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Review

Review

Recent Advances in the Potential of Positive Allosteric Modulators of the $GABA_B$ Receptor to Treat Alcohol Use Disorder

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Abstract

Aims: The effects of alcohol on gamma-aminobutyric acid (GABA) transmission are key for the development and maintenance of alcohol use disorder (AUD). Previous research consistently indicates that $GABA_B$ receptor agonists such as baclofen can attenuate addiction-related behaviors in preclinical models of AUD. More importantly, baclofen has also shown promise in clinical studies, particularly in severely alcohol-dependent patients. However, despite this promise, other clinical studies have not confirmed its efficacy and chiefly, larger clinical trials have not been conducted. Therefore, with the exception of France, baclofen is not approved for the treatment of AUD in any other country. Furthermore, it is also important to keep in mind that some patients treated with baclofen may experience important side-effects, including sedation, drowsiness and sleepiness.
Methods: This short review will first discuss the history of baclofen for AUD treatment. We will then summarize preclinical behavioral results that have investigated the efficacy of $GABA_B$ PAMs for addiction treatment, with a special focus on our recent work that investigated the effects of ADX71441, a novel $GABA_B$ PAM, on several alcohol-related behaviors in rats that model important aspects of human AUD. Finally, in light of the recent criticism about the translational value of animal models of addiction, the specific translational potential of our work and of other preclinical studies that have unanimously reported the efficacy of $GABA_B$ PAMs to attenuate multiple alcohol-related behaviors will be discussed.
Results: Positive allosteric modulators (PAMs) of the $GABA_B$ receptor offer an attractive alternative approach to baclofen and have the potential to achieve mechanistic and therapeutic effects similar to $GABA_B$ agonists, while avoiding the tolerance and toxicity issues associated with baclofen. To date, all preclinical behavioral results have invariably shown the efficacy of $GABA_B$ PAMs for addiction treatment.
Conclusions: Preclinical studies indicate that $GABA_B$ PAMs have a higher therapeutic index than orthosteric agonists, at least in terms of mitigating the sedative effects of $GABA_B$ agonism. This predicts that $GABA_B$ PAMs have a high translational potential in humans and merit being tested clinically, in particular in patients with severe AUD.

Excessive alcohol use remains a major cause of mortality and morbidity worldwide (Nutt *et al.*, 2010; Whiteford *et al.*, 2013). Strikingly, the harm from alcohol even exceeds that from illicit drugs such as heroin or cocaine (due to much greater prevalence of use) (Nutt *et al.*, 2010). Although pharmacotherapies exist that produce major clinical benefits in other addictions (Kakko *et al.*, 2003; Amato *et al.*, 2005),

medications for alcohol use disorder (AUD) are few (naltrexone, nalmefene, acamprosate, disulfiram), have limited efficacy, and have not been broadly adopted in clinical practice, making discovery of new therapeutics key to addressing extensive, currently unmet medical needs.

Gamma aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the brain (Sivilotti and Nistri, 1991; Bormann, 2000) is key for the development and maintenance of drug addiction. The synaptic actions of GABA are mediated by two major classes of receptors: the ionotropic receptors $GABA_A$ and $GABA_C$, which selectively increase chloride conductance, and the metabotropic receptors ($GABA_B$), which increase potassium conductance (Dutar and Nicoll, 1988; Bormann, 2000). $GABA_B$ receptors in particular have been long proposed as a potential candidate target for clinical treatment of addiction (Brebner *et al*., 2002; Cousins *et al*., 2002; Heilig and Egli, 2006; Addolorato *et al*., 2009).

The orthosteric $GABA_B$ receptor agonist baclofen, clinically used to treat spasticity, has, for example, been shown to attenuate the reinforcing properties of cocaine and the motivation to self-administer this drug in rodents (Roberts *et al*., 1996; Roberts and Andrews, 1997). Baclofen also dose-dependently decreases morphine-, cocaine- and nicotine-induced dopamine release in the nucleus accumbens shell (Fadda *et al*., 2003). However, the most extensive data for involvement of $GABA_B$ receptor in drug addiction are available for alcohol-related behaviors.

SUPPRESSING EFFECT OF BACLOFEN IN ANIMAL MODELS OF ALCOHOL ADDICTION

Perhaps, the first evidence of a potential role of $GABA_B$ receptors in mediating alcohol-related behaviors was reported in Göteborg, Sweden, by the group of Arvid Carlsson in 1976. In a study conducted in mice, the authors showed that an acute injection of a dose of 5 mg/kg of baclofen (intraperitoneally, i.p.) suppressed alcohol-induced locomotor stimulation (Cott *et al*., 1976). It was also able to influence dopamine metabolism in the striatum and limbic regions as baclofen initially stimulated the synthesis of 3,4-dihydroxyphenylalanine, the precursor of dopamine, followed by a significant decrease after 2.5 h. Ten years later, Daoust *et al*. (1987) found that baclofen but not muscimol (a $GABA_A$ receptor agonist) decreased voluntary consumption of alcohol in a two-bottle choice paradigm, suggesting a selective role of the metabotropic $GABA_B$ receptors in modulation of alcohol intake.

Following these seminal studies, numerous reports emerged in the mid-2000s providing further support for the notion that baclofen may be a candidate medication for AUD treatment. For instance, baclofen was shown to reduce alcohol operant self-administration and motivation for alcohol in non-dependent rats (Anstrom *et al*., 2003; Janak and Gill, 2003), dependent rats (Walker and Koob, 2007) as well as selectively bred strains of alcohol-preferring rats (Maccioni *et al*., 2005; Liang *et al*., 2006). In addition, baclofen prevented the acquisition of alcohol drinking behavior (Colombo *et al*., 2002) and suppressed extinction responding for alcohol in Sardinian alcohol-preferring rats (sP) (Colombo *et al*., 2003). The initial Swedish discovery that baclofen was able to suppress alcohol-induced locomotor stimulation was also confirmed and extended by several studies performed in alcohol-preferring rats (Quintanilla *et al*., 2008) and different lines and strains of mice (Humeniuk *et al*., 1993; Shen *et al*., 1998; Broadbent and Harless, 1999; Chester and Cunningham, 1999; Boehm *et al*., 2002; Holstein *et al*., 2009).

EFFECTS OF BACLOFEN IN CLINICAL STUDIES

Following initial validation in preclinical models, baclofen has also shown promising, although conflicting, results in clinical studies, in particular in patients with severe AUD. The first evidence that baclofen showed efficacy in humans was reported in an open-label study conducted in Italy by Addolorato *et al*. (2000). It included 10 alcohol-dependent patients who received baclofen (but no placebo group) administered orally for 4 weeks (at a dose of 15 mg/kg for the first 3 days, followed by an increased dose of 30 mg/day for the remaining 27 days of treatment) and found that the drug substantially reduced alcohol craving and alcohol drinking, up to complete abstinence throughout the experiment for seven patients. A follow-up study concluded that administration of low baclofen doses (30 mg/day) rapidly suppressed severe symptoms of alcohol withdrawal syndrome (Addolorato *et al*., 2002b). A randomized controlled trial (RCT) investigated in parallel the efficacy of baclofen to suppress drinking over a month in 39 alcohol-dependent subjects (Addolorato *et al*., 2002a) and found that baclofen reduced alcohol intake and craving. A case report that followed attracted considerable scientific and media attention on the potential of baclofen to treat AUD (Ameisen, 2005). Olivier Ameisen, a French physician, described how, after using all the available AUD medications with no success, he self-treated his own AUD using high dosage of baclofen (270 mg/day, nine times higher the dose used in previous trials). Ameisen (2005) reported a complete and prolonged abstinence and suppression of craving for alcohol. Due to somnolence, he progressively reduced the baclofen dose to 120 mg/day, a dose that permitted him to control his comorbid anxiety disorder. Finally, an ambitious RCT in severely alcohol-dependent patients with liver disease extended these observations and found that baclofen more than doubled the proportion of participants who achieved abstinence and maintained it for the 12-week duration of the study (Addolorato *et al*., 2007).

In marked contrast, an RCT conducted in the USA (Garbutt *et al*., 2010) was negative and did not find any difference between baclofen and placebo on the percentage of heavy drinking days, time to first drink or time to relapse. A possible reason for this apparent discrepancy is that the Italian study recruited patients with more severe AUD (14 mean daily drinks versus seven in the American study), which suggests that baclofen may be more efficacious in heavily dependent patients (Leggio *et al*., 2010). In an RCT conducted in veterans with chronic hepatitis C, baclofen did not improve the percentage of days of abstinence (Hauser *et al*., 2017), and several studies have also reported negative data (Krupitsky *et al*., 2015; Beraha *et al*., 2016; Reynaud *et al*., 2017).

Finally, two recent RCTs were in agreement with the Italian study and reported beneficial effect of baclofen. The first one, conducted in Australia, recruited a total of 104 severely alcohol-dependent patients (average level of 15 drinks by drinking day), both with and without liver disease (Morley *et al*., 2018). Baclofen treatment significantly reduced the time to lapse and relapse, while increasing the percentage of days of abstinence. The Bacloville study, conducted in France, recruited 320 patients throughout 62 primary care centers and aimed to test the efficacy of titrated baclofen for achieving low-risk alcohol consumption (Rigal *et al*., 2020). Baclofen was more effective than placebo in reducing daily alcohol consumption and increasing the number of abstinence days.

WHAT IS WRONG WITH BACLOFEN THEN?

Despite promising results in both preclinical models and clinical trials, baclofen itself has inherent limitations as a therapeutic for

alcohol addiction and is not approved for this indication by the relevant authorities (European Medicines Agency and the Food Drug Administration), with the noticeable recent exception of France. In October 2018, the French Medicines Agency authorized the use of baclofen to treat AUD under certain conditions (Rolland *et al*., 2019), namely, '... following failure of other available medical treatments in adults with alcohol dependence and high-risk alcohol consumption (>60 g/day for men or >40 g/day for women)', with a maximum authorized dose that should not exceed 80 mg/day.

First, contrary to the preclinical data, the clinical literature is overall conflicting, as evidenced by meta-analysis and systemic reviews aimed at examining the efficacy of baclofen for AUD treatment. These have yielded mixed results, but they were completed before these two recent RCTs (Leggio *et al*., 2010; Agabio and Leggio, 2018; Minozzi *et al*., 2018; Palpacuer *et al*., 2018). Consequently, in 2018, a panel of international experts met in Cagliari and reached a consensus statement that concluded that, 'baclofen remains a promising pharmacotherapy for AUD, however, baclofen's superiority versus placebo has not been established'. Current evidence indicates that the efficacy of baclofen is lower than that of already approved medications for AUD and further clinical trials are required (Agabio *et al*., 2018).

Second, another key reason baclofen has not been widely approved is that use of baclofen is limited by side effects. For example, in preclinical work, although baclofen successfully reduced alcohol self-administration in C57BL/6 J mice, doses that suppressed the reinforcing effects of alcohol also suppressed locomotor activity and potentiated the sedative properties of alcohol, even at alcohol doses that were not sedative per se (Besheer *et al*., 2004). In a clinical trial in cocaine-abusing male patients, baclofen administration was associated with headache, nausea, sedation and dizziness (Ling *et al*., 1998). Chronic administration of baclofen frequently results in tolerance to its effects because baclofen is an orthosteric agonist and, therefore, necessitates dose escalation (de Beaurepaire, 2014; Muller *et al*., 2015). The tolerance patients develop in response to baclofen heighten an already high risk for lethal intoxication that has also increased as its off-label prescription for AUD has grown (Leger *et al*., 2017). Notably, the Bacloville study also found that baclofen group had a greater number of serious adverse effects reported, mostly, drowsiness, fatigue and insomnia (85 versus 36 for placebo (Rigal *et al*., 2020)).

POSITIVE ALLOSTERIC MODULATORS: A UNIQUE OPPORTUNITY

To overcome these limitations, positive allosteric modulators (PAMs) were developed as an alternative pharmacological approach to targeting the same mechanism. In the early 2000s, the first *in vivo* PAMs of the $GABA_B$ receptors, CGP7930 and its close analog CGP13501, were synthetized at Novartis in Switzerland (Urwyler *et al*., 2001). PAMs indeed exert their effects on $GABA_B$ receptors through allosteric binding to a site that is topographically distinct from that bound by the endogenous ligand (orthosteric site) (May and Christopoulos, 2003; Conn *et al*., 2009). Upon binding, PAMs lack intrinsic activity and act by potentiating the signaling only when the endogenous ligand (GABA) activates the receptor. This mechanism offers several advantages over orthosteric agonists, and it was expected that PAMs would retain the positive and anti-addictive properties of the $GABA_B$ receptor agonists, while producing less of their undesirable, adverse effects.

It did not take long before the alcohol research community tested this exciting hypothesis. In 2005, the group led by Giancarlo Colombo in Cagliari (Italy) was the first to test the effect of two of these newly synthetized $GABA_B$ PAMs, CGP7930 and GS39783 (Urwyler *et al*., 2003; Orru *et al*., 2005), on acquisition and maintenance of alcohol drinking in selectively bred sP. Using a two-bottle choice paradigm, the authors found that repeated, daily administration of both $GABA_B$ PAMs dose-dependently prevented the acquisition and maintenance of alcohol drinking in alcohol-naïve sP rats, although this was more pronounced with acquisition of drinking. These results were replicated and extended to other preclinical models of AUD in subsequent studies.

EFFECTS OF GABAB PAMS ON PRECLINICAL MODELS OF EXCESSIVE AND RELAPSE-LIKE DRINKING

Several $GABA_B$ PAMs have also been tested on animal models of excessive drinking and binge drinking. Chronic treatment (once daily for 7 consecutive days) with rac-BHFF potently reduced alcohol intake (by 65% at the highest dose of 200 mg/kg (Loi *et al*., 2013). ADX71441, a novel $GABA_B$ PAM that had entered Phase 1 clinical testing, decreased alcohol intake in two different rodent models of binge drinking, the drinking-in-dark (DID) and intermittent access paradigms (Hwa *et al*., 2014), with no effect on water drinking. Interestingly, ADX71441 potently decreased binge-like drinking throughout the whole 4 h of the DID procedure, whereas naltrexone (used as a clinically available positive control) only transiently, and to a lesser extent, reduced intake during the first hour of the DID. In agreement with this investigation, both rac-BHFF and ORM-27669 (a $GABA_B$ PAM with lower agonist efficacy that was recently identified) potently reduced alcohol intake in C57BL/6 J mice in the DID paradigm (de Miguel *et al*., 2019). In a four-bottle choice paradigm with unpredictable daily 1 h sessions that promoted escalation of alcohol intake, all three doses of GS39783 selectively reduced alcohol drinking in sP rats (Colombo *et al*., 2015).

Finally, $GABA_B$ PAMs have also been shown to efficiently reduce relapse-like drinking. The alcohol deprivation effect (ADE) describes a phenomenon typically observed in animals with a long-term exposure to alcohol that occurs when alcohol solutions are presented again following a period of deprivation (Sinclair and Senter, 1967). In their seminal paper, Sinclair and Senter (1967) exposed rats that had been previously drinking a solution of 7% alcohol for a month to several weekly periods of alcohol deprivation and found that rats, when they were given back access to alcohol on the following week, drank significantly more alcohol. However, this effect was transient and drinking levels returned to normal after a few days. The ADE has been proposed as a relevant model to study relapse-like drinking with good predictive validity as it has been pharmacologically validated using the clinically approved compounds acamprosate (Spanagel *et al*., 1996, 2014), naltrexone (Holter and Spanagel, 1999) and nalmefene (Foo *et al*., 2019). The novel $GABA_B$ PAM CMPPE (2-{1-[2-(4-chlorophenyl)-5-methylpyrazolo[1,5-a]pyrimidin-7-yl]-2-piperidinyl}ethanol) was found to potently and dose-dependently (10 and 30 mg/kg, i.p.) attenuate relapse-like alcohol drinking following repeated exposure to deprivation period of alcohol in Wistar rats (Vengeliene *et al*., 2018).

EFFECTS OF GABAB PAMS ON ALCOHOL SELF-ADMINISTRATION

In parallel to the Italian study that assessed the effects of CGP7930 on drinking, Liang *et al.* (2006) found that, similarly to baclofen, an acute treatment with 10 and 20 mg/kg CGP7930 (i.p.) dose-dependently decreased 10% alcohol self-administration in alcohol-preferring Indiana P rats trained on a fixed ratio 3 (FR3). In agreement with these data, an acute treatment with CGP7930 (in a dose range of 2.5–10 mg/kg i.p.) also reduced operant self-administration of a solution of 15% alcohol in sP rats under an FR4 schedule (Maccioni and Colombo, 2019). Pretreatment with GS39783 (25–100 mg/kg given orally) also dose-dependently decreased responding for alcohol in sP under the same regimen of reinforcement, without affecting responding for a medium concentration of 0.3% sucrose (Maccioni *et al.*, 2007). Both BHF177 (Maccioni *et al.*, 2009) and COR659 (Maccioni *et al.*, 2017) reduced responding and the motivation for alcohol as shown by reduced breakpoint in a progressive ratio (PR) schedule (Hodos, 1961). Finally, the novel $GABA_B$ PAM CMPPE dose-dependently (2.5–10 mg/kg, i.p.) decreased 15% alcohol self-administration under an FR5 schedule of reinforcement, as well motivation for alcohol in female sP rats (Maccioni *et al.*, 2019).

PRECLINICAL VALIDATION OF THE NOVEL GABAB PAM ADX71441

In a recent paper from our group, we investigated the effect of ADX71441 (see Fig. 1 for a summary of the data) on a battery of alcohol-associated behaviors that model important aspects of human AUD (Augier *et al.*, 2017a). We first tested the effect of ADX71441 on 20% alcohol operant self-administration in outbred Wistar rats (Augier *et al.*, 2014, 2017b), a widely used behavioral procedure for assessing the primary reinforcement value of a substance. We found that treatment with the $GABA_B$ PAM dose-dependently suppressed alcohol self-administration, as well as potently decreased the motivation of the animals to consume alcohol. This effect was robust in non-dependent rats as a dose of 10 mg/kg of ADX71441 attenuated responding by >80%. Importantly, this dose did not affect locomotor activity.

Of note, ADX71441 also potently decreased operant self-administration of 0.2% saccharin, a non-caloric sweetener. This indicates that the drug may act by decreasing the immediate reinforcing value rather than the caloric value of liquid reinforcers and is not specific to alcohol reinforcer. This point is interesting as it is probably the only aspect of the $GABA_B$ PAM literature that has shown discrepancies between studies. Although most studies have reported specific effects on alcohol reward compared with water or food controls, COR659, for example, also suppressed responding for a sucrose solution (1–3% w/v) in sP rats under an FR4 and PR schedules, responding for a chocolate solution (5% w/v) in Wistar rats under the FR10 and PR schedules, and cue-induced reinstatement of chocolate seeking in Wistar rats (Maccioni *et al.*, 2017). In addition, rac-BHFF but not GS39783 also decreased lever pressing for a solution of 1% w/v sucrose, although this was to a lesser extent than with alcohol (Maccioni *et al.*, 2015). Altogether, these results suggest that the $GABA_B$ PAMs tested so far may not all share a similar pharmacological profile. For example, it has been suggested that COR659 also interacts with cannabinoid CB1 receptors (Maccioni *et al.*, 2017).

Of particular relevance, we also found that rats with a history of dependence showed increased sensitivity to suppression of alcohol self-administration by ADX71441. Using chronic intermittent alcohol vapor exposure, an established rat model in which repeated cycles of alcohol intoxication and withdrawal induce dependence and lead to neuroadaptations that persist past acute withdrawal (Rogers *et al.*, 1979), we observed that the dose of ADX71441 required to significantly affect responding for alcohol in non-dependent animals was 3 mg/kg, whereas a dose of 1 mg/kg was sufficient in animals with a history of dependence. This result is important as it may help explain the apparent discrepancy between the two major RCTs that investigated the efficacy of baclofen to treat AUD (Addolorato *et al.*, 2007; Garbutt *et al.*, 2010) and support the hypothesis that $GABA_B$ PAMs may be more efficient in severely dependent patients.

A critical challenge with human patients that have achieved abstinence is to prevent relapse, which can be triggered by drug-associated cues for example. It is estimated that >50% of newly abstinent AUD patients will relapse after 3 months (Hunt *et al.*, 1971). We therefore investigated the effect of the $GABA_B$ PAM on established preclinical models of relapse, namely extinction followed by cue- and stress-induced reinstatement of responding (Carroll and Comer, 1996). We found that treatment with ADX71441 suppressed reinstatement of alcohol seeking induced by both alcohol-predictive environmental (olfactory and visual) cues and exposure to a stressful event (intermittent footshock) in an animal model of relapse (Augier *et al.*, 2017a). In accordance with our findings, the novel $GABA_B$ PAM CMPPE also suppressed cue-induced alcohol seeking in both male (Vengeliene *et al.*, 2018) and female (Maccioni *et al.*, 2019) Wistar rats.

We further investigated the neural substrates through which ADX71441 suppresses stress-induced relapse to alcohol seeking by carrying out c-Fos mapping and identified a network consisting of the dorsal raphe nucleus, nucleus accumbens shell and medial prefrontal cortex within which activity was strongly correlated with responding during stress-induced reinstatement (Augier *et al.*, 2017a). Activity of this network accounted for >70% of the variance in reinstatement responding and was robustly suppressed by ADX71441, making this network a plausible neural substrate of ADX71441 activity to suppress stress-related relapse. Importantly, all these effects of ADX71441 are observed in the absence of significant sedative side effects. ADX71441 displays a 10-fold dose separation between specific behavioral effects and sedation, and therefore may have a better therapeutic index than baclofen for treatment of AUD.

CAN THESE RESULTS TRANSLATE TO PATIENTS?

Overall, $GABA_B$ PAMs merit being tested clinically since all $GABA_B$ PAMs tested to date on preclinical models of addiction have been shown to successfully attenuate alcohol-related behaviors and exert anti-addictive properties (Maccioni and Colombo, 2019). Despite these unanimously positive results, translating preclinical data to the clinic remains tricky and further validation may be needed before testing $GABA_B$ PAMs in a clinical situation. Even with significant progress and major advances in our understanding of the neurobiology of alcohol addiction, few preclinically validated findings have translated into clinically significant treatments (Heilig *et al.*, 2016a, 2016b). Promising targets that were identified in animal models of alcohol addiction, such as the corticotropin-releasing hormone 1

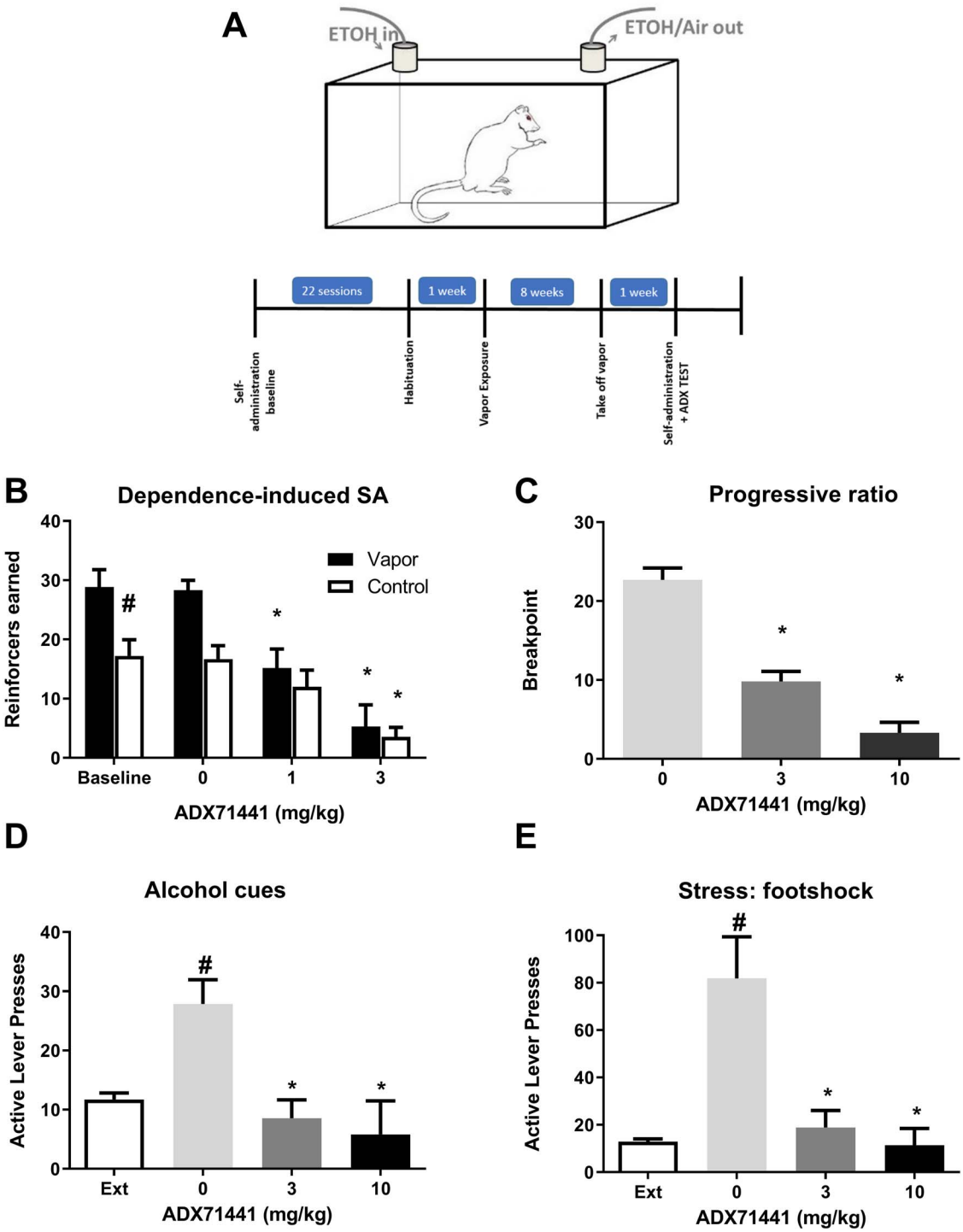

Fig. 1. ADX71441 strongly decreases a battery of alcohol-associated behaviors in rats A: Schematic representation of the vapor experiment **B**: Increased sensitivity to suppression of alcohol self-administration in rat-dependent-rat **C**: Potent reduction in motivation for alcohol **D**: ADX71441 blocks both cue-induced and stress-induced **E**: alcohol seeking. Adapted from Augier *et al*. (2017a) with permission.

receptor (also known as corticotropin-releasing factor 1), failed in clinical trials (Kwako *et al*., 2015; Schwandt *et al*., 2016; Shaham and de Wit, 2016), leading on one hand to increased criticism on the translational validity of animal models (Field and Kersbergen, 2020), but also on the other hand to the realization that research in model organisms may gain translational power from incorporating additional processes that are currently missing from most animal models (Ahmed, 2010; Heilig *et al*., 2016a).

AUD is indeed a complex disorder that cannot be solely defined as an excessive alcohol intake. It is more importantly characterized as a chronic relapsing disorder featuring compulsive alcohol use that is excessive and difficult to control despite negative consequences

(Wagner and Anthony, 2002). A critical problem in current addiction research is therefore to understand the transition between controlled and compulsive alcohol use, a hallmark feature of addiction. Importantly, only a small subset of users makes this transition to pathological drug abuse (Anthony, 2002; Grant *et al*., 2015). In marked contrast, in the operant self-administration paradigm (Weeks, 1962), a model that is the gold standard to assess in animals the reinforcing properties of drugs that are abused by humans, most rats will learn to produce instrumental responses in order to voluntarily administer addictive drugs and individual variation is often treated as random experimental error. Another limitation of most animal models of addiction is the fact that the availability of alternative non-drug rewards has been so far largely overlooked in studies investigating the neural substrates of addiction processes (Ahmed, 2010). The development of drug addiction is characterized by a shift in decision making, in which drugs become increasingly chosen over healthy rewards. Despite this, these factors have, with few exceptions, not been incorporated into neurobiological studies of drug addiction.

These points to the possibility that, focusing on self-administration alone, in the absence of healthy alternatives and at a group level, may not be optimal to identify crucial aspects of addiction (Robinson, 2004; Ahmed, 2010). Important advances and attempts to improve these shortcomings have recently been made in the addiction field. For instance, using a multicriteria-based approach, Deroche-Gamonet *et al*. (2004) have shown that rats self-administering cocaine during a prolonged period of 3 months developed behavioral traits that resemble three important criteria used to diagnose addiction in humans. Using a mutually exclusive choice procedure, the Ahmed group has shown that most rats trained to self-administer cocaine under extended access to the drug will abstain from cocaine when a valuable behavioral option is available, but that a subset of these animals keeps injecting the drug despite the opportunity to engage in an alternative and valuable behavior (Lenoir *et al*., 2007; Cantin *et al*., 2010). Interestingly, in both approaches, only a minority of animals developed an addiction-like phenotype, suggesting that focusing on this minority of animals could provide a better strategy to unlock the molecular mechanisms specific to drug addiction versus mere self-administration (Robinson, 2004; Ahmed, 2010).

IMPAIRED GABAERGIC TRANSMISSION IN PATHOLOGICAL ALCOHOL CHOICE

In a recent investigation, we therefore aimed to incorporate these aspects into a preclinical of alcohol addiction in order to investigate the molecular mechanisms underlying the choice of alcohol over an alternative reward (Augier *et al*., 2018). Using a discrete, mutually exclusive choice model, we screened over 600 rats for their choice behavior (Fig. 2) and found that, in accordance with previous work with other drugs of abuse (Cantin *et al*., 2010; Lenoir *et al*., 2013; Caprioli *et al*., 2015; Huynh *et al*., 2017), most of them, after having self-administered 20% alcohol for months, quickly stopped responding for the drug when they were given access to a potent alternative reward, a sweet solution of saccharin. However, about 15% of outbred rats choose alcohol over an alternative high-value reward, a rate similar to human alcohol addiction (Grant *et al*., 2015). In addition, alcohol-choosing rats showed traits reminiscent of clinical addiction (Deroche-Gamonet *et al*., 2004), such as high motivation to obtain alcohol as measured using a PR schedule (Hodos, 1961), and pursuit of alcohol despite adverse consequences (namely, an electric footshock contingently delivered with alcohol or alcohol adulteration with increasing concentrations of the bitter tastant, quinine).

Following the behavioral characterization of alcohol-choosing animals, we pursued a molecular discovery effort to investigate the processes in this minority of vulnerable individuals that promote choosing alcohol over a potent alternative reward in the context of developing addiction. Using a custom NanoString nCounter panel (Geiss *et al*., 2008) that contains around 400 transcripts previously hypothesized to be involved in drug addiction, we performed a differential gene expression screen and found minimal evidence for changes in gene expression between alcohol choosing versus non-choosing rats in several of the brain regions analyzed (including the nucleus accumbens, caudate–putamen, prelimbic and infralimbic prefrontal cortex as well as hippocampus). By contrast, we identified around 40 genes, including a GABAergic pathway, that were markedly dysregulated in the central amygdala (CeA) of alcohol-choosing rats. In particular, expression of the GABA transporter GAT-3 (*Slc6a11*) in this structure was down-regulated by >50%, accompanied by similarly down-regulated transcripts encoding several $GABA_A$ receptor subunits as well as other transporters of GAT family (GAT-1, *Slc6a1*; GAT-2, *Slc6a13*; GAT-3, *Slc6a11*; and BGT-1, *Slc6a12*). Low-GAT-3 transcript levels resulted in decreased expression of the transporter at the protein level, as well as elevated inhibitory GABA-tone due to impaired clearance of extracellular GABA by the transporter, as confirmed using slice electrophysiology. In agreement with this finding, we also observed higher anxiety-like behavior in alcohol-choosing animals.

In addition, a viral vector-mediated knockdown of GAT-3 in CeA of non-choosing rats markedly promoted their choice of alcohol over the alternative reward, converting saccharin-choosing rats into alcohol-choosing rats *in vivo*. This demonstrates a causal role of GAT-3 for alcohol choice. Finally, to assess whether these results may have translational relevance, we carried out an RNA-seq transcriptome analysis in *post mortem* brain tissue from patients with AUD and controls. GAT-3 expression was selectively decreased in CeA of patients with AUD compared with those who died of unrelated causes, which indicate that our findings may translate to humans.

DISCUSSION AND CONCLUSION

Altogether, our findings identified neuroadaptations affecting GABA signaling with the CeA as a causal contributing factor to the transition to alcohol addiction. Furthermore, they point to impaired GABA clearance within CeA as a molecular mechanism associated with core traits of addiction, which appears to translate between species and may offer targets for novel pharmacotherapies to treat AUD. As a direct follow-up, rescuing impaired GABA clearance due to suppressed GAT-3 expression indeed appears to be a strong candidate for a potential therapeutic mechanism in alcohol addiction. Directly targeting the GABA transporter will however require normalizing its expression or developing positive modulators of the transporter, which remains uncertain and requires years of additional work.

An alternative approach would be to evaluate existing drugs that normalize impaired GABAergic transmission through other mechanisms, as suggested by recent observations that presynaptic $GABA_B$ receptors such as baclofen inhibit GABA release within the CeA (Delaney *et al*., 2018). This offers an unexpected convergence with our previous work that investigated the effect of ADX71441 on

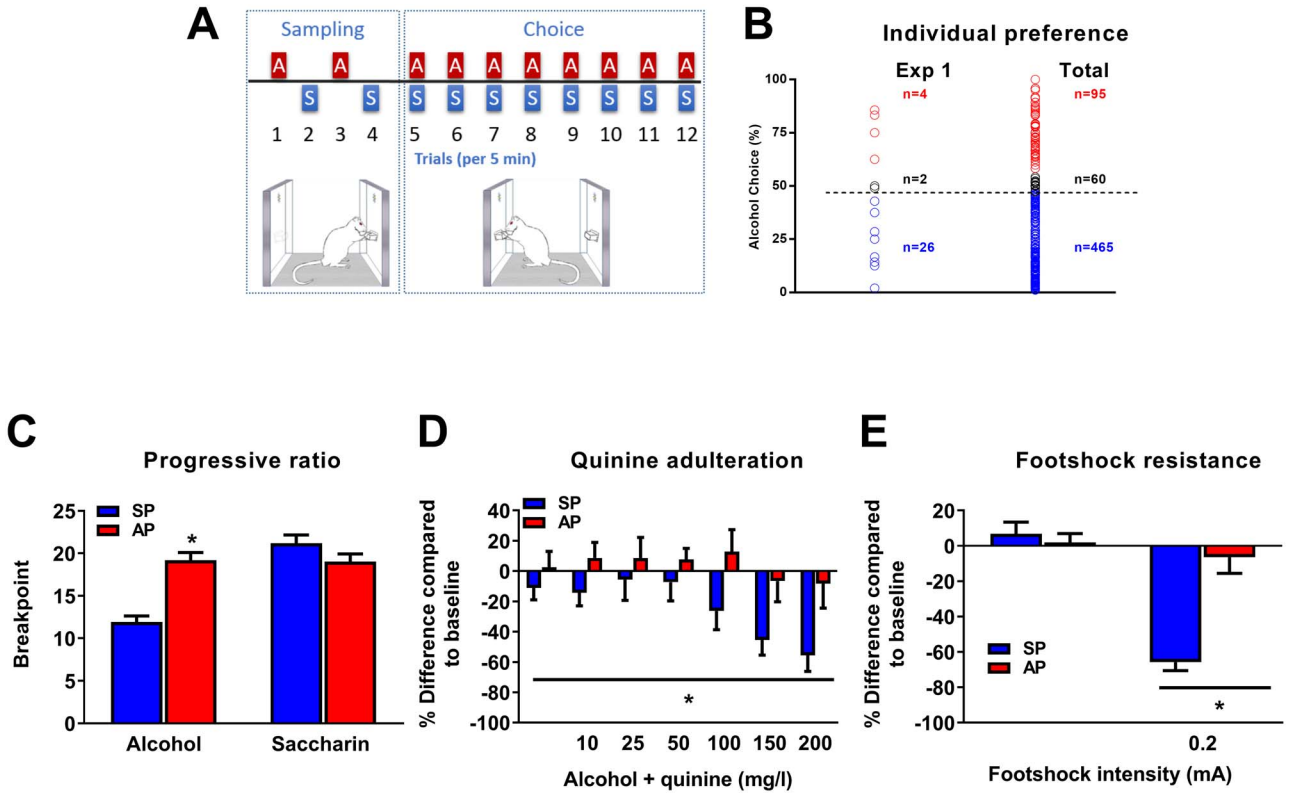

Fig. 2. Alcohol-choosing rats exert a constellation of addiction like A: Schematic representation of the discrete choice procedure **B**: Individual distribution **C**: Specific elevated motivation to obtain alcohol, but not saccharin in alcohol-choosing rats **D**: Compulsive alcohol drinking in alcohol-choosing rats, shown by resistance to quinine adulteration of the alcohol solution **E**: Compulsive alcohol drinking, shown by resistance to footshock. Adapted from Augier *et al.* (2018) with permission.

several alcohol-related behaviors (Augier *et al.*, 2017a), as it should be expected that the same mechanistic and therapeutic effect could also be achieved by $GABA_B$ PAMs. In agreement with this hypothesis, we found in preliminary data that treatment with ADX71441 potently, dose-dependently and selectively normalizes choice preference in the minority of rats that choose alcohol over a sweet reward, without affecting choice preference in saccharin-preferring animals (Augier and Heilig, unpublished results). We are currently working on replicating this preliminary finding with a larger population and extending it to female animals.

In conclusion, at the preclinical level, all $GABA_B$ PAM studies to date have consistently reported that $GABA_B$ PAMs exert 'anti-alcoholic' and therapeutic effects, retaining the efficacy of baclofen on a variety of alcohol-related behaviors that mimic several important features of human addiction. Furthermore, as expected from their respective mechanisms of action, $GABA_B$ PAMs have a higher therapeutic index than orthosteric agonists, at least in terms of mitigating the sedative effects of $GABA_B$ agonism. Most studies have reported a selective reduction of alcohol-related behaviors with no or little effect on other non-drug reinforcers, an effect that is achieved at doses that do not produce sedative effects or other locomotor impairment. Altogether, this predicts that $GABA_B$ PAMs have a high translational potential in humans and merit being tested clinically, in particular in patients with severe AUD. To our knowledge, at least two $GABA_B$ PAMs, ADX71441 and ODM-106, have entered the initial phases of clinical testing. Unfortunately, Addex Therapeutics recently announced that they will stop further clinical evaluation of ADX71441, but will continue, in collaboration with Indivior PLC, to work on the development of novel $GABA_B$ PAMs compounds that may progress to the clinic (Addex Therapeutics, 2019).

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CONFLICT OF INTEREST

None declared.

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