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Sigma Receptors and Alcohol Use Disorders

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Abstract

Although extensive research has focused on understanding the neurobiological mechanisms underlying alcohol addiction, pharmacological treatments for alcohol use disorders are very limited and not always effective. This constraint has encouraged the search for novel pharmacological targets for alcoholism therapy. Sigma receptors were shown to mediate some of the properties of cocaine and amphetamine, which was attributed to the direct binding of psychostimulants to these receptors. More recently, the role of sigma receptors in the rewarding and reinforcing effects of alcohol was also proposed, and it was suggested that their hyperactivity may result in excessive alcohol drinking. This chapter reviews current knowledge on the topic, and suggests that the sigma receptor system may represent a new therapeutic target for the treatment of alcohol use disorders.

Keywords

Addiction; Alcohol; Alcoholism; Alcohol dependence; Consumption; Drinking; Ethanol; Preferring; Withdrawal

1 Epidemiology and Associated Medical Conditions

The global status report on alcohol and health by the World Health Organization (WHO) indicates that worldwide alcohol consumption in 2010 was equal to 6.2 l of pure alcohol consumed per person aged 15 years or older per day (World Health Organization 2014). The WHO also indicates that in 2012, over 3 million deaths (~6% of all global deaths) were attributable to alcohol consumption (World Health Organization 2014). Globally, alcohol misuse is the first risk factor for premature death and disability for people between the ages of 15 and 49, and it is ranked fifth when all ages are accounted for. One-fourth of total deaths in people between 20 and 39 years are dependent on alcohol (World Health Organization 2014; Lim et al. 2012). In addition, estimates of the global economic burden of alcohol consumption suggest that alcohol is responsible for 1.3–3.3% of total health costs, 6.4–14.4% of total public order and safety costs, 0.3–1.4% of gross domestic product

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GDP for criminal damage costs, 1.0–1.7% of GDP for drunk driving costs, and 2.7–10.9% of GDP for workplace costs (e.g., absenteeism, unemployment, and premature mortality) (Baumberg 2006).

The adverse consequences on health associated with alcohol consumption are numerous. The WHO indicates that alcohol is a causal factor in 60 types of diseases and injury-related health conditions, including addiction, gastrointestinal diseases, cardiovascular diseases, cancers, fetal alcohol spectrum disease, and alcohol-related injuries (World Health Organization 2014).

Acute alcohol consumption is responsible for a variety of physiological and behavioral effects which are resultant of blood alcohol concentrations (BACs), (Koob and Le Moal 2005). At BACs of 10–50 mg/dl, alcohol increases locomotor activity, disinhibits behavior, and relieves anxiety. When BACs reach 80 mg/dl, alcohol impairs judgment, cognition, and motor function. Individuals with BACs of 150 mg/dl experience marked motor impairment and ataxia, memory lapse, as well as decreased reaction time. BACs of 300 mg/dl produce hypnosis and can cause general anesthesia and coma. At BACs of 400 mg/dl, death is observed in 50% of the people (Koob and Le Moal 2005).

Alcohol is responsible for a plethora of psychiatric disorders, the most relevant being alcohol use disorder (AUD). The diagnosis of AUD in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, American Psychiatric Association 2013) integrates in a single disorder the diagnoses of alcohol abuse and alcohol dependence previously described in the fourth edition of the manual. The manual lists 11 criteria for AUD, and the disorder is diagnosed as mild, moderate, or severe as a function of the number of criteria met (2–3 mild, 4–5 moderate, >5 severe). According to the DSM-5, the diagnosis of AUD is therefore based on the presence of impaired control, social impairment, risky use, as well as pharmacological indicators.

2 Definitions of Alcohol Use Disorders

Alcohol represents the most commonly used and abused substance in the world and it has been consumed for centuries in several cultures. Alcohol exerts beneficial effects when consumed in moderation, but it has abuse potential when consumed in excess. According to the Dietary Guidelines for Americans, moderate alcohol consumption is defined as up to one drink per day for women and up to two drinks per day for men. A standard drink is defined as 14 g of pure alcohol, which are equivalent to a 12-ounce can of beer, a 5-ounce glass of wine, or a 1.5-ounce glass of 80-proof liquor. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines binge drinking as a pattern of drinking which results in BAC levels of 80 mg/dL (NIAAA 2004). Binge drinking typically occurs with four drinks for women and five drinks for men in a time window of approximately 2 h. The Substance Abuse and Mental Health Services Administration (SAMHSA) defines binge drinking as drinking five or more alcoholic drinks on the same occasion on at least 1 day in the past 30 days, while heavy drinking is defined as drinking five or more drinks on the same occasion on each of 5 or more days in the past 30 days (Koob and Le Moal 2005).

3 Molecular Targets of Alcohol

The molecular mechanisms of action of alcohol are several and complex, and still not entirely understood. The complexity of alcohol mechanisms is mainly due to its molecular structure: alcohol is a very small molecule with both polar and nonpolar properties and as such it can easily travel through both hydrophilic and lipophilic molecular and cellular structures. As a consequence, alcohol interacts with both plasma membrane and intracellular proteins. Given the plethora of molecular effects that alcohol can produce, here we will limit our discussion to a brief description of the main mechanisms underlying ethanol's putative direct interaction with specific target proteins.

A well-known mechanism of action of alcohol is related to its direct interaction with ligand-gated ion channel membrane proteins, especially the pentameric (five subunits) Cys-loop superfamily of neurotransmitter receptors including GABAA receptor (GABAAR), nicotinic acetylcholine receptor (nAChRs), and glycine receptor (GlyR) (Olsen et al. 2014; Trudell et al. 2014). Alcohol directly binds and agonizes GABAAR, and the specific receptor subunit composition makes it more or less responsive to ethanol (Lobo and Harris 2008; Santhakumar et al. 2007; Mehta and Ticku 1988; Suzdak et al. 1988). α4β2δ, α4β3δ, and α6β3δ GABAARs are very sensitive to alcohol, with concentrations of 0.1–1 mM of ethanol significantly enhancing GABA currents (Sundstrom-Poromaa et al. 2002; Wallner et al. 2003). In addition, alcohol is hypothesized to directly act on nAChRs and the net effect of this interaction depends on the receptor subunit composition; alcohol enhances the function of α4β2, α4β4, α2β2, and α2β4 nAChRs, while it exerts no effect on α3β2 and α3β4 nAChRs, and inhibits α7 nAChRs (Narahashi et al. 1999; Cardoso et al. 1999; Davis and de Fiebre 2006). Furthermore, alcohol can bind and positively modulate GlyRs (Perkins et al. 2010).

Another well-described mechanism of action of alcohol is its antagonistic action on the N-methyl-D-aspartate glutamate receptor (NMDAR); alcohol is thought to interact allosterically with NMDARs, reducing the affinity of the agonist for the receptors (Lima-Landman and Albuquerque 1989; Wright et al. 1996).

Alcohol has also been demonstrated to directly interact with G-protein-gated inwardly rectifying potassium (GIRK) channels activating them through a direct binding to a hydrophobic pocket. Interestingly, GIRK channels can be occupied and activated by chemical groups different than those of alcohol (Bodhinathan and Slesinger 2013).

Sigma receptor (SigR) ligands have been shown to influence the effects of psychostimulants, in particular cocaine and methamphetamine, which were demonstrated to bind directly to SigR, although at low (micromolar) affinity (Brammer et al. 2006; Nguyen et al. 2005; Sharkey et al. 1988). For this reason, until a few years ago, only a few studies had examined the possibility of a SigR modulation of ethanol's actions. However, growing evidence indicates that indirect SigR-mediated effects may exist for other substances of abuse besides psychostimulants, including ethanol. Therefore it is conceivable that, for example in the context of cocaine, some of the molecular mechanisms described for SigR may also be common to those of alcohol. Important mechanisms include the described interactions of

SigR with dopamine D1 and D2 receptors, potassium channels and opioid receptors, as well as proteins of the nuclear envelope and histone deacetylases (Navarro et al. 2010, 2013; Kourrich et al. 2013; Tsai et al. 2015; Kim et al. 2010; Mei and Pasternak 2007).

4 Sigma Receptors and the Locomotor-Activating and Sedative Effects of Alcohol

Alcohol effects on locomotor activity are a direct function of the BACs attained. At low BACs, alcohol exerts locomotor-stimulating effects and increases locomotor activity, while at higher BACs, the depressant and sedative effects of alcohol become evident. The locomotor-stimulating properties of alcohol are interpreted as an index of its rewarding properties and abuse liability, and they are thought to be dependent on the activation of the mesolimbic dopaminergic system (Phillips and Shen 1996). In rodents, the locomotor-stimulating effects of alcohol and drugs are typically evaluated by placing subjects in an arena equipped with infrared sensor photobeams; the interruption of these photobeams, caused by the subjects' movement, is recorded by a computer and the number of interruptions is a direct index of the locomotor activity of the subjects.

The selective sigma-1 receptor (Sig-1R) antagonist N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino)ethylamine (BD1047), injected at doses of 3–30 mg/kg, dose-dependently blocked the locomotor-stimulating effects induced by 1 g/kg of ethanol in Swiss mice (Maurice et al. 2003). In the same study, it was shown that the selective Sig-1R agonist PRE-084, administered at doses of 1–10 mg/kg, failed to affect alcohol-induced locomotion stimulation. Interestingly, neither drug affected locomotor activity when administered alone (Maurice et al. 2003).

Accordingly, in a recent study, Valenza et al. (2015) found that C57BL/6J mice lacking the *SIGMAR1* (previously known as *Oprs1*) gene, which encodes the Sig-1R, were less sensitive to the locomotor-stimulant effects of 1.5 g/kg of ethanol as compared to the wild-type counterpart. Since the C57BL/6J strain is particularly insensitive to the locomotor-stimulant effects of ethanol, mice in this study were pretreated with the benzodiazepine (BDZ) partial inverse agonist Ro 15–4513 (Miczek and Weerts 1987), which is able to unmask the stimulant effects of ethanol by blocking the depressant properties of ethanol (Becker and Hale 1989). These observations, therefore, confirm the notion that Sig-1R is involved in mediating the locomotor-stimulating effects of alcohol. Together these studies suggest that Sig-1R activation may mediate or at least contribute to the locomotor-activating effects of ethanol, and therefore perhaps also to its abuse potential.

In the same study, the effects of *SIGMAR1* knockout (KO) on the sedative effects of high doses of alcohol were tested using the loss of righting reflex procedure. In this procedure, following the administration of a high dose of alcohol (4 g/kg), mice are placed on a V-shaped surface, and the latency to lose the righting reflex (inability to right itself from a supine position) and the sleep duration are recorded. *SIGMAR1* KO mice were shown not to differ from wild-type mice neither in the latency to lose the righting reflex nor in time spent sleeping, suggesting a similar sensitivity between the two genotypes and therefore opposing the involvement of Sig-1R in the sedative effects of alcohol (Valenza et al. 2015).

5 Sigma Receptors and the Rewarding Properties of Alcohol

Alcohol can increase the salience of the contextual stimuli, such as places in which positive alcohol effects are experienced. Once, through associative learning, contextual neutral stimuli have acquired rewarding properties, they can then exert powerful control over behavior. This mechanism plays a critical role in maintaining alcohol taking behavior, as approaching an alcohol-associated context can set the occasion for drinking to begin (Bardo and Bevins 2000). An experimental procedure to evaluate whether a substance has rewarding properties is place conditioning (also known as conditioned place preference), a task where a compartment equipped with specific contextual cues is repeatedly paired with a rewarding substance (in this case ethanol) and therefore becomes preferred versus a second, neutral compartment (Bardo and Bevins 2000). Even though technically challenging depending on the specific species and strain used, alcohol is able to induce conditioned place preference in rodents (Cunningham and Noble 1992). Pharmacological agents can be administered either before each of the conditioning sessions to assess their influence on the acquisition of place preference or before the post-conditioning test to instead assess their influence on the expression of place preference.

Sig-1R antagonism has been shown to successfully block the expression of the conditioned place preference induced by alcohol. Indeed, pretreatment with the selective Sig-1R antagonist BD1047 (3–30 mg/kg), administered during conditioning, has been shown to dose dependently block the acquisition of place preference induced by repeated injections of 2 g/kg of alcohol in male mice (Maurice et al. 2003). In the same study, the authors demonstrated a bidirectionality of the process, as the selective Sig-1R agonist 2-(4-morpholino) ethyl 1-phenylcyclohexane-1-carboxylate (PRE-084, 1–10 mg/kg), given before a dose of ethanol (0.5 g/kg) (which was per se inert), resulted in a dramatic dose-dependent facilitation of ethanol-induced place preference (Maurice et al. 2003). These results were confirmed and extended in a study in which Sig-1R ligands were administered intracerebroventricularly (Bhutada et al. 2012). In this study, BD1047 (0.1–10 μg/mouse) dose dependently blocked not only the acquisition, but also the expression of ethanol-induced conditioned place preference. It is important to note that both BD1047 and PRE-084 have been repeatedly shown not to exert any effect on place preference when administered alone (Romieu et al. 2000, 2002; Maurice et al. 2003).

6 Sigma Receptors and Alcohol Drinking

Strong evidence from both human and animal studies supports the overarching hypothesis that SigR activation modulates alcohol intake and proposes a role for Sig-1R antagonists as potential pharmacological agents for the treatment of alcohol-use disorder.

A functional relationship between alcoholism and polymorphisms in the human *SIGMAR1* gene has been shown in a study by Miyatake et al. (2004), who measured the differential representation of *SIGMAR1* functional polymorphisms in a Japanese population of alcoholic subjects. This study showed that the frequency of the A-485 allele and the TT-241–240/Pro2 haplotype, whose transcriptional activity was significantly reduced compared with that of the T-485 allele and the GC-241–240 allele, was higher in controls

relative to alcoholic subjects, suggesting that this polymorphism in *SIGMAR1* may act as protective factors for alcohol dependence.

At a preclinical level, a relatively large body of evidence has shown a bidirectional role for SigRs in regulating alcohol drinking, and these studies are reviewed below based on the experimental procedure used to assess alcohol drinking behavior: home cage vs. operant self-administration.

6.1 Home Cage Drinking

A procedure used to evaluate drinking in rats is the two-bottle choice. In this procedure, alcohol drinking is measured in rats that are provided continuous access (24-h day) in their home cage with two bottles: one containing a solution of ethanol (usually 10% *v/v*), and the other one water. Intake and preference are both measured.

In the context of SigR pharmacology, many studies using the two-bottle choice procedure have been performed in selectively bred Sardinian alcohol-preferring (sP) rat. Lines of rodents genetically selected for high alcohol intake and preference represent a successful tool to study the genetic factors underlying excessive alcohol consumption (Ciccocioppo and Hyytia 2006). In particular, rats of the sP rat line have been shown to voluntarily drink large quantities of ethanol, to have a strong innate preference for ethanol over water, and to possess a heritable component analog to human alcohol dependence (Cloninger et al. 1981; Prescott and Kendler 1999; Sigvardsson et al. 1996). Therefore, sP rats represent a model of genetic predisposition to high ethanol drinking and a tool for identifying potential pharmacotherapies for alcoholism (Colombo et al. 2006).

Sig-1Rs have been demonstrated to exert a key role in both the acquisition and the maintenance of excessive alcohol drinking in sP rats. Sabino and colleagues have shown that chronic systemic administration of the selective Sig-1R antagonist BD1063 (30 mg/kg) dramatically reduced the acquisition of alcohol-drinking behavior in sP rats, reducing both intake and preference for alcohol (Blasio et al. 2015). In this study, vehicle-treated sP rats rapidly escalated their alcohol intake to 6 g/kg of ethanol per day within the 2 weeks of observation. Ethanol drinking acquisition was also accompanied by a rapid increase in the preference for alcohol as the consumption of water gradually decreased to maintain a stable overall fluid intake. On the other hand, BD1063-treated sP rats showed a marked reduction in alcohol drinking accompanied by an increase in water intake. Notably, the drug treatment did not affect overall fluid intake and significantly decreased the preference for alcohol, indicating that Sig-1R antagonism is able to shift the innate inclination to drink alcohol over water of sP rats (Blasio et al. 2015). sP rats were also shown to have innately higher levels of Sig-1R protein in the nucleus accumbens (NAcc) as compared to outbred Wistar rats, which provides critical information about the genetic basis of high alcohol drinking (Blasio et al. 2015). Interestingly, increased Sig-1R levels in the NAcc were normalized by chronic alcohol consumption, which may be consistent with the reduced motivation to drink alcohol which follows recent alcohol consumption (Blasio et al. 2015).

Sig-1R antagonism has also been demonstrated to decrease the maintenance of alcohol drinking in sP rats (Sabino et al. 2009b). The selective Sig-1R antagonist NE100 (10–30

mg/kg) reduced the intake of alcohol consumed by sP rats when injected either acutely or chronically. Following acute administration, NE100 dramatically reduced excessive ethanol intake, and decreased the preference for alcohol by increasing the volume of water consumed without affecting total fluid intake. In addition, when sP rats were offered a two-bottle choice between sucrose and water, acute NE100 treatment did not decrease the consumption of sucrose. Overall, these results suggest that the effect of the drug was selective for alcohol and that it was not due to malaise or secondary to an overall behavioral deficit (Sabino et al. 2009b). In addition, the alcohol-suppressive effect of NE100 was not due to changes in ethanol pharmacokinetics, as drug treatment did not affect BACs when ethanol was administered by gavage (Sabino et al. 2009b). Chronic NE100 treatment to sP rats (30 mg/kg) also significantly reduced alcohol intake, with a peak reduction by the treatment day 3. Starting from day 6, some tolerance to NE100's effect was evident, similar to what was also observed with opioid receptor antagonists (e.g., naloxone and naltrexone), for which tolerance has been shown to develop after 5–14 days of treatment (Cowen et al. 1999; Overstreet et al. 1999; Parkes and Sinclair 2000). Chronic treatment with NE100 did not affect daily food intake (Sabino et al. 2009b).

NE100 treatment was also shown to fully block the increase in alcohol consumption observed when alcohol access is reinstated following a period of deprivation (Sabino et al. 2009b). This transient increase in alcohol consumption is referred to as "alcohol deprivation effect" and it has been posited to be an animal model for alcohol craving and relapse (Rodd-Henricks et al. 2000; Agabio et al. 2000). In this procedure, sP rats, trained under a two-bottle choice continuous access condition, were forced to abstain from alcohol for 1 week, and on the test day, either NE100 or vehicle was administered to the rats before access renewal. Under vehicle conditions, abstinent sP rats dramatically increased the intake of alcohol upon renewing access to the bottle of alcohol as compared to non-abstinent rats; this alcohol deprivation effect was fully prevented by pretreatment with the selective Sig-1R antagonist (Sabino et al. 2009b).

It has been recently shown that *SIGMAR1* KO mice show greater alcohol intake and greater alcohol preference in a two-bottle choice procedure as compared to WT mice (Valenza et al. 2015). Interestingly, the higher the concentration of alcohol provided (3%, 6%, and 20% *v/v*), the more pronounced the observed increase in alcohol intake was. Conversely, when mice were tested in two-bottle choice for either saccharin or quinine, neither the intake of the sweet nor of the bitter solution was changed in *SIGMAR1* KO mice, ruling out that the deletion of *SIGMAR1* results in altered taste perception or in a general increase in intake of fluids (Valenza et al. 2015). Results from this study seem to contradict the overarching hypothesis that Sig-1R activation mediates the effects of alcohol and that Sig-1R antagonism decreases excessive alcohol drinking (Sabino et al. 2009a, b, 2011). However, the species difference (mice vs. rats) may be responsible for the differential effects observed. In addition, it cannot be excluded that in whole-body KO mice developmental mechanisms play a counteradaptive role and may confound the results obtained.

6.2 Operant Self-Administration

The reinforcing effects of alcohol are studied using instrumental conditioning, a form of associative learning in which subjects (typically rats or mice) learn to self-administer alcohol (or water) by pressing a lever inside an operant chamber. Following a single press on one of the two levers (fixed ratio 1), a syringe pump containing the solution is activated and the respective fluid is dispensed into a drinking cup. In this procedure alcohol drinking is evaluated as the number of responses emitted on the alcohol lever.

Two major studies have been pivotal in demonstrating the bidirectional modulatory role of SigR in the reinforcing properties of alcohol.

In a first study, the effects of the selective Sig-1R antagonist BD1063 on alcohol reinforcement were evaluated in both a genetic and an environmental animal model of excessive alcohol drinking (Sabino et al. 2009a). The genetic animal model used in this study was the sP rats described above. The environmental animal model was outbred Wistar rats made dependent through the exposure to chronic intermittent ethanol (CIE). Briefly, rats were housed for a period of 4–6 weeks in sealed chambers into which ethanol vapor was intermittently introduced (for review, see Vendruscolo and Roberts 2014); BACs were kept at approximately 150–200 mg% across the exposure period. During acute withdrawal from alcohol, CIE rats show heightened levels of ethanol self-administration, anxiety-like behavior, and increased threshold in the intracranial self-stimulation, compared to control, air-exposed rats (Sabino et al. 2006; Funk et al. 2006; O'Dell et al. 2004). Results from this study showed that the selective Sig-1R antagonist BD1063 (3.3–11 mg/kg) dose dependently reduced excessive ethanol self-administration in both sP rats and CIE rats during acute withdrawal (Sabino et al. 2009a). BD1063 did not, however, reduce ethanol self-administration in control rats. In addition, BD1063 treatment did not affect responding for water or for an equally reinforcing solution of saccharin, suggesting that the Sig-1R antagonist effects were selective for alcohol (Sabino et al. 2009a).

In the same study, the effects of BD1063 were also tested in a progressive ratio schedule of reinforcement for alcohol, which represents a highly validated operant model to assess subjects' motivation for alcohol (Hodos 1961). In this procedure, the number of lever presses (ratio) required to obtain a single reinforcer increases progressively, with the last ratio defined as the "breakpoint." The breakpoint, therefore, represents the maximum effort a subject expends to obtain the desired reinforcing stimulus, and is an objective measure of the subject's motivation. Results from this study showed that BD1063 (3.3–11 mg/kg) dose dependently reduced the breakpoint for ethanol in sP rats (Sabino et al. 2009a).

Collectively, these data suggest that Sig-1Rs are recruited in conditions of excessive ethanol intake and/or heightened motivation, thus likely contributing to innate and ethanol-induced increases in susceptibility to drink excessively. In addition, the increase in the NAcc Sig-1R expression levels in sP rats compared to outbred Wistar rats observed by Blasio et al. (2015) can be speculated to explain the increased sensitivity of sP rats to pharmacological blockade with Sig-1R antagonists found in this study.

The results of a second study demonstrated the bidirectionality of the modulation of ethanol drinking exerted by the SigR system. Daily systemic treatment (2/day for 7 consecutive days) with the SigR agonist 1,3-di-(2-tolyl)guanidine (DTG) (15 mg/kg) was shown to increase ethanol self-administration in sP rats under a fixed ratio 1 schedule of responding (Sabino et al. 2011). Importantly, the increased self-administration in DTG-treated rats resulted in BACs exceeding 80 mg%, which can therefore be regarded as "binge-like" according to the definition provided by the National Institute on Alcohol Abuse and Alcoholism (NIAAA 2004). Importantly, SigR agonist treatment might represent a novel way to induce binge drinking in laboratory animals, which historically has been difficult to achieve (Sabino et al. 2011). Treatment with DTG also increased breakpoint for ethanol in a progressive ratio schedule of reinforcement, suggesting a greater motivation to work for alcohol. Notably, the DTG-induced increase in ethanol intake was reversed by a subthreshold dose of the Sig-1R antagonist BD1063, confirming that the Sig-1R subtype mediated the DTG effects (Sabino et al. 2011). In addition, considering that both sP rats and acutely withdrawn CIE rats show alterations of Sig-1R levels in the NAcc (Blasio et al. 2015; Sabino et al. 2009a), it is conceivable that Sig-1R of the NAcc may mediate the susceptibility to excessive drinking, both innate and induced by chronic alcohol exposure.

Repeated treatment with DTG induced an increase in μ- and δ-opioid receptor gene expression in the ventral tegmental area (VTA) of sP rats, suggesting that SigR agonists may facilitate ethanol's ability to activate the mesolimbic dopaminergic system through this mechanism which involved the endogenous opioid system of the VTA. These results suggest a key facilitatory role for SigR in the reinforcing effects of ethanol and identify a potential mechanism that contributes to excessive drinking.

7 Sigma Receptors and Alcohol Seeking

One of the major issues encountered in the treatment of alcohol addiction is relapse following abstinence. In alcoholic individuals, abstinence is accompanied by craving, a strong desire to engage in alcohol drinking often referred to as alcohol seeking behavior, which is in turn responsible for relapse (Martin-Fardon and Weiss 2013; Everitt and Robbins 2000; Le and Shaham 2002). Craving is typically triggered by a number of different factors, of which the most common are exposure to stress, exposure to alcohol (i.e., priming), and exposure to conditioned environmental stimuli previously associated with alcohol (i.e., conditioned cues). In this chapter, we focus on seeking behavior triggered by exposure to either priming or alcohol conditioned cues, as they are factors triggering relapse studied in relation to SigR system.

7.1 Priming-Induced Alcohol Seeking Behavior

In alcoholics, relapse and craving during abstinence are often triggered by acute reexposure to alcohol (Chutuape et al. 1994; Hodgson et al. 1979). Small amounts of alcohol can act much like *hors d'oeuvres*, thereby contributing to the "first-drink" relapse phenomenon (Ludwig et al. 1974). Literature suggests that SigRs are involved in the mechanisms underlying priming-induced alcohol seeking behavior. Indeed, Bhutada and colleagues examined the effects of SigR ligands on priming-induced reinstatement of

ethanol conditioned place preference (Bhutada et al. 2012). This procedure is based on the conditioned place paradigm described previously. Briefly, specific tactile and visual stimuli of one of the two compartments of a place preference apparatus are associated with the effects of alcohol, while the stimuli of the other compartment remain neutral. Once ethanol place preference has been established, subjects are repeatedly exposed to the alcohol-paired compartment until preference is gradually extinguished. Once the alcohol preference is extinguished, it can be reinstated by exposure to alcohol or to another pharmacological agent (i.e., cross-reinstatement). In this study, the authors demonstrated that alcohol seeking behavior could be reinstated by systemic administration of 1 g/kg of ethanol or cross-reinstated by intracerebroventricular microinfusion of the selective Sig-1R PRE-084 (1–10 μg/mouse). In addition, the selective Sig-1R antagonist BD1047 (1–10 μg/mouse), microinfused intracerebroventricularly, was able to dose dependently block both ethanol-induced reinstatement and the PRE-084-induced cross-reinstatement of ethanol-induced conditioned place preference, suggesting that reinstatement of ethanol conditioned place preference involves the activation of central Sig-1Rs (Bhutada et al. 2012).

7.2 Cue-Induced Alcohol Seeking Behavior

As previously mentioned, once contextual stimuli are associated with the positive effects of alcohol through Pavlovian conditioning, they can exert a strong control over behavior. These conditioned cues become particularly relevant in occasions in which the effects of alcohol are not being experienced (i.e., during abstinence), and can lead to resumption of alcohol drinking. In preclinical psychopharmacological research, different animal models of alcohol seeking behavior have been developed to study the influence of stimuli associated with alcohol. Here we will be describing two operant responding alcohol seeking procedures, which have been used to assess the role of SigRs in the modulation of the influence of alcohol-associated cues over behavior.

A classical experimental procedure used to assess seeking behavior is the cue-induced reinstatement of seeking behavior. In this task, subjects are trained to self-administer alcohol by pressing a lever, and each lever response is contiguously paired with a brief presentation of a conditioned stimulus (e.g., an olfactory stimulus, a light, a tone). Following the initial training, ethanol-reinforced responding is extinguished by withholding both alcohol delivery and presentation of the conditioned stimulus. Once extinction of lever responding is obtained, reinstatement of alcohol seeking behavior is induced by presenting the alcohol-associated conditioned stimulus. Using this procedure, Martin-Fardon and colleagues showed that the selective Sig-1R BD1047 (3–20 mg/kg) was able to block cue-induced reinstatement of alcohol seeking induced by presentation of an olfactory stimulus.

Another classical experimental procedure used to assess seeking behavior is the seeking-taking chain in a second-order schedule of reinforcement, where responding on a seeking lever is maintained not only by the self-administered reinforcer, but also by contingent presentation of reinforcer-paired stimuli that serve as conditioned reinforcers of instrumental behavior (Velazquez-Sanchez et al. 2015; Everitt and Robbins 2000; Giuliano et al. 2015). Typically, a second inactive lever is present and responses on this lever result in no consequences, but are recorded as an index of motor activity. This procedure has been

recently established employing alcohol as the reinforcer, and it has been used to determine the role of SigR in alcohol seeking behavior (Blasio et al. 2015). The selective Sig-1R antagonist BD1063 (3–30 mg/kg) systemically administered was shown to be able to dramatically and dose dependently reduce alcohol seeking behavior. All doses of BD1063 tested significantly decreased the number of lever presses and importantly BD1063 did not affect responding on the inactive lever, ruling out an overall behavioral suppression.

Altogether, these data suggest that the ability of alcohol-associated cues to induce seeking behavior involves the activation of Sig-1R.

8 Sigma Receptors and Cognitive Impairment During Alcohol Withdrawal

Withdrawal from chronic consumption of alcohol is characterized by a plethora of physical, motivational, cognitive, and emotional symptoms (Pitel et al. 2007; Beatty et al. 1995; McKeon et al. 2008; Koob 2003). Withdrawal symptoms can be unpleasant and intense, and can develop from several hours to a few days after the cessation (or reduction) of heavy and prolonged alcohol use; while certain symptoms may be short lasting, others can persist for months and contribute to relapse (Koob 2000, 2003; American Psychiatric Association 2013).

The impairment in cognitive function is a symptom associated with chronic alcohol exposure withdrawal (Beatty et al. 1995; Pitel et al. 2007), and has been demonstrated to involve the Sig-1R system (Meunier et al. 2006; Sabeti 2011; Sabeti and Gruol 2008). In a study conducted by Meunier and colleagues, mice were shown to develop cognitive dysfunction in a novel object recognition task, during a 16-day withdrawal period which followed 4 months of chronic alcohol consumption. In this task, mice were tested for their ability to habituate to familiar objects, to correctly locate familiar object in different spatial locations, and to recognize familiar vs. novel objects. Alcohol-withdrawn mice showed increased locomotion, anxiety, and object exploration, which impeded correct reaction to object habituation, spatial change, and novelty. Importantly the authors showed that treatment with either a nonselective Sig-1R agonist (igmesine) or a Sig-1R antagonist (BD1047) restored correct reactions to spatial change and novelty in mice (Meunier et al. 2006). In addition, these mice had upregulated Sig-1R expression in the hippocampus, which was attenuated following repeated administration of either Sig-1R ligand, suggesting that the increase in hippocampal Sig-1R levels may mediate the ethanol withdrawal-induced cognitive impairments (Meunier et al. 2006).

In addition, it was shown using slice electrophysiology that withdrawal from chronic intermittent ethanol vapors during adolescence significantly alters long-term potentiation in the hippocampus via a Sig-1R-related mechanism (Sabeti and Gruol 2008; Sabeti 2011). In a first study, authors examined how chronic ethanol exposure during adolescence affects long-term potentiation (LTP) mechanisms in the hippocampus (Sabeti and Gruol 2008). The study shows that the selective Sig-1R antagonist BD1047 blocked a slow-developing NMDAR-independent LTP in excitatory CA1 synapses in hippocampal slices at 24 h after CIE vapor exposure. In addition, in alcohol-withdrawn early-adolescent animals, authors

observed a Sig-1R-dependent increased presynaptic function during NMDAR-independent LTP induction.

In a second study, the same authors found that, in slices obtained from adolescent rats exposed to chronic intermittent alcohol, CA1 neurons responded to the induction of large-amplitude LTP stimulations with a reduced excitability during ethanol withdrawal compared to slices obtained from ethanol-naïve rats. Importantly these impairments, which manifested as decreased spike efficacy and impaired activity-induced field excitatory postsynaptic potential-to-spike (E-S) potentiation, were normalized by the Sig-1R antagonist BD1047. These data suggest that acute ethanol withdrawal recruits Sig-1Rs, which in turn act to depress the efficacy of excitatory inputs in triggering action potentials during LTP.

9 Concluding Remarks

As reviewed above, there is growing evidence that the Sig-1R system may represent a novel target for the pharmacological treatment of alcohol-use disorders. Sig-1R antagonists have proven effective in reducing excessive alcohol drinking and alcohol seeking behavior in multiple animal models, suggesting that Sig-1R activation mediates the susceptibility to drink high quantities of alcohol. However, the exact mechanisms through which the Sig-1R system influences the actions of alcohol are still not entirely clear. Therefore, mechanistic studies aimed at understanding the interaction between the Sig-1R system and alcohol are warranted to improve our understanding of the neurobiological bases of alcoholism and help develop novel therapeutic options for this disorder.

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