Neurobiological alterations in alcohol addiction: a review

Alteraciones neurobiológicas en el alcoholismo: revisión

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Resumen

Todavía se desconoce el mecanismo exacto mediante el cual el etanol produce sus efectos en el cerebro. Sin embargo, hoy en día se sabe que el etanol interactúa con proteínas específicas de la membrana neuronal, implicadas en la transmisión de señales, produciendo así alteraciones en la actividad neuronal. En este artículo de revisión se describen diferentes alteraciones neuroquímicas producidas por esta droga. En primer lugar, el etanol actúa sobre dos receptores de membrana: los receptores ionotrópicos $GABA_A$ y NMDA. El etanol potencia la acción del GABA y antagoniza la del glutamato, actuando de esta manera como un depresor del SNC. Además, el etanol afecta a la mayoría de sistemas neuroquímicos y endocrinos. En cuanto al sistema de recompensa, tanto el sistema opioide como el dopaminérgico se ven alterados por esta droga. Igualmente, los sistemas serotonérgico, noradrenérgico, cannabinoide y el sistema del factor liberador de corticotropina, tienen un papel importante en la neurobiología del alcoholismo. Por otro lado, el etanol también puede modular componentes citosólicos, entre los cuales se encuentran los segundos mensajeros. Asimismo, en este artículo de revisión se presentan los tratamientos farmacológicos actuales para el alcoholismo, así como diferentes tratamientos potenciales de futuro, basados en resultados de investigaciones en curso.

Palabras Clave: alcoholismo, neurobiologia, neurotransmisores, GABA, glutamato.

Abstract

The exact mechanism by which ethanol exerts its effects on the brain is still unknown. However, nowadays it is well known that ethanol interacts with specific neuronal membrane proteins involved in signal transmission, resulting in changes in neural activity. In this review different neurochemical alterations produced by ethanol are described. Primarily, ethanol interacts with two membrane receptors: $GABA_A$ and NMDA ion channel receptors. Ethanol enhances the GABA action and antagonizes glutamate action, therefore acting as a CNS depressant. In addition, ethanol affects most other neurochemical and endocrine systems. In regard to the brain reward system, both dopaminergic and opioid system are affected by this drug. Furthermore, the serotonergic, noradrenergic, corticotropin-releasing factor and cannabinoid systems seem to play an important role in the neurobiology of alcoholism. At last but not least, ethanol can also modulate cytoplasmic components, including the second messengers. We also review briefly the different actual and putative pharmacological treatments for alcoholism, based on the alterations produced by this drug.

Key Words: alcohol dependence, neurobiology, neurotransmitters, GABA, glutamate.

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Alcohol dependence is a costly and socially devastating illness. Ethanol produces a complex and multidimensional effect on health and the global burden related to alcohol consumption in terms of morbidity, mortality and disability is detrimental. According to the WHO, alcohol consumption is the world's third largest risk factor for disease and disability; in middle-income countries, it is the greatest risk. Almost 4% of all deaths worldwide are attributed to alcohol, greater than deaths caused by HIV/AIDS, violence or tuberculosis, resulting in approximately 2.5 million deaths each year (World Health Organization, 2011).

Biomedical research is actually making a major effort to clarify the mechanisms of action of ethanol, which are still largely unknown. Alcohol consumption produces a wide variety of physiological and behavioural effects in a dose-dependent manner; from lowest to highest dose: anxiolysis, myorelaxation, analgesia, sedation, amnesia, hypothermia and anaesthesia. It is well known that ethyl alcohol or ethanol is toxic to most body tissues, producing changes on the cardiovascular system, digestive system, central nervous system, peripheral nerves, muscle-skeletal system and the foetus. This article will focus on the alterations produced by ethanol on the central nervous system.

On the whole ethanol generates a deep depression of neuronal functions, concomitantly decreasing the glucose metabolism throughout the human brain (G. J. Wang et al., 2000). Nonetheless, the exact mechanism by which ethanol exerts its effects on the brain is still unknown. It was initially hypothesized the disruption of the neuronal membrane fluidity, caused by the lipophilicity of ethanol. This theory suggested that the acute effects of ethanol would be due to an increase in neuronal membrane fluidity; while chronic use, in a compensatory way, would increase the rigidity of the membrane, consequently altering the neuronal functions (Chin & Goldstein, 1981; Rottenberg, 1986). However, nowadays it is well known that ethanol interacts with specific neuronal membrane proteins involved in signal transmission, resulting in changes in neural activity (Harris, Trudell & Mihic, 2008)

Primarily, ethanol interacts with two membrane receptors: $GABA_A$ and NMDA ion channel receptors. GABA is considered the quintessential inhibitory neurotransmitter in the central nervous system (CNS), and by contrast, glutamate, the main excitatory neurotransmitter. The effect of ethanol on these two systems is based on the enhancement of GABA action and the antagonism of glutamate action, therefore acting as a CNS depressant (Grobin, Matthews, Devaud & Morrow, 1998; Wirkner et al., 1999). In addition, ethanol affects most other neurochemical and endocrine systems (Diamond & Gordon, 1997) (Figure 1). Thus, both dopaminergic and opioid system are affected by this drug, mainly in regard to the brain reward system. Furthermore, the serotonergic, noradrenergic, corticotropin-releasing factor and cannabinoid systems seem to play an important role in the neurobiology of alcoholism. At last but not least, ethanol can also modulate cytoplasmic components, including the second messengers.

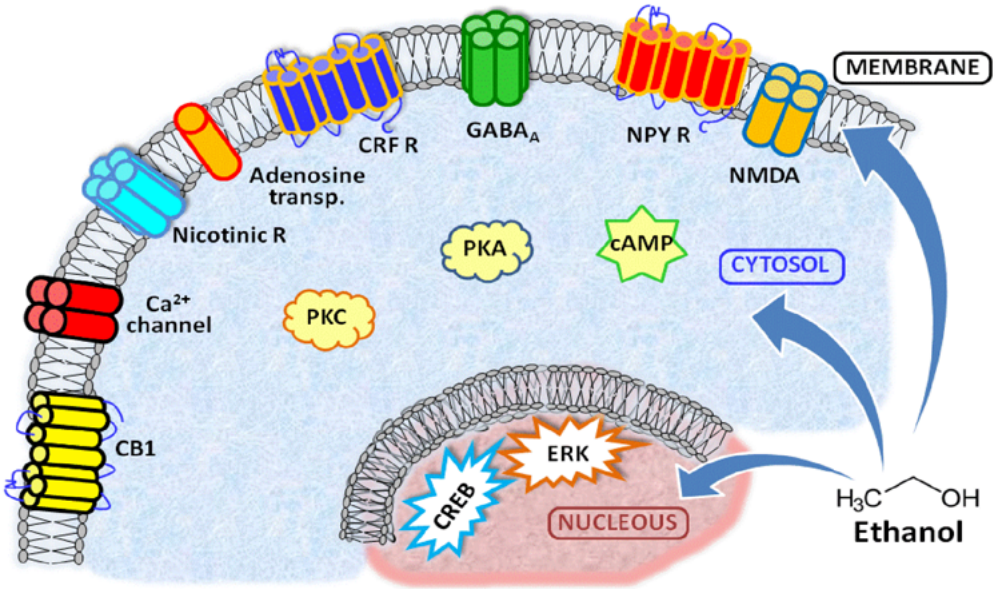

Figure 1. A representation of the great number of cellular components that are modulated by ethanol exposure directly or indirectly: membrane receptors, cytosolic signalling elements, and transcription factors in the nucleus. *R: receptor, NPY: neuropeptide Y, GABA: γ-amino-butyric acid, NMDA: N-methyl-D-aspartic acid, CRF: corticotrophin-releasing factor, CB1: Cannabinoid Receptor 1, PKC and PKA: protein kinase C and A, cAMP: cyclic adenosine monophosphate, ERK: extracellular-signal-regulated kinase , CREB: cAMP-responsive element binding protein.*

GABAergic system

GABA or γ-amino-butyric acid is the principal inhibitory neurotransmitter in the brain, and the GABAergic system plays an important role in the behavioural and pharmacological effects of ethanol. $GABA_A$ receptor protein complex is composed of five subunits, assembled to form a channel across the neuronal membrane for chloride ions. In addition to the main activator of this receptor, the GABA, there are many other substances that interact with this complex. These substances bind to different parts of the receptor, either in the extracellular region or in the channel domain, therefore modulating the anion channel activity. The receptor activation leads to the opening of the channel, allowing the entry of chloride ions, producing a hyperpolarization of the membrane and a consequent decrease in neuronal excitability (Baur, Minier & Sigel, 2006). Ethanol allosterically potentiates the action of GABA, or any other activator of this receptor as benzodiazepines or barbiturates, stimulating the flow of chloride induced by these $GABA_A$ receptors (Aguayo, Peoples, Yeh & Yevenes, 2002; Grobin et al., 1998). Even if the majority of studies suggest a direct allosteric modulation of the $GABA_A$ receptor by ethanol, phosphorylation/dephosphorylation mechanisms also seem to be important in the receptor modulation (Ravindran & Ticku, 2006).

Ethanol mediated $GABA_A$ potentiation does not occur in all brain regions, nor in all cell types in the same region; either even in all of $GABA_A$ receptors in a single neuron (Grobin, Papadeas & Morrow, 2000). This effect is attributed to the heterogeneity of the subunits that make up the receptors, for which seven families and different subtypes have been described. Only certain subtypes of some subunits appear to be sensitive to ethanol (Ravindran & Ticku, 2006).

Chronic ethanol consumption and repeated ethanol withdrawals produce many adaptations of $GABA_A$ receptor function. For instance, chronic exposure to ethanol results in a decrease in the sensitivity of $GABA_A$ receptor-mediated responses, including the sedative, motor incoordinating and acute cognitive-impairing effects of ethanol (Silvers, Tokunaga, Mittleman & Matthews, 2003). Additionally, chronic ethanol administration differentially alters the expression of distinct $GABA_A$ receptor subunit mRNA and protein levels in various brain regions, which would probably have significant functional consequences (Kumar et al., 2009). These adaptations of the $GABA_A$ receptor seem to be important in the marked increased CNS excitability that characterizes the withdrawal. Furthermore, several polymorfphisms in the $GABA_A$ gene have been found associated with alcohol dependence and characteristics of alcohol withdrawal and severity of alcohol dependence (Soyka et al., 2008).

On the other hand, $GABA_B$ receptor is a metabotropic transmembrane receptor for GABA that is linked to potassium and calcium channels via G-proteins. The activation of this receptor leads to an inhibition of the cation channels, resulting in a hyperpolarization of the membrane and a consequent decrease in neuronal excitability (Bowery et al., 2002). Ethanol enhances the $GABA_B$ induced synaptic responses and this phenomenon could be important in the altered mental and motor performance of individuals in an acute intoxication phase (Federici, Nistico, Giustizieri, Bernardi & Mercuri, 2009).

Glutamatergic system

Glutamate is the principal excitatory neurotransmitter in the brain and plays a crucial role in the pharmacological effects of the ethanol. Glutamate receptors can be divided into two groups according to the mechanism by which their activation gives rise to a postsynaptic current. Ionotropic glutamate receptors (NMDA or N-methyl-D-aspartic acid, AMPA or α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid, and kainate) form an ion channel pore that is activated when glutamate binds to the receptor (Traynelis et al., 2010). On the other hand, metabotropic glutamate receptors indirectly activate ion-channels on the plasma membrane through a signalling cascade that involves G-proteins (Niswender & Conn, 2010). The effect of ethanol over the glutamatergic systems lays on the modulation of the ionotropic glutamate receptors. Particularly the NMDA receptors are the most sensitive to the effects of ethanol, even if AMPA and kainate receptors are also modulated by this drug (Dodd, Beckmann, Davidson & Wilce, 2000).

The NMDA receptor, which is composed of four subunits, forms a cation channel. The activation of the receptor leads to increased permeability for Na^+, K^+, and mainly for Ca^{2+}, resulting in neuronal membrane depolarization (Traynelis et al., 2010). The acute action of ethanol on this receptor is to reduce the flow through the channel (Wirkner et al., 1999). This flow modification can alter many cellular functions, such as synaptic function, by inhibiting the release of neurotransmitters. Thus, ethanol inhibits the long-term potentiation phenomenon, which is important in learning and memory, probably through NMDA receptors (Givens & McMahon, 1995; Givens, 1995). On the other hand, chronic ethanol administration produces an adaptive up-regulation of NMDA receptor function in animal brains and in cultured cells (Hoffman & Tabakoff, 1994). During withdrawal, a rebound activation of these receptors occurs, playing an important role in the alcohol withdrawal syndrome, including delirium tremens and especially seizures (Hughes, 2009).

Nevertheless, the exact mechanism by which ethanol alters the functionality of this receptor remains still unknown. Almost certainly it does not exert any direct action on the different modulating sites so far known; neither seems to interact with the Mg^{2+} which is normally blocking the ion channel (Ron, 2004). The most likely mechanism of action is to interfere with the phosphorylation and compartmentalization of this receptor (Ron, 2004; Xu, Smothers & Woodward, 2011). As in the case of the $GABA_A$ receptor, there is a

great local and regional variability in the actions of ethanol on NMDA receptors. Ethanol does not inhibit the NMDA receptors in all brain regions and where it does inhibit, the inhibition occurs only in a subset of neurons (Yang, Criswell, Simson, Moy & Breese, 1996). This variability depends on the different subunits that form these tetrameric NMDA receptors, since only some seem to be responsible of the sensitivity to ethanol (Nagy, Kolok, Dezso, Boros, & Szombathelyi, 2003). At last, genetic studies have found variants in the NMDA receptor genes that are associated with alcoholism and related traits (Wernicke et al., 2003).

Dopaminergic system

Alcohol, like all other drugs of abuse, acutely activates the mesocorticolimbic dopamine system and, upon chronic administration, produces functional alterations of this important brain reward system. The anatomical core of the reward system are dopaminergic neurons of the ventral tegmental area (VTA) that project to the nucleus accumbens, amygdala, prefrontal cortex and other forebrain structures (Koob & Volkow, 2010). Available data suggest that the mesocorticolimbic dopamine system is involved both in the positive and negative reinforcing effects of ethanol (Soderpalm, Lof & Ericson, 2009). Firstly, ethanol was shown to cause dose-dependent excitation of dopaminergic VTA neurons *in vivo* and *in vitro* (Brodie, Shefner & Dunwiddie, 1990; Gessa, Muntoni, Collu, Vargiu & Mereu, 1985). Likewise, ethanol caused an increase of dopamine levels in the nucleus accumbens, which is another factor linking the mesolimbic dopamine system to reward (Boileau et al., 2003; Di Chiara & Imperato, 1988). In addition, behavioural studies have demonstrated that rodents self-administer ethanol directly in the VTA, further supporting the involvement of the reward system in the effects of alcohol (Rodd et al., 2004).

Nevertheless, dopaminergic lesion studies with the selective 6-hydroxydopamine neurotoxin consistently show that dopaminergic denervation of the nucleus accumbens does not interfere with ethanol consumption or maintenance of ethanol-reinforced responding (Ikemoto, McBride, Murphy, Lumeng & Li, 1997; Koistinen, Tuomainen, Hyytia & Kiianmaa, 2001). Similarly, elevation of dopamine levels in the accumbens by a selective dopamine reuptake inhibitor fails to alter ethanol self-administration (Engleman et al., 2000). These results indicate that ethanol self-administration is not dependent only on accumbal dopamine activation. Possibly, stimulation of this transmission is necessary for rewarding effects associated with low-dose stimulant actions of ethanol, but not essential for other aspects of reinforcing actions of the drug (e.g., anxiolytic effects) (Weiss & Porrino, 2002).

Many genes involved in the dopaminergic system show polymorphic variations in alcoholics. A variant of the tyrosine hydroxylase enzyme, which is involved in the synthesis of dopamine, is associated with early-onset alcoholism (Dahmen, Volp, Singer, Hiemke & Szegedi, 2005). Besides, certain variants in the genes encoding for dopamine metabolizing enzyme monoamine oxidase A and the dopamine D2 receptor are associated with the emergence of antisocial personality traits and a higher proneness for alcoholism (Parsian, 1999; T. J. Wang et al., 2007). The frequency of a polymorphism in the dopamine transporter gene was also significantly increased in alcoholics with severe alcohol withdrawal symptoms (Sander et al., 1997).

Opioid system

Ethanol reinforcement mechanisms involve, at least partially, the ethanol-induced activation of the endogenous opioid system. Ethanol may alter opioidergic transmission at different levels and several studies suggest that mu and delta opioid receptors, as well as the enkephalins and beta-endorphins, play a major role in ethanol's actions in the brain (Gianoulakis, 2009). The involvement of the opioid system in alcohol addiction interferes with mesolimbic dopamine transmission in the brain reward pathways. Thus, ethanol increases levels of endorphins in the nucleus accumbens (Olive, Koenig, Nannini & Hodge, 2001). In addition, the administration of opioid antagonists reduces the release of dopamine in the nucleus accumbens induced by ethanol (Gonzales & Weiss, 1998). However, there are other mechanisms that do not affect the dopaminergic transmission and contribute to the suppressive effects of opioid antagonists on the consumption of alcohol. In this regard, selective lesions of the dopaminergic terminals in the nucleus accumbens do not alter ethanol self-administration in rats, while naltrexone itself is able to reduce alcohol consumption in the same animals (Koistinen et al., 2001).

Many genetic studies have examined the association of the mu-opioid receptor gene with substance dependence, focusing on the A118G single-nucleotide polymorphism. One meta-analysis revealed that this SNP may contribute to the susceptibility of alcohol dependence in Asians but not in Caucasians (Chen et al., 2012); however, another one showed that it does not appear to affect the risk for substance disorder (Arias, Feinn & Kranzler, 2006). In any case, this polymorphism seems to be associated with naltrexone treatment response in alcohol addiction (Chamorro et al., 2012; Oslin et al., 2003).

Serotonergic system

Serotonin (5-hydroxytryptamine or 5-HT) has been implicated in several aspects of brain function including regulation of affective states, ingestive behaviour and addiction (Hayes & Greenshaw, 2011). Ethanol potentiates the function of the 5-HT_3 and the somatodendritic 5-HT_{1A} receptors (Lovinger, 1999). In addition, an increase in the extracellu-

lar serotonin levels has been reported in the nucleus accumbens after alcohol administration (Yan, 1999).

Studies in rodents selectively bred for alcohol preference have shown deficits in serotonin transmission, including low brain serotonin content, a decrease in serotonergic cells and fibers, and a compensatory up-regulation of 5-HT_{1A} receptors (Wong, Threlkeld, Lumeng & Li, 1990; Zhou, Pu, Murphy, Lumeng & Li, 1994). Moreover, reduced availability in serotonin transporters have been described in the brain of alcoholic subjects by a SPECT study (Heinz et al., 1998), and also in the *postmortem* caudate nucleus of alcoholic subjects (Storvik, Tiihonen, Haukijarvi, & Tupala, 2006). Since these deficits seem to represent a risk for developing abnormal drinking behaviour, alterations in serotonin transmission are thought to be more relevant to alcoholism type II, characterized by antisocial personality traits, higher hereditability and the early-onset form of the disease, compared to type I alcoholism, with anxious traits and social and late-onset (Cloninger et al., 1988). Consistent with this hypothesis, studies in humans have shown low cerebrospinal fluid content of the main serotonin metabolite 5-hydroxyindoleacetic acid predominantly in type II alcoholics (Fils-Aime et al., 1996; Virkkunen & Linnoila, 1993). Finally, there are genetic evidences for the association of a particular polymorphism of the serotonin transporter with alcohol addiction (Feinn, Nellissery & Kranzler, 2005).

Other systems

In addition, ethanol affects most other neurochemical and endocrine systems (Figure 1). Alcohol acts on nicotinic acetylcholine receptors, enhancing the function of some subtypes and inhibiting the activity of others (Davis & de Fiebre, 2006). Chronic exposure to ethanol also produces increased Ca^{2+} entry into neurons mainly via L-type calcium channels (Gerstin, McMahon, Dadgar & Messing, 1998), which is due to changes in the expression of some subunits that compose the channel (Katsura et al., 2006). An increase in the noradrenergic transmission has been observed at low doses of ethanol, while at high doses it produces a decrease (Rossetti, Longu, Mercuro, Hmaidan & Gessa, 1992). Besides, in patients with withdrawal syndrome, plasma and cerebrospinal fluid levels of noradrenaline are increased (Hawley, Major, Schulman & Linnoila, 1985) because of the overstimulation of noradrenergic neurons by the increased glutamate transmission and the loss of noradrenergic autoinhibition by reduced α_2-autoreceptor function (De Witte, Pinto, Ansseau, & Verbanck, 2003).

Corticotropin releasing factor (CRF) plays an important role during the development of alcohol addiction and stress-induced relapses to alcohol drinking (M. Heilig & Koob, 2007). For instance, alcohol-preferring rats displayed increased CRF release, which correlated with a high anxiety state (Richter, Zorrilla, Basso, Koob & Weiss, 2000). Similarly, a great number of evidences suggest a role for neuropeptide Y signalling in the regulation of anxiety-like behaviours and ethanol consumption (Thorsell, 2008). Thus, neuropeptide Y gene expression was significantly lower in the central nucleus of the amygdala of alcohol-preferring rats than non-preferring rats (Suzuki, Lumeng, McBride, Li & Hwang, 2004). Genetic data suggest that a polymorfphism in the neuropeptide Y gene may be associated with seizure during alcohol withdrawal (Okubo & Harada, 2001). A wide range of behavioral, pharmacological and genetic studies suggest that the endocannabinoid system is also implicated in the neurobiology of alcoholism (Erdozain & Callado, 2011, Erdozain et al, 2014).

Finally, several intracellular second messengers systems are also affected by ethanol (Moonat, Starkman, Sakharkar & Pandey, 2010) (Figure 1). Thus, acute ethanol could stimulate adenylyl cyclase activity and increase cAMP production, while chronic ethanol results in adenylyl cyclase down-regulation (Tabakoff et al., 1995). One of the mechanisms proposed for this acute stimulation by ethanol of the cAMP signalling involves the inhibition of a nucleoside transporter, which leads to the accumulation of extracellular adenosine, and thus the activation of the A_{2A} receptors coupled to G_s proteins (Newton & Messing, 2006). Furthermore, cAMP-responsive element binding protein (CREB) and its phosphorilated form seem to be increased after acute ethanol administration, while they are decreased during ethanol withdrawal (Moonat et al., 2010). Besides, several studies have implicated the protein kinase C family of serine-threonine kinases in mediating both acute and chronic responses to ethanol exposure (Newton & Ron, 2007). Finally, the signalling pathway of MAP kinases, and specifically the extracellular-signal-regulated kinase (ERK) subfamily are modulated by ethanol, since ERK phosphorylation is reduced after acute and chronic exposure in rats and mice (Zhai, Li, Wang & Lu, 2008) and also in postmortem brain of alcoholic subjects (Erdozain et al, 2014).

Pharmacological treatments for alcoholism

It is true that alcoholism cannot be treated without regard for its social, behavioural and motivational context. However, there is solid evidence today that pharmacological treatments can prolong the time to relapse following cessation of heavy drinking or decrease the number of heavy drinking days (Bouza, Angeles, Munoz & Amate, 2004). Nevertheless, the fact that ethanol interacts with a great number of neurotransmission systems, along with the genetic and individual factors of alcoholic patients, could explain that there is not a single effective treatment for alcohol dependence. Currently there are only three medications approved by the European Medicines Agency (EMEA) and the U.S. Food and Drug Administration (FDA) for the treatment of

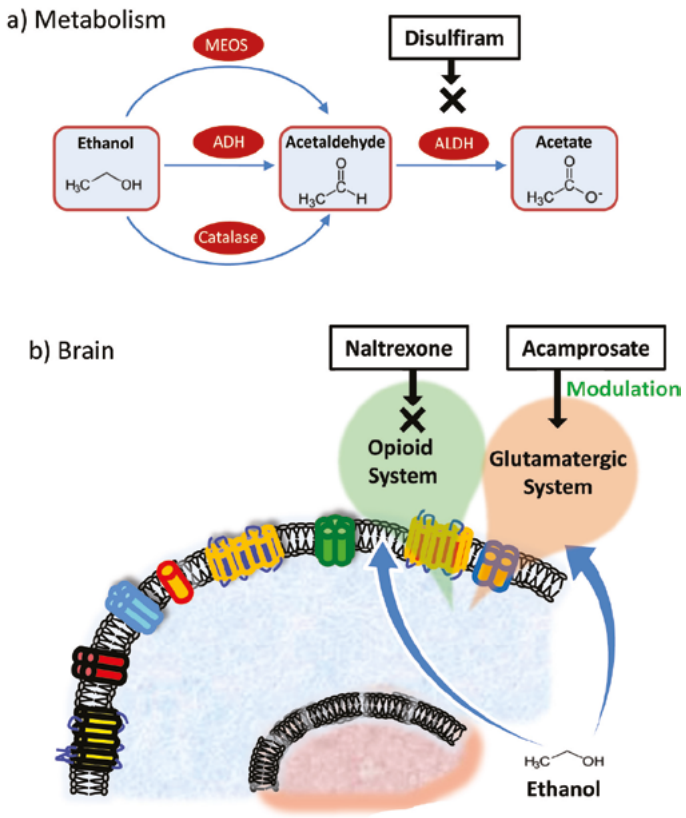

Figure 2. An illustration of the mechanism of action of the three medications currently approved by the European Medicines Agency (EMEA) and the U.S. Food and Drug Administration (FDA) for the treatment of alcohol abuse and alcoholism: disulfiram, naltrexone and acamprosate. **A)** Ethanol is metabolized to acetaldehyde mainly by the alcohol dehydrogenase (ADH) and in a lower extent by the microsomal ethanol oxidizing system (MEOS) and the hydrogen peroxide-catalase complex. The second step of the ethanol metabolism consists of the rapid conversion of the acetaldehyde to acetate, primarily though the aldehyde dehydrogenase (ALDH). Disulfiram inhibits the activity of aldehyde dehydrogenase. **B)** Naltrexone is a mixed opioid receptor antagonist with high affinity for μ-opioid receptors and acamprosate seems to restore the disrupted glutamatergic transmission that occurs after chronic alcohol use.

alcohol abuse and alcoholism: disulfiram, naltrexone and acamprosate (Figure 2). However, medication compliance issues, adverse side effects and the modest efficacy of these compounds reveal the need for developing safe and newer effective medications. Preclinical and clinical evidence suggest that other classes of medications might also be of potential use for alcoholism (Olive, 2010). In the next paragraphs a little review of each of these drugs is presented.

Disulfiram (Antabuse™), first approved by the FDA as a deterrent to alcohol consumption almost 60 years ago, inhibits the activity of aldehyde dehydrogenase, which metabolizes acetaldehyde to acetate. As a result, consumption of alcohol in the presence of this drug produces an accumulation of acetaldehyde in the periphery and central nervous system, which results in aversive reaction characterized by nausea, vomiting, severe headache, flushing, and other unpleasant autonomic and central nervous system disturbances. Despite its limitations, disulfiram remains a viable option as a treatment for alcohol dependence (Barth & Malcolm, 2010).

Naltrexone is a mixed opioid receptor antagonist with high affinity for μ-opioid receptors. The efficacy of naltrexone to suppress alcohol consumption, craving, and rates of relapse, albeit moderate, has attributed an important role to endogenous opioid peptides with affinity for the mu opioid receptor (endorphins and enkephalins) in mediating various alcohol-related effects and behaviours (Ray, Chin & Miotto, 2010).

Acamprosate is a homotaurine analogue with the ability to reduce alcohol consumption in rodents and promote abstinence in human alcoholics. While the precise neurobiological mechanisms of action of acamprosate have yet to be determined, the well-documented efficacy of this compound to reduce alcohol craving and relapse seems to lay on its ability to restore the disrupted glutamatergic transmission that occurs after chronic alcohol use (Mason & Heyser, 2010).

A great number of putative drugs for alcoholism are also being studied at the moment. $GABA_B$ receptor agonist baclofen, a nervous system depressant originally approved for use as a muscle relaxant and antispastic agent, represents a promising treatment for alcohol dependence. Preclinical animal studies have shown its action at various stages of the process of alcohol addiction, and clinical studies have already shown its efficacy on alcohol craving, intake, and relapse prevention (Gorsane et al., 2012). The anticonvulsivant topiramate also reduces alcohol consumption and relapse. Its possible mechanisms of action are hypothesized to be related to its ability to facilitate GABAergic transmission and antagonize AMPA and kainate glutamate receptor subtypes (De Sousa, 2010). Apart from its antipshychotic effects, aripiprazole is also able to reduce alcohol consumption in both rodents and human, probably as a result of its dopaminergic and serotonergic actions in frontal-subcortical circuits underlying alcohol reward and impulsivity (Vergne & Anton, 2010).

Both preclinical and clinical data provide evidence that nicotine administration increases alcohol intake, while nicotinic receptor antagonists, such as varenicline, recently approved for smoking cessation, reduce alcohol-mediated behaviours (Chatterjee & Bartlett, 2010). Antagonists of the primary receptor for the stress-related peptide CRF are able to reduce alcohol consumption and relapse-like behaviour in rodents, particularly in those with a history of ethanol dependence induced by prolonged alcohol vapour inhalation. These results show the importance of stress- and negative emotion-associated neural circuitry in mediating alcohol consumption and relapse (Zorrilla, Heilig, de Wit & Sha-

ham, 2013). Finally, the antagonism of the cannabinoid CB1 receptor is another putative treatment for alcoholism (Maccioni, Colombo & Carai, 2010).

At last, it is important to note that there is considerable heterogeneity among people with alcohol addiction, and that this heterogeneity suggests a need for personalized treatment approaches based on, among other factors, genetic variation. There is emerging literature on naltrexone pharmacogenetics, which has the potential to identify responders on the basis of particular genetic polymorphisms (Ray et al. 2010). Genetic variations on the corticotropin-releasing factor systems is also likely to moderate alcoholism treatment effects ((Markus Heilig, Goldman, Berrettini & O'Brien, 2011; Zorrilla et al., 2013).

Conclusion

The exact mechanism by which ethanol exerts its effects on the brain is still unknown. However, nowadays it is well known that ethanol interacts with specific neuronal membrane proteins involved in signal transmission, resulting in changes in neural activity. In this review different neurochemical alterations produced by ethanol have been described. Primarily, ethanol interacts with two membrane receptors: $GABA_A$ and NMDA ion channel receptors. Ethanol enhances the GABA action and antagonizes glutamate action, therefore acting as a CNS depressant. In addition, ethanol affects most other neurochemical and endocrine systems. In regard to the brain reward system, both dopaminergic and opioid system are affected by this drug. Furthermore, the serotonergic, noradrenergic, corticotropin-releasing factor and cannabinoid systems seem to play an important role in the neurobiology of alcoholism. Based on the alterations produced by this drug, different pharmacological treatments are already approved for alcoholism, and a great number of additional putative medications are being studied at the moment. At last, it is important to note that there is considerable heterogeneity among people with alcohol addiction, suggesting a need for personalized treatment approaches based on genetic variation.

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Conflict of Interest

The authors declare no conflict of interest.

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