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THERAPEUTIC TARGETS FOR ALCOHOLISM

L.A. Sorbera, S. Rajendran, C. Dulsat, N. Forns and E. Rosa

Thomson Reuters, Barcelona, Spain

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SUMMARY

Alcoholism is a chronic, progressive and relapsing disease characterized by craving for alcohol, continued use despite personal injury, inability to limit drinking, withdrawal syndrome when drinking stops and the development of tolerance. The mesocorticolimbic dopamine system in the brain is responsible for the rewarding properties of alcohol, with monoamines and their receptors playing a crucial role in the etiology of the disease. The pharmacological treatment of alcohol dependence to date includes sensitizing drugs, opioid antagonists, drugs acting on serotonergic and/or dopaminergic systems and drugs acting on glutamate receptors. Several factors determine the type and duration of treatment prescribed (e.g., dependence severity, history of previous treatment, presence of comorbid psychiatric or medical problems). However, treatment remains complicated and results vary for each individual. The search therefore continues for effective therapies for alcohol dependence. This article presents those drug targets that are currently under active investigation for the treatment of alcoholism.

INTRODUCTION

Ethyl alcohol, or ethanol, is an intoxicating ingredient produced by the fermentation of yeast, sugars and starches that can be found in beer, wine and liquor. Although alcohol has been recognized as an agent of abuse since the 17th century, the concept of alcoholism as a disease was not widely accepted until the second half of the 19th century. Alcoholism, also known as alcohol dependence, is a chronic, progressive and relapsing disease that is characterized by a strong craving for alcohol, continued use despite harm or personal injury, an inability to limit drinking, withdrawal syndrome when drinking stops, and the development of tolerance. According to the World Health Organization (WHO), there are 76.3 million persons with alcohol use disorders (1-6).

Correspondence: L.A. Sorbera, PhD, Thomson Reuters, Provença 388, 08025 Barcelona, Spain. E-mail: lisa.sorbera@thomsonreuters.com.

Alcohol modulates numerous neurotransmitters and receptors, and once consumed, it can affect every organ in the body. It is rapidly absorbed from the stomach and small intestine into the bloodstream, where it circulates through the liver. Enzymes in the liver metabolize alcohol, but only in small amounts at a time. Thus, excess alcohol is left to circulate throughout the body and the intensity of associated behavioral effects is directly related to the amount of alcohol consumed (1, 4, 7).

The mesocorticolimbic dopamine system in the brain is responsible for the rewarding properties of alcohol and other drugs of abuse. It begins in the ventral tegmental area and projects to the nucleus accumbens and forebrain. The nucleus accumbens is associated with motivation, while the dorsal striatum of the forebrain is implicated in learning and behavioral responses. In general, acute intake of alcohol results in alterations in excitatory and inhibitory neurotransmitters and their receptors, and effects are temporary and reversible. However, chronic exposure leads to long-lasting changes in receptors and signaling interactions; this process is known as neuroadaptation and involves changes at both the genetic and structural level. Monoamines are key players in the etiology of alcoholism. Dopamine has multiple actions on the reward center. Endogenous opioids, which are released after alcohol intake, attenuate stress and produce euphoria. Serotonin facilitates tolerance and can thereby cause an increase in alcohol consumption. In addition, alcohol can exert facilitating effects on the inhibitory action of GABA and attenuating effects on the stimulatory actions of glutamate (1, 8-11).

The treatment of alcoholism is notoriously difficult and is associated with a high failure rate. The complex nature of alcohol addiction requires medications to treat symptoms of alcohol withdrawal during detoxification, as well as a combined treatment approach incorporating both pharmacotherapy and psychosocial measures designed to promote abstinence and prevent relapse. Drugs used for treatment of alcohol dependence can be broadly classified into the following groups: sensitizing drugs, opioid antagonists, drugs acting on serotonergic and/or dopaminergic systems, and drugs acting on glutamate receptors. Disulfiram has been shown to be most effective for patients who believe in its efficacy and remain compliant with the treatment. The opioid antagonist naltrexone lowers relapse rate, reduces drinking days and prolongs periods of abstinence, while serotonin reuptake inhibitors and serotonin antagonists at best have equivocal efficacy. Acamprosate restores the normal activity of glutamate and GABA systems. However, not all patients respond

equally well to the same drugs and there remains a need for more effective therapies for alcoholism (1, 8, 11).

The search for effective treatment strategies for alcoholism continues, with research focusing on the identification of novel targets for drug development. Those targets which are currently under active investigation are discussed below (see Figure 1). Table I provides a selection of products under active development for each target and Table II includes selected patents.

TARGETS

α_1-Adrenoceptors

α_1-Adrenoceptors are a subtype of α-adrenoceptors that signal via $G_{\alpha q}$ proteins. Signaling involves phospholipase C (PLC)-mediated cleavage of phosphatidylinositol 4,5-bisphosphate (PIP2), resulting in an increase in inositol triphosphate (IP3) and diacylglycerol (DAG). DAG interacts with calcium channels of the endoplasmic and sarcoplasmic reticulum, increasing intracellular calcium release. The receptor also exerts excitatory signals in the central nervous system (CNS) and inhibition has been shown to suppress alcohol consumption. Antagonism of this receptor may be effective in the treatment of alcoholism (12-14).

Aldehyde dehydrogenase

Aldehyde dehydrogenases (ALDH; EC 1.2.1.3) are a group of enzymes that catalyze the oxidation of aliphatic and aromatic aldehydes using NADP as a cofactor. Studies have shown that polymorphisms in liver alcohol dehydrogenase and ALDH alter ethanol metabolism and elimination, and therefore influence the susceptibility to ethanol intake. Moreover, an inherited deficiency in ALDH class 2 in particular has been shown to decrease the risk for alcoholism. Thus,

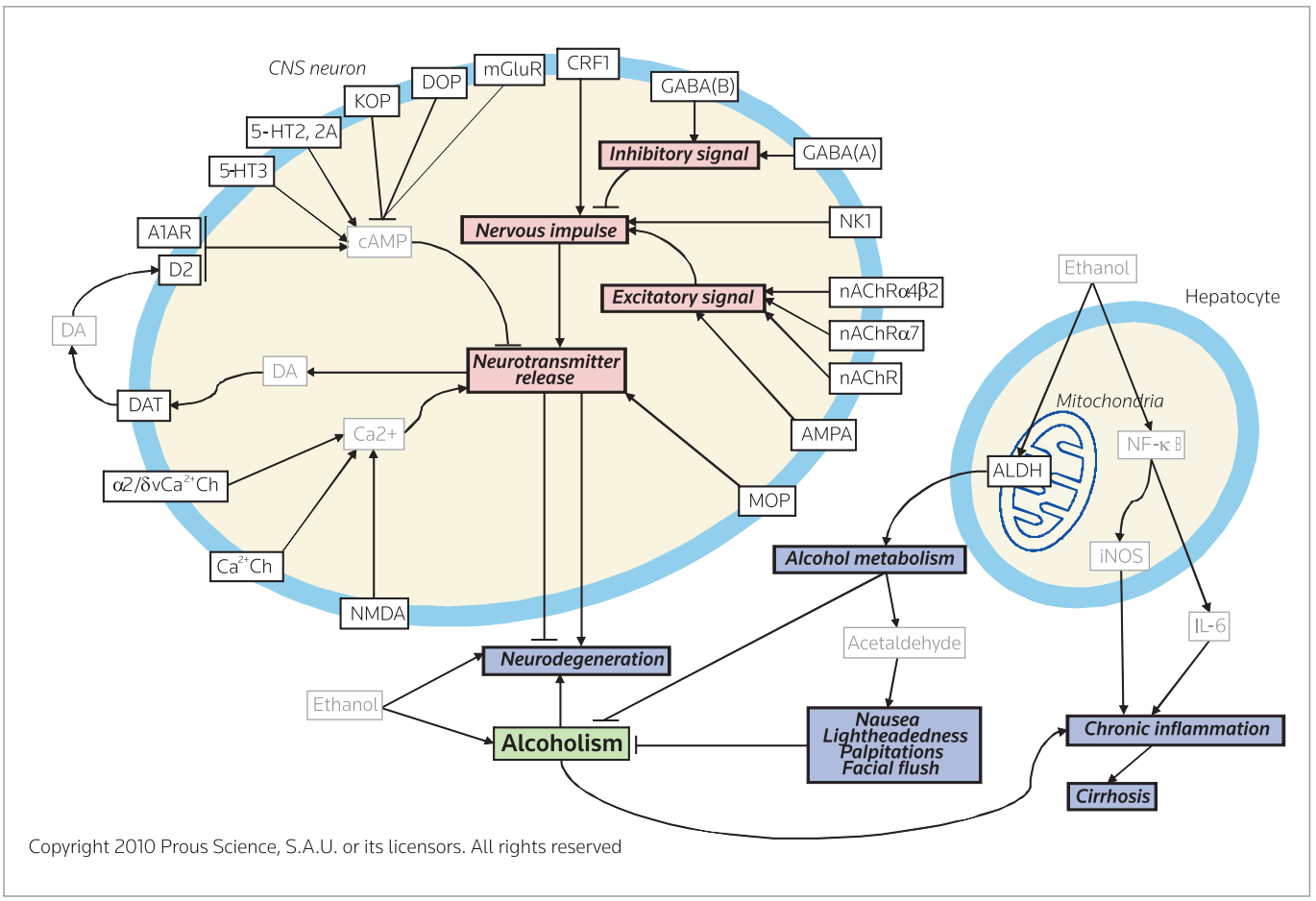

Figure 1. Alcoholism targetscape. A diagram showing an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of alcoholism and their biological actions. Gray or lighter symbols are targets that are not validated (i.e., targets not associated with a product that is currently under active development for alcoholism). Abbreviations: $\alpha 2/\delta$ vCa^{2+} Ch, calcium channel $\alpha 2/\delta$ subunit; A1AR, α_1-adrenoceptor; ALDH, aldehyde dehydrogenase; AMPA, AMPA receptor; Ca^{2+} Ch, calcium channel; cAMP, 3',5'-cyclic adenosine monophosphate; CRF1, corticotropin-releasing factor CRF_1 receptor; D2, dopamine D_2 receptor; DA: dopamine; DAT, dopamine transporter; DOP, δ opioid receptor; GABA(A), $GABA_A$ receptor; GABA(B), $GABA_B$ receptor; 5-HT2, 5-HT_2 receptor; 5-HT2A, 5-HT_{2A} receptor; 5-HT3, 5-HT_3 receptor; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; KOP, κ opioid receptor; mGluR, metabotropic glutamate receptor; MOP, μ opioid receptor; nAChR, nicotinic acetylcholine receptor; NF-κB, nuclear factor NF-kappaB; NK1, tachykinin NK_1 receptor; NMDA, NMDA receptor.

Table I. *Selected targets and products launched or being actively investigated for alcoholism (from Thomson Reuters Integrity℠).*

Target name	Product	Source	Phase
α_2-Adrenoceptor (nonspecified subtype)	Prazosin hydrochloride	Yale University	III
	Modafinil	National Institute on Drug Abuse	II
Aldehyde dehydrogenase (nonspecified subtype)	Disulfiram	Pfizer	L-1953
AMPA	Topiramate	National Institute on Alcohol Abuse and Alcoholism/Yale University	III
	Caroverine hydrochloride	Phafag	L-
Calcium channel subunit (nonspecified subtype)	Gabapentin	National Institute on Alcohol Abuse and Alcoholism	III
CRF_1 receptor	Verucerfont	National Institute on Alcohol Abuse and Alcoholism	II
Dopamine D_2 receptor	Quetiapine fumarate	University of Texas Southwestern Medical Center Dallas	III
	Aripiprazole	National Institute on Alcohol Abuse and Alcoholism	II/III
Dopamine transporter (DAT)	DOV-102677	Euthymics Bioscience	I
$GABA_A$ receptor	Diazepam	Roche	L-1963
$GABA_B$ receptor (nonspecified subtype)	ALKS-29	Alkermes	I/II
Metabotropic glutamate (mGlu) receptor (nonspecified subtype)	Acamprosate calcium	Merck-Lipha Sante	L-1989
Nicotinic acetylcholine receptor (nonspecified subtype)	Mecamylamine hydrochloride	Yale University	III
Nicotinic acetylcholine α4 receptor	Varenicline tartrate	National Institute on Drug Abuse	II
Nicotinic acetylcholine α7 receptor	Varenicline tartrate	National Institute on Drug Abuse	II
Nicotinic acetylcholine β2 receptor	Varenicline tartrate	National Institute on Drug Abuse	II
NMDA receptor	Acamprosate calcium	Merck-Lipha Sante	L-1989
Norepinephrine reuptake inhibitor	DOV-102677	Euthymics Bioscience	I
δ Opioid (DOP) receptor	ALKS-33	Alkermes	II
κ Opioid (KOP) receptor	Naltrexone hydrochloride	Bristol-Myers Squibb	L-1998
	Nalmefene	Biotie Therapies	Preregistered
	ALKS-33	Alkermes	II
μ Opioid (MOP) receptor (isoform MOR-1)	Naltrexone hydrochloride	Bristol-Myers Squibb	L-1998
	ALKS-33	Alkermes	II
Serotonin 5-HT_2 receptor	Melperone hydrochloride (FG-5111)	Lundbeck	L-
Serotonin 5-HT_{2A} receptor	Quetiapine	University of Texas Southwestern Medical Center Dallas	III
	Aripiprazole	National Institute on Alcohol Abuse and Alcoholism	II/III
Serotonin 5-HT_3 receptor	Olanzapine/ondansetron (TO-2060)	Transcept Pharmaceuticals	II
Serotonin 5-HT reuptake	Citalopram hydrobromide	National Institute on Drug Abuse	II
	DOV-102677	Euthymics Bioscience	I
Tachykinin NK_1 receptor	Aprepitant	National Institute on Drug Abuse	II
	LY-686017	Lilly/National Institute on Alcohol Abuse and Alcoholism	II

inhibitors of ALDH may be effective in reducing excessive alcohol consumption and relapse (15-17).

AMPA receptor

The AMPA receptor is a non-NMDA (*N*-methyl-D-aspartic acid)-type ionotropic transmembrane receptor for the excitatory neurotransmitter glutamate that is involved in learning and memory; AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) is the synthetic ligand for this receptor. Studies have shown that changes in the number of synaptic AMPA receptors may be responsible for synaptic plasticity (i.e., the neuronal mechanism required for learning and memory). The glutamate system plays a major role in mediating ethanol's effects on brain and behavior, and the AMPA receptor together with the NMDA receptor has been shown to mediate neuroadaptation to drugs of abuse and ethanol. The AMPA receptor in particular appears to play a prominent role in neuroplastic changes due to chronic ethanol exposure and in alcohol-seeking behavior and relapse. Antagonism of this receptor may be effective in the treatment of substance abuse, including alcoholism (18-20).

Calcium channels and the α2/δ subunit

Calcium channels are pore-forming proteins present in cell membranes that control the flow of ions, thereby establishing the small voltage gradient that exists across the membrane of cells. These

Table II. *Selected patents for targets being validated for alcoholism (from Thomson Reuters Integrity℠).*

Target	Patent	Source	Phase
$GABA_A$ receptor	WO 2006004945	WiSys Technology Foundation	Biological testing
	WO 2009143445	UWM Research Foundation	Biological testing
Metabotropic glutamate receptor	WO 2010011570	H. Lundbeck	Biological testing
δ Opioid (DOP) receptor	WO 2007027628	US Department of Health & Human Services	Biological testing
	WO 2008036980	AllTranz	Biological testing
κ Opioid (KOP) receptor	US 2009186873	Eli Lilly and Company	Biological testing
	WO 2008036980	AllTranz	Biological testing
	WO 2009130270	Janssen Pharmaceutica	Biological testing
	WO 2009130272	Janssen Pharmaceutica	Biological testing
	WO 2010063292	Biotie Therapies/H. Lundbeck	Biological testing
μ Opioid (MOP) receptor	WO 2007027628	US Department of Health & Human Services	Biological testing
	WO 2008036980	AllTranz	Biological testing
Sodium- and chloride-dependent glycine transporter 1	WO 2010092286	sanofi-aventis	Biological testing

voltage-gated channels (L-, N-, P/Q-, R- and T-type) are formed as a complex of several different subunits and are prominent throughout the nervous system, where they are responsible for triggering the release of neurotransmitters. It has been suggested that modulation of intracellular calcium levels by voltage-gated calcium channels may be involved in neuronal death and cognitive deficits. Selective inhibition of N- and T-type calcium channels has been shown to decrease acute ethanol intoxication and alcohol consumption. On the other hand, activation of the α2/δ subunit of voltage-gated calcium channels may reduce alcohol consumption, attenuate alcohol withdrawal and prevent relapse. The subunit regulates calcium current density and activation/inactivation kinetics of the channel. α2/δ is the regulatory subunit for the P/Q-type (*CACNA1A*), N-type (*CACNA1B*), L-type (*CACNA1C* or *CACNA1D*) and T-type calcium channels (*CACNA1G*). Several α2/δ subtypes are evident and are characterized by the presence of a δ1, δ2, δ3 or δ4 chain. Activation of this subunit is considered a therapeutic option for the treatment of alcoholism (21-24).

Dopamine D_2 receptor

The dopamine D_2 receptor is a G protein-coupled, seven-transmembrane-spanning receptor protein (G_i/G_o) that, like the D_1 receptor, binds dopamine present in the CNS in basal ganglia. The dopaminergic system originating in the midbrain ventral tegmental area appears to be crucial in the development of alcoholism and addiction to other drugs of abuse, with the D_2 receptor in particular playing an important role in the reinforcing and motivating effects of ethanol. The D_2 receptor inhibits cAMP synthesis by coupling to $G_{\alpha i/o}$ and also regulates calcium and potassium channels via PLC when it forms hetero-oligomers, particularly with the D_1 receptor. This D_1-D_2 receptor hetero-oligomer has been proposed to facilitate a distinctive dopamine-mediated Ca^{2+} signaling, with important effects on synaptic plasticity. In illnesses such as bipolar disorder, schizophrenia, Parkinson's disease and restless legs syndrome, transmission in discrete dopamine pathways may involve a range of hypoactivation to hyperactivation of dopamine receptors, particularly those of the D_2 subtype. Thus, antagonism of this receptor subtype may be an effective treatment approach. However, full agonists or pure D_2 receptor antagonists may not be optimal therapeutic approaches due to their inability to restore the aberrant dopamine pathways to a normal level of basal tone. D_2 receptor partial agonists, on the other hand, may stabilize activity in dopamine pathways by dampening excessive and/or by restoring deficient D_2 receptor stimulation and achieving a desired level of basal activity. The D_2 receptor is currently one of the most widely studied targets for antipsychotic drugs, and D_2 antagonists and D_2 partial agonists have been validated for alcoholism (25-28).

Dopamine transporter

The dopamine transporter (DAT) is a protein encoded by the dopamine transporter gene *DAT1* (*SLC6A3*), involved in the transport (reuptake) of dopamine. DAT binds to residual dopamine in the synaptic cleft following neurotransmission and is then repacked into synaptic vesicles and stored in the axon terminal of the presynaptic neuron for future use. Dopaminergic neurotransmission plays a crucial role in the development and maintenance of alcohol dependence, and targeting dopamine transport (reuptake) and/or decreasing dopamine signaling may be effective in the treatment of alcoholism (26, 29, 30).

$GABA_A$/$GABA_B$ receptors

GABA (γ-aminobutyric acid) is the major inhibitory neurotransmitter in the brain and spinal cord and acts via $GABA_A$, $GABA_B$ and $GABA_C$ receptors. The $GABA_A$ and $GABA_B$ subtypes have been suggested to play an important role in the development of alcoholism. $GABA_A$ receptors are widely distributed throughout the CNS and considered the major fast-acting inhibitory neurotransmitter system in the brain. They are ionotropic and can be activated by several different compounds. Studies suggest that the genes encoding $GABA_A$ receptor subunits (e.g., *GABRA2*) are linked to alcoholism. $GABA_B$ receptors are widely distributed throughout the CNS and in peripheral autonomic terminals and are metabotropic, thus distinguishing them from ionotropic $GABA_A$ receptors. $GABA_B$ receptors are coupled to G proteins and activation causes a decrease in Ca^{2+} and an increase in K^+ influx through the membrane. $GABA_B$-induced changes in Ca^{2+} conductance are thought to be associated with P/Q-type and N-type, and

possibly L-type, calcium channels and with several different types of potassium channels. Targeting of $GABA_A$ and $GABA_B$ receptors may be effective in the treatment of alcoholism (12, 23, 31-34).

Metabotropic glutamate receptor

Metabotropic glutamate (mGlu) receptors are a special subclass of glutamate receptors that are G protein-coupled receptors. They bind the excitatory amino acid glutamate and thus mediate several of its numerous functions in the central and peripheral nervous systems. There are eight different mGlu receptors ($mGlu_1$ to $mGlu_8$) which are classified into groups I, II and III. They are ubiquitously distributed throughout the CNS and multifunctional. They regulate neuronal excitability and synaptic transmission and play a role in many physiological and pathological conditions, including control of movements, schizophrenia, stress and anxiety, epilepsy, drug addiction, learning and memory, among others. Glutamate appears to play a crucial role in drug addiction and alcoholism and modulation of these receptors is a potential treatment for alcoholism (12, 35, 36).

Nicotinic acetylcholine receptors

Nicotinic acetylcholine receptors (nAChRs) are a class of acetylcholine (ACh) receptors that are activated by ACh and the alkaloid nicotine (which imitates the effects of ACh), which distinguishes this class of ACh receptors from the unrelated muscarinic acetylcholine receptors (mAChRs). nAChRs are linked to ion channels in the cell membrane and are divided into two subclasses: the ganglionic nicotinic receptors found in the central and peripheral nervous systems and the neuromuscular nicotinic receptor found in neuromuscular junctions of somatic muscles. Activation of the neuronal receptor through ligand binding causes depolarization of the plasma membrane, resulting in calcium entry and excitation of the presynaptic neurons. This induces neurotransmitter release and long-term potentiation through gene regulation. Studies suggest that glycine receptors in the nucleus accumbens and nAChRs in the ventral tegmental area participate in the mesocorticolimbic dopamine system, activating and reinforcing the effects of ethanol. There are several types of neuronal nAChRs that vary according to the arrangement of the several homologous subunits around the central ion channel. The $\alpha4$, $\alpha7$ and $\alpha4\beta2$, as well as the $\alpha3\beta2$, $\alpha3\beta4$ and $\alpha6$, subunits of the nAChR family have all been suggested to be potential therapeutic targets for the treatment of alcoholism (37-39).

NMDA receptor

The NMDA receptor is a subtype of glutamate receptor that binds the excitotoxic amino acid NMDA in neurons. Activation of the NMDA receptor results in the opening of an associated ion channel pore, allowing influx of Na^+, K^+ and Ca^{2+}, the latter thought to play a critical role in synaptic plasticity. Synaptic overactivity results in excessive glutamate release, thus overstimulating postsynaptic cell membrane receptors (i.e., the NMDA receptor), which, upon activation, open associated ion channel pores and increase ion influx. The consequence is neuronal cell injury and death. The glutamate system plays a major role in mediating the effects of ethanol on brain and behavior, and the NMDA receptor, together with the AMPA receptor, has been shown to mediate neuroadaptation to ethanol. Upregulation of NMDA receptors and downregulation of $GABA_A$ receptors may be responsible for the central effects of long-term ethanol consumption. Antagonism of the NMDA receptor may therefore be effective in the treatment of alcoholism (40-42).

Opioid receptors (μ, δ and κ)

Opioid receptors are a class of G protein-coupled receptors found in regions of the brain that bind morphine, as well as in areas that are unrelated (e.g., striatum) and related (e.g., along the aqueduct of Sylvius) to pain and reward. Subtypes include μ (MOP), δ (DOP), κ (KOP) and NOP receptors, which have all been shown to exert antinociceptive effects and appear to be involved in reward and compulsive drug/alcohol intake. Natural ligands for these receptors are the opiate peptide neurotransmitters (derived from proopiomelanocortin [POMC], proenkephalin, prodynorphin or pronociceptin/orphanin FQ), although opiates (e.g., morphine) are potent agonists that mimic the action of the natural transmitters. Agents (i.e., antagonists, agonists and partial agonists) targeting the μ, δ and κ opioid receptors may be effective in the treatment of alcoholism (9, 43, 44).

Serotonin 5-HT_2, 5-HT_{2A} and 5-HT_3 receptors

5-Hydroxytryptamine (5-HT; serotonin) is a biogenic amine neurotransmitter in the CNS that is synthesized in neurons of the raphe nucleus in the brainstem and present in high concentrations in the hypothalamus and basal ganglia. The serotonergic system innervates almost all areas of the brain and spinal cord, and 5-HT is involved in a wide variety of behaviors, including: affective state, sleep–wakefulness, feeding behavior, sexual behavior, temperature regulation, circadian rhythmicity, locomotion, neuroendocrine secretion, hallucinogenesis, pain and reward-seeking behavior. 5-HT acts via several receptors that belong to the class of phosphoinositide-specific PLC-linked receptors such as the 5-HT_2 receptors. The 5-HT_2 receptors are involved in tracheal smooth muscle contraction, bronchoconstriction, arterial occlusion and control of aldosterone production. The 5-HT_{2A} receptor is also a potential target in alcoholism since antagonists of 5-HT_2 receptors and the 5-HT_{2A} subtype in particular have been shown to reduce alcohol consumption and craving in diagnosed alcoholics. The 5-HT_3 receptor subtype has been shown to be potentiated by ethanol intake and appears to modulate reward. Antagonism of the 5-HT_3 receptor may also be effective in the treatment of alcoholism (19, 45-48).

Tachykinin NK_1 receptor

Tachykinins are a group of polypeptides or neurokinins including substance P, neurokinin A and neurokinin B, which share four of five carboxyl-terminal amino acids (Phe-Xaa-Gly-Leu-Met-NH_2). They are localized in both the central and peripheral nervous systems and cause hypotension, contraction of the smooth muscle of the gut and bladder, and secretion of saliva. The effects of tachykinins are mediated via three tachykinin receptor subtypes, NK_1, NK_2 and NK_3, which are members of the superfamily of G protein-coupled, seven transmembrane-spanning receptors. The NK_1 receptors have been shown to be involved in alcohol consumption and inactivation of this receptor type modulates alcohol reward and escalation. Thus, NK_1 antagonism may be effective in the treatment of alcoholism (49, 50).

DISCLOSURES

The authors state no conflicts of interest.

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