ABSTRACT

Over the past decade, there has been growing interest in understanding the neuroscientific basis of alcoholism and in developing effective therapeutic pharmacologic agents that target the underlying neurochemical processes that mediate alcohol-seeking behavior. Corticomesolimbic dopamine pathways are central to the development of alcohol reinforcement. Therefore, medications that can modulate dopamine by their actions at serotonin, opioid, gamma aminobutyric acid, and glutamate receptors have been considered as treatments for alcohol dependence. This overview will present knowledge on progress in developing a variety of medications for the treatment of alcohol dependence. (Adv Stud Nurs. 2004;2(2):48-53)

The significant and escalating problem of alcohol addiction, with its accompanying physical and psychosocial sequelae, has driven scientists and clinicians to attempt to augment the traditional psychotherapeutic and behavioral approaches with pharmacologic therapy. As with other psychiatric diagnoses, such as depression, it has now been learned that there is a neurobiologic basis to the disease of alcoholism. Understanding what happens at the level of the brain and exploring and developing pharmacotherapy based on this understanding promise to assist alcohol abusers in their attempts to stop drinking and to diminish their craving for this drug and potential for relapse. Four major issues have driven research efforts: (1) Up to 50% of alcohol-dependent patients relapse shortly after detoxification and/or nonpharmacologic treatment; (2) Knowledge has been gained in the past decade in the field of neurobiology with regard to the complex and multifaceted neurotransmitter systems within the brain that have been implicated in the desire for and addiction to alcohol; (3) Some individuals may possess a biologic predisposition to alcoholism based on abnormalities in brain chemistry that may be treatable via medication therapy; and (4) Programs that use psychosocial or behavioral models have raised questions about the potential for synergistic, additive, or even counteractive interactions with the pharmacologic dose of supposed therapeutic medications.

Of the biobehavioral processes that maintain alcohol-seeking behavior, reinforcement is the most reliable. In behavioral studies, alcohol, like other abused drugs, can serve as a reinforcer, increasing the probability that an individual will work on a contingent basis to acquire more and more of the substance. Few animal models exist, because animals do not tend to be attracted to ethanol in the same manner as humans; however, performing behavioral studies with animal models, whereby animals begin to selectively prefer alcohol to water, and then coupling these behavioral studies to neurochemical studies has been the mainstay for understanding the neuropharmacology of alcohol-seeking behavior. To make this connection, micropipettes are placed into the brain of the animal while the animal is pressing a lever for alcohol or another substance. Through microdialysis, fluids are obtained and measured to ascertain whether various neurochemicals are increased or decreased during alcohol-seeking behavior.

How does alcohol exert its influence on the brain? The focus of this discussion is to provide a fundamental understanding of what is known about the biologic basis of alcohol dependence and the pharmacologic agents that are being used, developed, and/or proposed as adjuncts to traditional treatment strategies.
**Alcohol's Mechanisms of Action**

Historically, it was believed that alcohol's intoxicating effects were a result of fluidization of the cell's phospholipid membrane, working in a manner similar to the way in which some general anesthetics or analgesics function. Unless given in high doses, however, alcohol is neither an effective anesthetic nor analgesic. In fact, alcohol's influence on membranes causes minimal fluctuations—ones that are within physiologic limits. Furthermore, ethanol, a large molecule, does not bind to a specific receptor. It binds to some hydrophobic pockets in close proximity to receptors but not to receptors themselves. The function of receptors is to recognize and bind specific ligands, which are ions, molecules, or a molecular group that bind to another chemical entity to form a larger complex. This then influences conversion of an extracellular signal to an intracellular signal. The processes by which this information is relayed are known collectively as signal transduction mechanisms.

Transmembrane receptors employ various types of signal transduction. The 2 receptor systems through which ethanol exerts its effects are the ligand-gated ion channels and the guanine nucleotide (G)-protein coupled receptors. The ligand-gated ion channels permit the fast movement of some ions, such as sodium, potassium, or chloride, across the lipid layer of the cell membrane via the use of a specific neurotransmitter; this influx of ions affects intracellular processes. The G-protein coupled receptors, which comprise multiple segments linked by G proteins, are more complex, involving hormones and other cellular messengers, such as calcium. Glutamate and gamma-aminobutyric acid (GABA)-A are 2 ligands used in the ligand-gated ion channels. Dopamine, serotonin, and GABA-B are among the ligands used in the G-protein coupled transmembrane signal transduction system.

To summarize, alcohol exerts its cellular effects via 2 main cell transport systems that use various receptors, including glutamate, voltage-gated calcium channels, serotonin (5-HT), GABA-A, and GABA-B (Figure 1). The acute and chronic effects of these receptor systems differ, accounting for the relative importance of alcohol reinforcement, tolerance, and withdrawal under these conditions.

**The Dopamine Theory of Addiction**

The most popular theory as to why humans self-administer potentially lethal drugs, such as alcohol, is that these chemicals activate the reinforcement system in the brain, which under normal circumstances is activated by substances and activities that are necessary to survival, such as food, water, and sex. Reinforcers are thought to increase the effect of dopamine at receptors in the mesolimbic system, which originates in the A10 ventral tegmental area, relay in the nucleus accumbens, and send efferent signals to the hippocampus and cortex (Figure 2A). In the nucleus accumbens, reinforcing such as ethanol increase the release of dopamine. Phillips et al found that that dopamine is released from the nucleus accumbens when a rat presses a lever that delivers reinforcing brain stimulation to its ventral tegmental area. Furthermore, if the dopamine system is lesioned by administering 6-hydroxy dopamine, which is toxic to the dopamine cells, the animal will show a tendency toward decreased alcohol consumption.

Microanalysis, lesioning via 6-hydroxy dopamine, and biobehavioral studies during self-administration reveal that contingent alcohol consumption increases mesocorticolimbic dopamine levels. Functionally, dopamine neurons discharge rhythmically, but alcohol induces a burst-firing pattern associated with increased reinforcement. In other words, increased levels of dopamine medi-
ate the rewarding or reinforcing effects of a drug of abuse, such as ethanol. The drive to drink is multifactorial and modulated by processes that are related to memory and learning but also to fear stimuli and primal fear impulses. Thus, the drive to drink is modulated by emotion and by cognitive processes. For example, individuals prefer to drink alcohol in a social setting surrounded by their friends, because the cognitive memories of these experiences modulate the rewarding effects of alcohol.

If high levels of dopamine are present when animals ingest alcohol, it would seem intuitive that introducing dopamine antagonists would eliminate the drive to take drugs or drink alcohol. In practice, however, this does not occur. In fact, after an initial transient suppression, the animal tends to drink more. This is because the neuroadaptive processes of postsynaptic receptor blockade are so high that an animal will attempt to overcome the blockade by drinking more. If, however, instead of attempting to block normative dopamine function, there is an attempt to modulate suprabasal dopamine functioning, the results may be more successful. To accomplish this task, the interactions between dopamine and other neurotransmitters must be understood and capitalized upon.

Dopamine does not mediate alcohol reinforcement on its own but receives neuromodulation from several other neurotransmitters. The most critical of these include tonic inhibition by 5-HT and modulation by opioid, GABA, and glutamate (n-methyl-D-aspartate/adenosine monophosphate-activated [AMP A]/kainate) receptors. Serotonin's influence on dopamine is complex and depends on its interactions with particular 5-HT receptor subtypes. For example, although 5-HT T2 receptors potentiate dopamine release, 5-HT T3 receptors inhibit midbrain dopamine release. GABA neurons inhibit dopamine neurons in the ventral tegmental area; however, midbrain dopamine release is facilitated by activation of glutamate receptors and opioid receptors.

Understanding dopamine neuromodulation has been an important target for medication development in the field of alcoholism research. All of these brain chemicals govern the drive to drink alcohol, which is influenced by cognitive processes and basal mood state—by what a person thinks and feels. Furthermore, an understanding that acute and chronic drinking have different effects on neurotransmitters (see Sidebar, page 51) is crucial to developing medications that target different types of drinking behaviors and different types of drinkers (eg, those who had early onset of alcoholism versus those who developed alcoholism later in life).

**Treatment Modalities Based on Biochemistry**

Because patients with different subtypes of alcoholism (eg, early onset versus late onset or those who have comorbidity, such as depression or anxiety) may have varying responses to pharmacologic therapies, continuing to explore how various neurotransmitters function in various types of alcohol-dependent patients and attempting to tailor treatment to each individual are ongoing goals. The following section describes various medications that target neurotransmitters—all of which modulate dopamine function but may be more or less effective and appropriate depending on the type of patient and that patient's history.

**Opioids (Naltrexone, Naloxone, and Nalmefene)**

Acute administration of alcohol has been shown in animal and human studies to stimulate the release of endogenous beta-endorphins. In individuals with a strong family history of alcohol abuse, there seems to be a larger than normal increase in the amount of beta-endorphins released when a drink is taken; this perhaps increases the risk of abusing alcohol because it induces a pleasurable sensation.
Naltrexone and naloxone antagonize opioid receptors (acting primarily on mu receptors) and work by decreasing the craving for alcohol, resulting in fewer relapses. Nalmefene is another opioid antagonist that blocks delta, kappa, and mu receptors. Multiple studies with these medications reveal that they attenuate ethanol consumption, and, in the case of naltrexone, this tendency is negatively correlated with baseline beta-endorphin levels. Gianoulakis found that in humans with a family history of alcoholism, alcohol intake is associated with a concomitant dose-dependent rise in beta-endorphin levels. Blockade at the mu receptor may therefore diminish alcohol abuse in this manner.

Another proposed mechanism of action for the opioids is via their effects on the mesocorticolimbic system, which plays an important—although not completely understood—role in reinforcement of drug and alcohol addictive behaviors. It may be that opioids serve as direct neuromodulators of dopamine discharge in the nucleus accumbens or facilitate the inhibitory discharge of GABA efferents located there. One final mechanism of action that has been proposed for naltrexone and related drugs is modulation of the hypothalamic-pituitary axis stress response.

Overall naltrexone is an effective treatment for alcohol dependence; however, there have been important negative studies and some limitations. Large-scale multicenter clinical trials showing efficacy are lacking (despite the aggregate findings from single-site trials), as are dose-response studies that might reveal better efficacy in higher doses. Few studies longer than 12 weeks in duration have been conducted. Studies targeting specific types of alcoholism, such as in those with a genetic predisposition, might reveal different efficacies for different populations of drinkers. One final drawback to the use of naltrexone is that its efficacy relies on medication compliance (in those 80% compliant, relapse rates were 14% versus 50% in patients taking placebo); thus, the practical aspects of assuring that the alcohol user takes medication as directed may be difficult to achieve outside of specialized facilities designed to cope with alcohol addiction. Nurses help patients taking this medication and their families by teaching them methods to increase adherence to long-term medication therapy and by offering psychosocial treatments that enhance motivation to remain sober.

SEROTONIN-RELATED MEDICATIONS (FLUOXETINE, BUSPIRONE, AND ONDANSETRON)

As many alcohol-dependent patients also have concomitant psychologic problems, such as depression, anxiety, and impulsivity, and because these emotional disorders are associated with serotonin dysfunction, preclinical and clinical research has explored serotonin deficiency as a proposed biologic mechanism of alcohol abuse. Animal studies have revealed that low levels of serotonin activity in the central nervous system are associated with an increase in alcohol drinking, and initial studies by Naranjo and colleagues have shown that selective serotonin reuptake inhibitors (SSRIs) are associated with less alcohol use. There has been some debate as to whether the actions of SSRIs may be nonspecific because these medications also increase satiety for food and water; however, even when food and water intake returns to normal, fluoxetine seems to continue to suppress alcohol consumption, suggesting that in animals, this drug is somehow reducing the reinforcing effects of alcohol and/or motivation to continue drinking.

Large-scale, well-conducted, double-blind clinical trials have demonstrated clearly that SSR1 medications may not be effective in a general population of alcohol-dependent individuals, especially among those with an early onset of disease or without comorbid emotional illnesses, such as depression or anxiety. Even for these individuals, in especially depressed patients for whom it was initially believed that serotonergic medications would be helpful, recent studies indicate that these medications may decrease depression without decreasing drinking. For individuals with anxiety, buspirone may reduce drinking behavior, but it is unclear if this is secondary to a reduc-
tion in anxiety alone or due to a direct neurochemical effect on the centers that control alcohol use in the brain. Ondansetron, a 5-HT3 receptor antagonist, is a promising medication for the treatment of early-onset alcoholism. The biomolecular explanation for why this drug appears to work for this subgroup of individuals may have to do with variations in the serotonin transporter that affects transmitter turnover rather than a simple serotonin deficiency state.

Thus, it is likely that the role of serotonin and serotonergic drugs in ethanol use is very complex, and that one possible method for explaining the interaction between serotonin and ethanol is via a complex interaction between alcohol drinking and polymorphic differences in the serotonin transporter. One avenue for the future may be to genetically screen alcohol-dependent individuals to determine to which serotonergic medication a particular individual might respond based on this data.

Glutamate Antagonism and GABA Enhancement (Acamprosate, Topiramate)

Widely studied and approved in Europe, acamprosate enhances GABA transmission by blocking glutamate receptors. In essence, by antagonizing glutamate, this decreases dopamine function, which in turn decreases the desire to increase ethanol intake. Glutamate antagonists can work hand in hand with medications that enhance GABA output, because GABA output decreases cell-body release of dopamine, leading to essentially the same end result: decreased ethanol intake.

A pharmacologic agent that combines both of these mechanisms of action is topiramate, a drug currently approved by the US Food and Drug Administration for use in seizure disorders. Topiramate antagonizes alcohol's rewarding effects associated with abuse by inhibiting mesocorticolumbic dopamine release via the facilitation of GABA and the inhibition of glutamate functions (Figure 2B). Its mechanism of action may be thought of as similar to a running faucet with a plugged-up drain. Excess dopamine is akin to water running from a tap into the sink. As long as the water (dopamine) is running, there is stimulation to drink. Opening the plug would reduce this excess water (dopamine) by letting it begin to drain (action of GABA). However, a continuous new supply of water (dopamine) is present as long as the faucet is running (excitation by glutamate). To turn off the water (dopamine), turning off the faucet (glutamate inhibition) is needed. Once this occurs, all of the water (dopamine) drains away (action of GABA) and no more can fill the sink (because glutamate has turned off the tap).

It is believed that individuals with chronic alcoholism might have more glutamate binding sites in the brain compared with those who are not alcohol dependent, and these binding sites could enhance dopamine transmission. Use of topiramate may reduce this activity and decrease the desire to drink, particularly in this subgroup of people. It is likely that topiramate has multiple mechanisms of action, including effects on voltage-gated calcium channels (reducing withdrawal symptoms), sodium channels, and the subtypes of glutamate (AMPA/kainate) that relate to its ability to potentiate GABA and reduce craving.

Johnson et al performed a double-blind, randomized, controlled, 12-week clinical trial comparing oral topiramate (in escalating doses ranging from 25 mg to 300 mg per day) to placebo in 150 patients, all of whom also

**Figure 2B. Glutamate Antagonists: Topiramate—Basic Science**

Midbrain to nucleus accumbens: increased GABA and decreased glutamate to ventral tegmental area = suppression of dopamine input to nucleus accumbens.
From nucleus accumbens to cortex: decreased glutamate hypersensitivity in hippocampus and cortex = reduced GABA/glutamate and inhibition of nucleus accumbens to cortex reward.
Sum: decreased facilitation of midbrain to cortex brain reward.
GABA = gamma-aminobutyric acid; GLU = glutamate; N Acc = nucleus accumbens; VTA = ventral tegmental area; DA = dopamine; HC = hippocampus.
Data from Johnson et al.
received brief behavioral treatment to maximize medication adherence. Patients were then interviewed about their drinking behaviors and received blood tests to determine plasma gamma-glutamyl transferase levels (GGT), an objective measure of alcohol consumption. At the conclusion of the study, patients taking topiramate had 2.88 fewer drinks per day ($P = .0006$), 3.10 fewer drinks per drinking day ($P = .0009$), 27.6% fewer heavy drinking days ($P = .0003$), 26.2% more abstinent days ($P = .0003$), lower GGT levels, and less self-reported craving. According to the authors, patients taking topiramate had significantly reduced craving due to drinking. The researchers concluded that topiramate in doses up to 300 mg per day is more effective than placebo as an adjunct to standardized medication compliance management in the treatment of alcoholism, with no differences seen between patients with late- versus early-onset alcoholism.

**Conclusion**

The complex interaction between neurotransmitters, alcohol, and various structures in the brain (in particular the mesocorticolimbic pathways) might hold the key toward a multifaceted approach to pharmacotherapy as an adjunct to psychotherapy and behavioral techniques in the management of alcoholism. As different subtypes of alcohol-dependent patients (eg, those with comorbid psychiatric conditions or those whose alcohol abuse was expressed at various stages of their lives) appear to respond to different drugs acting on dopamine via different associated brain chemicals, the way of the future seems to be to tailor pharmacotherapy according to each individual's specific history and perhaps genetic type. Furthermore, drugs that seem to work on more than one pathway (eg, topiramate with its dual action on glutamate and GABA), and combinations of therapies (eg, naltrexone and acamprosate being investigated in the Combining Medications and Behavioral Interventions [COMBINE] study) also hold scientific and clinical interest in an attempt to target both "state" and "trait" effects of drinking behavior and to reduce craving, the reward sensations, and tolerance, while improving abstinence and reducing the incidence of relapse and withdrawal symptoms. Although this seems an ambitious undertaking, continued progress in our understanding of the biologic basis of alcohol dependence may make this possible.

**REFERENCES**