

Acamprosate: Recent Findings and Future Research Directions

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This article explores the mechanisms of action and the potential responder profile of acamprosate, a compound efficacious in relapse prevention of alcoholism. New evidence at the molecular and cellular level suggests that acamprosate attenuates hyper-glutamatergic states that occur during early abstinence and involves ionotropic (NMDA)- and metabotropic (mGluR5) glutamate receptors along with augmented intracellular calcium release and electrophysiological changes. Thus mutant mice with enhanced glutamate levels exhibit higher alcohol consumption than wild type mice and respond better to acamprosate, demonstrating that acamprosate acts mainly on a hyper-glutamatergic system. This mode of action further suggests that acamprosate exhibits neuroprotective properties. In rats, cue-induced reinstatement behavior is significantly reduced by acamprosate treatment whereas cue-induced craving responses in alcohol-dependent patients seem not to be affected by this treatment. An ongoing study ("Project Predict") defines specific responder profiles for an individualized use of acamprosate and naltrexone. Neurophysiological as well as psychometric data are used to define 2 groups of patients: "reward cravers" and "relief cravers". While naltrexone should work better in the first group, acamprosate is hypothesized to be efficacious in the latter where withdrawal associated and/or cue induced hyper-glutamatergic states are thought to trigger relapse. Further research should target the definition of subgroups applying endophenotypic approaches, e.g. by detecting a hyperglutamatergic syndrome using MR spectroscopy.

Key Words: Alcoholism, Acamprosate, Pharmacodynamics, Craving, Glutamate, Ethanol, Meta-Analysis.

ACAMPROSATE: MOLECULAR MECHANISMS IN RELAPSE PREVENTION AND NEUROPROTECTION

Structural Considerations

A CAMPROSATE IS THE calcium salt of *N*-acetyl homotaurine, a small, highly flexible molecule with similarities to many amino acids, most notably glutamate, gamma-aminobutyric acid, aspartate, glycine, and taurine (Spanagel and Zieglansberger, 1997). As all the amino acids cited are neurotransmitters and/or neuromodulators, most research on the mechanism of action of acamprosate has assumed that amino acid transmitters are involved. However, many structurally similar compounds function as anti-oxidant/free-radical scavengers, and it has been suggested that acamprosate has similar effects on oxygen free radicals during alcohol intoxication (Dahchour et al., 2005).

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Effects of Acamprosate on Glutamate and GABA Transmission

Given these many potential actions it has been very difficult to focus on a single mechanism of acamprosate, and this may reflect the reality. Thus, although most recent work has focused on the glutamatergic system, homotaurine is a known GABA(A) receptor agonist, and studies on neuronal networks *in vivo* suggest that acamprosate may have differential effects on glutamate/NMDA receptors at low concentrations, with effects on GABA(A) receptors at higher concentrations (Pierrefiche et al., 2004). Acamprosate may have different actions at different concentrations, or in different brain areas dependent on receptor distribution and/or subtype. The reason for the recent focus on glutamate results from early electrophysiological studies in cortical neurons which identified inhibitory effects of acamprosate on glutamate responses that were consistent with a weak NMDAR antagonism (Zeise et al., 1993). Radioligand binding studies suggested that acamprosate had weak partial agonist effects on NMDA receptors through indirect actions on a polyamine site on the NMDAR complex (Al Qatari et al., 1998; Naassila et al., 1998). Such a mechanism might enhance or inhibit NMDAR function depending on the local concentration of endogenous polyamines and/or the regional distribution of different subunits of the NMDAR. However, subsequent electrophysiological examination of NMDAR function at the molecular level suggested that direct interactions of acamprosate with the NMDA receptor at a polyamine, or any other site were

limited to a very small proportion of neurons studied (Popp and Lovinger, 2000). Rammes et al. (2001) reported weak effects of acamprosate (250 and 350 μM) on NMDAR subtypes (NR1a/2A and NR1a/2B) expressed in *Xenopus* oocytes or HEK-293 cells. However, acamprosate did produce similar increases in NR1 and NR2B receptor expression *in vivo* to those seen following acute treatment with NMDAR antagonists (Rammes et al., 2001). Moreover, a recently published study that injected *Xenopus* oocytes with cDNAs or cRNAs encoding several candidate receptors for acamprosates' action including (among others) mGluR1 and 5, GABA(A) receptors, and various combinations of alpha and beta subunits of voltage-gated Na^+ channels, failed to show direct modulating effects of acamprosate (0.1 to 100 μM) on electrophysiological responses of these receptors and ion channels (Reilly et al., 2008).

All these results in combination might argue that acamprosate produces changes in the brain that mimic the effects of NMDAR antagonism by some indirect mechanism. This does not exclude changes in GABA transmission, effects on other amino acids in the CNS, or effects on oxidation stress. Of course, the important question is which (if any) of these potential molecular mechanisms underlies the anti-relapse action of acamprosate.

Neuroprotective Effects of Acamprosate

In cultures/fetal rat neocortical neurons, a model that has been used very commonly in studies of NMDAR-mediated neurotoxicity, increased glutamate-induced toxicity and Ca^{2+} entry occurs during withdrawal from ethanol *in vitro* (Al Qatari et al., 2001), as found by other workers. Acamprosate significantly, and concentration-dependently, inhibited the excess toxicity and Ca^{2+} entry associated with ethanol withdrawal. The neuroprotective effect of the drug was significantly greater than in control cultures (Al Qatari et al., 2001). Because glutamate was used as the stimulus in this model, and because mGluRs can modulate NMDAR function, protection against neurotoxicity by acamprosate could be produced either by an action on mGluRs (indirectly modulating NMDAR function) or by direct inhibition of NMDAR function. However, the slope of the relation between Ca^{2+} entry and neurotoxicity in the presence of acamprosate differed markedly from that obtained when NMDAR antagonists were used during ethanol withdrawal (Al Qatari et al., 2001). This suggests that acamprosate does not interact directly with the NMDAR in the same way that conventional antagonists do.

In a more complex model utilizing organotypic hippocampal cell cultures obtained from the neonatal rat, it is possible to obtain excitotoxicity during ethanol withdrawal in the absence of exogenous application of glutamate or NMDA. Thus the CA1 region of the culture (which is most susceptible to excitotoxic damage) can be shown to take up propidium iodide (PI) an index of neuronal damage, after medium change (Mayer et al., 2002a,b) or after ethanol withdrawal

into low Mg^{2+} buffer (10). In both cases the toxicity is believed to be a consequence of release of endogenous glutamate, resulting in activation of NMDARs, with flux of excess Ca^{2+} through NMDARs being the neurotoxic insult. Acamprosate inhibits the neurotoxicity, and Ca^{2+} entry, produced by both stimuli, i.e. medium change and ethanol withdrawal (Mayer et al., 2002a,b). However, the same concentration of acamprosate that inhibited withdrawal-induced neurotoxicity had no significant effect on the excess toxicity, or $^{45}\text{Ca}^{2+}$ entry, induced by NMDA either in control cultures or during withdrawal (Mayer et al., 2002a,b). This suggests that the inhibitory effects of acamprosate on withdrawal are not caused by a direct inhibitory effect on NMDARs (whether or not these NMDARs have been modified by chronic ethanol exposure). In contrast, acamprosate inhibited the neurotoxic effects of the mGluR agonist, trans-ACPD (Harris et al., 2002). ACPDs toxicity was increased during ethanol withdrawal (Harris et al., 2003) and this enhanced toxicity was inhibited by acamprosate (Harris et al., 2003). These results strongly suggest that, in this model, acamprosate is neuroprotective in ethanol withdrawal by causing indirect inhibition of NMDA receptors, and that some action on mGluRs is a strong candidate for the mechanism.

As acamprosate closely mimicked the effect of the relatively selective mGluR5 antagonist, SIB1893, in organotypic cultures where both inhibit ethanol withdrawal-induced toxicity and trans-ACPD toxicity, but not NMDA-induced toxicity (Harris et al., 2003), the neuroprotective effects of acamprosate may be explicable by an effect on mGluR5s, but this is not certain and other actions of acamprosate, including anti-oxidant effects (Dahchour et al., 2005) cannot be excluded.

Other Possible Pathways of Action of Acamprosate

With regard to studies on both animals and humans during alcohol dependence, acamprosate has been reported to prevent changes plasma in beta-endorphins (Kiefer et al., 2006; Zalewska-Kaszubska et al., 2005) that are associated with dependence. In addition, acamprosate prevented increases in leptin that were associated with craving and relapse during abstinence (Kiefer et al., 2005). These changes in plasma hormones may underlie effects of acamprosate in relapse; however, the exact mechanism of interaction of acamprosate with these hormones remains to be elucidated and may possibly reflect an epiphenomenon to an alteration in other transmitters in the CNS. The widespread distribution of amino acids and the structural similarities between acamprosate and amino acids suggests that molecular effects on amino acid receptors could explain these effects on circulating hormones, but this is conjecture. Similarly, acamprosate treatment has recently been reported to alter the characteristics of dopamine transmission in the mesolimbic system (Cano-Cebrián et al., 2003; Cowen et al., 2005). This is potentially very important in modifying the reinforcing effects of alcohol during relapse. The well-known intimate connections between glutamate

and NMDA receptors with dopaminergic neurons in the ventral tegmental area (Kauer and Malenka, 2007) makes actions on glutamate receptors a firm possibility, but other mechanisms (e.g., glutamate receptors onto dopaminoceptive neurons) cannot be excluded. New conditional mouse models with specific NMDA receptor deletion in either dopaminergic (Cre-recombinase controlled by the promoter of the dopamine transporter – DAT) or dopaminoceptive neurons (Cre-recombinase controlled by the promoter of the dopamine D1 receptor) have recently been generated (Lemberger et al., 2007; Parlato et al., 2006). In addition, a selective genetic deletion of mGluR5 receptors in dopaminoceptive neurons can be also achieved by this novel approach. These mouse models will be extremely helpful to elucidate the action of acamprosate and to get a better functional understanding of glutamate/dopamine interactions within the reinforcement system.

Behavioral Effects of Acamprosate in Animal Models

Different behavioral components of alcohol dependence can be modeled in experimental animals. For example, relapse-like drinking behavior and compulsive alcohol consumption can be assessed using a long-term alcohol self-administration model with repeated deprivation phases (Sanchis-Segura and Spanagel, 2006). The effect of acamprosate in this model has been evaluated. The results show that acamprosate completely abolishes relapse-like drinking behavior (Spanagel and Zieglgansberger, 1997).

The effects of acamprosate have also been tested in the “cue-induced reinstatement model” (Sanchis-Segura and Spanagel, 2006). In this model, rats are trained to lever press to receive either ethanol or water in response to olfactory cues during a first conditioning phase. Once stable response rates have been achieved, lever pressing behavior is extinguished by absence of cues and reward in a second experimental phase (extinction). Finally, in a third phase (reinstatement), re-exposure to the ethanol-paired cues from the conditioning phase in the absence of further ethanol availability elicits clear-cut recovery of responding, whereas no such effect is observed upon presentation of water-paired cues.

In this model, acamprosate dose-dependently attenuated reinstatement of alcohol-seeking elicited by ethanol-paired cues without affecting responding to water-paired cues (Bachteler et al., 2005). This suggests that acamprosate can selectively reduce alcohol-seeking elicited by environmental stimuli predictive of alcohol availability. Alcohol-seeking can be considered as 1 behavioral component of craving. However, there seems to be a mismatch between this particular finding in rats and the general observation in alcohol-dependent patients. Thus, acamprosate usually does not interfere with alcohol craving. Ooteman et al. (2007) have recently experimentally shown that cue-induced craving is not affected by acamprosate whereas a reduction of autonomic nervous system reactions to alcohol-related cues is seen in abstinent alcoholics following acamprosate treatment.

How Does Acamprosate Reduce Relapse-Like Drinking Behavior?

Over the last decade, a growing amount of data from animal studies shows that the activity of the glutamatergic system appears to be of importance in treatment responses to this drug. In particular, it is assumed that acamprosate specifically acts on a hyper-glutamatergic system (Spanagel and Kiefer, 2008; Spanagel and Zieglgansberger, 1997). The hyper-glutamatergic hypothesis suggests that acute alcohol exposure leads to a transient reduction of glutamatergic activity, which normalizes over time because of homeostatic regulatory counter-mechanisms. Withdrawal of ethanol is subsequently accompanied by a rebound surge in glutamatergic activity, as the up-regulated counter-mechanisms are no longer dampened by the presence of ethanol. The resulting hyper-glutamatergic state is thought to contribute to the hyper-excitability and craving seen during alcohol withdrawal. Thus, acamprosate is thought to reduce the activity of the glutamate system by interacting with glutamate receptors (Harris et al., 2002, 2003). This action prevents the emergence of a hyper-glutamatergic state during alcohol withdrawal and conditioned withdrawal responses. Direct evidence for this mode of action comes from *Per2* knockout mice that exhibit a hyper-glutamatergic system, because of alterations in glutamate transport from the synaptic cleft. In particular, these *Per2* knockout mice show decreased expression of the astrocytic glutamate transporter EAAT1, resulting in reduced uptake of glutamate into astrocytes and thus elevated extracellular glutamate concentrations in the brain (Spanagel et al., 2005). As hyperactivity of the glutamatergic system is believed to be an important neurophysiological mechanism underlying the emergence and maintenance of alcohol dependence, it was of interest to assess whether alcohol-seeking behaviors would be modified in *Per2* knockout mice. Indeed, these animals showed an increased alcohol intake compared with control littermates (Spanagel et al., 2005). In subsequent experiments, the effect of acamprosate on brain neurochemistry and alcohol consumption was evaluated in these mice. Acamprosate reduced extracellular glutamate levels to those observed in wild-type mice and completely abolished the elevation in alcohol consumption. These experiments provided direct evidence demonstrating that acamprosate acts by dampening a hyper-glutamatergic state/system, thereby reducing alcohol consumption and relapse drinking behavior.

A PROSPECTIVE APPROACH TO PREDICT RESPONSE TO ACAMPROSATE

Pharmacological relapse prevention in patients suffering from alcoholism is currently based on 2 extensively tested medications: acamprosate (Mann et al., 2004) and naltrexone (O'Brien, 2005). Concerning the combined treatment with both compounds, 3 trials have been published so far. Two of them (Feeney et al., 2006; Kiefer et al., 2003) found an

additive effect if both drugs were combined, indicating that there might be a synergistic effect. Alternatively, a differential effect could be assumed. Individualized treatment of the “right” patient with the “right” drug would then markedly increase effects size. However, the third and largest study (Combining Medications and Behavioral Interventions; COMBINE; Anton et al., 2006), a multiple arm study comparing treatment outcome in alcohol dependence with naltrexone and acamprosate found no additive effect of both drugs. Only naltrexone showed a significant but modest treatment effect on 1 predetermined endpoint (return to heavy drinking) but not on the other (percent days abstinent).

The next step in this scenario has to define subgroups of acamprosate or naltrexone responders both on a neurobiological and a psychopathological basis. This study is currently being performed. “Project PREDICT” is a randomized, double-blind, placebo-controlled trial involving 427 subjects recruited in 4 alcohol treatment centers at German universities. By courtesy of the COMBINE steering committee, the design and most of the questionnaires, instruments, etc. of this U.S. study could be applied in Project PREDICT as well. However, patients are randomized into 3 groups only. In a 2:2:1 ratio they receive acamprosate, naltrexone, or placebo, following a manualized inpatient detoxification program (Mann et al., 2006). All patients receive medication for 3 months together with low intensity supportive psychotherapy (“medical management”) aiming primarily at enhancing compliance. This is followed by 3 more months of “medical management” without medication. Follow-up visits assess drinking status at 9, 12, 15, and 18 months after inclusion. Patients are encouraged to participate in self-help groups throughout the 18 months study duration. Drinking outcome will be related to usual baseline variables but also to pharmacogenomic markers, neurophysiological variables, and fMRI data, to identify potential correlates of treatment response. In particular, the hypothesis will be tested that naltrexone may be more effective in patients whose urge to drink is characterized by reward craving, whereas acamprosate would be more effective in relapses following relief craving (Littleton, 1995; Verheul et al., 1999). In relief craving, the patients consume to avoid the negative feelings and mood states associated with withdrawal from alcohol or “pseudowithdrawal”, which can be triggered by cues and can occur even months after detoxification. The physiological substrate of relief craving is believed to consist in hyperactivity of excitatory glutamatergic neurotransmission in the central nervous system that occurs when ethanol (inhibiting glutamatergic neurotransmission) is no longer present in the brain. Acamprosate, which attenuates cue-induced conditioned withdrawal in experimental animals and down-regulates glutamatergic neurotransmission in neurons exposed to ethanol, is expected to be particularly efficacious in treating alcohol dependence in subjects in whom relief craving dominates the psychological drives for consumption.

Further studies are needed to enable clinicians to define the subpopulation of alcohol-dependent patients that display

hyperglutamatergic neurotransmission during withdrawal and cue-induced “pseudo-withdrawal”. One useful technique might be the glutamate spectroscopy (MRS) which allows direct, non-invasive, *in vivo* measurements of cerebral glutamate in patients with mental disorders (e.g., Gallinat et al., 2007; Hasler et al., 2007; Yucel et al., 2007), and that now is explored in an ongoing trial in alcohol-dependent patients (Mann et al., 2007). In 1995, Rossetti and Carboni demonstrated for the very first time that augmented glutamate levels occur during alcohol withdrawal. In this study, glutamate levels were measured in the striatum of freely moving rats using *in vivo* microdialysis. Within 12 hours of withdrawal, extracellular glutamate levels were enhanced by 255% as compared with control rats. Glutamate concentrations remained elevated for a subsequent 12 hours and returned to control levels within 36 hours. In a series of studies by the group of De Witte, rats were chronically exposed to alcohol vapor inhalation. Similar time profiles of augmented glutamate levels during withdrawal were observed in the nucleus accumbens and hippocampus (Dahchour and De Witte, 1999, 2003; Dahchour et al., 1998). It is important to note that changes in glutamate levels may be due to deficits in glutamate transport (Melendez et al., 2005) and are time-locked to the overt physical signs of withdrawal (Rossetti and Carboni, 1995). These findings suggest that increased extracellular levels of glutamate reflect an over-activity of excitatory neurotransmission during alcohol withdrawal. Furthermore, they provide a biochemical rationale for the use of acamprosate with regard to the treatment of the alcohol withdrawal syndrome and possibly relapse into alcohol drinking (Littleton, 1995). In particular, it is suggested that acamprosate acts on a hyper-glutamatergic state, having only a small effect on a “normal” glutamatergic state (De Witte et al., 2005; Littleton, 1995; Spanagel and Kiefer, 2008). Since at magnetic field strengths of 2.0 T and above it is possible to resolve glutamate sufficiently well to measure its concentration (Gallinat et al., 2007; Schubert et al., 2004), high-field spectroscopy could provide an ideal tool for longitudinal tracking of neurometabolic plasticity within glutamatergic systems that accompany alcohol withdrawal, abstinence and its interaction with acamprosate treatment.

CONCLUSION

The balance of evidence suggests that acamprosate is an inhibitory modulator of the NMDA receptor by a mechanism not fully understood up to now, perhaps involving mGluR5. This may be relevant to effects on protracted withdrawal (as above) which may in turn be relevant to relapse. In addition, alcohol-induced sensitization and reinforcement is also mediated by the NMDA receptor and mGluR5 (Kotlinska et al., 2006; Tzschentke, 2007), and there is a rapidly increasing literature documenting the role of these and other non-NMDA receptors in the amygdala in conditioned alcohol responses (Schulz et al., 2001; Walker and Davis, 2002; Zhu et al., 2007).

The relevance of a hyperactive glutamatergic system for the pathophysiology of alcoholism was demonstrated by transgenic animal models that showed enhanced glutamate levels and exhibited a higher free choice alcohol intake than wild type mice and responded better to acamprosate (Crabbe et al., 2006; Spanagel et al., 2005). However, this implicates that especially craving because of alcohol-associated stimuli and the so-called “withdrawal relief craving” going along with conditioned hyperglutamatergic states might be a relevant target for acamprosate treatment, none of the earlier trials nor the COMBINE study were designed to define treatment relevant subgroups of alcoholism. In particular, these studies did not include biological measures of subgroups of alcoholism and especially subtypes of craving (Anton et al., 2006). It showed no treatment effects of acamprosate on abstinence proportion; in contrast to the majority of the European studies on this topic (Mann et al., 2004). Patient characteristics suggest that mainly patients without a physical withdrawal syndrome requiring withdrawal treatment were included in the COMBINE study (Anton et al., 2006; Kiefer and Mann, 2006). Given the suggestion that acamprosate’s efficacy is associated with its ability to modulate withdrawal-induced hyperglutamatergic states inducing craving, the specific pharmacological target for acamprosate might have been absent in negative acamprosate trials. Hence, recent research on acamprosate focuses on the definition of biological predictors of efficacy of acamprosate using genetic and endophenotypic (MRS) approaches.

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