Weller RO, 2016. Vascular, glial, and lymphatic immune gateways of the central nervous system. Acta Neuropathol 132, 317–338 doi: 10.1007/s00401-016-1606-5 [PubMed: 27522506]

Erickson CK, Kochhar A, 1985. An animal model for low dose ethanol-induced locomotor stimulation: behavioral characteristics. Alcohol Clin Exp Res 9, 310–314 doi:10.1111/j.1530-0277.1985.tb05550.x [PubMed: 3901799]

Fahlke C, Hard E, Eriksson CJP, Engel JA, Hansen S, 1995. Amphetamine-induced hyperactivity: differences between rats with high or low preference for alcohol. Alcohol 12, 363–367 doi:10.1016/0741-8329(95)00019-N [PubMed: 7546334]

Fahlke C, Hansen S, Engel JA, Hard E, 1994. Effects of ventral striatal 6-OHDA lesions or amphetamine sensitization on ethanol consumption in the rat. Pharmacol Biochem Behav 47, 345–349 doi:10.1016/0091-3057(94)90020-5 [PubMed: 8146227]

Fairbanks J, Umbreit A, Kolla BP, Karpyak VM, Schneekloth TD, Loukianova LL, Sinha S, 2020. Evidence-based pharmacotherapies for alcohol use disorder: clinical pearls. Mayo Clin Proc 95, 1964–1977 doi:10.1016/j.mayocp.2020.01.030 [PubMed: 32446635]

Fantegrossi WE, Ciullo JR, Wakabayashi KT, De La Garza R, Traynor JR, Woods JH, 2008. A comparison of the physiological, behavioral, neurochemical and microglial effects of methamphetamine and 3,4-methylenedioxymethamphetamine in the mouse. Neuroscience 151, 533–543 doi:10.1016/j.neuroscience.2007.11.007 [PubMed: 18082974]

Felipo V, Butterworth RF, 2002. Neurobiology of ammonia. Prog Neurobiol 67, 259–279 doi:10.1016/s0301-0082(02)00019-9 [PubMed: 12207972]

Feller DJ, Crabbe JC, 1991. Effect of neurotransmitter-selective drugs in mice selected for differential sensitivity to the hypothermic actions of ethanol. J Pharmacol Exp Ther 256, 954–958 [PubMed: 1672379]

Feller DJ, Young ER, Riggan JP, Stuart J, Crabbe JC, 1993. Serotonin and genetic differences in sensitivity and tolerance to ethanol hypothermia. Psychopharmacology (Berl) 112:331–338 doi: 10.1007/BF02244929 [PubMed: 7871038]

Ferragud A, Velazquez-Sanchez C, Canales JJ, 2014. Modulation of methamphetamine's locomotor stimulation and self-administration by JHW 007, an atypical dopamine reuptake blocker. Eur J Pharmacol 731, 73–79 doi:10.1016/j.ejphar.2014.03.015 [PubMed: 24675149]

Fleming S, Toratani S, Shea-Donohue T, Kashiwabara Y, Vogel SN, Metcalf ES, 2001 Pro- and anti-inflammatory gene expression in the murine small intestine and liver after chronic exposure to alcohol. Alcohol Clin Exp Res 25, 579–589 [PubMed: 11329499]

Fultz EK, Martin DL, Hudson CN, Kippin TE, Szumlinski KK, 2017. Methamphetamine-alcohol interactions in murine models of sequential and simultaneous oral drug-taking. Drug Alcohol Depend 177, 178–186 doi:10.1016/j.drugalcdep.2017.03.026 [PubMed: 28601731]

Fultz EK, Szumlinski KK, 2018. Prior binge-drinking history promotes the positive affective valence of methamphetamine in mice. Drug Alcohol Depend 183, 150–154 doi:10.1016/j.drugalcdep.2017.10.034 [PubMed: 29253796]

Grace CE, Schaefer TL, Herring NR, Graham DL, Skelton MR, Gudelsky GA, Williams MT, Vorhees CV, 2010. Effect of a neurotoxic dose regimen of (+)-methamphetamine on behavior, plasma corticosterone, and brain monoamines in adult C57BL/6 mice. Neurotoxicol Teratol 32, 346–355 doi:10.1016/j.ntt.2010.01.006 [PubMed: 20096350]

Granado N, Ares-Santos S, Moratalla R, 2013. Methamphetamine and Parkinson's disease. Parkinsons Dis 308052. doi: 10.1155/2013/308052 [PubMed: 23476887]

Granholm L, Rowley S, Ellgren M, Segerstrom L, Nylander I, 2015. Impact of adolescent ethanol exposure and adult amphetamine self-administration on evoked striatal dopamine release in male rats. Psychopharmacology (Berl) 232, 4421–4431 doi:10.1007/s00213-015-4070-3 [PubMed: 26407601]

Guengerich FP, Avadhani NG, 2018. Roles of cytochrome P450 in metabolism of ethanol and carcinogens. Adv Exp Med Biol 1032, 15–35 doi: 10.1007/978-3-319-98788-0_2 [PubMed: 30362088]

Gutierrez-Lopez MD, Llopis N, Feng S, Barrett DA, O'Shea E, Colado MI, 2010. Involvement of 2-arachidonoyl glycerol in the increased consumption of and preference for ethanol of mice treated with neurotoxic doses of methamphetamine. Br J Pharmacol 160, 772–783 doi:10.1111/j.1476-5381.2010.00720.x [PubMed: 20590579]

Halpin LE, Yamamoto BK, 2012. Peripheral ammonia as a mediator of methamphetamine neurotoxicity. J Neurosci 32, 13155–13163. doi:10.1523/JNEUROSCI.2530-12.2012 [PubMed: 22993432]

Halpin LE, Gunning WT, Yamamoto BK, 2013. Methamphetamine causes acute hyperthermia-dependent liver damage. Pharmacol Res Perspect 1, e00008. doi:10.1002/prp2.8 [PubMed: 25505562]

Halpin LE, Northrop NA, Yamamoto BK, 2014. Ammonia mediates methamphetamine-induced increases in glutamate and excitotoxicity. Neuropsychopharmacology 39, 1031–1038. doi:10.1038/npp.2013.306 [PubMed: 24165886]

Hamida SB, Plute E, Cosquer B, Kelche C, Jones BC, Cassel JC, 2008. Interactions between ethanol and cocaine, amphetamine, or MDMA in the rat: thermoregulatory and locomotor effects. Psychopharmacology (Berl) 197, 67–82 doi:10.1007/s00213-007-1007-5 [PubMed: 18040665]

Haorah J, Knipe B, Gorantla S, Zheng J, Persidsky Y, 2007. Alcohol-induced blood-brain barrier dysfunction is mediated via inositol 1,4,5-triphosphate receptor (IP3R)-gated intracellular calcium release. J Neurochem 100, 324–336 doi:10.1111/j.1471-4159.2006.04245.x [PubMed: 17241155]

Harkness JH, Shi X, Janowsky A, Phillips TJ, 2015. Trace amine-associated receptor 1 regulation of methamphetamine intake and related traits. Neuropsychopharmacology 40, 2175–2184 doi:10.1038/npp.2015.61 [PubMed: 25740289]

Hastings TG, 1995. Enzymatic oxidation of dopamine: the role of prostaglandin H synthase. J Neurochemistry 64, 919–924 doi:10.1046/j.1471-4159.1995.64020919.x

Healey JC, Winder DG, Kash TL, 2008. Chronic ethanol exposure leads to divergent control of dopaminergic synapses in distinct target regions. Alcohol 42, 179–190 doi:10.1016/j.alcohol.2008.01.003 [PubMed: 18358675]

Henriques JF, Portugal CC, Canedo T, Relvas JB, Summavielle T, Socodato R, 2018. Microglia and alcohol meet at the crossroads: Microglia as critical modulators of alcohol neurotoxicity. Toxicol Lett 283, 21–31 doi:10.1016/j.toxlet.2017.11.002 [PubMed: 29129797]

Herbeck DM, Brecht ML, Lovinger K, Raihan A, Christou D, Sheaff P, 2013. Poly-drug and marijuana use among adults who primarily used methamphetamine. J Psychoactive Drugs 45, 132–140 doi:10.1080/02791072.2013.785824 [PubMed: 23909001]

Hitzemann R, Iancu OD, Reed C, Baba H, Lockwood DR, Phillips TJ, 2019. Regional analysis of the brain transcriptome in mice bred for high and low methamphetamine consumption. Brain Sci 9 doi:10.3390/brainsci9070155

Howes LG, Reid JL, 1986. The effects of alcohol on local, neural and humoral cardiovascular regulation. Clin Sci 71, 9–15 doi: 10.1042/cs0710009

Johnson TD, Berenson MM, 1991. Methamphetamine-induced ischemic colitis. J Clin Gastroenterol 13, 687–689 doi:10.1097/00004836-199112000-00015 [PubMed: 1761842]

Kamens HM, Burkhart-Kasch S, McKinnon CS, Li N, Reed C, Phillips TJ, 2005. Sensitivity to psychostimulants in mice bred for high and low stimulation to methamphetamine. Genes Brain Behav 4, 110–125 doi:10.1111/j.1601-183X.2004.00101.x [PubMed: 15720407]

Kamens HM, Burkhart-Kasch S, McKinnon CS, Li N, Reed C, Phillips TJ, 2006. Ethanol-related traits in mice selectively bred for differential sensitivity to methamphetamine-induced activation. Behav Neurosci 120, 1356–1366 doi:10.1037/0735-7044.120.6.1356 [PubMed: 17201481]

Kamijo Y, Soma K, Nishida M, Namera A, Ohwada T, 2002. Acute liver failure following intravenous methamphetamine. Vet Hum Toxicol 44, 216–217 [PubMed: 12136967]

Karjalainen K, Kuussaari K, Kataja K, Tigerstedt C, Hakkarainen P, 2017. Measuring concurrent polydrug use in general populations: a critical assessment. Eur Addict Res 23, 163–169 doi:10.1159/000477802 [PubMed: 28641293]

Karkhanis AN, Rose JH, Huggins KN, Konstantopoulos JK, Jones SR, 2015. Chronic intermittent ethanol exposure reduces presynaptic dopamine neurotransmission in the mouse nucleus accumbens. Drug Alcohol Depend 150, 24–30 doi:10.1016/j.drugalcdep.2015.01.019 [PubMed: 25765483]

Kays JS, Yamamoto BK, 2019. Evaluation of microglia/macrophage cells from rat striatum and prefrontal cortex reveals differential expression of inflammatory-related mRNA after methamphetamine. Brain Sci 9, 340. doi:10.3390/brainsci9120340

Kedia S, Sell MA, Relyea G, 2007. Mono- versus polydrug abuse patterns among publicly funded clients. Subst Abuse Treat Prev Policy 2, 33 doi:10.1186/1747-597X-2-33 [PubMed: 17996066]

King AC, Cao D, deWit H, O'Connor SJ, Hasin DS, 2019. The role of alcohol response phenotypes in the risk for alcohol use disorder. BJPsych Open 5, e38 doi:10.1192/bjo.2019.18 [PubMed: 31685074]

Kirkpatrick MG, Gunderson EW, Levin FR, Foltin RW, Hart CL, 2012. Acute and residual interactive effects of repeated administrations of oral methamphetamine and alcohol in humans. Psychopharmacology (Berl) 219, 191–204 doi:10.1007/s00213-011-2390-5 [PubMed: 21748253]

Kita T, Shimada K, Mastunari Y, Wagner GC, Kubo K, Nakashima T, 2000. Methamphetamine-induced striatal dopamine neurotoxicity and cyclooxygenase-2 protein expression in BALB/c mice. Neuropharmacology 39, 399–406 doi:10.1016/s0028-3908(99)00175-6 [PubMed: 10698006]

Kitanaka J, Kitanaka N, Tatsuta T, Miyoshi A, Koumoto A, Tanaka K, Nishiyama N, Morita Y, Takemura M, 2010. Pretreatment with l-histidine produces a shift from methamphetamine-induced stereotypical biting to persistent locomotion in mice. Pharmacol Biochem Behav 94, 464–470 doi:10.1016/j.pbb.2009.10.009 [PubMed: 19895842]

Kitanaka J, Kitanaka N, Tatsuta T, Morita Y, Takemura M, 2007. Blockade of brain histamine metabolism alters methamphetamine-induced expression pattern of stereotypy in mice via histamine H1 receptors. Neuroscience 147, 765–777 doi:10.1016/j.neuroscience.2007.05.006 [PubMed: 17570600]

Kitanaka N, Kitanaka J, Hall FS, Uhl GR, Watabe K, Kubo H, Takahashi H, Tanaka K, Nishiyama N, Takemura M, 2014. Agmatine attenuates methamphetamine-induced hyperlocomotion and stereotyped behavior in mice. Behav Pharmacol 25, 158–165 doi:10.1097/FBP.0000000000000030 [PubMed: 24557322]

Kohda H, Funahashi M, Shikata I, Kimura H, 1986. Decrease in d-methamphetamine sensitivity in mice due to ethanol: apparent inhibitory and stimulatory effects of ethanol on d-

methamphetamine-induced locomotor activity. Pharmacol Biochem Behav 25, 1035–1039 doi:10.1016/0091-3057(86)90082-1 [PubMed: 3786356]

Kousik SM, Napier TC, and Carvey PM, 2012. The effects of psychostimulant drugs on blood brain barrier function and neuroinflammation. Front Pharmacol 3, 121 doi: 10.3389/fphar.2012.00121 [PubMed: 22754527]

Lappin JM, Darke S, Farrell M, 2018. Methamphetamine use and future risk for Parkinson's disease: Evidence and clinical implications. Drug Alcohol Depend 187, 134–140 doi: 10.1016/j.drugalcdep.2018.02.032 [PubMed: 29665491]

Lawyer G, Bjerkan PS, Hammarberg A, Jayaram-Lindström N, Franck J, Agartz I, 2010. Amphetamine dependence and co-morbid alcohol abuse: associations to brain cortical thickness. BMC Pharmacol 10, 5 doi:10.1186/1471-2210-10-5 [PubMed: 20487539]

Leclercq S, Cani PD, Neyrinck AM, Stärkel P, Jamar F, Mikolajczak M, Delzenne NM, de Timary P, 2012. Role of intestinal permeability and inflammation in the biological and behavioral control of alcohol-dependent subjects. Brain Behav Immun 26, 911–918 doi:10.1016/j.bbi.2012.04.001 [PubMed: 22521198]

Le Moine O, Marchant A, DeGroote D, Azar C, Goldman M, Deviere J, 1995. Role of defective monocyte interleukin-10 release in tumor necrosis factor-alpha overproduction in alcoholic cirrhosis. Hepatology 22,1436–1439 doi:10.1002/hep.1840220516 [PubMed: 7590660]

Leslie EM, Smirnov A, Cherney A, Wells H, Legosz M, Kemp R, Najman JM, 2017. Simultaneous use of alcohol with methamphetamine but not ecstasy linked with aggression among young adult stimulant users. Addict Behav 70, 27–34 doi:10.1016/j.addbeh.2017.01.036 [PubMed: 28182965]

Letendre S, Paulino AD, Rockenstein E, Adame A, Crews L, Cherner M, Heaton R, Ellis R, Everall IP, Grant I, Masliah E, 2007. Pathogenesis of hepatitis C virus coinfection in the brains of patients infected with HIV. J Infect Dis 196, 361–370 doi:10.1086/519285 [PubMed: 17597450]

Li B, Wang Y, Zhang Y, Liu M, 2014. Effects of ethanol on the toxicokinetics of methamphetamine in rabbits. Iran J Pharm Res 13, 329–336 [PubMed: 24734088]

Liang M, Liu Y, Zheng N, Ananda S, Liu L, 2012. Distribution of methamphetamine and its metabolite amphetamine in acute and subacute ethanol-methamphetamine combination abuse model rats. J Anal Toxicol 36, 30–35 doi:10.1093/jat/bkr007 [PubMed: 22290750]

Lockwood AH, McDonald JM, Reiman RE, Gelbard AS, Laughlin JS, Duffy TE, Plum F, 1979. The dynamics of ammonia metabolism in man. Effects of liver disease and hyperammonemia. J Clin Invest 63, 449–460 doi:10.1172/JCI109322 [PubMed: 429564]

Loftis JM, Choi D, Hoffman W, Huckans MS, 2011. Methamphetamine causes persistent immune dysregulation: a cross-species, translational report. Neurotox Res 20, 59–68 doi:10.1007/s12640-010-9223-x [PubMed: 20953917]

Lograno DE, Matteo F, Trabucchi M, Govoni S, Cagiano R, Lacomba C, Cuomo V, 1993. Effects of chronic ethanol intake at a low dose on the rat brain dopaminergic system. Alcohol 10, 45–49 doi:10.1016/0741-8329(93)90052-p [PubMed: 8447966]

Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J, 2015. Structural and functional features of central nervous system lymphatic vessels. Nature 523, 337–341 doi: 10.1038/nature14432 [PubMed: 26030524]

Loxton D, Canales JJ, 2017. Long-term cognitive, emotional and neurogenic alterations induced by alcohol and methamphetamine exposure in adolescent rats. Prog Neuropsychopharmacol Biol Psychiatry 74, 1–8 doi:10.1016/j.pnpbp.2016.11.003 [PubMed: 27865801]

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

Maickel RP, Nash JF Jr., 1986. Drug interactions with ethanol. Effects on body temperature and motor impairment. Neuropharmacology 25, 315–322 doi:10.1016/0028-3908(86)90258-3 [PubMed: 3703179]

Manley SJ, Little HJ, 1997. Enhancement of amphetamine- and cocaine-induced locomotor activity after chronic ethanol administration. J Pharmacol Exp Ther 281, 1330–1339 [PubMed: 9190869]

Mark KA, Quinton MS, Russek SJ, Yamamoto BK, 2007. Dynamic changes in vesicular glutamate transporter 1 function and expression related to methamphetamine-induced glutamate release. J Neurosci 27, 6823–6831 doi:10.1523/JNEUROSCI.0013-07.2007 [PubMed: 17581970]

Mark KA, Soghomonian JJ, Yamamoto BK, 2004. High-dose methamphetamine acutely activates the striatonigral pathway to increase striatal glutamate and mediate long-term dopamine toxicity. J Neurosci 24, 11449–11456 doi:10.1523/JNEUROSCI.3597-04.2004 [PubMed: 15601951]

Mathurin P, Deng QG, Keshavarzian A, Choudhary S, Holmes EW, Tsukamoto H, 2000. Exacerbation of alcoholic liver injury by enteral endotoxin in rats. Hepatology 32,1008–1017 doi:10.1053/jhep.2000.19621 [PubMed: 11050051]

Matsumoto RR, Seminerio MJ, Turner RC, Robson MJ, Nguyen L, Miller DB, O'Callaghan JP, 2014. Methamphetamine-induced toxicity: an updated review on issues related to hyperthermia. Pharmacol Ther 144, 28–40 doi:10.1016/j.pharmthera.2014.05.001 [PubMed: 24836729]

Matuszewich L, Yamamoto BK, 1999. Modulation of GABA release by dopamine in the substantia nigra. Synapse 32, 29–36. doi:10.1002/(SICI)1098-2396(199904)32:1<29::AID-SYN4>3.0.CO;2-2 [PubMed: 10188635]

Mayfield J, Blednov YA, Harris RA, 2015. Behavioral and genetic evidence for GIRK channels in the CNS: Role in physiology, pathophysiology, and drug addiction. Int Rev Neurobiol 123, 279–313 doi:10.1016/bs.irn.2015.05.016 [PubMed: 26422988]

McColl ER, Piquette-Miller M, 2020. SLC neurotransmitter transporters as therapeutic targets for alcohol use disorder: a narrative review. Alcohol Clin Exp Res doi:10.1111/acer.14445

McCreary AC, Müller CP, Filip M, 2015. Psychostimulants: basic and clinical pharmacology. Int Rev Neurobiol 120, 41–83 doi: 10.1016/bs.irn.2015.02.008 [PubMed: 26070753]

McKinzie DL, McBride WJ, Murphy JM, Lumeng L, Li TK, 2002. Effects of amphetamine on locomotor activity in adult and juvenile alcohol-preferring and - nonpreferring rats. Pharmacol Biochem Behav 71, 29–36 doi:10.1016/s0091-3057(01)00610-4 [PubMed: 11812505]

Mendelson J, Jones RT, Upton R, Jacob P 3rd, 1995. Methamphetamine and ethanol interactions in humans. Clin Pharmacol Ther 57, 559–568 doi:10.1016/0009-9236(95)90041-1 [PubMed: 7768079]

Meyer PJ, Meshul CK, Phillips TJ, 2009. Ethanol- and cocaine-induced locomotion are genetically related to increases in accumbal dopamine. Genes Brain Behav 8, 346–355 doi: 10.1111/j.1601-183X.2009.00481.x [PubMed: 19220481]

Midanik LT, Tam TW, Weisner CC, 2007. Concurrent and simultaneous drug and alcohol use: Results of the 2000 National Alcohol Survey. Drug and Alcohol Dependence 90, 72–80 doi: 10.1016/j.drugalcdep.2007.02.024 [PubMed: 17446013]

Milesi-Halle A, Hendrickson HP, Laurenzana EM, Gentry WB, Owens SM, 2005. Sex-and dose-dependency in the pharmacokinetics and pharmacodynamics of (+)-methamphetamine and its metabolite (+)-amphetamine in rats. Toxicol Appl Pharmacol 209, 203–213 doi:10.1016/j.taap.2005.04.007 [PubMed: 15916788]

Miner NB, Elmore JS, Baumann MH, Phillips TJ, Janowsky A, 2017. Trace amine-associated receptor 1 regulation of methamphetamine-induced neurotoxicity. Neurotoxicology 63:57–69 doi: 10.1016/j.neuro.2017.09.006 [PubMed: 28919515]

Moeller SJ, Fink DS, Gbedemah M, Hasin DS, Galea S, Zvolensky MJ, Goodwin RD, 2018. Trends in illicit drug use among smokers and nonsmokers in the United States, 2002–2014. J Clin Psychiatry 79, 17m11718 doi:10.4088/JCP.17m11718

Mootz J, Miner NB, Phillips TJ, 2020. Differential genetic risk for methamphetamine intake confers differential sensitivity to the temperature-altering effects of other addictive drugs. Genes Brain Behav 19, e12640 doi:10.1111/gbb.12640 [PubMed: 31925906]

Mutter R, Ali MM, 2019. Factors associated with completion of alcohol detoxification in residential settings. J Subst Abuse Treat 98, 53–58 doi:10.1016/j.jsat.2018.12.009 [PubMed: 30665604]

Myers MG, Kelly JF, 2006. Cigarette smoking among adolescents with alcohol and other drug use problems. Alcohol Res Health 29, 221–227 [PubMed: 17373413]

Myles BJ, Jarrett LA, Broom SL, Speaker HA, Sabol KE, 2008. The effects of methamphetamine on core body temperature in the rat-part 1: chronic treatment and ambient temperature. Psychopharmcology (Berl) 198:301–311 doi: 10.1007/s00213-007-1061-z

Nash JF, Yamamoto BK, 1993. Effect of D-amphetamine on the extracellular concentrations of glutamate and dopamine in iprindole-treated rats. Brain Res 627, 1–8 doi:10.1016/0006-8993(93)90741-5 [PubMed: 7904885]

Nestby P, Vanderschuren LJ, De Vries TJ, Hogenboom F, Wardeh G, Mulder AH, Schoffelmeer AN, 1997. Ethanol, like psychostimulants and morphine, causes long-lasting hyperreactivity of dopamine and acetylcholine neurons of rat nucleus accumbens: possible role in behavioural sensitization. Psychopharmacology (Berl) 133, 69–76 doi:10.1007/s002130050373 [PubMed: 9335083]

Nickell JR, Siripurapu KB, Vartak A, Crooks PA, Dwoskin LP, 2014. The vesicular monoamine transporter-2: an important pharmacological target for the discovery of novel therapeutics to treat methamphetamine abuse. Adv Pharmacol 69, 71–106 doi:10.1016/B978-0-12-420118-7.00002-0 [PubMed: 24484975]

Nishiguchi M, Kinoshita H, Kasuda S, Takahase M, Yamamura T, Matsui K, Ouchi H, Minami T, Hishida S, Nishio H, 2010. Effects of dopamine antagonists on methamphetamine-induced dopamine release in high and low alcohol preference rats. Toxicol Mech Methods 20, 127–132 doi:10.3109/15376511003621658 [PubMed: 20163290]

Northrop NA, Yamamoto BK, 2012. Persistent neuroinflammatory effects of serial exposure to stress and methamphetamine on the blood-brain barrier. J Neuroimmune Pharmacol 7, 951–968 doi:10.1007/s11481-012-9391-y [PubMed: 22833424]

Northrop NA, Yamamoto BK, 2015. Methamphetamine effects on blood-brain barrier structure and function. Front Neurosci 9, 69 doi:10.3389/fnins.2015.00069 [PubMed: 25788874]

Nowak P, Dabrowska J, Bortel A, Izabela B, Kostrzewa RM, Brus R, 2006. Prenatal cadmium and ethanol increase amphetamine-evoked dopamine release in rat striatum. Neurotoxicol Teratol 28, 563–572 doi:10.1016/j.ntt.2006.07.002 [PubMed: 17005368]

O'Callaghan JP, Miller DB, 1994. Neurotoxicity profiles of substituted amphetamines in the C57BL/6J mouse. J Pharmacol Exp Ther 270, 741–751 [PubMed: 8071867]

Peacock A, Leung J, Larney S, Colledge S, Hickman M, Rehm J, Giovino GA, West R, Hall W, Griffiths P, Ali R, Gowing L, Marsden J, Ferrari AJ, Grebely J, Farrell M, Degenhardt L, 2018. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addiction 113, 1905–1926 doi:10.1111/add.14234 [PubMed: 29749059]

Phillips TJ, Reed C, 2014. Targeting GABAB receptors for anti-abuse drug discovery. Expert Opin Drug Discov 9, 1307–1317 doi:10.1517/17460441.2014.956076 [PubMed: 25195620]

Phillips TJ, Burkhart-Kasch S, Gwiazdon CC, Crabbe JC, 1992. Acute sensitivity of FAST and SLOW mice to the effects of abused drugs on locomotor activity. J Pharmacol Exp Ther 261, 525–533 [PubMed: 1578369]

Phillips TJ, Burkhart-Kasch S, Terdal ES, Crabbe JC, 1991. Response to selection for ethanol-induced locomotor activation: genetic analyses and selection response characterization. Psychopharmacology (Berl) 103, 557–566 doi:10.1007/BF02244259 [PubMed: 2062990]

Phillips TJ, Dudek BC, 1991. Locomotor activity responses to ethanol in selectively bred long- and short-sleep mice, two inbred mouse strains, and their F1 hybrids. Alcohol Clin Exp Res 15, 255–261 doi:10.1111/j.1530-0277.1991.tb01866.x [PubMed: 2058802]

Phillips TJ, Pastor R, Scibelli AC, Reed C, Tarragon E, 2011. Behavioral sensitization to addictive drugs: Clinical relevance and methodological aspects, in: Raber J (Ed.), Animal Models of Behavioral Analysis, Neuromethods 50. Springer Science+Business Media, pp. 267–305. doi:10.1007/978-1-60761-883-6_11

Phillips TJ, Shen EH, 1996. Neurochemical bases of locomotion and ethanol stimulant effects. Int Rev Neurobiol 39, 243–282 doi:10.1016/s0074-7742(08)60669-8 [PubMed: 8894850]

Pontesa H, Pinhoa PG, Fernandes E, Branco PS, Ferreira LM, Carmo H, Remião F, Carvalho F, Bastos ML, 2010. Metabolic interactions between ethanol and MDMA in primary cultured rat hepatocytes. Toxicology 270:150–157 doi: 10.1016/j.tox.2010.02.010 [PubMed: 20170704]

Popova NK, Ivanova EA, 2002. 5-HT(1A) receptor antagonist p-MPPI attenuates acute ethanol effects in mice and rats. Neurosci Lett 322:1–4 doi: 10.1016/s0304-3940(01)02519-8 [PubMed: 11958829]

Pratt OE, Rooprai HK, Shaw G, Thomson AD 1990. The genesis of alcoholic brain tissue injury. Alcohol Alcohol. 25, 217–230 doi:10.1093/oxfordjournals.alcalc.a044995 [PubMed: 2198037]

Prendergast C, Hassanein AH, Bansal V, Kobayashi L, 2014. Shock with intestinal ischemia: a rare complication of methamphetamine use. Am Surg 80, 101–102 [PubMed: 24401527]

Qin L, Crews FT, 2012. Chronic ethanol increases systemic TLR3 agonist-induced neuroinflammation and neurodegeneration. J Neuroinflammation 9, 130 doi:10.1186/1742-2094-9-130 [PubMed: 22709825]

Ramirez SH, Potula R, Fan S, Eidem T, Papugani A, Reichenbach N, Dykstra J, Weksler BB, Romero IA, Couraud PO, Persidsky Y, 2009. Methamphetamine disrupts blood-brain barrier function by induction of oxidative stress in brain endothelial cells. J Cereb Blood Flow Metab 29, 1933–1945 doi: 10.1038/jcbfm.2009.112 [PubMed: 19654589]

Reed C, Baba H, Zhu Z, Erk J, Mootz JR, Varra NM, Williams RW, Phillips TJ, 2018. A spontaneous mutation in *Taar1* impacts methamphetamine-related traits exclusively in DBA/2 mice from a single vendor. Front Pharmacol 8, 993 doi:10.3389/fphar.2017.00993 [PubMed: 29403379]

Ripley TL, Dunworth SJ, Stephens DN, 2002. Consequences of amygdala kindling and repeated withdrawal from ethanol on amphetamine-induced behaviours. Eur J Neurosci 16, 1129–1138 doi:10.1046/j.1460-9568.2002.02175.x [PubMed: 12383242]

Roberto M, Varodayan FP, 2017. Synaptic targets: Chronic alcohol actions. Neuropharmacology 122, 85–99 doi: 0.1016/j.neuropharm.2017.01.013 [PubMed: 28108359]

Robinson TE, Berridge KC, 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev 18, 247–291 doi:10.1016/0165-0173(93)90013-p [PubMed: 8401595]

Robinson TE, Berridge KC, 2000. The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction 95 Suppl 2, S91–117 doi:10.1080/09652140050111681

Robinson TE, Berridge KC, 2008. The incentive sensitization theory of addiction: some current issues. Philos Trans R Soc Lond B Biol Sci 363, 3137–3146 doi:10.1098/rstb.2008.0093 [PubMed: 18640920]

Rose ME, Grant JE, 2008. Pharmacotherapy for methamphetamine dependence: a review of the pathophysiology of methamphetamine addiction and the theoretical basis and efficacy of pharmacotherapeutic interventions. Ann Clin Psychiatry 20, 145–155 doi:10.1080/10401230802177656 [PubMed: 18633741]

Rosengren LE, Persson LI, 1979. Influence of ethanol and dexamethasone on blood–brain barrier dysfunction to albumin. Acta Neurol Scand 59, 119–126 doi:10.1111/j.1600-0404.1979.tb02918.x [PubMed: 572126]

Roussotte FF, Bramen JE, Nunez SC, Quandt LC, Smith L, O'Connor MJ, Bookheimer SY, Sowell ER, 2011. Abnormal brain activation during working memory in children with prenatal exposure to drugs of abuse: the effects of methamphetamine, alcohol, and polydrug exposure. Neuroimage 54, 3067–3075 doi:10.1016/j.neuroimage.2010.10.072 [PubMed: 21040792]

Ruiz P, Calliari A, Genovese P, Scorza C, Pautassi RM, 2018. Amphetamine, but not methylphenidate, increases ethanol intake in adolescent male, but not in female, rats. Brain Behav 8, e00939 doi:10.1002/brb3.939 [PubMed: 29670821]

Saloner R, Paolillo EW, Umlauf A, Moore DJ, Heaton RK, Grant I, Cherner M, Group T, 2019. Conditional effects of lifetime alcohol consumption on methamphetamine-associated neurocognitive performance. J Int Neuropsychol Soc 25, 787–799 doi:10.1017/S1355617719000493 [PubMed: 31179969]

Sanchez-Alavez M, Bortell N, Basova L, Samad F, Marcondes MCG, 2020. Macrophages and brown adipocytes cross-communicate to modulate a thermogenic program following methamphetamine exposure. Int J Hyperthermia 37:1368–1382 doi: 10.1080/02656736.2020.1849822 [PubMed: 33307890]

Scaplen KM, Mei NJ, Bounds HA, Song SL, Azanchi R, Kaun KR, 2019. Automated real-time quantification of group locomotor activity in Drosophila melanogaster. Sci Rep 9, 4427 doi:10.1038/s41598-019-40952-5 [PubMed: 30872709]

Schuckit MA, 2018. A critical review of methods and results in the search for genetic contributors to alcohol sensitivity. Alcohol Clin Exp Res 42, 822–835 doi:10.1111/acer.13628 [PubMed: 29623680]

Sern KR, Fultz EK, Coelho MA, Bryant CD, Szumlinski KK, 2020. A prior history of binge-drinking increases sensitivity to the motivational valence of methamphetamine in female C57BL/6J mice. Subst Abuse 14, 1178221819897073 doi:10.1177/1178221819897073 [PubMed: 32009790]

Shabani S, McKinnon CS, Reed C, Cunningham CL, Phillips TJ, 2011. Sensitivity to rewarding or aversive effects of methamphetamine determines methamphetamine intake. Genes Brain Behav 10, 625–636 doi:10.1111/j.1601-183X.2011.00700.x [PubMed: 21554535]

Sharma R, Sahota P, Thakkar MM, 2018. A single episode of binge alcohol drinking causes sleep disturbance, disrupts sleep homeostasis, and down-regulates equilibrative nucleoside transporter 1. J Neurochem 146, 304–321 doi: 10.1111/jnc.14470 [PubMed: 29804297]

Shen RY, Hannigan JH, Chiodo LA, 1995. The effects of chronic amphetamine treatment of prenatal ethanol-induced changes in dopamine receptor function: electrophysiological findings. J Pharmacol Exp Ther 274, 1054–1060 [PubMed: 7562468]

Singh AK, 2019. Alcohol interaction with cocaine, methamphetamine, opioids, nicotine, cannabis, and gamma-hydroxybutyric acid. Biomedicines 7 doi:10.3390/biomedicines7010016

Singh AK, Jiang Y, Gupta S, Benlhabib E, 2007. Effects of chronic ethanol drinking on the blood brain barrier and ensuing neuronal toxicity in alcohol-preferring rats subjected to intraperitoneal LPS injection. Alcohol Alcohol 42, 385–399 doi:10.1093/alcalc/agl120 [PubMed: 17341516]

Singh RA, Kosten TA, Kinsey BM, Shen X, Lopez AY, Kosten TR, Orson FM, 2012. Dose-dependent changes in the locomotor responses to methamphetamine in BALB/c mice: low doses induce hypolocomotion. Pharmacol Biochem Behav 103, 230–236 doi:10.1016/j.pbb.2012.08.013 [PubMed: 23010423]

Smith DE, Fischer CM, 1970. An analysis of 310 cases of acute high-dose methamphetamine toxicity in Haight-Ashbury. Clin Toxicol 3,117–124 doi:10.3109/15563657008990106 [PubMed: 5520384]

Stafford AM, Reed C, Baba H, Walter NA, Mootz JR, Williams RW, Neve KA, Fedorov LM, Janowsky AJ, Phillips TJ, 2019. *Taar1* gene variants have a causal role in methamphetamine intake and response and interact with *Oprm1*. Elife 8, e46472 doi:10.7554/eLife.46472 [PubMed: 31274109]

Stafford AM, Reed C, Phillips TJ, 2020. Non-genetic factors that influence methamphetamine intake in a genetic model of differential methamphetamine consumption. Psychopharmacology (Berl) doi:10.1007/s00213-020-05614-9

Steketee JD, Kalivas PW, 2011. Drug wanting: behavioral sensitization and relapse to drug-seeking behavior. Pharmacol Rev 63, 348–365 doi:10.1124/pr.109.001933 [PubMed: 21490129]

Substance Abuse and Mental Health Services Administration, 2014a. Results from the 2013 National Survey on Drug Use and Health: Summary of national findings, NSDUH Series H-48, HHS Publication No. (SMA) 14–4863. Rockville, MD: Substance Abuse and Mental Health Services Administration.

Substance Abuse and Mental Health Services Administration, 2014b. The DAWN Report: Alcohol and drug combinations are more likely to have a serious outcome than alcohol alone in emergency department visits involving underage drinking. Rockville, MD: Substance Abuse and Mental Health Services Administration.

Swan N, 1997. CDC Report highlights link between drug abuse and spread of HIV. NIDA Notes, Aids Research. 12.

Świątkiewicz M, Zaremba M, Joniec I, Członkowski A, Kurkowska-Jastrzębska I, 2013. Potential neuroprotective effect of ibuprofen, insights from the mice model of Parkinson's disease. Pharmacological Reports 65, 1227–1236 doi:10.1016/s1734-1140(13)71480-4 [PubMed: 24399718]

Szumlinski KK, Lominac KD, Campbell RR, Cohen M, Fultz EK, Brown CN, Miller BW, Quadir SG, Martin D, Thompson AB, von Jonquieres G, Klugmann M, Phillips TJ, Kippin TE, 2017 Methamphetamine addiction vulnerability: the glutamate, the bad, and the ugly. Biol Psychiatry 81:959–970 doi: 10.1016/j.biopsych.2016.10.005 [PubMed: 27890469]

Tan H, Liang D, Zhong N, Zhao Y, Chen Z, Zhao M, Jiang H, 2019. History of alcohol and opioid use impacts on the long-term recovery trajectories of methamphetamine-dependent patients. Front Psychiatry 10, 398 doi:10.3389/fpsyt.2019.00398 [PubMed: 31231256]

Tanaka K, Kunishige-Yamamoto A, Hashimoto H, Shintani N, Hayata A, Baba A, 2010. Increased ethanol preference and serotonin 1A receptor-dependent attenuation of ethanol-induced hypothermia in PACAP-deficient mice. Biochem Biophys Res Commun 391:773–777 doi: 10.1016/j.bbrc.2009.11.136 [PubMed: 19944672]

Thomas DM, Kuhn DM, 2005. Cyclooxygenase-2 is an obligatory factor in methamphetamine-induced neurotoxicity. J Pharmacol Exp Ther 313, 870–876 doi:10.1124/jpet.104.080242 [PubMed: 15718289]

Tschumi CW, Daszkowski AW, Sharpe AL, Trzeciak M, Beckstead MJ, 2020. A history of ethanol drinking increases locomotor stimulation and blunts enhancement of dendritic dopamine transmission by methamphetamine. Addict Biol 25, e12763 doi:10.1111/adb.12763 [PubMed: 31062485]

Uban KA, Comeau WL, Bodnar T, Yu WK, Weinberg J, Galea LA, 2015. Amphetamine sensitization and cross-sensitization with acute restraint stress: impact of prenatal alcohol exposure in male and female rats. Psychopharmacology (Berl) 232, 1705–1716 doi:10.1007/s00213-014-3804-y [PubMed: 25420606]

Uhrig S, Vandael D, Marcantoni A, Dedic N, Bilbao A, Vogt MA, Hirth N, Broccoli L, Bernardi RE, Schonig K, Gass P, Bartsch D, Spanagel R, Deussing JM, Sommer WH, Carbone E, Hansson AC, 2017. Differential roles for L-type calcium channel subtypes in alcohol dependence. Neuropsychopharmacology 42, 1058–1069 doi:10.1038/npp.2016.266 [PubMed: 27905406]

Vaghef L, Babri S, Vahed MM, 2014. The effect of escalating dose, multiple binge methamphetamine regimen and alcohol combination on spatial memory and oxidative stress markers in rat brain. J Alcohol Drug Depend 2 doi:10.4172/2329-6488.1000159

Wang Y, Jeng CH, Lin JC, Wang JY, 1995. Methamphetamine facilitates ethanol-induced depressions in cerebellar Purkinje neurons of prazocin- or DSP4-treated rats. Psychopharmacology (Berl) 121, 433–441 doi:10.1007/BF02246491 [PubMed: 8619006]

Wang L, Min JE, Krebs E, Evans E, Huang D, Liu L, Hser YI, Nosyk B, 2017. Polydrug use and its association with drug treatment outcomes among primary heroin, methamphetamine, and cocaine users. Int J Drug Policy 49, 32–40 doi:10.1016/j.drugpo.2017.07.009 [PubMed: 28888099]

Wang R, Shen YL, Hausknecht KA, Chang L, Haj-Dahmane S, Vezina P, Shen RY, 2019. Prenatal ethanol exposure increases risk of psychostimulant addiction. Behav Brain Res 356, 51–61 doi:10.1016/j.bbr.2018.07.030 [PubMed: 30076855]

Watson MR, James K, Mittleman G, Matthews DB, 2020. Impact of acute ethanol exposure on body temperatures in aged, adult and adolescent male rats. Alcohol 82:81–89 doi: 10.1016/j.alcohol.2019.08.001 [PubMed: 31408671]

Wearne TA, Cornish JL, 2019. Inhibitory regulation of the prefrontal cortex following behavioral sensitization to amphetamine and/or methamphetamine psychostimulants: A review of GABAergic mechanisms. Prog Neuropsychopharmacol Biol Psychiatry 95, 109681 doi:10.1016/j.pnpbp.2019.109681 [PubMed: 31255648]

Weeden CS, Roberts JM, Kamm AM, Kesner RP, 2015. The role of the ventral dentate gyrus in anxiety-based behaviors. Neurobiol Learn Mem 118, 143–149 doi:10.1016/j.nlm.2014.12.002 [PubMed: 25498221]

Wheeler JM, Reed C, Burkhart-Kasch S, Li N, Cunningham CL, Janowsky A, Franken FH, Wiren KM, Hashimoto JG, Scibelli AC, Phillips TJ, 2009. Genetically correlated effects of selective breeding for high and low methamphetamine consumption. Genes Brain Behav 8, 758–771 doi:10.1111/j.1601-183X.2009.00522.x [PubMed: 19689456]

Wijetunga M, Seto T, Lindsay J, Schatz I, 2003. Crystal methamphetamine-associated cardiomyopathy: tip of the iceberg? J Toxicol Clin Toxicol 41, 981–986 doi:10.1081/clt-120026521 [PubMed: 14705845]

Williams SB, Yorgason JT, Nelson AC, Lewis N, Nufer TM, Edwards JG, Steffensen SC, 2018. Glutamate transmission to ventral tegmental area GABA neurons is altered by acute and chronic ethanol. Alcohol Clin Exp Res 42, 2186–2195 doi:10.1111/acer.13883 [PubMed: 30204234]

Winkler MC, Greager EM, Stafford J, Bachtell RK, 2018. Methamphetamine self-administration reduces alcohol consumption and preference in alcohol-preferring P rats. Addict Biol 23, 90–101 doi:10.1111/adb.12476 [PubMed: 27860181]

Wise RA, Bozarth MA, 1987. A psychomotor stimulant theory of addiction. Psychological Review 94, 469–492 doi:10.1037/0033-295X.94.4.469 [PubMed: 3317472]

Wolf FW, Rodan AR, Tsai LT, Heberlein U, 2002. High-resolution analysis of ethanol-induced locomotor stimulation in Drosophila. J Neurosci 22, 11035–11044 doi:10.1523/JNEUROSCI.22-24-11035.2002 [PubMed: 12486199]

World Drug Report 2016 (United Nations publication, Sales No. E.16.XI.7).

World Drug Report 2019 (United Nations publication, Sales No. E.19.XI.8).

World Health Organization, 2018. Global status report on alcohol and health 2018. License: CC BY-NC-SA 3.0 IGO

Xu C, Shen RY, 2001. Amphetamine normalizes the electrical activity of dopamine neurons in the ventral tegmental area following prenatal ethanol exposure. J Pharmacol Exp Ther 297, 746–752 [PubMed: 11303066]

Yamamura T, Hishida S, Hatake K, Taniguchi T, Ouchi H, 1992. Effects of methamphetamine and ethanol on learning and brain neurotransmitters in rats. Pharmacol Biochem Behav 42, 389–400 doi:10.1016/0091-3057(92)90131-x [PubMed: 1357672]

Yates JW, Meij JT, Sullivan JR, Richtand NM, Yu L, 2007. Bimodal effect of amphetamine on motor behaviors in C57BL/6 mice. Neurosci Lett 427, 66–70 doi:10.1016/j.neulet.2007.09.011 [PubMed: 17920769]

Yoneyama N, Crabbe JC, Ford MM, Murillo A, Finn DA, 2008. Voluntary ethanol consumption in 22 inbred mouse strains. Alcohol 42, 149–160 doi:10.1016/j.alcohol.2007.12.006 [PubMed: 18358676]

Yu L, Cherng CF, Chen C, 2002. Melatonin in concentrated ethanol and ethanol alone attenuate methamphetamine-induced dopamine depletions in C57BL/6J mice. J Neural Transm (Vienna) 109, 1477–1490 doi:10.1007/s007020200096 [PubMed: 12486488]

Zou X, Huang H, Yang L, Liu H, Li Y, Xia Q, Yuan S, Yao S, 2018. Methamphetamine consumption and life-threatening abdominal complications: A case report. Medicine (Baltimore) 97, e0647 doi:10.1097/MD.0000000000010647 [PubMed: 29718879]

Highlights

- Comorbid alcohol and methamphetamine use amplifies deleterious consequences
- Brain development, cognition, motor function and physiology are adversely affected
- Neurotoxicity is augmented by comorbid use and involves glutamate excitotoxicity
- Needed is more research investigating motivation for comorbid use

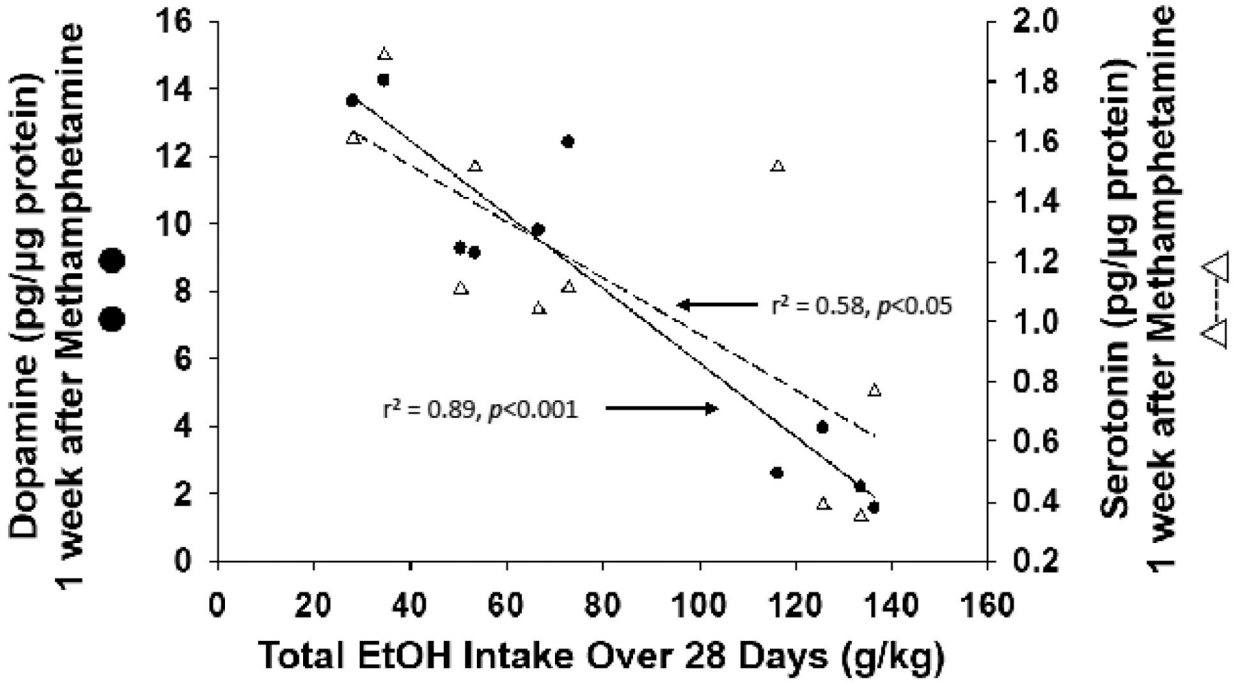

Figure 1.

MA-induced depletions of striatal dopamine and serotonin vs. EtOH intake. Data shown are for rats that had access to EtOH for 24 h, every other day, across a 28-day period. One day after the final EtOH drinking period, rats were administered the binge MA regimen (4 × 10 mg/kg MA, IP at 2 h intervals) and tissues were taken one week later for analysis by high-performance liquid chromatography. The magnitude of decreases in dopamine and serotonin content in the striatum were significantly correlated with the total amount of EtOH consumed over the 28 days. Blood ethanol concentration was 70.9 ± 1.9 mg/dL plasma when measured in the EtOH-drinking rats 4 hr into the dark cycle on Day 28 of intermittent EtOH drinking. Water drinking controls that received saline challenge had average striatal serotonin content of 3.0 pg/µg protein and dopamine content of 110 pg/µg protein (data not shown). EtOH, ethanol; MA, methamphetamine. Reprinted (with modification) by permission from Springer Nature, Journal of Neuroimmune Pharmacology, Methamphetamine-Induced Brain Injury and Alcohol Drinking, 13(1) 53–63, 2018, Amanda Blaker and Bryan Yamamoto COPYRIGHT 2018

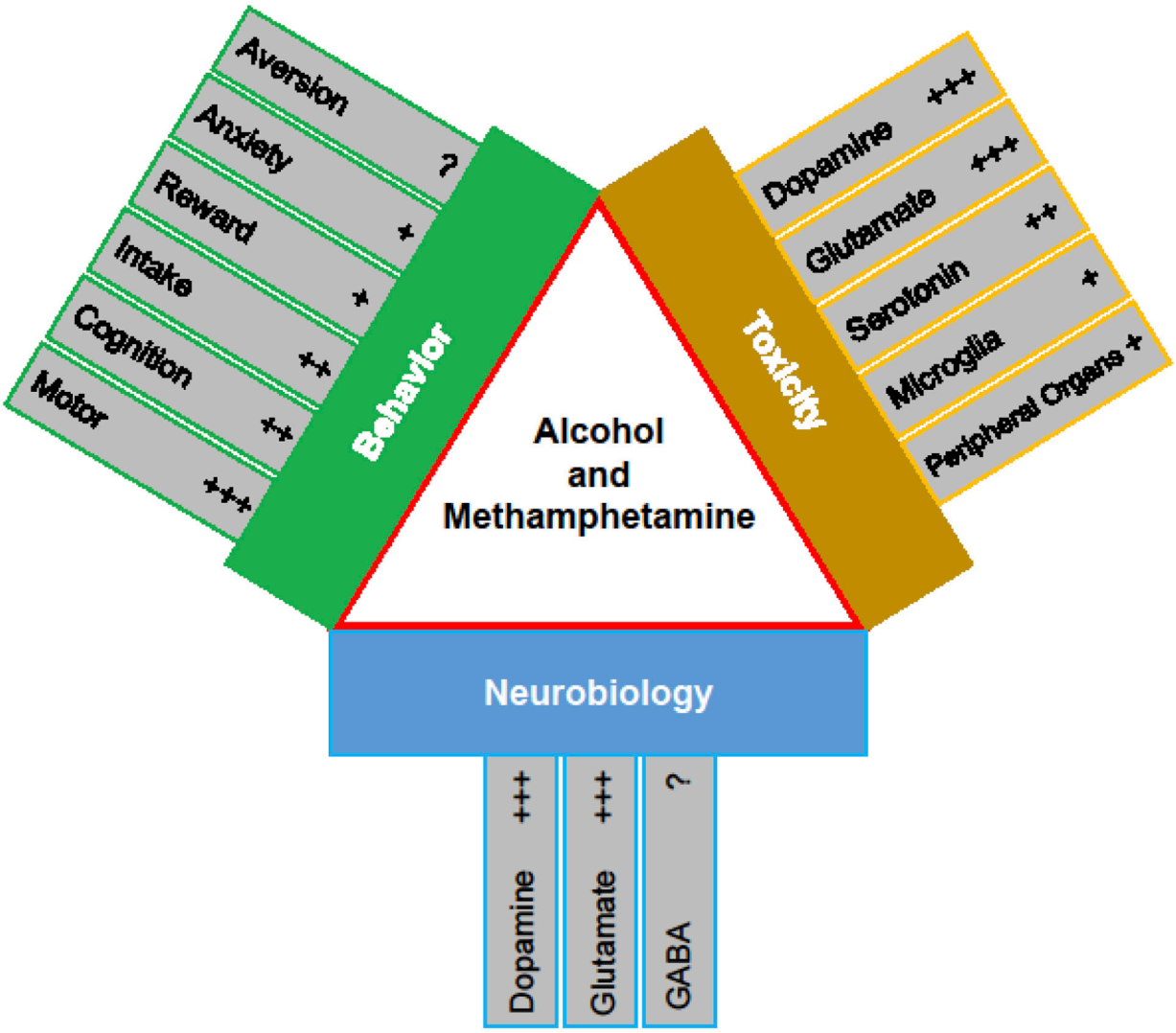

Figure 2.

Current state of knowledge about combined alcohol and methamphetamine effects from animal research studies. Data are reported for behavioral, neurobiological and toxicity effects. Categories of investigation in each of these areas, so far, are listed in the grey boxes. The number of plusses (+) is meant to represent the strength of support for an impact of combined alcohol and methamphetamine exposure. The impact of combined administration on aversion-related behaviors, compared to the effect of each drug alone, has not been investigated, as indicated by the question mark (?), but is relevant to continued use. Likewise, the impact of the combined drugs on GABAergic processes has not been investigated, but is a recommended area of investigation based on evidence for independent GABAergic effects of each drug as discussed in the review.

Table 1.

Effects of combined or sequential exposure to EtOH and MA.

EtOH and MA/AMP exposure	Strain / species	Behavior tested	Main findings	Reference
Simultaneous exposure (EtOH and MA administered or consumed together or in close succession)				
3BC EtOH drinking (water vs. 15% EtOH vs. 30% EtOH; 24 h/day) × 5 weeks and then for 1 additional week during saline or MA treatment (2.5 mg/kg, IP, every other day) for CPP and another week during CPP extinction	Male alcohol-preferring P rats	Locomotor activity during CPP	MA attenuated EtOH-associated reductions in activity	Althobaiti et al. 2019
		EtOH intake and preference	During conditioning, MA initially reduced EtOH intake and preference, which gradually recovered over days; there was no effect of MA on EtOH intake during the extinction phase	
		MA-induced CPP	MA-induced CPP; data were not analyzed for the potential effect of EtOH	
EtOH offered as only source of fluid (20% EtOH in 8% sucrose) + daily EtOH+MA treatment (1.6 g/kg EtOH + 2 mg/kg MA, IP) × 2 weeks then tested 1 day after the final treatment	Male BALB/c mice	Elevated plus maze	EtOH and MA co-administration produced an anxiogenic effect that was not observed with either drug alone	Chuang et al., 2011
MA + EtOH drinking (3 bottles containing 20% EtOH, 10 mg/L MA, and 20% EtOH + 10 mg/L MA; 2 h/day) × 3 days	Male B6 mice	Preference	Preference for EtOH+MA was greater than for EtOH or MA alone, and preference for EtOH alone was greater than for MA alone	Fultz et al., 2017
		MA intake	MA intake was greater from the EtOH+MA solution than from the MA alone solution	
		EtOH intake	No difference in EtOH intake from the EtOH+MA and EtOH alone solutions	
Saline or EtOH (1.5 g/kg, IP) + saline or d-AMP (1–2 mg/kg, IP) immediately before testing × 4 days	Male Long Evans rats	Locomotor activity	EtOH attenuated d-AMP stimulation	Hamida et al., 2008
Saline or EtOH (0.8–1.6 g/kg, IP) + saline or MA (1.5–7.5 mg/kg, SC) immediately before testing	Male ddY mice	Locomotor activity	EtOH inhibited low dose MA stimulation and enhanced high dose MA stimulation	Kohda et al., 1986
Saline, EtOH (1.5 g/kg), MA (2 mg/kg) or EtOH (1.5 g/kg) + MA (2 mg/kg) IG × 5 days, then tested 15 days after the final treatment	Male Long Evans rats	Elevated plus maze	All prior drug exposures increased anxiety-like behavior	Loxton and Canales, 2017
		Reference memory	Prior drug exposure effects were comparable and all produced reference memory deficits	
		Working memory	Working memory deficits were observed only for rats previously treated with EtOH + MA	
Placebo alone; EtOH alone (1.5–6 g/kg, IG); EtOH (1.5–6 g/kg, IG) + d-AMP (1–4 mg/kg, IP) immediately before testing	Male Swiss-Cox mice	Motor coordination on rotarod	d-AMP co-administration did not affect EtOH-induced motor impairment	Maickel and Nash, 1986
MA + EtOH drinking (3 bottles containing 3, 6, or 10% EtOH [4 days each], 20 mg/L MA [all days], and 3, 6, or 10% EtOH + 20 mg/L MA [4 days at each EtOH concentration]; 18 h/day) × 12 days	Male and female MAHDR mice	Preference	Preference for MA alone was greater than for EtOH alone or EtOH+MA in males, but females had equal preference for all 3 solutions	Stafford et al., 2020

EtOH and MA/AMP exposure	Strain / species	Behavior tested	Main findings	Reference
		MA intake	MA intake was greater from the MA alone solution than the EtOH+MA solution in males, but MA consumption was equal from the 2 solutions in females	
		EtOH intake	No difference in EtOH consumption from the EtOH+MA and EtOH alone solutions, regardless of sex	
2BC MA + EtOH drinking (water vs. 3, 6, or 10% EtOH + 20 mg/L MA [4 days at each EtOH concentration]; 18 h/day) × 12 days	Male and female MAHDR mice	MA intake	MA intake was reduced when mixed with EtOH	Stafford et al., 2020
		EtOH intake	EtOH intake was not impacted when mixed with MA	
Saline or MA (escalating doses from 0.1–4 mg/kg, SC 3 × daily for 14 days, then 6 mg/kg 4 × daily for 14 days) + saline or EtOH (2 g/kg, IG) on all 28 days, then tested 1 or 14 days after the final treatment	Male Wistar rats	Morris water maze	EtOH co-administration exacerbated MA-induced spatial memory impairments	Vaghef et al., 2014
2BC EtOH drinking (water vs. 10% or 20% EtOH; 24 h/day) × 5 days or 21 days, and then for 8 to 14 additional days + saline or MA self-administration (0.1 mg/kg/IV infusion; all days on FR1 or 6 days on FR1 then 5 days on FR5 then 3 days on PR; 2 h/day)	Male alcohol-preferring P rats	EtOH consumption	MA reduced EtOH consumption when EtOH drinking occurred prior to and during MA self-administration; when EtOH drinking was initiated 1 week after but concurrently with MA self-administration, MA initially reduced EtOH intake and then intake recovered over days	Winkler et al., 2018
Saline or MA self-administration (0.1 mg/kg/IV infusion; FR1; 2 h/day) × 5 days, and then for 10 additional days + 2BC EtOH drinking (water vs. 10% EtOH; 24 h/day)		MA self-administration	EtOH increased MA self-administration at FR1, when MA self-administration was initiated 1 week after EtOH drinking, but the effect did not persist at FR5 or PR	
Saline or MA (2 mg/kg, IP) + saline or EtOH (2 g/kg, IP) immediately before testing	Male Sprague Dawley rats	Shock avoidance learning	EtOH co-administration amplified MA-associated deficits in avoidance learning	Yamamura et al., 1992
Sequential exposure (effects of prior EtOH on MA responses)				
Saline or EtOH treatment (2.2 g/kg, IP) × 21 days then challenged with saline (IP) 5 days later, and then with MA (1 mg/kg, IP) 2 days after that, immediately before testing	Male Albino Swiss Webster mice	Locomotor activity	Prior EtOH exposure enhanced MA stimulation in mice classified as EtOH-sensitive prior to MA treatment; no effect in EtOH-insensitive mice	Abrahao et al., 2009
Early life water or EtOH exposure via maternal water or EtOH drinking during gestation and lactation (10% EtOH offered as only source of fluid) then 2 month old offspring treated with saline or d-AMP once (0.6–2.4 mg/kg, IP) or repeatedly (1.2 mg/kg, IP every 2 days for 15 days), immediately before testing	Male and/or female Sprague Dawley and Long Evans rats	Locomotor activity and sensitization	Early life EtOH exposure increased acute d-AMP and sensitization	Barbier et al., 2008; 2009
Intermittent 2BC EtOH drinking (water vs. 10% EtOH, every other day; 24 h/day) × 28 days then saline or neurotoxic MA “binge regimen” (4 × 10 mg/kg, IP at 2 h intervals) 1 day later; tested 7 days after MA treatment	Male Sprague Dawley rats	Motor coordination on rotarod	Motor dysfunction only occurred in rats exposed to both EtOH and MA	Blaker et al., 2019b
DID water or EtOH drinking (4 bottles containing 5%, 10%, 20%, and 40% EtOH; 2 h/day) × 14 days then once daily MA treatment (1–4 mg/kg, IP) during CPP × 4 days starting 5 or 10 days after the final EtOH	Male B6 mice	Locomotor activity	Prior EtOH exposure did not affect MA stimulation Prior	Fultz and Szumlinski, 2018

EtOH and MA/AMP exposure	Strain / species	Behavior tested	Main findings	Reference
drinking day; locomotor activity monitored during CPP sessions		Place preference	EtOH exposure increased MA-induced place preference	
DID water or EtOH drinking (4 bottles containing 5%, 10%, 20%, and 40% EtOH; 2 h/day) × 7 days then MA + EtOH drinking (3 bottles containing 20% EtOH, 10 mg/L MA, and 20% EtOH + 10 mg/L MA; 2 h/day) × 3 days starting 1 day after final EtOH drinking day	Male B6 mice	MA consumption	Prior EtOH exposure increased MA intake	Fultz et al., 2017
DID water or EtOH drinking (4 bottles containing 5%, 10%, 20%, and 40% EtOH; 2 h/day) × 10 days (or water control), then MA oral self-administration (10 days at FR1 then 5 days at FR2, then 5 days at FR5 [10 mg/L MA], followed by up to 5 days each at escalating MA concentrations [2.5–40 mg/L] at FR1; 1 h/day) starting 1 day after the final EtOH drinking day	Male and female B6 × 129×1/SvJ mice	MA self-administration	Prior EtOH exposure did not affect MA self-administration at FR1 or FR5, but reduced MA self-administration at FR2 and also when MA self-administration was examined at increasing concentrations	Fultz et al., 2017
Episodic water or EtOH treatment (2 g/kg, IG; 3 days/week) × 5 weeks then d-AMP self-administration (5 days at FR3 then 2 days at PR [0.1 mg/kg/IV infusion], followed by escalating doses of d-AMP [0.025–0.1 mg/kg/IV infusion] for 3 days each at FR3 then 2 days at PR [0.1 mg/kg/IV infusion]; 1 h/day)	Male Wistar rats	d-AMP self-administration	Prior EtOH exposure had no effect on d-AMP self-administration	Granholm et al., 2015
Sucrose or EtOH offered as only source of fluid (3% EtOH) × 8 weeks then challenged with saline or d-AMP (1 mg/kg, IP) 24 h later (15 min d-AMP pretreatment)	Male Wistar rats	Locomotor activity	Prior EtOH exposure heightened d-AMP stimulation	Lograno et al., 1993
Control or EtOH liquid diet (increasing from 3.5% to 8%) × 3 weeks then challenged with saline or AMP (1–5 mg/kg, IP) 1 day, 6 days, or 2 months after EtOH withdrawal (20 min AMP pretreatment)	Male TO mice	Locomotor activity	Prior EtOH exposure increased AMP stimulation at 6 days and 2 months after EtOH withdrawal, but not 1 day	Manley and Little, 1997
Non-EtOH or EtOH liquid diet (7% EtOH for 24 days) as sole nutrition, or repeated episodes of non-EtOH or EtOH liquid diet and withdrawal (24 days total; 7% EtOH removed for 8 h on days 11 and 18), and then treated with saline or d-AMP (0.25–1 mg/kg, IP) 5 days after withdrawal, immediately before testing	Male and female Hooded Lister rats	Locomotor activity	Single and repeated episodes of prior EtOH exposure did not alter d-AMP stimulation	Ripley et al., 2002
DID water or EtOH drinking (4 bottles containing 5%, 10%, 20%, and 40% EtOH; 2 h/day) × 14 days then once daily MA treatment (1–4 mg/kg, IP) during CPP × 4 days starting 5 or 10 days after the final EtOH drinking day; locomotor activity monitored during CPP sessions	Female B6 mice	Locomotor activity Place preference	Prior EtOH exposure did not affect MA stimulation Prior EtOH exposure increased MA-induced place preference	Sern et al., 2020
2BC EtOH drinking (water vs. 3, 6, and 10% EtOH for 4 days each; 18 h/day) × 12 days then 2BC MA drinking (water vs. 20, 40, and 80 mg/L for 4 days each; 18 h/day) × 12 days	Male and female MAHDR mice	MA intake	Prior EtOH exposure had no effect on MA intake	Stafford et al., 2020
DID water or EtOH drinking (20% EtOH; 4 h/day) × 14 days then challenged with saline or MA (3 injections: 1 mg/kg, then 2 mg/kg × 2; IP at 15 min intervals during testing for cumulative doses of 1, 3, and 5 mg/kg) 9, 11, and 13 days after the final EtOH drinking day	Male B6 mice	Locomotor activity	Prior EtOH consumption increased sensitivity to MA stimulation at 5 mg/kg, but not 1 or 3 mg/kg	Tschumi et al., 2020
Prenatal control or EtOH exposure via maternal non-EtOH or EtOH liquid diet (36% of total calories) during gestation, then adult offspring (70 ± 2.5 days) treated with saline or d-AMP repeatedly (1–2 mg/kg, IP every other day for 15 days) immediately before testing	Male and female Sprague Dawley rats	Locomotor sensitization	Prenatal EtOH exposure resulted in heightened sensitization to d-AMP	Uban et al., 2015
Prenatal control or EtOH exposure via maternal water or EtOH administration (6 g/kg/day, IG) during gestation then d-AMP self-administration (FR1; 0.1	Male Sprague Dawley rats	d-AMP self-administration	Prenatal EtOH exposure enhanced d-AMP self-administration	Wang et al., 2019

EtOH and MA/AMP exposure	Strain / species	Behavior tested	Main findings	Reference
mg/kg IV infusion × 3 days then 0.03 mg/kg/ IV infusion × 7 days; 3 h/day) during adulthood				
Sequential exposure (effects of prior MA on EtOH responses)				
Saline or MA treatment (1 g/kg, IP) × 10 days then challenged with saline (IP) 5 days later, and then EtOH (2.2 g/kg, IP) 2 days after that, immediately before testing	Male Albino Swiss Webster mice	Locomotor activity	Prior MA exposure had no effect on locomotor response to EtOH, regardless of whether mice were classified as sensitive or insensitive to MA prior to EtOH treatment	Abrahao et al., 2009
Saline or d-AMP treatment (twice daily; increased from 1–9 mg/kg, SC every 2–4 days) × 5 weeks then 2BC EtOH drinking (water vs. 2%, 4%, 6%, 8%, 10%, and 12% EtOH for 1 week each; 24 h/day) × 6 weeks starting 3 months after last d-AMP treatment	Female Wistar rats	EtOH intake	Prior d-AMP exposure increased EtOH intake, specifically at the higher EtOH concentrations (8–12%)	Fahlke et al., 1994
DID water or MA drinking (4 bottles containing 5, 10, 20, and 40 mg/L; 2 h/day) × 10 days then DID EtOH drinking (4 bottles containing 5%, 10%, 20%, and 40% EtOH; 2 h/day) × 7 days, starting the day after the final MA drinking day	Male B6 mice	EtOH consumption	Prior MA exposure increased EtOH consumption, specifically from the 40% EtOH bottle	Fultz et al., 2017
Saline or a neurotoxic MA treatment regimen (3 × 8 mg/kg, IP at 3 h intervals) then 2BC EtOH drinking (water vs. 3%, 6%, 10%, and 20% EtOH for 7 days each; 24 h/day), starting 7 days after MA treatment	Male B6 mice	EtOH consumption	Prior neurotoxic MA exposure increased EtOH consumption	Gutierrez-Lopez et al., 2010
Adolescent saline or AMP treatment (4 mg/kg, IP) × 5 days (PD 27–31), then 2BC EtOH drinking (water vs. 5% EtOH; 24 h/day) 4, 6 and 8 days after last AMP treatment	Male and female Wistar rats	EtOH consumption	Prior AMP exposure increased EtOH consumption in males, but not females	Ruiz et al., 2018
Saline or MA self-administration (FR1; 0.1 mg/kg/IV infusion; 2 h/day) × 10 days, and then 2BC EtOH drinking (water vs. 10% EtOH; 24 h/day) × 14 days starting 2 days after the last MA self-administration session	Male alcohol-preferring P rats	EtOH consumption	Prior MA self-administration had no effect on subsequent EtOH consumption	Winkler et al., 2018

2BC, two-bottle choice; 3BC; three-bottle choice; AMP, amphetamine; B6, C57BL/6J; CPP, conditioned place preference; d-AMP, d-amphetamine; DID, drinking-in-the-dark; EtOH, ethanol; FR, fixed ratio; IG, intragastric; IP, intraperitoneal; IV, intravenous; MA, methamphetamine; MAHDR, methamphetamine high drinking; PD, postnatal day; PR, progressive ratio; SC, subcutaneous

Table 2.

Shared genetic influences on behavioral, physiological, and neurobiological effects of EtOH and MA/AMP.

Genetic model	Drug treatment	Phenotype	Main findings	Reference
FAST vs. SLOW mice, selectively bred for high vs. low stimulant response to acute EtOH; male and female	Saline or MA treatment (1–8 mg/kg, IP) immediately before testing	Locomotor activity	FAST mice exhibited greater MA-induced stimulation than SLOW mice	Bergstrom et al., 2003
msP rats, selectively bred for high EtOH preference vs. non-selected genetically heterogeneous Wistar rats; male	Saline or AMP treatment (1 mg/kg, IP) during testing	Extracellular DA levels	msP rats exhibited a greater AMP-induced increase in extracellular DA in the NAc shell than Wistar rats	Bifone et al., 2019
	Saline or d-AMP treatment (0.5 mg/kg, IV) immediately before testing	Magnetic resonance imaging functional reactivity	msP rats exhibited increased functional reactivity in the NAc shell in response to d-AMP compared to Wistar rats	
sP vs. sNP rats, selectively bred for high vs. low EtOH preference; male and female	Saline or AMP treatment (1 mg/kg, IP) immediately before testing	Locomotor activity	sNP rats exhibited greater AMP stimulation than sP rats	D'Aquila et al., 2002
HOT vs. COLD mice, selectively bred for high vs. low hypothermia to EtOH; male and female	AMP treatment (1.25 – 10 mg/kg, IP) immediately after baseline temperature	Body temperature	HOT and COLD mice exhibited comparable dose-dependent hypothermic and hyperthermic responses	Feller and Crabbe, 1991
MAHDR vs. MALDR mice, selectively bred for high vs. low MA intake; male and female	Saline or EtOH treatment (2 or 4 g/kg, IP) immediately after baseline temperature	Body temperature	MAHDR and MALDR mice exhibited comparable dose-dependent hypothermic responses	Harkness et al., 2015
HMACT vs. LMACT mice, selectively bred for high vs. low stimulant response to acute MA; male and female	Saline or EtOH treatment (2 g/kg, IP) immediately before testing	Locomotor activity	HMACT mice exhibited greater EtOH stimulation than LMACT mice	Kamens et al., 2006
	2BC EtOH drinking (water vs. 3, 6, 10, and 20% EtOH for 4 days each; 24 h/day) × 16 days OR 2BC EtOH drinking (water vs. 10% EtOH; 24 h/day) × 10 days	EtOH intake	EtOH intake was greater in LMACT than HMACT mice	
	EtOH treatment (2 and 4 g/kg, IP) and tested periodically 5–180 min later	EtOH pharmacokinetics	LMACT mice had a modest increase in EtOH clearance rate for 2 g/kg, but not 4 g/kg EtOH, compared to HMACT mice	
P vs. NP rats, selectively bred for high vs. low EtOH preference; male and female	Saline or d-AMP treatment (0.3–1.2 mg/kg, SC) immediately before testing	Locomotor activity	NP rats exhibited greater d-AMP than P rats	McKinzie et al., 2002
HAP vs. LAP rats, selectively bred for high vs. low EtOH preference; male and female	Pre-treatment with vehicle or SCH23390 (0.3 μg, ICV) then MA treatment (1 mg/kg, IP) 10 min later	DA levels	D1 receptor antagonism with SCH23390 augmented the effect of MA on DA levels in the striatum in HAP, but not LAP, rats	Nishiguchi et al., 2010
FAST vs. SLOW mice, selectively bred for high vs. low stimulant response to acute EtOH; male and female	Saline or d-AMP treatment (2.5–10 mg/kg, IP) immediately before testing	Locomotor activity	FAST mice exhibited a shift to the right in the dose-response curve in an early selection generation (S11); there was no difference between the lines in a later generation (S14–15)	Phillips et al., 1992

2BC, two-bottle choice; AMP, amphetamine; d-AMP, d-amphetamine; DA, dopamine; EtOH, ethanol; HAP, high alcohol preference; HMACT, high MA activation; ICV, intracerebroventricular; IP, intraperitoneal; IV, intravenous; LAP, low alcohol preference; LMACT, low MA activation; MA, methamphetamine; msP, Marchigian Sardinian alcohol-preferring; NAc, nucleus accumbens; NP, alcohol-non-preferring; P, alcohol-preferring; SC, subcutaneous; sNP, Sardinian alcohol-non-preferring; sP, Sardinian alcohol-preferring

Table 3.

Physiological effects of combined or sequential exposure to EtOH and MA.

EtOH and MA/AMP exposure	Species	Physiological measure tested	Main findings	Reference
Simultaneous exposure (EtOH and MA administered or consumed together or in close succession)				
Saline or EtOH treatment (3 g/kg, IP) 30 min before saline or MA treatment (1–4 g/kg, IP); data collected 30 min after MA	Male albino mice	Body temperature	EtOH pretreatment reversed the hyperthermic effect of MA	Ageel and Ginawi, 1985
Saline or MA treatment (1–4 mg/kg, IP) 30 min before saline or EtOH treatment (3 g/kg, IP); data collected 30 min after EtOH		Body temperature	MA pretreatment attenuated the hypothermic effect of EtOH	
EtOH (3 g/kg, IG) alone or EtOH + MA (15 mg/kg, IG) vs. saline only control; samples collected periodically 30 min to 30 h post-treatment	Male rabbits	Blood and urine MA and AMP	EtOH co-administration accelerated MA absorption and the rate of metabolism of MA to AMP	Li et al., 2014
Water or EtOH offered as sole source of fluid (20% EtOH) × 4 weeks then for 5 or 14 additional days + saline or MA treatment (1 mg/kg, IP); samples collected 30 min after final MA injection	Male Sprague Dawley rats	Brain and organ MA and AMP	EtOH co-administration increased levels of MA and AMP in several organs including the brain	Liang et al., 2012
		Blood EtOH concentration	MA co-administration did not alter blood EtOH concentration	
2BC EtOH drinking (water vs. 10% or 20% EtOH, 24 h/day) × 5 days, then for 8 additional days + saline or MA self-administration (0.1 mg/kg/IV infusion; FR1; 2 h/day); samples collected following 8 days of saline or MA self-administration, 30 min after EtOH treatment (1 g/kg, IG)	Male alcohol-preferring P rats	Blood EtOH concentration	MA co-exposure had no impact on blood EtOH concentration	Winkler et al., 2018
Sequential exposure (effects of prior EtOH on MA responses)				
Saline or EtOH treatment (6 g/kg/day, IG) × 7 days, then saline or neurotoxic MA “binge regimen” (4 × 10 mg/kg, IP at 2 h intervals) 1 day later; data collected immediately after last MA injection	Male Wistar rats	Body temperature	Prior EtOH exposure did not alter the thermal response to MA	Althobaiti et al., 2016
Intermittent 2BC EtOH drinking (water vs. 10% EtOH, every other day; 24 h/day) × 28 days then neurotoxic MA “binge regimen” (4 × 10 mg/kg, IP at 2 h intervals) 1 day later; tested every 30 min during MA “binge regimen”	Male Sprague Dawley rats	MA thermal response	Prior EtOH exposure had no effect on the thermal response to MA	Blaker and Yamamoto, 2018 Blaker et al., 2019b
Sequential exposure (effects of prior MA on EtOH responses)				
Neurotoxic MA treatment regimen (3 × 8 mg/kg, IP at 3 h intervals) then EtOH treatment (3 g/kg, IP) 7 days later; tested periodically 30–270 min post-treatment	Male B6 mice	EtOH pharmacokinetics	Prior MA exposure did not alter EtOH clearance rate	Gutierrez-Lopez et al., 2010

In most of the studies described in this table, animals exposed to EtOH and MA/AMP simultaneously or sequentially were compared to a no-drug control group as well as EtOH- and MA/AMP-only groups. 2BC, two-bottle choice; AMP, amphetamine; EtOH, ethanol; FR, fixed ratio; IG, intragastric; IP, intraperitoneal; IV, intravenous; MA, methamphetamine

Table 4.

Neurobiological effects of combined or sequential exposure to EtOH and MA.

EtOH and MA/AMP exposure	Species	Neurobiological measure tested	Main findings	Reference
Simultaneous exposure (EtOH and MA administered or consumed together or in close succession)				
EtOH offered as only source of fluid (20% EtOH in 8% sucrose) + daily EtOH+MA treatment (1.6 g/kg EtOH + 2 mg/kg MA, IP) × 2 weeks; DA measured 30 h later	Male BALB/c mice	DA levels	No effect of EtOH+MA on DA levels in the striatum or PFC	Chuang et al., 2011
		5-HT levels	No effect of EtOH+MA on 5-HT levels in the striatum or PFC	
		Neuronal toxicity	Co-administration of EtOH and MA increased neuronal toxicity in the dentate gyrus, as measured by reduced numbers of NeuN-positive cells, which was not observed for either drug alone; co-administration of EtOH and MA did not further reduce NeuN-positive cells compared to either drug alone in the amygdala; no effects of EtOH+MA in the striatum or cortex	
		Glial toxicity	Co-administration of EtOH and MA did not further impact glial toxicity, as measured by reduction in GFAP-positive cells compared to either drug alone in the striatum, dentate gyrus, and amygdala; no effects of EtOH+MA in the PFC	
		Cell proliferation	Co-administration of EtOH and MA did not further decrease cell proliferation compared to either drug alone in the subventricular zone and dentate gyrus	
Saline, EtOH (1.5 g/kg), MA (2 mg/kg) or EtOH (1.5 g/kg) + MA (2 mg/kg) IG × 5 days; behavioral testing 15 days later for 12 days, then neurogenesis assessed 1 day later	Male Long Evans rats	Neurogenesis	Prior co-administration of EtOH and MA altered hippocampal neurogenesis, measured as number of doublecortin-void gaps; MA and EtOH = MA increased the length of doublecortin-void gaps	Loxton and Canales, 2017
Local application of EtOH (750 nM) + MA (10^{-8} M) in anesthetized rats; tested immediately after treatment	Male Sprague Dawley rats	Cerebellar Purkinje neuronal activity and the role of the noradrenergic system	MA co-application potentiated EtOH-induced depression in cerebellar Purkinje neuronal activity in the presence of an α-adrenergic receptor antagonist (prazocin, 1 mg/kg); this was potentiated by noradrenergic lesions	Wang et al., 1995
EtOH (escalating doses from 1–4 g/kg, IP over 26 days) + MA (escalating doses from 2–8 mg/kg, IP over 26 days); DA measured 11 days later	Male Sprague Dawley rats	DA levels	EtOH co-administration mitigated MA-induced DA depletions in the striatum (not statistically significant); in the hippocampus, EtOH decreased DA while MA increased DA, and the combination mitigated these independent effects; no effects in the cortex	Yamamura et al., 1992
		5-HT levels	EtOH co-administration rescued MA-induced 5-HT depletions to the level of EtOH alone in the hippocampus and striatum,	

EtOH and MA/AMP exposure	Species	Neurobiological measure tested	Main findings	Reference
			and reversed MA-induced 5-HT depletions in the cortex	
Neurotoxic MA "binge regimen" (4 × 10 mg/kg, IP at 2 h intervals) + EtOH treatment (0.292.34 g/kg, IP) 30 min before the 1st and 2nd MA injections, and 30 min after the 3rd MA injection; DA measured 2 weeks later	Male and female B6 mice	DA levels	EtOH co-administration mitigated MA-induced DA depletions in the striatum	Yu et al., 2002
Sequential exposure (effects of prior EtOH on MA responses)				
Water or EtOH offered as sole source of fluid (2% EtOH) × 8 weeks, then saline or neurotoxic MA "binge regimen" (4 × 10 mg/kg, IP at 2 h intervals) 1 day later; samples taken 72 h after MA treatment	Male C57BL/6 N mice	DA levels	Prior EtOH exposure did not affect MA-induced DA depletions in the striatum	
Water or EtOH treatment (6 g/kg, IG) × 7 days, then saline or neurotoxic MA "binge regimen" (4 × 10 mg/kg, IP at 2 h intervals) 1 day later; samples taken 48 h later	Male Wistar rats	DA levels	Prior EtOH exposure did not affect DA levels after MA in the striatum or hippocampus	Almalki et al., 2018
		5-HT levels	Prior EtOH exposure did not affect MA-induced 5-HT depletions in the striatum or hippocampus	
		Glutamate levels	Prior EtOH exposure reduced MA-induced increases in striatal glutamate levels; there were no effects of MA and/or EtOH on glutamate levels in the hippocampus	
Water or EtOH treatment (6 g/kg, IG) × 7 days, then saline or neurotoxic MA "binge regimen" (4 × 10 mg/kg, IP at 2 h intervals) 1 day later; samples obtained 48 h after MA treatment	Male Wistar rats	Glutamate transporter expression (GLT-1 and GLAST)	Prior EtOH exposure potentiated MA-induced downregulation of GLT-1 in the dorsal striatum and hippocampus; no effect of EtOH or MA on GLAST	Alshehri et al., 2017
Water or EtOH treatment (6 g/kg, IG) × 7 days, then saline or neurotoxic MA "binge regimen" (4 × 10 mg/kg, IP at 2 h intervals) 1 day later; samples obtained 48 h after MA treatment	Male Wistar rats	Glutamate transporter expression (GLT-1 and GLAST)	Prior EtOH exposure potentiated MA-induced downregulation of GLT-1 in the NAc but not PFC; no effect of EtOH or MA on GLAST	Althobaiti et al., 2016
Water only or intermittent 2BC EtOH drinking (water vs. 10% EtOH, every other day; 24 h/day) × 28 days or water or EtOH administration (6 g/kg, IG) × 7 days, then saline or neurotoxic MA "binge regimen" (4 × 10 mg/kg, IP at 2 h intervals) 1 day later; samples obtained 7 days after MA treatment	Male Sprague Dawley rats	DA and 5-HT levels	Prior EtOH exposure via drinking or gavage exacerbated long-term MA-induced DA and 5-HT depletions in the striatum, and 5-HT depletions in the PFC; this effect was reversed by cyclooxygenase inhibition during EtOH drinking	Blaker and Yamamoto, 2018
		DAT and SERT levels	Prior EtOH exposure via drinking or gavage exacerbated long-term MA-induced depletions of DAT in the striatum and SERT in the striatum and PFC	
Intermittent 2BC EtOH drinking (water vs. 10% EtOH, every other day; 24 h/day) × 28 days then neurotoxic MA "binge regimen" (4 × 10 mg/kg, IP at 2 h intervals) 1 day later; acute glutamate response was measured during MA treatment, and spectrin proteolysis and DA content was measured 7 days after MA treatment	Male Sprague Dawley rats	Acute extracellular glutamate levels	Prior EtOH exposure augmented the acute MA-induced increase in extracellular glutamate	Blaker et al., 2019a
		Long-term spectrin proteolysis and DA content	Prior EtOH exposure augmented the MA-induced long-term increase in spectrin proteolysis and long-term decrease in DA content in the striatum	
Water only or intermittent 2BC EtOH drinking (water vs. 10% EtOH, every other day; 24 h/day) × 28 days, then saline or neurotoxic MA "binge regimen" (4 × 10 mg/kg, IP at 2 h intervals) 1 day later; samples for microglia taken 2 h and 3	Male Sprague Dawley rats	Microglia cell counts and morphology	Sequential exposure to EtOH then MA produced microglia morphology changes in the substania nigra 2 h after MA treatment that were not observed	Blaker et al., 2019b

EtOH and MA/AMP exposure	Species	Neurobiological measure tested	Main findings	Reference
days after MA treatment; samples for dopaminergic apoptosis taken 3 days after MA treatment; samples for DAT and TH taken 7 days after MA treatment			with either drug alone; this effect was not present 3 days after MA treatment and there were no effects of sequential EtOH then MA exposure on microglia in the striatum at either time point	
		Dopaminergic apoptosis	Apoptosis in dopaminergic neurons in the substantia nigra was augmented by sequential exposure to EtOH then MA	
		DAT levels	Prior EtOH exacerbated long-term MA-induced depletions of DAT in the striatum	
		TH levels	Prior EtOH exposure in combination with binge MA exposure reduced TH in the substantia nigra, which was not observed for either drug alone	
Episodic EtOH treatment (2 g/kg, IG; 3 days/week) × 5 weeks (PD 28–59) then d-AMP treatment (2 mg/kg, IV) 3 weeks after EtOH treatment ended; evoked DA release measured 5 min after d-AMP treatment, and then every 10 min until 55 min post-treatment in anesthetized rats	Male Wistar rats	Evoked DA release	Prior EtOH exposure reduced evoked DA release in response to d-AMP in the dorsal striatum	Granholm et al., 2015
Prenatal EtOH exposure via maternal EtOH drinking during gestation (10% EtOH offered as only source of fluid) then AMP treatment (4 mg/kg, IP) at 3 months of age; DA measured immediately after AMP treatment every 20 min for 180 min in anesthetized rats	Male Wistar rats	DA levels	Prenatal EtOH exposure did not alter AMP-induced increases in DA in the striatum	Nowak et al., 2006
Prenatal control or EtOH exposure via maternal non-EtOH or EtOH liquid diet (35% of total calories) during gestation, then repeated saline or AMP treatment from PD 22 to 10–12 months of age (2 mg/kg/day, SC); electrophysiological recordings occurred 1924 h after last AMP injection in anesthetized rats	Male Long Evans rats	Sensitivity of somatodendritic DA autoreceptors in the VTA as measured by quinpirole-induced inhibition of DA neuron activity	Chronic, postnatal AMP exposure reversed prenatal EtOH exposure-induced heightened sensitivity of somatodendritic DA autoreceptors in the VTA	Shen et al., 1995
DID EtOH drinking (20% EtOH; 4 h/day; ~ 5.5 g/kg/day) × 14 days then 1 or 10 μM MA applied to horizontal midbrain slices 1 week later and immediately tested	Male B6 mice	Midbrain DA D2 receptor-mediated inhibitory postsynaptic current amplitude	Prior EtOH exposure blunted MA-induced increases in midbrain DA D2 receptor-mediated inhibitory postsynaptic current amplitude at the higher, but not lower MA concentration	Tschumi et al., 2020
Prenatal EtOH exposure via maternal EtOH administration (3 g/kg 2x daily during weekdays and 4 g/kg 1x daily during weekends, IG) during gestation then 6–8 weeks old offspring treated with d-AMP (cumulative doses of 0.05–12.8 mg/kg, IV); electrophysiological recordings occurred during d-AMP treatment in unanesthetized rats	Male Sprague Dawley rats	VTA DA neuron firing rate	Prenatal EtOH exposure enhanced sensitivity to d-AMP-induced reductions in VTA DA neuron firing rates	Xu and Shen, 2001

In most of the studies described in this table, animals exposed to EtOH and MA/AMP simultaneously or sequentially were compared to a no-drug control group as well as EtOH- and MA/AMP-only groups. 2BC, two-bottle choice; 5-HT, serotonin; AMP, amphetamine; B6, C57BL/6J; d-AMP, d-amphetamine; DA, dopamine; DAT, dopamine transporter; DID, drinking-in-the-dark; EtOH, ethanol; GFAP, glial fibrillary acidic protein; IG, intragastric; IP, intraperitoneal; IV, intravenous; MA, methamphetamine; NAc, nucleus accumbens; PD, postnatal day; PFC, prefrontal cortex; SC, subcutaneous; SERT, serotonin transporter; TH, tyrosine hydroxylase; VTA, ventral tegmental area